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Title:

High-definition transcranial infraslow pink noise stimulation for chronic low back pain: Protocol for a pilot, safety, and feasibility randomized control trial.

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ABSTRACT

Introduction: Chronic low back pain (CLBP) is a common disabling health condition. Current treatments demonstrate modest effects, warranting newer therapies. Brain imaging demonstrate altered electrical activities in cortical areas responsible for pain modulation, emotional, and sensory components of pain experience. Treatments targeting to change electrical activities of these key brain regions may produce clinical benefits. This pilot study aims to (a) evaluate feasibility, safety, and acceptability of a novel neuromodulation technique, high definition transcranial infraslow pink noise stimulation (HD-tIPNS), in people with CLBP, and (b) derive treatment estimates to support sample size calculation for a fully powered trial should trends of effectiveness be present.

Methods & analysis: A pilot, triple-blinded (participant, outcome assessor, and treating researcher) randomized two-arm placebo-controlled parallel trial. Participants with CLBP will be randomized to either sham stimulation or HD-tIPNS (targeting somatosensory cortex and dorsal and pregenual anterior cingulate cortex). Primary outcomes include feasibility and safety measures. Secondary measures include clinical (pain, function), psychological, quantitative sensory testing, and electroencephalography collected at baseline, immediately post-intervention, and at one-week, one-month and three-months post-intervention. Descriptives will be calculated for all measures. Linear mixed-effects model will be used to obtain treatment estimates on clinical outcomes. A nested qualitative study will assess participants perceptions about acceptability of intervention and analyzed thematically.

Ethics and dissemination: Ethical approval has been obtained from the Health and Disability Ethics Committee (Ref:20/NTB/67). Findings will be reported to regulatory and funding bodies, presented at conferences, and published in a scientific journal.

STRENGTH AND LIMITATIONS

- A triple-blinded randomized two-arm placebo-controlled parallel trial.
- A new neuromodulation technique will be pilot tested for treatment of CLBP.
- First study to simultaneously target cortical areas responsible for pain modulation, emotional and sensory components of pain experience.
- Not powered to test treatment effectiveness but will provide treatment estimates for a future fully powered trial.

INTRODUCTION

Chronic low back pain (CLBP) is a significant and growing health challenge, affecting individuals, the wider community, and the healthcare system.[1-3] Along with pain and impaired function, individuals with CLBP have significant psychological comorbidities and poor quality of life.[1-3] Currently available treatments for CLBP demonstrate at best small effect sizes.[4-6] Pharmacological interventions are not effective with a high risk of adverse outcomes.[7-9] Thus, new, innovative, evidence-based, safer therapies are warranted for the management of CLBP.

Resting-state cortical activity alterations have been demonstrated in individuals with CLBP.[10-13] The most notably involved cortical areas include the anterior cingulate cortex (ACC) and the primary somatosensory cortex (SSC), which are the central hubs of the pain processing brain networks.[10-18] The ACC, particularly the pregenual region (pgACC), is part of the descending pain modulatory system (or anti-nociceptive system), the activation of which releases μ-opioids that act to modulate incoming nociception information from the hyperactive, spinal cord circuits, thereby alleviating pain.[12,15,18-20] The SSC, along with the dorsal region of ACC (dACC), is part of ascending nociceptive (lateral and medial) pathways that are responsible for encoding the sensory (i.e. painfulness) and the emotional components (e.g. suffering) of the pain experience.[12,15,18-20] Recent evidence suggests that alterations in the functional connectivity patterns between the pain processing regions (pgACC, dACC, SSC) are critical for maintaining chronic pain and are associated with its clinical and psychological outcomes.[14,16,18, 21-28]

Neuromodulatory interventions targeted to alter activities in cortical pain processing areas may improve clinical outcomes. Transcranial electrical stimulation (TES), a non-invasive brain stimulation technique, can influence the electrical activity of targeted brain regions, promote cortical plasticity, and improve the functional connectivity to/from the targeted area, thereby improving pain modulation. Evidence for effect of TES for treatment of CLBP is limited (n=9 pilot studies[29-37], n=2 protocols[38,39] and have demonstrated mixed results.[40,41] Previous TES studies targeted altering cortical electrical activity of a single superficial brain region[29-32,34-37] (e.g., Motor cortex or dorsolateral prefrontal cortex) using transcranial direct current stimulation (tDCS), except one study[33] that targeted a deeper brain region (dACC). None of the studies has simultaneously targeted multiple-brain regions (pgACC, dACC, SSC) responsible for the descending and ascending modulation of nociceptive sensory information. Further, the stimulation technique used in the previous TCS studies involved applying two large scalp electrode pads that deliver currents to diffuse areas of the brain, making focalized stimulation of targeted brain regions less feasible. Focal and simultaneous stimulation of multiple brain regions could help improve clinical outcomes with larger effect sizes, similar to invasive neuromodulatory interventions[42].

We propose determining the feasibility and safety of a novel high definition transcranial infraslow pink noise stimulation (HD-tIPNS) technique, targeting the pgACC, dACC, and SSC regions simultaneously in people with CLBP. This protocol outlines the methods and analysis used in the pilot randomized controlled trial. The specific aims are to (a) evaluate the feasibility, safety, and acceptability of the HD-tIPNS technique in people with CLBP, and (b) provide estimates of clinical outcome measures to

support a sample size calculation for a fully powered trial should the trend of effectiveness be present.

METHODS AND ANALYSIS

The following guides have been used to prepare this study protocol: Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement[43], the template for intervention description and replication (TIDieR) checklist[44], and IMMPACT Recommendations[45-49]. In addition, this trial has been prospectively registered (Table 1).

Study design:

The proposed study will be a triple blinded pilot randomized placebo-controlled parallel trial with two intervention arms. The outcome measures will be collected at baseline, immediately post-intervention, and at follow-up periods: one week, one month, and three months post-intervention (Fig. 1).

Randomization: A research administrator, not involved in other procedures, will randomize participants on a 1:1 basis using a computerized open-access randomization software program to:

- Group 1: HD-tIPNS, or
- Group 2: Sham stimulation

The randomization schedule will be concealed in sequentially numbered, sealed opaque envelopes and provided to participants at their first treatment session.

Blinding: Participants, outcome assessor, and treating researchers will be blinded to group allocation. Stimulation programs on Starstim device will be designed and controlled by an independent researcher to allow blinding of the treating researcher. The success of blinding will be assessed after the completion of the intervention and follow-up phases. The participant, and the outcome assessor, and treating researcher will be asked "What type of treatment they believe that they/the participant received respectively?" and will be required to choose between three options: active, sham, or don't know. The confidence in their judgement will also be assessed on an 11-point numeric rating scale *(0=Not at all confident to 10=Extremely confident)*, with the reason for their judgement being noted and whether the intervention was revealed to them. Unblinding will be permissible only in the case of an adverse event or any unexpected event.

Study setting: This study will be conducted in the Department of Surgical Sciences laboratory, Dunedin School of Medisine, Dunedin hospital, New Zealand.

Participants and eligibility criteria:

Adults with CLBP will be eligible to participate.

Inclusion criteria: Age between 18 to 75 years, pain in the lower back (the region between 12th rib and gluteal fold) for ≥3 months, and bad enough to limit usual activities or change daily routine for >1 day, a score of >4 on an 11-point numeric pain rating scale (NPRS, 0=*No pain* to 10=*Worst pain imaginable*) in the week prior to enrolment, a disability score of ≥5 on Roland–Morris Disability Questionnaire[50,51]. These cut-off scores are used as an indication that CLBP significantly impacts daily functioning, are

by International Association of Study of Pain guidelines and are in line with optimal Delphi definitions of LBP prevalence (DOLBaPP).[3,50-53]

Exclusion criteria: Participants with the following self-reported health conditions will be excluded: Inflammatory arthritis, auto-immune conditions, acute back pain, underwent spinal surgery or lumbar epidural injections in past six months, waiting/scheduled for any interventional procedures in the next six months, neurological diseases, substance abuse, unstable medical or psychiatric conditions, peripheral neuropathy, vascular disorders, cognitive impairments [a score of <24 on the mini-mental status examination conducted at baseline], psychiatric illnesses, electronic/metal body implants (around the head/neck region), and recent or current pregnancy.

Sample size:

This proposed research is a pilot exploratory study, which will be executed to make a power estimate for a future phase II study should the intervention appear feasible, safe, acceptable, and show trends of effectiveness.

Recruitment and study enrolment:

Participants will be primarily recruited through broadcasting in the public media (e.g., newspapers and social media). Participants attending healthcare providers will also be invited to participate. The total recruitment period will be a one-year (June'21 to May'22). Advertisements will be placed in the local newspapers twice a month and social media once a month (Sponsored Facebook ad, for one week). Advertisement fliers will be placed around a tertiary hospital, regional healthcare practices, and

supermarkets. A recruitment email will be sent to the local tertiary educational university/polytechnic staff and students once every two months.

All volunteers will complete an online screening form. Potential participants will be contacted by a researcher with a health professional background (Trained Musculoskeletal Physiotherapist) to undergo further screening over the phone to confirm eligibility prior to study enrolment. The study information sheet will be emailed to eligible participants. Written informed consent will be obtained before baseline testing. At the baseline session, all participants will complete questionnaires to capture demographics, clinical characteristics of CLBP, including presence of central sensitivity (Central Sensitization Inventory)[54,55], neuropathic pain quality (PainDETECT)[56], pain personification[57], and treatment expectancy and credibility[58].

Intervention procedures(Table 2):

The intervention will be administered five times a week (30 minutes/session) for four weeks by an assistant research fellow trained by the primary investigator experienced in neuromodulation techniques. A battery-driven wireless transcranial electrical stimulator (Starstim-Home TES®, Neuroelectrics, Spain) will be used to deliver stimulation while participants are comfortably and quietly seated. Eight electrodes will be placed on a neoprene head cap following the International 10-20 EEG system to simultaneously target pgACC, dACC, and SSC(Fig. 2).

For HD-tIPNS group, the stimulation will be delivered at a current strength of a maximum of 2mA for 30min, with 60s ramp up and ramp down at the beginning and end of each stimulation session, with continuous stimulation in between. The pink

noise stimulation at a current strength of a maximum of 0.6mA will be superimposed on the infraslow (0.1Hz sinusoidal) waveform of a current intensity of 1mA. The current strength at each electrode will never exceed the maximum safety limit of 2mA. The intervention dosage is chosen based on the previous TES studies in CLBP[29-39] and follows safety guidelines[59-61].

For the sham stimulation group, to create an identical skin sensation to active stimulation, we will use the Actisham protocol created by the Neuroelectrics.[62] The current will be applied for a 60s ramp up and 60s ramp down at the beginning and end of each stimulation session, without any current for the remainder of the session. The duration of the sham session will be like HD-tIPNS session to blind the procedure appropriately. Participants in both groups will be informed that they may or may not perceive any sensations during the stimulation treatment. The previous TES studies have used this sham procedure and are shown to effectively blind participants to the stimulation condition, as it can induce the same scalp sensations perceived during active stimulation, both in terms of intensity and localization. Further, the Actisham protocol will prevent the currents from reaching the cortex, thus avoiding causing any brain excitability changes.[62]

Usual care/concomitant treatments: Participants will be permitted to continue their medications/exercises/other concomitant treatments for the duration of the trial, with the type and dosage being recorded at the baseline session. Any changes to their concomitant treatments will be recorded at every treatment and assessment session. Participants will be advised not to change any of their concomitant treatments for the

duration of the trial. Participants with the intention of taking new medications or changing their treatment in the next three months will be excluded.

Outcome measures:

An assessor, blinded to the group allocation, will collect outcomes at baseline (T_B), immediately post-intervention (T_{im}), and at follow-up of one week (T_{1wk}), one month (T_{1m}) and three months (T_{3m}) post-intervention. The chosen secondary measures have good psychometric properties, are used in clinical trials involving people with CLBP and are by recommendations[45-49].

Primary outcomes:

Feasibility:

- Recruitment rate, the number of participants recruited per month. Participants will be recruited over one year, with no threshold placed on the recruitment rate for each month.
- The proportion of participants recruited from the total number screened (with reasons for exclusion), expressed as a percentage.
- Adherence to intervention measured as number of treatment sessions attended by each participant expressed as a percentage of total number of sessions.
- Drop-out rates, measured as the number of participants who dropped out in each group, expressed as a percentage of the total number of participants enrolled in the study.

Safety:

At each treatment and follow-up session, the treating researcher will record any adverse effects that likely have a causal relationship with the intervention. The following variables will be recorded:

- Worsening or improvement of symptoms: The Discontinuation-Emergent Sign and Symptom (DESS)[63], will be used to record worsening or improving side effects compared to status prior to previous session.
- Qualitative description and intensity of each symptom on a Likert scale (0=none to 10=extreme)
- Relation of symptom to treatment, measured on a scale ranging from 1=unrelated to 5=strongly related.
- Duration and time taken for resolution of each symptom expressed in minutes.
- Any drop-outs due to adverse effects and how the adverse effects were managed.

Acceptability:

Participant acceptability of the intervention will also be recorded quantitatively on an 11-point NRS (0=Not at all acceptable to 10=Very acceptable).

Secondary measures (Table 3):

Pain intensity and interference: using Brief Pain Inventory[64], a standardized, validated questionnaire for CLBP.

Pain unpleasantness (affective component) measured using an 11-point unpleasantness NRS (0=not at all unpleasant to 10=most unpleasant imaginable).[65,66]

Pain bothersomeness: measured using an 11-point bothersomeness NRS (0=not at all bothering to 10=most bothering).[65,66] A categorical question will also be used “In

the last one week, how bothersome has your low back pain been?'' with five choises: "not at all", "slightly", "moderately", "very much", and "extremely".[67,68]

Physical Function: *Roland–Morris Disability Questionnaire*[50,51] will be used to assess self-reported functional abilities. *International Physical Activity Questionnaire—short form*[69], will be used to assess physical activity levels.

Movement related pain[70]*:* assessed using repeated spinal bending tasks (forward and backward bending). Participants will complete 20 repetitions of forward and backwards bending tasks each, with the cue to pick up a pencil placed on the floor in front of them and to view a marker placed on the ceiling behind them, respectively.[70-72] Repeated forward and backward bending tasks will be conducted independently, with at least 10-15minutes rest in between. The number of repetitions completed by each participant will be recorded. Pain intensity will be recorded on an NRS (0=no pain to 100=worst pain imaginable) before commencing movements, then following every five repetitions.

The global rate of change[73]*:* assessed using the question *"Compared to the beginning of treatment, how would you describe your back at this moment?"* Participants will rate their perceived change on an 11-point scale (-5=much worse, through 0=unchanged, to +5=completely, recovered).

Quality of life and wellbeing: will be assessed using *European Quality of Life–5 Dimensions* scale[74] and *World Health Organisation- Five Well-Being Index*[75] respectively.

Psychological measures: will include *Depression, Anxiety, and Stress Scale*[76]*,* to measure those three psychological constructs, *Pain Catastrophizing Scale*[77]*,* to measure extent of catastrophic thoughts and feelings about their pain[78], *Pain Vigilance*

and Awareness Questionnaire[79] to measure frequency of habitual 'attention to pain', *Pain self-efficacy*[80] to assess pain self-efficacy beliefs, *Positive and Negative Affect Schedule-short form*[81,82] to measure two dominant dimensions of affect style, *Emotion Regulation Questionnaire*[83] to quantify two self-reported emotional regulation strategies, *Brief Illness Perception Questionnaire*[84] to assess cognitive perceptions, *Five-Facet Mindfulness Questionnaire*-15[85,86] to assess elements of mindfulness, *Revised Chronic Pain Acceptance Questionnaire*[87,88] to measure acceptance of pain, and *Coping Strategies Questionnaire*[89] to assess coping strategies used for pain management.

Sleep: Medical Outcomes Study-Sleep Scale (MOS-Sleep)[90,91] will be used for assessing key constructs of sleep quality and quantity.

Measures of peripheral and central sensitization:

Quantitative sensory testing will be conducted and reported in accordance with the guidelines[92,93] and our previous study[94].

- *Mechanical temporal summation (MTS):* will be assessed using a nylon monofilament (Semmes monofilament 6.65, 300 g). Brief ten repetitive contacts will be delivered at a rate of 1 Hz, externally cued by auditory stimuli. The participants will be asked to rate the level of pain experienced on 11-point NRS (0=No pain to 100=Extreme pain) immediately after the first contact and to rate their greatest pain intensity after the 10th contact. Three trials will be conducted for each of the two regions (i.e., symptomatic low back and non-dominant wrist) in random order. The location of these areas will be recorded using bony landmarks to ensure that same areas are re-assessed during follow-up. MTS will be calculated as difference

between NRS rating after the first contact and the highest pain rating after the 10th contact for each trial. This score presents the maximum amount of MTS across ten contact points. Average of three trials will be calculated, with a positive score indicating an increase in MTS. The MTS index will be defined as the ratio of "follow-up" pain rating divided by "baseline" pain rating.[94-96]

- *Pressure pain threshold (PPT):* A computerized, handheld digital algometer (AlgoMed; Medoc, Ramat Yishai, Israel) will be used to measure three trials of PPT over two regions (symptomatic low back and non-dominant wrist) in random order. Two familiarization trials will be performed at dominant mid-forearm before formal trials. The 1-cm^2 algometer probe will be pressed over marked test site perpendicularly to the skin at a rate of 30kPa/s. Participants will be instructed to press algometer trigger button in the patient control unit when pressure sensation changes to first pain.[97] Once patient-controlled unit is activated, the trial is automatically terminated, and amount of pressure will be recorded. If participants did not report pain at maximum pressure level which is set at 1000kPa for safety reasons, the procedure would be terminated, and a score of 1000kpa will be assigned for that trial. The average of three trials will be calculated and used for analysis.[98]
- Condition pain modulation (CPM) is the most frequently administered procedure for exploring the endogenous pain modulatory system.[97,99] CPM test procedure will be administered at least 15 to 20 minutes after the MTS and PPT procedures with the previously published recommendations of testing.[97,99]
  - ❖ The conditioning stimulus will consist of a cold pressor task. The participants will immerse their dominant hand (until mid-forearm) in a thermos containing circulating cold water for a maximum period of 2 minutes. The cold water

temperature will be maintained at ~5° centigrade and will be recorded immediately before and after the immersion procedure. Participants will be asked to continue hand immersion until the end of 2 minutes or until it is too uncomfortable to be kept immersed (NPRS~80%). Participant's pain during conditioning stimulus will be recorded on 11-point NPRS (0=No pain to 100=Extreme pain) at every 15s interval. A similar conditioning stimulus protocol has been used in previous studies showing a significant CPM effect.[100]

- Test stimulus: A computerized, handheld digital algometer (AlgoMed; Medoc, Ramat Yishai, Israel) will be used to measure suprathreshold PPT (pain40) at the non-dominant leg region (tibialis anterior muscle). Two familiarization trials will be performed at mid-forearm before the formal trials. The 1-cm^2 algometer probe will be pressed over the marked test site perpendicularly to the skin at a rate of 30 kPa/s. The participants will be instructed to press the algometer trigger button in the patient control unit when the pressure sensation changes to a pain intensity of 40 out of 100 on the NPRS. Once the patient-controlled unit is activated, the trial is automatically terminated, and the amount of pressure (kPa) will be recorded. Suppose participants did not report pain at the maximum pressure level which is set at 1000 kPa for safety reasons, the assessor will terminate the procedure, and a score of 1000 kpa will be assigned for that trial. Two PPT (pain40) trials will be recorded before conditioning stimulus and will be averaged to obtain a baseline score. In addition, three PPT (pain40) trials will be recorded in the same region at 30, 60, and 90 seconds immediately after the conditioning stimulus.
- Calculation of CPM: A percent change score will be calculated for each time point (i.e., CPM30sec, CPM60sec, and CPM90sec), with a positive score indicating an

increase in PPTs (pain40) after the conditioning stimulus and thus the presence of CPM effect.

$$\text{CPM percent change score} = \frac{\text{Post score} - \text{Pre score}}{\text{Pre score}} \text{ x } 100$$

Measures of cortical electrical activity:

Resting-state electroencephalogram (EEG) will be obtained in a quiet room while the participant is sitting upright in a comfortable chair by an independent researcher blinded to the treatment group. Participants will be asked to refrain from caffeinated drinks. EEG data will be collected using the SynAmps RT Amplifier (Compudemics Neuroscan). The EEG will be sampled with 64 electrodes placed in the standard 10–20 International placement, and impedances will be checked to remain below 5 kΩ. The EEG data will then be resampled to 128 Hz, band-pass filtered (fast Fourier transform filter) to 0.01–44 Hz and re-referenced to the average reference using the EEGLAB function in Matlab. The data will then be plotted in EEGLAB for a careful inspection of artifacts and manual rejection.

- *Source localization:* Standardized low-resolution brain electromagnetic tomography (sLORETA) will be used to estimate intracerebral electrical sources that generate scalp-recorded activity in each of the following ten frequency bands, i.e., infraslow (0.01-0.1Hz), slow (0.2-1.5Hz), delta (2–3.5Hz), theta (4–7.5Hz), alpha1 (8–10Hz), alpha2 (10.5–12Hz), beta1 (12.5–18Hz), beta2 (18.5–21Hz), beta3 (21.5–30Hz), and gamma (30.5–44Hz).(116) Comparisons will be made between pre-and post-treatment measurements on a whole-brain by sLORETA statistical contrast maps through multiple voxel-by-voxel comparisons in a logarithm of t-ratio.[101-102]

- *Lagged phase connectivity:* will be used as a measure of coherence and will be calculated for all ten frequency bands as above.[103] Regions of interest will be defined based upon all brain areas obtained in previous whole-brain analyses and targeted brain regions (pgACC, dACC, and SSC) for different frequencies. Comparisons will be made between pre-and post-treatment measurements using sLORETA statistical contrast maps through multiple voxel-by-voxel comparisons in a logarithm of t-ratio.

Statistical analysis:

SPSS version 27.0 will be used for all statistical analyses. Descriptive statistics will be used to analyze feasibility, safety, and acceptability measures. Linear mixed-effects model analysis will be used to obtain estimates of treatment effects on secondary measures. We will define intervention group as a between-subject factor, assessment time-points as a within-subject factor, participants as a random factor, and baseline prognostic indicators as covariates. An independent model will be conducted for each outcome variable as preliminary exploratory assessments to determine any trend in between-group comparisons. We will calculate a 75% confidence interval for pain and disability measures as the probability threshold to inform worthiness of conducting a full trial. The mean difference between HD-tIPNS and Sham stimulation will need to be greater than the minimal clinically important difference for either pain or disability, to consider sufficient preliminary evidence of a treatment effect. Individual participants change in secondary measures across time points and groups will be illustrated by using modified Brinley plots[104].

A nested qualitative study

We will include a nested qualitative study to explore participant's experiences and acceptability of intervention procedures. Semi-structured in-depth interviews will be conducted by a researcher, blinded to treatment allocation, immediately post-intervention. All participants will be invited to participate. The aims of this study are explorative in nature and will evaluate participant's experiences, exploring difficulties and barriers faced, perception towards intervention/research process, acceptability of intervention, perceived value and positive aspects of the study, and any other issues that arise during interviews. The interviews will be audio-recorded and fully transcribed. The analysis will be guided by General Inductive Approach[105,106], which provides a pragmatic framework for identifying shared and individual experiences and embraces findings derived from both research objectives (deductive) and those arising directly from analysis of raw data (inductive). A constant comparison process will be used; researchers will reflect on and discuss completed interviews and revise the questions schedule accordingly to ensure a broad capture of new important information. The results of qualitative study will be published separately.

Patient and Public involvement:

No patient involved.

DISCUSSION

The proposed research will be the first randomized placebo-controlled pilot study to explore a novel HD-tIPNS technique targeting multiple brain regions simultaneously in individuals with CLBP. The HD-tIPNS technique is developed to specifically modulate the infraslow electrical activity (0-0.1 Hz) in the brain. The infraslow electrical activity, a fundamental frequency range of the brain, re-organizes neurons and improves the electrical connectivity of the brain-wide functional networks.[107-110] The pink noise frequency spectrum resembles the naturally occurring signals in the self-organization of the brain, thus can be more effective than standard tDCS electrical parameters used in previous studies.[111,112] We, therefore, believe that specifically and simultaneously targeting the fundamental infraslow activity at key nodes of pain processing networks, using a novel HD-tIPNS technique, could normalize brain-wide electrical activity and functional connectivity between areas of interest, promoting better pain modulation and producing more meaningful clinical benefits.

Our proposed pilot research will provide preliminary evidence on safety, feasibility, acceptability, and trends of effectiveness of HD-tIPNS for CLBP treatment. Evidence for effect of targeting infraslow wave electrical activity on pain and function will result in creation of new knowledge and provide further evidence to develop novel interventions for improved health outcomes in individuals with CLBP. Our study is not powered to test treatment effectiveness. However, if trends of effectiveness are present, these data will support a fully powered trial in future.

ETHICS, DATA SAFETY, AND DISSEMINATION

Ethical approval has been obtained from Health and Disability Ethics Committee (Ref:20/NTB/67), who may also audit the study investigators during or after the study. Any deviations from protocol will require Ethical amendment and will be updated in the registry. To protect participant confidentiality, any personal information collected will be destroyed at the end of the project. Each participant will be given a unique identification code, and the data will be linked to that code only. All study data will be securely stored in a locked filing cabinet or electronically with password protection, such that only those involved in the research program will have access to it. As required by the University's research policy, any unidentified raw data on which the results of the project depend will be kept in secure storage for ten years, after which it will be destroyed.

An independent Data and Safety Monitoring Committee will monitor the safety of the study. A serious adverse event (SAE) is defined as any untoward medical occurrence or effect that results in death, is life-threatening, requires hospitalisation, results in persistent or significant disability or incapacity.The study will be discontinued if there is any unexpected SAE, other unexpected events, or if funding is completed/ insufficient.

Study findings will be reported to the regulatory and funding bodies, presented at the local, national, and international conferences, and disseminated by peer-review publication in a scientific journal.

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The authors have no conflicts of interest to declare.

REFERENCES:

1. Clark S, Horton R. Low back pain: a major global challenge. Lancet 2018;391(10137):2302.

2. Hoy D. The global burden of low back pain: estimates from the Global Burden of Disease 2010 study. Ann Rheum Dis 2014;73(6):968-74.

3. Treede RD, Rief W, Barke A, Aziz Q, Bennett MI, Benoliel R, Cohen M, Evers S, Finnerup NB, First MB, Giamberardino MA. A classification of chronic pain for ICD-11. Pain 2015;156(6):1003.

4. Chou R, Deyo R, Friedly J, Skelly A, Hashimoto R, Weimer M, Fu R, Dana T, Kraegel P, Griffin J, Grusing S. Nonpharmacologic therapies for low back pain: a systematic review for an American College of Physicians Clinical Practice Guideline. Ann Intern Med 2017;166(7):493-505.

5. Coulter ID, Crawford C, Hurwitz EL, Vernon H, Khorsan R, Booth MS, Herman PM. Manipulation and mobilization for treating chronic low back pain: a systematic review and meta-analysis. Spine J 2018;18(5):866-79.

6. Rubinstein SM, De Zoete A, Van Middelkoop M, Assendelft WJ, De Boer MR, Van Tulder MW. Benefits and harms of spinal manipulative therapy for the treatment of chronic low back pain: systematic review and meta-analysis of randomised controlled trials. BMJ 2019;364:l689.

7. Chou R, Turner JA, Devine EB, Hansen RN, Sullivan SD, Blazina I, Dana T, Bougatsos C, Deyo RA. The effectiveness and risks of long-term opioid therapy

for chronic pain: a systematic review for a National Institutes of Health Pathways to Prevention Workshop. Ann Intern Med 2015;162(4):276-86.

8. Koes BW, Backes D, Bindels PJ. Pharmacotherapy for chronic non-specific low back pain: current and future options. Expert Opin Pharmaco 2018;19(6):537-45.

9. Pavelka K, Jarosova H, Sleglova O, Svobodova R, Votavova M, Milani L, Prochazka Z, Kotlarova L, Kostiuk P, Sliva J, Meroni AM. Chronic Low Back Pain: Current Pharmacotherapeutic Therapies and a New Biological Approach. Curr Med Chem 2019;26(6):1019-26.

10. Konno SI, Sekiguchi M. Association between brain and low back pain. J Orthop Sci 2018;23(1):3-7.

11. Kregel J, Meeus M, Malfliet A, Dolphens M, Danneels L, Nijs J, Cagnie B. Structural and functional brain abnormalities in chronic low back pain: A systematic review. Semin Arthritis Rheu 2015;45(2):229-237.

12. Kucyi A, Davis KD. The dynamic pain connectome. Trends Neurosci 2015;38(2):86-95.

13. Ng SK, Urquhart DM, Fitzgerald PB, Cicuttini FM, Hussain SM, Fitzgibbon BM. The relationship between structural and functional brain changes and altered emotion and cognition in chronic low back pain brain changes. Clin J Pain 2018;34(3):237-61.

14. De Ridder D, Vanneste S. The Bayesian brain in imbalance: Medial, lateral and descending pathways in tinnitus and pain: A perspective. Prog Brain Res 2020;262:309-34.

15. Li T, Zhang S, Kurata J. Suppressed descending pain modulatory and enhanced sensorimotor networks in patients with chronic low back pain. J Anesth 2018;32(6):831-43.

16. Vanneste S, De Ridder D. Chronic pain as a brain imbalance between pain input and pain suppression. Brain Commun 2021;3(1):fcab014.

17. Yuan C, Shi H, Pan P, Dai Z, Zhong J, Ma H, Sheng L. Gray Matter Abnormalities Associated With Chronic Back Pain. Clin J Pain 2017;33(11):983-90.

18. De Ridder D, Adhia D, Vanneste S. The anatomy of pain and suffering in the brain and its clinical implications. Neuroscience & Biobehavioral Reviews. 2021 Aug 16.

19. Bushnell MC, Čeko M, Low LA. Cognitive and emotional control of pain and its disruption in chronic pain. Nat Rev Neurosci 2013;14(7):502.

20. De Ridder D, Vanneste S. Burst and tonic spinal cord stimulation: different and common brain mechanisms. Neuromodulation: Technology at the Neural Interface 2016;19(1):47-59.

21. Baliki MN, Petre B, Torbey S, Herrmann KM, Huang L, Schnitzer TJ, Fields HL, Apkarian AV. Corticostriatal functional connectivity predicts transition to chronic back pain. Nat Neurosci 2012;15(8):1117.

22. Coppieters I, Meeus M, Kregel J, Caeyenberghs K, De Pauw R, Goubert D, Cagnie B. Relations between brain alterations and clinical pain measures in chronic musculoskeletal pain: a systematic review. J Pain 2016;17(9):949-62.

