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Effect of Anodal Transcranial Direct Current Stimulation Combined with Exercise in Adults with Chronic Non-specific Low Back Pain: Protocol for a Randomized Controlled Trial

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Abstract:

Background: *Chronic Low back pain (LBP) is a prevalent condition associated with significant disability and high costs to society. Although exercise protocols have proven benefit to relief pain symptoms, their effectiveness are often limited. Transcranial direct current stimulation (tDCS), a non-invasive brain stimulation technique, has shown promising results on reducing pain scores in different conditions. However, there is still weak evidence of its clinical impact on chronic LBP.*

Objective: *To evaluate the efficacy of tDCS plus exercise compared to sham-tDCS plus exercise in adults with chronic nonspecific LBP.*

Methods: *We propose a single-center, randomized, double-blind, placebo-controlled, phase II trial, with parallel design, including 117 patients aged 18-65 years with > 12 weeks of LBP and a baseline pain score of ≥ 3 in the Numerical Pain Rating Scale (NPRS). Participants will be randomized by blocks to one of the treatment arms (active-tDCS + exercise or sham-tDCS + exercise), with 4 weeks of intervention. Our main outcome will be pain intensity as assessed by NPRS. Secondary outcomes will be: (1) functional disability (Roland Morris Disability Questionnaire); (2) quality of life (SF-36); (3) parameters related to central pain processing (endogenous pain inhibition and facilitation, and central sensitization). Follow-up assessments will be performed at 1 and 3 months after the intervention period.*

Conclusions: *The proposed study will contribute to previous literature by testing an innovative and non-invasive technique to treat chronic LBP. Despite potential methodological challenges, the analyses of clinical and neurophysiological markers will bring valuable information to the understanding of this burdensome condition.*

Keywords: *chronic low back pain, transcranial direct current stimulation, exercise, clinical trial, protocol.*

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INTRODUCTION

Chronic low back pain (LBP) is associated with significant disability and a decrease in quality of life (Tsuji et al., 2016). According to England's National Health Service, LBP incurs health care costs estimated to be around £1.3 million per day (Foster et al., 2018). From 1990-2015, LBP was responsible for approximately 60 million disability adjusted life years, with an increase of 54% during that time period (Hartyigsen, JanBuchbinder, Rachelle et al., 2018). LBP is also the leading cause of years lived with disability in Brazil: from 1990 to 2015 the number of years people lived with disability increased by 79.7% (Martins-Melo et al., 2016). The pathophysiology for LBP is still not well understood (Herndon et al., 2015). The lack of an effective standard treatment for LBP calls

for further investigations to find evidence-based interventions for this common condition.

Transcranial direct current stimulation (tDCS) is a non-invasive brain stimulation technique that has been shown to reduce chronic low back pain when used in conjunction with other interventions (Hazime et al., 2017; Straudi et al., 2018). To date, it is known that tDCS modulates neuronal excitability in a polarity dependent manner which influences brain plasticity. However, its effect on pain-related neural circuits is not fully understood (Brunoni et al., 2012; Jacobson et al., 2012). The mechanism is partially explained through its direct effect on polarization of neural cell membranes promoting long-term synaptic potentiation (Luedtke et al., 2015). Consequently, having a positive effect on pain-related networks such as: primary and sensory motor cortex, anterior cingulate cortex and the thalamus. However current evidence shows that TDCS has a low to moderate effect size on pain disorders (O'Connell et al., 2018), and some authors believe the combination of tDCS with other active therapies is an approach worth of investigation to increase the effect sizes of these interventions (Straudi et al., 2018).

Exercise has been shown to be effective for chronic non-specific LBP and is nowadays recommended as first-line care for this prevalent condition (Foster et al., 2018). However, there is no consensus over the type and the duration of exercise which is most suitable to treat LBP. Some evidence suggests that the mechanism of exercise in pain relief is that physical activities produces analgesia through activation of centrally-located pain inhibition pathways. Also, it is believed that exercise enhances the phosphorylation of NMDA receptors in the thalamus, nucleus reticularis dorsallis (SRD) (Rostral Ventromedial Medulla) and the caudal medullary raphe nuclei. Those parts of the brain (which produces 5-HT) and the connections with M1 and S1 areas are involved in the pain relief process (Bobinski et al., 2015). Additionally, exercise influences various aspects of bodily function, including a large neural circuit via efferent input (bottom-up) from medulla to cortical regions as well as a neuroendocrine response (Schwarz et al., 1992; Goldfarb et al., 1997; Kramer et al., 2007). This concept is known as exercise-induced hypoalgesia and is supported by animal and human studies and involves cortical-thalamic-SRD circuits including the insula (Holschneider et al., 2007; Williamson et al., 1985).

The main rationale for the optimized clinical effects of the combined intervention is the "top-down" (from cortical: primary sensory motor cortex, cingulate cortex and insula; to subcortical: thalamus) enhancement on neural excitability elicited by tDCS and complemented by a "bottom-up" effect (from subcortical: thalamus, cerebellum to cortical: sensorimotor cortex, insula and dorsolateral prefrontal cortex) elicited by exercise. These two mechanisms of action strengthen the endogenous pain control system and normalize thalamocortical circuits. Furthermore, at the molecular level, they have an effect on the glutamatergic system and calcium signaling as well as on the long-term potentiation.

Treatments involving tDCS in association with exercise are safe and can be implemented in clinical practice. The efficacy of this combination was demonstrated especially in patients with low back pain who present predominantly with a central sensitization mechanism (Nijs et al., 2015). Therefore, in recent years, both interventions separately have emerged as a promising tool to target brain regions related to central chronic pain (Zaghi et al., 2009). However, because of the heterogeneity of pathology, uncertainty of disease progression and treatment response combined with the variety of subjective outcomes, evidence from randomized controlled trials is still lacking (Luedtke et al., 2015).

In this study, we aim to test the efficacy of a combined intervention of tDCS plus exercise compared to sham-tDCS and exercise on pain intensity measured by a numeric pain rating scale in patients with chronic nonspecific LBP. We hypothesize that a combined intervention will result in greater pain reduction compared to only one intervention. Moreover, this study also investigates if the combined intervention has an effect on quality of life, on functional disability and on measures of central sensitization.

MATERIALS AND METHODS

We propose a single center, randomized, double-blind, placebo-controlled phase II trial. Adults with chronic non-specific LBP will be randomized in a 1x1 parallel design. The intervention is active-tDCS + exercise and the control is sham tDCS + exercise. The main outcome is pain intensity measured 1 month after the end of the intervention. The study will take place at the Laboratory of Pain and Neuromodulation, Porto Alegre Teaching Hospital, Rio Grande do Sul, Brazil.

Eligibility Criteria

Patients will be interviewed by the study's blinded assessor (a family doctor) who will determine eligibility. Eligible patients will be informed about the objectives of the study and asked to sign the consent form.

Inclusion criteria:

(1) Age 18-65 years.

(2) Chronic non-specific LBP (defined as pain or discomfort localized below the costal margin and above the inferior gluteal folds, persisting for more than 12 weeks, without recognizable cause). A family physician will make the clinical triage - assessing every subject to exclude those with nerve root compromise or serious spinal pathology (see below in exclusion criteria)
(3) Pain intensity ≥ 3 (measured by Pain Numerical Rating Scale)
(4) Able to provide informed consent

Exclusion criteria:

(1) Nerve root compromise (i.e., one or more of motor, reflex or sensation deficit)
(2) Serious spinal pathology (such as fracture, infection, tumor, inflammatory disorder, cauda equina syndrome)
(3) Spinal surgery within the previous six months
(4) Mini-Mental Status Examination (MMSE) less than 24/30
(5) Contra-indications to tDCS: uncontrolled epilepsy, implantable devices in the skull, severe cardiopulmonary, renal and hepatic diseases or pregnancy.
(6) clinically significant or unstable medical or psychiatric disorder,
(7) Increased risk of cardiovascular complication due to exercise as defined by the American college of sports medicine (ACSM) criteria (ACSM, 2015; Garber et al., 2011) and in this case not cleared by a physician.

If patients become ineligible during the trial by any of the above circumstances they will be dropped out and the Institutional Review Board will be informed.

Recruitment and Adherence

Both targeted and broad-based strategies will be used. Physicians and physical therapists from private and public pain clinics in Porto Alegre (and neighbor cities) will be informed about the study via email. The email will include educational material and the research group contact information. Group presentations will be designed to provide health care providers education and to ensure longitudinal awareness about the study. Broad based strategies include flyers targeting the accessible population and health care providers in recruitment centers and also social media/Google ads.

Measures will be taken to enhance adherence to the tDCS intervention and to the exercise protocol:

(1) Reimbursement for study related expenses (parking and travel expenses).
(2) 3 missing visits are permitted (3 non-consecutive or 2 consecutive visits)
(3) Free childcare during the study visit
(4) Prior confirmation of appointments as part of adherence monitoring
(5) Open label treatment will be offered to the control group at the end of the trial

Randomization and Allocation Concealment

Randomization sequences will be created using a pre-specified computer-generated web-based blocked randomization scheme (SAS/STAT® 9.2 Proc Plan Permuted-block randomization, Institute Inc. Cary, NC, USA) with blocks of variable sizes (4 and 6). All patients who give consent for participation and fulfill the inclusion criteria will be randomized. Randomization will be requested by the staff member responsible for recruitment. In order to ensure concealment of the allocation process, we will use an interactive web response system (IWRS). An administrative assistant will call the IWRS and will provide the treatment codes according to the randomization scheme and will record the assignment in a confidential log. The randomization list will remain at the coordinator center of the study and the central randomization system service and will be kept strictly confidential for the investigators for the duration of the study. This will minimize any influence from the principal investigator, evaluators, and therapists during the conducted randomizations.

Blinding

This study will be double blinded (i.e., evaluators, device operators and trial participants will be blinded). Raters will not be present during tDCS applications and trial participants will be admitted in different rooms and scheduled for outpatient follow up on different days. The set-up of tDCS application will be performed in a way so the subject will not be able to see the tDCS device and parameters. The sensation during an active tDCS session or sham tDCS will be equal (Brunoni et al., 2017; Chapman et al., 2011), avoiding that participants realize which treatment they are receiving. Finally, to ensure the blinding of the operators, the active or sham stimulation mode will be chosen by using different number codes that only the administrative assistant will know, in other words, the operator is not aware of the stimulation mode assigned for each code.

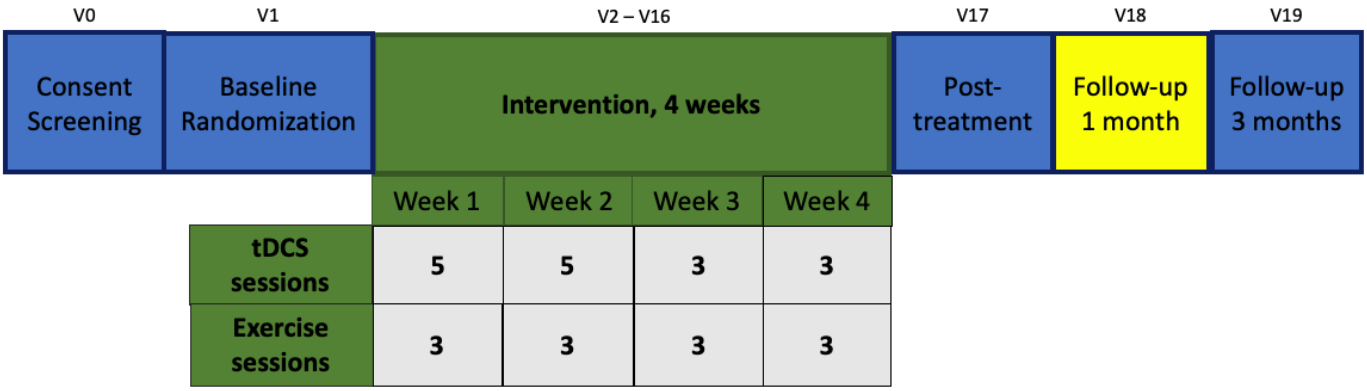

Fig. 1. Yellow color: V18 - Primary Outcome is Pain Intensity (NPRS). Duration: V0: around 1 hour; V1, V17, V18 and V19: around 2 hours; V2-V16: around 1 hour.

The principal investigator will be responsible for reporting all adverse events (during the tDCS or exercise) or medical emergencies to the Institutional Review Board and/or Data Safety Monitoring Committee (DSMC). In the rare event of unblinding due to an adverse event, the physicians involved in the inpatient and outpatient care will not be informed of the patient's group allocation. An administrative assistant in collaboration with an independent statistician will prepare data reports for the DSMC. In the end of the trial, the effectiveness of blinding will be assessed by asking participants which intervention they received (active or sham-tDCS).

Intervention

As described in the timeline below (figure 1), TDCS will be performed on a daily basis for 2 weeks followed by 3 times a week for 2 weeks with a total of 16 sessions. Exercise will be performed 3 times a week for 4 weeks with a total of 12 sessions. Whenever there is an exercise session, tDCS will be performed concomitantly (participant will start the exercise and the stimulation at the same time).

TDCS: Active-tDCS: We will apply tDCS using a 1x1 low-intensity DC Stimulator that uses coding and a portable battery to deliver direct low amplitude and current. In the active (anodal) stimulation, rubber electrodes in a saline soaked sponge (35cm^2) will be placed over the dominant motor cortex (M1), while the reference (cathodal) saline-soaked sponge electrode (35cm^2) will be placed in a frontal position above the contralateral supraorbital area. Primary motor cortex will be localized using the 10/20 EEG system (C3 or C4), a reliable method for the technique of tDCS (Gandiga et al., 2016). The current will be ramped up over 30 seconds to reach the target stimulation intensity of 2mA. This will last for 30 minutes while patients are performing exercise therapy.

Sham-tDCS: Sham tDCS will be applied on the primary motor cortex with the same montage and parameters of active tDCS as described above. The current will be ramped up over 30 seconds to reach 2mA and then turned off. The sham stimulation procedure was chosen based on previous studies that have shown that perceived sensations on the scalp such as tingling usually fade out in the first 30 seconds of tDCS (Brunoni et al., 2017; Chapman et al., 2011).

Exercise: We will use a strengthening program adapted from the regimens designed by Richardson et al. (1995), McGill (1998) and Hicks et al. (2005). Initially participants will be taught to contract deep trunk muscle that are important spine stabilizers, and that have been shown to be dysfunctional in low back pain patients (Richardson et al., 1995). Then, patients will do exercises that will progressively challenge larger superficial trunk muscle while minimizing spinal compressive loads (Callaghan et al., 1998; McGill 1998). Each group will perform 12 sessions of half hour of supervised exercise over a 4-week period, i.e. 3 sessions/week. The exercise regimen will comprise two phases – Phase 1 and Phase 2.

Phase1- exercises will focus on activating deep stabilizing muscle of the spine. Participants will be taught to perform an isolated contraction of transversus abdominus by doing the hollow-in maneuver (HIM). Participants will be oriented to avoid the activity of superficial muscle and also to avoid breath holding while doing the HIM. Patients will choose their most comfortable position (lying supine, prone or side lying) and will be encouraged to gently perform the HIM, aiming for a sustained contraction of 10 seconds (with 10 seconds of rest between each contraction). The final goal of the Phase 1 (first 2 to 3 visits, week 1) is to be able to sustain 10 isometric contractions of 10 seconds with good technical execution (no superficial muscle activation, normal breathing).

When patients achieve that, they will be ready to progress to phase 2.

Phase 2 - participants will progress to more challenging positions - they will be asked to do the HIM in sitting (with neutral posture) and advance to standing as soon as they are able to perform 10 holds of 10s in sitting with proper technique. Concomitantly in phase 2 we will add more challenging exercises that aim to strengthen superficial stabilizers of the spine as well (quadratus lumborum, oblique abdominal, superficial multifidus and erector spine muscles). All the exercises of phase 2 will be done with co-activation of deep spine stabilizers (through HIM). Phase 2 will be divided into three subphases of progressively more challenging exercises (subphase 2a, 2b and 2c). Criteria for progression: whenever participants are able to do 20 repetitions of 8-s holds of all exercises of a subphase, they will be considered ready to progress to the next subphase. See the exercise sequence in figure 2.

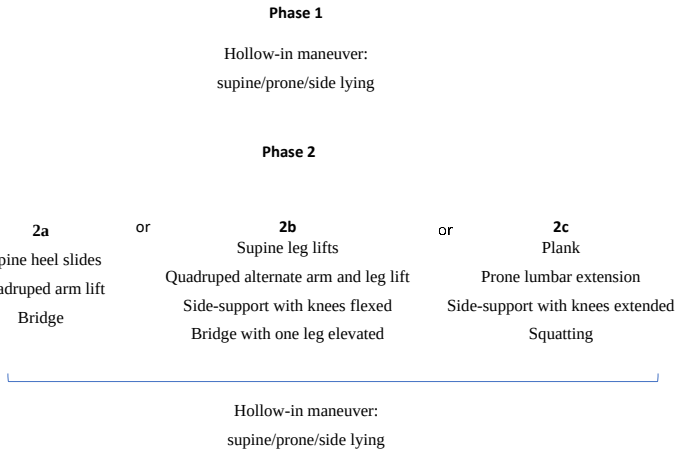

Fig. 2. Exercise sequence

At the end of the intervention phase (one month), all patients will be given a leaflet with home exercises, and they will be asked to keep doing the exercises (30-minute sessions, three times a week) throughout the entire follow-up period (3 months). In order to check for home exercise compliance, all participants will be asked to complete a compliance log that will be collected at 1 month and 3 months follow-up.

Outcomes

All clinical outcomes will be measured at baseline (Visit 1), immediately after intervention period (Visit 17), one month after intervention period (Visit 18) and 3 months after intervention period (Visit 19)

Primary Outcomes:

Our primary outcome will be Pain Intensity measured by the Numerical Pain Rating Scale (NPRS) one month after the intervention period (Visit 18). NPRS has been shown to be a valid, reliable and responsive scale for pain measurement in low back pain patients (Childs et al., 2005), and its use was recommended by a recent Delphi study for pain intensity assessment in nonspecific LBP trials (Chiarotto et al., 2018) The NPRS is a 11-point numerical scale ranging from 0 (no pain) to 10 (worst pain imaginable). Patients will be asked to verbally rate their average pain in the last seven days.

Secondary Outcomes:

Pain intensity (NPRS) immediately after intervention period (V17) and 3 months after the intervention period (V19).

All the following secondary outcomes will be assessed at V17, V18 and V19:

Functional Disability – measured with the Roland Morris Disability Questionnaire, a validated questionnaire designed to assess the degree of disability in participants with lower back pain (Ostelo et al., 2005; Ware et al., 1992). It consists of 24 items that measure the interference of low back pain in different domains (mobility, dressing, working, standing, sleeping, mood, recreation, appetite, etc.) Each item has a binary response (yes / no), and the final score is obtained by the total of positive responses (maximum score of 24). The higher the score, the more severe the disability caused by low back pain (Neblett et al., 2013).

Quality of Life – measured by SF-36 – a valid tool for assessing quality of life. SF-36 is easy to administer and understand and consists of a multidimensional questionnaire with 36 items encompassed in eight scales or domains, which are: functional capacity, physical aspects, pain, general health, vitality, social aspects, emotional aspects and mental health. It presents a final score from zero to 100.

Central Sensitization – measured by the Central Sensitization Inventory (CSI), a 25-item questionnaire that assesses health-related symptoms common to Central Sensitivity Syndromes, rated on a Likert-scale (0 = "never" to 4 = "always"). The maximum score is 100. Scores higher than 40 indicate presence of Central Sensitization (indicating hyperexcitability of the pain system). The CSI is a reliable and valid tool to assess Central Sensitization (Marchand and Arsenault, 2012; Staud et al., 2014).

Endogenous Pain Inhibition – measured by the Conditioned Pain Modulation (CPM) paradigm. The CPM is a reliable method to assess descending endogenous pain control. It involves two stimuli, the conditioning

stimulus and the test stimulus. We will use thermal pain thresholds (TPTs) for the test stimuli, which will be applied using a Peltier thermode on the subjects' forearm. (Marchand and Arsenault, 2012) The initial temperature will be 32 °C and will be increased gradually at 0.3°C per second. During the procedure, the subject will be instructed to say aloud when their sensation first changes from heat to a painful stimulus; the temperature at this moment will be recorded as the TPT. This same procedure will be repeated 3 times, and the average of the three values will be recorded as the TPT*pre*. For the conditioning stimulus, the forearm of the subject will be immersed for 2 minutes in a bath of water set at 12°C. At that point, the previously described thermal stimuli will again be applied over the subject's left forearm in the same way described for the test stimuli. The temperature when heat first become pain is recorded again. This measure is repeated three times, and the average is the TPT*pos*. Conditioned pain modulation (CPM) will be the difference between TPT*pre* and TPT*pos.*

Endogenous Pain Facilitation - measured by Temporal Slow Pain Summation (TSPS) – TSPS is elicited by repeated painful stimuli of various types, including heat, mechanical or electric, and is considered the human form of Mendell's "wind-up" phenomenon - an important spinal cord dorsal horn excitatory pain mechanism considered critical for the development of chronic pain (Staud et al., 2014). Heat pulses will be generated by a TSA-II Stimulator delivered to the right dominant proximal volar forearm using an appropriate size embedded HP-thermode. We will follow the adapted protocol suggested by Staud et al. (2014) in which the HP-thermode was programmed to deliver pulses rising/fall of 1-2-s, depending on subject's heat-evoked pain threshold, from adapting temperatures to peak temperatures, with a plateau of .7-s. Subjects will be trained to rate how painful (with numerical rating scale) single heat pulses at 44°C, 46°C, and 48°C (these temperatures provoke mild to moderate pain in most people)(Staud et al., 2014). Subsequently, they will receive 3 trains of 5 repetitive painful heat stimuli at 0.4 Hz to the same area to produce TSPS without inducing peripheral sensitization (Vierck et al., 1997). The interval between heat stimuli trains will be 30-s. Patients will be asked to rate the heat pain intensity of each painful stimulus using a numerical rating scale (ranging from 0 to 10); TSPS will be calculated as the difference between heat pain rating of the 5th stimulus minus the 1st stimulus, and the average of the three measures will be used.

Data Management and Monitoring

Data handling will be managed by a third-party agency. Investigators, patients, clinical staff applying the therapies and raters will not have access to the raw data until the data analysis is finished.

The DCM (Data Monitoring Committee) will be established according to the Brazilian Health Surveillance Agency (ANVISA) rules. It will comprise of a data manager, database programmer/designer, medical coder, clinical data coordinator, quality control associate, and data entry associate.

Personal data will be encrypted in a virtual database, secured and password protected, DCM will have access to the information during the clinical trial. An ID (identification number) will be given to each subject during the study in case of SUSAR (suspected unexpected serious adverse reaction).

SUSAR will be defined as adverse events that were life-threatening/disabling, required hospitalization and/or resulted in death. They will be collected during the trial, using standard adverse event forms for brain stimulation currently used in other studies and also standard adverse events for exercises. DCM will have unblinded access to all data of the subjects and will discuss the adverse events at an additional meeting.

Sample Size Calculation

The sample size is calculated based on a pilot study by Straudi et al. (Straudi et al., 2018). The statistically significant variation of pain level from baseline to one month of follow-up comparing exercise combined with active tDCS vs. exercise combined with sham for chronic low back pain had an effect size of Cohen's d 0.84. In addition, two more studies combining tDCS and other interventions for LBP have found an effect size of 0.33 and 0.79 respectively (Hazime et al., 2017; Luedtke et al., 2015). Due to the possible overestimation of effect size in pilot studies (Straudi et al., 2018) and as a mean value across studies, a more conservative approach was chosen estimating an effect size of 0.6 for the present study. We considered an effect size for linear regression of f2 = 0.15, which is in accordance with an expected medium effect size, alpha of 5%, power of 80% and two covariates in a multiple regression model (baseline pain intensity, baseline disability) (Cohen, 1998) with the estimated sample size of 97 participants. We added approximately 20% to that sample size to account for possible dropouts in the study (e.g., loss to follow-up, consent withdrawal, missed appointments). Our final sample size estimation is a total of 116 patients, 58 patients in each group. The estimated effect size is also in accordance with Green (Green et al., 1991), when it is suggested that the sample

size for multiple linear regression should follow the following equation: N = 104 + number of covariates. According to this estimation we determined a required sample size of 106. Therefore, the sample size of 116 patients is adequate for an 80% statistical power.

Statistical Analysis

For statistical analysis of primary and secondary outcome measures, we aim to apply an a priori defined repertoire of statistical models by comparing the intervention arm (tDCS + exercise therapy) against the control arm (sham tDCS + exercise therapy). In general, we will apply a linear mixed effect regression model, thus having both random and fixed effects, hereby enabling to control for important covariates (baseline pain intensity and baseline disability level).

Baseline characteristics of participants with chronic non-specific low back pain will be analyzed and compared among both arms by applying independent t-tests and two-way repeated measures ANOVA for continuous variables as well as Fisher`s exact test for categorical variables. Thus, ensuring to exclude potential detected differences between both treatment arms which might be related to differences in baseline values.

Regarding the statistical assessment of the primary outcome (pain intensity at V18 measured by NPRS), we will apply a multiple linear regression model to compare both study groups by considering pain intensity (assessed by the NPRS) as a continuous variable and adjusting for baseline pain.

For secondary outcomes, normally distributed variables (e.g. CPM & TSPS) will be statistically assessed via parametric tests, such as Student`s t-test or ANOVA, while non-normal distributed variables (e.g. CSI as dichotomized variable) will be assessed by non-parametric tests, such as chi-square test/Fisher`s exact test. Consequently, CSI scores will be assessed in a binomial fashion where scores higher than cutoff of 40 will represent the presence of central sensitization and scores below 40 points cutoff the absence of it. A chi-square or Fisher`s exact test will be used to compare CSI scores between both arms. For analyzing pain intensity (assessed by the NPRS) at V17 and V19, we will apply the identical multiple linear regression model as described and justified for primary outcome analysis. Moreover, SF-36 scores will be compared to determine the total reduction in scores between both arms. Previous studies have shown that the use of parametric or non-parametric tests have no effect on the outcome analysis of SF-36 (Torrance et al., 2009). Based on this justification we decided to apply t-test. Regarding statistically assessing functional disability, the Roland-Morris questionnaire linear regression will be conducted to compare values between groups, adjusting for baseline disability levels.

Unless stated otherwise, all results are presented as means and standard deviation and statistical significance refers to a two-tailed p value with alpha level of significance < 0.05.

Missing Data

A low dropout rate is expected due to our strategies to increase and maintain adherence. To deal with data missing-at-random, we will use the multiple imputation method.

DISCUSSION

This study will investigate an important public health problem, as non-specific low-back pain is a difficult to treat condition that affects several million people worldwide and is associated with a considerable low quality of life (Duarte et al., 2018). Therefore, we designed a placebo-controlled, double blind, parallel study aiming to investigate the effects of tDCS combined with exercise on pain intensity in patients with non-specific low back pain. Our main rationale is to try to generate a change in the pain-treatment paradigm. This is done by enhancing sensory processing by inducing neuroplasticity to positively influence the endogenous pain modulation. We expect this novel targeted method will shed light on the effect of this combined intervention on the regulation of dysfunctional central pain processing mechanisms. This will be detectable by clinical and neurophysiological outcomes (pain, CSI, CPM, TSPS).

In summary, tDCS and strengthening exercises coupled with these measures of central pain processing will help to unravel the mechanism of non-specific low back pain through the neurobiological changes produced by the intervention.

CONCLUSION

In view of the encouraging results observed with tDCS and exercise on chronic pain the present work may help further advance the understanding of the pathophysiology behind the condition and create treatment alternatives for lower back pain. Given the design of our trial we can expect a broad range in response to treatment taking into consideration the clinical and neurophysiological measures beings used and possible correlation with pain relief. Despite positive and negative scenarios this upcoming clinical trial will contribute significantly to the existing knowledge on chronic pain syndromes.

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