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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

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BMJ Open 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

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ABSTRACT

Introduction Chronic low back pain (LBP) is a common and costly health problem yet current treatments demonstrate at best, small effects. The concurrent application of treatments with synergistic clinical and mechanistic effects may improve outcomes in chronic LBP. This pilot trial aims to (1) determine the feasibility, safety and perceived patient response to a combined transcranial direct current stimulation (tDCS) and sensorimotor retraining intervention in chronic LBP and (2) provide data to support a sample size calculation for a fully powered trial should trends of effectiveness be present.

Methods and analysis A pilot randomised, assessor and participant-blind, sham-controlled trial will be conducted. Eighty participants with chronic LBP will be randomly allocated to receive either (1) active tDCS + sensorimotor retraining or (2) sham tDCS + sensorimotor retraining. tDCS (active or sham) will be applied to the primary motor cortex for 20 min immediately prior to 60 min of supervised sensorimotor retraining twice per week for 10 weeks. Participants in both groups will complete home exercises three times per week. Feasibility, safety, pain, disability and pain system function will be assessed immediately before and after the 10-week intervention. Analysis of feasibility and safety will be performed using descriptive statistics. Statistical analyses will be conducted based on intention-to-treat and per protocol and will be used to determine trends for effectiveness.

Ethics and dissemination Ethical approval has been gained from the institutional human research ethics committee (H10184). Written informed consent will be provided by all participants. Results from this pilot study will be submitted for publication in peer-reviewed journals.

Trial registration number ACTRN12616000624482

INTRODUCTION

Low back pain (LBP) is one of the most common reasons for people to seek healthcare.¹ Of those that report LBP, 44%–78% experience a re-occurrence within 12 months,² and approximately 25% of individuals develop chronic pain.³ Despite high

Strengths and limitations of this study

- A randomised, assessor and participant-blind, sham-controlled trial that will provide the first information on the feasibility and safety of a combined transcranial direct current stimulation and sensorimotor retraining intervention in chronic low back pain.
- This pilot trial is not powered to determine treatment effectiveness. However, if trends of effectiveness are present, these data will support a fully powered trial in future.
- The treating physiotherapist is not blinded to group allocation.

prevalence, current treatments for chronic LBP demonstrate, at best, small effect sizes.^{4,5} One avenue to improve outcomes in chronic LBP is through the application of combined treatments with synergistic clinical and mechanistic effects.

Sensorimotor retraining is a novel treatment that incorporates motor control exercise and lumbar tactile retraining and has been shown to be effective in early randomised controlled trials and case studies of chronic LBP.^{6–9} The mechanism underpinning improvements in pain and function with sensorimotor retraining is thought to involve normalisation of motor and sensory cortical changes and improved pain system function.^{6,9} The addition of a second treatment approach that targets synergistic mechanisms may boost the effectiveness of sensorimotor retraining in people with chronic LBP.

Transcranial direct current stimulation (tDCS), a form of non-invasive brain stimulation, is thought to promote cortical plasticity^{10–12} and improve pain system function through direct effects on the cortex and

thalamus,^{13–19} as well as ‘downstream’ effects on the anterior cingulate cortex and upper brainstem.^{20–21} Studies of healthy individuals and people with some forms of chronic pain suggest that anodal tDCS applied to the primary motor cortex can reduce pain.^{18–22–24} Indeed, a recent systematic review in fibromyalgia demonstrates the effects on pain that are analogous to those of FDA-approved pharmaceuticals with considerably fewer side effects.²⁵ In addition, the cortical effects of tDCS are hypothesised to increase the brain’s receptiveness to other treatments, a phenomenon known as priming.^{26–27} Based on these mechanisms, tDCS may optimise the responsiveness of the brain to sensorimotor retraining as well as target synergistic mechanisms of sensorimotor cortex reorganisation promoted by sensorimotor retraining. The complementary mechanistic targets of these treatments may summate to improve clinical outcomes beyond that which can be achieved with sensorimotor retraining alone. Despite this, no study has examined the effect of a combined tDCS and sensorimotor retraining therapy in chronic pain.^{28–30}