23. Hashmi JA, Baliki MN, Huang L, Baria AT, Torbey S, Hermann KM, Schnitzer TJ, Apkarian AV. Shape shifting pain: chronification of back pain shifts brain representation from nociceptive to emotional circuits. Brain 2013;136(9):2751-68.

24. Hemington KS, Rogachov A, Cheng JC, Bosma RL, Kim JA, Osborne NR, Inman RD, Davis KD. Patients with chronic pain exhibit a complex relationship triad between pain, resilience, and within-and cross-network functional connectivity of the default mode network. Pain 2018;159(8):1621-30.

25. Kim J, Mawla I, Kong J, Lee J, Gerber J, Ortiz A, Kim H, Chan ST, Loggia ML, Wasan AD, Edwards RR. Somatotopically specific primary somatosensory connectivity to salience and default mode networks encodes clinical pain. Pain 2019;160(7):1594-605.

26. Kong J, Spaeth RB, Wey HY, Cheetham A, Cook AH, Jensen K, Tan Y, Liu H, Wang D, Loggia ML, Napadow V. S1 is associated with chronic low back pain: a functional and structural MRI study. Mol Pain 2013;9(1):43.

27. Ossipov MH, Morimura K, Porreca F. Descending pain modulation and chronification of pain. Curr Opin Support Palliat Care 2014;8(2):143.

28. Tu Y, Jung M, Gollub RL, Napadow V, Gerber J, Ortiz A, Lang C, Mawla I, Shen W, Chan ST, Wasan AD. Abnormal medial prefrontal cortex functional connectivity and its association with clinical symptoms in chronic low back pain. Pain 2019;160(6):1308-18.

29. Ahn S, Prim JH, Alexander ML, McCulloch KL, Fröhlich F. Identifying and engaging neuronal oscillations by transcranial alternating current stimulation in

patients with chronic low back pain: a randomized, crossover, double-blind, sham-controlled pilot study. J Pain 2019;20(3):277-e1.

30. Hazime FA, Baptista AF, de Freitas DG, Monteiro RL, Maretto RL, Hasue RH, Joao SM. Treating low back pain with combined cerebral and peripheral electrical stimulation: A randomized, double-blind, factorial clinical trial. Eur J Pain 2017;21(7):1132-43.

31. Jafarzadeh A, Ehsani F, Yosephi MH, Zoghi M, Jaberzadeh S. Concurrent postural training and M1 anodal transcranial direct current stimulation improve postural impairment in patients with chronic low back pain. J Clin Neurosci 2019;68:224-34.

32. Luedtke K, Rushton A, Wright C, Jürgens T, Polzer A, Mueller G, May A. Effectiveness of transcranial direct current stimulation preceding cognitive behavioural management for chronic low back pain: sham controlled double blinded randomised controlled trial. BMJ 2015;350:h1640.

33. Mariano TY, Burgess FW, Bowker M, Kirschner J, van't Wout-Frank M, Jones RN, Halladay CW, Stein M, Greenberg BD. Transcranial Direct Current Stimulation for Affective Symptoms and Functioning in Chronic Low Back Pain: A Pilot Double-Blinded, Randomized, Placebo-Controlled Trial. Pain Med 2018;20(6):1166-77.

34. O'Connell NE, Cossar J, Marston L, Wand BM, Bunce D, De Souza LH, Maskill DW, Sharp A, Moseley GL. Transcranial direct current stimulation of the motor cortex in the treatment of chronic nonspecific low back pain: a randomized, double-blind exploratory study. Clin J Pain 2013;29(1):26-34.

35. Schabrun SM, Burns E, Thapa T, Hodges P. The response of the primary motor cortex to neuromodulation is altered in chronic low back pain: a preliminary study. Pain Med 2017;19(6):1227-36.

36. Schabrun SM, Jones E, Cancino EL, Hodges PW. Targeting chronic recurrent low back pain from the top-down and the bottom-up: a combined transcranial direct current stimulation and peripheral electrical stimulation intervention. Brain Stimul 2014;7(3):451-9.

37. Straudi S, Buja S, Baroni A, Pavarelli C, Pranovi G, Fregni F, Basaglia N. The effects of transcranial direct current stimulation (tDCS) combined with group exercise treatment in subjects with chronic low back pain: a pilot randomized control trial. Clin Rehabil 2018;32(10):1348-56.

38. Larie M, Esfandiarpour F, Riahi F, Derisfard F, Parnianpour M. Effects of Cortical and Peripheral Electrical Stimulation on Brain Activity in Individuals with Chronic Low Back Pain. Phys Treat- Speci Phys Ther J 2019;9(1):39-46.

39. Ouellette AL, Liston MB, Chang WJ, Walton DM, Wand BM, Schabrun SM. Safety and feasibility of transcranial direct current stimulation (tDCS) combined with sensorimotor retraining in chronic low back pain: a protocol for a pilot randomised controlled trial. BMJ Open 2017;7(8):e013080.

40. O'Connell NE, Marston L, Spencer S, DeSouza LH, Wand BM. Non-invasive brain stimulation techniques for chronic pain. Cochrane Database Syst Rev 2018;3(3):CD008208.

41. Pinto CB, Costa BT, Duarte D, Fregni F. Transcranial direct current stimulation as a therapeutic tool for chronic pain. J ECT 2018;34(3):e36-50.

42. Lima MC, Fregni F. Motor cortex stimulation for chronic pain: systematic review and meta-analysis of the literature. Neurology 2008;70(24):2329-37.

43. Chan AW, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin JA, Doré CJ. SPIRIT 2013 statement: defining standard protocol items for clinical trials. Ann Intern Med 2013;158(3):200-7.

44. Hoffmann TC, Glasziou PP, Boutron I, Milne R, Perera R, Moher D, Altman DG, Barbour V, Macdonald H, Johnston M, Lamb SE. Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide. BMJ 2014;348:g1687.

45. Edwards RR, Dworkin RH, Turk DC, Angst MS, Dionne R, Freeman R, Hansson P, Haroutounian S, Arendt-Nielsen L, Attal N, Baron R. Patient phenotyping in clinical trials of chronic pain treatments: IMMPACT recommendations. Pain 2016;157(9):1851.

46. Gewandter JS, Dworkin RH, Turk DC, Devine EG, Hewitt D, Jensen MP, Katz NP, Kirkwood AA, Malamut R, Markman JD, Vrijens B. Improving study conduct and data quality in clinical trials of chronic pain treatments: IMMPACT recommendations. J Pain 2020;21(9-10):931-42.

47. Smith SM, Dworkin RH, Turk DC, Baron R, Polydefkis M, Tracey I, Borsook D, Edwards RR, Harris RE, Wager TD, Arendt-Nielsen L. The potential role of sensory testing, skin biopsy, and functional brain imaging as biomarkers in chronic pain clinical trials: IMMPACT considerations. J Pain 2017;18(7):757-77.

48. Smith SM, Dworkin RH, Turk DC, McDermott MP, Eccleston C, Farrar JT, Rowbotham MC, Bhagwagar Z, Burke LB, Cowan P, Ellenberg SS. Interpretation

of chronic pain clinical trial outcomes: IMMPACT recommended considerations. Pain 2020;161(11):2446-61.

49. Taylor AM, Phillips K, Patel KV, Turk DC, Dworkin RH, Beaton D, Clauw DJ, Gignac MA, Markman JD, Williams DA, Bujanover S. Assessment of physical function and participation in chronic pain clinical trials: globalPACT/OMERACT recommendations. Pain 2016 Sep;157(9):1836.

50. Roland M, Morris R. A study of the natural history of back pain. Part I: development of a reliable and sensitive measure of disability in low-back pain. Spine 1983;8(2):141-4.

51. Roland M, Morris R. A study of the natural history of low-back pain. Part II: development of guidelines for trials of treatment in primary care. Spine 1983;8(2):145-50.

52. Dionne CE, Dunn KM, Croft PR, Nachemson AL, Buchbinder R, Walker BF, Wyatt M, Cassidy JD, Rossignol M, Leboeuf-Yde C, Hartvigsen J. A consensus approach toward the standardization of back pain definitions for use in prevalence studies. Spine 2008;33(1):95-103.

53. Grotle M, Brox JI, Vollestad NK. Concurrent comparison of responsiveness in pain and functional status measurements used for patients with low back. Spine 2004;29(21):E492-E501.

54. Mayer TG, Neblett R, Cohen H, Howard KJ, Choi YH, Williams MJ, Perez Y, Gatchel RJ. The development and psychometric validation of the central sensitization inventory. Pain Prac 2012;12(4):276-85.

55. Neblett R, Cohen H, Choi Y, Hartzell MM, Williams M, Mayer TG, Gatchel RJ. The Central Sensitization Inventory (CSI): establishing clinically significant values for identifying central sensitivity syndromes in an outpatient chronic pain sample. J Pain 2013;14(5):438-45.

56. Freynhagen R, Tölle TR, Gockel U, Baron R. The painDETECT project–far more than a screening tool on neuropathic pain. Current medical research and opinion. 2016;32(6):1033-57.

57. Schattner E, Shahar G. Role of pain personification in pain-related depression: An object relations perspective. Psychiatry 2011;74(1):14-20.

58. Devilly GJ, Borkovec TD. Psychometric properties of the credibility/expectancy questionnaire. J Behav Ther Exp Psychiatry 2000;31(2):73-86.

59. Lefaucheur JP, Antal A, Ayache SS, Benninger DH, Brunelin J, Cogiamanian F, Cotelli M, De Ridder D, Ferrucci R, Langguth B, Marangolo P. Evidence-based guidelines on the therapeutic use of transcranial direct current stimulation (tDCS). Clin Neurophysiol 2017;128(1):56-92.

60. Nikolin S, Huggins C, Martin D, Alonzo A, Loo CK. Safety of repeated sessions of transcranial direct current stimulation: a systematic review. Brain Stimul 2018;11(2):278-88.

61. Woods AJ, Antal A, Bikson M, Boggio PS, Brunoni AR, Celnik P, Cohen LG, Fregni F, Herrmann CS, Kappenman ES, Knotkova H. A technical guide to tDCS, and related non-invasive brain stimulation tools. Clin Neurophysiol 2016;127(2):1031-48.

62. Neri F, Mencarelli L, Menardi A, Giovannelli F, Rossi S, Sprugnoli G, Rossi A, Pascual-Leone A, Salvador R, Ruffini G, Santarnecchi E. A novel tDCS sham approach based on model-driven controlled shunting. Brain Stimul 2020;13(2):507-16.

63. Rosenbaum JF, Fava M, Hoog SL, Ascroft RC, Krebs WB. Selective serotonin reuptake inhibitor discontinuation syndrome: a randomized clinical trial. Biol Psychiatry 1998;44(2):77-87.

64. Song CY, Lin SF, Huang CY, Wu HC, Chen CH, Hsieh CL. Validation of the Brief Pain Inventory in patients with low back pain. Spine 2016;41(15):E937-42.

65. Price DD, Bush FM, Long S, Harkins SW. A comparison of pain measurement characteristics of mechanical visual analogue and simple numerical rating scales. Pain 1994;56(2):217-26.

66. Price DD, McGrath PA, Rafii A, Buckingham B. The validation of visual analogue scales as ratio scale measures for chronic and experimental pain. Pain 1983;17(1):45-56.

67. Deyo RA, Battie M, Beurskens AJ, Bombardier C, Croft P, Koes B, Malmivaara A, Roland M, Von Korff M, Waddell G. Outcome measures for low back pain research: a proposal for standardized use. Spine 1998;23(18):2003-13.

68. Dunn KM, Croft PR. Classification of low back pain in primary care: using “bothersomeness” to identify the most severe cases. Spine 2005;30(16):1887-92.

69. Maddison R, Mhurchu CN, Jiang Y, Vander Hoorn S, Rodgers A, Lawes CM, Rush E. International physical activity questionnaire (IPAQ) and New Zealand

physical activity questionnaire (NZPAQ): a doubly labelled water validation. Int J Behav Nutr Phys Act 2007;4(1):62.

70. Rabey M, Smith A, Beales D, Slater H, O'Sullivan P. Differing psychologically derived clusters in people with chronic low back pain are associated with different multidimensional profiles. Clin J Pain 2016;32(12):1015-27.

71. Brouwer S, Reneman MF, Dijkstra PU, Groothoff JW, Schellekens JM, Göeken LN. Test–retest reliability of the Isernhagen work systems functional capacity evaluation in patients with chronic low back pain. J Occup Rehab 2003;13(4):207-18.

72. O'Sullivan P. Diagnosis and classification of chronic low back pain disorders: maladaptive movement and motor control impairments as underlying mechanism. Man Ther 2005;10(4):242-55.

73. Costa LO, Maher CG, Latimer J, Ferreira PH, Ferreira ML, Pozzi GC, Freitas LM. Clinimetric testing of three self-report outcome measures for low back pain patients in Brazil: which one is the best?. Spine 2008;33(22):2459-63.

74. Herdman M, et al. (2011). Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res 2011;20(10):1727-36.

75. Topp CW, Østergaard SD, Søndergaard S, Bech P. The WHO-5 Well-Being Index: a systematic review of the literature. Psychother Psychosom 2015;84(3):167-76.

76. Parkitny L, McAuley JH, Walton D, Costa LO, Refshauge KM, Wand BM, Di Pietro F, Moseley GL. Rasch analysis supports the use of the depression,

anxiety, and stress scales to measure mood in groups but not in individuals with chronic low back pain. J Clin Epidemiol 2012;65(2):189-98.

77. Osman A, Barrios FX, Gutierrez PM, Kopper BA, Merrifield T, Grittmann L. The Pain Catastrophizing Scale: further psychometric evaluation with adult samples. J Behav Med 2000;23(4):351-65.

78. MM, Eugster R, Held U, Steurer J, Kofmehl R, Weiser S. Catastrophizing—a prognostic factor for outcome in patients with low back pain: a systematic review. Spine J 2014;14(11):2639-57.

79. Roelofs J, Peters ML, McCracken L, Vlaeyen JW. The pain vigilance and awareness questionnaire (PVAQ): further psychometric evaluation in fibromyalgia and other chronic pain syndromes. Pain 2003;101(3):299-306.

80. Nicholas MK, McGuire BE, Asghari A. A 2-item short form of the Pain Self-efficacy Questionnaire: development and psychometric evaluation of PSEQ-2. J Pain 2015;16(2):153-63.

81. Thompson ER. Development and validation of an internationally reliable short-form of the positive and negative affect schedule (PANAS). J Coss-Cult Psychol 2007;38(2):227-42.

82. Watson D, Clark LA, Tellegen A. Development and validation of brief measures of positive and negative affect: the PANAS scales. J Pers Soc Psychol 1988;54(6):1063.

83. Gross JJ, John OP. Individual differences in two emotion regulation processes: implications for affect, relationships, and well-being. J Pers Soc Psychol 2003;85(2):348.

84. Broadbent E, Petrie KJ, Main J, Weinman J. The brief illness perception questionnaire. J Psychosom Res 2006;60(6):631-7.

85. Baer RA, Smith GT, Lykins E, Button D, Krietemeyer J, Sauer S, Walsh E, Duggan D, Williams JM. Construct validity of the five facet mindfulness questionnaire in meditating and nonmeditating samples. Assessment 2008;15(3):329-42

86. Gu J, Strauss C, Crane C, Barnhofer T, Karl A, Cavanagh K, Kuyken W. Examining the factor structure of the 39-item and 15-item versions of the Five Facet Mindfulness Questionnaire before and after mindfulness-based cognitive therapy for people with recurrent depression. Psychol Assess 2016;28(7):791.

87. McCracken LM, Vowles KE, Eccleston C. Acceptance of chronic pain: component analysis and a revised assessment method. Pain 2004;107(1-2):159-66.

88. Vowles KE, McCracken LM, McLeod C, Eccleston C. The Chronic Pain Acceptance Questionnaire: confirmatory factor analysis and identification of patient subgroups. Pain 2008;140(2):284-91.

89. Jensen MP, Keefe FJ, Lefebvre JC, Romano JM, Turner JA. One-and two-item measures of pain beliefs and coping strategies. Pain 2003;104(3):453-69.

90. Stewart AL, Ware JE. Measuring functioning and well-being: the medical outcomes study approach. Duke University Press; 1992.

91. Stewart AL, Ware JE, Brook RH, Davies AR. Conceptualization and measurement of health for adults in the Health Insurance Study. Vol II. Physical

health in terms of functioning. Santa Monica (CA): The RAND Corporation; 1978. p. 236–359.

92. Rolke R, Baron R, Maier CA, Tölle TR, Treede RD, Beyer A, Binder A, Birbaumer N, Birklein F, Bötefür IC, Braune S. Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): standardized protocol and reference values. Pain 2006;123(3):231-43.

93. Uddin Z, MacDermid JC. Quantitative sensory testing in chronic musculoskeletal pain. Pain Med 2016;17(9):1694-703.

94. Mani R, Adhia DB, Leong SL, Vanneste S, De Ridder D. Sedentary behaviour facilitates conditioned pain modulation in middle-aged and older adults with persistent musculoskeletal pain. Pain Rep 2019;4:e773.

95. Goodin BR, Bulls HW, Herbert MS, Schmidt J, King CD, Glover TL, Sotolongo A, Sibille KT, Cruz-Almeida Y, Staud R, Fessler BJ. Temporal summation of pain as a prospective predictor of clinical pain severity in adults aged 45 years and older with knee osteoarthritis: Ethnic differences. Psychosom Med 2014;76(4):302-10.

96. Hubscher M, Moloney N, Leaver A, Rebbeck T, McAuley JH, Refshauge KM. Relationship between quantitative sensory testing and pain or disability in people with spinal pain-a systematic review and meta-analysis. Pain 2013;154(9):1497-504.

97. Yarnitsky D, Bouhassira D, Drewes AM, Fillingim RB, Granot M, Hansson P, Landau R, Marchand S, Matre D, Nilsen KB, Stubhaug A, Treede RD, Wilder-Smith OH. Recommendations on practice of conditioned pain modulation (CPM) testing. Eur J Pain 2015;19:805–6.

98. Suokas AK, Walsh DA, McWilliams DF, Condon L, Moreton B, Wylde V, Arendt-Nielsen L, Zhang W. Quantitative sensory testing in painful osteoarthritis: a systematic review and meta-analysis. Osteoarthr Cartil 2012;20:1075–85.

99. Yarnitsky D, Arendt-Nielsen L, Bouhassira D, Edwards RR, Fillingim RB, Granot M, Hansson P, Lautenbacher S, Marchand S, Wilder-Smith O. Recommendations on terminology and practice of psychophysical DNIC testing. Eur J Pain 2010;14:339.

100. Kennedy DL, Kemp HI, Ridout D, Yarnitsky D, Rice AS. Reliability of conditioned pain modulation: a systematic review. Pain 2016;157:2410–19.

101. Nichols TE, Holmes AP. Nonparametric permutation tests for functional neuroimaging: a primer with examples. Human brain mapping. 2002;15(1):1-25.

102. Pascual-Marqui RD. Standardized low-resolution brain electromagnetic tomography (sLORETA): technical details. Methods Find Exp Clin Pharmacol 2002;24(Suppl D):5-12.

103. Pascual-Marqui RD. Discrete, 3D distributed, linear imaging methods of electric neuronal activity. Part 1: exact, zero error localization. arXiv preprint 2007;arXiv 0710.3341.

104. Black SR, Blampied N, Arnold LE, Fristad MA. Is evidence-based treatment helping my patient? Utilizing modified Brinley plots to measure clinical change. Clin Psychol Sci 2019;26(1):e12272.

105. Braun V, Clarke V. Using thematic analysis in psychology. Qual Res Psychol 2006;3(2):77-101.

106. Thomas DR. A general inductive approach for analyzing qualitative evaluation data. Am J Eval 2006;27(2):237-46.

107. Brookes MJ, Woolrich M, Luckhoo H, Price D, Hale JR, Stephenson MC, Barnes GR, Smith SM, Morris PG. Investigating the electrophysiological basis of resting state networks using magnetoencephalography. Proc Natl Acad Sci 2011;108(40):16783-8.

108. Mitra A, Raichle ME. How networks communicate: propagation patterns in spontaneous brain activity. Philos Trans R Soc B: Biol Sci 2016;371(1705):20150546.

109. Watson BO. Cognitive and Physiologic Impacts of the Infraslow Oscillation. Front Syst Neurosci 2018;12:44.

110. Wilckens KA, Ferrarelli F, Walker MP, Buysse DJ. Slow-wave activity enhancement to improve cognition. Trends Neurosci 2018;41(7):470-82.

111. Leong SL, De Ridder D, Vanneste S, Sutherland W, Ross S, Manning P. High definition transcranial pink noise stimulation of anterior cingulate cortex on food craving: An explorative study. Appetite 2018;120:673-8.

112. Whittington F, De Ridder D, & Adhia, D. (2021). High definition transcranial infraslow pink noise stimulation for improving executive functioning in healthy older adults: A pilot safety trial. *New Zealand Medical Journal;*134(1537):115-116.

113. DaSilva AF, Truong DQ, DosSantos MF, Toback RL, Datta A, Bikson M. State-of-art neuroanatomical target analysis of high-definition and conventional tDCS montages used for migraine and pain control. Front Neuroanat 2015;9:89.

114. Datta A, Bansal V, Diaz J, Patel J, Reato D, Bikson M. Gyri-precise head model of transcranial direct current stimulation: improved spatial focality using a ring electrode versus conventional rectangular pad. Brain Stimul 2009;2(4):201-7.

115. Dmochowski JP, Datta A, Bikson M, Su Y, Parra LC. Optimized multi-electrode stimulation increases focality and intensity at target. J Neural Eng 2011;8(4):046011.

116. Minhas P, Bansal V, Patel J, Ho JS, Diaz J, Datta A, Bikson M. Electrodes for high-definition transcutaneous DC stimulation for applications in drug delivery and electrotherapy, including tDCS. J Neurosci Methods 2010;190(2):188-97.

117. To WT, Eroh J, Hart J, Vanneste S. Exploring the effects of anodal and cathodal high definition transcranial direct current stimulation targeting the dorsal anterior cingulate cortex. Sci Rep 2018;8(1):4454.

118. Ploner M, Sorg C, Gross J. Brain rhythms of pain. Trends Cogn Sci 2017;21(2):100-10.

119. Zhang B, Jung M, Tu Y, Gollub R, Lang C, Ortiz A, Park J, Wilson G, Gerber J, Mawla I, Chan ST. Identifying brain regions associated with the neuropathology of chronic low back pain: a resting-state amplitude of low-frequency fluctuation study. Br J Anaesth 2019;123(2):e303-11.

120. Zhou F, Gu L, Hong S, Liu J, Jiang J, Huang M, Zhang Y, Gong H. Altered low-frequency oscillation amplitude of resting state-fMRI in patients with discogenic low-back and leg pain. J Pain Res 2018;11:165.

121. Ruffini G, Fox MD, Ripolles O, Miranda PC, Pascual-Leone A. Optimization of multifocal transcranial current stimulation for weighted cortical pattern targeting from realistic modeling of electric fields. Neuroimage 2014;89:216-25.

122. Ruffini G, Wendling F, Sanchez-Todo R, Santarnecchi E. Targeting brain networks with multichannel transcranial current stimulation (tCS). Curr Opin Biomed Eng 2018;8:70-7.

TABLES

Table 1. WHO trial registration data set (v.1.3.1).

Item	Information
Primary registry and trial Identifying number	Australian and New Zealand Clinical Trials Registry- ACTRN 12620000505909p
Date of registration in primary registry	23/04/2020
Universal Trial Number	U1111-1250-1177
Source of monetary or material support	Health Research Council of New Zealand Emerging Researcher First Grant, The Healthcare Otago Charitable trust, Lottery Health Research equipment grant, Brain Health Research Centre, and the Neurological foundation of New Zealand.
Primary Sponsor	University of Otago
Contact for public queries	Dr Divya Adhia, Department of Surgical Sciences, Otago Medical School, University of Otago.
Contact for scientific queries	Dr Divya Adhia, Department of Surgical Sciences, Otago Medical School, University of Otago.

Item	Information
Public title	Non-invasive brain stimulation for chronic low back pain.
Scientific title	Safety and feasibility of transcranial electrical stimulation for chronic low back pain.
Country of recruitment	New Zealand.
Health condition or problem studied	Chronic low back pain.
Interventions	High-definition transcranial infraslow pink noise stimulation.
Key eligibility criteria	Adults between the ages of 18-75 years, with chronic low back pain.
Study type	Interventional, exploratory randomised placebo-controlled parallel pilot trial; Allocation ratio = 1:1.
Date of first enrolment	1st June 2021
Sample size	Not calculated. This pilot study will be executed to make a power estimate for a future phase II study.
Recruitment status	Recruiting

Item	Information
Primary outcomes	Feasibility (measured as recruitment rate, proportion of participants recruited, adherence to intervention, and drop-out rates) Safety (measured as any adverse events that have a likely causal relationship with the intervention) Acceptability of the intervention (assessed quantitatively as well as qualitatively)
Secondary measures	Pain: Brief pain Inventory, pain unpleasantness and bothersomeness, global rate of change score. Function: Roland-Morris disability questionnaire, International physical activity questionnaire, Movement related pain. Wellbeing: European quality of life–5 dimensions, World Health Organisation- five wellbeing index. Psychological measures: Depression, anxiety and stress scale, pain catastrophising scale, pain vigilance and awareness questionnaire, pain self-efficacy, positive and negative affect scale, emotional regulation questionnaire, Brief Illness Perception Questionnaire, Five-Facet Mindfulness Questionnaire-15, Revised Chronic Pain

Item	Information
	Acceptance Questionnaire, Coping Strategies Questionnaire, and Sleep.
Mechanistic measures	Quantitative sensory testing: mechanical temporal summation, pressure pain threshold, and conditioned pain modulation. Resting-state electroencephalogram: current density and functional connectivity.
Ethical Review	Status: Approved, Date of Approval: 28th July 2020; Committee: Health and Disability Ethics Committee (HDEC, Ref: 20/NTB/67)

Table 2: Description of the HD-tIPNS intervention, as per the template for intervention description and replication.

Item number and Item	Description
1. BRIEF NAME Provide the name or a phrase that describes the intervention.	High-definition transcranial infraslow pink noise stimulation (HD-tIPNS).
2. WHY Describe any rationale, theory, or goal of the elements essential to the intervention.	The HD technique uses arrays of multiple small electrodes whose configuration can be optimized for focally targeting specific brain regions.[111-117] The HD-tIPNS technique is developed to specifically modulate the infraslow electrical activity (0-0.1 Hz) in the brain. The infraslow electrical activity, a fundamental frequency range of the brain, re-organizes neurons and improves the electrical connectivity of the brain-wide functional networks.[107-110] Optimizing the infraslow frequency can normalize the electrical activity in the higher frequency bands known to be affected in individuals with chronic pain.[107-110] Recent imaging studies have also

	demonstrated alterations in the infraslow oscillations in individuals with CLBP in descending (pgACC) and ascending (dACC, SSC) pain pathways.[118-120] Research shows that pink noise stimulation can influence the infraslow electrical activity (0-0.1 Hz) in the brain.[111,112] The pink noise frequency spectrum resembles the naturally occurring signals in the self-organization of the brain, thus can be more effective than standard tDCS electrical parameters. [111,112] We, therefore, hypothesize that specifically and simultaneously targeting the fundamental infraslow activity at the key nodes of pain processing networks, using a novel HD-tIPNS technique, could normalize brain-wide electrical activity and functional connectivity between areas of interest, promoting better pain modulation and producing more meaningful clinical benefits.
3. WHAT Materials: Describe any physical or informational materials used in the intervention, including those	A battery-driven wireless transcranial electrical stimulator (Starstim-Home TES®, Neuroelectrics, Spain) will be used to deliver stimulation while participants are comfortably and quietly seated. Eight electrodes will be

provided to participants or used in intervention delivery or in training of intervention providers. Provide information on where the materials can be accessed (e.g. online appendix, URL).	placed on a neoprene head cap following the International 10-20 EEG system to simultaneously target pgACC, dACC, and SSC (Fig. 2).
4. Procedures: Describe each of the procedures, activities, and/or processes used in the intervention, including any enabling or support activities.	The treating researcher will place the neoprene cap with the eight electrodes attached to it on the participant's head while they are comfortably seated in a chair. The reference electrode will be placed on the right ear. Electrogel will be applied to the scalp at the locations of the electrodes for reducing the impedance. The NIC2 software uses a traffic light signal indicator (red, yellow, green) for impedance. All electrodes will be prepared to have the lowest impedance (green colour). All the cables will be attached to the stimulating electrodes and the neckbox. The stimulator will be connected to the NIC2 software using its wifi function. The participant will be comfortably positioned in a half-lying position with their eyes closed. The participant will

	be asked to relax, and the stimulation intervention will be delivered for 30 minutes.
5. WHO PROVIDED For each category of intervention provider (e.g. psychologist, nursing assistant), describe their expertise, background and any specific training given.	Two independent researchers will be involved in the delivery of the intervention. A researcher (R1) with a health professional background (physiotherapist) will design and control the Starstim-Home device and set up the stimulation programs in the NIC2 (neuroelectrics software), to allow blinding of the treating researcher (R2). The program will be uploaded to the online portal and the treatment will be scheduled for each participant by R1. Another independent researcher (assistant research fellow, R2) with considerable experience in administering neuromodulation techniques will prepare the participants for treatment and administer the stimulation intervention using the iPad of the Starstim-Home TES system. During the stimulation period, the iPad screen presents only a green bar for indicating the duration of the stimulation session and no other stimulation parameters

	are presented. This allows for appropriate blinding of the treating researcher (R2).
6. HOW Describe the modes of delivery (e.g. face-to-face or by some other mechanism, such as internet or telephone) of the intervention and whether it was provided individually or in a group.	All participants will receive individual face-to-face sessions.
7. WHERE Describe the type(s) of location(s) where the intervention occurred, including any necessary infrastructure or relevant features.	Interventions will be delivered at a clinical laboratory in the Otago Medical School, Department of Surgical Sciences, located in the Dunedin Hospital, Dunedin, New Zealand.
8. WHEN and HOW MUCH Describe the number of times the intervention was delivered and over what period of time including	All participants will receive the intervention (based on their randomized group) for a total of 20 sessions, five times a week for four consecutive weeks. Each stimulation session will last for 30 minutes duration.

the number of sessions, their schedule, and their duration, intensity or dose.	
9. TAILORING If the intervention was planned to be personalized, titrated or adapted, then describe what, why, when, and how.	The interventions will not be tailored to individual participant's brain states. All participants in HD-tIPNS group will receive the same stimulation waveform, pink noise stimulation at a current strength of a maximum of 0.6mA superimposed on the infraslow (0.1Hz sinusoidal) waveform of a current intensity of 1mA.
10. MODIFICATIONS If the intervention was modified during the course of the study, describe the changes (what, why, when, and how).	Not applicable. This is a protocol for a pilot trial.
11. HOW WELL Planned: If intervention adherence or fidelity was assessed, describe how and by whom, and if any	Adherence to intervention will be one of the primary outcomes for the study and will be recorded by the treating researcher. Adherence rates will be calculated once the treatment phase is completed. The number of treatment

strategies were used to maintain or improve fidelity, describe them.	sessions attended by each participant and expressed as a percentage of the total number of sessions.
12. Actual: If intervention adherence or fidelity was assessed, describe the extent to which the intervention was delivered as planned.	Not applicable. This is a protocol for a pilot trial.

