Brain Stimulation xxx (2014) 1–9

Contents lists available at ScienceDirect

Brain Stimulation

journal homepage: www.brainstimjrnl.com

Original Research

Targeting Chronic Recurrent Low Back Pain From the Top-down and the Bottom-up: A Combined Transcranial Direct Current Stimulation and Peripheral Electrical Stimulation Intervention

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ARTICLE INFO

Article history:
Received 21 December 2013
Received in revised form 20 January 2014
Accepted 26 January 2014
Available online xxx

Keywords:
Chronic low back pain
Transcranial direct current stimulation
Treatment
Peripheral electrical stimulation

ABSTRACT

Background: Mechanisms such as neural sensitization and maladaptive cortical organization provide novel targets for therapy in chronic recurrent low back pain (CLBP).
Objective: We investigated the effect of a transcranial direct current stimulation (tDCS) and peripheral electrical stimulation (PES) treatment on pain, cortical organization, sensitization and sensory function in CLBP.
Methods: Using a placebo-controlled crossover design, 16 individuals received four treatments in separate sessions: i) anodal tDCS/PES; ii) anodal tDCS/sham PES; iii) sham tDCS/PES; or iv) sham tDCS/sham PES. Pain was assessed at baseline, immediately following, and at 1 and 3 days after treatment. Motor cortical organization, sensitization and sensory function were measured before and immediately after treatment.
Results: Combined tDCS/PES reduced pain and sensitization, normalized motor cortical organization and improved sensory function. The reduction in pain was greater in individuals with more pronounced sensitization. Applied alone, tDCS or PES also reduced pain. However, with the exception of improved sensory function and reduced map volume following PES, clinical and neurophysiological outcomes were unaltered by tDCS or PES applied separately. No changes were observed following sham treatment.
Conclusion: Our data suggest a combined tDCS/PES intervention more effectively improves CLBP symptoms and mechanisms of cortical organization and sensitization, than either intervention applied alone or a sham control.

Introduction

Termed a 'Western epidemic,' chronic recurrent low back pain (CLBP) is a leading cause of disability in the developed world. Lifetime prevalence is as high as 79% in adults [1] and 84% in adolescents [2]. Significant social and economic costs are associated with poor rates of recovery (58% at 1 month) and high rates of recurrence (73% in 12 months) [3]. Despite the tremendous scale of the problem, CLBP remains challenging to treat. Systematic reviews of existing therapies report, at best, small effects [4,5]. There is a critical need for innovative therapies that improve recovery and reduce symptom recurrence in LBP.

Advances in understanding CLBP have revealed new biological targets for therapy. Mechanisms such as increased sensitivity of cortical and spinal neurons to sensory stimuli ('central sensitization'), and maladaptive reorganization of the complex network of brain regions involved in the experience of pain (i.e. 'pain neuromatrix'), are thought to contribute to persistent pain [6–9]. Yet, few non-pharmacological interventions have been trialed that target these mechanisms. Transcranial direct current stimulation (tDCS) and peripheral electrical stimulation (PES) are two interventions with the potential to desensitize the nervous system and regulate brain organization via complementary 'top-down' and 'bottom-up' effects [10–18]. The combined application of these techniques provides a novel opportunity to bombard multiple pain systems, across multiple levels of the nervous system, simultaneously and

Financial disclosures: This work was supported by a Program Grant from the National Health and Medical Research Council (NHMRC) of Australia (ID631717), an NHMRC Clinical Research Fellowship (ID631612) to SMS and an NHMRC Senior Principal Research Fellowship (ID1002190) to PWH. There are no conflicts of interest to declare.

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http://dx.doi.org/10.1016/j.brs.2014.01.058

may improve clinical outcomes. Further, there is the possibility of synergistic effects when tDCS and PES are combined. For example, PES is known to reduce cortical excitability [19], potentially shifting the synaptic threshold toward long-term depression (LTD) and favoring the increased cortical excitability induced by anodal tDCS. This phenomenon, whereby one intervention can increase the brain's receptiveness to another, is known as 'priming' [20].

If the combined mechanisms of tDCS/PES can be harnessed, this intervention may provide clinical benefits for people with CLBP. However, it is unknown how a combined intervention affects organization of the motor regions of the brain, sensitization of the nervous system or higher sensory functions, each of which is known to be modified in CLBP, or how changes to these mechanisms may relate to clinical outcomes.

This study aimed to investigate the immediate effect of a combined tDCS/PES intervention on: i) pain, ii) organization of the motor cortex, iii) sensitization (central and peripheral), and iv) higher sensory function in people with recurring episodes of LBP and to compare this effect with tDCS and PES applied alone and a sham treatment control. We also aimed to undertake additional exploratory analysis to consider whether the response to each treatment differed between individuals based on signs of primary and secondary hyperalgesia or features of motor cortex organization. We hypothesized that the combined intervention would reduce pain and sensitization, normalize cortical organization and improve higher sensory function, to a greater extent than each intervention applied alone or a sham intervention control.

Materials and methods

Study design

A placebo-controlled crossover design with participant blinding was used. Individuals with CLBP received four interventions, across separate sessions, in random order: i) anodal tDCS/PES ('tDCS/PES'); ii) anodal tDCS/sham PES ('tDCS alone'); iii) sham tDCS/PES ('PES alone'); or iv) sham tDCS/sham PES ('sham'). Subsequent interventions were applied no less than 7 days apart. All outcome measures were performed immediately before and after application of each intervention. Pain severity was further assessed at day 1 and 3 following each intervention.