This pilot randomised controlled trial (RCT) protocol will outline study methods and resources required to determine the feasibility, acceptability and safety³¹ of tDCS combined with sensorimotor retraining for people with chronic LBP. This protocol uses a pain and neuroscience mechanisms approach to combine two treatments with the potential to produce complementary and additive effects on sensorimotor cortical organisation and pain system function. The specific aims are to (1) determine the feasibility, safety, perceived patient response to, and acceptability of, a combined tDCS and sensorimotor training intervention in chronic LBP and (2) provide data to support a sample size calculation for a fully powered trial should trends of effectiveness be present.

METHODS AND ANALYSIS

Trial design

We will use a pilot randomised, participant and assessor-blind controlled trial design. The trial will be conducted and reported according to the Consolidated Standards of Reporting Trials (CONSORT) statement for non-pharmacological treatment standards and the Template for Intervention Description and Replication checklist and guide.³² The trial has been prospectively registered with the Australian and New Zealand Clinical Trials Registry (ACTRN12616000624482).

Participants

Participants aged between 18 and 60 years with chronic LBP will be recruited from the Western Sydney suburbs, in New South Wales, Australia. Chronic LBP is defined as pain occurring between the bottom rib and the gluteal fold, which has been present for more than 12 weeks.^{2–4–33} Participants will be required to have an average pain score greater than or equal to 4/10 on a numerical rating scale in the week prior to enrolment³⁴ and a minimum score of 4 points on the Roland Morris Disability Questionnaire

(RMDQ) to limit the potential for floor effects.⁶ Participants will be excluded if they (1) present with specific spinal pathology (tumour, spondylolythsis, fracture, etc), nerve root pain or co-existing major muscular, joint, neurological or psychiatric conditions; (2) have undergone back surgery; (3) are currently undertaking a structured exercise programme for LBP; or (4) present with contraindications to tDCS (eg, cuts or blisters under the electrode sites) or conditioned pain modulation techniques (eg, loss of sensation). Participants can continue to use their normal medication for the duration of the trial. The type of medication and dosage used will be recorded at the baseline assessment.

Recruitment

Participants will be recruited from local healthcare providers (eg, medical practitioners, chiropractors and physiotherapists), support groups, social media and newspaper advertisements. Potential participants will first complete an online screening questionnaire with those who meet the inclusion criteria contacted by the investigators to arrange baseline assessment. Participants will then provide written informed consent on arrival at the baseline assessment. The number of people screened and enrolled in the trial, as well as reasons for ineligibility, will be recorded.

Randomisation

Participants will be individually randomised on a 1:1 basis to the active or control groups in equal numbers. The randomisation schedule will be concealed in consecutively numbered, sealed opaque envelopes. An investigator not involved in recruitment, treatment or assessment will provide the envelope to the treating clinician who will reveal group allocation.

Blinding

Participants, the therapist and the outcome assessor will be blind to group allocation. The tDCS unit used to deliver the direct current stimulation includes a blinded study mode that allows the therapist to enter only a blinded randomisation code to determine whether active or sham stimulation is delivered. Set-up of the randomisation code, and programming of the tDCS unit, will be performed by an investigator not involved in the trial. The success of participant blinding will be assessed at follow-up assessment using a yes/no response to the question, ‘Do you feel you received the real brain stimulation?’ and a 10cm visual analogue scale of the individual’s confidence in that judgement.^{35–36} Participants will also be asked, ‘Why do you believe you received the real/sham brain stimulation?’ and, ‘Was it divulged to you whether you were receiving real brain stimulation or not?’ The success of therapist and assessor blinding will be determined at the completion of the follow-up assessment for each participant using a yes/no response to the question, ‘Did you know the intervention group to



which the participant was assigned before trial completion?' and, 'If you answer "yes", how was it divulged to you?'.³⁵