Table 3: List of the measure's domains, their construct, measurement tools, and assessment time points

Measure's Domains	Constructs	Measurement tools	Timepoints
Pain	Severity	Brief Pain Inventory Short form Severity subscale in the past 24 hours.	T_B, T_{im}, T_{1wk}, T_{1m}, T_{3m}
		0-10 NRS of the worst pain in the past 24 hours	T_B, T_{im}, T_{1wk}, T_{1m}, T_{3m}
		0-10 NRS of the worst pain in the past four weeks	T_B, T_{1m}, T_{3m}
		0-10 NRS of average pain in the past 24 hours	T_B, T_{im}, T_{1wk}, T_{1m}, T_{3m}
		0-10 NRS of average pain in past four weeks	T_B, T_{1m}, T_{3m}
	Unpleasantness	0-10 NRS of unpleasantness in the past 24 hours	T_B, T_{im}, T_{1wk}, T_{1m}, T_{3m}
		0-10 NRS of unpleasantness in past four weeks	T_B, T_{1m}, T_{3m}
	Bothersomeness	0-10 NRS of bothersomeness in past 24 hours	T_B, T_{im}, T_{1wk}, T_{1m}, T_{3m}
		0-10 NRS of bothersomeness in past four weeks	T_B, T_{1m}, T_{3m}

Physical functioning	Pain interference	Brief Pain Inventory Short form Interference subscale in the past 24 hours.	T_B, T_{im}, T_{1wk}, T_{1m}, T_{3m}
	Disability	Roland–Morris Disability Questionnaire	T_B, T_{im}, T_{1wk}, T_{1m}, T_{3m}
	Physical activity levels	International Physical Activity Questionnaire–short form in the last seven days	T_B, T_{im}, T_{1wk}, T_{1m}, T_{3m}
	Movement evoked pain	0-100 NRS on repeated forward and backward bending	T_B, T_{im}, T_{1wk}, T_{1m}, T_{3m}
Global change	Global perceived change	Perceived change in the back region on an 11-point scale (-5=much worse, through 0=unchanged, to +5=completely, recovered	T_{1wk}, T_{1m}, T_{3m}
Effectiveness	Perceived effectiveness	Perceived treatment effectiveness on an 0-10 NRS	T_{im}
Satisfaction	Extent of satisfaction	Perceived treatment satisfaction on an 0-10 NRS	T_{im}
Psychological functioning	Depression	Depression, Anxiety, and Stress Scale	T_B, T_{im}, T_{1wk}, T_{1m}, T_{3m}
	Catastrophising	Pain Catastrophising Scale	T_B, T_{im}, T_{1wk}, T_{1m}, T_{3m}
	Attention to pain	Pain Vigilance and Awareness Questionnaire	T_B, T_{im}, T_{1wk}, T_{1m}, T_{3m}
	Self-efficacy	Pain Self Efficacy Questionnaire (two-item)	T_B, T_{im}, T_{1wk}, T_{1m}, T_{3m}

	Control of emotions	Emotional Regulation Questionnaire	T_B, T_{im}, T_{1wk}, T_{1m}, T_{3m}
	Affect style	Positive and Negative Affect Scale	T_B, T_{im}, T_{1wk}, T_{1m}, T_{3m}
	Illness perception	Brief Illness Perception Questionnaire	T_B, T_{im}, T_{1wk}, T_{1m}, T_{3m}
	Mindfulness	Five-Facet Mindfulness Questionnaire	T_B, T_{im}, T_{1wk}, T_{1m}, T_{3m}
	Acceptance	Revised Chronic Pain Acceptance Questionnaire	T_B, T_{im}, T_{1wk}, T_{1m}, T_{3m}
	Coping	Coping Strategies Questionnaire	T_B, T_{im}, T_{1wk}, T_{1m}, T_{3m}
General Health	Quality of life	European Quality of Life- 5D	T_B, T_{im}, T_{1wk}, T_{1m}, T_{3m}
	Well-being	World Health Organisation-Five Well-Being Index	T_B, T_{im}, T_{1wk}, T_{1m}, T_{3m}
Sleep	Sleep quality and quantity	Medical Outcomes Study-Sleep Scale	T_B, T_{im}, T_{1wk}, T_{1m}, T_{3m}
T_B: At baseline, T_{im}: Immediately post-intervention, T_{1wk}: One-week post-intervention, T_{1m}: One-month post-intervention, T_{3m}: Three-months post-intervention			

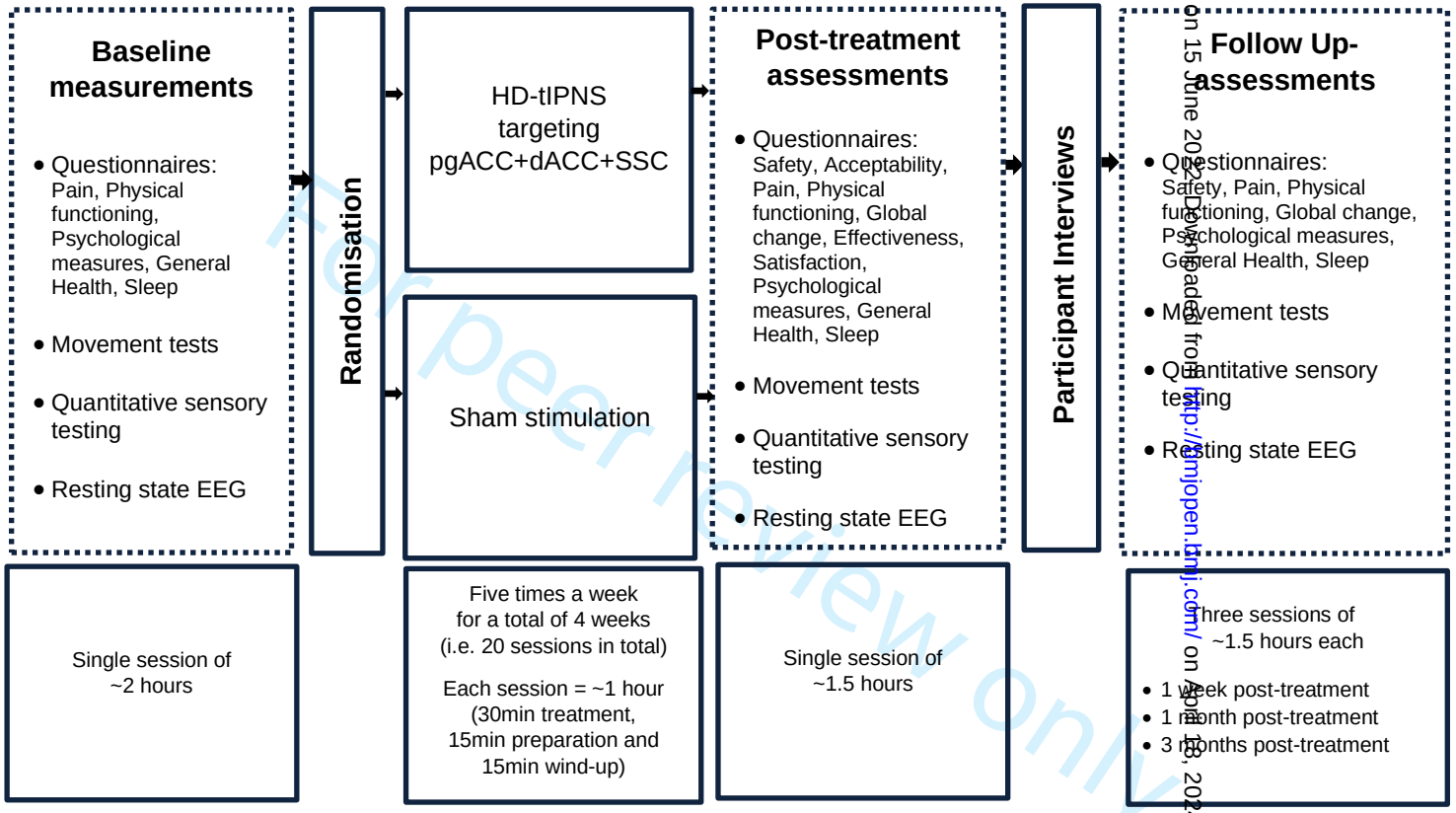
FIGURE LEGEND

Figure 1. Study design and timelines

EEG: Electroencephalography, HD-tIPNS: high definition transcranial infraslow pink noise stimulation, pgACC: pregenual anterior cingulate cortex, dACC: dorsal anterior cingulate cortex, SSC: primary somatosensory cortex.

Figure 2. Electrode positions and targeted brain regions

This figure presents results of the optimization that was created using the Stimweaver software by the Neuroelectrics company for targeting the activity of pgACC, dACC, and SSC.(121,122) From Left to right: Normal component of the E-field En (V/m), target E-field (V /m), target weight and ERNI* (mV 2/m2) for grey matter. The optimal montage consists of 8-channels that will be placed on the scalp following the international 10-20 EEG system.



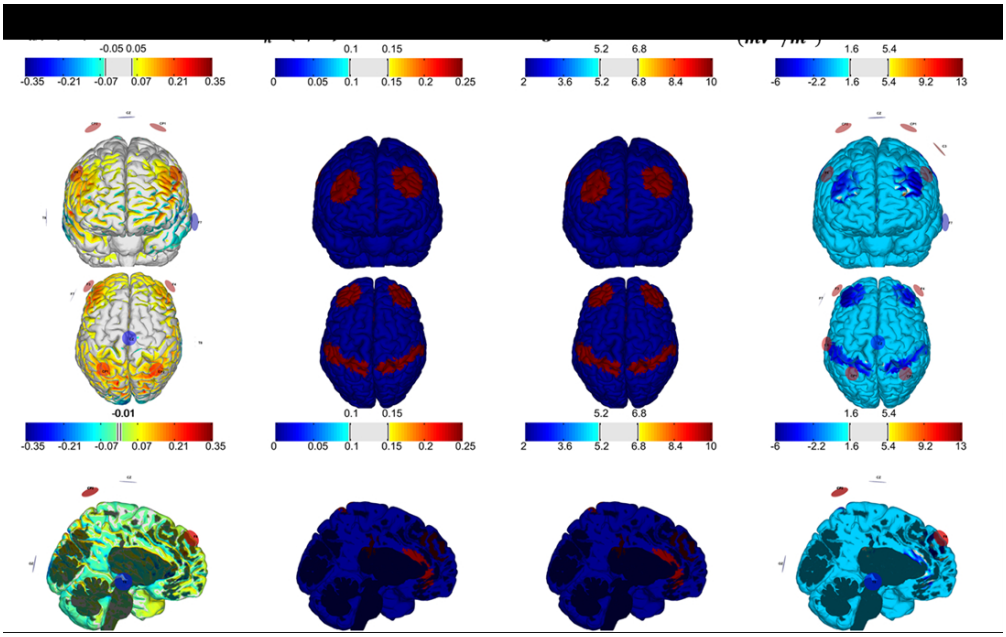


Figure 2. Electrode positions and targeted brain regions.

235x147mm (118 x 118 DPI)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	ItemNo	Description	Check/Details
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	✓ (Main Document, p. 1)
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	✓ (Table 1)
	2b	All items from the World Health Organization Trial Registration Data Set	✓ (Table 1)
Protocol version	3	Date and version identifier	✓ (Table 1)
Funding	4	Sources and types of financial, material, and other support	✓ (Main Document, p. 23)
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	✓ (Main Document, p. 1)
	5b	Name and contact information for the trial sponsor	✓ (Included in registry)
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	None.

	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	✓ (Main Document, p. 22)
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	✓ (Main Document, p. 5-7)
	6b	Explanation for choice of comparators	✓ (Main Document, p. 6)
Objectives	7	Specific objectives or hypotheses	✓ (Main Document, p. 6)
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	✓ (Main Document, p. 7, and Fig. 1)
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	✓ (Main Document, p. 8)
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	✓ (Main Document, p. 8-9)
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	✓ (Main Document, p. 10-11, Table 2, Fig.2)

		11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	✓ (Main Document, p. 22)
		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	✓ (Main Document, p. 12)
		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	✓ (Main Document, p. 11)
	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	✓ (Main Document, p. 12-19, Table 3)
	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	✓ (Fig. 1)
	Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	✓ (Main Document, p. 9)
	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	✓ (Main Document, p. 9-10)
Methods: Assignment of interventions (for controlled trials)				
Allocation:				

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	✓ (Main Document, p. 7-8)
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	✓ (Main Document, p. 7-8)
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	✓ (Main Document, p. 7-10)
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	✓ (Main Document, p. 8)
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	✓ (Main Document, p. 8)
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	✓ (Main Document, p. 12-19, Table 3)

	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	✓ (Main Document, p. 12-20, Table 3)
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	✓ (Main Document, p. 12-20, 22, Table 3)
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	✓ (Main Document, p. 19)
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	✓ (Main Document, p. 19)
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	✓ (Main Document, p. 19)
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	✓ (Main Document, p.22)
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	✓ (Main Document, p. 22)

Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	✓ (Main Document, p. 22)
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	✓ (Main Document, p. 22)
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	✓ (Main Document, p. 22)
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	✓ (Main document, p. 22)
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	✓ (Main document, p. 10)
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Not applicable.
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	✓ (Main document, p. 22)
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	✓ (Main Document, p. 22)

Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	✓ (Main document, p. 22)
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	None.
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	✓ (Main Document, p. 22)
	31b	Authorship eligibility guidelines and any intended use of professional writers	✓
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	✓ (Included in registry)
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	✓ (Approved by Ethics Committee)
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Not applicable.

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

High-definition transcranial infraslow pink noise stimulation for chronic low back pain: Protocol for a pilot, safety, and feasibility randomized placebo-controlled trial.

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Complete List of Authors:	Adhia, Divya; University of Otago - Dunedin Campus, Surgical Sciences Mani, Ramakrishnan; University of Otago , School of physiotherapy Reynolds, John; University of Otago - Dunedin Campus, Anatomy Vanneste, Sven; Trinity College Dublin, DeRidder, Dirk; University of Otago
Primary Subject Heading:	Neurology
Secondary Subject Heading:	Complementary medicine, Medical management, Neurology
Keywords:	Back pain < ORTHOPAEDIC & TRAUMA SURGERY, Pain management < ANAESTHETICS, Neurology < INTERNAL MEDICINE, Neurological pain < NEUROLOGY, Spine < ORTHOPAEDIC & TRAUMA SURGERY

Title:

High-definition transcranial infraslow pink noise stimulation for chronic low back pain: Protocol for a pilot, safety, and feasibility randomized placebo-controlled trial.

Authors: Divya Bharatkumar Adhia[a,e,*], Ramakrishnan Mani[b,e], John Reynolds[c], Sven Vanneste[d], Dirk De Ridder[a,e]

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Low back pain, Transcranial electrical stimulation, Randomised controlled trial, Safety, Feasibility

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(Word count includes Abstract, Strengths/Limitation, Funding and Competing Interests Statement, author contributions, and changes to registry section)

ABSTRACT

Introduction: Chronic low back pain (CLBP) is a common disabling health condition. Current treatments demonstrate modest effects, warranting newer therapies. Brain imaging demonstrates altered electrical activities in cortical areas responsible for pain modulation, emotional, and sensory components of pain experience. Treatments targeting to change electrical activities of these key brain regions may produce clinical benefits. This pilot study aims to (a) evaluate feasibility, safety, and acceptability of a novel neuromodulation technique, high definition transcranial infraslow pink noise stimulation (HD-tIPNS), in people with CLBP, (b) explore the trend of effect of HD-tIPNS on pain and function, and (c) derive treatment estimates to support sample size calculation for a fully powered trial should trends of effectiveness be present.

Methods & analysis: A pilot, triple-blinded randomized two-arm placebo-controlled parallel trial. Participants (n=40) with CLBP will be randomized to either sham stimulation or HD-tIPNS (targeting somatosensory cortex and dorsal and pregenual anterior cingulate cortex). Primary outcomes include feasibility and safety measures, and clinical outcomes of pain (Brief Pain Inventory) and disability (Roland-Morris disability questionnaire). Secondary measures include clinical, psychological, quantitative sensory testing, and electroencephalography collected at baseline, immediately post-intervention, and at one-week, one-month and three-months post-intervention. All data will be analysed descriptively. A nested qualitative study will assess participants perceptions about acceptability of intervention and analyzed thematically.

Ethics and dissemination: Ethical approval has been obtained from Health and Disability Ethics Committee(Ref:20/NTB/67). Findings will be reported to regulatory

and funding bodies, presented at conferences, and published in a scientific journal. Registration: Prospectively registered in Australian and New Zealand Clinical Trials Registry (ACTRN12620000505909).

STRENGTH AND LIMITATIONS

- This study will use a novel neuromodulation technique (HD-tIPNS) tosimultaneously target cortical areas responsible for pain modulation, emotional, and sensory components of pain experience.
- The use of Starstim-Home transcranial electrical stimulation system allows appropriate blinding of the treating researcher, and the possibility of a high-quality triple-blinded (participant, treatment therapist, and outcome assessor) randomized placebo-controlled trial.
- Sample size estimation has not been conducted in this feasibility and safety study design.

INTRODUCTION

Chronic low back pain (CLBP) is a significant and growing health challenge, affecting individuals, the wider community, and the healthcare system.[1-3] Along with pain and impaired function, individuals with CLBP have significant psychological comorbidities and poor quality of life.[1-3] Currently available treatments for CLBP demonstrate at best small effect sizes.[4-6] Pharmacological interventions are not effective with a high risk of adverse outcomes.[7-9] Thus, new, innovative, evidence-based, safer therapies are warranted for the management of CLBP.

Resting-state cortical activity alterations have been demonstrated in individuals with CLBP.[10-13] The most notably involved cortical areas include the anterior cingulate cortex (ACC) and the primary somatosensory cortex (SSC), which are the central hubs of the pain processing brain networks.[10-18] The ACC, particularly the pregenual region (pgACC), is part of the descending pain modulatory system (or anti-nociceptive system), the activation of which releases μ-opioids that act to modulate incoming nociception information from the hyperactive, spinal cord circuits, thereby alleviating pain.[13 16 17 19 20] The SSC, along with the dorsal region of ACC (dACC), is part of ascending nociceptive (lateral and medial) pathways that are responsible for encoding the sensory (i.e. painfulness) and the emotional components (e.g. suffering) of the pain experience.[13 16 17 19 20] Recent evidence suggests that alterations in the functional connectivity patterns between the pain processing regions (pgACC, dACC, SSC) are critical for maintaining chronic pain and are associated with its clinical and psychological outcomes.[14-16 21-28]

Neuromodulatory interventions targeted to alter activities in cortical pain processing areas may improve clinical outcomes. Transcranial electrical stimulation (TES), a non-invasive brain stimulation technique, can influence the electrical activity of targeted brain regions, promote cortical plasticity, and improve the functional connectivity to/from the targeted area, thereby improving pain modulation. Recent systematic reviews and meta-analyses demonstrate positive effects of the TES techniques in chronic pain conditions (e.g., fibromyaligia, migraine, spinal cord injury)[29-32] However, the evidence for effect of TES for treatment of CLBP is limited (n=10 pilot studies[33-42], n=2 protocols[43 44]) and have demonstrated mixed results.[45 46] Previous TES studies targeted altering cortical electrical activity of a single superficial brain region[33-36 38-42] (e.g., Motor cortex or dorsolateral prefrontal cortex) using transcranial direct current stimulation (tDCS), except one study[37] that targeted a deeper brain region (dACC). None of the studies has simultaneously targeted multiple-brain regions (pgACC, dACC, SSC) responsible for the descending and ascending modulation of nociceptive sensory information. Further, the stimulation technique used in the previous TCS studies involved applying two large scalp electrode pads that deliver currents to diffuse areas of the brain, making focalized stimulation of targeted brain regions less feasible. Focal and simultaneous stimulation of multiple brain regions could help improve clinical outcomes with larger effect sizes, similar to invasive neuromodulatory interventions[47].

We propose determining the feasibility and safety of a novel high definition transcranial infraslow pink noise stimulation (HD-tIPNS) technique, targeting the pgACC, dACC, and SSC regions simultaneously in people with CLBP. The HD-tIPNS technique was developed to specifically modulate the infraslow electrical activity (0.0-0.1 Hz) in the

brain. The infraslow electrical activity, a fundamental frequency range of the brain, re-organizes neurons and improves the electrical connectivity of the brain-wide functional networks.[48-51] The ISF plays a profound role in modulating and synchronizing high-frequency cortical activity that are known to be affected in chronic pain[50 52-54], and is also critically involved in mediating pain perception[55]. Evidence from imaging studies also demonstarte alterations in the infraslow oscillations in individuals with CLBP in the pain processing brain regions (pgACC, dACC, SSC).[56 57] The pink noise frequency spectrum resembles the naturally occurring signals in the self-organization of the brain, thus can be more effective than standard tDCS electrical parameters used in previous studies.[58 59] We, therefore, believe that specifically and simultaneously targeting the fundamental infraslow activity at key nodes of pain processing networks, using a novel HD-tIPNS technique, could normalize brain-wide electrical activity and functional connectivity between areas of interest, promoting better pain modulation and producing more meaningful clinical benefits. This protocol outlines the methods and analysis used in the pilot randomized controlled trial. The specific aims are to (a) evaluate the feasibility, safety, and acceptability of the HD-tIPNS technique in people with CLBP, (b) explore the trend of effect of HD-tIPNS on pain and function, and (c) provide estimates of clinical outcome measures to support a sample size calculation for a fully powered trial should the trend of effectiveness be present.

METHODS AND ANALYSIS

The following guides have been used to prepare this study protocol: Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement[60], the template for intervention description and replication (TIDieR) checklist[61], and IMMPACT

Recommendations[62-66]. In addition, this trial has been prospectively registered (Table 1).

Study design:

The proposed study will be a triple blinded pilot randomized placebo-controlled parallel trial with two intervention arms. The outcome measures will be collected at baseline, immediately post-intervention, and at follow-up periods: one week, one month, and three months post-intervention (Fig. 1).

Randomization: A research administrator, not involved in other procedures, will randomize participants on a 1:1 basis using a computerized open-access randomization software program to:

- Group 1: HD-tIPNS, or
- Group 2: Sham stimulation

The randomization schedule will be concealed in sequentially numbered, sealed opaque envelopes and provided to participants at their baseline measurements.

Blinding: Participants, outcome assessor, and treating researchers will be blinded to group allocation. Stimulation programs on Starstim device will be designed and controlled by an independent researcher to allow blinding of the treating researcher. The success of blinding will be assessed after the completion of the intervention and follow-up phases. The participant, and the outcome assessor, and treating researcher will be asked “What type of treatment they believe that they/the participant received respectively?” and will be required to choose between three options: active, sham, or

don't know. The confidence in their judgement will also be assessed on an 11-point numeric rating scale *(0=Not at all confident to 10=Extremely confident)*, with the reason for their judgement being noted and whether the intervention was revealed to them. Unblinding will be permissible only in the case of an adverse event or any unexpected event.

Study setting: This study will be conducted in the Department of Surgical Sciences laboratory, Dunedin School of Medicine, Dunedin hospital, New Zealand.

Participants and eligibility criteria:

Adults with CLBP will be eligible to participate.

Inclusion criteria: Capable of understanding and signing an informed consent form, age between 18 to 75 years on the day of the consent, pain in the lower back (the region between 12th rib and gluteal fold) that occurs everyday for ≥3 months, a score of ≥4 on an 11-point numeric pain rating scale (NPRS, 0=*No pain* to 10=*Worst pain imaginable*) in the past four weeks prior to enrolment, a disability score of ≥5 on Roland–Morris Disability Questionnaire[67 68]. These cut-off scores are used as an indication that CLBP significantly impacts daily functioning, are by International Association of Study of Pain guidelines and are in line with optimal Delphi definitions of LBP prevalence (DOLBaPP).[3 67-70]

Exclusion criteria: Participants with the following self-reported health conditions will be excluded: Inflammatory arthritis, undergoing any therapy from a health professional (e.g. physiotherapist or chiropractor), recent soft tissue injuries of the back in the last

3 months, history of surgery to the back region or waiting/scheduled for any procedures within the next six months, current intake of any centrally-acting medications or intention of taking new medications in the next three months, steroid injections to the back in past six months, radicular pain and radiculopathy, history of neurological diseases, unstable medical or psychiatric conditions, history of epilepsy or seizures, peripheral neuropathy, vascular disorders, substance abuse, dyslipidemia, cognitive impairments [dementia, post-traumatic stress disorders, Alzheimer's disease; assessed as a score of <24 on the mini-mental status examination conducted at baseline], history of uncontrolled/untreated hypertension, presence of any pacemaker or defibrillator or electronic/metal body implants (around the head/neck region), and recent or current pregnancy.

Sample size:

This proposed research is a pilot exploratory study, which will be executed to make a power estimate for a future phase II study should the intervention appear feasible, safe, acceptable, and show trends of effectiveness. Hence a sample size calculation was not performed. Based on statistical advice, a sample of 40 participants (20/group) was considered enough to determine feasibility issues and obtain treatment estimates for designing a full trial.

Recruitment and study enrolment:

Participants will be primarily recruited through broadcasting in the public media (e.g., newspapers and social media). Participants attending healthcare providers will also be invited to participate. The total recruitment period will be one-year (June'21 to

May'22). Advertisements will be placed in the local newspapers twice a month and social media once a month (Sponsored Facebook ad, for one week). Advertisement fliers will be placed around a tertiary hospital, regional healthcare practices, and supermarkets. A recruitment email will be sent to the local tertiary educational university/polytechnic staff and students once every two months.

All volunteers will complete an online screening form. Potential participants will be contacted by a researcher with a health professional background (Trained Musculoskeletal Physiotherapist) to undergo further screening over the phone to confirm eligibility prior to study enrolment. The study information sheet (Supplementary file) will be emailed to eligible participants. Written informed consent will be obtained before baseline testing. At the baseline session, all participants will complete questionnaires to capture demographics, clinical characteristics of CLBP, including presence of central sensitivity (Central Sensitization Inventory)[71 72], neuropathic pain quality (PainDETECT)[73], pain personification[74], and treatment expectancy and credibility[75].

Intervention procedures(Table 2):

The intervention will be administered five times a week (30 minutes/session) for four weeks by an assistant research fellow trained by the primary investigator experienced in neuromodulation techniques. A battery-driven wireless transcranial electrical stimulator (Starstim-Home TES®, Neuroelectrics, Spain) will be used to deliver stimulation while participants are comfortably and quietly seated (Fig. 2). Eight small electrodes (~4cm^2) will be placed on a neoprene head cap following the International 10-20 EEG system to simultaneously target pgACC, dACC, and SSC (Fig. 2).

For HD-tIPNS group, the stimulation will be delivered at a current strength of a maximum of 2mA for 30min, with 60s ramp up and ramp down at the beginning and end of each stimulation session, with continuous stimulation in between. The pink noise stimulation at a current strength of a maximum of 0.6mA will be superimposed on the infraslow (0.1Hz sinusoidal) waveform of a current intensity of 1mA. The current strength at each electrode will never exceed the maximum safety limit of 2mA. The intervention dosage is chosen based on the previous TES studies in CLBP[33-41 43 44] and follows safety guidelines[76-78].

For the sham stimulation group, to create an identical skin sensation to active stimulation, we will use the Actisham protocol created by the Neuroelectrics.[79] The current will be applied for a 60s ramp up and 60s ramp down at the beginning and end of each stimulation session, without any current for the remainder of the session. The duration of the sham session will be like HD-tIPNS session to blind the procedure appropriately. Participants in both groups will be informed that they may or may not perceive any sensations during the stimulation treatment. The previous TES studies have used this sham procedure and are shown to effectively blind participants to the stimulation condition, as it can induce the same scalp sensations perceived during active stimulation, both in terms of intensity and localization. Further, the Actisham protocol will prevent the currents from reaching the cortex, thus avoiding causing any brain excitability changes.[79]

Treatment fidelity will be assessed by the principal investigator at each session, who will supervise that the treatment is delivered in a standardized manner as planned.

The treatment delivered for each participant for each session will be saved on the NIC2 computer software.

Usual care/concomitant treatments: Participants will be permitted to continue their medications/exercises/other concomitant treatments for the duration of the trial, with the type and dosage being recorded at the baseline session. Any changes to their concomitant treatments will be recorded at every treatment and assessment session. Participants will be advised not to change any of their concomitant treatments for the duration of the trial. Participants with the intention of taking new medications or changing their treatment in the next three months will be excluded.

Outcome measures:

An assessor, blinded to the group allocation, will collect outcomes at baseline (T_B), immediately post-intervention (T_{im}), and at follow-up of one week (T_{1wk}), one month (T_{1m}) and three months (T_{3m}) post-intervention. The chosen secondary measures have good psychometric properties, are used in clinical trials involving people with CLBP and are by recommendations[62-66].

Primary outcomes:

Feasibility measures:

- Recruitment rate, the number of participants recruited per month. Participants will be recruited over one year, with no threshold placed on the recruitment rate for each month. The recruitment rate will be recorded every week since the release of the

advertisements, as wll as the number of advertisements and the time period required to achieve the desired sample size (n=40).

- The proportion of participants eligible and recruited from the total number screened (with reasons for exclusion), expressed as a percentage.
- Adherence to intervention measured as number of treatment sessions attended by each participant expressed as a percentage of total number of sessions. Adherence rates will be calculated once the treatment phase is completed.
- Drop-out rates, measured as the number of participants who dropped out in each group, expressed as a percentage of the total number of participants enrolled in the study. Drop-outs rates will be calculated once the follow-up phase is completed.

Safety measures:

At each treatment and follow-up session, the treating researcher will record any adverse effects that likely have a causal relationship with the intervention. The following variables will be recorded:

- Qualitative description and intensity of each symptom on a Likert scale (0=none to 10=extreme)
- Relation of symptom to treatment, measured on a scale ranging from 1=unrelated to 5=strongly related.
- Duration and time taken for resolution of each symptom expressed in minutes.
- Worsening or improvement of symptoms: The Discontinuation-Emergent Sign and Symptom (DESS)[80], will be used to record worsening or improving side effects compared to status prior to previous session.
- Any drop-outs due to adverse effects and how the adverse effects were managed.

