Transcranial Direct Current Stimulation of the Motor Cortex in the Treatment of Chronic Nonspecific Low Back Pain

A Randomized, Double-blind Exploratory Study

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Objectives: To test the proof of principle that active anodal transcranial direct current stimulation (tDCS) applied to the motor cortex reduces pain significantly more than sham stimulation in a group of participants with chronic nonspecific low back pain.

Methods: The study utilized a within-participants sham-controlled, interrupted time series design. A sample of 8 participants was recruited. After 3 days of baseline measures, patients entered a 15-day experimental period (Mondays to Fridays) for 3 consecutive weeks. During this period each patient received sham stimulation daily until a randomly allocated day when active stimulation was commenced. Active stimulation was then given daily for the remaining days of the experimental period. Both the participants and the assessors were blinded. The primary outcomes were average pain intensity and unpleasantness in the last 24 hours measured using a visual analogue scale. Secondary outcomes included self-reported disability, depression and anxiety, a battery of cognitive tests to monitor for unwanted effects of stimulation, and patients' perceptions of whether they had received active or sham stimulation. Data were analyzed using generalized estimating equations.

Results: No significant effect was seen in the primary outcomes between active and sham stimulation (average pain intensity $P = 0.821$, unpleasantness $P = 0.937$) or across any other clinical variables. There was evidence that patients may have been able to distinguish between the active and sham conditions ($P = 0.035$).

Discussion: These results do not provide evidence that tDCS is effective in the treatment of chronic back pain. The use of a small convenience sample limits the generalizability of these findings and precludes definitive conclusions on the efficacy of tDCS in chronic nonspecific low back pain.

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Chronic low back pain (CLBP) is a widespread and costly problem for which few interventions are effective.[1] Brain stimulation techniques have been used to address a variety of pathologic pain conditions. Both invasive brain stimulation, in which electrodes are surgically implanted epidurally within the cortex and noninvasive stimulation techniques, such as repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) have been developed. All of these techniques seek to alter activity in brain regions by an electrical stimulation of the brain.[2]

The precise mechanisms by which brain stimulation may alleviate pain are not clear. Imaging studies in humans suggest that invasive stimulation of the motor cortex may reduce pain by modulation of activity in cortical and subcortical brain areas involved in pain processing, for example the orbitofrontal cortex, cingulate cortex, and the thalamus and by facilitating descending noxious inhibitory mechanisms.[3] Both tDCS and rTMS have been shown to modulate brain activity specific to the site of application and the parameters of stimulation. Evidence suggests that the observed alterations in cortical excitability after rTMS and tDCS, which last beyond the time of stimulation, are the result of long-term synaptic changes.[2] Pain relief after rTMS has been associated with the restoration of decreased intracortical inhibition in patients with neuropathic pain[4] and an increase in excitatory neurotransmitter levels in patients with chronic visceral pain.[5] Conversely, tDCS led to a decrease in intracortical inhibition in a group of patients with chronic pain of mixed etiology.[6] Although both rTMS and epidural motor cortex stimulation present challenges to the implementation of effective sham conditions in efficacy studies, tDCS has a methodological advantage and it is more likely that a sham treatment will be indistinguishable from the active treatment condition.[7]

A recent Cochrane review into the efficacy of noninvasive brain stimulation methods for chronic pain[8] found preliminary evidence of efficacy for active tDCS applied to the motor cortex. However, because of significant clinical and statistical heterogeneity it was not possible to accurately estimate the effect size. To date, 1 study has investigated this method in a group of 12 participants that included 8 with chronic back pain[6] and found a reduction

in pain after 5 daily active stimulation sessions with a concurrent reduction in intracortical inhibition. The aim of this exploratory study was to test whether daily treatments of active anodal tDCS applied to the motor cortex reduces pain significantly more than sham stimulation in a group of patients with chronic nonspecific low back pain.

MATERIALS AND METHODS

This study had full approval from the School of Health Sciences and Social Care Research Ethics Committee, Brunel University, the NHS Research Ethics Service (reference number 07/H0808/172) and the Hillingdon Hospitals NHS Trust Research and Development Office. A sham-controlled, interrupted time series design was utilized with randomized multiple baselines. This design is considered advantageous to a parallel or cross-over randomized controlled trial in studies with small samples as it enhances statistical power while still providing a degree of control over nonspecific treatment effects and other biases.[9] In addition, the design was chosen to allow for exploration of the effect of varying the number of stimulation sessions, which no study to date has addressed. To reduce bias both the patients and the assessor were blinded to the intervention status (ie, sham or active stimulation).

Patients

A convenience sample of patients with back pain was recruited from the physiotherapy department and spinal diagnostic clinic of a general hospital in west London, UK. Patients referred to this department who met the inclusion criteria were invited to take part in the study. The inclusion criteria were as follows: aged over 18 years, proficient in written and spoken English, and a history of nonspecific low back pain (as defined by the European guidelines on low back pain[10]) of greater than 6 months duration. The exclusion criteria were: evidence of specific spinal pathology (fractures, neoplasm, deformity, Scheuermann disease, spinal infections, spondylolisthesis/lysis, radiculopathy), a history of spinal surgery within the year before commencing the study, known neurological disease, identifiable psychotic illness or other mental illness, pregnancy, or involvement in any other ongoing research project relating to their low back pain.

tDCS Stimulation

tDCS was delivered using a battery driven CX-6650 ramp controlled DC stimulator (Rolf Schneider Electronics, Germany). Current was delivered by electrodes encased in sponge pads soaked with 1% saline solution. The machine was kept behind the participant and out of their view at all times. For both the active and sham conditions, the anode was placed over the motor cortex of the patient and the cathode was placed over the contralateral supraorbital region. Electrodes were secured using soft elastic straps. For patients whose pain was predominantly on 1 side of their back, the contralateral hemisphere was stimulated. For patients whose pain was not predominantly on 1 side, the hemisphere contralateral to the patient's self-nominated dominant hand was stimulated. This approach is consistent with previous clinical studies.[11,12]

The location of the motor cortex was estimated using the international 10-20 EEG system and placing the centre of the electrode pad at a point 1 cm anterior and 4 cm lateral to the vertex. We have previously identified this location as the motor cortex representation of the lumbar paravertebral muscles in a TMS mapping study.[13]

In the active stimulation condition a constant current of 2 mA intensity was applied for 20 minutes with a 5-second ramp phase at the beginning. In the sham stimulation condition the machine was activated for 30 seconds using identical parameters but was then switched off, without the patient's knowledge. This sham control is commonly employed[5,6,11,12,14–16] because over the initial 30 seconds of stimulation, an initial sensation of tingling under the electrode fades away. Patients are less likely to distinguish active from sham conditions if the initial period of tingling is present in both.

Outcome Measures

Primary Outcomes

The primary outcomes were average self-reported pain intensity and unpleasantness over the last 24 hours. Both were measured on separate 10 cm visual analogue scales (VAS). For intensity, the left anchor was "no pain" and the right anchor was "worst pain imaginable." For unpleasantness, the left anchor was "not bad at all" and the right anchor was "the most unpleasant feeling imaginable." Both measures were taken once daily during the baseline period, before stimulation on each day of the experimental phase, and once at each follow-up point.

Secondary Outcomes

To investigate any immediate effect of brain stimulation on pain intensity or unpleasantness, both were assessed using the same VAS, but in response to the question "How would you rate your pain (intensity/unpleasantness) at the moment?", immediately before and after each session. We measured self-reported disability using the Roland and Morris Disability Questionnaire[17] and anxiety and depression using the Hospital Anxiety and Depression Scale.[18] These were collected daily during the baseline and follow-up periods and every fifth day during the experimental phase. We also investigated whether the sham condition was distinguishable from active stimulation using a 0 to 10-cm VAS with the left anchor 0 cm = "100% sure the machine was switched on" and the right anchor "100% sure the machine was switched off." This was measured immediately after each stimulation session.

Adverse events: patients were asked, at the start of each day of the stimulation period and immediately after each stimulation session whether they experienced any adverse events or noticed any unexpected side effects. Patients were asked daily to report their analgesic medication.

Cognitive Function: to assess for any unwanted effects of stimulation on cognitive function, we employed a battery of cognitive tests to monitor performance over a range of cognitive domains. These were taken daily during the baseline and follow-up period and prestimulation and poststimulation on each day of the experimental period. These tests were performed by the patients on a laptop computer using E-Prime software (Psychology Software Tools, Sharpsburg). The following tests were undertaken:

Stroop color-word task: patients were required to respond to the ink color (red, blue, yellow, or green) of the printed words "Red," "Blue," "Yellow," and "Green" presented on a monitor using the appropriate keyboard key. Sixteen practice trials were administered, followed by 96 pseudorandomized test trials, half of which were congruent (word-color matched), and half incongruent (word-color

not matched). Measures of mean reaction time and accuracy (proportion of errors) were computed for this task.

Word recognition task for episodic memory: a list of 40 semantically unrelated nouns was created. Twenty target words were presented at a rate of 5 s/word on a monitor. After a distracter reaction time task, the 20 target words were randomly intermixed with 20 distracter words, and individually presented on a monitor for 5 seconds each. Patients were instructed to respond "Yes" for target words and "No" for distracter words using designated keyboard keys. On any given testing day, 1 of 8 possible lists of nouns was used to minimize the risk of patients learning the words over the course of the study. Mean reaction time and accuracy (proportion of correct responses) were analyzed.

Two-choice and 4-choice reaction time tasks: in the 2-choice version of the task, a black disc was presented on a monitor either left or right of a central fixation cross in a pseudorandom order. In the 4-choice version of the task, the black disc was presented in 1 of 4 locations (lower or upper left or right). Patients were required to press designated keyboard keys that mapped spatially onto the position of the disc on the screen as quickly but as accurately as possible. In each condition, 20 practice trials were administered before 48 test trials. On each testing day, 1 of these tasks was used as the distracter for the word memory recognition test. Mean reaction time and accuracy (proportion of errors) were analyzed.

Procedure

Patients gave their informed consent. The study included a 3-day baseline period, followed by a 15-day stimulation period during which patients received either real or sham stimulation, then a 3-day follow-up period. Outcomes were assessed again 3 weeks later. Figure 1 shows a flow chart of the study process. All testing and stimulation was carried out in a laboratory on a university campus.

After consent, each patient attended for 3 days (the "baseline period"). All outcome measures were completed daily but no interventions were given. The patient was then randomly allocated a specific day, which was not revealed to them, within the following 15-day period (the "experimental period") during which active stimulation would commence. The 15 days of the experimental period were Mondays to Fridays for 3 consecutive weeks. Each patient received sham stimulation daily until the day randomly allocated for active stimulation to commence. Active stimulation was then given daily for the remaining days of the experimental period.

Randomization and Blinding

The day for commencing active stimulation was randomized using a computer generated random numbers list that avoided replication (ie, no 2 patients could be randomized to commence active stimulation on the same day). The treatment allocations for each patient were generated and sealed in an opaque envelope. This process was completed by an independent administrator before recruitment of the first patient. The treatment schedule was revealed to the researcher who applied the stimulation on the first day of the stimulation period but was not revealed to the patients or any other member of the research team including the researcher who oversaw all outcome assessments. Blinding was maintained until all data for all patients had been collected for all patients and extracted and entered into a spreadsheet for analysis.

Data Analysis

Overall summary statistics were calculated, as were summary statistics by stimulation condition. Outcomes were modeled using generalized estimating equations[19] to determine whether there was a difference in outcome by condition (active vs. sham). These allow for the 2-level structure (patients being tested at multiple time points) to be modeled and results are given as coefficients and 95% confidence intervals (CI). These give marginal estimates (population average), which can be interpreted as the effect for the average person. The correlation structure was set to exchangeable (equal correlation within patients, but independence between patients). Bonferroni correction for multiple comparisons was not used because of the exploratory nature of the study and because we wished to minimize the likelihood of not detecting an effect that was actually there (type I error). All analyses were performed using Stata version 11 (Statacorp LP).

RESULTS

Patients

Eleven patients volunteered for the study but 3 were excluded at the recruitment stage, 2 because they had undergone back surgery within the last year, and 1 because of a marked congenital structural deformity of the spine. Table 1 shows the demographic characteristics of patients and details of the stimulation that they received. The mean age was 45 (SD, 10) years. Seven of the 8 patients were female. All patients completed the study including the 3-week follow-up although in addition to weekends, some gaps (maximum 6 d for 1 participant) were experienced during the study process because of uncontrollable circumstances including: heavy snow (3 patients), other illness (unrelated to back pain) (1 patient), family bereavement (1 patient), car breakdown (1 patient), and a national election in which 1 patient had a supervisory role and was unable to attend. Where days were missed for any reason (including weekends) the stimulation period was continued from the same point when the patient returned. The minimum number of active stimulation sessions that a participant received was 3 and the maximum was 14 (mean, 9) (SD, 4).

Table 2 gives the summary statistics across all variables by treatment condition. Table 3 shows the coefficients with 95% confidence intervals (CI) for the active treatment compared with the sham with P values.

The Effect of tDCS on Back Pain

Active tDCS had no effect on average 24-hour back pain intensity (coefficient, −0.070; 95% CI, −0.682 to 0.541; $P = 0.821$) nor on pain unpleasantness (coefficient, −0.026; 95% CI, −0.683 to 0.630; $P = 0.937$; number of included test occasions (n) = 109). Active TDCS provided no more pain relief presession to postsession than sham TDCS (intensity: coefficient, 0.008; 95% CI, −0.314 to 0.331; $P = 0.959$; unpleasantness: coefficient, 0.061; 95% CI, −0.290 to 0.411; $P = 0.735$; n = 117).

Figure 2 illustrates the change in pain intensity for each participant across the course of the study. Analysis of individual patients' pain intensity scores demonstrated that at the end of the last active stimulation no patients had experienced a reduction in pain of $\geq 20\%$ of their mean pain score after sham stimulation sessions.

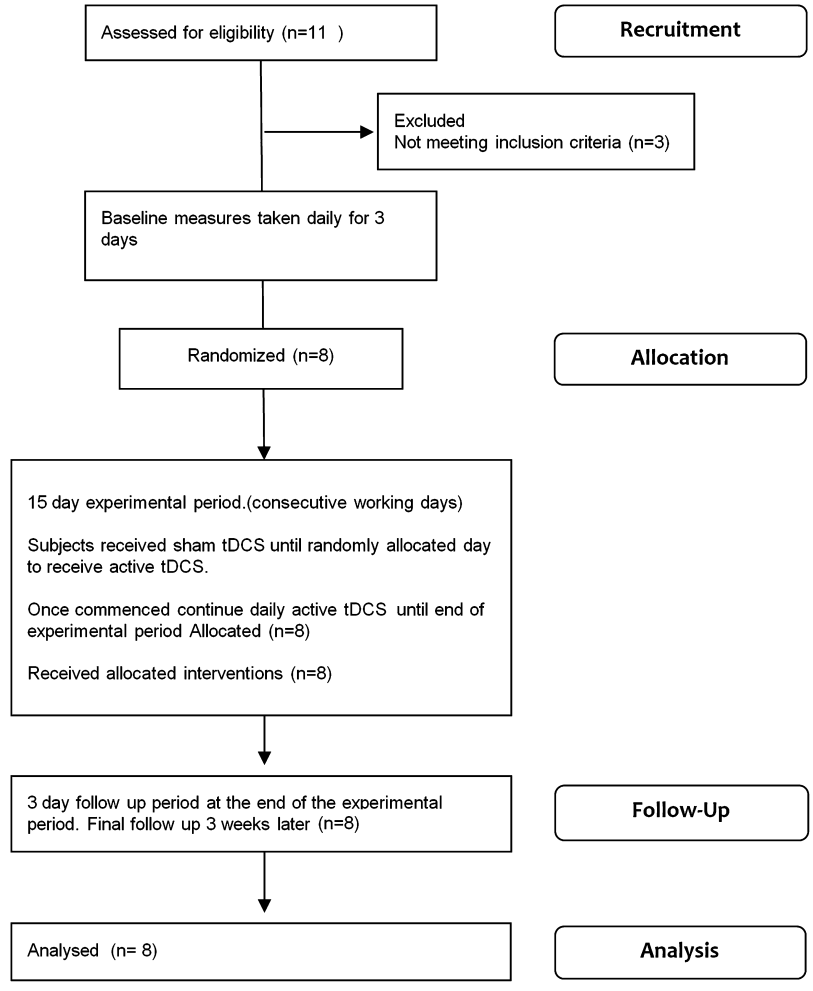

FIGURE 1. A flow chart illustrating the study process. tDCS indicates transcranial direct current stimulation.

Secondary Outcome Variables

Anxiety and depression scores were not entered into the analysis as there were insufficient data from each condition.

How Effectively did the Sham Condition Mimic Active Stimulation?

Patients scored higher on their perception of whether they had received active or sham treatment after active stimulation [mean (SD) active stimulation 6.47(1.22), sham stimulation 5.24(2.54); coefficient, 0.935; 95% CI 0.068 to 1.802; $P = 0.035$) (n = 117). This may indicate that the difference between the active and sham conditions was detectable.

Cognitive Tests

No deterioration was seen in patients' performance on any of the cognitive tests (n = 117). Accuracy in the word recognition task improved after active stimulation compared with sham (coefficient, 0.026; 95% CI, 0.001 to 0.051; $P = 0.042$).

Sensitivity Analysis

The models for pain outcomes were reanalyzed without controlling for patients' perceptions of the treatment condition and then, separately, with time (entered as the day of the stimulation period 1 to 15) included as a controlling variable. This made no difference to the outcome of the analyses. The model for participants' judgement as to the treatment condition was reanalyzed controlling for time and initial voltage. Once time and initial voltage were controlled for there was no significant relationship between patients' judgements and the stimulation condition (coefficient, 1.090; 95% CI, −0.173 to 2.353; $P = 0.091$).

Power Analysis

A post hoc power analysis based on a simple paired pretest-posttest study design suggests that to detect a moderately clinically important difference (a 30% reduction from baseline[20]) in average 24-hour back pain intensity, with 80% power at a significance level of $P = < 0.05$ would require a sample size of 15 patients. However, in the current study design additional power is conferred by the collection of multiple data points per patient.

Adverse Events

One patient reported dizziness, which lasted for a few minutes, immediately after stimulation. This was reported on 5 consecutive stimulation days and always after sham stimulation. Four patients on 1 occasion each reported

TABLE 1. Demographic Characteristics Participants and Details of the Stimulation Received

Subjects	Sex	Age (y)	Duration of Pain (y)	Location of Pain	Prior Clinical Management	Pain Medication	Hemisphere Stimulated	Day of Stimulation Period Active Stimulation Commenced (1-15)	No. Days Active Stimulations Received
1	F	34	5	Lumbar spine left side dominant, bilateral legs to below knee	Physiotherapy, analgesics	Ibuprofen as required	Right	2	14
2	F	39	3	Lumbar spine bilateral, no dominant side	Physiotherapy, analgesics Facet joint injections	None	Left	6	10
3	F	43	5	Lumbar spine left side dominant and left leg to below knee	Physiotherapy, analgesics, Facet joint injections, epidural.	Citalopram (20 md/d) Co-dydramol as required	Right	9	6
4	F	48	> 20	Lumbar spine, right side dominant	Chiropractic, analgesics	Ibuprofen, co-dydramol as required	Left	4	12
5	F	61	> 20	Lumbar spine, right side dominant	Spinal fusion (1994), physiotherapy, analgesics	Paracetomol as required	Left	11	5
6	F	57	13	Lumbar spine, right side dominant and right leg to below knee	Physiotherapy, pain management program, analgesics	Ibuprofen as required	Left	12	3
7	M	42	> 20	Lumbar spine bilateral, no dominant side	Physiotherapy, analgesics	None	Left	8	7
8	F	35	1-4	Lumbar spine, left sided dominance, left leg to below knee	Physiotherapy, facet joint injections, epidural, ultrasound, TENS, acupuncture	Ibuprofen, paracetomol, co-codamol, diclofenac as required	Right	5	11

headache after the stimulation. Two of the headaches were reported after sham stimulation and 2 after active stimulation. One patient noted headaches on 5 separate days during the stimulation period, 1 after sham stimulation and 4 after active stimulation. That patient also reported a long history of regular headaches. One patient on 1 occasion reported an increase in a preexisting ear pain after active stimulation. Through the course of the study 1 patient reported that she had notably fewer cravings for high-fat content foods.

DISCUSSION

The aim of this study was to explore whether anodal tDCS applied to the motor cortex has analgesic effects in patients with CLBP. The results do not provide evidence that anodal tDCS applied to the motor cortex is effective in CLBP. In fact the overall change in pain and other clinical outcomes throughout the course of the study, while generally demonstrating a trend towards improvement, is minimal. These findings are not consistent with those of existing studies of tDCS in other chronic pain conditions.[5,6,11,12,15–17] All previous studies have concluded in favor of tDCS over sham. Notably these studies gave treatment courses of up to 5 stimulation sessions. In the current study all but 1 patient received 5 active stimulation sessions or more and 4 patients received 10 or more active stimulations. Our results also demonstrate no significant change in current pain scores immediately after active stimulation. These findings contrast with those of Boggio et al[14] who found that a single dose of active tDCS led to an immediate reduction of pain in 8 patients with chronic neuropathic pain.

What might explain the difference between our results and the existing literature? The literature in tDCS is dominated by small studies investigating tDCS for a variety of chronic pain conditions and the risk of bias in these studies is frequently difficult to assess.[8] Although small in terms of patient numbers the current study was rigorously controlled with comparable statistical power to existing studies and utilized a recommended statistical approach.[19] It is recognized that at such an early developmental stage of research, small study effects and publication bias may also influence the evidence base for this modality with a propensity for negative studies to not reach full publication.[21,22]

One possible contributor to differential effects between studies is that the effects of tDCS may be specific to certain types of painful conditions. A recent meta-analysis of individual patient data from studies of rTMS for chronic neuropathic pain[23] reported a trend towards greater efficacy

TABLE 2. Summary Statistics by Treatment Condition

	Baseline	Sham	Active	Follow-up
Variables	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**
24 h average pain intensity (VAS, 0-10 cm)	5.25 (2.16)	5.19 (2.05)	5.03 (1.85)	4.57 (2.26)
24 h average pain unpleasantness (VAS, 0-10 cm)	5.33 (2.08)	5.29 (2.22)	5.16 (1.91)	4.63 (2.50)
Current pain intensity prestimulation (VAS, 0-10 cm)	4.35 (2.42)	4.53 (2.45)	4.27 (2.08)	3.97 (2.43)
Current pain unpleasantness prestimulation (VAS, 0-10 cm)	4.26 (2.65)	4.52 (2.57)	4.34 (2.14)	3.98 (2.43)
Current pain intensity poststimulation (VAS, 0-10 cm)	—	4.02 (2.13)	3.88 (2.20)	—
Current pain unpleasantness poststimulation (VAS, 0-10 cm)	—	3.97 (2.26)	3.88 (2.27)	—
Participants' judgement as to whether active or sham stimulation (VAS, 0-10 cm)	—	5.24 (2.54)	6.47 (1.22)	—
Disability (RMDQ) (score, 0-24)	10.7 (4.5)	10.2 (4.2)	9.0 (5.2)	7.8 (4.8)
Anxiety (HADS-A) (score, 0-18)	7.2 (3.4)	6.4 (3.7)	6.1 (4.0)	5.0 (4.1)
Depression (HADS-D) (score, 0-18)	4.5 (2.7)	4.1 (3.0)	3.4 (2.9)	3.6 (2.9)
Stroop test accuracy prestimulation*	0.01 (0.02)	0.02 (0.02)	0.02 (0.02)	0.02 (0.02)
Stroop test accuracy poststimulation*	—	0.02 (0.05)	0.02 (0.02)	—
Stroop test reaction time prestimulation (ms)	771.05 (110.97)	665.12 (68.87)	648.20 (69.76)	648.79 (91.07)
Stroop test reaction time poststimulation (ms)	—	660.19 (68.08)	645.02 (71.01)	—
Word memory test accuracy prestimulation†	0.86 (0.07)	0.87 (0.08)	0.88 (0.08)	0.92 (0.09)
Word memory test accuracy poststimulation†	—	0.86 (0.11)	0.89 (0.09)	—
Word memory test reaction time prestimulation (ms)	858.16 (102.78)	752.69 (65.36)	744.48 (61.38)	720.57 (56.00)
Word memory test reaction time poststimulation (ms)	—	747.56 (81.56)	730.12 (52.62)	—
4-choice reaction time accuracy prestimulation*	0.05 (0.06)	0.03 (0.02)	0.03 (0.02)	0.03 (0.02)
4-choice reaction time accuracy poststimulation*	—	0.03 (0.03)	0.03 (0.02)	—
4-choice reaction time, reaction time, prestimulation (ms)	449.67 (110.30)	399.55 (73.88)	380.50 (68.63)	377.56 (81.52)
4-choice reaction time, reaction time, poststimulation (ms)	—	397.33 (77.87)	378.72 (72.75)	—
2-choice reaction time accuracy prestimulation*	0.02 (0.02)	0.02 (0.01)	0.04 (0.05)	0.02 (0.02)
2-choice reaction time accuracy poststimulation*	—	0.03 (0.02)	0.02 (0.02)	—
2-choice reaction time, reaction time, prestimulation (ms)	297.02 (44.67)	283.18 (36.72)	280.87 (33.14)	283.83 (32.48)
2-choice reaction time, reaction time, poststimulation (ms)	—	280.75 (34.52)	280.83 (30.57)	—
Voltage when stimulator initially turned on (V)	—	9 (4)	10 (4)	—

*Outcome is proportion of incorrect responses.
†Outcome is proportion correct responses.
HADS Indicates Hospital Anxiety and Depression Scale; RMDQ, Roland and Morris Disability Questionnaire; VAS, visual analogue scale.

in patients with centrally maintained compared with peripherally maintained pain states. Currently there is insufficient data related to tDCS for a similar analysis to be performed. Fregni et al[12] demonstrated significant improvements in pain in patients with fibromyalgia, a chronic pain syndrome that, like CLBP, is characterized by ongoing pain without a clear structural diagnosis or specific neurological insult, but that is associated with alterations in brain structure and function.[24,25] Most recently, Antal et al[6] noted a trend towards a smaller effect of tDCS on back pain than on pain associated with arthrosis, but the small sample size used did not support a formal analysis of the influence of condition on efficacy. As such the data regarding the specificity of treatment effects from noninvasive brain

TABLE 3. Coefficients (95% Confidence Interval) for Active Treatment (Compared With Sham)—Time not Included

Outcomes	Coefficient	95% CI	*P*
24 h average pain intensity*	−0.070	−0.682 to 0.541	0.821
24 h average pain unpleasantness*	−0.026	−0.683 to 0.630	0.937
Current pain intensity poststimulation†	0.008	−0.314 to 0.331	0.959
Current pain unpleasantness poststimulation†	0.061	−0.290 to 0.411	0.735
Participants' judgement as to whether active or sham stimulation‡	0.935	0.068 to 1.802	0.035
Stroop test accuracy†‖	−0.016	−0.046 to 0.014	0.302
Stroop test reaction time†	−7.445	−19.611 to 4.720	0.230
Word memory test accuracy†§	0.026	0.001 to 0.051	0.042
Word memory test reaction time†	−28.497	−58.171 to 1.178	0.060
4 choice reaction time accuracy†‖	−0.004	−0.013 to 0.006	0.455
4 choice reaction time, reaction time†	−12.554	−24.289 to −0.819	0.036
2 choice reaction time accuracy†‖	−0.001	−0.011 to 0.010	0.892
2 choice reaction time, reaction time†	−2.666	−10.299 to 4.968	0.494

*Controlling for the patients' perception from the previous day of whether they are receiving active treatment or sham on a 0 to 10 VAS.
†Controlling for pretest score of the given variable.
‡Controlling for the voltage when the stimulator is initially switched on.
§Outcome is proportion correct.
‖Outcome is proportion incorrect.

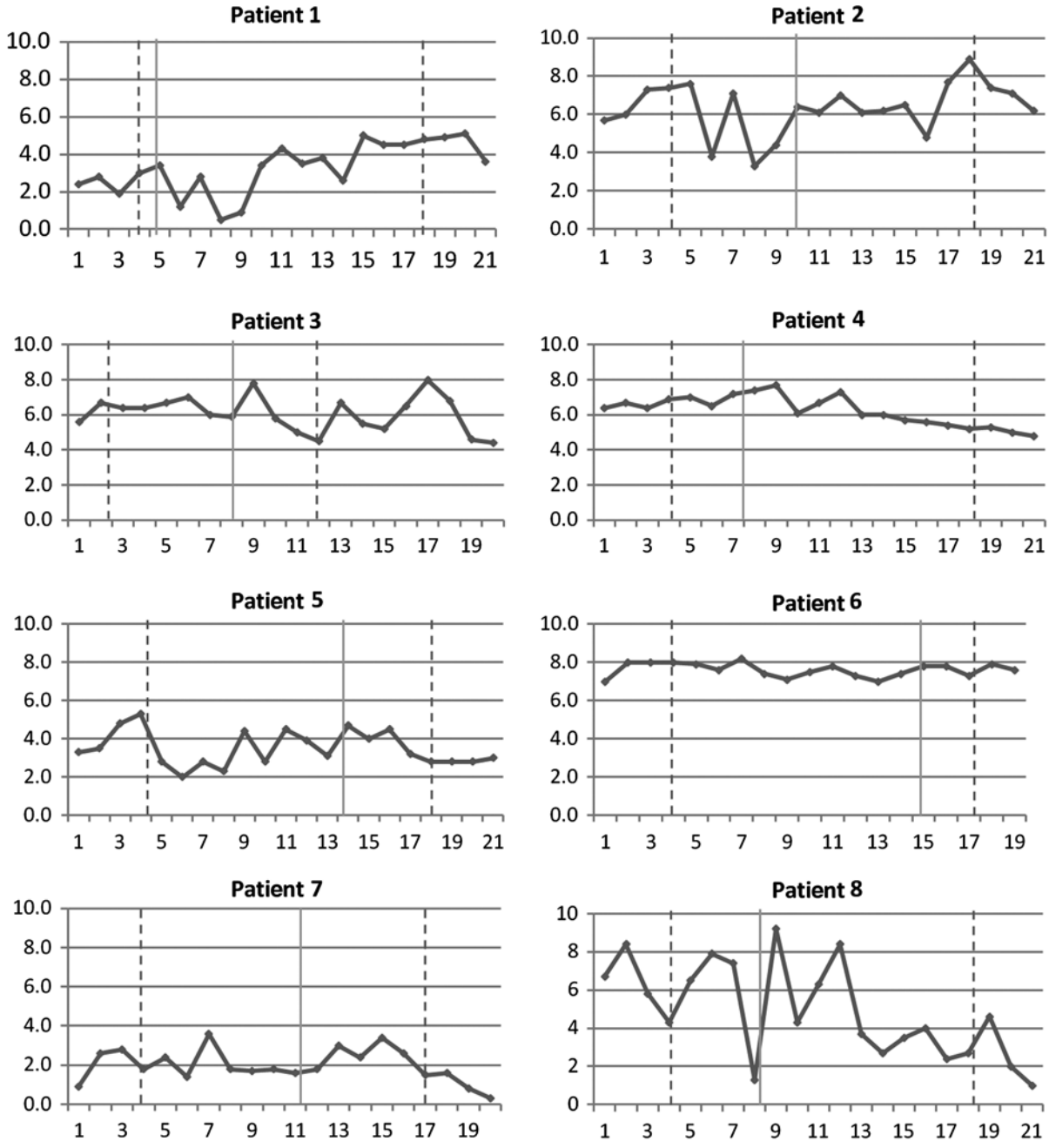

FIGURE 2. The change in pain intensity through the course of the study for each patient. The *y* axis represents the average pain intensity over the previous 24 hours measured on a 0 to 10-cm visual analogue scale, the *x* axis represents the session number. The vertical dashed lines indicate the beginning and end of the stimulation period. The vertical solid line indicates the day of onset of active stimulation.

stimulation for different conditions are both incomplete and inconclusive. Although it is possible that tDCS might be specifically ineffective for CLBP, it is not clear what factors might underpin such an interpretation.

We observed little change in patients' clinical symptoms under either stimulation condition, indicating a negligible placebo effect. Indeed the mean reduction in average 24-hour pain intensity was < 1 cm on a 10-cm VAS across both the active and sham stimulation conditions. However, our analysis suggests that at least some patients may have been able to distinguish between the active and sham conditions. It is possible that as the stimulation period progressed patients may have been more likely to suspect that they were receiving active stimulation and that this might have contributed to the significant difference observed. Factoring time into the analysis removed the effect of stimulation condition on patients' judgements regarding the treatment condition ($P = 0.091$). It is arguable therefore that patients were successfully blinded. Nonetheless the trend observed in this small sample indicates that a more

rigorous assessment of the validity of sham tDCS at intensities of ≥ 2 mA is justified.

This raises the question of whether the blinding of patients used in existing clinical studies can be considered robust. Previous validation of the sham condition at intensities of 1 mA was provided by Gandiga et al.[7] In the current study and all existing clinical studies of tDCS for the treatment of pain, intensities of 2 mA have been applied, which may elicit stronger sensations. If the blinding of this sham condition is not truly robust this might have led some studies to exaggerate the efficacy of tDCS. One might expect blinding to be more of an issue in studies that utilize cross-over designs where patients have a direct comparison between active-stimulation and sham-stimulation conditions. Nonetheless in the report of the recent parallel trial by Mori et al[16] the authors allude to having difficulties with blinding at intensities of 2 mA, although, unfortunately, they do not specify what they were and no other studies have reported a formal assessment of blinding success.

We observed no serious or lasting adverse effects, which is consistent with previous studies. Transient headaches and nausea were reported under both active and sham conditions by a number of patients, which means at least some of them can be considered "nocebo" responses. In addition, no deterioration was seen in performance of any of the cognitive tests and these results add to the growing body of evidence indicating that tDCS using the same stimulation parameters is a safe intervention.

Study Limitations

The main limitation of the current study is its small sample size. Perhaps our study was underpowered to detect the effect of active tDCS over sham. Our sample was similar in size to those used in previous studies that have demonstrated an effect. Moreover, we used a repeated measures design and analytical approaches that mitigate this limitation to some degree. Importantly the data show no clear trend that a larger group would have returned a different outcome. The use of a small convenience sample significantly limits the generalizability of the findings. It is plausible that through chance all of our patients were nonresponders and that a different population may have demonstrated an effect.

Another possible confounder is that the basic order of delivery of treatment condition was uniform across patients (ie, sham followed by active). Given that patients may have deduced that as the study progressed the probability of receiving active stimulation increased this factor might be predicted to have artificially advantaged the active stimulation condition, although the study still returned a negative outcome.

We estimated the location of the motor cortex without assistance from neuroimaging techniques. This is a limitation of all of the published studies of tDCS for chronic pain. This method is less accurate than fMRI-based stereotactic guidance,[26] however, the common use of large electrodes such as those employed in the current study makes it unlikely that this would have significantly affected our results or those of previous studies. In addition, more sophisticated neuronavigation techniques are unlikely to be available or affordable in standard clinical practice.

Throughout the course of the study a number of patients missed treatment sessions because of unavoidable events (in addition to weekends) and where this interrupted treatment on consecutive days it may arguably have detracted from the clinical efficacy of stimulation. This reflects the common clinical reality. Notably, patients who did not miss sessions did not have a better response to those who did.

The results of this exploratory study do not provide evidence that tDCS is effective in reducing CLBP. This is the first study to investigate this treatment modality on CLBP and the results are not consistent with existing studies of tDCS in chronic pain conditions. The use of a small convenience sample limits the generalizability of these findings and precludes definitive conclusions. There is some preliminary evidence that the sham controls regularly employed in clinical trials of tDCS may not be optimal in terms of participant blinding.

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