

**Medial Prefrontal High-Definition Transcranial Direct Current Stimulation to Improve Pain Modulation in Chronic Low Back Pain**

*A Pilot Randomized Double-blinded Placebo-Controlled Crossover Trial*

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## Medial Prefrontal High-Definition Transcranial Direct Current Stimulation to Improve Pain Modulation in Chronic Low Back Pain: A Pilot Randomized Double-blinded Placebo-Controlled Crossover Trial --Manuscript Draft--

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Abstract:	<p>Chronic low back pain (CLBP) is highly disabling, but often without identifiable source. Focus has been on impaired anti-nociceptive mechanisms contributing to pain maintenance, though methods of targeting this impairment remain limited. This randomised-controlled cross-over pilot trial used active versus sham medial prefrontal cortex (mPFC) high-definition transcranial direct current stimulation (HD-tDCS) for three-consecutive days to improve descending pain inhibitory function. Twelve CLBP patients were included with an average visual analogue scale (VAS) pain intensity of <math>3.0 \pm 1.5</math> and pain duration of <math>5.3 \pm 2.6</math> years. Pressure pain thresholds (PPTs), conditioned pain modulation (CPM), and temporal summation of pain (TSP) assessed by cuff algometry, as well as pain symptomatology (intensity, unpleasantness, quality, disability) and related psychological features (pain catastrophizing, anxiety, affect), were assessed on Day1 before three consecutive days of HD-tDCS sessions (each 20 min), at 24-hours (Day4) and 2-weeks (Day21) following final HD-tDCS. Blinding was successful. No significant differences in psychophysical (PPT, CPM, TSP), symptomatology or psychological outcomes were observed between active and sham HD-tDCS on Day4 and Day21. CPM-effects at Day1 negatively correlated with change in CPM-effect at Day4 following active HD-tDCS (<math>P=0.002</math>). Lack of efficacy was attributed to several factors, not least that patients did not display impaired CPM at baseline.</p>

**Medial Prefrontal High-Definition Transcranial Direct Current Stimulation to Improve Pain Modulation in Chronic Low Back Pain: A Pilot Randomized Double-blinded Placebo-Controlled Crossover Trial**

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## **ABSTRACT**

Chronic low back pain (CLBP) is highly disabling, but often without identifiable source. Focus has been on impaired anti-nociceptive mechanisms contributing to pain maintenance, though methods of targeting this impairment remain limited. This randomised-controlled cross-over pilot trial used active versus sham medial prefrontal cortex (mPFC) high-definition transcranial direct current stimulation (HD-tDCS) for three-consecutive days to improve descending pain inhibitory function. Twelve CLBP patients were included with an average visual analogue scale (VAS) pain intensity of  $3.0 \pm 1.5$  and pain duration of  $5.3 \pm 2.6$  years. Pressure pain thresholds (PPTs), conditioned pain modulation (CPM), and temporal summation of pain (TSP) assessed by cuff algometry, as well as pain symptomatology (intensity, unpleasantness, quality, disability) and related psychological features (pain catastrophizing, anxiety, affect), were assessed on Day1 before three consecutive days of HD-tDCS sessions (each 20 min), at 24-hours (Day4) and 2-weeks (Day21) following final HD-tDCS. Blinding was successful. No significant differences in psychophysical (PPT, CPM, TSP), symptomatology or psychological outcomes were observed between active and sham HD-tDCS on Day4 and Day21. CPM-effects at Day1 negatively correlated with change in CPM-effect at Day4 following active HD-tDCS ( $P=0.002$ ). Lack of efficacy was attributed to several factors, not least that patients did not display impaired CPM at baseline.

**Trial registration:** ClinicalTrials.gov (NCT03864822)

**Perspective:** Medial prefrontal HD-tDCS did not alter pain, psychological nor psychophysical outcomes, though correlational analysis suggested response may depend on baseline pain inhibitory efficacy, with best potential effects in patients with severe impairments in descending pain inhibitory mechanisms. Future work should focus on appropriate patient selection and optimising stimulation targeting.

**Key words:** Low back pain, non-invasive brain stimulation, conditioned pain modulation, medial prefrontal cortex, randomized crossover trial

## INTRODUCTION

Chronic low back pain (CLBP) is well-known to be a costly and disabling condition, for which clear pathophysiology is lacking in the majority of cases[33; 43; 89]. ~~Hence~~As a result, increased focus has been placed on psychosocial factors and central pain processing mechanisms ~~are often implicated as possible contributors to~~ ~~in~~ the development and maintenance of the condition[26; 74]. Prior work has shown both that CLBP commonly co-occurs with affective disturbances[17; 47], and that CLBP patients generally show impairments in anti-nociceptive mechanisms (e.g. Conditioned Pain Modulation (CPM)) related to LBP duration, extent, and severity[15; 22; 52]. Although behavioural interventions can be used by experienced clinicians to successfully address these affective and psychosocial factors[83], there remains little conclusive evidence on whether impaired anti-nociceptive mechanisms can be restored.

One approach could be to intervene with factors associated to impairments in ~~central pain processing mechanisms~~CPM[28; 55]; e.g. by reducing stress, restoring sleep quality and/or increasing physical activity. However, it is difficult to acutely alter these factors in ~~a standardised and~~ a repeatable manner. Another more standardised approach to acutely improving anti-nociceptive mechanisms may be through~~alternatively,~~ transcranial direct current stimulation (tDCS), which is a non-invasive method of altering cortical excitability, that has been used to acutely enhance CPM in healthy individuals[18]. In CLBP populations, tDCS trials have not focussed on targeting anti-nociceptive mechanisms specifically, though trials for this purpose in other pain populations are ongoing[8]. Instead, most existing clinical studies aim to reduce pain and disability by stimulating either the primary motor or dorsolateral prefrontal cortex~~which may be able to improve pain inhibitory mechanisms and reduce clinical pain, especially when applied over several consecutive days~~[1; 69]. So far, these approaches have had limited success[1], which could be due to the lack of relevant stimulation targeting. In-line, studies have shown that anodal tDCS targeted at the motor cortex can acutely improve CPM in healthy individuals[18] possibly through modulation of thalamic and prefrontal activity, though trials for this purpose in pain patients are ongoing[8].

In the present work, it was therefore hypothesized that targeting cortical regions involved in both affective regulation and pain modulation, as commonly shown to be altered in CLBP patients, may be more efficacious~~of relevance~~.

The medial prefrontal cortex (mPFC) has recently been highlighted as a prime locus for this affect and anti-nociception[37], due to its role in encoding pain affect[70], and its connections with the periaqueductal gray (PAG) and thus descending inhibitory circuitry[4; 86]. Among CLBP

patients, abnormal functional connectivity has been observed between areas of the mPFC and PAG[49; 81; 90; 91], with reduced connectivity seen during clinical LBP exacerbation[90] and experimental pain provocation[49]. Such alterations in connectivity have been shown to correlate with pain intensity[90] and other clinical parameters[81], and have been speculated to indicate impaired cortical initiation of descending inhibition[90].

So far, no pain studies have targeted the mPFC to enhance anti-nociceptive mechanisms using tDCS. However, a prior study used high-definition tDCS (HD-tDCS), posited to enhance focal accuracy and current penetration compared to conventional tDCS[84], to target the anterior cingulate cortex (ACC, a mPFC subregion), showing differential effects on specific cognitive tasks[80]. Computer modelling of this array demonstrates current spreading generally in the mPFC[80], hence it was deemed appropriate to use in the present study.

In this randomized crossover pilot trial, the primary objective was to assess effects of active versus sham HD-tDCS, applied to the mPFC for three consecutive days, on descending pain inhibition ~~as~~ measured by CPM. Secondary objectives were to assess active HD-tDCS effects on other psychophysical testing measures (pressure pain thresholds and temporal summation of pain), along with symptomatology (pain severity and disability) and psychological features (affect, anxiety, pain catastrophizing). It was hypothesized that active HD-tDCS would improve CPM effects, reduce negative affective features, and reduce LBP.

## METHODS

### *Participants*

Participants with chronic low back pain (CLBP) were recruited through advertisements on social media and local noticeboards, and initially screened for eligibility via email and over the phone.

~~Using G\*Power (v3.1.9.2) an A-priori sample size calculation was performed; assuming a modest correlation between repeated measures ( $R=0.6$ ), with 9 assessment sessions, 12 participants were required to detect a moderate effect size ( $f=0.25$ ) with 80% power at a 0.05 alpha level.~~

Participants were required to be 18-60 years old, speak English fluently, and complain of CLBP, defined as: Pain experienced primarily posteriorly between the inferior border of the 12<sup>th</sup> rib and the lower gluteal fold that had been continuously present (>3 days/week) for more than 3 months and was of sufficient intensity to limit daily activity. Participants were excluded if they were currently seeking active treatment, were routinely taking analgesics or other neuropsychotropic drugs, had red flag symptoms (i.e. fever, malaise, progressive neurologic deficit, significant trauma, prolonged corticosteroid use or osteoporosis, urinary or faecal incontinence, or

unintended weight loss), had other current or previous neurologic, musculoskeletal, mental or pain disorders that may affect the trial, or did not pass the transcranial stimulation safety screen[6]. All participants received written and verbal information about the study prior to recruitment and provided written informed consent prior to commencing the study. This study was pre-registered on ClinicalTrials.gov (NCT03864822), approved by the local ethical committee (VN-20170034) and conducted in accordance with the Declaration of Helsinki. All data was collected in the laboratories of the Center for Neuroplasticity and Pain (CNAP) at Aalborg University throughout 2019 by a trained experimenter (MEM).

### *Study Design and Procedure*

This pilot study was designed as a randomized double-blind placebo-controlled experimental crossover trial. Once enrolled, participants were assigned a treatment order based on a computer-generated random number sequence and were scheduled for 9 experimental sessions (Fig. 1). This was -broken into 2 blocks-phases of 5 sessions on Days 1, 2, 3, 4 and 21, where baseline assessment on Day 1 of phase 2 acted as the Day 21 session for phase 1. of 4 consecutive days and a final follow-up session, with each block separated by at least 14 days (to avoid carry-over effects)-In each phase, participants received 3 consecutive days of either active or sham HD-tDCS for 20 minutes (including 60s ramp on and off, respectively) to the medial prefrontal region. Prior to and following stimulation on the first day (Day1) of each phase, as well as immediately following stimulation on the third day (Day3), 24 hours after (Day4) and over 2 weeks after (Day21) end stimulation, a series of physical examination and psychophysical assessments of pain sensitivity were completed. Questionnaire data was obtained at the beginning of each session to track daily fluctuations in e.g. pain, mood, and sleep, and before and after each stimulation session to capture immediate changes in e.g. pain, anxiety, affective state and arousal (supplementary material).

----- Figure 1 -----

### *Demographics and Questionnaire Data*

At the start of the first session, participants reported their age, gender, height, weight, hand and leg dominance, and then completed a series of questionnaires. These included basic questions about their pain history (e.g. pain onset, duration, aggravating and easing factors, prior healthcare utilisation, prior investigations, beliefs), sleep duration (hours slept on preceding night), menstruation (current day of cycle) and mood (current and past week on the Face Scale[39]);



along with the International Physical Activity Questionnaire[10] (IPAQ, rates daily activity in three categories to give an estimate of daily energy expenditure), Pain Catastrophizing Scale[78] (PCS, gives an indication of pain-related distress by rating the frequency of 13 catastrophic thought patterns), State-Trait Anxiety Inventory[76] (STAI, indicates present state and general trait anxiety levels through agreement with 40 self-depictions), Positive and Negative Affective Schedule[88] (PANAS, quantifies current positive and negative affect through degree of present experience of 20 different affective descriptors), and Beck Depression Inventory II[5] (BDI-II, classifies degree of depressive symptoms through 20 five-item scales of behaviours). Questionnaires were repeated as detailed in Fig. 1.

### *Low Back Pain and Disability Ratings*

In addition, in the Day1 and Day4 session of each phase, participants rated their current LBP intensity and unpleasantness, along with their average and maximum LBP in the preceding 24 hours, on paper visual analogue scales (VAS, 0 cm: no pain/not unpleasant at all; 10 cm: worst pain imaginable/most unpleasant sensation imaginable). Average 24-hour pain ratings were also collected at the beginning of sessions on the second and third days, and current pain ratings (supplementary material) were obtained immediately prior to and following HD-tDCS. Participants also completed the Roland-Morris Disability Questionnaire[73] (RMDQ, quantifies disability based on dichotomous responses to 24 statements of functional task impairment), Start-back Screening Questionnaire[29] (SBSQ, classifies risk of chronification based on dichotomous response to 9 statements), and the Pain-DETECT questionnaire[19] (aims to identify presence of neuropathic symptoms based on temporal and spatial pain pattern and presence of different sensory qualities), and chose pain descriptors from the 72-word table of the McGill Pain Questionnaire[54]. The SBSQ and Pain-Detect were only completed in the very first session, whereas the RMDQ and McGill Pain Questionnaire ~~were~~ repeated on Day1 and Day4 in each phase.

### *Physical Examination*

Participants underwent a brief patient history to reconfirm eligibility for study inclusion, and explore their LBP history, prior investigations or interventions trialled, and beliefs about the condition. They then completed a basic physical examination including flexion, extension and lateral flexion, straight leg raise testing, and the Back Performance Scale[42; 77] to quantify function and movement-evoked pain (BPS, 5 standardised functional tasks with pain during the task rated by the participant and performance quality rated by the observer).

### *High-Definition Transcranial Direct Current Stimulation*

Direct current was delivered through five circular Ag/AgCl electrodes, placed with conductive electrode gel in 4 x 1 configuration in a neoprene EEG cap (NE056 Headcap in medium or large dependent on participant's head size, Neuroelectronics, Spain), using a battery-powered multichannel neurostimulator (Starstim R32, Neuroelectronics, Spain). The Cz channel of the EEG cap was placed at the vertex (measured midpoint between nasion and inion, and preauricular points), orientation of the cap was checked for symmetry and was secured under the ears of participants. The anode was placed at Fz with four surrounding cathodes on the forehead at Fp1, Fp2, F7 and F8 ~~as well as a reference electrode on the earlobe~~ as determined by the International 10-20 Electroencephalography System (Fig. 2), and as has been used previously to target subregions of the mPFC[80]. Prior to each stimulation session, electrical impedance was checked using the Neuroelectronics Instrument Controller (NIC2, Neuroelectronics, Spain) and electrodes were adjusted until good impedance (below 10k $\Omega$ ) was achieved for all stimulating electrodes. During each active stimulation session, participants were asked to sit quietly with their eyes open. ~~current~~ Current ramped up over 60 s to the target intensity of 2 mA for the anode (and -500 $\mu$ A at each cathode), where it remained for 18 minutes, then ramped down again over 60 s (20-minute total stimulation period). During each sham stimulation session, the stimulation ramped up over 60 s to 2 mA, then immediately ramped down again over 60 s and remained off for the subsequent 18 minutes to match the active stimulation period (Fig. 2). The electrical field distribution from this HD-tDCS array was modelled on a sample interface ('Ernie' dataset with prespecified scalp and cortical impedances), using the stimulation and electrode parameters detailed above, in SimNIBS software for MatLab as per prior recommendations[79] (Fig. 2).

----- Figure 2 -----

### *Blinding Procedure and Assessment*

Participants and the experimenter (MEM) were blinded to the HD-tDCS protocol applied in each phase. The experimenter initially set up the active and sham protocols in the HD-tDCS software (Neuroelectronics, Spain), after which a colleague who was not involved in the study, renamed the protocols to Protocol 1 and Protocol 2 and turned on the software's password protected double-blind feature. This meant the experimenter could select to apply Protocol 1 or Protocol 2 in the software but could not see any additional details about the protocol parameters nor any activity in the hardware during stimulation that would indicate which protocol was the Active or Sham

condition. Participants were informed of the cross-over design and that they would experience two different stimulation paradigms, one of which was expected to have an effect (Active) and the other of which was not (Sham). Beyond this, participants were informed prior to every stimulation session about the likely course of sensations (initially increasing itching, tingling or warmth on the top of the head for the first 1-2 minutes, that then fades away slowly), but were not given any further details about the stimulation protocol parameters or intended effects.

At the beginning of the first session in each phase, participants were asked whether they expected active HD-tDCS to have positive effects. Participants were further asked to rate which protocol they believed that they received immediately following each HD-tDCS session. Following assessment on Day 4 of each phase, participants completed a debriefing interview where they were asked: which protocol they believed they had received in the present phase, how certain (from 1: 'not at all' to 5: 'completely') they were about their protocol guess, when they recalled believing it was that protocol, why they believed this, sensations felt during stimulation, and side effects attributed to the stimulation. As this study used a novel montage targeting non-motor areas, it was deemed important to ensure that all potential adverse effects were captured and reported. Therefore, after these unstructured side effect reports, participants were then explicitly asked if they experienced any of the following adverse effects (based on previous HD-tDCS/tDCS literature[48; 65; 71]) during the present phase that they attributed to the stimulation: itching, tingling, burning, numbness, skin discomfort or redness, headache, change in movement control or visual perception, nausea, dizziness, difficulty concentrating, fatigue, nervousness, insomnia, mood swings.

#### *Handheld Pressure Algometry*

A 1 cm<sup>2</sup> rubber-tipped handheld pressure algometer (Somedic, Sweden) was used to assess pressure pain thresholds (PPTs) bilaterally over the extensor carpi radialis (ECR: 3 cm distal to the lateral epicondyle along a line toward the radial condyle), upper trapezius (UT: midway between the C7 spinous process and the acromion), lumbar extensors at the levels of the first and fifth lumbar vertebrae (L1 and L5: 3.5 cm lateral to the L1 and L5 spinous processes, over the erector spinae muscle/fascial bulk), and gastrocnemius (GAS: midway between the popliteal line and calcaneal tuberosity) muscles. This combination of sites has been used previously in LBP patients and healthy individuals[51] and allows for assessment of local (L1/L5) pressure sensitivity, as well as pressure sensitivity in regional (GAS), related (UT) and distant (ECR) areas to the low back. Further, all tests can be completed with the participant in a relaxed prone position, hence limiting

positional changes and potential pain provocation during assessment. Pressure was applied at 30 kPa/s perpendicular to each muscle belly until the participant indicated that the pressure became painful by pressing a button. Two measurements were repeated at each site, with >2 mins interval between testing of the same site and were averaged across repetitions and sides for analysis.

### *Cuff Pressure Algometry*

A computer-controlled cuff algometry system (Nocitech, Denmark), paired with two 10 cm-wide tourniquet pressure cuffs (VBM, Germany) and an electronic visual analogue scale (eVAS; anchored at 0 cm: 'no pain', 10 cm: 'worst pain imaginable'), was used to assess cuff pressure pain detection (cPDT) and tolerance (cPTT) thresholds, along with suprathreshold ratings, TSP and CPM.

This cuff algometry system offers reliable, validated, user-independent assessment of deep-tissue sensitivity[12; 24; 25], assumed to be of relevance to musculoskeletal pain conditions like CLBP.

Cuffs were placed firmly over the widest portion of each calf, approximately 5-cm distal to the tibial tuberosity. For cPDT and cPTT, pressure was increased at a rate of 1 kPa/s to a maximum of 100 kPa (safety limit) during which participants were asked to begin sliding the VAS dial upward when the pressure first became painful (cPDT, extracted at VAS = 1 cm), keep rating the intensity of pain on the eVAS as the pressure increased, and then press the 'stop' button when the pressure became intolerable (cPTT).

### *Suprathreshold Ratings*

Pressure was applied to the dominant leg at a rate of 100 kPa/s to cPTT intensity 3 times for 1 s with a 10 s break between stimuli. Participants were to rate the pain intensity of each stimulus on the eVAS then return the dial to 0 before next stimulation, with the maximum eVAS value for each stimulus extracted and averaged across repetitions for analysis.

### *Temporal Summation of Pain*

Ten sequential 1-s cuff inflations were applied to the dominant leg with 1 s interval in-between (100 kPa/s inflation rate). Participants were to rate the pain intensity (eVAS) of the first stimulus, leave the dial stationary, then adjust from this point if subsequent stimuli were perceived to be more or less painful. eVAS ratings after each stimulus were extracted and normalised by subtraction to the first stimulus rating, then averaged into three epochs of the second to fourth (I), fifth to seventh (II) and eighth to tenth inflations (III).

### *Conditioned Pain Modulation*

Four sequential assessments of cPDT and cPTT were applied on the dominant leg (test stimuli). Simultaneous to the third assessment, a conditioning stimulus was applied to the non-dominant leg via tonic cuff pressure inflation at 70% of cPTT, as assessed immediately prior to the CPM paradigm. Participants were asked to verbally rate the pain intensity of this conditioning stimulus on a numeric rating scale anchored in the same manner as the VAS. The second to fourth cPDT and cPTT values were normalised by subtraction to the first assessment, with the second ramp showing habituation effects of stimulus repetition, and the third (parallel) and fourth (sequential) representing CPM effects, as described previously[50; 51].

### *Statistics*

Using G\*Power (v3.1.9.2) an A-priori sample size calculation was performed; assuming a modest correlation between repeated measures ( $R=0.6$ ), with 9 assessment sessions, 12 participants were required to detect a moderate effect size ( $f=0.25$ ) with 80% power at a 0.05 alpha-level. Data were checked for normality using Shapiro-Wilks and parametric or non-parametric analysis was then used accordingly. Data are presented as mean (standard deviation (SD)) or median (interquartile range (IQR)) in tables and mean (+ standard error of the mean (SEM)) in figures. Blinding success was checked using a binomial test compared to chance (50%) for dichotomous protocol guesses, and using Wilcoxon signed rank tests for guess certainty, timing, and side effect reports. Data analyses regarding immediate effects of HD-tDCS on pain, questionnaire, and psychophysical outcomes recorded post-stimulation on Day1 and Day3 are reported in supplementary material and summarized here. To understand changes in baseline values over time and thus possible carry-over effects (regardless of HD-tDCS phase), questionnaire (pain intensity and unpleasantness VAS, RMDQ, BPS, sleep, mood, IPAQ, PCS, STAI, PANAS and BDI) and psychophysical data (PPTs, cPDT, cPTT, STR, TSP, and CPM) from the first (Day1 first completed phase), fifth (Day1 second completed phase) and ninth (Day21) sessions were compared using paired t-test, Wilcoxon signed rank test, repeated-measures analysis of variance (RM-ANOVA) or Friedman's ANOVA as appropriate. To investigate effects of HD-tDCS on questionnaire data (average and maximum 24 hour pain intensity and unpleasantness VAS, RMDQ, BPS, sleep, mood, PCS, STAI, and PANAS) for outcomes collected at the beginning of Day1, Day4, and Day21, using ANOVA or Friedman's ANOVA as appropriate. To investigate effects of HD-tDCS on psychophysical (PPTs, cPDT, cPTT, STR, TSP-epochs, and CPM-effects) outcomes, data from Day1, Day4, and Day21 in each phase were compared using RM-ANOVA or Friedman's ANOVA as appropriate. Finally, exploratory

Spearman's Rho correlations between CPM-effects at baseline (parallel ramp) and change in CPM (Day4 minus Day1 and Day21 minus Day1) due to Active or Sham HD-tDCS were conducted to understand variation in responses to stimulation. RM-ANOVAs were Greenhouse-Geisser corrected in the event of lacking sphericity on Mauchly's W testing. All post-hoc comparisons were Bonferroni corrected with significance set at  $P < 0.05$ .

## RESULTS

### *Patient Characteristics*

Twelve chronic LBP patients were included in the study and all completed both 4-day phases. One participant did not return for the final follow-up session (Day21) and one participant ceased the active stimulation at 10-minutes on Day3 due to intolerable scalp sensation (described as strong burning and pulling pain), though remaining data collection was still completed and included for this participant. Full analysis was completed on 11 participants, as the inclusion of the 12<sup>th</sup> participant (who did not return for Day21 in the second phase) did not change results for Day1 to Day4 comparisons. Generally, these patients were young (Table 1), though reported having had LBP for a number of years, with all having sought care for this pain in the past and approximately half having had an X-ray and/or MRI of their back taken previously (no abnormalities reported). All reported pain primarily in the lower back region with no patients reporting referral into the legs, but occasional (n = 4) reports of related pain in the upper back or neck.

----- Table 1 -----

### *Blinding*

Two more participants guessed the protocol correctly in the second phase than the first, and in the Active than the Sham HD-tDCS condition, but accuracy was not statistically different to chance in any condition ( $P > 0.38$ , Table 2). No differences were noted for guessing certainty ( $Z = -0.368$ ,  $P = 0.71$ ), guess timing ( $Z = -0.740$ ,  $P = 0.45$ ), or how commonly sensations (All  $P > 0.18$ ) or side effects ( $P = 0.831$ ) were reported between Active and Sham conditions (Table 2). On qualitative assessment, participants typically reported guessing they had received Active HD-tDCS when they had perceived stronger sensations during and/or a reduction in LBP intensity, but these associations were frequently incorrect (Table 2).

----- Table 2 -----

### Questionnaire Data

Baseline Differences: When baseline pain, disability, sleep, mood, IPAQ, PCS, STAI, PANAS and BDI data for the first (Day1, phase 1), fifth (Day1, phase 2) and ninth (Day21, phase 2) session (chronological irrespective of stimulation protocol) were compared, only a difference in RMDQ was observed ( $X^2=6.9$ ,  $P<0.04$ ), where disability scores were lower in session 5 than session 1 ( $Z=-2.53$ ,  $P=0.011$ ). No other significant differences were observed between baseline sessions for any variable (all  $P>0.1$ , Table 3) suggesting no carry-over effects between phases.

Effects of HD-tDCS: No significant effects of HD-tDCS (active, sham) or days (Day1, Day4, Day21) were observed for past 24 hour average pain intensity or unpleasantness VAS scores, maximum pain intensity or unpleasantness VAS scores, McGill scores, RMDQ, sleep time, current mood, mood over the past week, PCS, STAI-state, STAI-Trait, PANAS-positive or PANAS-negative scores (All  $P>0.1$ , Table 3). A significant *HD-tDCS\*Day* interaction ( $F_{2,20}=4.12$ ,  $P=0.032$ ,  $\eta^2=0.29$ , Table 3) was observed for BPS pain ratings, reflecting movement-evoked pain in functional tasks, whereby pain ratings were higher in the Sham than Active phase at the Day1 baseline assessment ( $P=0.021$ ), and were reduced at Day21 compared to Day1 in the Sham phase ( $P=0.043$ ).

----- Table 3 -----

### Psychophysical Data

Baseline Differences: When the first (Day1, phase 1), fifth (Day1, phase2) and ninth (Day21, phase 2) sessions were compared, no significant differences were noted in any of the psychophysical measures (PPT, cPDT, cPTT, STR, TSP and CPM). Only that TSP-epochs and CPM-effects were both present, with significant main effects of *Epoch* ( $F_{2,20}=15.33$ ,  $P<0.001$ ,  $\eta^2=0.60$ ), showing significant increases in ratings in each subsequent epoch (Post-hoc:  $1<2<3$ ,  $P<0.03$ ), and *Ramp* ( $F_{2,20}=5.25$ ,  $P=0.015$ ,  $\eta^2=0.34$ ), showing that cPDT and cPTT were higher on the third than second ramp, (Post-hoc: 3<sup>rd</sup> ramp (parallel CPM) > 2<sup>nd</sup> ramp (habituation),  $P=0.03$ ), respectively.

Effects of HD-tDCS: For PPTs, a *HD-tDCS\*Day* interaction was observed ( $F_{2,20}=3.60$ ,  $P=0.046$ ,  $\eta^2=0.26$ ). However, no significant differences were observed on post-hoc testing, but this effect was likely driven by slightly lower PPTs on Day1 in the sham compared with active (Day1 Active minus Sham =  $87.2 \pm 41.9$  kPa,  $P=0.064$ , Fig. 3A).

For cPTT, there was a main effect of *Day* ( $F_{1,2,11.7}=7.00$ ,  $P=0.018$ ,  $\eta^2=0.41$ , Fig. 3B), whereby cPTT was higher on Day21 than Day1 (Day21 minus Day1 =  $3.3 \pm 1.1$  kPa,  $P=0.043$ ). No significant effects were observed for cPDT ( $F<2.17$ ,  $P>0.14$ ,  $\eta^2<0.18$ ), nor were any significant effects observed for STR ( $F<0.49$ ,  $P>0.60$ ,  $\eta^2<0.05$ , Fig. 3C).

For TSP, there was a main effect of *Epoch* ( $F_{2,20}=11.21$ ,  $P=0.001$ ,  $\eta^2<0.53$ , Fig. 3D), showing an increase in eVAS scores on each subsequent *Epoch* (I<II<III,  $P<0.04$ ), but no significant differences between *HD-tDCS* or *Days* were noted.

There was a main effect of *Ramp* for CPM effects on both cPDT ( $F_{2,20}=4.39$ ,  $P=0.026$ ,  $\eta^2<0.31$ ) and cPTT ( $F_{2,20}=11.91$ ,  $P<0.001$ ,  $\eta^2<0.54$ , Fig. 3E). Post-hoc tests were non-significant for CPM effects on cPDT, but CPM effects on cPTT showed greater inhibition of ramps during (3<sup>rd</sup> Ramp (parallel CPM) > 2<sup>nd</sup> Ramp (habituation),  $P=0.005$ ) and following (4<sup>th</sup> Ramp (sequential CPM) > 2<sup>nd</sup> Ramp (habituation),  $P=0.005$ ) conditioning compared to the ramp prior, indicating CPM was present in these CLBP patients. No significant differences were observed between *HD-tDCS* or *Days* despite the visual trend evident in Fig. 3.

----- Figure 3 -----

#### *Exploratory Correlation Analysis*

A moderate negative correlation was observed between CPM at baseline (absolute first session, Day1) and the change in CPM following Active HD-tDCS (Day4,  $R_s=-0.79$ ,  $P=0.002$ , Fig. 4), suggesting those with the least efficient CPM at baseline responded most positively to the Active stimulation. The corresponding correlation analysis for changes in CPM following Sham HD-tDCS was in the opposing direction (positive) and non-significant (Day4,  $R_s=0.53$ ,  $P=0.075$ , Fig. 4). However, it should be noted, that in the majority of participants CPM was efficient at baseline, so mean effects of Active HD-tDCS on CPM in this sample were not significant.

----- Figure 4 -----

#### *Immediate Effects of HD-tDCS*

HD-tDCS had an immediate effect on pain intensity and unpleasantness, with a greater reduction in pain intensity observed on Day1 than Day2 and Day3 ( $P<0.03$ , Supplementary Material). No significant immediate effects were observed for short-form versions of the McGill, PCS, STAI, or PANAS, or for Valence and Arousal ratings. PPTs at the ECR showed greater reduction after Active than Sham HD-tDCS ( $P<0.04$ ), and both cPTT and STR showed greater increases on Day3 than Day1 ( $P<0.04$ ), but no immediate effects on cPDT, TSP or CPM were observed ( $P>0.06$ , Supplementary Material).



## DISCUSSION

Active versus sham HD-tDCS was directed at the mPFC in CLBP patients, primarily aiming to improve CPM, as well as ;possibly reducing -affective disturbances, and clinical pain. Blinding of HD-tDCS protocol was successfully achieved despite the cross-over design. However, even though various characteristics were assessed through questionnaire and psychophysical testing, no meaningful differences were observed between Active and Sham HD-tDCS. General temporal effects on cuff pain tolerance thresholds were evident, as well as immediate reductions in LBP ratings following both HD-tDCS paradigms on the first day. An interesting exploratory association was identified, suggesting that HD-tDCS paradigms targeting the mPFC may have potential for improving CPM in patients with severe impairments in this mechanism, however these findings need replication and further validation.

### *CLBP patient characteristics*

A comprehensive profile of CLBP patients was obtained, including sensory and affective LBP features, pain duration, self-reported disability, observer quantified function, state and trait psychological factors, past care-seeking behaviours, aggravating and easing factors, and prognostic and mechanistic classifications. As no meaningful changes were observed across the study in any of these outcomes on a group level, it is unlikely that this HD-tDCS paradigm alone has interventional potential in this specific population. Prior trials have suggested that combined tDCS and peripheral interventions can provide enhanced and maintained analgesic effects[27], and these possibilities remain to be explored with this new stimulation montage. However, there are also sample characteristics that are important to consider in relation to the lack of efficacy seen here. For example, despite reporting having had CLBP for several years, the patients included here reported minimal pain during testing sessions with even maximum past 24-hour pain ratings rarely exceeded 6/10; which is considerably lower than CLBP patients attending pain clinics[56]. The majority of included CLBP patients also reported levels of pain-catastrophizing[78], anxiety[34], and affect[5; 11] consistent with prior control data[51] and mostly below clinical cut-off scores. It was not the intention to recruit individuals with low pain scores, as this can produce floor effects, where clinically meaningful pain relief is challenging to demonstrate. However, it is possible that a relatively low-disability sample should have been expected given the intensive involvement required for the study (potentially preventing working individuals and those with reduced mobility from participating).

### *Psychophysical assessments of pro- and anti-nociception*

CLBP patient populations have previously been shown to have impaired CPM, facilitated TSP and reduced PPTs at local and distant sites, at least on a group level[15; 52]. However, CLBP patients represent a highly heterogeneous group, both in terms of symptomatology and ~~regarding~~ CPM impairment. Prior studies ~~tend to~~ suggest that CPM may be more impaired in patients with severe, widespread and/or longer lasting pain[21-23]. Hence, given the mild localised pain and limited disability reported in the present sample, it may be unsurprising that the majority (75%) demonstrated efficient CPM. In fact, both mean CPM and TSP observed here are of similar magnitude to control participants assessed ~~in prior work using with~~ the same methodology[24; 25; 30; 50]. PPTs over the lumbar sites were low in comparison to prior studies in controls[50; 67; 87], but fluctuations in PPT often occur with pain presence[51; 61; 66; 75], especially locally, and do not necessarily represent a pathological feature of the broader condition[14]. Based on these findings, it may be that these patients simply did not have ~~had~~ the problems usually associated with CLBP[53] that the HD-tDCS was intended to target ~~and thus no clear changes could be observed~~.

### *HD-tDCS targeting in CLBP*

Most prior non-invasive brain stimulation studies in chronic pain conditions have targeted the motor cortex[18]. However, it was hypothesized here that better effects might be observed if stimulation was directed to areas involved in affective processing and descending pain modulation, where impairments have previously been reported in CLBP patients[3; 49; 52; 90]. A previous study using similar justification targeted the ACC using conventional unilateral tDCS and showed reduced pain interference, intensity and disability after 6-weeks in CLBP patients[44]. However, this study did not assess CPM, used 10 sessions (as opposed to 3 here), a cathodal array, and a sample population of primarily older adult males with greater pain and disability levels, which may explain differences in results.

Polarity-dependent effects on cortical excitability and experimental pain perception have previously been observed for the motor[57; 92], sensory[82] and dorsolateral prefrontal[60] cortices, with anodal stimulation considered excitatory and cathodal inhibitory[13]. However, polarity effects are not always clear when targeting frontal regions[45; 46; 58] or when assessing pain perception in patients, where both cathodal and anodal stimulation may show similar effects[40; 85]. Anodal stimulation was selected here to target prefrontal connections to the periaqueductal gray[9], theorised to be involved in affective regulation of descending inhibition.

However, interplay between prefrontal regions is complex[68] and these regions can exert modulatory effects on pain through multiple distinct mechanisms[4; 86], including aforementioned PAG-mediated descending inhibition, descending facilitation of nociceptive transmission[93], or supraspinal effects on affective pain processing[16; 59]. There are also various subregions within the mPFC which show differential activation during pain[37], so although current direction is likely important, determining effects on specific subregions is challenging. Hence, even though HD-tDCS improves electrical field focality, it is likely that greater specificity in targeting is still needed.

It is also important to consider that alterations in functional connectivity observed between the mPFC and PAG in CLBP patients, which were suggested to indicate impaired descending pain modulation in these patients[90], seem to depend on current attentional, affective and pain state features[36]. As HD-tDCS paradigms are applied at rest, and as conversely heightened mPFC activity and connectivity to other pain processing regions has been observed at rest in CLBP patients[94], it may instead be more effective to use cathodal HD-tDCS to inhibit the mPFC. This approach may better reduce pain perception and/or unpleasantness more generally, consistent with the prior CLBP study[44] and with effects seen following brief TMS-induced disruption of the mPFC[35], though this would no longer ~~fit with targeting target~~ descending inhibitory connections and hence expected effects on CPM are unclear.

#### *Differential effects of HD-tDCS depending on baseline CPM*

It is interesting to consider why opposing effects were seen between patients with differing CPM efficacy at baseline. This may be the result of individual differences in resting brain activity and/or connectivity prior to the tDCS session, as has previously been shown to influence tDCS response[62]. For example, if efficient CPM reflects that mPFC-PAG pathways are already active in these patients, an additional excitatory tDCS paradigm may then produce an inhibitory homeostatic response[41] and have a negative effect on CPM. Whereas patients with severe CPM impairment, potentially reflecting reduced mPFC-PAG activity, may benefit from this HD-tDCS paradigm. This, along with the influence of individual brain states prior to treatment, requires further exploration.

Enhanced tDCS effects may also be observed if ~~appropriately~~ targeted stimulation was combined with other relevant training[69]. This is currently being tested in a large cohort of CLBP patients using tDCS in combination with functional motor and sensory training[2], but results are yet to come. In the specific case of CPM, it is possible that combinations of mPFC HD-tDCS

paradigms with other strategies to improve descending inhibition, such as tapentadol, duloxetine, artificial mood enhancement, stress reduction or sleep restoration could be successful. However, future work is needed to explore ~~the efficacy of these combinations~~this and further validate the pathophysiological importance of CPM impairment as a treatment target in CLBP.

### *Blinding*

~~Unfortunately, due~~Due to the small sample size, it was not possible to examine expected/believed HD-tDCS protocol effects; however, it appeared that HD-tDCS guesses were often wrong and hence blinding was well maintained throughout the trial. This is important to highlight, as ~~this is~~blinding has been reported to be problematic, especially in HD-tDCS studies ~~due to increased current density~~[20; 31], and in cross-over trials where participants are able to compare sensations[63; 64]. Prior studies attempting to develop sham strategies have shown clear differences in reported sensations during stimulation, unless a shunting technique (~~i.e.~~ using adjacent electrodes to shunt current through the scalp) was used[20; 72]. The central electrode array used in the present study was not conducive to this approach, so instead a longer ramp up and down phase was used to mimic the sensation-timeline reported during pilots in the active condition. Recall accuracy of painful sensations has been suggested to be substantially diminished after several days[7], hence the two-three week gap between phases here would have made comparison between stimulation paradigms challenging. Other factors likely contributing to blinding success here include using a trained investigator to place electrodes, concurrent experimenter blinding, neglecting specific information about the stimulation paradigms, and providing equally strong reinforcement of expected sensations during both phases. This successful blinding strengthens conclusions, and also supports prior work[20] indicating that crossover designs, which minimise sample size and ~~thus~~ exposure to experimental treatment, are appropriate for pilot testing new HD-tDCS paradigms.

### *Limitations*

Beyond influences of patient characteristics a few limitations should be noted. This pilot trial was adequately powered to show differences in psychophysical testing but only used a small sample of heterogeneous CLBP patients. As well, inherent issues with tDCS such as varying head size and hair thickness, unknown cognitive processes potentially performed by participants during stimulation, and interindividual e.g. anatomical, neurochemical and genetic variation which may influence current flow and precise electrode placement, that have been discussed previously[32; 38], were

presumably also evident here. Finally, this study only assessed patients on the days during, immediately following and on Day21 post-stimulation, so latent effects as observed in prior studies may have been missed.

### *Conclusion*

This study has shown no significant effects of active mPFC HD-tDCS on anti-nociceptive mechanisms, nor on other psychophysical tests, clinical LBP features or psychological characteristics. Blinding was maintained throughout the trial, ~~despite the crossover design,~~ suggesting ~~this a crossover study~~ design is appropriate for pilot testing new experimental paradigms. Future work should focus on ~~appropriate~~ patient screening and selection strategies to study effects on patients with true deficiencies in anti-nociceptive mechanisms, as well as optimising stimulation targeting, exploring different arrays and current directions, and looking at effects combined with mechanistically justified complementary interventions.

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**Figure 1:** Trial protocol showing (A) timeline of all sessions in the full protocol and (B) procedures involved on each day of each phase, as then repeated for alternate HD-tDCS paradigm. FAs seen in (A) for the second phase, the first assessment on Day1 acts as Day21 for the first phase, whereas in the second phase it is a separate Day21 session. In (A), orange circles indicate sessions with HD-tDCS and grey circles represent sessions with measurement only. In (B), faded boxes represent data either reported in supplementary material (immediate effects on pain, short-form questionnaires, and psychophysical testing) or not reported here (grey-empty grey boxes representing resting-state electroencephalography and affective/attentional outcomes). IPAQ: International Physical Activity Questionnaire. PCS: Pain Catastrophizing Scale. STAI: State-Trait Anxiety Inventory. PANAS: Positive and Negative Affective Schedule. BDI-II: Beck Depression Inventory. MPQ: McGill Pain Questionnaire. RMDQ: Roland-Morris Disability Questionnaire. SBSQ: Start Back Screening Questionnaire. SLR: Straight Leg Raise. PPT: Pressure Pain Threshold. ECR: extensor carpi radialis. UT: upper trapezius. L1/L5: 1<sup>st</sup> and 5<sup>th</sup> lumbar segments. GAS: gastrocnemius. PDT/PTT: pain detection/tolerance threshold. STR: suprathreshold rating. TSP: temporal summation of pain. CPM: conditioned pain modulation. HD-tDCS: high density transcranial direct current stimulation. SFQ: short-form questionnaires. PS: pain sensitivity assessment. EX: physical examination.

**Figure 2:** Depiction of A) HD-tDCS stimulation protocol for Active (60 s ramp ON, 18 min anodal HD-tDCS, 60s ramp OFF) and Sham (60 s ramp ON, 60 s ramp OFF); B) placement and current amplitude for anode, cathodes and reference electrode in relation to the 10-20 International EEG System; and C) electrical field modelling of 2mA anodal stimulation paradigm generated with SimNIBS as per prior simulations[79].

**Figure 3:** Mean (+SEM) psychophysical outcomes on Day1, Day4, and Day21 in both Active (yellow) and Sham (blue) HD-tDCS conditions: A) pressure pain thresholds, B) cuff pain detection (cPDT) and cuff tolerance threshold (cPTT), C) suprathreshold ratings, D) temporal summation of pain, and E) conditioned pain modulation. ECR=extensor carpi radialis, UT=upper trapezius, GAS=gastrocnemius. R2-4=Ramp 2-4 (2: prior to conditioning, 3: during conditioning, 4: post-conditioning). Significant between-epoch difference from Epoch 1 or between-ramp difference from

Ramp 2 is shown (\*,  $P < 0.03$ ). Main effect of Day with significant increase compared to Day1 is indicated (#,  $P < 0.04$ ).

**Figure 4:** Spearman's Rho correlations between mean CPM (parallel, ramp-3 minus ramp-1, average of effects on cPDT and cPTT) at baseline Day1 and the change in mean CPM from Day1 to Day4 within each HD-tDCS condition (Active/Sham). Individual participant data shown in orange for the 6 patients with least efficient CPM and in green for the 6 patients with most efficient CPM at baseline.

**Medial Prefrontal High-Definition Transcranial Direct Current Stimulation to Improve Pain Modulation in Chronic Low Back Pain: A Pilot Randomized Double-blinded Placebo-Controlled Crossover Trial**

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## **ABSTRACT**

Chronic low back pain (CLBP) is highly disabling, but often without identifiable source. Focus has been on impaired anti-nociceptive mechanisms contributing to pain maintenance, though methods of targeting this impairment remain limited. This randomised-controlled cross-over pilot trial used active versus sham medial prefrontal cortex (mPFC) high-definition transcranial direct current stimulation (HD-tDCS) for three-consecutive days to improve descending pain inhibitory function. Twelve CLBP patients were included with an average visual analogue scale (VAS) pain intensity of  $3.0 \pm 1.5$  and pain duration of  $5.3 \pm 2.6$  years. Pressure pain thresholds (PPTs), conditioned pain modulation (CPM), and temporal summation of pain (TSP) assessed by cuff algometry, as well as pain symptomatology (intensity, unpleasantness, quality, disability) and related psychological features (pain catastrophizing, anxiety, affect), were assessed on Day1 before three consecutive days of HD-tDCS sessions (each 20 min), at 24-hours (Day4) and 2-weeks (Day21) following final HD-tDCS. Blinding was successful. No significant differences in psychophysical (PPT, CPM, TSP), symptomatology or psychological outcomes were observed between active and sham HD-tDCS on Day4 and Day21. CPM-effects at Day1 negatively correlated with change in CPM-effect at Day4 following active HD-tDCS ( $P=0.002$ ). Lack of efficacy was attributed to several factors, not least that patients did not display impaired CPM at baseline.

**Trial registration:** ClinicalTrials.gov (NCT03864822)

**Perspective:** Medial prefrontal HD-tDCS did not alter pain, psychological nor psychophysical outcomes, though correlational analysis suggested response may depend on baseline pain inhibitory efficacy, with best potential effects in patients with severe impairments in descending pain inhibitory mechanisms. Future work should focus on appropriate patient selection and optimising stimulation targeting.

**Key words:** Low back pain, non-invasive brain stimulation, conditioned pain modulation, medial prefrontal cortex, randomized crossover trial

## INTRODUCTION

Chronic low back pain (CLBP) is well-known to be a costly and disabling condition, for which clear pathophysiology is lacking in the majority of cases[33; 43; 89]. As a result, increased focus has been placed on psychosocial factors and central pain processing mechanisms as possible contributors to the development and maintenance of the condition[26; 74]. Prior work has shown both that CLBP commonly co-occurs with affective disturbances[17; 47], and that CLBP patients generally show impairments in anti-nociceptive mechanisms (e.g. Conditioned Pain Modulation (CPM)) related to LBP duration, extent, and severity[15; 22; 52]. Although behavioural interventions can be used by experienced clinicians to successfully address these affective and psychosocial factors[83], there remains little conclusive evidence on whether impaired anti-nociceptive mechanisms can be restored.

One approach could be to intervene with factors associated to impairments in CPM[28; 55]; e.g. by reducing stress, restoring sleep quality and/or increasing physical activity. However, it is difficult to acutely alter these factors in a repeatable manner. Another more standardised approach to acutely improving anti-nociceptive mechanisms may be through transcranial direct current stimulation (tDCS), which is a non-invasive method of altering cortical excitability, that has been used to acutely enhance CPM in healthy individuals[18]. In CLBP populations, tDCS trials have not focussed on targeting anti-nociceptive mechanisms specifically, though trials for this purpose in other pain populations are ongoing[8]. Instead, most existing clinical studies aim to reduce pain and disability by stimulating either the primary motor or dorsolateral prefrontal cortex[1; 69]. So far, these approaches have had limited success[1], which could be due to the lack of relevant stimulation targeting. In the present work, it was therefore hypothesized that targeting cortical regions involved in both affective regulation and pain modulation, as commonly shown to be altered in CLBP patients, may be more efficacious.

The medial prefrontal cortex (mPFC) has recently been highlighted as a prime locus for affect and anti-nociception[37], due to its role in encoding pain affect[70], and its connections with the periaqueductal gray (PAG) and thus descending inhibitory circuitry[4; 86]. Among CLBP patients, abnormal functional connectivity has been observed between areas of the mPFC and PAG[49; 81; 90; 91], with reduced connectivity seen during clinical LBP exacerbation[90] and experimental pain provocation[49]. Such alterations in connectivity have been shown to correlate with pain intensity[90] and other clinical parameters[81], and have been speculated to indicate impaired cortical initiation of descending inhibition[90].

So far, no pain studies have targeted the mPFC to enhance anti-nociceptive mechanisms using tDCS. However, a prior study used high-definition tDCS (HD-tDCS), posited to enhance focal accuracy and current penetration compared to conventional tDCS[84], to target the anterior cingulate cortex (ACC, a mPFC subregion), showing differential effects on specific cognitive tasks[80]. Computer modelling of this array demonstrates current spreading generally in the mPFC[80], hence it was deemed appropriate to use in the present study.

In this randomized crossover pilot trial, the primary objective was to assess effects of active versus sham HD-tDCS, applied to the mPFC for three consecutive days, on descending pain inhibition as measured by CPM. Secondary objectives were to assess active HD-tDCS effects on other psychophysical testing measures (pressure pain thresholds and temporal summation of pain), along with symptomatology (pain severity and disability) and psychological features (affect, anxiety, pain catastrophizing). It was hypothesized that active HD-tDCS would improve CPM effects, reduce negative affective features, and reduce LBP.

## **METHODS**

### *Participants*

Participants with chronic low back pain (CLBP) were recruited through advertisements on social media and local noticeboards, and initially screened for eligibility via email and over the phone. Participants were required to be 18-60 years old, speak English fluently, and complain of CLBP, defined as: Pain experienced primarily posteriorly between the inferior border of the 12<sup>th</sup> rib and the lower gluteal fold that had been continuously present (>3 days/week) for more than 3 months and was of sufficient intensity to limit daily activity. Participants were excluded if they were currently seeking active treatment, were routinely taking analgesics or other neuropsychotropic drugs, had red flag symptoms (i.e. fever, malaise, progressive neurologic deficit, significant trauma, prolonged corticosteroid use or osteoporosis, urinary or faecal incontinence, or unintended weight loss), had other current or previous neurologic, musculoskeletal, mental or pain disorders that may affect the trial, or did not pass the transcranial stimulation safety screen[6]. All participants received written and verbal information about the study prior to recruitment and provided written informed consent prior to commencing the study. This study was pre-registered on ClinicalTrials.gov (NCT03864822), approved by the local ethical committee (VN-20170034) and conducted in accordance with the Declaration of Helsinki. All data was collected in the laboratories of the Center for Neuroplasticity and Pain (CNAP) at Aalborg University throughout 2019 by a trained experimenter (MEM).



### *Study Design and Procedure*

This pilot study was designed as a randomized double-blind placebo-controlled experimental crossover trial. Once enrolled, participants were assigned a treatment order based on a computer-generated random number sequence and were scheduled for 9 experimental sessions (Fig. 1). This was broken into 2 phases of 5 sessions on Days 1, 2, 3, 4 and 21, where baseline assessment on Day 1 of phase 2 acted as the Day 21 session for phase 1. In each phase, participants received 3 consecutive days of either active or sham HD-tDCS for 20 minutes (including 60s ramp on and off, respectively) to the medial prefrontal region. Prior to and following stimulation on the first day (Day1) of each phase, as well as immediately following stimulation on the third day (Day3), 24 hours after (Day4) and over 2 weeks after (Day21) end stimulation, a series of physical examination and psychophysical assessments of pain sensitivity were completed. Questionnaire data was obtained at the beginning of each session to track daily fluctuations in e.g. pain, mood, and sleep, and before and after each stimulation session to capture immediate changes in e.g. pain, anxiety, affective state and arousal (supplementary material).

----- *Figure 1* -----

### *Demographics and Questionnaire Data*

At the start of the first session, participants reported their age, gender, height, weight, hand and leg dominance, and then completed a series of questionnaires. These included basic questions about their pain history (e.g. pain onset, duration, aggravating and easing factors, prior healthcare utilisation, prior investigations, beliefs), sleep duration (hours slept on preceding night), menstruation (current day of cycle) and mood (current and past week on the Face Scale[39]); along with the International Physical Activity Questionnaire[10] (IPAQ, rates daily activity in three categories to give an estimate of daily energy expenditure), Pain Catastrophizing Scale[78] (PCS, gives an indication of pain-related distress by rating the frequency of 13 catastrophic thought patterns), State-Trait Anxiety Inventory[76] (STAI, indicates present state and general trait anxiety levels through agreement with 40 self-depictions), Positive and Negative Affective Schedule[88] (PANAS, quantifies current positive and negative affect through degree of present experience of 20 different affective descriptors), and Beck Depression Inventory II[5] (BDI-II, classifies degree of depressive symptoms through 20 five-item scales of behaviours). Questionnaires were repeated as detailed in Fig. 1.

### *Low Back Pain and Disability Ratings*

In addition, in the Day1 and Day4 session of each phase, participants rated their current LBP intensity and unpleasantness, along with their average and maximum LBP in the preceding 24 hours, on paper visual analogue scales (VAS, 0 cm: no pain/not unpleasant at all; 10 cm: worst pain imaginable/most unpleasant sensation imaginable). Average 24-hour pain ratings were also collected at the beginning of sessions on the second and third days, and current pain ratings (supplementary material) were obtained immediately prior to and following HD-tDCS. Participants also completed the Roland-Morris Disability Questionnaire[73] (RMDQ, quantifies disability based on dichotomous responses to 24 statements of functional task impairment), Start-back Screening Questionnaire[29] (SBSQ, classifies risk of chronification based on dichotomous response to 9 statements), and the Pain-DETECT questionnaire[19] (aims to identify presence of neuropathic symptoms based on temporal and spatial pain pattern and presence of different sensory qualities), and chose pain descriptors from the 72-word table of the McGill Pain Questionnaire[54]. The SBSQ and Pain-Detect were only completed in the very first session, whereas the RMDQ and McGill Pain Questionnaire were repeated on Day1 and Day4 in each phase.

### *Physical Examination*

Participants underwent a brief patient history to reconfirm eligibility for study inclusion, and explore their LBP history, prior investigations or interventions trialled, and beliefs about the condition. They then completed a basic physical examination including flexion, extension and lateral flexion, straight leg raise testing, and the Back Performance Scale[42; 77] to quantify function and movement-evoked pain (BPS, 5 standardised functional tasks with pain during the task rated by the participant and performance quality rated by the observer).

### *High-Definition Transcranial Direct Current Stimulation*

Direct current was delivered through five circular Ag/AgCl electrodes, placed with conductive electrode gel in 4 x 1 configuration in a neoprene EEG cap (NE056 Headcap in medium or large dependent on participant's head size, Neuroelectronics, Spain), using a battery-powered multichannel neurostimulator (Starstim R32, Neuroelectronics, Spain). The Cz channel of the EEG cap was placed at the vertex (measured midpoint between nasion and inion, and preauricular points), orientation of the cap was checked for symmetry and was secured under the ears of participants. The anode was placed at Fz with four surrounding cathodes on the forehead at Fp1, Fp2, F7 and F8 as determined by the International 10-20 Electroencephalography System (Fig. 2), and as has been

used previously to target subregions of the mPFC[80]. Prior to each stimulation session, electrical impedance was checked using the Neuroelectronics Instrument Controller (NIC2, Neuroelectronics, Spain) and electrodes were adjusted until good impedance (below 10k $\Omega$ ) was achieved for all stimulating electrodes. During each active stimulation session, participants were asked to sit quietly with their eyes open. Current ramped up over 60 s to the target intensity of 2 mA for the anode (and -500 $\mu$ A at each cathode), where it remained for 18 minutes, then ramped down again over 60 s (20-minute total stimulation period). During each sham stimulation session, the stimulation ramped up over 60 s to 2 mA, then immediately ramped down again over 60 s and remained off for the subsequent 18 minutes to match the active stimulation period (Fig. 2). The electrical field distribution from this HD-tDCS array was modelled on a sample interface ('Ernie' dataset with prespecified scalp and cortical impedances), using the stimulation and electrode parameters detailed above, in SimNIBS software for MatLab as per prior recommendations[79] (Fig. 2).

----- Figure 2 -----

#### *Blinding Procedure and Assessment*

Participants and the experimenter (MEM) were blinded to the HD-tDCS protocol applied in each phase. The experimenter initially set up the active and sham protocols in the HD-tDCS software (Neuroelectronics, Spain), after which a colleague who was not involved in the study, renamed the protocols to Protocol 1 and Protocol 2 and turned on the software's password protected double-blind feature. This meant the experimenter could select to apply Protocol 1 or Protocol 2 in the software but could not see any additional details about the protocol parameters nor any activity in the hardware during stimulation that would indicate which protocol was the Active or Sham condition. Participants were informed of the cross-over design and that they would experience two different stimulation paradigms, one of which was expected to have an effect (Active) and the other of which was not (Sham). Beyond this, participants were informed prior to every stimulation session about the likely course of sensations (initially increasing itching, tingling or warmth on the top of the head for the first 1-2 minutes, that then fades away slowly), but were not given any further details about the stimulation protocol parameters or intended effects.

At the beginning of the first session in each phase, participants were asked whether they expected active HD-tDCS to have positive effects. Participants were further asked to rate which protocol they believed that they received immediately following each HD-tDCS session. Following assessment on Day 4 of each phase, participants completed a debriefing interview where they

were asked: which protocol they believed they had received in the present phase, how certain (from 1: 'not at all' to 5: 'completely') they were about their protocol guess, when they recalled believing it was that protocol, why they believed this, sensations felt during stimulation, and side effects attributed to the stimulation. As this study used a novel montage targeting non-motor areas, it was deemed important to ensure that all potential adverse effects were captured and reported. Therefore, after these unstructured side effect reports participants were then explicitly asked if they experienced any of the following adverse effects (based on previous HD-tDCS/tDCS literature[48; 65; 71]) during the present phase that they attributed to the stimulation: itching, tingling, burning, numbness, skin discomfort or redness, headache, change in movement control or visual perception, nausea, dizziness, difficulty concentrating, fatigue, nervousness, insomnia, mood swings.

#### *Handheld Pressure Algometry*

A 1 cm<sup>2</sup> rubber-tipped handheld pressure algometer (Somedic, Sweden) was used to assess pressure pain thresholds (PPTs) bilaterally over the extensor carpi radialis (ECR: 3 cm distal to the lateral epicondyle along a line toward the radial condyle), upper trapezius (UT: midway between the C7 spinous process and the acromion), lumbar extensors at the levels of the first and fifth lumbar vertebrae (L1 and L5: 3.5 cm lateral to the L1 and L5 spinous processes, over the erector spinae muscle/fascial bulk), and gastrocnemius (GAS: midway between the popliteal line and calcaneal tuberosity) muscles. This combination of sites has been used previously in LBP patients and healthy individuals[51] and allows for assessment of local (L1/L5) pressure sensitivity, as well as pressure sensitivity in regional (GAS), related (UT) and distant (ECR) areas to the low back. Further, all tests can be completed with the participant in a relaxed prone position, hence limiting positional changes and potential pain provocation during assessment. Pressure was applied at 30 kPa/s perpendicular to each muscle belly until the participant indicated that the pressure became painful by pressing a button. Two measurements were repeated at each site, with >2 mins interval between testing of the same site and were averaged across repetitions and sides for analysis.

#### *Cuff Pressure Algometry*

A computer-controlled cuff algometry system (Nocitech, Denmark), paired with two 10 cm-wide tourniquet pressure cuffs (VBM, Germany) and an electronic visual analogue scale (eVAS; anchored at 0 cm: 'no pain', 10 cm: 'worst pain imaginable'), was used to assess cuff pressure pain detection (cPDT) and tolerance (cPTT) thresholds, along with suprathreshold ratings, TSP and CPM.

This cuff algometry system offers reliable, validated, user-independent assessment of deep-tissue sensitivity[12; 24; 25], assumed to be of relevance to musculoskeletal pain conditions like CLBP. Cuffs were placed firmly over the widest portion of each calf, approximately 5-cm distal to the tibial tuberosity. For cPDT and cPTT, pressure was increased at a rate of 1 kPa/s to a maximum of 100 kPa (safety limit) during which participants were asked to begin sliding the VAS dial upward when the pressure first became painful (cPDT, extracted at VAS = 1 cm), keep rating the intensity of pain on the eVAS as the pressure increased, and then press the 'stop' button when the pressure became intolerable (cPTT).

### *Suprathreshold Ratings*

Pressure was applied to the dominant leg at a rate of 100 kPa/s to cPTT intensity 3 times for 1 s with a 10 s break between stimuli. Participants were to rate the pain intensity of each stimulus on the eVAS then return the dial to 0 before next stimulation, with the maximum eVAS value for each stimulus extracted and averaged across repetitions for analysis.

### *Temporal Summation of Pain*

Ten sequential 1-s cuff inflations were applied to the dominant leg with 1 s interval in-between (100 kPa/s inflation rate). Participants were to rate the pain intensity (eVAS) of the first stimulus, leave the dial stationary, then adjust from this point if subsequent stimuli were perceived to be more or less painful. eVAS ratings after each stimulus were extracted and normalised by subtraction to the first stimulus rating, then averaged into three epochs of the second to fourth (I), fifth to seventh (II) and eighth to tenth inflations (III).

### *Conditioned Pain Modulation*

Four sequential assessments of cPDT and cPTT were applied on the dominant leg (test stimuli). Simultaneous to the third assessment, a conditioning stimulus was applied to the non-dominant leg via tonic cuff pressure inflation at 70% of cPTT, as assessed immediately prior to the CPM paradigm. Participants were asked to verbally rate the pain intensity of this conditioning stimulus on a numeric rating scale anchored in the same manner as the VAS. The second to fourth cPDT and cPTT values were normalised by subtraction to the first assessment, with the second ramp showing habituation effects of stimulus repetition, and the third (parallel) and fourth (sequential) representing CPM effects, as described previously[50; 51].

## *Statistics*

Using G\*Power (v3.1.9.2) an A-priori sample size calculation was performed; assuming a modest correlation between repeated measures ( $R=0.6$ ), with 9 assessment sessions, 12 participants were required to detect a moderate effect size ( $f=0.25$ ) with 80% power at a 0.05 alpha-level. Data were checked for normality using Shapiro-Wilks and parametric or non-parametric analysis was then used accordingly. Data are presented as mean (standard deviation (SD)) or median (interquartile range (IQR)) in tables and mean (+ standard error of the mean (SEM)) in figures. Blinding success was checked using a binomial test compared to chance (50%) for dichotomous protocol guesses, and using Wilcoxon signed rank tests for guess certainty, timing, and side effect reports. Data analyses regarding immediate effects of HD-tDCS on pain, questionnaire, and psychophysical outcomes recorded post-stimulation on Day1 and Day3 are reported in supplementary material and summarized here. To understand changes in baseline values over time and thus possible carry-over effects (regardless of HD-tDCS phase), questionnaire (pain intensity and unpleasantness VAS, RMDQ, BPS, sleep, mood, IPAQ, PCS, STAI, PANAS and BDI) and psychophysical data (PPTs, cPDT, cPTT, STR, TSP, and CPM) from the first (Day1 first completed phase), fifth (Day1 second completed phase) and ninth (Day21) sessions were compared using paired t-test, Wilcoxon signed rank test, repeated-measures analysis of variance (RM-ANOVA) or Friedman's ANOVA as appropriate. To investigate effects of HD-tDCS on questionnaire data (average and maximum 24 hour pain intensity and unpleasantness VAS, RMDQ, BPS, sleep, mood, PCS, STAI, and PANAS) for outcomes collected at the beginning of Day1, Day4, and Day21, using ANOVA or Friedman's ANOVA as appropriate. To investigate effects of HD-tDCS on psychophysical (PPTs, cPDT, cPTT, STR, TSP-epochs, and CPM-effects) outcomes, data from Day1, Day4, and Day21 in each phase were compared using RM-ANOVA or Friedman's ANOVA as appropriate. Finally, exploratory Spearman's Rho correlations between CPM-effects at baseline (parallel ramp) and change in CPM (Day4 minus Day1 and Day21 minus Day1) due to Active or Sham HD-tDCS were conducted to understand variation in responses to stimulation. RM-ANOVAs were Greenhouse-Geisser corrected in the event of lacking sphericity on Mauchly's W testing. All post-hoc comparisons were Bonferroni corrected with significance set at  $P<0.05$ .

## **RESULTS**

### *Patient Characteristics*

Twelve chronic LBP patients were included in the study and all completed both 4-day phases. One participant did not return for the final follow-up session (Day21) and one participant ceased the active stimulation at 10-minutes on Day3 due to intolerable scalp sensation (described as strong burning and pulling pain), though remaining data collection was still completed and included for this participant. Full analysis was completed on 11 participants, as the inclusion of the 12<sup>th</sup> participant (who did not return for Day21 in the second phase) did not change results for Day1 to Day4 comparisons. Generally, these patients were young (Table 1), though reported having had LBP for a number of years, with all having sought care for this pain in the past and approximately half having had an X-ray and/or MRI of their back taken previously (no abnormalities reported). All reported pain primarily in the lower back region with no patients reporting referral into the legs, but occasional (n = 4) reports of related pain in the upper back or neck.

----- Table 1 -----

### *Blinding*

Two more participants guessed the protocol correctly in the second phase than the first, and in the Active than the Sham HD-tDCS condition, but accuracy was not statistically different to chance in any condition ( $P > 0.38$ , Table 2). No differences were noted for guessing certainty ( $Z = -0.368$ ,  $P = 0.71$ ), guess timing ( $Z = -0.740$ ,  $P = 0.45$ ), or how commonly sensations (All  $P > 0.18$ ) or side effects ( $P = 0.831$ ) were reported between Active and Sham conditions (Table 2). On qualitative assessment, participants typically reported guessing they had received Active HD-tDCS when they had perceived stronger sensations during and/or a reduction in LBP intensity, but these associations were frequently incorrect (Table 2).

----- Table 2 -----

### *Questionnaire Data*

Baseline Differences: When baseline pain, disability, sleep, mood, IPAQ, PCS, STAI, PANAS and BDI data for the first (Day1, phase 1), fifth (Day1, phase 2) and ninth (Day21, phase 2) session (chronological irrespective of stimulation protocol) were compared, only a difference in RMDQ was observed ( $\chi^2 = 6.9$ ,  $P < 0.04$ ), where disability scores were lower in session 5 than session 1 ( $Z = -2.53$ ,  $P = 0.011$ ). No other significant differences were observed between baseline sessions for any variable (all  $P > 0.1$ , Table 3) suggesting no carry-over effects between phases.

Effects of HD-tDCS: No significant effects of HD-tDCS (active, sham) or days (Day1, Day4, Day21) were observed for past 24 hour average pain intensity or unpleasantness VAS scores,

maximum pain intensity or unpleasantness VAS scores, McGill scores, RMDQ, sleep time, current mood, mood over the past week, PCS, STAI-state, STAI-Trait, PANAS-positive or PANAS-negative scores (All  $P > 0.1$ , Table 3). A significant  $HD-tDCS \times Day$  interaction ( $F_{2,20}=4.12$ ,  $P=0.032$ ,  $\eta^2=0.29$ , Table 3) was observed for BPS pain ratings, reflecting movement-evoked pain in functional tasks, whereby pain ratings were higher in the Sham than Active phase at the Day1 baseline assessment ( $P=0.021$ ), and were reduced at Day21 compared to Day1 in the Sham phase ( $P=0.043$ ).

----- Table 3 -----

### *Psychophysical Data*

**Baseline Differences:** When the first (Day1, phase 1), fifth (Day1, phase2) and ninth (Day21, phase 2) sessions were compared, no significant differences were noted in any of the psychophysical measures (PPT, cPDT, cPTT, STR, TSP and CPM). Only that TSP-epochs and CPM-effects were both present, with significant main effects of *Epoch* ( $F_{2,20}=15.33$ ,  $P<0.001$ ,  $\eta^2=0.60$ ), showing significant increases in ratings in each subsequent epoch (Post-hoc:  $1<2<3$ ,  $P<0.03$ ), and *Ramp* ( $F_{2,20}=5.25$ ,  $P=0.015$ ,  $\eta^2=0.34$ ), showing that cPDT and cPTT were higher on the third than second ramp, (Post-hoc: 3<sup>rd</sup> ramp (parallel CPM) > 2<sup>nd</sup> ramp (habituation),  $P=0.03$ ), respectively.

**Effects of HD-tDCS:** For PPTs, a  $HD-tDCS \times Day$  interaction was observed ( $F_{2,20}=3.60$ ,  $P=0.046$ ,  $\eta^2=0.26$ ). However, no significant differences were observed on post-hoc testing, but this effect was likely driven by slightly lower PPTs on Day1 in the sham compared with active (Day1 Active minus Sham =  $87.2 \pm 41.9$  kPa,  $P=0.064$ , Fig. 3A).

For cPTT, there was a main effect of *Day* ( $F_{1,2,11.7}=7.00$ ,  $P=0.018$ ,  $\eta^2=0.41$ , Fig. 3B), whereby cPTT was higher on Day21 than Day1 (Day21 minus Day1 =  $3.3 \pm 1.1$  kPa,  $P=0.043$ ). No significant effects were observed for cPDT ( $F<2.17$ ,  $P>0.14$ ,  $\eta^2<0.18$ ), nor were any significant effects observed for STR ( $F<0.49$ ,  $P>0.60$ ,  $\eta^2<0.05$ , Fig. 3C).

For TSP, there was a main effect of *Epoch* ( $F_{2,20}=11.21$ ,  $P=0.001$ ,  $\eta^2<0.53$ , Fig. 3D), showing an increase in eVAS scores on each subsequent *Epoch* (I<II<III,  $P<0.04$ ), but no significant differences between  $HD-tDCS$  or *Days* were noted.

There was a main effect of *Ramp* for CPM effects on both cPDT ( $F_{2,20}=4.39$ ,  $P=0.026$ ,  $\eta^2<0.31$ ) and cPTT ( $F_{2,20}=11.91$ ,  $P<0.001$ ,  $\eta^2<0.54$ , Fig. 3E). Post-hoc tests were non-significant for CPM effects on cPDT, but CPM effects on cPTT showed greater inhibition of ramps during (3<sup>rd</sup> Ramp (parallel CPM) > 2<sup>nd</sup> Ramp (habituation),  $P=0.005$ ) and following (4<sup>th</sup> Ramp (sequential CPM) > 2<sup>nd</sup> Ramp (habituation),  $P=0.005$ ) conditioning compared to the ramp prior, indicating CPM was



present in these CLBP patients. No significant differences were observed between *HD-tDCS* or *Days* despite the visual trend evident in Fig. 3.

----- *Figure 3* -----

#### *Exploratory Correlation Analysis*

A moderate negative correlation was observed between CPM at baseline (absolute first session, Day1) and the change in CPM following Active HD-tDCS (Day4,  $R_s = -0.79$ ,  $P = 0.002$ , Fig. 4), suggesting those with the least efficient CPM at baseline responded most positively to the Active stimulation. The corresponding correlation analysis for changes in CPM following Sham HD-tDCS was in the opposing direction (positive) and non-significant (Day4,  $R_s = 0.53$ ,  $P = 0.075$ , Fig. 4). However, it should be noted, that in the majority of participants CPM was efficient at baseline, so mean effects of Active HD-tDCS on CPM in this sample were not significant.

----- *Figure 4* -----

#### *Immediate Effects of HD-tDCS*

HD-tDCS had an immediate effect on pain intensity and unpleasantness, with a greater reduction in pain intensity observed on Day1 than Day2 and Day3 ( $P < 0.03$ , Supplementary Material). No significant immediate effects were observed for short-form versions of the McGill, PCS, STAI, or PANAS, or for Valence and Arousal ratings. PPTs at the ECR showed greater reduction after Active than Sham HD-tDCS ( $P < 0.04$ ), and both cPTT and STR showed greater increases on Day3 than Day1 ( $P < 0.04$ ), but no immediate effects on cPDT, TSP or CPM were observed ( $P > 0.06$ , Supplementary Material).

## **DISCUSSION**

Active versus sham HD-tDCS was directed at the mPFC in CLBP patients, primarily aiming to improve CPM, as well as possibly reducing affective disturbances, and clinical pain. Blinding of HD-tDCS protocol was successfully achieved despite the cross-over design. However, even though various characteristics were assessed through questionnaire and psychophysical testing, no meaningful differences were observed between Active and Sham HD-tDCS. General temporal effects on cuff pain tolerance thresholds were evident, as well as immediate reductions in LBP ratings following both HD-tDCS paradigms on the first day. An interesting exploratory association was identified, suggesting that HD-tDCS paradigms targeting the mPFC may have potential for

improving CPM in patients with severe impairments in this mechanism, however these findings need replication and further validation.

### *CLBP patient characteristics*

A comprehensive profile of CLBP patients was obtained, including sensory and affective LBP features, pain duration, self-reported disability, observer quantified function, state and trait psychological factors, past care-seeking behaviours, aggravating and easing factors, and prognostic and mechanistic classifications. As no meaningful changes were observed across the study in any of these outcomes on a group level, it is unlikely that this HD-tDCS paradigm alone has interventional potential in this specific population. Prior trials have suggested that combined tDCS and peripheral interventions can provide enhanced and maintained analgesic effects[27], and these possibilities remain to be explored with this new stimulation montage. However, there are also sample characteristics that are important to consider in relation to the lack of efficacy seen here. For example, despite reporting having had CLBP for several years, the patients included here reported minimal pain during testing sessions with even maximum past 24-hour pain ratings rarely exceeded 6/10; which is considerably lower than CLBP patients attending pain clinics[56]. The majority of included CLBP patients also reported levels of pain-catastrophizing[78], anxiety[34], and affect[5; 11] consistent with prior control data[51] and mostly below clinical cut-off scores. It was not the intention to recruit individuals with low pain scores, as this can produce floor effects, where clinically meaningful pain relief is challenging to demonstrate. However, it is possible that a relatively low-disability sample should have been expected given the intensive involvement required for the study (potentially preventing working individuals and those with reduced mobility from participating).

### *Psychophysical assessments of pro- and anti-nociception*

CLBP patient populations have previously been shown to have impaired CPM, facilitated TSP and reduced PPTs at local and distant sites, at least on a group level[15; 52]. However, CLBP patients represent a highly heterogeneous group, both in terms of symptomatology and CPM impairment. Prior studies suggest that CPM may be more impaired in patients with severe, widespread and/or longer lasting pain[21-23]. Hence, given the mild localised pain and limited disability reported in the present sample, it may be unsurprising that the majority (75%) demonstrated efficient CPM. In fact, both mean CPM and TSP observed here are of similar magnitude to control participants assessed with the same methodology[24; 25; 30; 50]. PPTs over the lumbar sites were low in

comparison to prior studies in controls[50; 67; 87], but fluctuations in PPT often occur with pain presence[51; 61; 66; 75], especially locally, and do not necessarily represent a pathological feature of the broader condition[14]. Based on these findings, it may be that these patients simply did not have the problems usually associated with CLBP[53] that the HD-tDCS was intended to target.

#### *HD-tDCS targeting in CLBP*

Most prior non-invasive brain stimulation studies in chronic pain conditions have targeted the motor cortex[18]. However, it was hypothesized here that better effects might be observed if stimulation was directed to areas involved in affective processing and descending pain modulation, where impairments have previously been reported in CLBP patients[3; 49; 52; 90]. A previous study using similar justification targeted the ACC using conventional unilateral tDCS and showed reduced pain interference, intensity and disability after 6-weeks in CLBP patients[44]. However, this study did not assess CPM, used 10 sessions (as opposed to 3 here), a cathodal array, and a sample population of primarily older adult males with greater pain and disability levels, which may explain differences in results.

Polarity-dependent effects on cortical excitability and experimental pain perception have previously been observed for the motor[57; 92], sensory[82] and dorsolateral prefrontal[60] cortices, with anodal stimulation considered excitatory and cathodal inhibitory[13]. However, polarity effects are not always clear when targeting frontal regions[45; 46; 58] or when assessing pain perception in patients, where both cathodal and anodal stimulation may show similar effects[40; 85]. Anodal stimulation was selected here to target prefrontal connections to the periaqueductal gray[9], theorised to be involved in affective regulation of descending inhibition. However, interplay between prefrontal regions is complex[68] and these regions can exert modulatory effects on pain through multiple distinct mechanisms[4; 86], including aforementioned PAG-mediated descending inhibition, descending facilitation of nociceptive transmission[93], or supraspinal effects on affective pain processing[16; 59]. There are also various subregions within the mPFC which show differential activation during pain[37], so although current direction is likely important, determining effects on specific subregions is challenging. Hence, even though HD-tDCS improves electrical field focality, it is likely that greater specificity in targeting is still needed.

It is also important to consider that alterations in functional connectivity observed between the mPFC and PAG in CLBP patients, which were suggested to indicate impaired descending pain modulation in these patients[90], seem to depend on current attentional, affective and pain state

features[36]. As HD-tDCS paradigms are applied at rest, and as conversely heightened mPFC activity and connectivity to other pain processing regions has been observed at rest in CLBP patients[94], it may instead be more effective to use cathodal HD-tDCS to inhibit the mPFC. This approach may better reduce pain perception and/or unpleasantness more generally, consistent with the prior CLBP study[44] and with effects seen following brief TMS-induced disruption of the mPFC[35], though this would no longer target descending inhibitory connections and hence expected effects on CPM are unclear.

#### *Differential effects of HD-tDCS depending on baseline CPM*

It is interesting to consider why opposing effects were seen between patients with differing CPM efficacy at baseline. This may be the result of individual differences in resting brain activity and/or connectivity prior to the tDCS session, as has previously been shown to influence tDCS response[62]. For example, if efficient CPM reflects that mPFC-PAG pathways are already active in these patients, an additional excitatory tDCS paradigm may then produce an inhibitory homeostatic response[41] and have a negative effect on CPM. Whereas patients with severe CPM impairment, potentially reflecting reduced mPFC-PAG activity, may benefit from this HD-tDCS paradigm. This, along with the influence of individual brain states prior to treatment, requires further exploration.

Enhanced tDCS effects may also be observed if targeted stimulation was combined with other relevant training[69]. This is currently being tested in a large cohort of CLBP patients using tDCS in combination with functional motor and sensory training[2], but results are yet to come. In the specific case of CPM, it is possible that combinations of mPFC HD-tDCS paradigms with other strategies to improve descending inhibition, such as tapentadol, duloxetine, artificial mood enhancement, stress reduction or sleep restoration could be successful. However, future work is needed to explore this and further validate the pathophysiological importance of CPM impairment as a treatment target in CLBP.

#### *Blinding*

Due to the small sample size, it was not possible to examine expected/believed HD-tDCS protocol effects; however, it appeared that HD-tDCS guesses were often wrong and hence blinding was well maintained throughout the trial. This is important to highlight, as blinding has been reported to be problematic, especially in HD-tDCS studies[20; 31], and in cross-over trials where participants are able to compare sensations[63; 64]. Prior studies attempting to develop sham strategies have

shown clear differences in reported sensations during stimulation, unless a shunting technique (using adjacent electrodes to shunt current through the scalp) was used[20; 72]. The central electrode array used in the present study was not conducive to this approach, so instead a longer ramp up and down phase was used to mimic the sensation-timeline reported during pilots in the active condition. Recall accuracy of painful sensations has been suggested to be substantially diminished after several days[7], hence the two-three week gap between phases here would have made comparison between stimulation paradigms challenging. Other factors likely contributing to blinding success here include using a trained investigator to place electrodes, concurrent experimenter blinding, neglecting specific information about the stimulation paradigms, and providing equally strong reinforcement of expected sensations during both phases. This successful blinding strengthens conclusions, and also supports prior work[20] indicating that crossover designs, which minimise sample size and exposure to experimental treatment, are appropriate for pilot testing new HD-tDCS paradigms.

### *Limitations*

Beyond influences of patient characteristics a few limitations should be noted. This pilot trial was adequately powered to show differences in psychophysical testing but only used a small sample of heterogeneous CLBP patients. As well, inherent issues with tDCS such as varying head size and hair thickness, unknown cognitive processes potentially performed by participants during stimulation, and interindividual e.g. anatomical, neurochemical and genetic variation which may influence current flow and precise electrode placement, that have been discussed previously[32; 38], were presumably also evident here. Finally, this study only assessed patients on the days during, immediately following and on Day21 post-stimulation, so latent effects as observed in prior studies may have been missed.

### *Conclusion*

This study has shown no significant effects of active mPFC HD-tDCS on anti-nociceptive mechanisms, nor on other psychophysical tests, clinical LBP features or psychological characteristics. Blinding was maintained throughout the trial, suggesting a crossover design is appropriate for pilot testing new experimental paradigms. Future work should focus on patient screening and selection strategies to study effects on patients with true deficiencies in anti-nociceptive mechanisms, as well as optimising stimulation targeting, exploring different arrays and

current directions, and looking at effects combined with mechanistically justified complementary interventions.

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**Figure 1:** Trial protocol showing (A) timeline of all sessions in the full protocol and (B) procedures involved on each day of each phase. As seen in (A) for the second phase, the first assessment on Day1 acts as Day21 for the first phase, whereas in the second phase it is a separate Day21 session. In (A), orange circles indicate sessions with HD-tDCS and grey circles represent sessions with measurement only. In (B), faded boxes represent data either reported in supplementary material (immediate effects on pain, short-form questionnaires, and psychophysical testing) or not reported here (empty grey boxes representing resting-state electroencephalography and affective/attentional outcomes). IPAQ: International Physical Activity Questionnaire. PCS: Pain Catastrophizing Scale. STAI: State-Trait Anxiety Inventory. PANAS: Positive and Negative Affective Schedule. BDI-II: Beck Depression Inventory. MPQ: McGill Pain Questionnaire. RMDQ: Roland-Morris Disability Questionnaire. SBSQ: Start Back Screening Questionnaire. SLR: Straight Leg Raise. PPT: Pressure Pain Threshold. ECR: extensor carpi radialis. UT: upper trapezius. L1/L5: 1<sup>st</sup> and 5<sup>th</sup> lumbar segments. GAS: gastrocnemius. PDT/PTT: pain detection/tolerance threshold. STR: suprathreshold rating. TSP: temporal summation of pain. CPM: conditioned pain modulation. HD-tDCS: high density transcranial direct current stimulation. SFQ: short-form questionnaires. PS: pain sensitivity assessment. EX: physical examination.

**Figure 2:** Depiction of A) HD-tDCS stimulation protocol for Active (60 s ramp ON, 18 min anodal HD-tDCS, 60s ramp OFF) and Sham (60 s ramp ON, 60 s ramp OFF); B) placement and current amplitude for anode, cathodes and reference electrode in relation to the 10-20 International EEG System; and C) electrical field modelling of 2mA anodal stimulation paradigm generated with SimNIBS as per prior simulations[79].

**Figure 3:** Mean (+SEM) psychophysical outcomes on Day1, Day4, and Day21 in both Active (yellow) and Sham (blue) HD-tDCS conditions: A) pressure pain thresholds, B) cuff pain detection (cPDT) and cuff tolerance threshold (cPTT), C) suprathreshold ratings, D) temporal summation of pain, and E) conditioned pain modulation. ECR=extensor carpi radialis, UT=upper trapezius, GAS=gastrocnemius. R2-4=Ramp 2-4 (2: prior to conditioning, 3: during conditioning, 4: post-conditioning). Significant between-epoch difference from Epoch I or between-ramp difference from Ramp 2 is shown (\*,  $P < 0.03$ ). Main effect of Day with significant increase compared to Day1 is indicated (#,  $P < 0.04$ ).

**Figure 4:** Spearman's Rho correlations between mean CPM (parallel, ramp-3 minus ramp-1, average of effects on cPDT and cPTT) at baseline Day1 and the change in mean CPM from Day1 to Day4 within each HD-tDCS condition (Active/Sham). Individual participant data shown in orange for the 6 patients with least efficient CPM and in green for the 6 patients with most efficient CPM at baseline.

Fig. 1

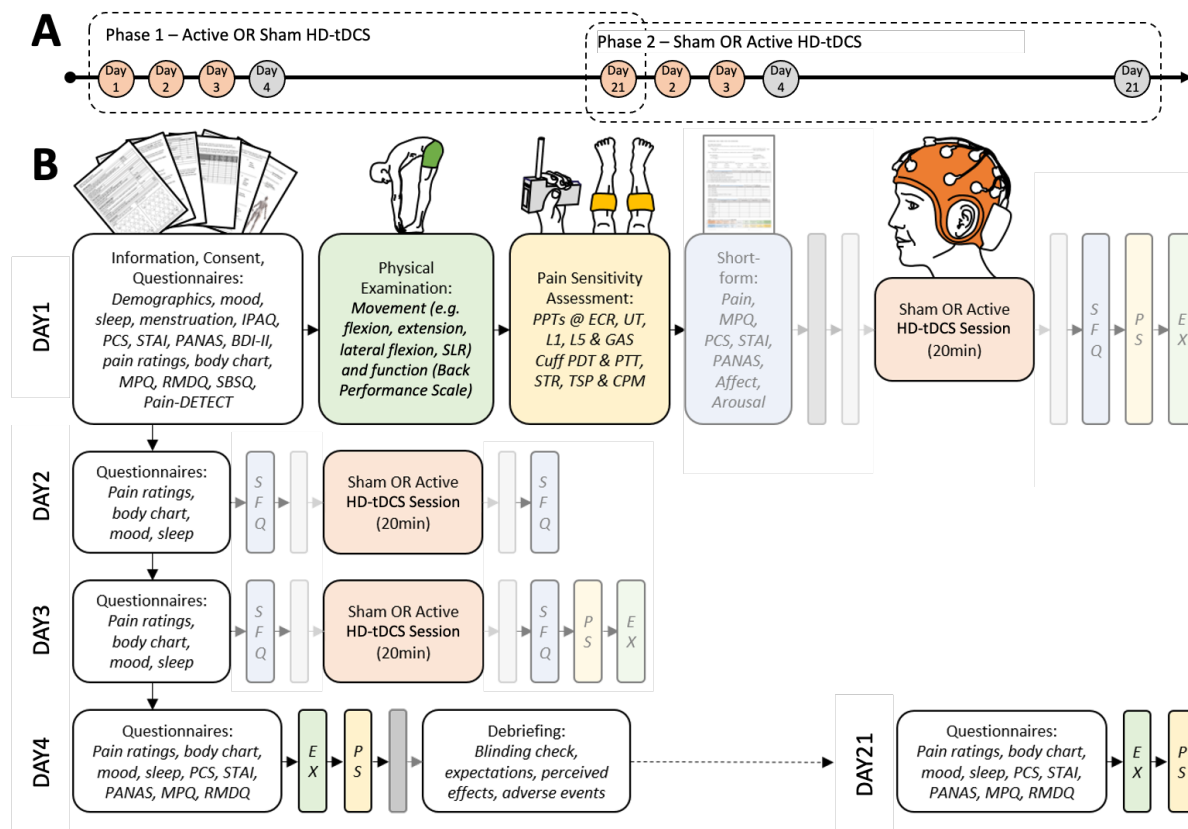


Fig. 2

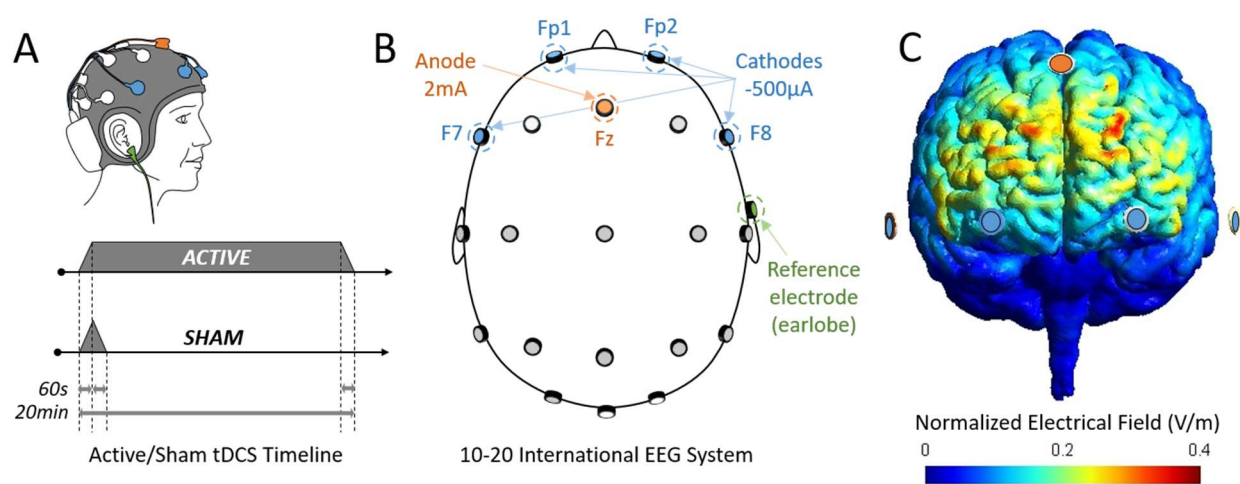


Fig. 3

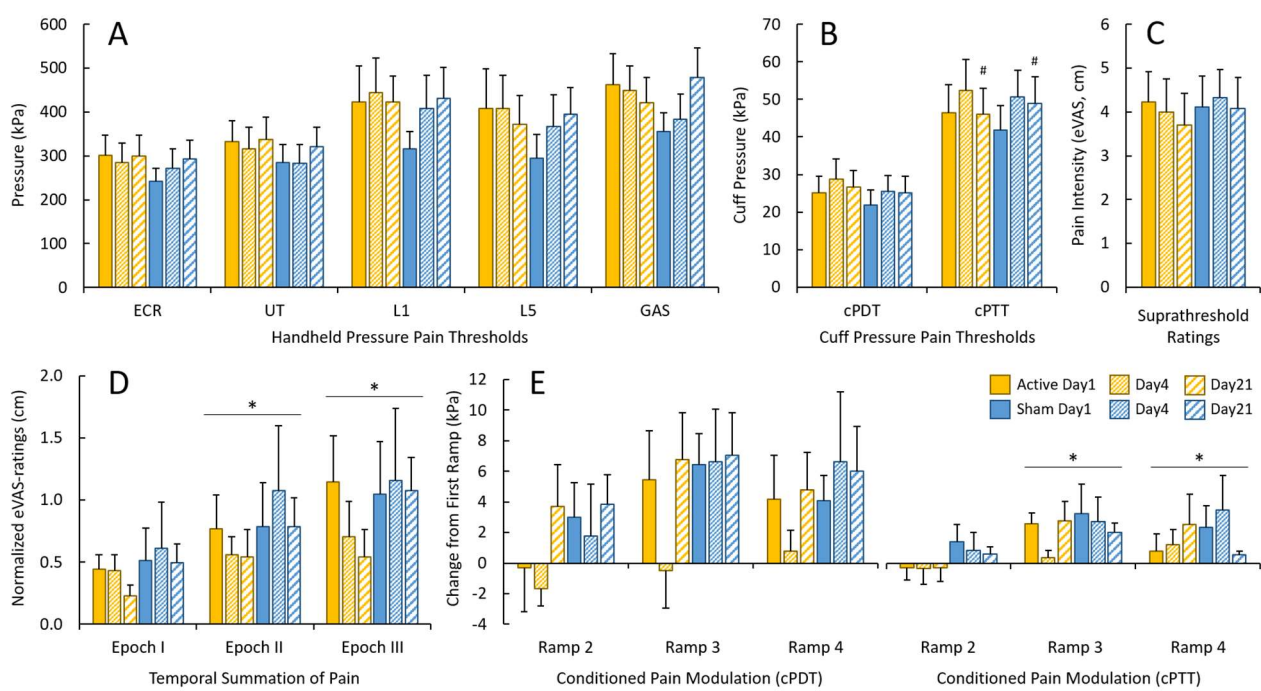
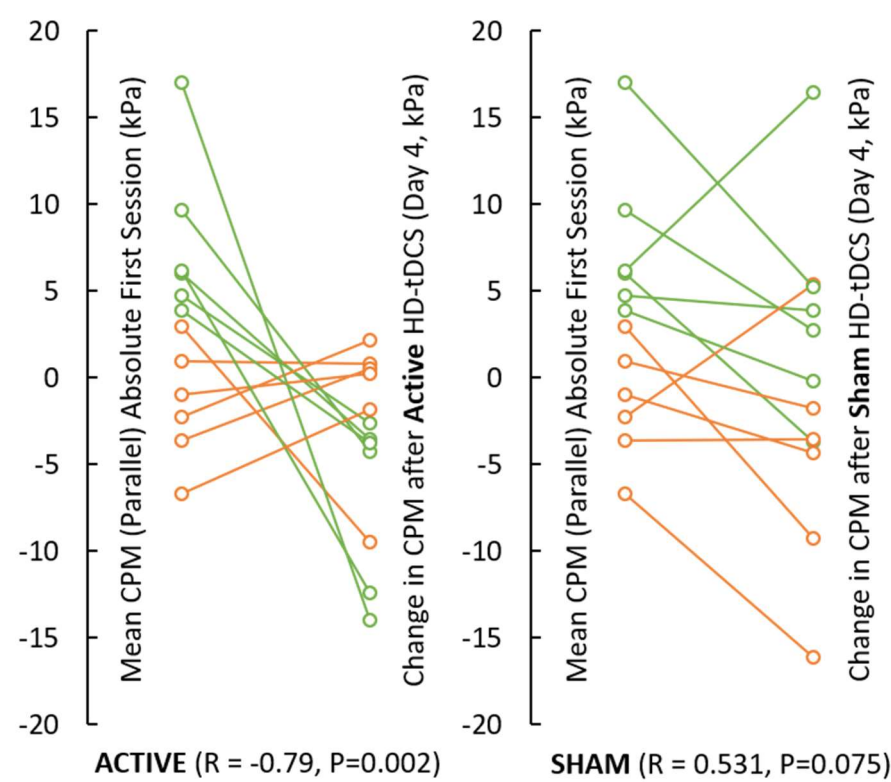




Fig. 4



**Table 1:** Baseline Demographics and Low Back Pain Characteristics

Characteristic (units)	CLBP Patients (n = 12)
<b>Age</b> (years)	28.6 ± 5.9
<b>Gender</b> (female : male)	9 : 3
<b>Height</b> (cm)	172.6 ± 9.4
<b>Weight</b> (kg)	75.4 ± 16.1
<b>Duration with Chronic LBP</b> (years)	5.3 ± 2.6
<b>Past healthcare sought</b> (n [%]):	
<i>General Practitioner</i>	8 [67]
<i>Physiotherapist</i>	5 [42]
<i>Chiropractor</i>	4 [33]
<i>Other (Massage / Acupuncture / etc.)</i>	3 [25]
<b>Investigations</b> (n [%]):	
<i>Imaging offered but not obtained</i>	2 [17]
<i>Plain radiographs (X-ray)</i>	5 [42]
<i>Magnetic Resonance Imaging (MRI)</i>	6 [50]
<i>Surgical investigation or treatment</i>	0 [0]
<b>Beliefs about Low Back Pain</b> (n [%]):	
Resolution: <i>Yes, I believe (or hope) it will go away</i>	5 [42]
Fear of exacerbation: <i>I avoid X because of my back</i>	6 [50]
<b>Start Back Questionnaire (Low / Moderate / High)</b>	7 / 4 / 1
<b>Pain DETECT</b>	9.4 ± 5.0

**Table 2:** Results of blinding and side effect assessment separated by phases (chronological) and HD-tDCS (Active/Sham). Median (Interquartile range).

	Phase One N = 12	Phase Two N = 12	Active HD-tDCS N = 12	Sham HD-tDCS N = 12
<b>Protocol Assignment</b>				
<i>Protocol Actually Applied (Active / Sham)</i>	6 / 6	6 / 6	12 / 0	0 / 12
<i>Participant Belief of Protocol Applied (Active / Sham)</i>	6 / 6	8 / 4	8 / 4	6 / 6
<i>Percentage Correct (% Overall)</i>	50%	67%	67%	50%
<b>Participant Certainty of Protocol Guess</b>				
<i>1: not at all certain – 5: completely certain</i>	2 (1)	3 (1.25)	2 (1)	3 (1.25)
<b>Time when Protocol Guess Decided</b>				
<i>n, Day1 / Day 2 / Day3 / Day4 when forced to choose</i>	3 / 1 / 3 / 5	6 / 3 / 0 / 3	3 / 3 / 2 / 4	6 / 1 / 1 / 4
<b>Reasons for Protocol Guessed</b>				
<i>Active Guessed</i>	Felt burning/ other scalp sensation during (n = 4), no reason (n = 2)	Felt longer or more intense sensation during (n = 5), reduced back pain (n = 2), no reason (n = 1)	<i>*CORRECT*</i> Felt stimulation/ more intense sensation during (n = 4), reduced back pain (n = 2), no reason (n = 2)	<i>*INCORRECT*</i> Felt burning/ more intense sensation during (n = 3), reduced back pain (n = 2), no reason (n = 1)
<i>Sham Guessed</i>	Did not feel much during (n = 3), no change in back pain (n = 2), bad luck (n = 1)	Less sensation felt during stimulation (n = 4)	<i>*INCORRECT*</i> Did not feel stimulation or less felt during (n = 2), bad luck (n = 1), no change in back pain (n = 1)	<i>*CORRECT*</i> Did not feel stimulation or less felt during (n = 5), no change in back pain (n = 1)
<b>Sensations Reported During Stimulation (N[%])</b>				
<i>Heat / warmth / burning</i>	5 [42]	4 [33]	4 [33]	5 [42]
<i>Itching</i>	9 [75]	8 [67]	10 [83]	7 [58]
<i>Tingling</i>	6 [50]	2 [17]	6 [50]	2 [17]
<i>Pins and needles / pricking</i>	0 [0]	2 [17]	0 [0]	2 [17]
<i>Nothing felt</i>	1 [8]	2 [17]	1 [8]	2 [17]
<b>Side Effects Reported Post-Stimulation* (N[%])</b>				
<i>Skin discomfort / hypersensitivity</i>	4 [33]	0 [0]	3 [25]	1 [8]
<i>Skin redness</i>	1 [8]	1 [8]	1 [8]	1 [8]
<i>Headache</i>	4 [33]	2 [17]	4 [33]	2 [17]
<i>Nausea</i>	1 [8]	0 [0]	0 [0]	1 [8]
<i>Dizziness</i>	1 [8]	0 [0]	0 [0]	1 [8]
<i>Difficulty concentrating</i>	2 [17]	1 [8]	1 [8]	2 [17]
<i>Increased fatigue</i>	2 [17]	1 [8]	1 [8]	2 [17]
<i>Increased energy</i>	1 [8]	0 [0]	1 [8]	0 [0]
<i>Difficulty sleeping / increased nightly waking</i>	2 [17]	1 [8]	1 [8]	2 [17]
<i>Increased sleep</i>	1 [8]	0 [0]	1 [8]	0 [0]
<b>Expectation of Positive Effect if Active (Yes, N[%])</b>	6 [50]	6 [50]	7 [58]	5 [42]

\*When initially questioned for unstructured responses, participants did not report any side effects beyond the sensations described during stimulation

**Table 3:** Individual characteristics organised by Session (Chronological baselines) and HD-tDCS (Active/Sham) as Mean  $\pm$  Standard Deviation or Median (Interquartile range)

Chronological Order				Characteristics by HD-tDCS							
	Session 1	Session 5	Session 9	Statistics	Active			Sham			Statistics
	(Day1)	(Day1)	(Day21)		Day 1	Day 4	Day 21	Day 1	Day 4	Day 21	
	N = 12	N = 12	N = 11		N = 12	N = 12	N = 11	N = 12	N = 12	N = 11	
Low Back Pain VAS Ratings (Past 24 hours):											
Average Pain Intensity (cm)	3.0 ± 1.5	2.9 ± 1.0	2.2 ± 1.2	F<1.8, P>0.2	2.9 ± 1.4	2.3 ± 2.3	2.8 ± 1.2	2.9 ± 1.2	2.4 ± 1.9	2.2 ±1.0	F<2.1, P>0.1
Average Pain Unpleasantness (cm)	3.1 ± 1.8	3.1 ± 1.6	3.4 ± 1.2	F<1.1, P>0.3	3.2 ± 1.7	2.6 ± 2.7	3.0 ± 1.6	3.0 ± 1.7	2.6 ± 2.0	2.6 ± 1.3	F<1.1, P>0.3
Maximum Pain Intensity (cm)	3.8 ± 1.3	4.0 ± 1.4	3.8 ± 1.3	F<0.7, P>0.9	3.8 ± 1.2	3.7 ± 2.8	4.0 ±1.5	4.0 ± 1.5	3.8 ± 2.2	2.7 ± 1.1	F<0.6, P>0.6
Maximum Pain Unpleasantness (cm)	4.0 ± 1.6	4.1 ± 1.9	4.2 ± 1.4	F<0.6, P>0.9	3.9 ± 1.8	3.8 ± 3.1	4.4 ± 1.7	4.2 ± 1.7	4.1 ± 2.1	3.8 ± 1.7	F<0.6, P>0.5
McGill Pain Score	16 (7)	10.5 (9.5)	17 (14.5)	X²=4.1, P=0.1	14 (8.5)	11 (9.5)	11 (11.3)	13.5 (9.25)	11 (12.5)	10 (12.5)	X²=7.3, P=0.2
Roland-Morris Disability Questionnaire (/24)	5 (3)	3 (1.75)*	4 (3.5)	X²=6.9, P<0.04	4 (2.25)	4 (2.25)	3.5 (2.5)	3 (2.25)	4.5 (3.5)	3 (2.5)	X²=6.1, P=0.3
Back Performance Scale											
Score (Sum)	2.5 (2.5)	2.5 (3)	2 (3.5)	X²=0.1, P=0.96	2 (3)	2 (3)	2 (4)	2 (4)	2 (3)	1 (3)	X²=7.5, P=0.2
Pain Ratings (mean across movement tasks)	1.2 ± 1.5	1.4 ± 1.9	1.4 ± 2.3	F<0.4, P>0.9	1.0 ± 1.4#	1.5 ± 2.4	2.0 ± 2.6	1.6 ± 1.9	1.3 ± 1.7	0.7 ± 1.0*	F=4.1, P=0.03
Sleep Duration (hours)	6.7 ± 1.2	6.8 ± 1.9	6.6 ± 0.8	F=0.0, P=1.0	7.2 ± 1.0	7.8 ± 1.1	6.2 ± 1.7	6.2 ± 1.8	7.4 ± 1.3	7.0 ± 1.2	F<4.1, P>0.07
Mood (/20)											
Current	5 (3.5)	4 (3.3)	4 (4.5)	X²=3.9, P=0.1	4 (4)	5 (4)	4 (4)	5 (4)	4 (4)	4 (4)	X²=10.6, P=0.06
Past week	3.5 (4.3)	3.5 (3.8)	5 (3.5)	X²=0.5, P=0.7	4 (3)	4 (7)	4 (3)	5 (5)	6 (5)	4 (8)	X²=3.3, P=0.6
IPAQ Physical Activity (MET-mins/week)	6100.1 ± 4399.5	5210.2 ± 5994.5	3755.9 ± 2959.6	F<3.2, P>0.6	4441.1 ± 3407.0	-	-	6869.2 ± 6395.2	-	-	t=-1.4, P=0.2
IPAQ Weekday Sitting Time (mins)	385.0 ± 206.6	362.5 ± 194.2	368.2 ± 187.9	F<0.6, P>0.9	380.0 ± 186.4	-	-	367.5 ± 214.1	-	-	t=0.2, P=0.8
Pain Catastrophizing Scale (/52)	13.9 ± 8.2	11.8 ± 8.5	12.6 ± 9.1	F<0.6, P>0.5	13.7 ± 7.2	13.3 ± 10.5		12.0 ± 9.4	11.9 ± 8.2		F<1.5, P>0.2
State-Trait Anxiety Inventory											
State Anxiety	34.9 ± 8.4	36.5 ± 10.4	39.0 ± 10.9	F<0.8, P>0.4	36.4 ± 8.6	38.5 ± 13.2		35.0 ± 10.3	35.9 ± 10.1		F<1.8, P>0.1
Trait Anxiety	41.2 ± 6.1	39.4 ± 6.5	41.7 ± 8.1	F<0.9, P>0.4	40.9 ± 7.2	41.5 ± 7.3		39.7 ± 5.4	41.2 ± 6.3		F<2.2, P>0.1
Positive and Negative Affective Schedule											
Positive Affect	26.5 ± 7.8	23.8 ± 7.8	23.8 ± 11.3	F<0.8, P>0.4	24.3 ± 8.9	22.3 ± 11.5		26.0 ± 6.8	25.3 ± 9.0		F<2.5, P>0.1
Negative Affect	12.9 ± 3.1	12.5 ± 2.9	11.4 ± 5.2	F<0.3, P>0.7	12.8 ± 3.0	12.1 ± 2.3		12.7 ± 2.9	11.9 ± 2.8		F<0.8, P>0.4
Beck Depression Inventory:											
Total score	8.7 ± 4.2	8.9 ± 5.0	6.4 ± 4.1	F<2.2, P>0.1	8.1 ± 3.8	-	-	9.5 ± 5.2	-	-	t=-1.0, P=0.3
Classification (Min. / Mild / Mod. / Sev.)	10 / 2 / 0 / 0	10 / 2 / 0 / 0	11 / 0 / 0 / 0		11 / 1 / 0 / 0			9 / 3 / 0 / 0			

\*Denotes significant differences between Sessions/Days (P<0.05), #denotes significant difference between Active/Sham HD-tDCS (P<0.03). VAS: visual analogue scale.

**Supplementary Material – Analysis of Immediate HD-tDCS Effects**

to

**Medial Prefrontal High-Definition Transcranial Direct Current Stimulation to Improve Pain Modulation in Chronic Low Back Pain: A Pilot Randomized Double-blinded Placebo-Controlled Crossover Trial**

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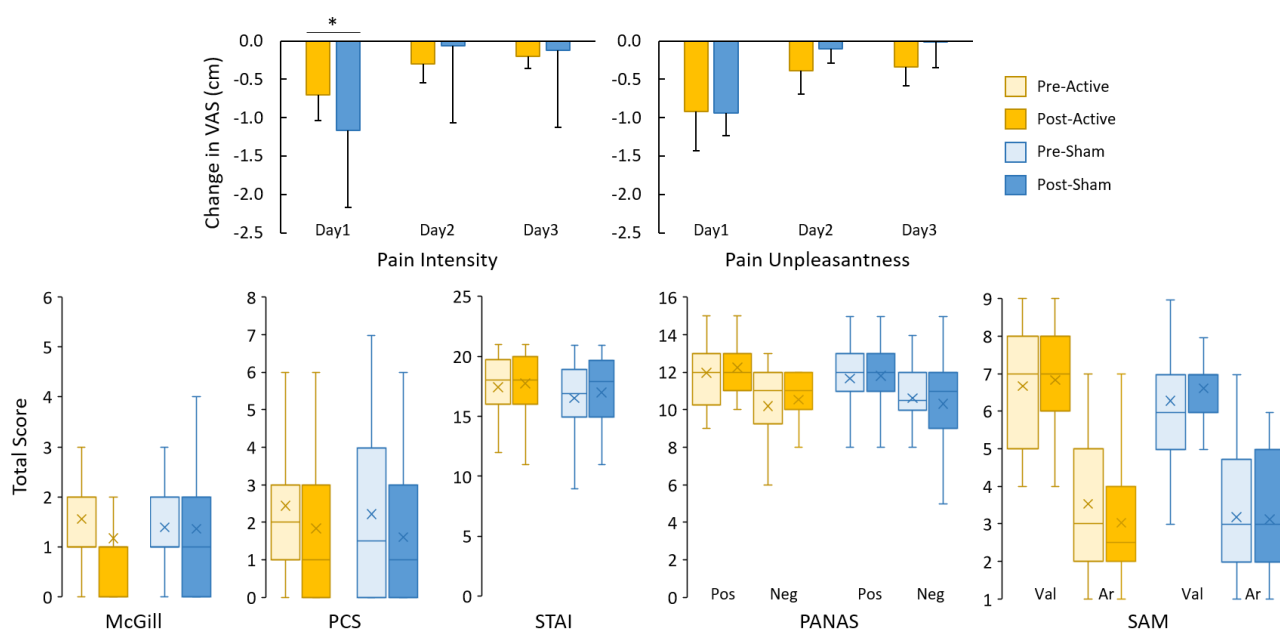
E-mail: [tgn@hst.aau.dk](mailto:tgn@hst.aau.dk)

## Methods for Capturing Immediate Effects of HD-tDCS

To capture immediate changes in response to HD-tDCS, ratings of current pain intensity and pain unpleasantness on a paper visual analogue scale (VAS) were collected. As well, validated short-form versions of the McGill pain descriptors, PCS, STAI, PANAS, along with a 9-point rating of valence (1: most negative to 9: most positive) and arousal (1: most calm to 9: most aroused) from the Self-Assessment Mannikin were used to assess psychological state immediately prior to and following HD-tDCS stimulation. In all cases, pre-HD-tDCS ratings were subtracted from post-HD-tDCS ratings on Day1, Day2, and Day3, and analysed using repeated measures analysis of variance (ANOVA) or Friedman's ANOVAs as appropriate. ANOVAs were Greenhouse-Geisser corrected in the event of lacking sphericity on Mauchly's W testing. All post-hoc comparisons were Bonferroni corrected with significance set at  $P < 0.05$ .

## Immediate Effects of HD-tDCS on Current State (Short-form Pain Scores and Questionnaires)

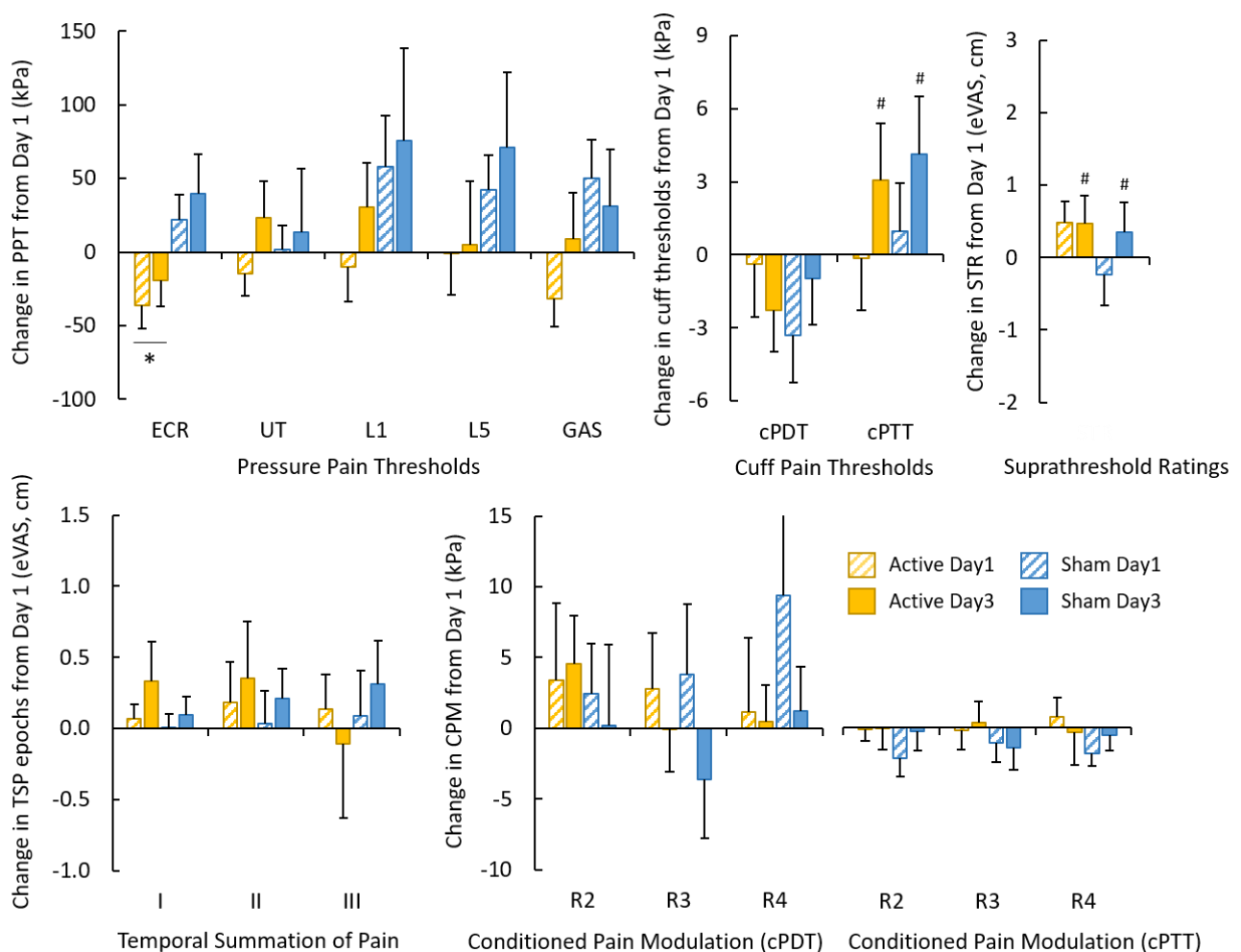
Short-form data collected prior to HD-tDCS were subtracted from data recorded immediately following each HD-tDCS session and compared across days (Day1, Day2, Day3) and HD-tDCS protocol (Active vs Sham). A main effect of Day on pain intensity ( $F_{2,22}=7.96$ ,  $P=0.003$ ,  $\eta^2=0.42$ ) and pain unpleasantness ( $F_{2,22}=3.89$ ,  $P=0.036$ ,  $\eta^2=0.26$ ) VAS scores was noted, with greater reduction in VAS scores on Day1 than Day2 ( $P=0.028$ ) and Day3 ( $P=0.030$ ) for pain intensity, but no significant post-hoc findings for pain unpleasantness (Fig. 3). No significant differences were observed between HD-tDCS protocols. Further, no significant differential effects of HD-tDCS protocol were noted for McGill, PCS, STAI, PANAS, Valence or Arousal scores ( $P > 0.05$ , Fig. 1).



**Supplementary Figure 1:** Change in pain intensity and unpleasantness VAS scores following and scores from short-form questionnaires immediately prior to and following Active and Sham HD-tDCS sessions. PCS = Pain Catastrophizing Scale (6-item). STAI = State Trait Anxiety Scale (4-item). PANAS = Positive (Pos) and Negative (Neg) Affective Schedule (6-item). SAM = Self-Assessment Mannikin. Val = Valence. Ar = Arousal. Significantly greater reduction in pain intensity VAS scores following stimulation on Day1 compared to Day2 and Day3 (\*,  $P < 0.03$ ).

### Immediate Effects of HD-tDCS on Psychophysical Outcomes

Psychophysical outcomes collected in the first session (Day1-Pre) were subtracted from outcomes collected immediately following HD-tDCS on Day1 and Day3 in the Active and Sham conditions and compared across days and HD-tDCS protocol (active/sham). PPTs at the ECR site showed a main effect of HD-tDCS protocol ( $F_{1,11}=5.64$ ,  $P=0.037$ ,  $\eta^2=0.33$ ) whereby reduction of PPTs was observed in the Active phase compared to Sham. No other significant differences in PPTs were noted (All  $P>0.15$ ). For cuff thresholds, no differences were observed for cPDT, but cPTT showed a main effect of Day ( $F_{1,11}=8.19$ ,  $P=0.015$ ,  $\eta^2=0.43$ , Fig. 2) with greater increase in cPTT on Day3 compared to Day1. STR also showed a main effect of Day ( $F_{1,11}=5.72$ ,  $P=0.036$ ,  $\eta^2=0.34$ , Fig. 2) with greater increase in eVAS ratings on Day3 than Day1. No significant effects or interactions were observed for TSP ( $P>0.06$ ) or CPM ( $P>0.15$ ).



**Supplementary Figure 2:** Mean (+SEM) immediate change in psychophysical outcomes from Day1 to Day1-post and Day3 for both Active and Sham protocols. ECR=extensor carpi radialis. UT=upper trapezius. GAS=gastrocnemius. cPDT/cPTT=cuff pain detection/tolerance threshold. TSP=temporal summation of pain. CPM=conditioned pain modulation. R2-4=Ramp 2-4 (2: prior to conditioning, 3: during conditioning, 4: post-conditioning). Significant between-protocol difference (\*,  $P<0.04$ ). Significant main effect of Day with larger increase in cPTT and STR at Day3 than Day1 overall (#,  $P<0.04$ ).



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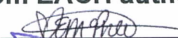

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## CONSORT 2010 checklist of information to include when reporting a randomised trial\*

Section/Topic	Item No	Checklist item	Reported on page No
<b>Title and abstract</b>			
	1a	Identification as a randomised trial in the title	Title page
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	Abstract
<b>Introduction</b>			
Background and objectives	2a	Scientific background and explanation of rationale	1-2
	2b	Specific objectives or hypotheses	2
<b>Methods</b>			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	2-3
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	NA
Participants	4a	Eligibility criteria for participants	2
	4b	Settings and locations where the data were collected	2
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	3-4
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	3-7
	6b	Any changes to trial outcomes after the trial commenced, with reasons	NA
Sample size	7a	How sample size was determined	2
	7b	When applicable, explanation of any interim analyses and stopping guidelines	NA
<b>Randomisation:</b>			
Sequence generation	8a	Method used to generate the random allocation sequence	2
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	3
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	5
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	5
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	5

		assessing outcomes) and how	
Statistical methods	11b	If relevant, description of the similarity of interventions	4-5
	12a	Statistical methods used to compare groups for primary and secondary outcomes	7-8
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	8
<b>Results</b>			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	8
	13b	For each group, losses and exclusions after randomisation, together with reasons	8
Recruitment	14a	Dates defining the periods of recruitment and follow-up	2
	14b	Why the trial ended or was stopped	NA
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table 1
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	Table 2-3
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	Table 3, Figure 3
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	NA
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	8
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	Table 2
<b>Discussion</b>			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	14
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	11-14
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	11-14
<b>Other information</b>			
Registration	23	Registration number and name of trial registry	2
Protocol	24	Where the full trial protocol can be accessed, if available	2
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	15

\*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see [www.consort-statement.org](http://www.consort-statement.org).