Acceptability and satisfaction:

Participant acceptability and satisfaction of the intervention will also be recorded quantitatively on an 11-point NRS (0=Not at all acceptable/satisfied to 10=Very acceptable/satisfied respectively).

Clinical measures:

Pain intensity and interference: using Brief Pain Inventory[81], a standardized, validated questionnaire for CLBP.

Physical Function: *Roland–Morris Disability Questionnaire*[67 68] will be used to assess self-reported functional abilities.

Secondary outcomes (Table 3):

Measures of peripheral and central sensitization: Quantitative sensory testing will be conducted and reported in accordance with the guidelines[82 83] and our previous study[84].

- *Mechanical temporal summation (MTS):* will be assessed using a nylon monofilament (Semmes monofilament 6.65, 300 g). Brief ten repetitive contacts will be delivered at a rate of 1 Hz, externally cued by auditory stimuli. The participants will be asked to rate the level of pain experienced on NRS (0=No pain to 100=Extreme pain) immediately after the first contact and to rate their greatest pain intensity after the 10th contact. Three trials will be conducted for each of the two regions (i.e., symptomatic low back and non-dominant wrist) in random order. The

location of these areas will be recorded using bony landmarks to ensure that same areas are re-assessed during follow-up. MTS will be calculated as difference between NRS rating after the first contact and the highest pain rating after the 10th contact for each trial. This score presents the maximum amount of MTS across ten contact points. Average of three trials will be calculated, with a positive score indicating an increase in MTS. The MTS index will be defined as the ratio of "follow-up" pain rating divided by "baseline" pain rating.[84-86]

- *Pressure pain threshold (PPT):* A computerized, handheld digital algometer (AlgoMed; Medoc, Ramat Yishai, Israel) will be used to measure three trials of PPT over two regions (symptomatic low back and non-dominant wrist) in random order. Two familiarization trials will be performed at dominant mid-forearm before formal trials. The 1-cm^2 algometer probe will be pressed over marked test site perpendicularly to the skin at a rate of 30kPa/s. Participants will be instructed to press algometer trigger button in the patient control unit when pressure sensation changes to first pain.[87] Once patient-controlled unit is activated, the trial is automatically terminated, and amount of pressure will be recorded. If participants did not report pain at maximum pressure level which is set at 1000kPa for safety reasons, the procedure would be terminated, and a score of 1000kpa will be assigned for that trial. The average of three trials will be calculated and used for analysis.[88]
- Condition pain modulation (CPM) is the most frequently administered procedure for exploring the endogenous pain modulatory system.[87 89] CPM test procedure will be administered at least 15 to 20 minutes after the MTS and PPT procedures with the previously published recommendations of testing.[87 89]

- The conditioning stimulus will consist of a cold pressor task. The participants will immerse their dominant hand (until mid-forearm) in a thermos containing circulating cold water for a maximum period of 2 minutes. The cold water temperature will be maintained at ~5° centigrade and will be recorded immediately before and after the immersion procedure. Participants will be asked to continue hand immersion until the end of 2 minutes or until it is too uncomfortable to be kept immersed (NPRS~80%). Participant's pain during conditioning stimulus will be recorded on NPRS (0=No pain to 100=Extreme pain) at every 15s interval. A similar conditioning stimulus protocol has been used in previous studies showing a significant CPM effect.[90]
- Test stimulus: A computerized, handheld digital algometer (AlgoMed; Medoc, Ramat Yishai, Israel) will be used to measure suprathreshold PPT (pain40) at the non-dominant leg region (tibialis anterior muscle). Two familiarization trials will be performed at mid-forearm before the formal trials. The 1-cm^2 algometer probe will be pressed over the marked test site perpendicularly to the skin at a rate of 30 kPa/s. The participants will be instructed to press the algometer trigger button in the patient control unit when the pressure sensation changes to a pain intensity of 40 out of 100 on the NRS. Once the patient-controlled unit is activated, the trial is automatically terminated, and the amount of pressure (kPa) will be recorded. Suppose participants did not report pain at the maximum pressure level which is set at 1000 kPa for safety reasons, the assessor will terminate the procedure, and a score of 1000 kpa will be assigned for that trial. Two PPT (pain40) trials will be recorded before conditioning stimulus and will be averaged to obtain a baseline score. In addition, three PPT (pain40) trials will be

recorded in the same region at 30, 60, and 90 seconds immediately after the conditioning stimulus.

- Calculation of CPM: A percent change score will be calculated for each time point (i.e., CPM30sec, CPM60sec, and CPM90sec), with a positive score indicating an increase in PPTs (pain40) after the conditioning stimulus and thus the presence of CPM effect.

$$\text{CPM percent change score} = \frac{\text{Post score} - \text{Pre score}}{\text{Pre score}} \text{ x } 100$$

Psychological measures: will include *Depression, Anxiety, and Stress Scale*[91], to measure those three psychological constructs, *Pain Catastrophizing Scale*[92], to measure extent of catastrophic thoughts and feelings about their pain[93], and *Pain Vigilance and Awareness Questionnaire*[94] to measure frequency of habitual 'attention to pain'.

Pain unpleasantness (affective component) measured using an 11-point unpleasantness NRS (0=not at all unpleasant to 10=most unpleasant imaginable).[95 96]

Pain bothersomeness: measured using an 11-point bothersomeness NRS (0=not at all bothering to 10=most bothering).[95 96] A categorical question will also be used "In the last one week, how bothersome has your low back pain been?'' with five choices: "not at all", "slightly", "moderately", "very much", and "extremely".[97 98]

The global rate of change[99]*:* assessed using the question *"Compared to the beginning of treatment, how would you describe your back at this moment?"* Participants will rate

their perceived change on an 11-point scale (-5=much worse, through 0=unchanged, to +5=completely, recovered).

Quality of life and wellbeing: will be assessed using *European Quality of Life–5 Dimensions* scale[100] and *World Health Organisation- Five Well-Being Index*[101] respectively.

Measures of cortical electrical activity: Resting-state electroencephalogram (EEG) (~10 minutes, eyes-closed) will be obtained in a quiet room while the participant is sitting upright in a comfortable chair by an independent researcher blinded to the treatment group. Participants will be asked to refrain from caffeinated drinks. EEG data will be collected using the SynAmps RT Amplifier (Compudemics Neuroscan). The EEG will be sampled with 64 electrodes placed in the standard 10–10 International placement, and impedances will be checked to remain below 5 kΩ. The EEG data will then be resampled to 128 Hz, band-pass filtered (fast Fourier transform filter) to 0.01–44 Hz and re-referenced to the average reference using the EEGLAB function in Matlab. The data will then be plotted in EEGLAB for a careful inspection of artifacts and manual rejection.

Standardized low-resolution brain electromagnetic tomography (sLORETA) will be used to estimate intracerebral electrical sources that generate scalp-recorded activity in each of the following ten frequency bands, i.e., infraslow (0.01-0.1Hz), slow (0.2-1.5Hz), delta (2–3.5Hz), theta (4–7.5Hz), alpha1 (8–10Hz), alpha2 (10.5–12Hz), beta1 (12.5–18Hz), beta2 (18.5–21Hz), beta3 (21.5–30Hz), and gamma (30.5–44Hz). The following three analyses will be used to explore the specific (i.e. at the targeted cortical regions) and non-specific (i.e. other cortical regions) effects of the HD-tIPNS on cortical activity and connectivity:

- *Whole-brain analysis:* will be used to explore the overall (specific and non-specific) changes in the current density in the cortical regions. Comparisons will be made between pre-and post-treatment measurements on a whole-brain by sLORETA statistical contrast maps through multiple voxel-by-voxel comparisons in a logarithm of t-ratio.[102-104]
- *Region of interest analysis:* will be used to calculate and compare the log transformed current density changes at the targeted brain regions (pgACC, dACC, and SSC). The ROI maker 1 function in sLORETA will be used to define the region of interest. A seed point will be provided for each region of interest and all voxels within a radius of 10mm will be averaged to calculate the current density.
- *Lagged phase connectivity:* will be used as a measure of coherence and will be calculated between all the regions of interest for all the ten frequency bands as described above.[102-104] Comparisons will be made between pre-and post-treatment measurements using sLORETA statistical contrast maps through multiple voxel-by-voxel comparisons in a logarithm of t-ratio.[102-104]

Statistical analysis:

SPSS version 27.0 will be used for all statistical analyses. Descriptive statistics will be used to analyze feasibility, safety, and acceptability measures. As this is a feasibility study, tests for significance to compare clinical or secondary measures between study groups will not performed, but descriptive statistics will be calculated.

All measures will be analyzed based on intention-to-treat principle and as per the originally assigned groups. Last observation carried forward methodology will be used to compute missing data. Mean±SDs and Mean differences (95% CI), will be calculated from baseline to each interim and primary endpoint (T_{3m}).

Percentage change to baseline will be calculated for primary pain (BPI) and functional (RMDQ) measures as below (e.g., for T_{3m}):

$$\text{Percent change to baseline} = \frac{\text{T3m} - \text{T0}}{\text{T0}} \text{x} 100$$

A ≥30% decrease will be considered as a meaningful clinical important difference (MCID). Proportion of participants with changes ≥MCID will be calculated and descriptively compared between groups.

A nested qualitative study

We will include a nested qualitative study to explore participant's experiences and acceptability of intervention procedures. Semi-structured in-depth interviews will be conducted by a researcher, blinded to treatment allocation, immediately post-intervention. All participants will be invited to participate. The aims of this study are explorative in nature and will evaluate participant's experiences, exploring difficulties and barriers faced, perception towards intervention/research process, acceptability of intervention, perceived value and positive aspects of the study, and any other issues that arise during interviews. Table 4 presents the questions that will be used as a guide for the interview. The interviews will be audio-recorded and fully transcribed. The analysis will be guided by General Inductive Approach[105 106], which provides a pragmatic framework for identifying shared and individual experiences and embraces findings derived from both research objectives (deductive) and those arising directly from analysis of raw data (inductive). A constant comparison process will be used; researchers will reflect on and discuss completed interviews and revise the questions

schedule accordingly to ensure a broad capture of new important information. The results of qualitative study will be published separately.

Patient and Public involvement:

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

DISCUSSION

The proposed research will be the first randomized placebo-controlled pilot study to explore a novel HD-tIPNS technique targeting multiple brain regions simultaneously in individuals with CLBP. This pilot research will provide preliminary evidence on feasibility, safety, and acceptability of the HD-tIPNS technique for treatment of CLBP. Assessment of feasibility and acceptability of new interventions and study procedures is essential to determine parameters required to inform the study design of a future fully-powered randomised controlled trial.[107] The HD-tIPNS is a novel intervention technique, and there are only a limited number of studies evaluating the TES interventions in people with CLBP. To the best of our knowledge, none of these studies have assessed the acceptability of the TES in people with CLBP. Our study will incorporate detailed mixed method approach to assess the feasibility and the acceptability of the HD-tIPNS techqniue and help inform interventions, study procedures, and refinements and the planning of a future definitive randomised controlled trial. Further although our study is not powered to test effectiveness, it will provide treatment estimates to design the sample characteristics and numbers for a fully powered randomised controlled trial in future.

ETHICS, DATA SAFETY, AND DISSEMINATION

Ethical approval has been obtained from Health and Disability Ethics Committee (Ref:20/NTB/67), who may also audit the study investigators during or after the study. Any deviations from protocol will require Ethical amendment and will be updated in the registry. To protect participant confidentiality, any personal information collected will be destroyed at the end of the project. Each participant will be given a unique

identification code, and the data will be linked to that code only. All study data will be securely stored in a locked filing cabinet or electronically with password protection, such that only those involved in the research program will have access to it. As required by the University's research policy, any unidentified raw data on which the results of the project depend will be kept in secure storage for ten years, after which it will be destroyed.

An independent Data and Safety Monitoring Committee will monitor the safety of the study. A serious adverse event (SAE) is defined as any untoward medical occurrence or effect that results in death, is life-threatening, requires hospitalisation, results in persistent or significant disability or incapacity.The study will be discontinued if there is any unexpected SAE, other unexpected events, or if funding is completed/ insufficient.

Study findings will be reported to the regulatory and funding bodies, presented at the local, national, and international conferences, and disseminated by peer-review publication in a scientific journal.

FUNDING AND COMPETING INTERESTS STATEMENT

This work is supported by NZ Health Research Council (20/618), Healthcare Otago Charitable Trust (Grant number: N/A), Lottery Health Research (20959), and Brain Health Research Centre (Grant number: N/A). The funding bodies were not involved in the study conceptualization or design; and will not be involved in the collection,

analysis, and interpretation of data; in the writing of the report; and in the decision to submit the article for publication.

There are no competing interests for any author.

AUTHORS' CONTRIBUTIONS:

Conceptualization: DBA, DDR, RM, JR, and SV; Methodology/Design of the work: DBA, DDR, RM, JR and SV; Writing—original draft preparation: DBA, DDR and RM; writing—critically reviewing and revising: DBA, DDR, RM, SV, and JR. All authors have critically read and agreed to the final version of the submitted manuscript and agree to be accountable for all aspects of the work.

CHANGES TO REGISTRY:

The following changes were made to the registered protocol based on the ethical review and the peer reviewer comments. *Eligibility criteria:* The age bracket for participant inclusion was expanded to 18 to 75 years instead of the originally planned 35 to 70 years. *Secondary outcomes:* The MTS and PPT tests will be evaluated at two sites (symptomatic low back and non-dominant wrist region) rather than the originally planned three regions (i.e., symptomatic low back region, non-symptomatic low back region, and the distant non-dominant wrist). Also, for the CPM procedure, the test site was changed to the non-dominant leg region, rather than the originally planned most painful low back region. *Outcomes:* Some of the secondary clinical measures and mechanistic measures (eg., pain unpleasantness, pain bothersomeness, global rate of change, quality of life, wellbeing, and resting state EEG) were included in the study

protocol but not in the registry. These have been added to the registry. All these changes to the protocol were made before the participant enrolment commenced, and are updated in the ANZCTR trial registry (https://anzctr.org.au/Trial/Registration/TrialReview.aspx?ACTRN=12620000505909).

Table 1. WHO trial registration data set (v.1.3.1).

Item	Information
Primary registry and trial Identifying number	Australian and New Zealand Clinical Trials Registry- ACTRN 12620000505909
Date of registration in primary registry	23/04/2020
Universal Trial Number	U1111-1250-1177
Source of monetary or material support	Health Research Council of New Zealand Emerging Researcher First Grant, The Healthcare Otago Charitable trust, Lottery Health Research equipment grant, Brain Health Research Centre, and the Neurological foundation of New Zealand.
Primary Sponsor	University of Otago
Contact for public queries	Dr Divya Adhia, Department of Surgical Sciences, Otago Medical School, University of Otago.
Contact for scientific queries	Dr Divya Adhia, Department of Surgical Sciences, Otago Medical School, University of Otago.
Public title	Non-invasive brain stimulation for chronic low back pain.
Scientific title	Safety and feasibility of transcranial electrical stimulation for chronic low back pain.
Country of recruitment	New Zealand.
Health condition or problem studied	Chronic low back pain.
Interventions	High-definition transcranial infraslow pink noise stimulation.
Key eligibility criteria	Adults between the ages of 18-75 years, with chronic low back pain.
Study type	Interventional, exploratory randomised placebo-controlled parallel pilot trial; Allocation ratio = 1:1.
Date of first enrolment	1st June 2021 (Note: Delayed from the planned enrolment date of 15th July 2020 as indicated in registry, due to equipment breakdown and delay in recruitment of research staff).
Sample size	Not calculated. This pilot study will be executed to make a power estimate for a future phase II study. Based on statistical advise,

Item	Information
	40 participants (20 per group) will be enough to determine feasibility measures for a fully powered trial.
Recruitment status	Recruiting (Recruitment period: June'21 to May'22)
Primary outcomes	Feasibility (measured as recruitment rate, proportion of participants eligible and recruited, adherence to intervention, and drop-out rates) Safety (measured as any adverse events that have a likely causal relationship with the intervention) Acceptability of the intervention (assessed quantitatively as well as qualitatively) Pain and disability: Brief pain Inventory and Roland-Morris disability questionnaire. (Note: Feasibility measures and treatment acceptability are primary measures that are listed under secondary outcome section in the ANZCTR due to limit of the primary outcomes that could be included in the registry).
Secondary measures	Quantitative sensory testing: mechanical temporal summation, pressure pain threshold, and conditioned pain modulation. Psychological measures: Depression, anxiety and stress scale, pain catastrophising scale, and pain vigilance and awareness questionnaire. Pain measures: Pain unpleasantness and bothersomeness, global rate of change score. Wellbeing: European quality of life–5 dimensions, World Health Organisation- five wellbeing index. Resting-state electroencephalogram: current density and functional connectivity.
Ethical Review	Status: Approved, Date of Approval: 28th July 2020; Committee: Health and Disability Ethics Committee (HDEC, Ref: 20/NTB/67)

Table 2: Description of the HD-tIPNS intervention, as per the template for intervention description and replication.

Item number and Item	Description
1. BRIEF NAME	High-definition transcranial infraslow pink noise stimulation (HD-tIPNS).
2. WHY	The HD technique uses arrays of multiple small electrodes whose configuration can be optimized for focally targeting specific brain regions.[58 59 108-112] The HD-tIPNS technique is developed to specifically modulate the infraslow electrical activity (0-0.1 Hz) in the brain. The infraslow electrical activity, a fundamental frequency range of the brain, re-organizes neurons and improves the electrical connectivity of the brain-wide functional networks.[48-51] Optimizing the infraslow frequency can normalize the electrical activity in the higher frequency bands known to be affected in individuals with chronic pain.[48-51] Recent imaging studies have also demonstrated alterations in the infraslow oscillations in individuals with CLBP in descending (pgACC) and ascending (dACC, SSC) pain pathways.[54 56 57] Research shows that pink noise stimulation can influence the infraslow electrical activity (0-0.1 Hz) in the brain.[58 59] The pink noise frequency spectrum resembles the naturally occurring signals in the self-organization of the brain, thus can be more effective than standard tDCS electrical parameters.[58 59] We, therefore, hypothesize that specifically and simultaneously targeting the fundamental infraslow activity at the key nodes of pain processing networks, using a novel HD-tIPNS technique, could normalize brain-wide electrical activity and functional connectivity between areas of interest, promoting better pain modulation and producing more meaningful clinical benefits.
3. WHAT	A battery-driven wireless transcranial electrical stimulator (Starstim-Home TES®, Neuroelectrics, Spain) will be used to deliver stimulation while participants are comfortably and quietly seated. Eight electrodes will be placed on a neoprene head cap following the International 10-20 EEG system to simultaneously target pgACC, dACC, and SSC (Fig. 2 and 3).
4. Procedures:	At each session, participant's scalp will be cleaned with alcohol wipes. The treating researcher will place the neoprene cap with the eight electrodes attached to it on the participant's head while they are comfortably seated in a chair. The reference electrode will be placed on the right ear. Electrogel will be applied to the scalp at the locations of the electrodes for reducing the impedance. The NIC2 software uses a traffic light signal indicator (red, yellow, green) for impedance. All electrodes will be prepared to have the lowest impedance (green colour). All the cables will be attached to the stimulating electrodes and the neckbox. The stimulator will be connected to the NIC2 software using its wifi function. The participant will be comfortably

	positioned in a half-lying position with their eyes closed. The participant will be asked to relax, and the stimulation intervention will be delivered for 30 minutes.
5. WHO PROVIDED	Two independent researchers will be involved in the delivery of the intervention. A researcher (R1) with a health professional background (physiotherapist) will design and control the Starstim-Home device and set up the stimulation programs in the NIC2 (neuroelectrics software), to allow blinding of the treating researcher (R2). The program will be uploaded to the online portal and the treatment will be scheduled for each participant by R1. Another independent researcher (assistant research fellow, R2) with considerable experience in administering neuromodulation techniques will prepare the participants for treatment and administer the stimulation intervention using the iPad of the Starstim-Home TES system. During the stimulation period, the iPad screen presents only a green bar for indicating the duration of the stimulation session and no other stimulation parameters are presented. This allows for appropriate blinding of the treating researcher (R2).
6. HOW	All participants will receive individual face-to-face sessions.
7. WHERE	Interventions will be delivered at a clinical laboratory in the Otago Medical School, Department of Surgical Sciences, located in the Dunedin Hospital, Dunedin, New Zealand.
8. WHEN and HOW MUCH	All participants will receive the intervention (based on their randomized group) for a total of 20 sessions, five times a week for four consecutive weeks. Each stimulation session will last for 30 minutes duration.
9. TAILORING	The interventions will not be tailored to individual participant's brain states. All participants in HD-tIPNS group will receive the same stimulation waveform, pink noise stimulation at a current strength of a maximum of 0.6mA superimposed on the infraslow (0.1Hz sinusoidal) waveform of a current intensity of 1mA.
10. MODIFICATIONS	Not applicable. This is a protocol for a pilot trial.
11. HOW WELL	Adherence to intervention will be one of the primary outcomes for the study and will be recorded by the treating researcher. Adherence rates will be calculated once the treatment phase is completed. The number of treatment sessions attended by each participant and expressed as a percentage of the total number of sessions.
12. Actual: describe the extent to which the intervention was delivered as planned.	Not applicable. This is a protocol for a pilot trial.

Table 3: List of the measure's domains, their construct, measurement tools, and assessment time points

Measure's Domains	Constructs	Measurement tools	Timepoints
Pain	Severity (primary clinical outcome)	Brief Pain Inventory Short form Severity subscale in the past 24 hours. 0-10 NRS of the worst pain in the past 24 hours 0-10 NRS of average pain in the past 24 hours	$T_B, T_{im}, T_{1wk}, T_{1m}, T_{3m}$ $T_B, T_{im}, T_{1wk}, T_{1m}, T_{3m}$ $T_B, T_{im}, T_{1wk}, T_{1m}, T_{3m}$
	Unpleasantness	0-10 NRS of unpleasantness in the past 24 hours	$T_B, T_{im}, T_{1wk}, T_{1m}, T_{3m}$
	Bothersomeness	0-10 NRS of bothersomeness in past 24 hours	$T_B, T_{im}, T_{1wk}, T_{1m}, T_{3m}$
Physical functioning	Pain interference (primary clinical outcome)	Brief Pain Inventory Short form Interference subscale in the past 24 hours.	$T_B, T_{im}, T_{1wk}, T_{1m}, T_{3m}$
	Disability (primary clinical outcome)	Roland–Morris Disability Questionnaire	$T_B, T_{im}, T_{1wk}, T_{1m}, T_{3m}$
Global change	Global perceived change	Perceived change in the back region on an 11-point scale (-5=much worse, through 0=unchanged, to +5=completely, recovered	T_{1wk}, T_{1m}, T_{3m}
Satisfaction	Extent of satisfaction	Perceived treatment satisfaction on an 0-10 NRS	T_{im}
Psychological functioning	Depression	Depression, Anxiety, and Stress Scale	$T_B, T_{im}, T_{1wk}, T_{1m}, T_{3m}$
	Catastrophising	Pain Catastrophising Scale	$T_B, T_{im}, T_{1wk}, T_{1m}, T_{3m}$
	Attention to pain	Pain Vigilance and Awareness Questionnaire	$T_B, T_{im}, T_{1wk}, T_{1m}, T_{3m}$
General Health	Quality of life	European Quality of Life- 5D	$T_B, T_{im}, T_{1wk}, T_{1m}, T_{3m}$
	Well-being	World Health Organisation-Five Well-Being Index	$T_B, T_{im}, T_{1wk}, T_{1m}, T_{3m}$

T_B: At baseline, T_{im}: Immediately post-intervention, T_{1wk}: One-week post-intervention, T_{1m}: One-month post-intervention, T_{3m}: Three-months post-intervention

Table 4: Interview guide

Questions for Participants	Follow up / prompting questions
Tell us what it's been like attending the assessment and treatment (brain stimulation) sessions.	
What obstacles have you had to face throughout the trial period?	What aspects/areas were challenging? How did it affect your back pain?
What is your perception of these brain stimulation sessions?	Do you feel the brain stimulation sessions was worth the time and effort/worthwhile? Why/why not?
Was it acceptable to you?	
Do you feel like you have gained anything from this experience? If so what?	What have you learned? How has this brain stimulation and the overall study experience changed your pain or function? Is there anything you'd identify as lacking in the treatment programme? What would you tell someone else thinking about participating in the same intervention?
Is there anything else you would like to share about the experience?	

REFERENCES:

1. Clark S, Horton R. Low back pain: a major global challenge. *The Lancet* 2018;391(10137):2302.
2. Hoy D, March L, Brooks P, et al. The global burden of low back pain: estimates from the Global Burden of Disease 2010 study. *Annals of the rheumatic diseases* 2014;73(6):968-74.
3. Treede R-D, Rief W, Barke A, et al. A classification of chronic pain for ICD-11. *Pain* 2015;156(6):1003.
4. Chou R, Deyo R, Friedly J, et al. Nonpharmacologic therapies for low back pain: a systematic review for an American College of Physicians clinical practice guideline. *Annals of internal medicine* 2017;166(7):493-505.
5. Coulter ID, Crawford C, Hurwitz EL, et al. Manipulation and mobilization for treating chronic low back pain: a systematic review and meta-analysis. *The Spine Journal* 2018;18(5):866-79.
6. Rubinstein SM, De Zoete A, Van Middelkoop M, et al. Benefits and harms of spinal manipulative therapy for the treatment of chronic low back pain: systematic review and meta-analysis of randomised controlled trials. *bmj* 2019;364
7. Chou R, Turner JA, Devine EB, et al. The effectiveness and risks of long-term opioid therapy for chronic pain: a systematic review for a National Institutes of Health Pathways to Prevention Workshop. *Annals of internal medicine* 2015;162(4):276-86.
8. Koes BW, Backes D, Bindels PJ. Pharmacotherapy for chronic non-specific low back pain: current and future options. *Expert opinion on pharmacotherapy* 2018;19(6):537-45.
9. Pavelka K, Jarosova H, Sleglova O, et al. Chronic low back pain: Current pharmacotherapeutic therapies and a new biological approach. *Current medicinal chemistry* 2019;26(6):1019-26.
10. Ng SK, Urquhart DM, Fitzgerald PB, et al. The relationship between structural and functional brain changes and altered emotion and cognition in chronic low back pain brain changes. *The Clinical journal of pain* 2018;34(3):237-61.
11. Konno S-i, Sekiguchi M. Association between brain and low back pain. *Journal of Orthopaedic Science* 2018;23(1):3-7.
12. Structural and functional brain abnormalities in chronic low back pain: A systematic review☆. Seminars in arthritis and rheumatism; 2015. Elsevier.
13. Kucyi A, Davis KD. The dynamic pain connectome. *Trends in neurosciences* 2015;38(2):86-95.
14. Vanneste S, De Ridder D. Chronic pain as a brain imbalance between pain input and pain suppression. *Brain Communications* 2021;3(1):fcab014.
15. De Ridder D, Vanneste S. The Bayesian brain in imbalance: Medial, lateral and descending pathways in tinnitus and pain: A perspective. Progress in Brain Research: Elsevier 2021:309-34.
16. De Ridder D, Adhia D, Vanneste S. The anatomy of pain and suffering in the brain and its clinical implications. *Neuroscience & Biobehavioral Reviews* 2021
17. Li T, Zhang S, Kurata J. Suppressed descending pain modulatory and enhanced sensorimotor networks in patients with chronic low back pain. *Journal of anesthesia* 2018;32(6):831-43.
18. Yuan C, Shi H, Pan P, et al. Gray matter abnormalities associated with chronic back pain. *The Clinical journal of pain* 2017;33(11):983-90.
19. De Ridder D, Vanneste S. Burst and tonic spinal cord stimulation: different and common brain mechanisms. *Neuromodulation: Technology at the Neural Interface* 2016;19(1):47-59.
20. Bushnell MC, Čeko M, Low LA. Cognitive and emotional control of pain and its disruption in chronic pain. *Nature Reviews Neuroscience* 2013;14(7):502-11.
21. Baliki MN, Petre B, Torbey S, et al. Corticostriatal functional connectivity predicts transition to chronic back pain. *Nature neuroscience* 2012;15(8):1117-19.
22. Coppieters I, Meeus M, Kregel J, et al. Relations between brain alterations and clinical pain measures in chronic musculoskeletal pain: a systematic review. *The Journal of Pain* 2016;17(9):949-62.
23. Hashmi JA, Baliki MN, Huang L, et al. Shape shifting pain: chronification of back pain shifts brain representation from nociceptive to emotional circuits. *Brain* 2013;136(9):2751-68.

