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High-definition transcranial infraslow pink noise stimulation for chronic low back pain: protocol for a pilot, safety and feasibility randomised 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 (1) evaluate feasibility, safety and acceptability of a novel neuromodulation technique, high-definition transcranial infraslow pink noise stimulation (HD-tIPNS), in people with CLBP, (2) explore the trend of effect of HD-tIPNS on pain and function, and (3) derive treatment estimates to support sample size calculation for a fully powered trial should trends of effectiveness be present.

Methods and analysis A pilot, triple-blinded randomised two-arm placebo-controlled parallel trial. Participants (n=40) with CLBP will be randomised 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 postintervention, and at 1-week, 1-month and 3 months postintervention. All data will be analysed descriptively. A nested qualitative study will assess participants perceptions about acceptability of intervention and analysed 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.

Trial registration number ACTRN12620000505909p.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study will use a novel neuromodulation technique (high-definition transcranial infraslow pink noise stimulation) to simultaneously 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) randomised 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 (ie, painfulness) and the emotional components (eg, 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 (eg, 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] (eg, 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 focalised 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, reorganises neurons and improves the electrical connectivity of the brain-wide functional networks.[48–51] The infraslow frequency plays a profound role in modulating and synchronising 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-organisation 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 normalise 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 randomised controlled trial. The specific aims are to (1) evaluate the feasibility, safety and acceptability of the HD-tIPNS technique in people with CLBP, (2) explore the trend of effect of HD-tIPNS on pain and function, and (3) 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 statement,[60] the template for intervention description and replication 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 randomised placebo-controlled parallel trial with two intervention arms. The outcome measures will be collected at baseline, immediately postintervention, and at follow-up periods: 1-week, 1-month and 3 months postintervention (figure 1).

Randomisation

A research administrator, not involved in other procedures, will randomise participants on a 1:1 basis using a computerised open-access randomisation software programme to:

- Group 1: HD-tIPNS.
- Group 2: Sham stimulation.

The randomisation 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 programmes 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

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

Item	Information
Primary registry and trial identifying no	Australian and New Zealand Clinical Trials Registry-ACTRN 12620000505909
Date of registration in primary registry	23 April 2020
Universal trial no	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	1 June 2021 (Note: Delayed from the planned enrolment date of 15 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, 40 participants (20 per group) will be enough to determine feasibility measures for a fully powered trial.
Recruitment status	Recruiting (recruitment period: June 2021 to May 2022)
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. Well-being: European quality of life-five dimensions, WHO-five well-being index. Resting-state electroencephalogram: current density and functional connectivity.
Ethical review	Status: Approved, Date of Approval: 28 July 2020; Committee: Health and Disability Ethics Committee (HDEC, Ref: 20/NTB/67)

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 (NRS) (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 and 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 4 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.[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 (eg, 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 6 months, current intake of any centrally-acting medications or intention of taking new medications in the next 3 months, steroid injections to the back in past 6 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, dyslipidaemia, cognitive impairments (dementia, post-traumatic stress disorders, Alzheimer's disease; assessed as a score of <24 on the Mini-Mental State 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.