All procedures were approved by the institutional Medical Research Ethics Committee and conformed to the Declaration of Helsinki. Participants provided written, informed consent and were free to withdraw from the study at any time.

Participants

Sixteen right-handed individuals with recurring episodes of non-specific LBP, defined as at least 2 episodes in the last 12 months [21], participated. Individuals were included if they experienced episodic pain in their low back (with or without buttock pain), sufficient to limit function, with a current pain intensity greater than 3 on an 11-point numerical rating scale (NRS) anchored with "no pain" at zero and "worst pain imaginable" at 10. Participant characteristics are provided in Table 1. Individuals were excluded from participation if they had a history of major circulatory, neurological or psychiatric conditions, previous spinal surgery, recent or current pregnancy, analgesic or anti-inflammatory medication in the last month or had received treatment from a health professional in the last month. No participant reported beginning a new treatment during the course of the study.

Table 1
Participant characteristics.

Characteristic	Mean ± standard error
Age (years)	30 ± 2.0
Gender (female:male)	7:9
Weight	73.6 ± 6.0
Height	175.4 ± 3.9
Baseline pain NRS (0–10 cm)	5.3 ± 0.4
Pain duration (years)	4.2 ± 0.7
Side of worst pain (right:left)	11:5

Electromyography (EMG)

Surface EMG was recorded from the back muscles at two sites: 3 cm lateral to the spinous process of L3, and 1 cm lateral to the spinous process of L5. Recordings were made on the side of worst pain using silver–silver chloride disposable electrodes (Noraxon USA Inc, AZ, USA). These sites are appropriate for recording general EMG from the back muscles [22] and are appropriate for evaluation of features of the motor cortical map of the paraspinal muscles [3,23]. The ground electrode was positioned over the anterior superior iliac spine. EMG data were amplified 1000×, filtered 20–1000 Hz and sampled at 2000 Hz using a Micro1401 data acquisition system and Spike2 software (Cambridge Electronic Design, Cambridge, UK).

Interventions

Interventions were applied for 30 min. This is based on previous research that demonstrates reduced cortical excitability after 30 min of PES applied at noxious intensity [19] and tDCS literature that uses common application times of between 20 and 40 min [24].

Transcranial direct current stimulation (tDCS)

Delivered using a direct current stimulator (constant current of 1 mA; DC stimulator plus; Magstim UK) via two 35 cm^2 (5 × 7 cm) saline-soaked surface sponge electrodes. Based on previous studies of the motor cortical representation of the back muscles [23,25], the center of the active electrode was positioned over the approximate location of the motor cortical representation of the back muscles (1 cm anterior and 4 cm lateral to the vertex) contralateral to the side of worst pain and the reference electrode over the contralateral supraorbital region. Current intensity was ramped up (0–1 mA) and down (1–0 mA) over 10 s at the beginning and end of the 30-min stimulation period. The sham tDCS condition involved electrodes placed in an identical position to that used for active stimulation. In this condition the stimulation was turned on for 15 s and then off to provide participants with the initial "itching" sensation but without current for the remainder of the "stimulation" period. This procedure has been shown to effectively blind participants to the stimulation condition [26].

Peripheral electrical stimulation (PES)

Applied to the area of worst pain using a Chattanooga Intelect Advanced therapy system (Chattanooga Group, Vista, USA). Stimulation was delivered using the same electrodes used for recording EMG. A biphasic waveform (0.1 ms pulse duration) was delivered at a frequency of 2 Hz. Stimulation intensity was set at 2–3× perceptual threshold to produce a strong, tingling sensation that was just below pain threshold. These parameters are commonly used in rehabilitation settings for the treatment of chronic pain [19,27–29]. Habituation to the stimulus was monitored verbally every 5 min. If the participant indicated a reduced sensation, current intensity was increased until the subject indicated a consistent

level of noxious sensation had again been achieved. The same electrode position was used for sham PES, for which the machine was turned on and all treatment parameters set, but stimulus intensity was left at 0 mA. To ensure blinding, participants were told different stimulus intensities were under investigation and they may or may not perceive sensations during the intervention [30]. The machine's display was faced away from the participant for both conditions.

Outcome measures

Pain severity

Current pain intensity was measured using the 11-point NRS.

Motor cortical organization

Single-pulse transcranial magnetic stimulation (TMS) was delivered to the primary motor cortex contralateral to the side of worst pain (Magstim 200 stimulator/figure-of-eight coil; Magstim Co. Ltd. Dyfed, UK). The coil was positioned along the sagittal midline with the handle facing posteriorly. This orientation has been shown to minimize current spread to the opposite hemisphere and elicit consistent responses (motor evoked potentials, MEPs) in paraspinal muscles [31]. The vertex was determined using the 10/20 International EEG Electrode Placement system and this point registered using a Brainsight2 neuronavigation system (Rogue Resolutions Ltd, Cardiff, UK). Starting at the vertex, five magnetic stimuli were delivered at 1-cm intervals on a 6 × 7 cm grid (0–5 cm lateral and from 1 cm posterior to 5 cm anterior, where the vertex is point 0,0 cm). Accurate coil placement at each grid site was determined using neuronavigation. Stimuli were applied at 100% of stimulator output with an inter-stimulus interval of 6 s. All TMS procedures adhered to the TMS checklist for methodological quality [32].