24. Hemington KS, Rogachov A, Cheng JC, et al. Patients with chronic pain exhibit a complex relationship triad between pain, resilience, and within-and cross-network functional connectivity of the default mode network. *Pain* 2018;159(8):1621-30.
25. Kim J, Mawla I, Kong J, et al. Somatotopically-specific primary somatosensory connectivity to salience and default mode networks encodes clinical pain. *Pain* 2019;160(7):1594.
26. Kong J, Spaeth B, Wey H-Y, et al. S1 is associated with chronic low back pain: a functional and structural MRI study. *Molecular pain* 2013;9:1744-8069-9-43.
27. Ossipov MH, Morimura K, Porreca F. Descending pain modulation and chronification of pain. *Current opinion in supportive and palliative care* 2014;8(2):143.
28. Tu Y, Jung M, Gollub RL, et al. Abnormal medial prefrontal cortex functional connectivity and its association with clinical symptoms in chronic low back pain. *Pain* 2019;160(6):1308.
29. Nascimento RMD, Cavalcanti RL, Souza CG, et al. Transcranial direct current stimulation combined with peripheral stimulation in chronic pain: a systematic review and meta-analysis. *Expert Rev Med Devices* 2022:1-20. doi: 10.1080/17434440.2022.2039623 [published Online First: 2022/02/09]
30. Pinto CB, Teixeira Costa B, Duarte D, et al. Transcranial Direct Current Stimulation as a Therapeutic Tool for Chronic Pain. *J ect* 2018;34(3):e36-e50. doi: 10.1097/yct.0000000000000518 [published Online First: 2018/06/29]
31. Knotkova H, Hamani C, Sivanesan E, et al. Neuromodulation for chronic pain. *Lancet* 2021;397(10289):2111-24. doi: 10.1016/s0140-6736(21)00794-7 [published Online First: 2021/06/02]
32. Lloyd DM, Wittkopf PG, Arendsen LJ, et al. Is Transcranial Direct Current Stimulation (tDCS) Effective for the Treatment of Pain in Fibromyalgia? A Systematic Review and Meta-Analysis. *The Journal of Pain* 2020;21(11):1085-100. doi: https://doi.org/10.1016/j.jpain.2020.01.003
33. Ahn S, Prim JH, Alexander ML, et al. Identifying and Engaging Neuronal Oscillations by Transcranial Alternating Current Stimulation in Patients With Chronic Low Back Pain: A Randomized, Crossover, Double-Blind, Sham-Controlled Pilot Study. *J Pain* 2019;20(3):277.e1-77.e11. doi: 10.1016/j.jpain.2018.09.004 [published Online First: 2018/10/01]
34. Hazime FA, Baptista AF, de Freitas DG, et al. Treating low back pain with combined cerebral and peripheral electrical stimulation: A randomized, double-blind, factorial clinical trial. *Eur J Pain* 2017;21(7):1132-43. doi: 10.1002/ejp.1037 [published Online First: 2017/04/26]
35. Jafarzadeh A, Ehsani F, Yosephi MH, et al. Concurrent postural training and M1 anodal transcranial direct current stimulation improve postural impairment in patients with chronic low back pain. *J Clin Neurosci* 2019;68:224-34. doi: 10.1016/j.jocn.2019.07.017 [published Online First: 2019/07/28]
36. Luedtke K, Rushton A, Wright C, et al. Effectiveness of transcranial direct current stimulation preceding cognitive behavioural management for chronic low back pain: sham controlled double blinded randomised controlled trial. *Bmj* 2015;350:h1640. doi: 10.1136/bmj.h1640 [published Online First: 2015/04/18]
37. Mariano TY, Burgess FW, Bowker M, et al. Transcranial Direct Current Stimulation for Affective Symptoms and Functioning in Chronic Low Back Pain: A Pilot Double-Blinded, Randomized, Placebo-Controlled Trial. *Pain Med* 2019;20(6):1166-77. doi: 10.1093/pm/pny188 [published Online First: 2018/10/26]
38. O'Connell NE, Cossar J, Marston L, et al. Transcranial direct current stimulation of the motor cortex in the treatment of chronic nonspecific low back pain: a randomized, double-blind exploratory study. *Clin J Pain* 2013;29(1):26-34. doi: 10.1097/AJP.0b013e318247ec09 [published Online First: 2012/12/12]
39. Schabrun SM, Burns E, Thapa T, et al. The Response of the Primary Motor Cortex to Neuromodulation is Altered in Chronic Low Back Pain: A Preliminary Study. *Pain Med* 2018;19(6):1227-36. doi: 10.1093/pm/pnx168 [published Online First: 2017/10/11]

40. Schabrun SM, Jones E, Elgueta Cancino EL, et al. Targeting chronic recurrent low back pain from the top-down and the bottom-up: a combined transcranial direct current stimulation and peripheral electrical stimulation intervention. *Brain Stimul* 2014;7(3):451-9. doi: 10.1016/j.brs.2014.01.058 [published Online First: 2014/03/04]
41. Straudi S, Buja S, Baroni A, et al. The effects of transcranial direct current stimulation (tDCS) combined with group exercise treatment in subjects with chronic low back pain: a pilot randomized control trial. *Clin Rehabil* 2018;32(10):1348-56. doi: 10.1177/0269215518777881 [published Online First: 2018/05/23]
42. Jiang N, Wei J, Li G, et al. Effect of dry-electrode-based transcranial direct current stimulation on chronic low back pain and low back muscle activities: A double-blind sham-controlled study. *Restor Neurol Neurosci* 2020;38(1):41-54. doi: 10.3233/rnn-190922 [published Online First: 2019/11/07]
43. Larie Ms, Esfandiarpour F, Riahi F, et al. Effects of Cortical and Peripheral Electrical Stimulation on Brain Activity in Individuals with Chronic Low Back Pain. *Physical Treatments - Specific Physical Therapy* 2019;9(1):39-46. doi: 10.32598/ptj.9.1.39
44. Ouellette AL, Liston MB, Chang WJ, et al. Safety and feasibility of transcranial direct current stimulation (tDCS) combined with sensorimotor retraining in chronic low back pain: a protocol for a pilot randomised controlled trial. *BMJ Open* 2017;7(8):e013080. doi: 10.1136/bmjopen-2016-013080 [published Online First: 2017/08/23]
45. Patricio P, Roy JS, Rohel A, et al. The Effect of Noninvasive Brain Stimulation to Reduce Nonspecific Low Back Pain: A Systematic Review and Meta-analysis. *Clin J Pain* 2021;37(6):475-85. doi: 10.1097/ajp.0000000000000934 [published Online First: 2021/05/06]
46. O'Connell NE, Marston L, Spencer S, et al. Non-invasive brain stimulation techniques for chronic pain. *Cochrane Database Syst Rev* 2018;3(3):Cd008208. doi: 10.1002/14651858.CD008208.pub4 [published Online First: 2018/03/17]
47. Lima MC, Fregni F. Motor cortex stimulation for chronic pain: systematic review and meta-analysis of the literature. *Neurology* 2008;70(24):2329-37. doi: 10.1212/01.wnl.0000314649.38527.93 [published Online First: 2008/06/11]
48. Brookes MJ, Woolrich M, Luckhoo H, et al. Investigating the electrophysiological basis of resting state networks using magnetoencephalography. *Proceedings of the National Academy of Sciences* 2011;108(40):16783-88.
49. Mitra A, Raichle ME. How networks communicate: propagation patterns in spontaneous brain activity. *Philosophical Transactions of the Royal Society B: Biological Sciences* 2016;371(1705):20150546.
50. Watson BO. Cognitive and physiologic impacts of the infraslow oscillation. *Frontiers in systems neuroscience* 2018;12:44.
51. Wilckens KA, Ferrarelli F, Walker MP, et al. Slow-wave activity enhancement to improve cognition. *Trends in neurosciences* 2018;41(7):470-82.
52. Chan AW, Mohajerani MH, LeDue JM, et al. Mesoscale infraslow spontaneous membrane potential fluctuations recapitulate high-frequency activity cortical motifs. *Nature communications* 2015;6(1):1-12.
53. Pan W-J, Thompson GJ, Magnuson ME, et al. Infraslow LFP correlates to resting-state fMRI BOLD signals. *Neuroimage* 2013;74:288-97.
54. Ploner M, Sorg C, Gross J. Brain rhythms of pain. *Trends in cognitive sciences* 2017;21(2):100-10.
55. Alshelh Z, Di Pietro F, Youssef AM, et al. Chronic neuropathic pain: it's about the rhythm. *Journal of Neuroscience* 2016;36(3):1008-18.
56. Zhang B, Jung M, Tu Y, et al. Identifying brain regions associated with the neuropathology of chronic low back pain: a resting-state amplitude of low-frequency fluctuation study. *British journal of anaesthesia* 2019;123(2):e303-e11.
57. Zhou F, Gu L, Hong S, et al. Altered low-frequency oscillation amplitude of resting state-fMRI in patients with discogenic low-back and leg pain. *Journal of pain research* 2018;11:165.

58. Leong SL, De Ridder D, Vanneste S, et al. High definition transcranial pink noise stimulation of anterior cingulate cortex on food craving: An explorative study. *Appetite* 2018;120:673-78.
59. Whittington F, De Ridder D, Adhia DB. High definition transcranial infraslow pink noise stimulation for improving executive functioning in healthy older adults – A pilot safety trial. Otago Medical School Research Society Summer Student Sepeaker Awards: New Zealand Medical Journal, 2021.
60. Chan A-W, Tetzlaff JM, Altman DG, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. *Annals of internal medicine* 2013;158(3):200-07.
61. Hoffmann TC, Glasziou PP, Boutron I, et al. Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide. *Bmj* 2014;348
62. Edwards RR, Dworkin RH, Turk DC, et al. Patient phenotyping in clinical trials of chronic pain treatments: IMMPACT recommendations. *Pain* 2016;157(9):1851.
63. Gewandter JS, Dworkin RH, Turk DC, et al. Improving study conduct and data quality in clinical trials of chronic pain treatments: IMMPACT recommendations. *The journal of pain* 2020;21(9-10):931-42.
64. Smith SM, Dworkin RH, Turk DC, et al. The potential role of sensory testing, skin biopsy, and functional brain imaging as biomarkers in chronic pain clinical trials: IMMPACT considerations. *The Journal of Pain* 2017;18(7):757-77.
65. Smith SM, Dworkin RH, Turk DC, et al. Interpretation of chronic pain clinical trial outcomes: IMMPACT recommended considerations. *Pain* 2020;161(11):2446-61.
66. Taylor AM, Phillips K, Patel KV, et al. Assessment of physical function and participation in chronic pain clinical trials: IMMPACT/OMERACT recommendations. *Pain* 2016;157(9):1836.
67. Roland M, Morris R. A study of the natural history of low-back pain. Part II: development of guidelines for trials of treatment in primary care. *Spine* 1983;8(2):145-50.
68. Roland M, Morris R. A study of the natural history of back pain. Part I: development of a reliable and sensitive measure of disability in low-back pain. Spine (Phila Pa 1976). 1983; 8 (2): 141-4. *dx doi org/101097/00007632-198303000-00004*
69. Dionne CE, Dunn KM, Croft PR, et al. A consensus approach toward the standardization of back pain definitions for use in prevalence studies. *Spine* 2008;33(1):95-103.
70. Grotle M, Brox JI, Vøllestad NK. Concurrent comparison of responsiveness in pain and functional status measurements used for patients with low back pain. *Spine* 2004;29(21):E492-E501.
71. Neblett R, Cohen H, Choi Y, et al. The Central Sensitization Inventory (CSI): establishing clinically significant values for identifying central sensitivity syndromes in an outpatient chronic pain sample. *J Pain* 2013;14(5):438-45. doi: 10.1016/j.jpain.2012.11.012 [published Online First: 2013/03/16]
72. Mayer TG, Neblett R, Cohen H, et al. The development and psychometric validation of the central sensitization inventory. *Pain Pract* 2012;12(4):276-85. doi: 10.1111/j.1533-2500.2011.00493.x [published Online First: 2011/09/29]
73. Freynhagen R, Tölle TR, Gockel U, et al. The painDETECT project–far more than a screening tool on neuropathic pain. *Current medical research and opinion* 2016;32(6):1033-57.
74. Schattner E, Shahar G. Role of pain personification in pain-related depression: An object relations perspective. *Psychiatry: Interpersonal & Biological Processes* 2011;74(1):14-20.
75. Devilly GJ, Borkovec TD. Psychometric properties of the credibility/expectancy questionnaire. *Journal of behavior therapy and experimental psychiatry* 2000;31(2):73-86.
76. Lefaucheur J-P, Antal A, Ayache SS, et al. Evidence-based guidelines on the therapeutic use of transcranial direct current stimulation (tDCS). *Clinical Neurophysiology* 2017;128(1):56-92.
77. Nikolin S, Huggins C, Martin D, et al. Safety of repeated sessions of transcranial direct current stimulation: a systematic review. *Brain stimulation* 2018;11(2):278-88.
78. Woods AJ, Antal A, Bikson M, et al. A technical guide to tDCS, and related non-invasive brain stimulation tools. *Clinical neurophysiology* 2016;127(2):1031-48.

79. Neri F, Mencarelli L, Menardi A, et al. A novel tDCS sham approach based on model-driven controlled shunting. *Brain stimulation* 2020;13(2):507-16.
80. Rosenbaum JF, Fava M, Hoog SL, et al. Selective serotonin reuptake inhibitor discontinuation syndrome: a randomized clinical trial. *Biological psychiatry* 1998;44(2):77-87.
81. Song C-Y, Lin S-F, Huang C-Y, et al. Validation of the Brief Pain Inventory in Patients With Low Back Pain. *Spine (Philadelphia, Pa 1976)* 2016;41(15):E937-E42. doi: 10.1097/BRS.0000000000001478
82. Uddin Z, MacDermid JC. Quantitative Sensory Testing in Chronic Musculoskeletal Pain. *Pain Med* 2016;17(9):1694-703. doi: 10.1093/pm/pnv105 [published Online First: 2016/02/20]
83. Rolke R, Baron R, Maier Ca, et al. Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): standardized protocol and reference values. *Pain* 2006;123(3):231-43.
84. Mani R, Adhia DB, Leong SL, et al. Sedentary behaviour facilitates conditioned pain modulation in middle-aged and older adults with persistent musculoskeletal pain: a cross-sectional investigation. *Pain reports* 2019;4(5):e773-e73. doi: 10.1097/PR9.0000000000000773
85. Goodin BR, Bulls HW, Herbert MS, et al. Temporal summation of pain as a prospective predictor of clinical pain severity in adults aged 45 years and older with knee osteoarthritis: ethnic differences. *Psychosomatic medicine* 2014;76(4):302-10. doi: 10.1097/PSY.0000000000000058
86. Hübscher M, Moloney N, Leaver A, et al. Relationship between quantitative sensory testing and pain or disability in people with spinal pain—a systematic review and meta-analysis. *PAIN®* 2013;154(9):1497-504.
87. Yarnitsky D, Bouhassira D, Drewes AM, et al. Recommendations on practice of conditioned pain modulation (CPM) testing. *Eur J Pain* 2015;19(6):805-6. doi: 10.1002/ejp.605 [published Online First: 2014/10/21]
88. Suokas AK, Walsh DA, McWilliams DF, et al. Quantitative sensory testing in painful osteoarthritis: a systematic review and meta-analysis. *Osteoarthritis Cartilage* 2012;20(10):1075-85. doi: 10.1016/j.joca.2012.06.009 [published Online First: 2012/07/17]
89. Yarnitsky D, Arendt-Nielsen L, Bouhassira D, et al. Recommendations on terminology and practice of psychophysical DNIC testing. *Eur J Pain* 2010;14(4):339. doi: 10.1016/j.ejpain.2010.02.004 [published Online First: 2010/03/17]
90. Kennedy DL, Kemp HI, Ridout D, et al. Reliability of conditioned pain modulation: a systematic review. *Pain* 2016;157(11):2410-19. doi: 10.1097/j.pain.0000000000000689 [published Online First: 2016/10/19]
91. Parkitny L, McAuley JH, Walton D, et al. Rasch analysis supports the use of the depression, anxiety, and stress scales to measure mood in groups but not in individuals with chronic low back pain. *J Clin Epidemiol* 2012;65(2):189-98. doi: 10.1016/j.jclinepi.2011.05.010 [published Online First: 2011/09/06]
92. Osman A, Barrios FX, Gutierrez PM, et al. The Pain Catastrophizing Scale: further psychometric evaluation with adult samples. *J Behav Med* 2000;23(4):351-65. doi: 10.1023/a:1005548801037 [published Online First: 2000/09/14]
93. Wertli MM, Eugster R, Held U, et al. Catastrophizing-a prognostic factor for outcome in patients with low back pain: a systematic review. *Spine J* 2014;14(11):2639-57. doi: 10.1016/j.spinee.2014.03.003 [published Online First: 2014/03/13]
94. Roelofs J, Peters ML, McCracken L, et al. The pain vigilance and awareness questionnaire (PVAQ): further psychometric evaluation in fibromyalgia and other chronic pain syndromes. *Pain* 2003;101(3):299-306. doi: 10.1016/s0304-3959(02)00338-x [published Online First: 2003/02/14]
95. Price DD, McGrath PA, Rafii A, et al. The validation of visual analogue scales as ratio scale measures for chronic and experimental pain. *Pain (Amsterdam)* 1983;17(1):45-56. doi: 10.1016/0304-3959(83)90126-4

96. Price DD, Bush FM, Long S, et al. A comparison of pain measurement characteristics of mechanical visual analogue and simple numerical rating scales. *Pain* 1994;56(2):217-26.
97. Deyo RA, Battie M, Beurskens AJHM, et al. Outcome measures for low back pain research : A proposal for standardized use. *Spine (Philadelphia, PA 1976)* 1998;23(18):2003-13. doi: 10.1097/00007632-199809150-00018
98. Dunn KM, Croft PR. Classification of low back pain in primary care : Using bothersomeness to identify the most severe cases. *Spine (Philadelphia, Pa 1976)* 2005;30(16):1887-92. doi: 10.1097/01.brs.0000173900.46863.02
99. Kamper SJ, Maher CG, Mackay G. Global rating of change scales: a review of strengths and weaknesses and considerations for design. *Journal of Manual & Manipulative Therapy* 2009;17(3):163-70.
100. Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res* 2011;20(10):1727-36. doi: 10.1007/s11136-011-9903-x [published Online First: 2011/04/12]
101. Topp CW, Østergaard SD, Søndergaard S, et al. The WHO-5 Well-Being Index: a systematic review of the literature. *Psychother Psychosom* 2015;84(3):167-76. doi: 10.1159/000376585 [published Online First: 2015/04/04]
102. Pascual-Marqui RD. Standardized low-resolution brain electromagnetic tomography (sLORETA): technical details. *Methods Find Exp Clin Pharmacol* 2002;24 Suppl D:5-12. [published Online First: 2003/02/11]
103. Nichols TE, Holmes AP. Nonparametric permutation tests for functional neuroimaging: a primer with examples. *Human brain mapping* 2002;15(1):1-25.
104. Pascual-Marqui RD. Discrete, 3D distributed, linear imaging methods of electric neuronal activity. Part 1: exact, zero error localization. *arXiv preprint arXiv:07103341* 2007
105. Braun V, Clarke V. Using thematic analysis in psychology. *Qualitative research in psychology* 2006;3(2):77-101.
106. Thomas DR. A general inductive approach for analyzing qualitative evaluation data. *American journal of evaluation* 2006;27(2):237-46.
107. Eldridge SM, Lancaster GA, Campbell MJ, et al. Defining feasibility and pilot studies in preparation for randomised controlled trials: development of a conceptual framework. *PloS one* 2016;11(3):e0150205.
108. Minhas P, Bansal V, Patel J, et al. Electrodes for high-definition transcutaneous DC stimulation for applications in drug delivery and electrotherapy, including tDCS. *Journal of neuroscience methods* 2010;190(2):188-97.
109. DaSilva AF, Truong DQ, DosSantos MF, et al. State-of-art neuroanatomical target analysis of high-definition and conventional tDCS montages used for migraine and pain control. *Frontiers in neuroanatomy* 2015;9:89.
110. Datta A, Bansal V, Diaz J, et al. Gyri-precise head model of transcranial direct current stimulation: improved spatial focality using a ring electrode versus conventional rectangular pad. *Brain stimulation* 2009;2(4):201-07. e1.
111. Dmochowski JP, Datta A, Bikson M, et al. Optimized multi-electrode stimulation increases focality and intensity at target. *Journal of neural engineering* 2011;8(4):046011.
112. To WT, Eroh J, Hart J, et al. Exploring the effects of anodal and cathodal high definition transcranial direct current stimulation targeting the dorsal anterior cingulate cortex. *Scientific reports* 2018;8(1):1-16.
113. Ruffini G, Fox MD, Ripolles O, et al. Optimization of multifocal transcranial current stimulation for weighted cortical pattern targeting from realistic modeling of electric fields. *Neuroimage* 2014;89:216-25.
114. Ruffini G, Wendling F, Sanchez-Todo R, et al. Targeting brain networks with multichannel transcranial current stimulation (tCS). *Current Opinion in Biomedical Engineering* 2018;8:70-77.

FIGURE LEGEND

Figure 1. Study design and timelines

EEG: Electroencephalography, HD-tIPNS: high definition transcranial infraslow pink noise stimulation, pgACC: pregenual anterior cingulate cortex, dACC: dorsal anterior cingulate cortex, SSC: primary somatosensory cortex.

Figure 2. The transcranial electrical stimulation set-up

Figure 3. Electrode positions and targeted brain regions

This figure presents results of the optimization that was created using the Stimweaver software by the Neuroelectrics company for targeting the activity of pgACC, dACC, and SSC.113, 114 From Left to right: Normal component of the E-field En (V/m), target E-field (V /m), target weight and ERNI* (mV 2/m2) for grey matter. The optimal montage consists of 8-channels that will be placed on the scalp following the international 10-20 EEG system.

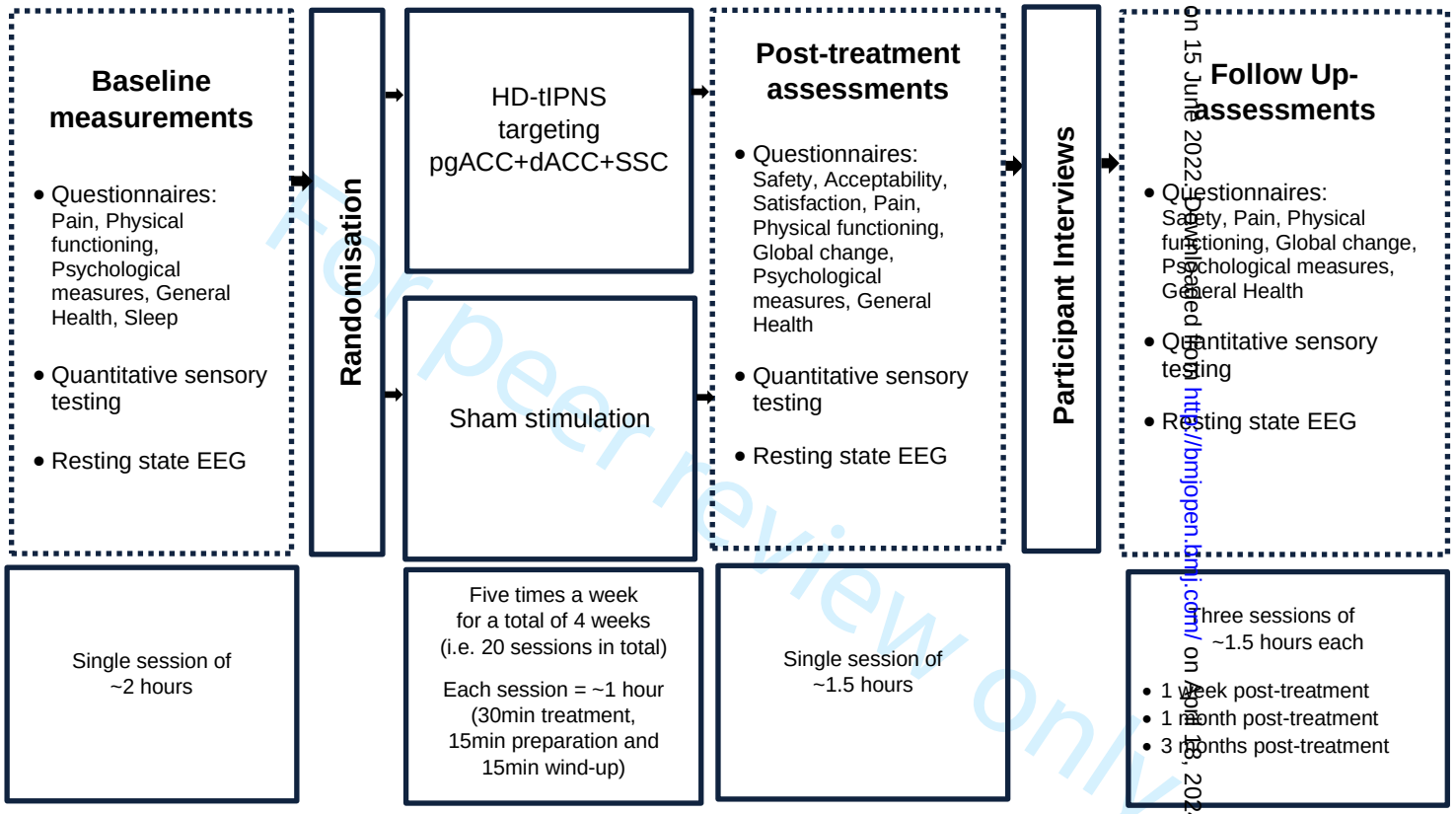
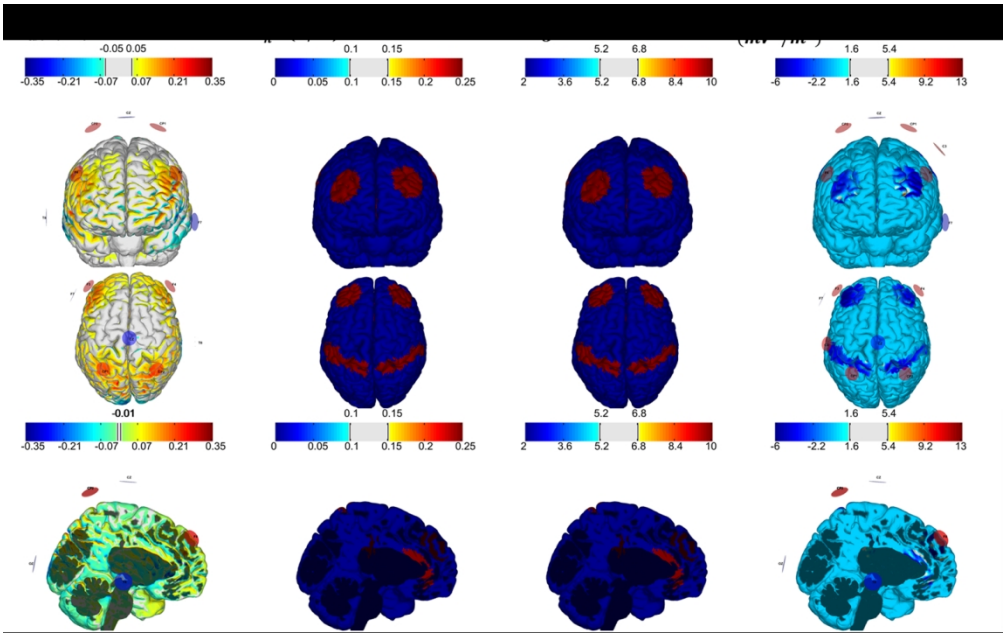


Figure 2. The transcranial electrical stimulation set-up

191x70mm (118 x 118 DPI)



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339x213mm (118 x 118 DPI)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	ItemNo	Description	Check/Details
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	✓ (Main Document, p. 1)
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	✓ (Main Document, p.4, and Table 1)
	2b	All items from the World Health Organization Trial Registration Data Set	✓ (Table 1)
Protocol version	3	Date and version identifier	✓ (Table 1)
Funding	4	Sources and types of financial, material, and other support	✓ (Table 1)
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	✓ (Main Document, p. 1)
	5b	Name and contact information for the trial sponsor	✓ (Table 1)
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	None.

	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	✓ (Main Document, p. 24)
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	✓ (Main Document, p. 5-7)
	6b	Explanation for choice of comparators	✓ (Main Document, p. 5-6)
Objectives	7	Specific objectives or hypotheses	✓ (Main Document, p. 7)
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	✓ (Main Document, p. 8, and Fig. 1)
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	✓ (Main Document, p. 9)
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	✓ (Main Document, p. 9-10)
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	✓ (Main Document, p. 11-13, Table 2, Fig.2 and Fig 3)

	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	✓ (Main Document, p. 23-24)
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	✓ (Main Document, p. 13)
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	✓ (Main Document, p. 13)
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	✓ (Main Document, p. 13-20, Table 3)
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	✓ (Fig. 1)
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	✓ (Main Document, p. 10)
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	✓ (Main Document, p. 10-11)

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	✓ (Main Document, p. 8-9)
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	✓ (Main Document, p. 8-9)
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	✓ (Main Document, p. 8-9)
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	✓ (Main Document, p. 8-9)
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	✓ (Main Document, p. 8-9)
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	✓ (Main Document, p. 13-20, Table 3)

	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	✓ (Main Document, p. 13-20, Table 3)
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	✓ (Main Document, p. 13-20, 23-24)
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	✓ (Main Document, p. 20)
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	✓ (Main Document, p. 20)
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	✓ (Main Document, p. 20-21)
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	✓ (Main Document, p.24)
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	✓ (Main Document, p. 23-24)

Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	✓ (Main Document, p. 23-24)
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	✓ (Main Document, p. 23-24)
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	✓ (Main Document, p. 23-24)
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	✓ (Main document, p. 23-24)
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	✓ (Main document, p. 15)
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Not applicable.
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	✓ (Main document, p. 23-24)
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	✓ (Main document, p. 24)

Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	✓ (Main document, p. 23-24)
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	None.
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	✓ (Main Document, p. 24)
	31b	Authorship eligibility guidelines and any intended use of professional writers	✓
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	✓ (Included in registry)
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	✓ (Approved by Ethics Committee)
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Not applicable.

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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High-definition transcranial infraslow pink noise stimulation for chronic low back pain: Protocol for a pilot, safety, and feasibility randomized placebo-controlled trial.

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Title:

High-definition transcranial infraslow pink noise stimulation for chronic low back pain: Protocol for a pilot, safety, and feasibility randomized placebo-controlled trial.

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ABSTRACT

Introduction: Chronic low back pain (CLBP) is a common disabling health condition. Current treatments demonstrate modest effects, warranting newer therapies. Brain imaging demonstrates altered electrical activities in cortical areas responsible for pain modulation, emotional, and sensory components of pain experience. Treatments targeting to change electrical activities of these key brain regions may produce clinical benefits. This pilot study aims to (a) evaluate feasibility, safety, and acceptability of a novel neuromodulation technique, high definition transcranial infraslow pink noise stimulation (HD-tIPNS), in people with CLBP, (b) explore the trend of effect of HD-tIPNS on pain and function, and (c) derive treatment estimates to support sample size calculation for a fully powered trial should trends of effectiveness be present.

Methods & analysis: A pilot, triple-blinded randomized two-arm placebo-controlled parallel trial. Participants (n=40) with CLBP will be randomized to either sham stimulation or HD-tIPNS (targeting somatosensory cortex and dorsal and pregenual anterior cingulate cortex). Primary outcomes include feasibility and safety measures, and clinical outcomes of pain (Brief Pain Inventory) and disability (Roland-Morris disability questionnaire). Secondary measures include clinical, psychological, quantitative sensory testing, and electroencephalography collected at baseline, immediately post-intervention, and at one-week, one-month and three-months post-intervention. All data will be analysed descriptively. A nested qualitative study will assess participants perceptions about acceptability of intervention and analyzed thematically.

Ethics and dissemination: Ethical approval has been obtained from Health and Disability Ethics Committee(Ref:20/NTB/67). Findings will be reported to regulatory

and funding bodies, presented at conferences, and published in a scientific journal. Registration: Prospectively registered in Australian and New Zealand Clinical Trials Registry (ACTRN12620000505909).

STRENGTH AND LIMITATIONS

- This study will use a novel neuromodulation technique (HD-tIPNS) tosimultaneously target cortical areas responsible for pain modulation, emotional, and sensory components of pain experience.
- The use of Starstim-Home transcranial electrical stimulation system allows appropriate blinding of the treating researcher, and the possibility of a high-quality triple-blinded (participant, treatment therapist, and outcome assessor) randomized placebo-controlled trial.
- Sample size estimation has not been conducted in this feasibility and safety study design.

INTRODUCTION

Chronic low back pain (CLBP) is a significant and growing health challenge, affecting individuals, the wider community, and the healthcare system.[1-3] Along with pain and impaired function, individuals with CLBP have significant psychological comorbidities and poor quality of life.[1-3] Currently available treatments for CLBP demonstrate at best small effect sizes.[4-6] Pharmacological interventions are not effective with a high risk of adverse outcomes.[7-9] Thus, new, innovative, evidence-based, safer therapies are warranted for the management of CLBP.