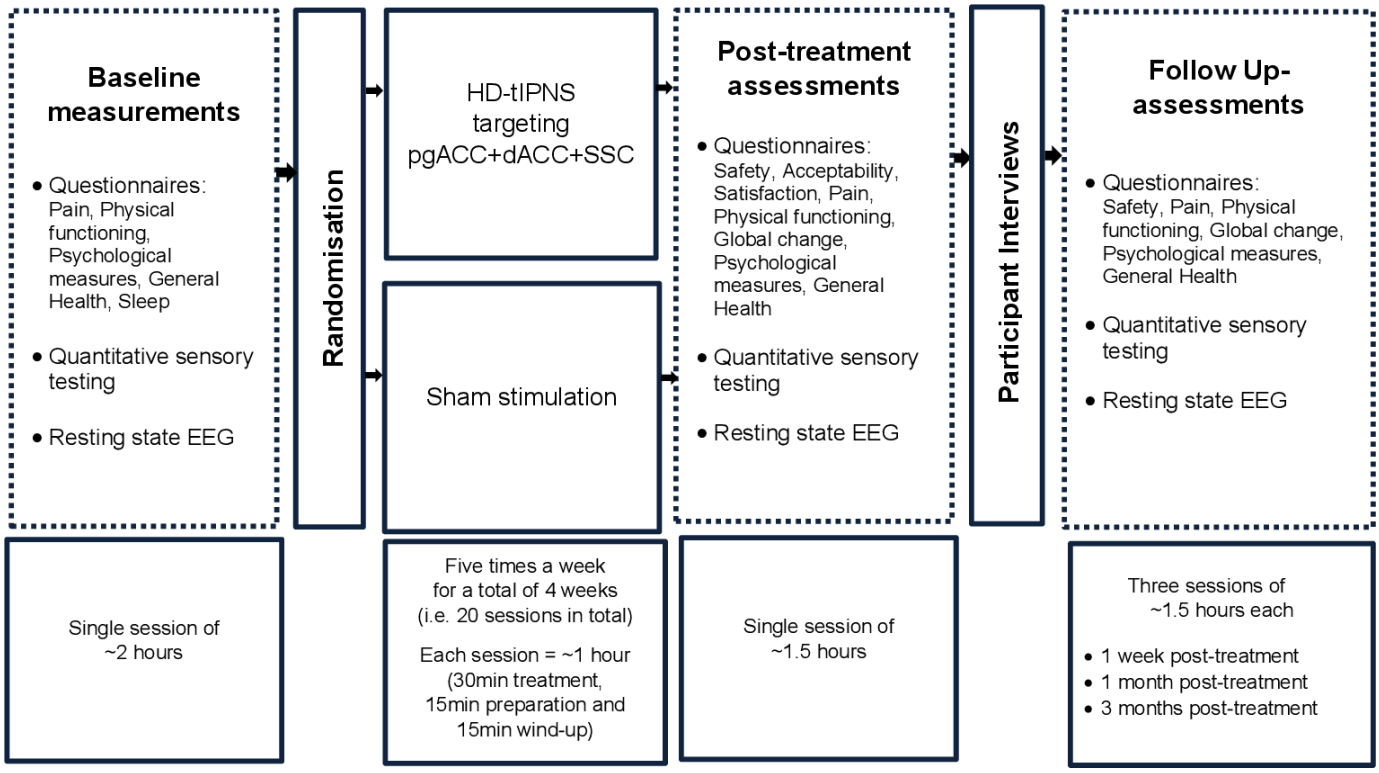

Figure 1 Study design and timelines. dACC, dorsal anterior cingulate cortex; EEG, electroencephalography; HD-tIPNS, high-definition transcranial infraslow pink noise stimulation; pgACC, pregenual anterior cingulate cortex; SSC, primary somatosensory cortex.

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 (eg, newspapers and social media). Participants attending healthcare providers will also be invited to participate. The total recruitment period will be 1 year (June 2021 to May 2022). Advertisements will be placed in the local newspapers twice a month and social media once a month (Sponsored Facebook ad, for 1 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 2 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 (online supplemental 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 Sensitisation Inventory),[71 72] neuropathic pain quality (PainDETECT),[73] pain personification,[74] and treatment expectancy and credibility.[75]

Intervention procedures

The intervention will be administered five times a week (30 min/session) for 4 weeks by an assistant research fellow trained by the primary investigator experienced in neuromodulation techniques. A battery-driven wireless TES (Starstim-Home TES, Neuroelectrics, Spain) will be used to deliver stimulation while participants are comfortably and quietly seated (figure 2). The HD technique uses arrays of multiple small electrodes whose configuration can be optimised for focally targeting specific brain regions.[58 59 76–80] Eight small

Figure 2 The transcranial electrical stimulation set-up.