Intervention

Participants will be randomly allocated to receive either (1) active tDCS + sensorimotor retraining or (2) sham tDCS + sensorimotor retraining. The intervention will be delivered twice a week for 10 weeks and will consist of 20 min of active or sham tDCS immediately followed by 1 hour of supervised sensorimotor retraining. A 10-week intervention has been chosen as this duration has led to improved outcomes in people with chronic LBP following a sensorimotor retraining intervention in a previous study.⁶ A qualified physiotherapist, trained in the use of tDCS, will deliver both the tDCS intervention and the sensorimotor retraining in a consulting room of Western Sydney University. To replicate typical clinical practice, participants in both groups will also complete home exercise three times per week. Outcome measures will be assessed immediately before and immediately after the 10-week intervention.

Transcranial direct current stimulation

tDCS will be delivered to the primary motor cortex using a DC-STIMULATOR PLUS, (NeuroConn, Ilmenau, Germany), while participants are comfortably and quietly seated. Direct current will be delivered for 20 min via two 35 cm² surface sponge electrodes. The active electrode (anode) will be positioned over the primary motor cortex using the International 10–20 system contralateral to the side of worst LBP. The reference electrode (cathode) will be positioned over the contralateral supraorbital region ipsilateral to the side of pain. The primary motor cortex has emerged as one of the most effective and reliable sites for tDCS in the treatment of pain, producing improvements in pain analogous to those of FDA-approved pharmaceuticals in other musculoskeletal pain conditions with considerably fewer side effects.²⁵ Using standard tDCS parameters,²⁵ current intensity will be ramped up (0–1 mA) and down (1–0 mA) over 10 s at the beginning and end of the 20 min stimulation period. For sham stimulation, electrodes will be placed in an identical position. To provide the initial itching sensation, stimulation will be turned on for 15 s and then off. Participants will be informed that they may or may not perceive any sensation during the treatment. This procedure has been shown to effectively blind participants to the stimulation condition at intensities of 1 mA.³⁷

Sensorimotor retraining

Immediately following the active or sham tDCS intervention, participants will commence a graded sensorimotor retraining programme informed by a previously published protocol.^{6,7} Components of the protocol include progressive tactile localisation, tactile discrimination and graphaesthesia training, laterality recognition, imagined movements, precision focused and feedback enriched

movement training (including full range movements, isometric local muscle recruitment and co-contraction and dissociation exercises) and precision focused and feedback enriched functional retraining.⁶ Five stages exist for each of the sensory and motor retraining elements. Participants will be progressed through each stage by the physiotherapist based on specific, previously published criteria.⁶

Participants will be provided with a home exercise diary containing visual and written instructions for each exercise (including dosage) and will be asked to practice the training at home for 30 min, 3 times per week. The exercise diary will include space for participants to outline which exercises were completed, how many repetitions were performed and any comments regarding the home exercise programme (eg, whether pain was present, whether any exercises were difficult and if applicable, the reason why exercises were unable to be completed). The exercise diary will be returned to the investigator at the postintervention assessment session.

OUTCOME MEASURES

Measures of feasibility, safety and adherence will be collected throughout the pilot study, while endpoint measures of pain and function (Brief Pain Inventory, RMDQ) as well as pain mechanisms will be measured 1 week prior to the participant commencing, and within 1 week of completion, of the 10-week intervention. All measures will be performed in the research laboratories of Western Sydney University.

Primary outcomes

Feasibility

The number of participants that (1) meet the inclusion criteria, (2) agree to be randomised, (3) complete the intervention and (4) attend the postintervention assessment will be calculated in accordance with CONSORT guidelines. Feasibility will be measured as (1) the number of treatment sessions attended by each participant, (2) number of drop-outs in each group, (3) proportion of participants recruited from the total number screened, (4) willingness of each participant to undergo therapy on an 11-point numerical rating scale with 'not at all willing' at 0 and 'very willing' at 10 (measured at baseline) and (5) the number of home exercise sessions completed.

Safety

Safety will be assessed as any adverse effect, defined as 'a response to an intervention which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function' and that likely has a causal relationship with the intervention,³⁸ reported on verbal questioning by the treating physiotherapist at each session. A mild tingling or itching sensation under the electrodes, fatigue, headache, nausea and insomnia have been reported as potential adverse reactions

following tDCS.³⁹ Potential adverse reactions as a result of sensorimotor retraining may include increased pain or muscle soreness in the back. The treating physiotherapist will record a description of any adverse effects along with the severity and duration of symptoms and how the adverse effect was managed.

Secondary outcomes

Questionnaires

The Brief Pain Inventory will be used to measure pain severity and disability. To assess pain, participants will be asked to complete four numerical rating scales anchored with 0 ('no pain') and 10 ('worst pain imaginable') for pain at its (1) most intense over the last week, (2) least intense over the last week, (3) average intensity over the last week and (4) right now. Scores from each scale will be averaged to calculate a final pain severity score out of 10.⁴⁰ To assess function, participants will complete seven numerical rating scales to describe how their back pain interfered with daily life (eg, general activity and mood) in the past week. Each scale will be anchored with 0 ('does not interfere with daily life') and 10 ('completely interferes'). Scores from the seven scales will be averaged to give a final pain interference score out of 10.⁴¹ The Brief Pain Inventory has been shown to be valid and reliable in the chronic LBP population.⁴⁰ Self-reported disability will also be measured using the 24-point RMDQ that has been shown to be valid and reliable in people with LBP.^{42 43} Finally, the global perceived effect of treatment scale, where each participant's perceived response to therapy is assessed using an 11-point Likert scale ranging from 'vastly worsened' to 'completely recovered', will be completed.⁴⁴

Measures of pain mechanisms

Measures of pain mechanisms will be performed in the same order for all participants.

Secondary outcomes of pain mechanisms

Pressure pain thresholds (PPTs)

Pressure pain thresholds (PPTs) will be measured using a hand-held pressure algometer (Algometer Type II, SBMEDIC Electronics, Sweden) with a probe size of 1 cm². The probe will be applied perpendicular to the skin (rate 40 kPa/s) until the participant first reports that the sensation of pressure has changed to pain. PPTs will be measured three times, in random order, at each of nine sites on a 3×3 grid (spacing 2 cm between points, 27 stimuli in total) centred at the site of worst pain. Participants will be asked to locate the site of worst pain at baseline for positioning of the grid. The location of this site will be recorded using bony landmarks to ensure that the same site is targeted in the follow-up assessment. In addition, three PPTs will be measured at the contralateral thumbnail. The average of the three measurements at each site will be used for analyses. PPT measures have been shown to be reliable in chronic LBP.^{45 46}

Heat pain thresholds

Heat pain thresholds (HPT) will be measured using a Thermal Sensory Analyzer system (TSA-2001, Q-Sens-CPM, Medoc, Ramat Yishai, Israel). A 30×30 mm Peltier-based thermode will be placed on the skin. The temperature will start at 32°C and increase at a rate of 0.5°C/s. Participants will push a button when the sensation of heat first turns to a sensation of pain. HPTs will be measured at (1) the site of worst pain, (2) the lumbar site contralateral to the side of pain and (3) the ventral aspect of the forearm contralateral to the side of pain (10 cm distal from the elbow crest). Three measurements will be recorded at each site and the average analysed. HPT measures are reliable in chronic LBP.^{45 47}

Conditioned pain modulation

Conditioned pain modulation (CPM) is examined as a change in the pain perceived in one body region (test stimulation) as a result of pain induced in another body region (conditioned stimulation). It is a safe measure of pain processing that is thought to indicate the function of descending pain control systems. We will use pressure pain (PPTs) as the test stimulation and heat pain (1°C above HPT) as the conditioned stimulation (Thermal Sensory Analyzer, TSA-2001, Q-Sense-CPM, Medoc, Ramat Yishai, Israel). Three PPTs will be measured before the application of heat pain. Heat pain will then be applied via a 30×30 mm thermode with three sequential PPT measures taken after 30 s of the conditioning (heat) stimulus. The heat stimulus will then be removed. Participants will be asked to rate their pain during conditioning (heat) stimulation on a numeric rating scale (0–100) at 0 s, 30 s and at the end of the trial. Pain scores will be maintained between 50 and 80/100 for the conditioned stimulus during testing. Participants will complete two trials in random order: (1) test stimulation applied at the most painful lumbar region (indicated by the participant) and conditioned stimulation at the contralateral forearm and (2) test stimulation at the forearm ipsilateral to the site of pain and conditioned stimulation at the contralateral lumbar region. The CPM paradigm is reliable in chronic LBP.^{45 48 49}

Temporal summation

Temporal summation (TS) will be assessed using a 26 g nylon monofilament (Aesthesio: DanMic Global) to apply repeated mechanical stimulation according to the Standardized Evaluation of Pain protocol.⁵⁰ The participant will be asked whether a single filament stimulus provokes pain. If the answer is 'yes', the participant will then be asked to rate the pain on a numeric rating scale (0–100). If the answer is 'no', a 'zero' will be recorded on a numeric rating scale. The filament will then be applied to the skin at a rate of 1 Hz for 30 s. The participant will be asked to rate the pain on the numeric rating scale again at the end of the 30 stimuli. TS will be tested on the most painful area and the dorsal aspect of the non-dominant wrist joint. Previous work has recommended using TS of



mechanical pain to assess endogenous pain modulation in chronic LBP populations.⁵¹ TS of mechanical pain is a reliable test.⁵²

Data and statistical analyses

Data for feasibility and safety will be analysed using descriptive statistics. Trends for effectiveness will be determined in two ways: (1) to assess within group changes in pain, function and pain mechanisms, a one-way repeated measures analysis of variance will be performed to compare baseline and 10-week follow-up scores for each outcome, in each group; (2) to assess between-group changes in pain, function and pain mechanisms, an analysis of covariance will be performed where group allocation is the fixed factor and the corresponding baseline outcome values are included as covariates.⁵³ Post hoc Bonferroni tests will be applied where appropriate. Effect sizes will be determined using partial η^2 from planned contrasts. Alpha will be set at 0.05. As this is a pilot trial, missing data will not be replaced.

The size of the treatment effects will be used to determine whether a full randomised controlled trial is warranted.^{54 55} Means and SD for measures of pain, disability and pain mechanisms will be used to perform a sample size estimate. Power will be set at 80% to detect between-group differences with an alpha of 0.05 and a drop-out rate based on that of the pilot trial. SigmaPlot software will be used to analyse all data.

Sample size

This is a pilot study that will be used to generate data to inform a future full-scale randomised controlled trial should the intervention appear feasible, safe and show trends of effectiveness. As a result, a prospective sample size calculation was not conducted. Based on projected recruitment rates within the study timeframe, a sample size of 40 participants per group (80 in total) has been selected.

ETHICS AND DISSEMINATION

Western Sydney University Human Research Ethics Committee has approved this trial (H10184). All participants will provide written informed consent following verbal and written explanation of the study protocol and the opportunity to ask questions. Results will be presented at scientific meetings and published in peer-reviewed journals. All publications and presentations related to the study will be authorised and reviewed by the study investigators.

TRIAL STATUS

This trial will begin recruitment in September 2017 and is expected to be complete (including follow-up testing) by December 2018.

Contributors ALO, MBL, W-JC, DW, BMW and SMS were each involved in the conception, design, writing and editing of the study protocol. ALO, MBL, WJC, DW, BMW and SMS approved the final protocol.

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Competing interests None declared.

Ethics approval Western Sydney University (H10184).

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