Resting-state cortical activity alterations have been demonstrated in individuals with CLBP.[10-13] The most notably involved cortical areas include the anterior cingulate cortex (ACC) and the primary somatosensory cortex (SSC), which are the central hubs of the pain processing brain networks.[10-18] The ACC, particularly the pregenual region (pgACC), is part of the descending pain modulatory system (or anti-nociceptive system), the activation of which releases μ-opioids that act to modulate incoming nociception information from the hyperactive, spinal cord circuits, thereby alleviating pain.[13 16 17 19 20] The SSC, along with the dorsal region of ACC (dACC), is part of ascending nociceptive (lateral and medial) pathways that are responsible for encoding the sensory (i.e. painfulness) and the emotional components (e.g. suffering) of the pain experience.[13 16 17 19 20] Recent evidence suggests that alterations in the functional connectivity patterns between the pain processing regions (pgACC, dACC, SSC) are critical for maintaining chronic pain and are associated with its clinical and psychological outcomes.[14-16 21-28]

Neuromodulatory interventions targeted to alter activities in cortical pain processing areas may improve clinical outcomes. Transcranial electrical stimulation (TES), a non-invasive brain stimulation technique, can influence the electrical activity of targeted brain regions, promote cortical plasticity, and improve the functional connectivity to/from the targeted area, thereby improving pain modulation. Recent systematic reviews and meta-analyses demonstrate positive effects of the TES techniques in chronic pain conditions (e.g., fibromyaligia, migraine, spinal cord injury).[29-32] However, the evidence for effect of TES for treatment of CLBP is limited (n=10 pilot studies[33-42], n=2 protocols[43 44]) and have demonstrated mixed results. Recent systematic reviews and meta-analyses suggests that there is very low quality evidence that a single session of TES have short term effects for improving pain in people with CLBP.[45 46] Previous TES studies targeted altering cortical electrical activity of a single superficial brain region[33-36 38-42] (e.g., Motor cortex or dorsolateral prefrontal cortex) using transcranial direct current stimulation (tDCS), except one study[37] that targeted a deeper brain region (dACC). None of the studies has simultaneously targeted multiple-brain regions (pgACC, dACC, SSC) responsible for the descending and ascending modulation of nociceptive sensory information. Further, the stimulation technique used in the previous TCS studies involved applying two large scalp electrode pads that deliver currents to diffuse areas of the brain, making focalized stimulation of targeted brain regions less feasible. Focal and simultaneous stimulation of multiple brain regions could help improve clinical outcomes with larger effect sizes, similar to invasive neuromodulatory interventions[47].

We propose determining the feasibility and safety of a novel high definition transcranial infraslow pink noise stimulation (HD-tIPNS) technique, targeting the pgACC, dACC,

and SSC regions simultaneously in people with CLBP. The HD-tIPNS technique was developed to specifically modulate the infraslow electrical activity (0.0-0.1 Hz) in the brain. The infraslow electrical activity, a fundamental frequency range of the brain, re-organizes neurons and improves the electrical connectivity of the brain-wide functional networks.[48-51] The ISF plays a profound role in modulating and synchronizing high-frequency cortical activity that are known to be affected in chronic pain[50 52-54], and is also critically involved in mediating pain perception[55]. Evidence from imaging studies also demonstarte alterations in the infraslow oscillations in individuals with CLBP in the pain processing brain regions (pgACC, dACC, SSC).[56 57] The pink noise frequency spectrum resembles the naturally occurring signals in the self-organization of the brain, thus can be more effective than standard tDCS electrical parameters used in previous studies.[58 59] We, therefore, believe that specifically and simultaneously targeting the fundamental infraslow activity at key nodes of pain processing networks, using a novel HD-tIPNS technique, could normalize brain-wide electrical activity and functional connectivity between areas of interest, promoting better pain modulation and producing more meaningful clinical benefits. This protocol outlines the methods and analysis used in the pilot randomized controlled trial. The specific aims are to (a) evaluate the feasibility, safety, and acceptability of the HD-tIPNS technique in people with CLBP, (b) explore the trend of effect of HD-tIPNS on pain and function, and (c) provide estimates of clinical outcome measures to support a sample size calculation for a fully powered trial should the trend of effectiveness be present.

METHODS AND ANALYSIS

The following guides have been used to prepare this study protocol: Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement[60], the template

for intervention description and replication (TIDieR) checklist[61], and IMMPACT Recommendations[62-66]. In addition, this trial has been prospectively registered (Table 1).

Study design:

The proposed study will be a triple blinded pilot randomized placebo-controlled parallel trial with two intervention arms. The outcome measures will be collected at baseline, immediately post-intervention, and at follow-up periods: one week, one month, and three months post-intervention (Fig. 1).

Randomization: A research administrator, not involved in other procedures, will randomize participants on a 1:1 basis using a computerized open-access randomization software program to:

- Group 1: HD-tIPNS, or
- Group 2: Sham stimulation

The randomization schedule will be concealed in sequentially numbered, sealed opaque envelopes and provided to participants at their baseline measurements.

Blinding: Participants, outcome assessor, and treating researchers will be blinded to group allocation. Stimulation programs on Starstim device will be designed and controlled by an independent researcher to allow blinding of the treating researcher. The success of blinding will be assessed after the completion of the intervention and follow-up phases. The participant, and the outcome assessor, and treating researcher will be asked “What type of treatment they believe that they/the participant received

respectively?" and will be required to choose between three options: active, sham, or don't know. The confidence in their judgement will also be assessed on an 11-point numeric rating scale *(0=Not at all confident to 10=Extremely confident)*, with the reason for their judgement being noted and whether the intervention was revealed to them. Unblinding will be permissible only in the case of an adverse event or any unexpected event.

Study setting: This study will be conducted in the Department of Surgical Sciences laboratory, Dunedin School of Medicine, Dunedin hospital, New Zealand.

Participants and eligibility criteria:

Adults with CLBP will be eligible to participate.

Inclusion criteria: Capable of understanding and signing an informed consent form, age between 18 to 75 years on the day of the consent, pain in the lower back (the region between 12th rib and gluteal fold) that occurs everyday for ≥3 months, a score of ≥4 on an 11-point numeric pain rating scale (NPRS, 0=*No pain* to 10=*Worst pain imaginable*) in the past four weeks prior to enrolment, a disability score of ≥5 on Roland–Morris Disability Questionnaire[67 68]. These cut-off scores are used as an indication that CLBP significantly impacts daily functioning, are by International Association of Study of Pain guidelines and are in line with optimal Delphi definitions of LBP prevalence (DOLBaPP).[3 67-70]

Exclusion criteria: Participants with the following self-reported health conditions will be excluded: Inflammatory arthritis, undergoing any therapy from a health professional

(e.g. physiotherapist or chiropractor), recent soft tissue injuries of the back in the last 3 months, history of surgery to the back region or waiting/scheduled for any procedures within the next six months, current intake of any centrally-acting medications or intention of taking new medications in the next three months, steroid injections to the back in past six months, radicular pain and radiculopathy, history of neurological diseases, unstable medical or psychiatric conditions, history of epilepsy or seizures, peripheral neuropathy, vascular disorders, substance abuse, dyslipidemia, cognitive impairments [dementia, post-traumatic stress disorders, Alzheimer's disease; assessed as a score of <24 on the mini-mental status examination conducted at baseline], history of uncontrolled/untreated hypertension, presence of any pacemaker or defibrillator or electronic/metal body implants (around the head/neck region), and recent or current pregnancy.

Sample size:

This proposed research is a pilot exploratory study, which will be executed to make a power estimate for a future phase II study should the intervention appear feasible, safe, acceptable, and show trends of effectiveness. Hence a sample size calculation was not performed. Based on statistical advice, a sample of 40 participants (20/group) was considered enough to determine feasibility issues and obtain treatment estimates for designing a full trial.

Recruitment and study enrolment:

Participants will be primarily recruited through broadcasting in the public media (e.g., newspapers and social media). Participants attending healthcare providers will also

be invited to participate. The total recruitment period will be one-year (June'21 to May'22). Advertisements will be placed in the local newspapers twice a month and social media once a month (Sponsored Facebook ad, for one week). Advertisement fliers will be placed around a tertiary hospital, regional healthcare practices, and supermarkets. A recruitment email will be sent to the local tertiary educational university/polytechnic staff and students once every two months.

All volunteers will complete an online screening form. Potential participants will be contacted by a researcher with a health professional background (Trained Musculoskeletal Physiotherapist) to undergo further screening over the phone to confirm eligibility prior to study enrolment. The study information sheet (Supplementary file) will be emailed to eligible participants. Written informed consent will be obtained before baseline testing. At the baseline session, all participants will complete questionnaires to capture demographics, clinical characteristics of CLBP, including presence of central sensitivity (Central Sensitization Inventory)[71 72], neuropathic pain quality (PainDETECT)[73], pain personification[74], and treatment expectancy and credibility[75].

Intervention procedures(Table 2):

The intervention will be administered five times a week (30 minutes/session) for four weeks by an assistant research fellow trained by the primary investigator experienced in neuromodulation techniques. A battery-driven wireless transcranial electrical stimulator (Starstim-Home TES®, Neuroelectrics, Spain) will be used to deliver stimulation while participants are comfortably and quietly seated (Fig. 2). The HD technique uses arrays of multiple small electrodes whose configuration can be

optimized for focally targeting specific brain regions.[58 59 76-80] Eight small electrodes (~4cm^2) will be placed on a neoprene head cap following the International 10-20 EEG system to simultaneously target pgACC, dACC, and SSC (Fig. 2 and Fig. 3). [81, 82]

For HD-tIPNS group, the stimulation will be delivered at a current strength of a maximum of 2mA for 30min, with 60s ramp up and ramp down at the beginning and end of each stimulation session, with continuous stimulation in between. The pink noise stimulation at a current strength of a maximum of 0.6mA will be superimposed on the infraslow (0.1Hz sinusoidal) waveform of a current intensity of 1mA. The current strength at each electrode will never exceed the maximum safety limit of 2mA. The intervention dosage is chosen based on the previous TES studies in CLBP[33-41 43 44] and follows safety guidelines[83-85].

For the sham stimulation group, to create an identical skin sensation to active stimulation, we will use the Actisham protocol created by the Neuroelectrics.[86] The current will be applied for a 60s ramp up and 60s ramp down at the beginning and end of each stimulation session, without any current for the remainder of the session. The duration of the sham session will be like HD-tIPNS session to blind the procedure appropriately. Participants in both groups will be informed that they may or may not perceive any sensations during the stimulation treatment. The previous TES studies have used this sham procedure and are shown to effectively blind participants to the stimulation condition, as it can induce the same scalp sensations perceived during active stimulation, both in terms of intensity and localization. Further, the Actisham protocol will prevent the currents from reaching the cortex, thus avoiding causing any brain excitability changes.[86]

Treatment fidelity will be assessed by the principal investigator at each session, who will supervise that the treatment is delivered in a standardized manner as planned. The treatment delivered for each participant for each session will be saved on the NIC2 computer software.

Usual care/concomitant treatments: Participants will be permitted to continue their medications/exercises/other concomitant treatments for the duration of the trial, with the type and dosage being recorded at the baseline session. Any changes to their concomitant treatments will be recorded at every treatment and assessment session. Participants will be advised not to change any of their concomitant treatments for the duration of the trial. Participants with the intention of taking new medications or changing their treatment in the next three months will be excluded.

Outcome measures:

An assessor, blinded to the group allocation, will collect outcomes at baseline (T_B), immediately post-intervention (T_{im}), and at follow-up of one week (T_{1wk}), one month (T_{1m}) and three months (T_{3m}) post-intervention. The chosen secondary measures have good psychometric properties, are used in clinical trials involving people with CLBP and are by recommendations[62-66].

Primary outcomes:

Feasibility measures:

- Recruitment rate, the number of participants recruited per month. Participants will be recruited over one year, with no threshold placed on the recruitment rate for each month. The recruitment rate will be recorded every week since the release of the advertisements, as wll as the number of advertisements and the time period required to achieve the desired sample size (n=40).
- The proportion of participants eligible and recruited from the total number screened (with reasons for exclusion), expressed as a percentage.
- Adherence to intervention measured as number of treatment sessions attended by each participant expressed as a percentage of total number of sessions. Adherence rates will be calculated once the treatment phase is completed.
- Drop-out rates, measured as the number of participants who dropped out in each group, expressed as a percentage of the total number of participants enrolled in the study. Drop-outs rates will be calculated once the follow-up phase is completed.

Safety measures:

At each treatment and follow-up session, the treating researcher will record any adverse effects that likely have a causal relationship with the intervention. The following variables will be recorded:

- Qualitative description and intensity of each symptom on a Likert scale (0=none to 10=extreme)
- Relation of symptom to treatment, measured on a scale ranging from 1=unrelated to 5=strongly related.
- Duration and time taken for resolution of each symptom expressed in minutes.

- Worsening or improvement of symptoms: The Discontinuation-Emergent Sign and Symptom (DESS)[87], will be used to record worsening or improving side effects compared to status prior to previous session.
- Any drop-outs due to adverse effects and how the adverse effects were managed.

Acceptability and satisfaction:

Participant acceptability and satisfaction of the intervention will also be recorded quantitatively on an 11-point NRS (0=Not at all acceptable/satisfied to 10=Very acceptable/satisfied respectively).

Clinical measures:

Pain intensity and interference: using Brief Pain Inventory[88], a standardized, validated questionnaire for CLBP.

Physical Function: *Roland–Morris Disability Questionnaire*[67 68] will be used to assess self-reported functional abilities.

Secondary outcomes (Table 3):

Measures of peripheral and central sensitization: Quantitative sensory testing will be conducted and reported in accordance with the guidelines[89 90] and our previous study[91].

- *Mechanical temporal summation (MTS):* will be assessed using a nylon monofilament (Semmes monofilament 6.65, 300 g). Brief ten repetitive contacts will

be delivered at a rate of 1 Hz, externally cued by auditory stimuli. The participants will be asked to rate the level of pain experienced on NRS (0=No pain to 100=Extreme pain) immediately after the first contact and to rate their greatest pain intensity after the 10th contact. Three trials will be conducted for each of the two regions (i.e., symptomatic low back and non-dominant wrist) in random order. The location of these areas will be recorded using bony landmarks to ensure that same areas are re-assessed during follow-up. MTS will be calculated as difference between NRS rating after the first contact and the highest pain rating after the 10th contact for each trial. This score presents the maximum amount of MTS across ten contact points. Average of three trials will be calculated, with a positive score indicating an increase in MTS. The MTS index will be defined as the ratio of "follow-up" pain rating divided by "baseline" pain rating.[91-93]

- *Pressure pain threshold (PPT):* A computerized, handheld digital algometer (AlgoMed; Medoc, Ramat Yishai, Israel) will be used to measure three trials of PPT over two regions (symptomatic low back and non-dominant wrist) in random order. Two familiarization trials will be performed at dominant mid-forearm before formal trials. The 1-cm^2 algometer probe will be pressed over marked test site perpendicularly to the skin at a rate of 30kPa/s. Participants will be instructed to press algometer trigger button in the patient control unit when pressure sensation changes to first pain.[94] Once patient-controlled unit is activated, the trial is automatically terminated, and amount of pressure will be recorded. If participants did not report pain at maximum pressure level which is set at 1000kPa for safety reasons, the procedure would be terminated, and a score of 1000kpa will be assigned for that trial. The average of three trials will be calculated and used for analysis.[95]

- Condition pain modulation (CPM) is the most frequently administered procedure for exploring the endogenous pain modulatory system.[94 96] CPM test procedure will be administered at least 15 to 20 minutes after the MTS and PPT procedures with the previously published recommendations of testing.[94 96]
  - ❖ The conditioning stimulus will consist of a cold pressor task. The participants will immerse their dominant hand (until mid-forearm) in a thermos containing circulating cold water for a maximum period of 2 minutes. The cold water temperature will be maintained at ~5° centigrade and will be recorded immediately before and after the immersion procedure. Participants will be asked to continue hand immersion until the end of 2 minutes or until it is too uncomfortable to be kept immersed (NPRS~80%). Participant's pain during conditioning stimulus will be recorded on NPRS (0=No pain to 100=Extreme pain) at every 15s interval. A similar conditioning stimulus protocol has been used in previous studies showing a significant CPM effect.[97]
  - ❖ Test stimulus: A computerized, handheld digital algometer (AlgoMed; Medoc, Ramat Yishai, Israel) will be used to measure suprathreshold PPT (pain40) at the non-dominant leg region (tibialis anterior muscle). Two familiarization trials will be performed at mid-forearm before the formal trials. The 1-cm^2 algometer probe will be pressed over the marked test site perpendicularly to the skin at a rate of 30 kPa/s. The participants will be instructed to press the algometer trigger button in the patient control unit when the pressure sensation changes to a pain intensity of 40 out of 100 on the NRS. Once the patient-controlled unit is activated, the trial is automatically terminated, and the amount of pressure (kPa) will be recorded. Suppose participants did not report pain at the maximum pressure level which is set at 1000 kPa for safety reasons, the assessor will

terminate the procedure, and a score of 1000 kpa will be assigned for that trial. Two PPT (pain40) trials will be recorded before conditioning stimulus and will be averaged to obtain a baseline score. In addition, three PPT (pain40) trials will be recorded in the same region at 30, 60, and 90 seconds immediately after the conditioning stimulus.

- Calculation of CPM: A percent change score will be calculated for each time point (i.e., CPM30sec, CPM60sec, and CPM90sec), with a positive score indicating an increase in PPTs (pain40) after the conditioning stimulus and thus the presence of CPM effect.

$$\text{CPM percent change score} = \frac{\text{Post score} - \text{Pre score}}{\text{Pre score}} \text{ x } 100$$

Psychological measures: will include *Depression, Anxiety, and Stress Scale*[98], to measure those three psychological constructs, *Pain Catastrophizing Scale*[99], to measure extent of catastrophic thoughts and feelings about their pain[100], and *Pain Vigilance and Awareness Questionnaire*[101] to measure frequency of habitual 'attention to pain'.

Pain unpleasantness (affective component) measured using an 11-point unpleasantness NRS (0=not at all unpleasant to 10=most unpleasant imaginable).[102 103]

Pain bothersomeness: measured using an 11-point bothersomeness NRS (0=not at all bothering to 10=most bothering).[102 103] A categorical question will also be used "In the last one week, how bothersome has your low back pain been?'' with five choices: "not at all", "slightly", "moderately", "very much", and "extremely".[104 105]

The global rate of change[106]*:* assessed using the question *"Compared to the beginning of treatment, how would you describe your back at this moment?"* Participants will rate their perceived change on an 11-point scale (-5=much worse, through 0=unchanged, to +5=completely, recovered).

Quality of life and wellbeing: will be assessed using *European Quality of Life–5 Dimensions* scale[107] and *World Health Organisation- Five Well-Being Index*[108] respectively.

Measures of cortical electrical activity: Resting-state electroencephalogram (EEG) (~10 minutes, eyes-closed) will be obtained in a quiet room while the participant is sitting upright in a comfortable chair by an independent researcher blinded to the treatment group. Participants will be asked to refrain from caffeinated drinks. EEG data will be collected using the SynAmps RT Amplifier (Compudemics Neuroscan). The EEG will be sampled with 64 electrodes placed in the standard 10–10 International placement, and impedances will be checked to remain below 5 kΩ. The EEG data will then be resampled to 128 Hz, band-pass filtered (fast Fourier transform filter) to 0.01–44 Hz and re-referenced to the average reference using the EEGLAB function in Matlab. The data will then be plotted in EEGLAB for a careful inspection of artifacts and manual rejection.

Standardized low-resolution brain electromagnetic tomography (sLORETA) will be used to estimate intracerebral electrical sources that generate scalp-recorded activity in each of the following ten frequency bands, i.e., infraslow (0.01-0.1Hz), slow (0.2-1.5Hz), delta (2–3.5Hz), theta (4–7.5Hz), alpha1 (8–10Hz), alpha2 (10.5–12Hz), beta1 (12.5–18Hz), beta2 (18.5–21Hz), beta3 (21.5–30Hz), and gamma (30.5–44Hz). The following three analyses will be used to explore the specific (i.e. at the targeted cortical

regions) and non-specific (i.e. other cortical regions) effects of the HD-tIPNS on cortical activity and connectivity:

- *Whole-brain analysis:* will be used to explore the overall (specific and non-specific) changes in the current density in the cortical regions. Comparisons will be made between pre-and post-treatment measurements on a whole-brain by sLORETA statistical contrast maps through multiple voxel-by-voxel comparisons in a logarithm of t-ratio.[109-111]
- *Region of interest analysis:* will be used to calculate and compare the log transformed current density changes at the targeted brain regions (pgACC, dACC, and SSC). The ROI maker 1 function in sLORETA will be used to define the region of interest. A seed point will be provided for each region of interest and all voxels within a radius of 10mm will be averaged to calculate the current density.
- *Lagged phase connectivity:* will be used as a measure of coherence and will be calculated between all the regions of interest for all the ten frequency bands as described above.[109-111] Comparisons will be made between pre-and post-treatment measurements using sLORETA statistical contrast maps through multiple voxel-by-voxel comparisons in a logarithm of t-ratio.[109-111]

Statistical analysis:

SPSS version 27.0 will be used for all statistical analyses. Descriptive statistics will be used to analyze feasibility, safety, and acceptability measures. As this is a feasibility study, tests for significance to compare clinical or secondary measures between study groups will not performed, but descriptive statistics will be calculated.

All measures will be analyzed based on intention-to-treat principle and as per the originally assigned groups. Last observation carried forward methodology will be used to compute missing data. Mean±SDs and Mean differences (95% CI), will be calculated from baseline to each interim and primary endpoint (T_{3m}).

Percentage change to baseline will be calculated for primary pain (BPI) and functional (RMDQ) measures as below (e.g., for T_{3m}):

$$\text{Percent change to baseline} = \frac{\text{T3m} - \text{T0}}{\text{T0}} \text{x} 100$$

A ≥30% decrease will be considered as a meaningful clinical important difference (MCID). Proportion of participants with changes ≥MCID will be calculated and descriptively compared between groups.

A nested qualitative study

We will include a nested qualitative study to explore participant's experiences and acceptability of intervention procedures. Semi-structured in-depth interviews will be conducted by a researcher, blinded to treatment allocation, immediately post-intervention. All participants will be invited to participate. The aims of this study are explorative in nature and will evaluate participant's experiences, exploring difficulties and barriers faced, perception towards intervention/research process, acceptability of intervention, perceived value and positive aspects of the study, and any other issues that arise during interviews. Table 4 presents the questions that will be used as a guide for the interview. The interviews will be audio-recorded and fully transcribed. The analysis will be guided by General Inductive Approach[112 113], which provides a

pragmatic framework for identifying shared and individual experiences and embraces findings derived from both research objectives (deductive) and those arising directly from analysis of raw data (inductive). A constant comparison process will be used; researchers will reflect on and discuss completed interviews and revise the questions schedule accordingly to ensure a broad capture of new important information. The results of qualitative study will be published separately.

Patient and Public involvement:

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

DISCUSSION

To date, there are only a limited number of studies evaluating the TES interventions in people with CLBP.[45 46] A recent meta-analysis demonstrates that there is moderate quality evidence suggesting that neither repeated sessions of non-invasive brain stimulation nor its combination with other treatments significantly improves pain or disability in people with CLBP.[45] As most studies evaluating tDCS of single brain region demonstrated little success in improving pain and disability in people with CLBP, future trials focusing on different TES techniques, targeting multiple cortical areas, using various parameters are warranted and recommended. The proposed research will be the first randomized placebo-controlled pilot study to explore a novel HD-tIPNS technique targeting multiple brain regions simultaneously in individuals with CLBP.

This pilot research will provide preliminary evidence on feasibility, safety, and acceptability of the novel HD-tIPNS technique for treatment of CLBP. Assessment of feasibility and acceptability of new interventions and study procedures is essential to determine parameters required to inform the study design of a future fully-powered randomised controlled trial.[114] Further, to the best of our knowledge, none of the previous studies have assessed the acceptability of the TES in people with CLBP. Our study will incorporate detailed mixed method approach to assess the feasibility and the acceptability of the HD-tIPNS techqniue and help inform interventions, study procedures, and refinements and the planning of a future definitive randomised controlled trial. Additionally although our study is not powered to test effectiveness, it will provide treatment estimates to design the sample characteristics and numbers for a fully powered randomised controlled trial in future.

ETHICS, DATA SAFETY, AND DISSEMINATION

Ethical approval has been obtained from Health and Disability Ethics Committee (Ref:20/NTB/67), who may also audit the study investigators during or after the study. Any deviations from protocol will require Ethical amendment and will be updated in the registry. To protect participant confidentiality, any personal information collected will be destroyed at the end of the project. Each participant will be given a unique identification code, and the data will be linked to that code only. All study data will be securely stored in a locked filing cabinet or electronically with password protection, such that only those involved in the research program will have access to it. As required by the University's research policy, any unidentified raw data on which the results of the project depend will be kept in secure storage for ten years, after which it will be destroyed.

An independent Data and Safety Monitoring Committee will monitor the safety of the study. A serious adverse event (SAE) is defined as any untoward medical occurrence or effect that results in death, is life-threatening, requires hospitalisation, results in persistent or significant disability or incapacity.The study will be discontinued if there is any unexpected SAE, other unexpected events, or if funding is completed/ insufficient.

Study findings will be reported to the regulatory and funding bodies, presented at the local, national, and international conferences, and disseminated by peer-review publication in a scientific journal.

FUNDING AND COMPETING INTERESTS STATEMENT

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There are no competing interests for any author.

AUTHORS' CONTRIBUTIONS:

Conceptualization: DBA, DDR, RM, JR, and SV; Methodology/Design of the work: DBA, DDR, RM, JR and SV; Writing—original draft preparation: DBA, DDR and RM; writing—critically reviewing and revising: DBA, DDR, RM, SV, and JR. All authors have critically read and agreed to the final version of the submitted manuscript and agree to be accountable for all aspects of the work.

CHANGES TO REGISTRY:

The following changes were made to the registered protocol based on the ethical review and the peer reviewer comments. *Eligibility criteria:* The age bracket for participant inclusion was expanded to 18 to 75 years instead of the originally planned 35 to 70 years. *Secondary outcomes:* The MTS and PPT tests will be evaluated at two sites (symptomatic low back and non-dominant wrist region) rather than the originally

planned three regions (i.e., symptomatic low back region, non-symptomatic low back region, and the distant non-dominant wrist). Also, for the CPM procedure, the test site was changed to the non-dominant leg region, rather than the originally planned most painful low back region. *Outcomes:* Some of the secondary clinical measures and mechanistic measures (eg., pain unpleasantness, pain bothersomeness, global rate of change, quality of life, wellbeing, and resting state EEG) were included in the study protocol but not in the registry. These have been added to the registry. All these changes to the protocol were made before the participant enrolment commenced, and are updated in the ANZCTR trial registry (https://anzctr.org.au/Trial/Registration/TrialReview.aspx?ACTRN=12620000505909) .

Table 1. WHO trial registration data set (v.1.3.1).

Item	Information
Primary registry and trial Identifying number	Australian and New Zealand Clinical Trials Registry- ACTRN 12620000505909
Date of registration in primary registry	23/04/2020
Universal Trial Number	U1111-1250-1177
Source of monetary or material support	Health Research Council of New Zealand Emerging Researcher First Grant, The Healthcare Otago Charitable trust, Lottery Health Research equipment grant, Brain Health Research Centre, and the Neurological foundation of New Zealand.
Primary Sponsor	University of Otago
Contact for public queries	Dr Divya Adhia, Department of Surgical Sciences, Otago Medical School, University of Otago.
Contact for scientific queries	Dr Divya Adhia, Department of Surgical Sciences, Otago Medical School, University of Otago.
Public title	Non-invasive brain stimulation for chronic low back pain.
Scientific title	Safety and feasibility of transcranial electrical stimulation for chronic low back pain.
Country of recruitment	New Zealand.
Health condition or problem studied	Chronic low back pain.
Interventions	High-definition transcranial infraslow pink noise stimulation.
Key eligibility criteria	Adults between the ages of 18-75 years, with chronic low back pain.
Study type	Interventional, exploratory randomised placebo-controlled parallel pilot trial; Allocation ratio = 1:1.
Date of first enrolment	1st June 2021 (Note: Delayed from the planned enrolment date of 15th July 2020 as indicated in registry, due to equipment breakdown and delay in recruitment of research staff).
Sample size	Not calculated. This pilot study will be executed to make a power estimate for a future phase II study. Based on statistical advise,

Item	Information
	40 participants (20 per group) will be enough to determine feasibility measures for a fully powered trial.
Recruitment status	Recruiting (Recruitment period: June'21 to May'22)
Primary outcomes	Feasibility (measured as recruitment rate, proportion of participants eligible and recruited, adherence to intervention, and drop-out rates) Safety (measured as any adverse events that have a likely causal relationship with the intervention) Acceptability of the intervention (assessed quantitatively as well as qualitatively) Pain and disability: Brief pain Inventory and Roland-Morris disability questionnaire. (Note: Feasibility measures and treatment acceptability are primary measures that are listed under secondary outcome section in the ANZCTR due to limit of the primary outcomes that could be included in the registry).
Secondary measures	Quantitative sensory testing: mechanical temporal summation, pressure pain threshold, and conditioned pain modulation. Psychological measures: Depression, anxiety and stress scale, pain catastrophising scale, and pain vigilance and awareness questionnaire. Pain measures: Pain unpleasantness and bothersomeness, global rate of change score. Wellbeing: European quality of life–5 dimensions, World Health Organisation- five wellbeing index. Resting-state electroencephalogram: current density and functional connectivity.
Ethical Review	Status: Approved, Date of Approval: 28th July 2020; Committee: Health and Disability Ethics Committee (HDEC, Ref: 20/NTB/67)

Table 2: Description of the HD-tIPNS intervention, as per the template for intervention description and replication.

Item number and Item	Description
1. BRIEF NAME	High-definition transcranial infraslow pink noise stimulation (HD-tIPNS).
2. WHY	The HD technique uses arrays of multiple small electrodes whose configuration can be optimized for focally targeting specific brain regions.[58 59 76-80] The HD-tIPNS technique is developed to specifically modulate the infraslow electrical activity (0-0.1 Hz) in the brain. The infraslow electrical activity, a fundamental frequency range of the brain, re-organizes neurons and improves the electrical connectivity of the brain-wide functional networks.[48-51] Optimizing the infraslow frequency can normalize the electrical activity in the higher frequency bands known to be affected in individuals with chronic pain.[48-51] Recent imaging studies have also demonstrated alterations in the infraslow oscillations in individuals with CLBP in descending (pgACC) and ascending (dACC, SSC) pain pathways.[54 56 57] Research shows that pink noise stimulation can influence the infraslow electrical activity (0-0.1 Hz) in the brain.[58 59] The pink noise frequency spectrum resembles the naturally occurring signals in the self-organization of the brain, thus can be more effective than standard tDCS electrical parameters.[58 59] We, therefore, hypothesize that specifically and simultaneously targeting the fundamental infraslow activity at the key nodes of pain processing networks, using a novel HD-tIPNS technique, could normalize brain-wide electrical activity and functional connectivity between areas of interest, promoting better pain modulation and producing more meaningful clinical benefits.
3. WHAT	A battery-driven wireless transcranial electrical stimulator (Starstim-Home TES®, Neuroelectrics, Spain) will be used to deliver stimulation while participants are comfortably and quietly seated. Eight electrodes will be placed on a neoprene head cap following the International 10-20 EEG system to simultaneously target pgACC, dACC, and SSC (Fig. 2 and 3).
4. Procedures:	At each session, participant's scalp will be cleaned with alcohol wipes. The treating researcher will place the neoprene cap with the eight electrodes attached to it on the participant's head while they are comfortably seated in a chair. The reference electrode will be placed on the right ear. Electrogel will be applied to the scalp at the locations of the electrodes for reducing the impedance. The NIC2 software uses a traffic light signal indicator (red, yellow, green) for impedance. All electrodes will be prepared to have the lowest impedance (green colour). All the cables will be attached to the stimulating electrodes and the neckbox. The stimulator will be connected to the NIC2 software using its wifi function. The participant will be comfortably

	positioned in a half-lying position with their eyes closed. The participant will be asked to relax, and the stimulation intervention will be delivered for 30 minutes.
5. WHO PROVIDED	Two independent researchers will be involved in the delivery of the intervention. A researcher (R1) with a health professional background (physiotherapist) will design and control the Starstim-Home device and set up the stimulation programs in the NIC2 (neuroelectrics software), to allow blinding of the treating researcher (R2). The program will be uploaded to the online portal and the treatment will be scheduled for each participant by R1. Another independent researcher (assistant research fellow, R2) with considerable experience in administering neuromodulation techniques will prepare the participants for treatment and administer the stimulation intervention using the iPad of the Starstim-Home TES system. During the stimulation period, the iPad screen presents only a green bar for indicating the duration of the stimulation session and no other stimulation parameters are presented. This allows for appropriate blinding of the treating researcher (R2).
6. HOW	All participants will receive individual face-to-face sessions.
7. WHERE	Interventions will be delivered at a clinical laboratory in the Otago Medical School, Department of Surgical Sciences, located in the Dunedin Hospital, Dunedin, New Zealand.
8. WHEN and HOW MUCH	All participants will receive the intervention (based on their randomized group) for a total of 20 sessions, five times a week for four consecutive weeks. Each stimulation session will last for 30 minutes duration.
9. TAILORING	The interventions will not be tailored to individual participant's brain states. All participants in HD-tIPNS group will receive the same stimulation waveform, pink noise stimulation at a current strength of a maximum of 0.6mA superimposed on the infraslow (0.1Hz sinusoidal) waveform of a current intensity of 1mA.
10. MODIFICATIONS	Not applicable. This is a protocol for a pilot trial.
11. HOW WELL	Adherence to intervention will be one of the primary outcomes for the study and will be recorded by the treating researcher. Adherence rates will be calculated once the treatment phase is completed. The number of treatment sessions attended by each participant and expressed as a percentage of the total number of sessions.
12. Actual: describe the extent to which the intervention was delivered as planned.	Not applicable. This is a protocol for a pilot trial.

Table 3: List of the measure's domains, their construct, measurement tools, and assessment time points

Measure's Domains	Constructs	Measurement tools	Timepoints
Pain	Severity (primary clinical outcome)	Brief Pain Inventory Short form Severity subscale in the past 24 hours. 0-10 NRS of the worst pain in the past 24 hours 0-10 NRS of average pain in the past 24 hours	$T_B, T_{im}, T_{1wk}, T_{1m}, T_{3m}$ $T_B, T_{im}, T_{1wk}, T_{1m}, T_{3m}$ $T_B, T_{im}, T_{1wk}, T_{1m}, T_{3m}$
	Unpleasantness	0-10 NRS of unpleasantness in the past 24 hours	$T_B, T_{im}, T_{1wk}, T_{1m}, T_{3m}$
	Bothersomeness	0-10 NRS of bothersomeness in past 24 hours	$T_B, T_{im}, T_{1wk}, T_{1m}, T_{3m}$
Physical functioning	Pain interference (primary clinical outcome)	Brief Pain Inventory Short form Interference subscale in the past 24 hours.	$T_B, T_{im}, T_{1wk}, T_{1m}, T_{3m}$
	Disability (primary clinical outcome)	Roland–Morris Disability Questionnaire	$T_B, T_{im}, T_{1wk}, T_{1m}, T_{3m}$
Global change	Global perceived change	Perceived change in the back region on an 11-point scale (-5=much worse, through 0=unchanged, to +5=completely, recovered	$T_{im}, T_{1wk}, T_{1m}, T_{3m}$
Satisfaction	Extent of satisfaction	Perceived treatment satisfaction on an 0-10 NRS	T_{im}
Psychological functioning	Depression	Depression, Anxiety, and Stress Scale	$T_B, T_{im}, T_{1wk}, T_{1m}, T_{3m}$
	Catastrophising	Pain Catastrophising Scale	$T_B, T_{im}, T_{1wk}, T_{1m}, T_{3m}$
	Attention to pain	Pain Vigilance and Awareness Questionnaire	$T_B, T_{im}, T_{1wk}, T_{1m}, T_{3m}$
General Health	Quality of life	European Quality of Life- 5D	$T_B, T_{im}, T_{1wk}, T_{1m}, T_{3m}$
	Well-being	World Health Organisation-Five Well-Being Index	$T_B, T_{im}, T_{1wk}, T_{1m}, T_{3m}$
T_B: At baseline, T_{im}: Immediately post-intervention, T_{1wk}: One-week post-intervention, T_{1m}: One-month post-intervention, T_{3m}: Three-months post-intervention			

Table 4: Interview guide

Questions for Participants	Follow up / prompting questions
Tell us what it's been like attending the assessment and treatment (brain stimulation) sessions.	
What obstacles have you had to face throughout the trial period?	What aspects/areas were challenging? How did it affect your back pain?
What is your perception of these brain stimulation sessions?	Do you feel the brain stimulation sessions was worth the time and effort/worthwhile? Why/why not?
Was it acceptable to you?	
Do you feel like you have gained anything from this experience? If so what?	What have you learned? How has this brain stimulation and the overall study experience changed your pain or function? Is there anything you'd identify as lacking in the treatment programme? What would you tell someone else thinking about participating in the same intervention?
Is there anything else you would like to share about the experience?	

REFERENCES:

1. Clark S, Horton R. Low back pain: a major global challenge. *The Lancet* 2018;391(10137):2302.
2. Hoy D, March L, Brooks P, et al. The global burden of low back pain: estimates from the Global Burden of Disease 2010 study. *Annals of the rheumatic diseases* 2014;73(6):968-74.
3. Treede R-D, Rief W, Barke A, et al. A classification of chronic pain for ICD-11. *Pain* 2015;156(6):1003.
4. Chou R, Deyo R, Friedly J, et al. Nonpharmacologic therapies for low back pain: a systematic review for an American College of Physicians clinical practice guideline. *Annals of internal medicine* 2017;166(7):493-505.
5. Coulter ID, Crawford C, Hurwitz EL, et al. Manipulation and mobilization for treating chronic low back pain: a systematic review and meta-analysis. *The Spine Journal* 2018;18(5):866-79.
6. Rubinstein SM, De Zoete A, Van Middelkoop M, et al. Benefits and harms of spinal manipulative therapy for the treatment of chronic low back pain: systematic review and meta-analysis of randomised controlled trials. *bmj* 2019;364
7. Chou R, Turner JA, Devine EB, et al. The effectiveness and risks of long-term opioid therapy for chronic pain: a systematic review for a National Institutes of Health Pathways to Prevention Workshop. *Annals of internal medicine* 2015;162(4):276-86.
8. Koes BW, Backes D, Bindels PJ. Pharmacotherapy for chronic non-specific low back pain: current and future options. *Expert opinion on pharmacotherapy* 2018;19(6):537-45.
9. Pavelka K, Jarosova H, Sleglova O, et al. Chronic low back pain: Current pharmacotherapeutic therapies and a new biological approach. *Current medicinal chemistry* 2019;26(6):1019-26.
10. Ng SK, Urquhart DM, Fitzgerald PB, et al. The relationship between structural and functional brain changes and altered emotion and cognition in chronic low back pain brain changes. *The Clinical journal of pain* 2018;34(3):237-61.
11. Konno S-i, Sekiguchi M. Association between brain and low back pain. *Journal of Orthopaedic Science* 2018;23(1):3-7.
12. Structural and functional brain abnormalities in chronic low back pain: A systematic review☆. Seminars in arthritis and rheumatism; 2015. Elsevier.
13. Kucyi A, Davis KD. The dynamic pain connectome. *Trends in neurosciences* 2015;38(2):86-95.
14. Vanneste S, De Ridder D. Chronic pain as a brain imbalance between pain input and pain suppression. *Brain Communications* 2021;3(1):fcab014.
15. De Ridder D, Vanneste S. The Bayesian brain in imbalance: Medial, lateral and descending pathways in tinnitus and pain: A perspective. Progress in Brain Research: Elsevier 2021:309-34.
16. De Ridder D, Adhia D, Vanneste S. The anatomy of pain and suffering in the brain and its clinical implications. *Neuroscience & Biobehavioral Reviews* 2021
17. Li T, Zhang S, Kurata J. Suppressed descending pain modulatory and enhanced sensorimotor networks in patients with chronic low back pain. *Journal of anesthesia* 2018;32(6):831-43.
18. Yuan C, Shi H, Pan P, et al. Gray matter abnormalities associated with chronic back pain. *The Clinical journal of pain* 2017;33(11):983-90.
19. De Ridder D, Vanneste S. Burst and tonic spinal cord stimulation: different and common brain mechanisms. *Neuromodulation: Technology at the Neural Interface* 2016;19(1):47-59.
20. Bushnell MC, Čeko M, Low LA. Cognitive and emotional control of pain and its disruption in chronic pain. *Nature Reviews Neuroscience* 2013;14(7):502-11.
21. Baliki MN, Petre B, Torbey S, et al. Corticostriatal functional connectivity predicts transition to chronic back pain. *Nature neuroscience* 2012;15(8):1117-19.
22. Coppieters I, Meeus M, Kregel J, et al. Relations between brain alterations and clinical pain measures in chronic musculoskeletal pain: a systematic review. *The Journal of Pain* 2016;17(9):949-62.
23. Hashmi JA, Baliki MN, Huang L, et al. Shape shifting pain: chronification of back pain shifts brain representation from nociceptive to emotional circuits. *Brain* 2013;136(9):2751-68.

24. Hemington KS, Rogachov A, Cheng JC, et al. Patients with chronic pain exhibit a complex relationship triad between pain, resilience, and within-and cross-network functional connectivity of the default mode network. *Pain* 2018;159(8):1621-30.
25. Kim J, Mawla I, Kong J, et al. Somatotopically-specific primary somatosensory connectivity to salience and default mode networks encodes clinical pain. *Pain* 2019;160(7):1594.
26. Kong J, Spaeth B, Wey H-Y, et al. S1 is associated with chronic low back pain: a functional and structural MRI study. *Molecular pain* 2013;9:1744-8069-9-43.
27. Ossipov MH, Morimura K, Porreca F. Descending pain modulation and chronification of pain. *Current opinion in supportive and palliative care* 2014;8(2):143.
28. Tu Y, Jung M, Gollub RL, et al. Abnormal medial prefrontal cortex functional connectivity and its association with clinical symptoms in chronic low back pain. *Pain* 2019;160(6):1308.
29. Nascimento RMD, Cavalcanti RL, Souza CG, et al. Transcranial direct current stimulation combined with peripheral stimulation in chronic pain: a systematic review and meta-analysis. *Expert Rev Med Devices* 2022:1-20. doi: 10.1080/17434440.2022.2039623 [published Online First: 2022/02/09]
30. Pinto CB, Teixeira Costa B, Duarte D, et al. Transcranial Direct Current Stimulation as a Therapeutic Tool for Chronic Pain. *J ect* 2018;34(3):e36-e50. doi: 10.1097/yct.0000000000000518 [published Online First: 2018/06/29]
31. Knotkova H, Hamani C, Sivanesan E, et al. Neuromodulation for chronic pain. *Lancet* 2021;397(10289):2111-24. doi: 10.1016/s0140-6736(21)00794-7 [published Online First: 2021/06/02]
32. Lloyd DM, Wittkopf PG, Arendsen LJ, et al. Is Transcranial Direct Current Stimulation (tDCS) Effective for the Treatment of Pain in Fibromyalgia? A Systematic Review and Meta-Analysis. *The Journal of Pain* 2020;21(11):1085-100. doi: https://doi.org/10.1016/j.jpain.2020.01.003
33. Ahn S, Prim JH, Alexander ML, et al. Identifying and Engaging Neuronal Oscillations by Transcranial Alternating Current Stimulation in Patients With Chronic Low Back Pain: A Randomized, Crossover, Double-Blind, Sham-Controlled Pilot Study. *J Pain* 2019;20(3):277.e1-77.e11. doi: 10.1016/j.jpain.2018.09.004 [published Online First: 2018/10/01]
34. Hazime FA, Baptista AF, de Freitas DG, et al. Treating low back pain with combined cerebral and peripheral electrical stimulation: A randomized, double-blind, factorial clinical trial. *Eur J Pain* 2017;21(7):1132-43. doi: 10.1002/ejp.1037 [published Online First: 2017/04/26]
35. Jafarzadeh A, Ehsani F, Yosephi MH, et al. Concurrent postural training and M1 anodal transcranial direct current stimulation improve postural impairment in patients with chronic low back pain. *J Clin Neurosci* 2019;68:224-34. doi: 10.1016/j.jocn.2019.07.017 [published Online First: 2019/07/28]
36. Luedtke K, Rushton A, Wright C, et al. Effectiveness of transcranial direct current stimulation preceding cognitive behavioural management for chronic low back pain: sham controlled double blinded randomised controlled trial. *Bmj* 2015;350:h1640. doi: 10.1136/bmj.h1640 [published Online First: 2015/04/18]
37. Mariano TY, Burgess FW, Bowker M, et al. Transcranial Direct Current Stimulation for Affective Symptoms and Functioning in Chronic Low Back Pain: A Pilot Double-Blinded, Randomized, Placebo-Controlled Trial. *Pain Med* 2019;20(6):1166-77. doi: 10.1093/pm/pny188 [published Online First: 2018/10/26]
38. O'Connell NE, Cossar J, Marston L, et al. Transcranial direct current stimulation of the motor cortex in the treatment of chronic nonspecific low back pain: a randomized, double-blind exploratory study. *Clin J Pain* 2013;29(1):26-34. doi: 10.1097/AJP.0b013e318247ec09 [published Online First: 2012/12/12]
39. Schabrun SM, Burns E, Thapa T, et al. The Response of the Primary Motor Cortex to Neuromodulation is Altered in Chronic Low Back Pain: A Preliminary Study. *Pain Med* 2018;19(6):1227-36. doi: 10.1093/pm/pnx168 [published Online First: 2017/10/11]

40. Schabrun SM, Jones E, Elgueta Cancino EL, et al. Targeting chronic recurrent low back pain from the top-down and the bottom-up: a combined transcranial direct current stimulation and peripheral electrical stimulation intervention. *Brain Stimul* 2014;7(3):451-9. doi: 10.1016/j.brs.2014.01.058 [published Online First: 2014/03/04]
41. Straudi S, Buja S, Baroni A, et al. The effects of transcranial direct current stimulation (tDCS) combined with group exercise treatment in subjects with chronic low back pain: a pilot randomized control trial. *Clin Rehabil* 2018;32(10):1348-56. doi: 10.1177/0269215518777881 [published Online First: 2018/05/23]
42. Jiang N, Wei J, Li G, et al. Effect of dry-electrode-based transcranial direct current stimulation on chronic low back pain and low back muscle activities: A double-blind sham-controlled study. *Restor Neurol Neurosci* 2020;38(1):41-54. doi: 10.3233/rnn-190922 [published Online First: 2019/11/07]
43. Larie Ms, Esfandiarpour F, Riahi F, et al. Effects of Cortical and Peripheral Electrical Stimulation on Brain Activity in Individuals with Chronic Low Back Pain. *Physical Treatments - Specific Physical Therapy* 2019;9(1):39-46. doi: 10.32598/ptj.9.1.39
44. Ouellette AL, Liston MB, Chang WJ, et al. Safety and feasibility of transcranial direct current stimulation (tDCS) combined with sensorimotor retraining in chronic low back pain: a protocol for a pilot randomised controlled trial. *BMJ Open* 2017;7(8):e013080. doi: 10.1136/bmjopen-2016-013080 [published Online First: 2017/08/23]
45. Patricio P, Roy JS, Rohel A, et al. The Effect of Noninvasive Brain Stimulation to Reduce Nonspecific Low Back Pain: A Systematic Review and Meta-analysis. *Clin J Pain* 2021;37(6):475-85. doi: 10.1097/ajp.0000000000000934 [published Online First: 2021/05/06]
46. O'Connell NE, Marston L, Spencer S, et al. Non-invasive brain stimulation techniques for chronic pain. *Cochrane Database Syst Rev* 2018;3(3):Cd008208. doi: 10.1002/14651858.CD008208.pub4 [published Online First: 2018/03/17]
47. Lima MC, Fregni F. Motor cortex stimulation for chronic pain: systematic review and meta-analysis of the literature. *Neurology* 2008;70(24):2329-37. doi: 10.1212/01.wnl.0000314649.38527.93 [published Online First: 2008/06/11]
48. Brookes MJ, Woolrich M, Luckhoo H, et al. Investigating the electrophysiological basis of resting state networks using magnetoencephalography. *Proceedings of the National Academy of Sciences* 2011;108(40):16783-88.
49. Mitra A, Raichle ME. How networks communicate: propagation patterns in spontaneous brain activity. *Philosophical Transactions of the Royal Society B: Biological Sciences* 2016;371(1705):20150546.
50. Watson BO. Cognitive and physiologic impacts of the infraslow oscillation. *Frontiers in systems neuroscience* 2018;12:44.
51. Wilckens KA, Ferrarelli F, Walker MP, et al. Slow-wave activity enhancement to improve cognition. *Trends in neurosciences* 2018;41(7):470-82.
52. Chan AW, Mohajerani MH, LeDue JM, et al. Mesoscale infraslow spontaneous membrane potential fluctuations recapitulate high-frequency activity cortical motifs. *Nature communications* 2015;6(1):1-12.
53. Pan W-J, Thompson GJ, Magnuson ME, et al. Infraslow LFP correlates to resting-state fMRI BOLD signals. *Neuroimage* 2013;74:288-97.
54. Ploner M, Sorg C, Gross J. Brain rhythms of pain. *Trends in cognitive sciences* 2017;21(2):100-10.
55. Alshelh Z, Di Pietro F, Youssef AM, et al. Chronic neuropathic pain: it's about the rhythm. *Journal of Neuroscience* 2016;36(3):1008-18.
56. Zhang B, Jung M, Tu Y, et al. Identifying brain regions associated with the neuropathology of chronic low back pain: a resting-state amplitude of low-frequency fluctuation study. *British journal of anaesthesia* 2019;123(2):e303-e11.
57. Zhou F, Gu L, Hong S, et al. Altered low-frequency oscillation amplitude of resting state-fMRI in patients with discogenic low-back and leg pain. *Journal of pain research* 2018;11:165.

58. Leong SL, De Ridder D, Vanneste S, et al. High definition transcranial pink noise stimulation of anterior cingulate cortex on food craving: An explorative study. *Appetite* 2018;120:673-78.
59. Whittington F, De Ridder D, Adhia DB. High definition transcranial infraslow pink noise stimulation for improving executive functioning in healthy older adults – A pilot safety trial. Otago Medical School Research Society Summer Student Sepeaker Awards: New Zealand Medical Journal, 2021.
60. Chan A-W, Tetzlaff JM, Altman DG, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. *Annals of internal medicine* 2013;158(3):200-07.
61. Hoffmann TC, Glasziou PP, Boutron I, et al. Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide. *Bmj* 2014;348
62. Edwards RR, Dworkin RH, Turk DC, et al. Patient phenotyping in clinical trials of chronic pain treatments: IMMPACT recommendations. *Pain* 2016;157(9):1851.
63. Gewandter JS, Dworkin RH, Turk DC, et al. Improving study conduct and data quality in clinical trials of chronic pain treatments: IMMPACT recommendations. *The journal of pain* 2020;21(9-10):931-42.
64. Smith SM, Dworkin RH, Turk DC, et al. The potential role of sensory testing, skin biopsy, and functional brain imaging as biomarkers in chronic pain clinical trials: IMMPACT considerations. *The Journal of Pain* 2017;18(7):757-77.
65. Smith SM, Dworkin RH, Turk DC, et al. Interpretation of chronic pain clinical trial outcomes: IMMPACT recommended considerations. *Pain* 2020;161(11):2446-61.
66. Taylor AM, Phillips K, Patel KV, et al. Assessment of physical function and participation in chronic pain clinical trials: IMMPACT/OMERACT recommendations. *Pain* 2016;157(9):1836.
67. Roland M, Morris R. A study of the natural history of low-back pain. Part II: development of guidelines for trials of treatment in primary care. *Spine* 1983;8(2):145-50.
68. Roland M, Morris R. A study of the natural history of back pain. Part I: development of a reliable and sensitive measure of disability in low-back pain. Spine (Phila Pa 1976). 1983; 8 (2): 141-4. *dx doi org/101097/00007632-198303000-00004*
69. Dionne CE, Dunn KM, Croft PR, et al. A consensus approach toward the standardization of back pain definitions for use in prevalence studies. *Spine* 2008;33(1):95-103.
70. Grotle M, Brox JI, Vøllestad NK. Concurrent comparison of responsiveness in pain and functional status measurements used for patients with low back pain. *Spine* 2004;29(21):E492-E501.
71. Neblett R, Cohen H, Choi Y, et al. The Central Sensitization Inventory (CSI): establishing clinically significant values for identifying central sensitivity syndromes in an outpatient chronic pain sample. *J Pain* 2013;14(5):438-45. doi: 10.1016/j.jpain.2012.11.012 [published Online First: 2013/03/16]
72. Mayer TG, Neblett R, Cohen H, et al. The development and psychometric validation of the central sensitization inventory. *Pain Pract* 2012;12(4):276-85. doi: 10.1111/j.1533-2500.2011.00493.x [published Online First: 2011/09/29]
73. Freynhagen R, Tölle TR, Gockel U, et al. The painDETECT project–far more than a screening tool on neuropathic pain. *Current medical research and opinion* 2016;32(6):1033-57.
74. Schattner E, Shahar G. Role of pain personification in pain-related depression: An object relations perspective. *Psychiatry: Interpersonal & Biological Processes* 2011;74(1):14-20.
75. Devilly GJ, Borkovec TD. Psychometric properties of the credibility/expectancy questionnaire. *Journal of behavior therapy and experimental psychiatry* 2000;31(2):73-86.
76. Minhas P, Bansal V, Patel J, et al. Electrodes for high-definition transcutaneous DC stimulation for applications in drug delivery and electrotherapy, including tDCS. *Journal of neuroscience methods* 2010;190(2):188-97.
77. DaSilva AF, Truong DQ, DosSantos MF, et al. State-of-art neuroanatomical target analysis of high-definition and conventional tDCS montages used for migraine and pain control. *Frontiers in neuroanatomy* 2015;9:89.

78. Datta A, Bansal V, Diaz J, et al. Gyri-precise head model of transcranial direct current stimulation: improved spatial focality using a ring electrode versus conventional rectangular pad. *Brain stimulation* 2009;2(4):201-07. e1.
79. Dmochowski JP, Datta A, Bikson M, et al. Optimized multi-electrode stimulation increases focality and intensity at target. *Journal of neural engineering* 2011;8(4):046011.
80. To WT, Eroh J, Hart J, et al. Exploring the effects of anodal and cathodal high definition transcranial direct current stimulation targeting the dorsal anterior cingulate cortex. *Scientific reports* 2018;8(1):1-16.
81. Ruffini G, Fox MD, Ripolles O, et al. Optimization of multifocal transcranial current stimulation for weighted cortical pattern targeting from realistic modeling of electric fields. *Neuroimage* 2014;89:216-25.
82. Ruffini G, Wendling F, Sanchez-Todo R, et al. Targeting brain networks with multichannel transcranial current stimulation (tCS). *Current Opinion in Biomedical Engineering* 2018;8:70-77.
83. Lefaucheur J-P, Antal A, Ayache SS, et al. Evidence-based guidelines on the therapeutic use of transcranial direct current stimulation (tDCS). *Clinical Neurophysiology* 2017;128(1):56-92.
84. Nikolin S, Huggins C, Martin D, et al. Safety of repeated sessions of transcranial direct current stimulation: a systematic review. *Brain stimulation* 2018;11(2):278-88.
85. Woods AJ, Antal A, Bikson M, et al. A technical guide to tDCS, and related non-invasive brain stimulation tools. *Clinical neurophysiology* 2016;127(2):1031-48.
86. Neri F, Mencarelli L, Menardi A, et al. A novel tDCS sham approach based on model-driven controlled shunting. *Brain stimulation* 2020;13(2):507-16.
87. Rosenbaum JF, Fava M, Hoog SL, et al. Selective serotonin reuptake inhibitor discontinuation syndrome: a randomized clinical trial. *Biological psychiatry* 1998;44(2):77-87.
88. Song C-Y, Lin S-F, Huang C-Y, et al. Validation of the Brief Pain Inventory in Patients With Low Back Pain. *Spine (Philadelphia, Pa 1976)* 2016;41(15):E937-E42. doi: 10.1097/BRS.0000000000001478
89. Uddin Z, MacDermid JC. Quantitative Sensory Testing in Chronic Musculoskeletal Pain. *Pain Med* 2016;17(9):1694-703. doi: 10.1093/pm/pnv105 [published Online First: 2016/02/20]
90. Rolke R, Baron R, Maier Ca, et al. Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): standardized protocol and reference values. *Pain* 2006;123(3):231-43.
91. Mani R, Adhia DB, Leong SL, et al. Sedentary behaviour facilitates conditioned pain modulation in middle-aged and older adults with persistent musculoskeletal pain: a cross-sectional investigation. *Pain reports* 2019;4(5):e773-e73. doi: 10.1097/PR9.0000000000000773
92. Goodin BR, Bulls HW, Herbert MS, et al. Temporal summation of pain as a prospective predictor of clinical pain severity in adults aged 45 years and older with knee osteoarthritis: ethnic differences. *Psychosomatic medicine* 2014;76(4):302-10. doi: 10.1097/PSY.0000000000000058
93. Hübscher M, Moloney N, Leaver A, et al. Relationship between quantitative sensory testing and pain or disability in people with spinal pain—a systematic review and meta-analysis. *PAIN®* 2013;154(9):1497-504.
94. Yarnitsky D, Bouhassira D, Drewes AM, et al. Recommendations on practice of conditioned pain modulation (CPM) testing. *Eur J Pain* 2015;19(6):805-6. doi: 10.1002/ejp.605 [published Online First: 2014/10/21]
95. Suokas AK, Walsh DA, McWilliams DF, et al. Quantitative sensory testing in painful osteoarthritis: a systematic review and meta-analysis. *Osteoarthritis Cartilage* 2012;20(10):1075-85. doi: 10.1016/j.joca.2012.06.009 [published Online First: 2012/07/17]
96. Yarnitsky D, Arendt-Nielsen L, Bouhassira D, et al. Recommendations on terminology and practice of psychophysical DNIC testing. *Eur J Pain* 2010;14(4):339. doi: 10.1016/j.ejpain.2010.02.004 [published Online First: 2010/03/17]

97. Kennedy DL, Kemp HI, Ridout D, et al. Reliability of conditioned pain modulation: a systematic review. *Pain* 2016;157(11):2410-19. doi: 10.1097/j.pain.0000000000000689 [published Online First: 2016/10/19]
98. Parkitny L, McAuley JH, Walton D, et al. Rasch analysis supports the use of the depression, anxiety, and stress scales to measure mood in groups but not in individuals with chronic low back pain. *J Clin Epidemiol* 2012;65(2):189-98. doi: 10.1016/j.jclinepi.2011.05.010 [published Online First: 2011/09/06]
99. Osman A, Barrios FX, Gutierrez PM, et al. The Pain Catastrophizing Scale: further psychometric evaluation with adult samples. *J Behav Med* 2000;23(4):351-65. doi: 10.1023/a:1005548801037 [published Online First: 2000/09/14]
100. Wertli MM, Eugster R, Held U, et al. Catastrophizing-a prognostic factor for outcome in patients with low back pain: a systematic review. *Spine J* 2014;14(11):2639-57. doi: 10.1016/j.spinee.2014.03.003 [published Online First: 2014/03/13]
101. Roelofs J, Peters ML, McCracken L, et al. The pain vigilance and awareness questionnaire (PVAQ): further psychometric evaluation in fibromyalgia and other chronic pain syndromes. *Pain* 2003;101(3):299-306. doi: 10.1016/s0304-3959(02)00338-x [published Online First: 2003/02/14]
102. Price DD, McGrath PA, Rafii A, et al. The validation of visual analogue scales as ratio scale measures for chronic and experimental pain. *Pain (Amsterdam)* 1983;17(1):45-56. doi: 10.1016/0304-3959(83)90126-4
103. Price DD, Bush FM, Long S, et al. A comparison of pain measurement characteristics of mechanical visual analogue and simple numerical rating scales. *Pain* 1994;56(2):217-26.
104. Deyo RA, Battie M, Beurskens AJHM, et al. Outcome measures for low back pain research : A proposal for standardized use. *Spine (Philadelphia, PA 1976)* 1998;23(18):2003-13. doi: 10.1097/00007632-199809150-00018
105. Dunn KM, Croft PR. Classification of low back pain in primary care : Using bothersomeness to identify the most severe cases. *Spine (Philadelphia, Pa 1976)* 2005;30(16):1887-92. doi: 10.1097/01.brs.0000173900.46863.02
106. Kamper SJ, Maher CG, Mackay G. Global rating of change scales: a review of strengths and weaknesses and considerations for design. *Journal of Manual & Manipulative Therapy* 2009;17(3):163-70.
107. Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res* 2011;20(10):1727-36. doi: 10.1007/s11136-011-9903-x [published Online First: 2011/04/12]
108. Topp CW, Østergaard SD, Søndergaard S, et al. The WHO-5 Well-Being Index: a systematic review of the literature. *Psychother Psychosom* 2015;84(3):167-76. doi: 10.1159/000376585 [published Online First: 2015/04/04]
109. Pascual-Marqui RD. Standardized low-resolution brain electromagnetic tomography (sLORETA): technical details. *Methods Find Exp Clin Pharmacol* 2002;24 Suppl D:5-12. [published Online First: 2003/02/11]
110. Nichols TE, Holmes AP. Nonparametric permutation tests for functional neuroimaging: a primer with examples. *Human brain mapping* 2002;15(1):1-25.
111. Pascual-Marqui RD. Discrete, 3D distributed, linear imaging methods of electric neuronal activity. Part 1: exact, zero error localization. *arXiv preprint arXiv:07103341* 2007
112. Braun V, Clarke V. Using thematic analysis in psychology. *Qualitative research in psychology* 2006;3(2):77-101.
113. Thomas DR. A general inductive approach for analyzing qualitative evaluation data. *American journal of evaluation* 2006;27(2):237-46.
114. Eldridge SM, Lancaster GA, Campbell MJ, et al. Defining feasibility and pilot studies in preparation for randomised controlled trials: development of a conceptual framework. *PloS one* 2016;11(3):e0150205.

FIGURE LEGEND

Figure 1. Study design and timelines

EEG: Electroencephalography, HD-tIPNS: high definition transcranial infraslow pink noise stimulation, pgACC: pregenual anterior cingulate cortex, dACC: dorsal anterior cingulate cortex, SSC: primary somatosensory cortex.

Figure 2. The transcranial electrical stimulation set-up

Figure 3. Electrode positions and targeted brain regions

This figure presents results of the optimization that was created using the Stimweaver software by the Neuroelectrics company for targeting the activity of pgACC, dACC, and SSC.81, 82 From Left to right: Normal component of the E-field En (V/m), target E-field (V /m), target weight and ERNI* (mV 2/m2) for grey matter. The optimal montage consists of 8-channels that will be placed on the scalp following the international 10-20 EEG system.

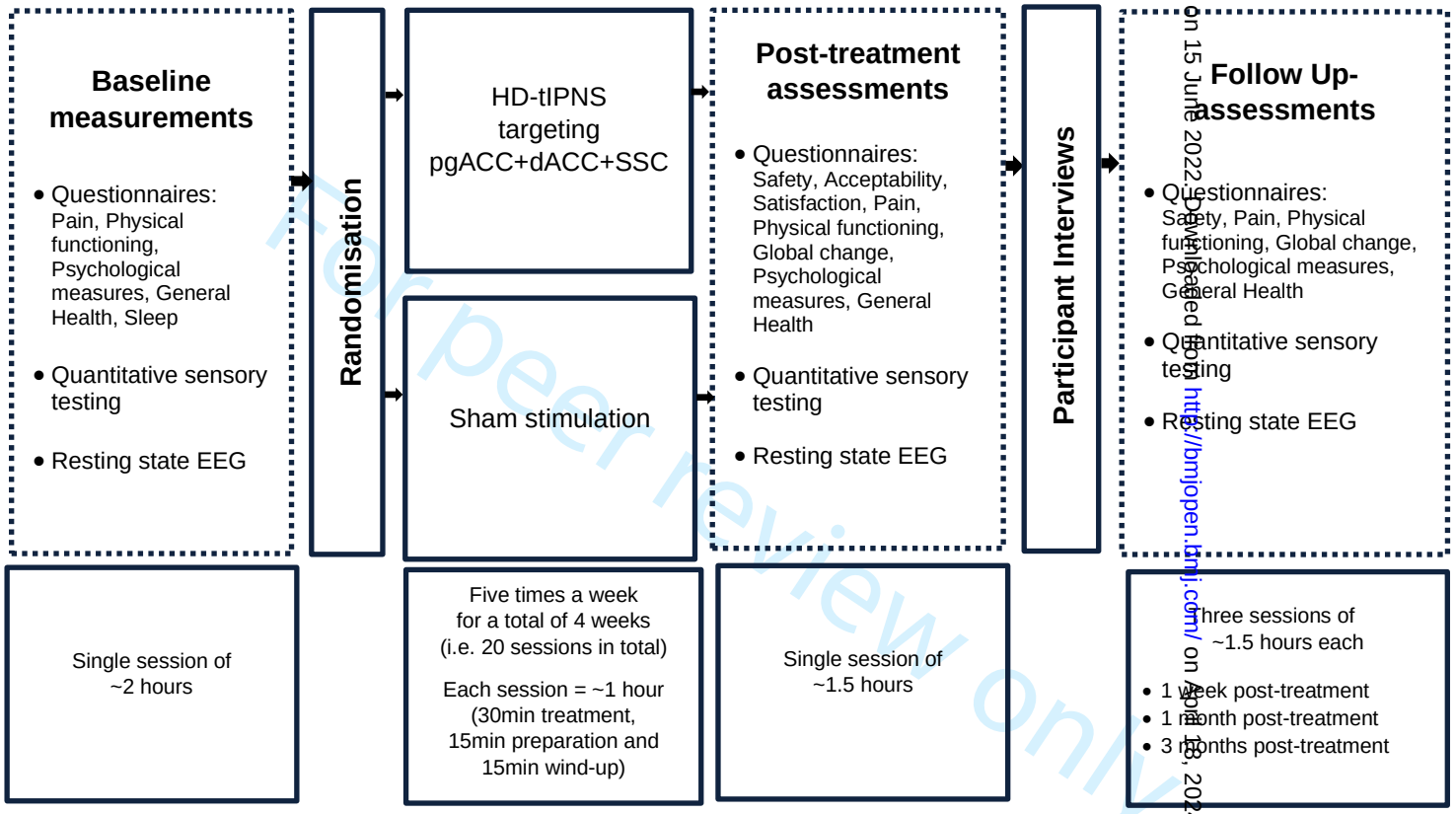


Figure 2. The transcranial electrical stimulation set-up

191x70mm (118 x 118 DPI)

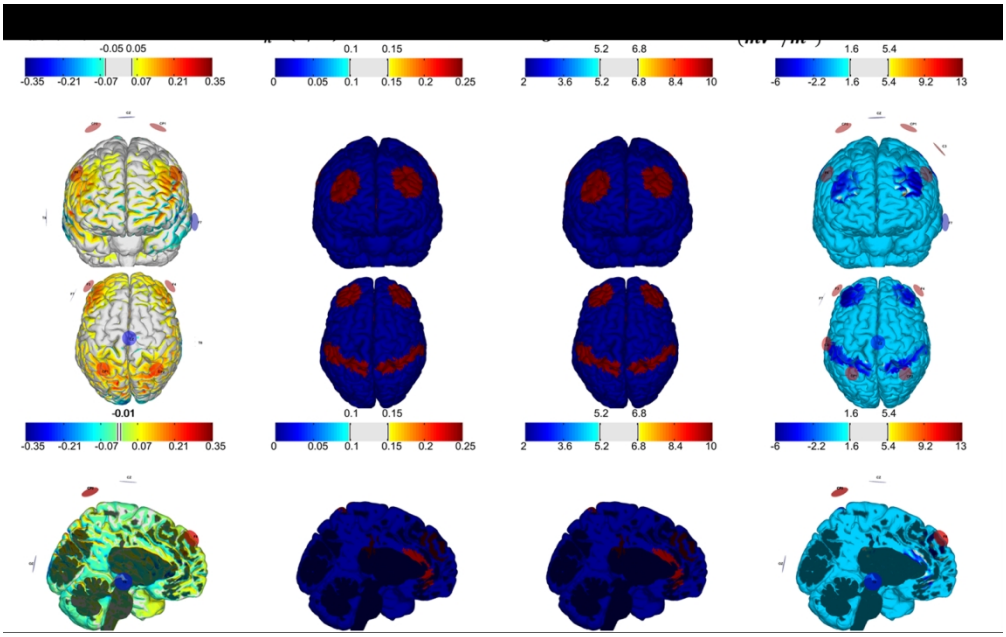


Figure 3. Electrode positions and targeted brain regions
This figure presents results of the optimization that was created using the Stimweaver software by the Neuroelectrics company for targeting the activity of pgACC, dACC, and SSC.113, 114 From Left to right: Normal component of the E-field En (V/m), target E-field (V /m), target weight and ERNI* (mV 2/m2) for grey matter. The optimal montage consists of 8-channels that will be placed on the scalp following the international 10-20 EEG system.

339x213mm (118 x 118 DPI)

Participant Information Sheet

Study title: Brain stimulation for chronic low back pain.

Locality: Dunedin School of Medicine, University of Otago, New Zealand.

Ethics committee ref.: 20/NTB/67

Lead investigator(s): Dr. Divya Adhia & Prof. Dirk De Ridder

Contact phone number: 03 470 9337

You are invited to take part in a study evaluating the safety and exploring the effect of a brain stimulation technique for improving pain and function in individuals with chronic low back pain. Whether or not you take part is your choice. If you don't want to take part, you don't have to give a reason, and it won't affect the care you receive. If you do want to take part now, but change your mind later, you can pull out of the study at any time.

This Participant Information Sheet will help you decide if you would like to take part. It sets out why we are doing the study, what your participation would involve, what the benefits and risks to you might be, and what would happen after the study ends. We will go through this information with you and answer any questions you may have. You do not have to decide today whether or not you will participate in this study. Before you decide, you may want to talk about the study with other people, such as family, whānau, friends, or healthcare providers. Feel free to do this.

If you agree to take part in this study, you will be asked to sign the Consent Form on the last page of this document. You will be given a copy of both the Participant Information Sheet and the Consent Form to keep.

This document is 9 pages long, including the Consent Form. Please make sure you have read and understood all the pages.

WHAT IS THE PURPOSE OF THE STUDY?

The purpose of this study is to evaluate the safety and to explore the effect of a brain stimulation technique on pain and function in individuals with a diagnosis of chronic low back pain. This study will involve stimulating the activity in the brain regions that have been demonstrated to be altered in individuals with chronic low back pain. The results obtained from this study will help us to develop new treatments for improving pain and function in individuals with chronic low back pain.

WHO ARE WE SEEKING TO PARTICIPATE IN THE PROJECT?

We are seeking approximately 40 adults (aged 18-75 years) with a clinical diagnosis of chronic low back pain, and with significant pain (present daily) and functional difficulties for a minimum duration of three months.

You are not eligible to participate if you have any of the following:

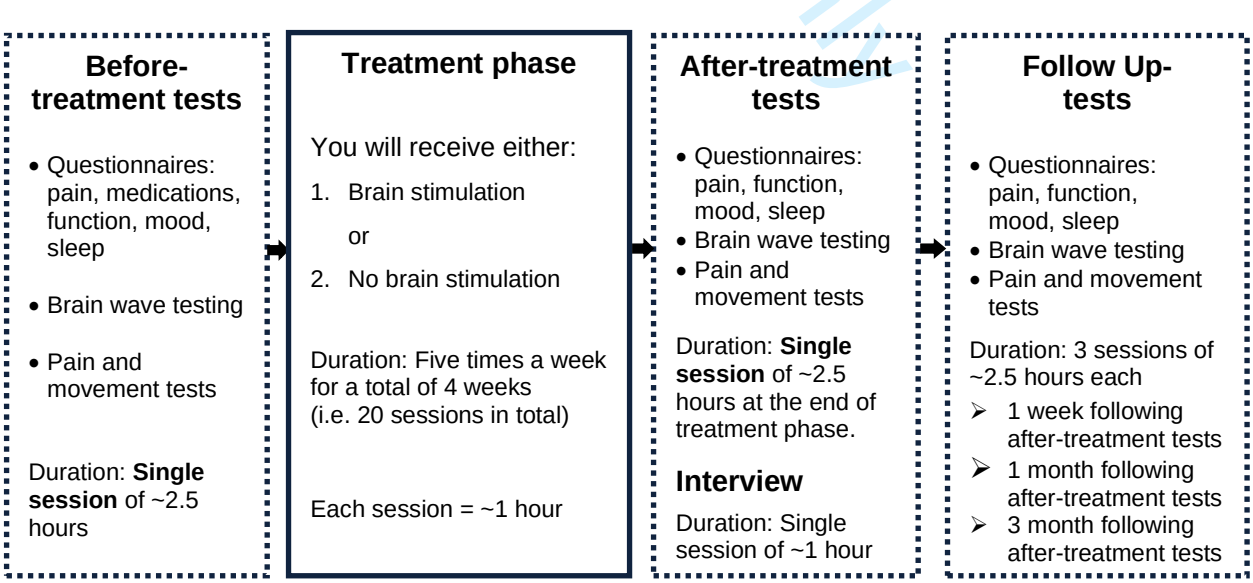
- Inflammatory arthritis (e.g. Rheumatoid arthritis, Fibromyalgia, Gout)
- Undergoing any therapy from a health professional (e.g. physiotherapist or chiropractor)
- Recent soft tissue injuries (e.g. muscle sprain) of the back in the last 3 months
- Recent steroid injections to your low back (in the past 6 months)
- History of surgery to the back region, radicular pain or radiculopathy (e.g. Sciatica, pain going down the leg with numbness and weakness of the leg, nerve compression)
- Waiting/scheduled for any procedures (e.g. surgery or steroid injection) within the next six months
- Currently taking steroid medications, antidepressants, anti-epileptics, or neuropathic pain drugs (e.g. Amitriptyline, Gabapentin, or Duloxetine)
- History of neurological conditions (e.g. Stroke, Multiple sclerosis, Spinal cord or peripheral nerve injuries or neuropathy) or vascular (i.e. blood vessel) problems
- Cognitive impairments (dementia, Alzheimer's disease)
- Unstable medical or psychiatric conditions, dyslipidaemia, uncontrolled/untreated hypertension, history of epilepsy or seizures, or alcohol or substance abuse
- Presence of electronic implants or metal implant in the body (particularly head and neck)
- Recent or current pregnancy (i.e. in the last 6 months)

You will be screened by the study investigator for your eligibility to participate in this study. You will be allowed to continue your pain medications for the duration of the trial, but the type and dosage and any change in the medications will be recorded throughout the duration of the trial.

You will also be asked to provide contact details of your GP or other current provider. We will contact your GP, or other current provider, to determine your eligibility for participation in the study, to notify them of your participation in the study, and to inform them if any incidental findings are recorded during assessments.

WHAT WILL MY PARTICIPATION IN THE STUDY INVOLVE?

As shown in Picture 1, you will be required to attend the following four study phases: Before-treatment tests, Treatment phase, After-treatment tests and Interview, Follow-up tests



Picture 1. Study phases and time-commitment for each phase

Before-treatment tests: will take ~2.5 hours at the Dunedin hospital. The following tests will be conducted after obtaining written informed consent.

- **Questionnaires:** You will be asked to complete questionnaires about yourself (age, gender, education, ethnicity, well-being), and your pain (location, nature, intensity, type) and how much pain affects your functional activities, quality of life and well-being, psychological states (e.g., mood, mindfulness, emotional regulation), current medication history (including pain relief), the presence of other health issues if any (e.g. diabetes), and sleep. You will also be asked about your thoughts associated with pain.

- **Brain wave testing:** After completing the questionnaires, you will be asked to wear a cap with electrodes attached to it (see Picture 2). According to Māori culture, the head is considered sacred *"he tapu te upoko"* and the brain is regarded as the *wairua* (soul). The researcher will obtain permission from you before touching your head. You will rest in a comfortable chair with your eyes closed for 10 minutes and your brain activity will be recorded. Following this, your brain will also be recorded for additional 2 minutes, while a researcher applies repeated light touches to your back region using a thin and blunted nylon filament. An electrode will also be placed on your chest to record your heart activity.

Picture 2. Brain wave testing cap with electrodes

- **Movement testing:** You will be asked to perform forward and backward bending movements repeatedly for 20 times. For the forward bending test, you will be asked to pick up a pencil placed on the floor and then place it back to the floor again repetitively. For the backward bending test, you will be asked to see a mark placed on the ceiling behind you repetitively. You can stop performing the repetitions of movements if your pain gets worse. You will also be asked to rate your intensity of pain on a 0-100 point scale, where 0 = No pain and 100 = Worst imaginable pain, at the start of the test and following every 5 repetitions.

- **Pain sensation testing:** Following brain wave testing, simple test procedures recording your perception of pain sensation will be tested over your low back regions and the wrist region (i.e. a non-painful body part for comparison purposes). The following test procedures will be administered.

  - **Repeated light touches** with a thin and blunted nylon filament - You will be asked to tell us whether you are feeling a sensation of touch or of pain. If you feel pain on repeated contacts, you will be asked to rate your intensity of pain on a 0-100 point scale, where 0 = No pain and 100 = Worst imaginable pain.

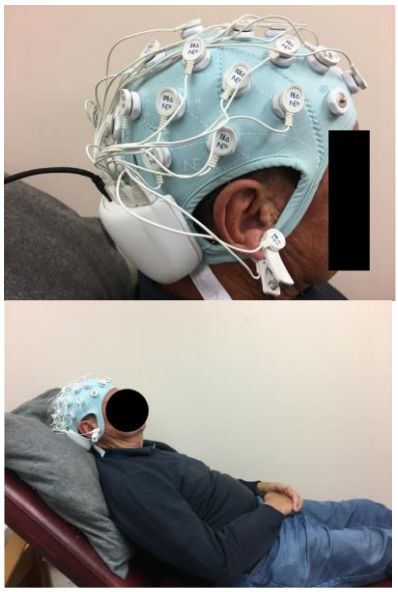
  - **Pressure to pain sensation testing** - Pressure will be gradually applied using a rubber-tipped pressure device. You will be asked to indicate immediately when the pressure sensation changes to discomfort or when you first feel pain. This procedure will be carried out when you are resting, as well as immediately following 2 minutes of hand immersion in a cold-water bath maintained at ~5^{o}C.

Treatment phase:

- **Randomisation:** Following the before-treatment tests, you will be randomly assigned to receive one of the two treatment conditions as below:
  - Brain stimulation, or
  - No brain stimulation

  You will have equal chances of being assigned to one of the two treatment groups, and you cannot change group.

- **Treatment sessions:** You will be required to attend a total of **twenty** treatment sessions (1-hour each, five sessions per week, for four consecutive weeks), at the Dunedin School of Medicine laboratory (Room 626, 6th floor Dunedin Hospital, 201 Great King Street). At each session, your scalp will be cleaned with alcohol wipes and you will have to wear a cap with electrodes attached to it on your head (see Picture 3). The researcher will ask permission before touching your head at each session. The researcher will apply electrode gel to your scalp to capture better signal quality. During this time, you will be asked to fill in some questionnaires about any side effects that you might have perceived from the previous sessions. Following the setup, you will receive treatment for 30min at each session, while you rest (see Picture 3). You will be asked to close your eyes and relax for 30min without falling asleep. You will be asked to report any sensations (e.g. itching, tingling) that you feel during treatment and rate the intensity of the sensation on a 0-10 point scale, where 0=None & 10=Worst imaginable, at intervals of 5min.



Picture 3. Brain stimulation device and the treatment position

- **Blinding:** You and the researchers conducting the before-treatment tests will not know if you are receiving neurofeedback treatment or not, i.e., you will be blinded to the treatment you receive. This blinding will help us to find out whether any changes in the pain and function tests are due to the brain stimulation treatment itself.

After-treatment tests: will take ~2.5 hours at the Dunedin hospital and will be done after the final treatment session is completed. The same tests that were done before the treatment sessions will be repeated.

Interview: After completion of the after-treatment tests, you will be invited to take part in an interview about your experiences with the brain stimulation treatment. The interview will use open-ended questions. You will be able to talk freely. You can refuse to answer any particular question(s) if you wish. The interview will be recorded with audio-recorders. The recording will be written out word for word. You can comment on your written-out interview if you wish. After completion of the written-out interview, the audio recording will be deleted.

Follow-up tests: You will be required to attend three test sessions of ~2.5 hours at the Dunedin hospital, 1 week, 1 month and 3 months following the after-treatment tests. The same tests that were done before the treatment sessions will be repeated.

WHAT I CAN AND CANNOT DO DURING THE STUDY PHASES?

As electrical activity of the brain can be affected by various factors, we request that you ***avoid***:

- Eating large meals for 2 hours before the session (Light snacking is OK)
- Drinking alcohol for 24 hours before the session
- Smoking for 4 hours before the session
- Consuming caffeinated drinks for 1 hour before the session
- Applying any hair products (oil, gel) before the session

You will be provided with some refreshments (e.g. crackers, tea, or juice) after each session.

WHAT ARE THE POSSIBLE BENEFITS AND RISKS OF THIS STUDY?

Previous studies show that this type of brain stimulation is a safe procedure. The common side-effects reported by previous studies include headache, fatigue, nausea, mild tingling sensation, or itching under the stimulation electrodes. Most side effects are mild and disappear soon after the stimulation.

Other minimal risks include the onset of seizures. In the unlikely event that this occurs, the treatment will be stopped immediately. We have previously tested the same stimulation design in healthy people and it was safe, with **no** reported case of seizures.

For pain sensation testing, we do not anticipate any form of discomfort that would last following the test procedures. You may feel mild pain, tingling, or pins and needles sensation in your hand during or immediately following immersion in a cold-water bath. These ranges of sensations should usually disappear quickly following the testing. A slight reddening of the skin may stay following the pressure to pain sensation testing, and it should go within hours of testing.

Some of the psychological questionnaires might cause distress, in which case your GP or current health provider will be notified and you will be referred to a psychologist if needed.

Other risks include that there may be no benefits and the brain stimulation treatment may not improve your pain or functional levels, or any initial improvements may wear off.

You will be closely monitored for your responses during all the testing procedures, and sufficient rest will be provided between each testing procedure. Any side effects of the treatment will be formally recorded and addressed if medical attention is required.

WHO PAYS FOR THE STUDY?

This study is partly funded by the Healthcare Otago Charitable trust, Health Research Council, and the Neurological Foundation of New Zealand.

There will be no costs to you for participating in the study. You will receive in total $350 petrol vouchers as a reimbursement for your travel and parking expenses. We will give you $250 petrol vouchers after completion of your after-treatment tests and the rest $100 at the last follow-up test (i.e. 3 months following after-treatment tests). In addition a $50 grocery voucher will be provided as a koha at the last follow-up test.

WHAT IF SOMETHING GOES WRONG?

If you were injured in this study, you would be eligible **to apply** for compensation from ACC just as you would be if you were injured in an accident at work or at home. This does not mean that your claim will automatically be accepted. You will have to lodge a claim with ACC, which may take some time to assess. If your claim is accepted, you will receive funding to assist in your recovery.

If you have private health or life insurance, you may wish to check with your insurer that taking part in this study won't affect your cover.

WHAT ARE MY RIGHTS?

- Your participation in this study is voluntary.
- You may withdraw from this project at any time and without any disadvantage to you of any kind. Besides, the study staff may decide to withdraw you from the study if there are any side effects from the treatment or if they have any other concerns.
- You have the right to access the information collected about you as part of the study.
- You will have full rights to correct or withdraw the information until the research is completed or until we begin to analyse the data.
- We will inform you if any new information becomes available during the study that may impact your health.

WHAT HAPPENS AFTER THE STUDY OR IF I CHANGE MY MIND?

As outlined above, we will collect various measures (e.g., pain, function, mood, response to pain testing, brain activity) by way of questionnaires, assessments, and interview. The study data will be securely stored in a locked filing cabinet or electronically with password protection, such that only those involved in the research program will have access to it. Personal information such as contact details and names will be destroyed at the end of the project. However, as required by the University's research policy, any raw data on which the results of the project depend will be kept in secure storage for ten years, after which it will be destroyed.

The study results will be published in an international scientific journal. Only a summary of the data will be mentioned in the research publication. The data included in the publication will in no way be linked to any specific person, and your identity will not be recorded with the data. Only study personnel will have access to any personal information. At the testing session, you will be given a unique identification code, and your data will be linked to that code only. You are most welcome to request a copy of the study results. These will be available once all the data is analysed, approximately 2 years following the commencement of the study, nominally in the first quarter of 2022.

The data collected from this study may be useful for future research. Any new study would have to get ethical approval.

WHO DO I CONTACT FOR MORE INFORMATION OR IF I HAVE CONCERNS?

If you have any questions, concerns, or complaints about the study at any stage, you can contact:

Name: Dr. Divya Adhia **Position**: Research Fellow **Department:** Department of Surgical Sciences, University of Otago, Dunedin.	**Phone number:** 03 470 9337 **Email**: divya.adhia@otago.ac.nz
Name: Professor Dirk De Ridder **Position**: Chair, Neurosurgery **Department:** Department of Surgical Sciences, University of Otago, Dunedin.	**Phone number:** 03 470 9337 **Email**: dirk.deridder@otago.ac.nz
Name: Dr Ramakrishnan Mani **Position:** Senior Lecturer **Department:** Centre for Health, Activity and Rehabilitation Research, School of Physiotherapy, University of Otago, Dunedin	**Phone number:** 03 479 3485 **Email:** ramakrishnan.mani@otago.ac.nz
Name: Professor John Reynolds **Position**: Associate Director, Brain Research NZ Centre of Research Excellence. **Department:** Department of Anatomy, University of Otago, Dunedin.	**Phone number:** 03 479 5781 **Email**: john.reynolds@otago.ac.nz
Name: Professor Paul Glue **Position**: Study Psychologist **Department:** Department of Psychological Medicine, University of Otago, Dunedin.	**Phone number:** 03 470 9430 **Email**: paul.glue@otago.ac.nz

If you want to talk to someone who isn't involved with the study, you can contact an independent health and disability advocate on:

Phone: 0800 555 050
Fax: 0800 2 SUPPORT (0800 2787 7678).
Email: advocacy@advocacy.org.nz
Website: https://www.advocacy.org.nz/

For Māori health support, please contact :

Name, position: Mark Brunton, Kaitakawaenga Rangahau Māori
(Facilitator Research Māori)
Telephone number: 03 479 8738
Email: mark.brunton@otago.ac.nz

You can also contact the health and disability ethics committee (HDEC) that approved this study on:

Phone: 0800 4 ETHICS
Email: hdecs@moh.govt.nz

This project has been reviewed and approved by the Health and Disability Ethics Committee (Ref: 20/NTB/67).

Consent Form

By signing this form, you indicate your consent to the following:

I have read, or have had read to me, and I understand the Participant Information Sheet.		
I have had enough time to think about whether or not to participate in this study.		
I have had a chance to use a legal representative, whanau/ family support, or a friend to help me ask questions and understand the study.		
I am satisfied with the answers I have been given regarding the study, and I have a copy of this consent form and information sheet.		
I understand that taking part in this study is voluntary (my choice) and that I may pull out from the study at any time without this affecting my medical care.		
I consent to the research staff collecting and processing my information, including information about my health.		
I understand the risks associated with the testing and treatment procedures, which are explained in the Participant Information Sheet.		
I understand that my participation in this study is confidential and that no material, which could identify me personally, will be used in any reports on this study.		
I know that I will be given petrol vouchers (*a total value of $350,* in parts) to cover travel expenses associated with study participation.		
I understand the compensation provisions in case of injury during the study.		
I know whom to contact if I have any questions about the study in general.		
I understand my responsibilities as a study participant.		
I agree with my GP or other current provider being informed of my participation in this study.		
I agree for the researchers to contact my GP or other current provider if needed to determine my eligibility for participation in the study, and to be notified if any incidental findings is recorded.		
I understand data collected from me in this study may be used for future research.		
If I decide to withdraw from the study, I agree that the information collected about me up to the point when I withdraw may continue to be processed.	Yes ☐	No ☐
I wish to receive a summary of the results of the study.	Yes ☐	No ☐

Declaration by participant:

I hereby consent to take part in this study.

Participant's name:

Signature: Date:

Emergency contact / Support person:

Please specify a contact person (a friend or a relative), in case of an emergency during the study participation. The contact details will be deleted from the file following completion of the study phases.

Name of a friend or relative:

Contact number:

Declaration by a member of the research team:

I have given a verbal explanation of the research project to the participant, and have answered the participant's questions about it.

I believe that the participant understands the study and has given informed consent to participate.

Researcher's name:

Signature: Date:

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	ItemNo	Description	Check/Details
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	✓ (Main Document, p. 1)
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	✓ (Main Document, p.4, and Table 1)
	2b	All items from the World Health Organization Trial Registration Data Set	✓ (Table 1)
Protocol version	3	Date and version identifier	✓ (Table 1)
Funding	4	Sources and types of financial, material, and other support	✓ (Table 1)
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	✓ (Main Document, p. 1)
	5b	Name and contact information for the trial sponsor	✓ (Table 1)
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	None.

	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	✓ (Main Document, p. 24)
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	✓ (Main Document, p. 5-7)
	6b	Explanation for choice of comparators	✓ (Main Document, p. 5-6)
Objectives	7	Specific objectives or hypotheses	✓ (Main Document, p. 7)
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	✓ (Main Document, p. 8, and Fig. 1)
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	✓ (Main Document, p. 9)
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	✓ (Main Document, p. 9-10)
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	✓ (Main Document, p. 11-13, Table 2, Fig.2 and Fig 3)

		11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	✓ (Main Document, p. 23-24)
		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	✓ (Main Document, p. 13)
		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	✓ (Main Document, p. 13)
	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	✓ (Main Document, p. 13-20, Table 3)
	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	✓ (Fig. 1)
	Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	✓ (Main Document, p. 10)
	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	✓ (Main Document, p. 10-11)
Methods: Assignment of interventions (for controlled trials)				
Allocation:				

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	✓ (Main Document, p. 8-9)
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	✓ (Main Document, p. 8-9)
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	✓ (Main Document, p. 8-9)
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	✓ (Main Document, p. 8-9)
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	✓ (Main Document, p. 8-9)
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	✓ (Main Document, p. 13-20, Table 3)

		18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	✓ (Main Document, p. 13-20, Table 3)
	Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	✓ (Main Document, p. 13-20, 23-24)
	Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	✓ (Main Document, p. 20)
		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	✓ (Main Document, p. 20)
		20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	✓ (Main Document, p. 20-21)
	Methods: Monitoring			
	Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	✓ (Main Document, p.24)
		21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	✓ (Main Document, p. 23-24)

Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	✓ (Main Document, p. 23-24)
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	✓ (Main Document, p. 23-24)
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	✓ (Main Document, p. 23-24)
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	✓ (Main document, p. 23-24)
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	✓ (Main document, p. 15)
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Not applicable.
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	✓ (Main document, p. 23-24)
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	✓ (Main document, p. 24)

Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	✓ (Main document, p. 23-24)
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	None.
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	✓ (Main Document, p. 24)
	31b	Authorship eligibility guidelines and any intended use of professional writers	✓
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	✓ (Included in registry)
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	✓ (Approved by Ethics Committee)
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Not applicable.

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.