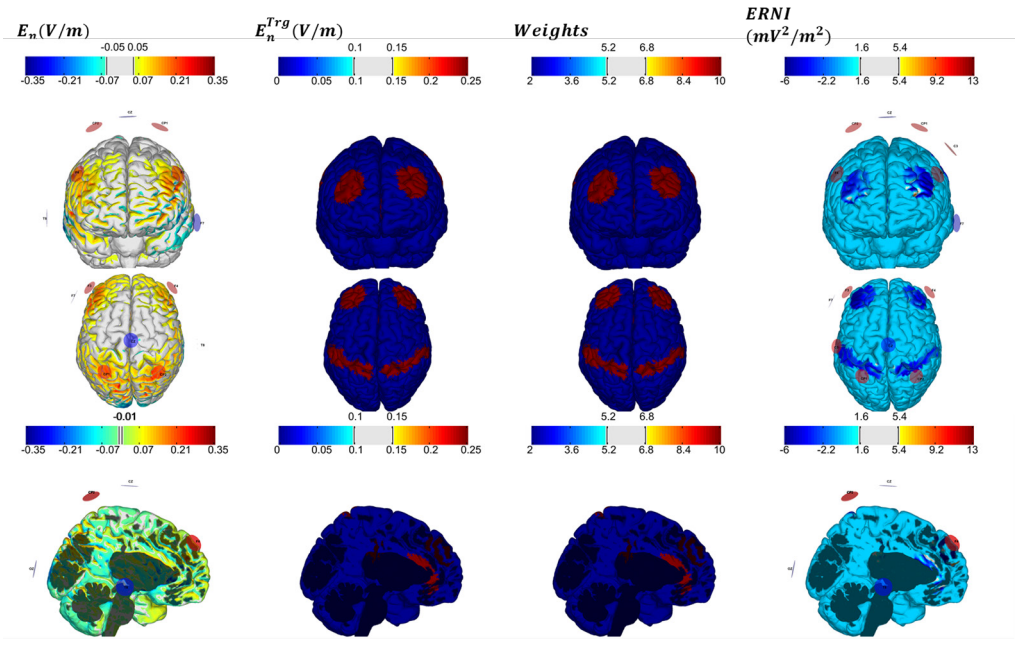

Figure 3 Electrode positions and targeted brain regions. This figure presents results of the optimisation thatwas created using the Stimweaver software by the Neuroelectrics company for targeting the activity of pgACC, dACC and SSC.[81 82] From left to right: Normal component of the E-field En (V/m), target E-field (V /m), target weight and ERNI (mV 2/m2) for grey matter. The optimal montage consists of eight channels that will be placed on the scalp following the international 10-20 EEG system. dACC, dorsal anterior cingulate cortex; EEG, electroencephalography; ERNI, Error Relative to No Intervention; pgACC, pregenual anterior cingulate cortex; SSC, primary somatosensory cortex.

electrodes (~4 cm^2) will be placed on a neoprene head cap following the International 10–20 electroencephalogram (EEG) system to simultaneously target pgACC, dACC and SSC (figures 2 and 3) (table 2).[81 82]

For HD-tIPNS group, the stimulation will be delivered at a current strength of a maximum of 2mA for 30 min, with 60 s 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 (0.1 Hz 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 60 s ramp up and 60 s 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 localisation. 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 standardised 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 3 months will be excluded.

Outcome measures

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

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

Item no and Item	Description
1.Brief name	HD-tIPNS
2.Why	The HD technique uses arrays of multiple small electrodes whose configuration can be optimised 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, reorganises neurons and improves the electrical connectivity of the brain-wide functional networks.[48–51] Optimising the infraslow frequency can normalise 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-organisation of the brain, thus can be more effective than standard tDCS electrical parameters.[58 59] We, therefore, hypothesise that specifically and simultaneously targeting the fundamental infraslow activity at the key nodes of pain processing networks, using a novel HD-tIPNS technique, could normalise 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 (figures 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 min.
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 programmes in the NIC2 (neuroelectrics software), to allow blinding of the treating researcher (R2). The programme 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 randomised group) for a total of 20 sessions, five times a week for four consecutive weeks. Each stimulation session will last for 30 min 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 0.6 mA superimposed on the infraslow (0.1 Hz sinusoidal) waveform of a current intensity of 1 mA.
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 will be recorded and expressed as a percentage of the total no 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.

ACC, anterior cingulate cortex; CLBP, chronic low back pain; dACC, dorsal region of ACC; EEG, electroencephalogram; HD-tIPNS, high-definition transcranial infraslow pink noise stimulation; pgACC, pregenual region ACC; SSC, somatosensory cortex; tDCS, transcranial direct current stimulation; TES, transcranial electrical stimulation.

Primary outcomes

Feasibility measures

- Recruitment rate, the number of participants recruited per month. Participants will be recruited over 1 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 well 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[87] will be used to record worsening or improving side effects compared with 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 (BPI),[88] a standardised, validated questionnaire for CLBP.

Physical function

Roland-Morris Disability Questionnaire[67 68] will be used to assess self-reported functional abilities.

Secondary outcomes

Measures of peripheral and central sensitisation

Quantitative sensory testing will be conducted and reported in accordance with the guidelines[89 90] and our previous study (table 3).[91]

- Mechanical temporal summation (MTS): will be assessed using a nylon monofilament (Semmes monofilament 6.65, 300 g). Brief 10 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 (ie, symptomatic low back and non-dominant wrist) in random order. The location of these areas will be recorded using bony

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.	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 average pain in the past 24 hours	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 a 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	WHO-Five Well-Being Index	T_B, T_{im}, T_{1wk}, T_{1m}, T_{3m}

NRS, Numeric Rating Scale; T_B, at baseline; T_{im}, immediately postintervention; T_{1m}, 1-month postintervention; T_{3m}, 3 months postintervention; T_{1wk}, 1-week postintervention.