As in previous studies, it was not possible to elicit clear and reliable MEPs from the paraspinal muscles at rest [23,31]. Thus, participants activated the paraspinal muscles to 20% of their maximum voluntary contraction (MVC) force during mapping. The target EMG amplitude was determined as 20% of the highest root mean square (RMS) EMG for 1 s during three, 3-s maximal trunk efforts performed against manual resistance in sitting. Visual feedback was provided on a computer monitor and the 20% MVC target achieved by sitting forward with the back straight [23,33]. To minimize fatigue, participants were instructed to rest for 3–5 min following completion of a sequence of stimuli along each row on the scalp (0–5 cm lateral). To ensure that the prolonged sitting and high TMS stimulator output required during the mapping procedure did not exacerbate LBP symptoms, pain severity was monitored verbally throughout, and evaluated on completion of TMS mapping using an 11-point NRS.

Sensitization

Estimated using tests of pressure pain thresholds (PPTs) and pain-free range of lumbar flexion (Schober test).

(i) Pressure pain thresholds (PPTs): A handheld pressure algometer (Somedic, Hörby, Sweden, probe size 1 cm^2) was applied at the site of pain (to estimate primary hyperalgesia) and over a remote site on the thumbnail contralateral to the side of pain. Although more variable [34], evaluation of the response at the thumbnail has been argued to reflect overall pressure-pain sensitivity [35] and was included as an estimate of secondary hyperalgesia (sensitivity to pain outside the painful region) and a reflection of central sensitization. Pressure was applied at a rate of ~40 Kpa/s and participants used a hand-held trigger to indicate when the sensation of pressure first changed to one of pain. Three measures were made at each site before and after each intervention and averaged for analysis.

(ii) Schober's test was used as a second measure of primary hyperalgesia by evaluation of the "threshold" range of lumbar flexion required to increase pain. This was measured before and after each intervention. The midline of the lumbar spine was marked at a level aligned to the inferior posterior superior iliac spine (PSIS) and 15 cm above this point. The participant was asked to bend forward as far as possible without increasing pain. The distance between the two landmarks was measured to the nearest millimeter. Three trials were performed before and after each intervention and averaged for analysis.

Higher sensory function

Measured as the threshold for two-point discrimination (TPD) using a caliper ruler positioned between the first lumbar vertebra and the iliac crest on the side of worst pain before and after each intervention [36,37]. TPD threshold was defined as the caliper separation at which the participant could clearly perceive two points instead of one. This threshold was estimated as the separation (average of three trials) at which the participants could first or last identify two points as the separation was increased or decreased, respectively, in 5 mm increments (in the vertical and horizontal direction). To limit bias calipers were occasionally expanded or contracted out of sequence during testing.

Data analyses

Analysis of TMS map data was performed using MATLAB 7 (The Mathsworks, USA). EMG was full-wave rectified and the five MEPs at each scalp site averaged. MEP onset and offset were visually identified from the averaged traces and MEP amplitude calculated as the RMS EMG amplitude between the onset and offset [31,38–41]. Background EMG from 55 to 5 ms prior to stimulation was subtracted [31,39,40]. MEP amplitudes were superimposed over the respective scalp sites to produce a topographical representation of the target paraspinal muscle EMG recording and normalized to the peak amplitude of the baseline map for each intervention. Consistent with previous studies, normalized values less than 25% of the peak response were removed and the remaining values rescaled from 0 to 100% [31].

Three parameters were calculated from the normalized maps. First, map volume, a measure of the total excitability of the cortical representation, was calculated as the sum of the mean normalized MEP amplitude at all active sites. To be considered active, a scalp site was required to have a normalized MEP amplitude of equal to or greater than 25% of the peak response. Second, the centre of gravity (CoG) was defined as the amplitude weighted centre of the map [42,43] and was calculated for each muscle using the formula: $\sum V_i \times X_i / \sum V_i, \quad \sum V_i \times Y_i / \sum V_i$ where V_i = mean MEP amplitude at each site with the coordinates X_i, Y_i. The CoG is a valid and reliable measure of a motor cortical representation [42,44]. Finally, the number of discrete peaks in the TMS map before and after each intervention was determined. A peak was identified if its amplitude was at least 60% of the maximum MEP amplitude for an individual's map and was separated from adjacent areas in the anterior–posterior plane of amplitude greater than 60% maximum MEP by a trough of at least 20%. These criteria were based on previous investigation of TMS maps in people with CLBP [31].

Statistical analyses

Measures of (i) pain severity, (ii) motor cortical organization (TMS map parameters), (iii) sensitization (local and remote PPTs, Schober test), and (iv) higher sensory function (TPD) were compared between interventions (tDCS/PES, tDCS alone, PES alone and

Table 2
LBP group data (mean ± standard error) pain scores.

Intervention	Pre	Post	Day 1	Day 3
tDCS/PES	4.6 ± 0.4	1.8 ± 0.5*	2.3 ± 0.5*	3.1 ± 0.5*
tDCS alone	4.2 ± 0.6	1.7 ± 0.4*	2.5 ± 0.5*	3.2 ± 0.4*
PES alone	3.8 ± 0.5	1.3 ± 0.3*	2.8 ± 0.5*	3.3 ± 0.6*
Sham	3.6 ± 0.4	2.9 ± 0.5	2.8 ± 0.4	3.3 ± 0.4

*$P < 0.05$ comparison to baseline.

sham) and time-points (pre, immediately post) using repeated measures analyses of variance (ANOVA). To evaluate the maintenance effect of each intervention on pain severity, a repeated measures ANOVA was used to compare between interventions (tDCS/PES, tDCS alone, PES alone and sham) and each follow-up time-point (pre vs. day 1 and pre vs. day 3 after the intervention). To determine if prolonged sitting and the high stimulator output required during the mapping procedure exacerbated LBP symptoms prior to the delivery of each intervention, pain severity was compared before and immediately after TMS mapping using a 1-way ANOVA. Significant interactions were further explored using Holm–Sidak post-hoc tests.

One-way ANOVAs were used to explore differences in the effect of treatment on pain severity (change on the NRS from baseline to immediately after each intervention) between individuals who presented with higher vs. lower (relative to the group median) signs of both primary and secondary hyperalgesia (high primary hyperalgesia defined as local PPT less than the median value of all baseline measures [538 kPa] and high secondary hyperalgesia as remote PPT less than the median value of all baseline measures [366 kPa]). Similarly, one-way ANOVAs were used to explore differences in the effect of treatment on pain severity (change on the NRS from baseline to immediately post each intervention) between individuals who displayed a single peak in the cortical map and those who displayed two discrete peaks. A possible linear association between signs of primary and secondary hyperalgesia at baseline was evaluated using Pearson's correlation coefficient. Significance was set at $P < 0.05$.

Results

Two participants completed only two sessions (tDCS alone and sham) and were excluded from the analysis. TMS mapping data were excluded for one subject where responses were unable to be evoked with the stimulator at 100% output. There was no difference in pain severity following the mapping procedure (pre mapping 4.0 ± 2.0; post mapping 3.8 ± 2.0), suggesting the prolonged sitting and high TMS stimulator output required during this test did not exacerbate LBP symptoms prior to delivery of the intervention (main effect – time; $P = 0.57$). No participant reported the TMS procedure to be painful.

Pain severity

Pain severity reduced, on average, by 2.5–2.8 points on the NRS (Table 2), immediately following each of the three active interventions (interaction – intervention × time; $P = 0.03$; tDCS/PES post-hoc $P < 0.001$, tDCS alone post-hoc $P < 0.001$ and PES alone post-hoc $P < 0.001$) but not following the sham intervention (average reduction 0.7 points on the NRS; post-hoc $P = 0.1$). There was no difference between baseline pain severity across the four interventions (post-hoc tests all; $P = 0.12$–0.78). The reduction in pain was maintained for each of the active interventions at day 1 (main effect – time; $P < 0.001$) and day 3 (main effect – time; $P = 0.01$) follow-up.

There was a strong positive association between low PPT at the site of CLBP (indicative of primary hyperalgesia) and low PPT at the remote thumbnail site (indicative of secondary hyperalgesia; $r = 0.68$, $P < 0.001$; Fig. 1A). When pain severity data were considered between those with low PPT in both regions ($n = 7$) and those without ($n = 9$), individuals with low PPT displayed a greater reduction in pain immediately following the combined tDCS/PES intervention than individuals with high PPT ($P = 0.04$, Fig. 1B). Changes in pain severity immediately following each of the remaining interventions did not differ between individuals with high and low PPTs (main effect: Pain hyperalgesia subgroup – tDCS alone $P = 0.73$, PES alone $P = 0.62$, sham, $P = 0.19$).

Motor cortical organization

Average cortical maps of paraspinal muscle responses to TMS before and after each intervention are shown in Fig. 2. Motor cortical maps displayed a single 'hotspot', usually located posteriorly, at baseline across all interventions. However, the number of discrete map peaks was influenced by the type of intervention (intervention × time interaction $P = 0.042$). Following the combined tDCS/PES intervention two discrete map peaks ($P < 0.001$; from 1.1 ± 0.35 to 1.7 ± 0.45 peaks) were observed. A single peak remained following tDCS alone ($P = 0.23$, from 1.2 ± 0.45 to 1.4 ± 0.51 peaks), PES alone ($P = 0.42$, from 1.2 ± 0.45 to 1.4 ± 0.51

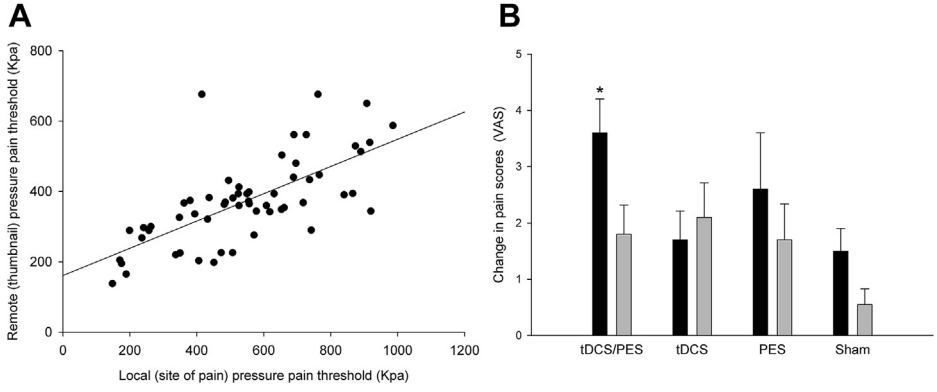

Figure 1. A) Association between primary (site of pain) and secondary (thumbnail) hyperalgesia across all four protocols at baseline. Note those with high sensitivity to pressure at the site of pain also displayed high sensitivity to pressure at the remote thumbnail site. B) Group change (mean ± standard error) in pain scores from baseline to immediately after each intervention in those with (black bars) and without (gray bars) sensitivity to pressure. The combined tDCS/PES intervention reduced pain to a greater extent in those with high pressure sensitivity. *$P < 0.05$.

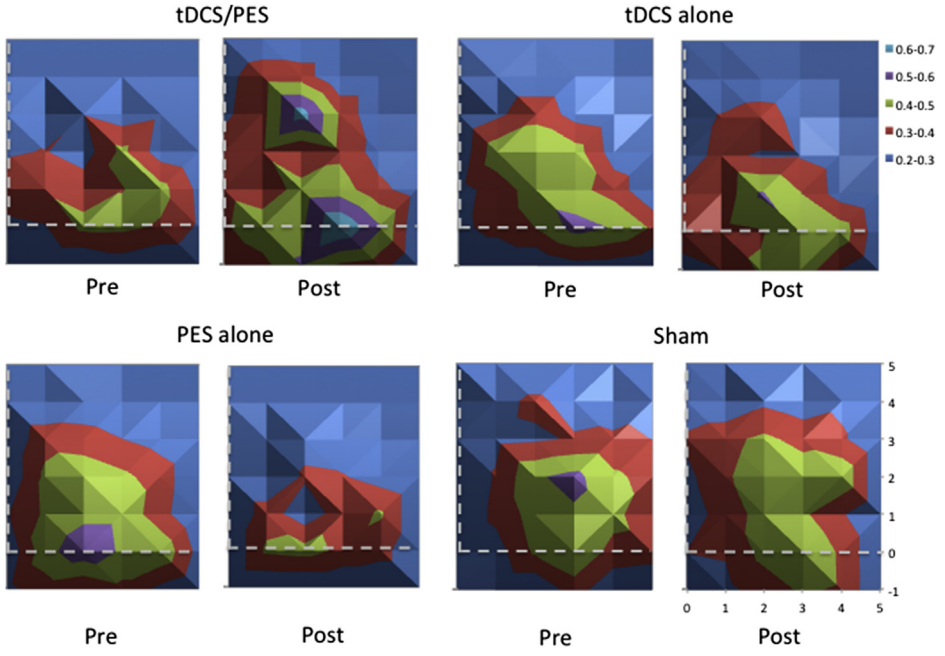

Figure 2. Average normalized motor cortical maps before and after each intervention. The horizontal dashed line represents the inter-aural line and the vertical dashed line the line from the nasion to the inion. Each square represents 1 × 1 cm. Note the presence of one 'hotspot' in each of the baseline maps and the differentiation of the motor cortical map into two discrete peaks following the combined tDCS/PES intervention.

peaks) and sham ($P = 0.69$, from 1.2 ± 0.45 to 1.2 ± 0.41 peaks). The proportion of individual maps containing two peaks before and after each intervention was: tDCS/PES pre 13%, post 69%; tDCS alone pre 25%, post 44%; PES alone pre 25%, post 38%; sham pre 25%, post 19%. The number of map peaks was not associated with the change in pain severity following any treatment (main effect: motor cortex map subgroup − tDCS/PES $P = 0.56$, tDCS alone $P = 1.0$, PES alone $P = 0.15$, sham $P = 0.55$).

Map volume was increased when tDCS and PES were combined (intervention × time interaction $P = 0.013$, post-hoc $P = 0.025$), decreased when PES was applied alone (post-hoc $P = 0.024$) and unchanged with tDCS applied alone (post-hoc $P = 0.73$) and sham (post-hoc $P = 0.59$; Fig. 3). The position of the CoG (intervention × time interaction x-coordinate $P = 0.32$; y-coordinate $P = 0.25$; main effect of time x-coordinate $P = 0.31$; y-coordinate $P = 0.66$) was not altered by any intervention.

Sensitization

Figure 4 shows group data for the Schober test before and after each intervention. The combined tDCS/PES intervention led to an increased range of motion of forward flexion (intervention × time interaction $P = 0.02$; post-hoc $P = 0.002$). Other interventions produced no effect on the Schober test (post-hoc tDCS alone $P = 0.89$; PES alone $P = 0.78$; sham $P = 0.1$). There was no difference in the Schober test at baseline across the four interventions (post-hoc tests between interventions at baseline all $P > 0.68$).

PPT increased at the site of pain when tDCS was combined with PES (intervention × time interaction $P = 0.03$; post-hoc $P = 0.001$), but was unaltered with each of the other interventions (post-hoc tDCS alone $P = 0.55$; PES alone $P = 0.21$; sham $P = 0.55$; Fig. 4). There was no difference in PPTs at the site of pain at baseline across the four interventions (post-hoc tests between interventions at baseline all $P > 0.52$). PPT at the remote thumbnail site was unaffected by any intervention (intervention × time interaction $P = 0.72$; main effect of time $P = 0.37$).

Higher sensory function

TPD on the side of worst pain reduced in both the vertical (intervention × time interaction $P < 0.001$) and horizontal (intervention × time interaction $P = 0.01$) directions immediately following the combined tDCS/PES intervention (vertical post-hoc $P = 0.003$; horizontal post-hoc $P = 0.006$) and following PES applied alone (vertical post-hoc $P < 0.001$; horizontal post-hoc $P = 0.001$; Fig. 4). The reduction in TPD did not differ between the tDCS/PES and PES alone interventions (tDCS/PES vs. PES vertical post-hoc $P = 0.48$; horizontal $P = 0.31$). There was no difference in TPD at baseline across the four interventions (post-hoc tests

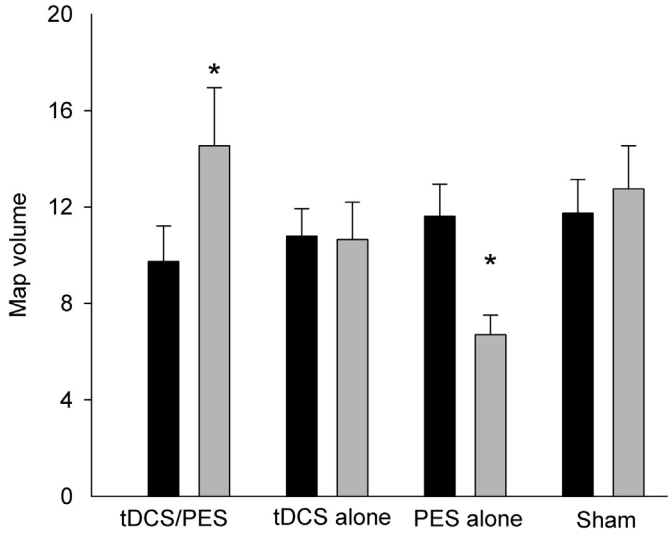

Figure 3. Map volume (group data mean ± standard error) before (black bars) and after (gray bars) each intervention. Map volume was increased following tDCS/PES and reduced when PES was applied alone. *$P < 0.05$.

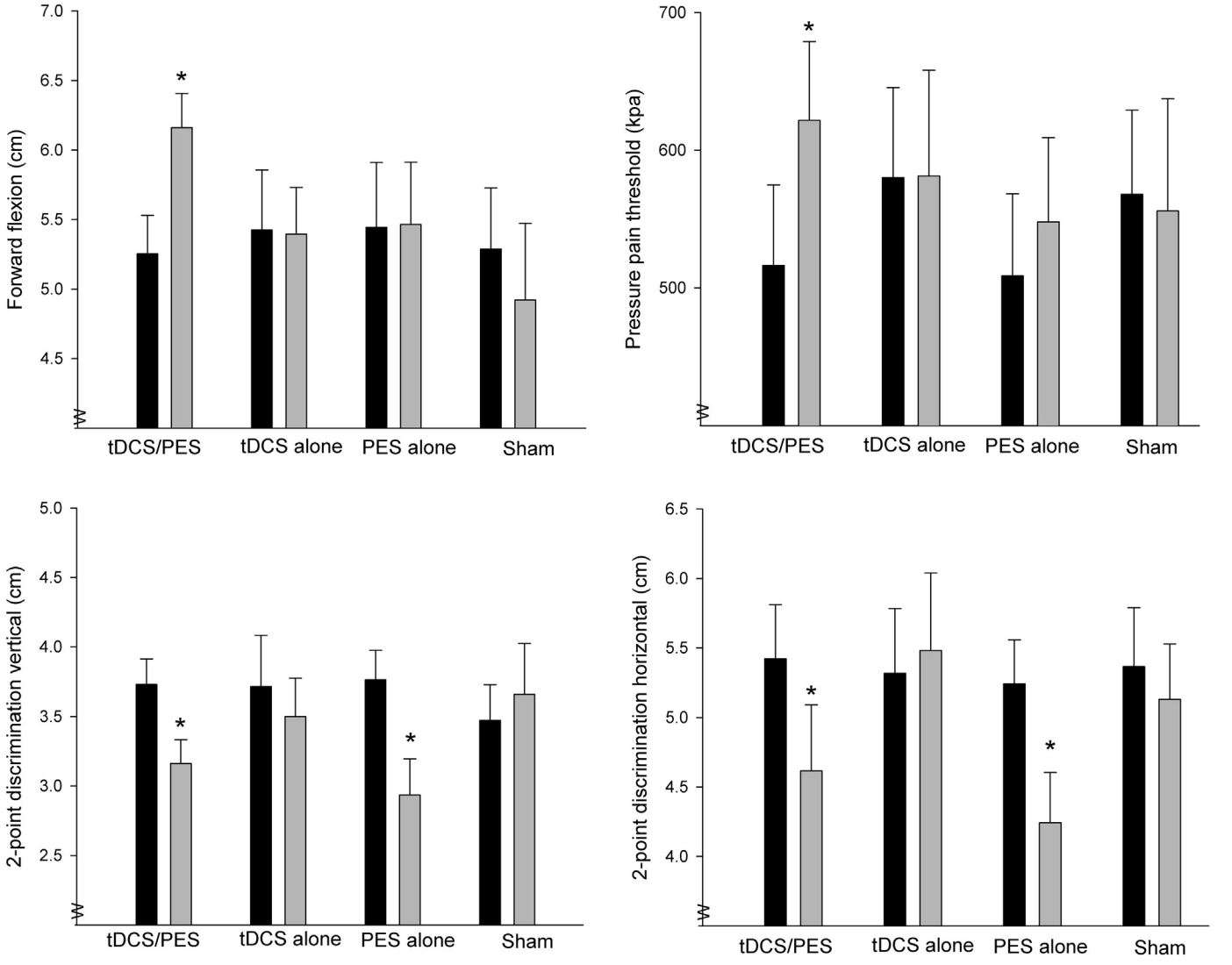

Figure 4. Group data (mean ± standard error) for forward flexion (top left), pressure pain thresholds at the site of pain (top right), 2-point discrimination vertical (bottom left) and 2-point discrimination horizontal (bottom right) before (black bars) and after (gray bars) each intervention. The combined tDCS/PES intervention increased forward flexion range of motion, increased pressure pain thresholds and reduced 2-point discrimination. PES applied alone also reduced 2-point discrimination. tDCS applied alone and sham did not alter any clinical measure. $^{*}P < 0.05$.

between interventions at baseline vertical all $P > 0.25$, horizontal all $P > 0.31$). There was no change following tDCS applied alone (vertical post-hoc $P = 0.4$; horizontal post-hoc $P = 0.9$) or the sham intervention (vertical post-hoc $P = 0.1$; horizontal post-hoc $P = 0.4$).

Discussion

This study is the first to show a combined tDCS and PES intervention reduces pain and sensitization normalizes aspects of organization of the motor cortex and improves higher sensory function in CLBP. The reduction in pain was greater in individuals with more pronounced primary and secondary hyperalgesia. When applied alone, tDCS or PES also reduced pain. However, with the exception of reduced TPD and reduced map volume following PES, additional clinical and neurophysiological outcomes were unaltered by tDCS and PES treatments applied separately. The sham treatment did not influence any clinical or neurophysiological measure. Taken together, these data suggest a combined tDCS/PES intervention more effectively improves symptoms of CLBP and mechanisms of cortical organization and sensitization, than either intervention applied alone or a sham intervention control.

Clinical outcomes are improved by a combined tDCS/PES intervention

Pain reduced immediately following all three active interventions and improvements were maintained for at least 3 days. The absence of a change in pain severity with the sham treatment indicates reduced pain was unlikely to be explained by time effects. Although evaluation of the organization of the motor cortex after the combined tDCS/PES indicated a shift toward that previously observed in pain-free controls (i.e. two discrete map peaks) [31], there was no relationship between the number of cortical map peaks and the change in pain severity. This implies the mechanisms that mediate pain severity in CLBP involve processes in addition to, or independent of, motor cortical reorganization. However, we did not include an outcome measure to probe motor behavior related to cortical organization. Discrete cortical organization of muscle representations in the sensorimotor cortex is thought to provide the

physiological basis for isolated movement control [45]. A lack of discrete cortical organization, as reported in focal hand dystonia [46,47] and CLBP [31,40], is associated with a loss of isolated movement (contraction of muscles *en masse*) and impaired motor function [47–49]. Thus, greater differentiation of the cortical representation of the back muscles in response to tDCS/PES might be expected to be associated with improved isolated movement. Further work is required to determine whether reorganization of the motor cortex is associated with enhanced motor behavior.

Previous studies have demonstrated a change in the position of the CoG of trunk muscles in CLBP following targeted motor skill training [39]. It is unclear why the interventions tested here did not alter the position of the CoG. However, several possibilities exist. First, the nature of changes in the cortical representation of the paraspinal and abdominal muscles is different; CoG of the abdominal muscles is shifted, whereas for the paraspinal muscles, the cortical representation is characterized by smudging of the usual two distinct cortical areas. Thus, similar changes with treatment for both muscle groups would not be expected. Second, targeted motor skill training may have a more direct influence on isolated movement control and thus, a larger effect on the differentiation of motor cortical representations, than the more global interventions (that do not directly target motor control) used here. Third, these differences may be explained by the use of different EMG recording techniques (fine wire vs. surface EMG recordings) and muscles tested (transversus abdominus vs. paraspinal muscles). The use of fine wire electrodes may provide greater resolution to observe changes in the differentiation of motor cortical representations related to specific muscle fascicles than surface EMG recordings. This requires investigation in future studies.

The combined tDCS/PES intervention more effectively reduced pain in individuals who displayed greater pressure sensitivity at local (primary hyperalgesia) and remote (secondary hyperalgesia) sites. Similarly, tDCS/PES was the only intervention to increase PPTs at the site of pain, and reduce pain sensitivity during forward flexion. These data suggest tDCS/PES may ameliorate sensitization in individuals with CLBP and this may contribute to reduced pain. The fact that reported tonic pain intensity also reduced with tDCS and PES applied alone, but without changes in measures of sensitivity, suggests possible summation of the mechanisms activated by the two interventions.

Possible mechanisms of action of PES

PES targets mechanisms of sensitization such as activation of descending antinociceptive pathways [11,12], activation of inhibitory neural circuits in the spinal cord [13], enhanced opioid and inhibitory neurotransmitter receptor activity [14,15] and consequently, spinal upregulation of inhibitory neurotransmitter release [15]. Consistent with reduced map volume in the present study, PES (when applied as a tonic sensory input) has also been shown to decrease neural excitability in both the primary sensory and primary motor cortex [19,50,51]. The biological substrate is thought to involve *reduced* synaptic efficacy and *increased* GABAergic cortical inhibition [52]. As chronic pain is hypothesized to involve overactivity in a widespread pain neuromatrix (characterized by *enhanced* synaptic efficacy and *reduced* cortical inhibition [7]), it is possible that PES reduced CLBP by dampening activity in this network. Reduced excitability of the primary sensory cortex in response to PES may also explain reduced TPD. Previous studies have shown that increased excitability of the primary sensory cortex is associated with impaired tactile acuity [53], suggesting that cortical excitability may have an important role in this aspect of behavior. Alternatively, this finding could be explained by an increased awareness of the area following PES or by the introduction of noise into muscle spindles that has been shown to improve sensitivity [54]. Further work is needed to determine the precise mechanisms through which PES reduces CLBP and improves sensory function.

Possible mechanisms of action of tDCS

Depending on the flow of current, tDCS can increase or decrease neuronal excitability. The effects are dependent on the polarity of stimulation; anodal tDCS induces membrane depolarization and enhanced excitability of cortical neurons, whereas cathodal tDCS induces membrane hyperpolarization and reduced excitability of cortical neurons [18,55]. Consistent with most [56–58], but not all [25], preliminary work in chronic pain, we demonstrate reduced pain with anodal tDCS. Evidence suggests tDCS of the primary motor cortex may relieve pain through inhibition of thalamic sensory neurons and disinhibition of neurons located in the periaqueductal gray [16]. Interestingly, anodal tDCS did not induce the characteristic increase in corticospinal excitability (i.e. map volume) reported in previous studies [59]. This difference is likely explained by the location of the paraspinal muscle representation deep in the motor cortex. The depth of the paraspinal muscle representation may have prevented electrical current from reaching appropriate cells, reducing the potential for neuronal depolarization [60].

Possible mechanisms of action of combined tDCS/PES

The combined tDCS/PES intervention increased map volume (corticospinal excitability) and normalized motor cortical representations in CLBP. This finding is interesting given that PES alone reduced, and tDCS alone had no effect on, map volume. The combined intervention was also the only paradigm to influence measures of sensitization. The absent or opposite effects obtained when PES and tDCS were applied alone compared with the combined intervention suggests a priming effect, where one intervention increased the receptiveness of the brain and spinal cord to the second intervention. For example, according to the principles of homeostatic metaplasticity; low neural activity biases synaptic modifications toward long-term potentiation (LTP; increased excitability), whereas high levels of activity favor long-term depression (LTD; decreased excitability) [61]. Although this mechanism has traditionally been proposed to regulate the effect of sequential and not concurrent interventions, recent evidence challenges this assertion and suggests that longer stimulation periods may behave similarly to sequential applications and induce homeostatic effects [59,62,63]. As PES is thought to reduce corticospinal excitability via LTD-like mechanisms, the application of this intervention may slide the synaptic threshold toward low neural activity, biasing synaptic modifications toward increased excitability when tDCS is applied. This mechanism may explain why tDCS alone has no effect on map volume, but with the addition of PES, neural networks are made more susceptible to the depolarizing currents of anodal tDCS and map volume is increased. In conjunction with this mechanism, it is possible that superior clinical effects obtained with the combined intervention reflect a bombardment of multiple 'top-down' and 'bottom-up' pain systems that, when modulated simultaneously, produce a greater reduction in pain sensitivity (as observed by increased PPTs and increased forward flexion ROM with tDCS/PES). In support of this premise, preliminary evidence demonstrates additive effects on pain thresholds in healthy individuals when a top-down (tDCS) and bottom-up (central pain modulation) therapies are combined [17]. Similarly, a preliminary study in chronic pain (8 individuals with arm pain) reported a greater immediate reduction in pain when

tDCS and PES (applied at an intensity below sensory threshold) were combined (37% reduction in ongoing pain) than application of tDCS alone (16% reduction) or a sham treatment (~3% increase) [56]. These data support the findings of our current study, although interpretation of data from the previous study is limited by the absence of assessment of the underlying mechanisms of a combined tDCS/PES application and no comparison to PES applied alone.

Clinical implications

Our data suggest a combined tDCS/PES intervention may produce clinical benefits that are greater than those obtained with either intervention applied alone. Greater clinical improvements with the combined protocol may reflect a priming mechanism that ameliorates pain sensitivity and normalizes cortical organization. Interestingly, the combined intervention produced greater improvements in those who presented with primary and secondary hyperalgesia, suggesting that this sub-group may derive greater benefits from neuromodulatory therapies. These findings require replication in a large, randomized, controlled trial. Notably, more robust clinical outcomes are likely to be achieved with a greater number of simulation sessions [64] and future studies should seek to explore this possibility. Finally, it should be noted that this study included individuals with recurrent LBP and our findings may not be generalizable to other forms of LBP.

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