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 10 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 computerised, 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 familiarisation 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 30 kPa/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 1000 kPa for safety reasons, the procedure would be terminated, and a score of 1000 kpa 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 15–20 min 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 min. 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 min 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 15 s interval. A similar conditioning stimulus protocol has been used in previous studies showing a significant CPM effect.[97]
  - Test stimulus: A computerised, 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 familiarisation 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 s immediately after the conditioning stimulus.
  - Calculation of CPM: A per cent change score will be calculated for each time point (ie, CPM30 s, CPM 60 s and CPM 90 s), with a positive score indicating an increase in PPTs (pain40) after the conditioning stimulus and thus the presence of CPM effect.

$$CPMpercentchangescore = \frac{Postscore - Prescore}{Prescore} x100$$

Psychological measures

Will include Depression, Anxiety and Stress Scale,[98] to measure those three psychological constructs, Pain Catastrophising 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'.

Secondary pain measures

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 1 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 with 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 well-being

Will be assessed using European Quality of Life-5 Dimensions scale[107] and WHO-Five Well-Being Index,[108] respectively.

Measures of cortical electrical activity

Resting-state EEG (~10 min, 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 artefacts and manual rejection.

Standardised low-resolution brain electromagnetic tomography (sLORETA) will be used to estimate intracerebral electrical sources that generate scalp-recorded activity in each of the following 10 frequency bands, that is, infraslow (0.01–0.1 Hz), slow (0.2–1.5 Hz), delta (2–3.5 Hz), theta (4–7.5 Hz), alpha1 (8–10 Hz), alpha2 (10.5–12 Hz), beta1 (12.5–18 Hz), beta2 (18.5–21 Hz), beta3 (21.5–30 Hz) and gamma (30.5–44 Hz). The following three analyses will be used to explore the specific (ie, at the targeted cortical regions) and non-specific (ie, 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 prereatment 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 10 mm 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 10 frequency bands as described above.[109–111] Comparisons will be made between pretreatment 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 V.27.0 will be used for all statistical analyses. Descriptive statistics will be used to analyse 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 analysed 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 (eg, for T_{3m}):

$$PercentChangeToBaseline = \frac{T3m - T0}{T0} x100$$

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. Semistructured in-depth interviews will be conducted by a researcher, blinded to treatment allocation, immediately postintervention. 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 audiorecorded 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 randomised placebo-controlled pilot study

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?	

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 programme 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 10 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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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.

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

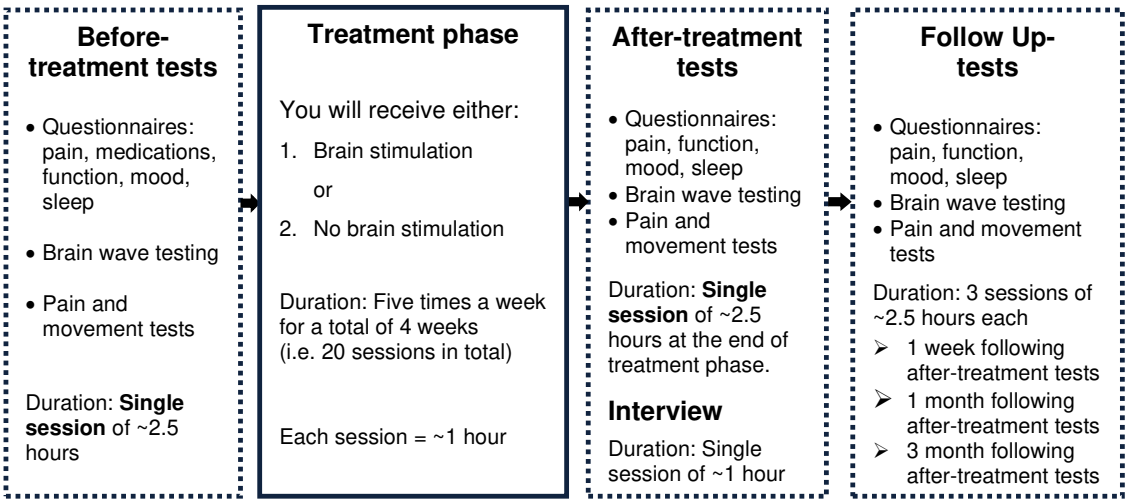
- Inflammatory arthritis (e.g. Rheumatoid arthritis, Fibromyalgia, Gout)
- Undergoing any therapy from a health professional (e.g. physiotherapist or chiropractor)
- Recent soft tissue injuries (e.g. muscle sprain) of the back in the last 3 months
- Recent steroid injections to your low back (in the 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 ~5ºC.

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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.

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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:
