Effectiveness of transcranial direct current stimulation alone or preceding cognitive-behavioral management for chronic low back pain: a sham-controlled, double blinded randomized controlled trial

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Effectiveness of transcranial direct current stimulation preceding cognitive behavioural management for chronic low back pain: sham controlled double blinded randomised controlled trial

Kerstin Luedtke,1 Alison Rushton,2 Christine Wright,2 Tim Jürgens,1 Astrid Polzer,1 Gerd Mueller,3 Arne May1

ABSTRACT

OBJECTIVE
To evaluate the effectiveness of transcranial direct current stimulation alone and in combination with cognitive behavioural management in patients with non-specific chronic low back pain.

DESIGN
Double blind parallel group randomised controlled trial with six months’ follow-up conducted May 2011–March 2013. Participants, physiotherapists, assessors, and analyses were blinded to group allocation.

SETTING
Interdisciplinary chronic pain centre.

PARTICIPANTS
135 participants with non-specific chronic low back pain >12 weeks were recruited from 225 patients assessed for eligibility.

INTERVENTION
Participants were randomised to receive anodal (20 minutes to motor cortex at 2 mA) or sham transcranial direct current stimulation (identical electrode position, stimulator switched off after 30 seconds) for five consecutive days immediately before cognitive behavioural management (four week multidisciplinary programme of 80 hours).

MAIN OUTCOMES MEASURES
Two primary outcome measures of pain intensity (0-100 visual analogue scale) and disability (Oswestry disability index) were evaluated at two primary endpoints after stimulation and after cognitive behavioural management.

RESULTS
Analyses of covariance with baseline values (pain or disability) as covariates showed that transcranial direct current stimulation was ineffective for the reduction of pain (difference between groups on visual analogue scale 1 mm (99% confidence interval −8.69 mm to 6.3 mm; P=0.68)) and disability (difference between groups 1 point (−1.73 to 1.98; P=0.86)) and did not influence the outcome of cognitive behavioural management (difference between group 3 mm (−10.32 mm to 6.73 mm); P=0.58; difference between groups on Oswestry disability index 0 point (−2.45 to 2.62); P=0.92). The stimulation was well tolerated with minimal transitory side effects.

CONCLUSIONS
This results of this trial on the effectiveness of transcranial direct current stimulation for the reduction of pain and disability do not support its clinical use for managing non-specific chronic low back pain.

TRIAL REGISTRATION
Current controlled trials ISRCTN89874874.

Introduction
Low back pain is one of the most prevalent and expensive musculoskeletal conditions.1 It is generally benign,2 with 74-89% patients recovering after three to six months,3 though about 9-28% develop chronic pain.4-7 Non-specific chronic low back pain does not have a defined source,2 and the pathogenesis is not fully understood. In the absence of a peripheral pathology, central sensitisation has been hypothesised to explain the development and maintenance of non-specific chronic low back pain.9,10 Main mechanisms are an increased release of excitatory neurotransmitters at spinal level, influencing pain perception via the spinothalamic pathway and altered top down pain control from the brain.11,12

International guidelines recommend multimodal cognitive behavioural therapy programmes, defined as structured interventions designed to modify dysfunctional thinking and behaviour,13 as the most effective available intervention for reduction of pain and disability.8,14-16 A recent systematic review identified moderate evidence for the short term effectiveness of cognitive behavioural interventions.17 The pooled effect size for pain reduction compared with other active interventions, however, was low (12 mm on a 0-100 mm visual analogue scale). Adjunct approaches that modulate excitability of the central nervous system have been proposed to enhance the effects of cognitive

WHAT IS ALREADY KNOWN ON THIS TOPIC
Numerous small studies have suggested that transcranial direct current stimulation can reduce chronic pain
Until now evidence from appropriately powered randomised controlled trials has been lacking
Systematic reviews and meta-analyses indicated a small beneficial effect but also highlighted the high risk of bias of existing trials

WHAT THIS STUDY ADDS
This is the first adequately powered trial, with low risk of bias, to evaluate transcranial direct current stimulation for pain reduction
Transcranial direct current stimulation over the motor cortex has no benefit for the reduction of pain and disability in patients with non-specific chronic low back pain
Furthermore, transcranial direct current stimulation applied immediately before a cognitive behavioural group intervention does not influence the outcome of the intervention
behavioural management on non-specific chronic low back pain.18,20

Transcranial direct current stimulation is a non-invasive technique to electrically stimulate the brain. It can be applied to different target areas on the skull by attachment of sponge electrodes soaked in saline solution. It is hypothesised that this influences cortical excitability by inducing positively or negatively charged currents through the skull,21 thereby modulating a widespread neural network of areas associated with pain processing including the thalamic nuclei, limbic system, brainstem nuclei, and spinal cord.22 Pain reducing effects of transcranial direct current stimulation are attributed to modulation of the endogenous opioid system,23 emotional appraisal of pain,24 and descending pain inhibition.23,25

Systematic reviews and meta-analyses on the effectiveness of anodal transcranial direct current stimulation reported a small pain reducing effect with stimulation of the motor cortex.26,27 The overall level of evidence, however, was low to very low26,27 because of an overall unclear or high risk of bias and inadequate sample sizes in all included trials. Recent research reported that pain reduction after traditional interventions was enhanced by the application of transcranial direct current stimulation as an adjunct intervention—that is, as a priming technique to repetitive transcranial magnetic stimulation,28 combined with transcutaneous electrical nerve stimulation29 or with a multidisciplinary programme.30

We evaluated the effectiveness of transcranial direct current stimulation on non-specific chronic low back pain and investigated its use as an adjunct intervention before cognitive behavioural management.

Methods
Study design and participants
This double blind parallel group randomised controlled trial was conducted in Germany. Trial design and its reporting followed the internationally recognised recommendations published by the CONSORT group,31 the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use,32 and the World Medical Association’s Declaration of Helsinki.33

Participants were adults aged 18-65 with non-specific chronic low back pain persisting for more than 12 weeks as defined in the European guidelines8 who met the eligibility criteria for cognitive behavioural management at a back pain clinic in Germany. All participants presented with a minimum of 15 mm on a 0-100 visual analogue scale for pain or 8 points on the Oswestry disability index. Eligibility for the cognitive behavioural management programme required the patient to understand and speak German. Patients had to be motivated to return to work and had to be physically fit enough to tolerate a four week physical training programme. An orthopaedic consultant, a psychologist, and a physiotherapist confirmed a participant’s eligibility for cognitive behavioural management by following a standard screening procedure. Participants were excluded if they presented with other chronic pain syndromes, neurological disease, or psychiatric disease; had had spinal surgery in the previous six months; were pregnant or trying to become pregnant; or misused alcohol, drugs, or prescription drugs.

Randomisation and blinding
Randomisation to anodal or sham stimulation was conducted in permuted blocks of 20 to allow for equal numbers in each study arm at various time points16-37 and stratified for baseline pain intensity.38 We randomised 160 stimulation codes (80 triggering active stimulation, 80 triggering sham stimulation) by custom written software into two separate lists for low (20-50 mm) and high (51-100 mm) pain intensity at baseline on a visual analogue scale. An independent researcher created the randomisation lists. To achieve allocation concealment the recruiter provided participants with the next unused stimulation code from the randomised lists. The recruiter had no access to the randomisation list. Blinding of participants and the treating physiotherapist was achieved by using a sham paradigm identical to the anodal stimulation procedure except that the direct current stimulator automatically switched off after 30 seconds after slowly reducing the stimulation intensity (5 second fade out). Stimulation mode (anodal/sham) was preprogrammed with five digit stimulation codes that triggered the active or sham procedure. The machine display continued to indicate the time and the impedance in the same manner for both procedures. Because of the initial brief stimulation period, associated skin sensation, and identical machine display, this method has previously been regarded as a reliable placebo condition for double blind trial designs.39-41 More recent debate, however, questioned the reliability of participant and assessor blinding with this sham paradigm.42

We therefore evaluated the success of blinding by asking participants after each stimulation session which type of stimulation they believed they had received. Additionally, the assessor recorded which stimulation type she believed the participant had received. To evaluate whether participants and investigator could guess the stimulation type better than would be expected by chance, we determined the κ coefficient of agreement for each day of stimulation.42,43 Blinding during data analysis was achieved by labelling participants “group A” and “group B” (performed by an independent researcher).

Interventions
Transcranial direct current stimulation
Participants received 20 minutes of anodal or sham stimulation over the left motor cortex with an intensity of 2 mA on five consecutive days. We chose this stimulation paradigm based on results from our systematic review, which identified it as the most effective in chronic pain trials with the lowest risk of bias.27 Transcranial direct current stimulation was produced by a small battery driven stimulator device and applied to the skull via saline solution (0.9%) soaked sponge electrodes (7×5 cm=35 cm²). The anode was...
placed over the left motor cortex, while the cathode was placed supraorbitally on the contralateral side, and both were held in place by elastic bandages. The electricity was slowly increased to 2 mA at the beginning of the stimulation (eight seconds fade in) and slowly decreased at the end of the stimulation (eight seconds fade out) to reduce skin sensations under-neath the electrodes. Single pulse transcranial magnetic stimulation (Magstim Company, Dyfed, UK) was applied to accurately determine the location of the left motor cortex (abductor digiti minimi) with a standard protocol.

Cognitive behavioural management
Immediately after the stimulation period all participants started a cognitive behavioural management programme. A maximum of eight patients per group received physically challenging sessions, including cardiovascular exercises, machine assisted muscle strength training, specific muscle stabilisation exercises for the trunk muscles, and work hardening sessions, as well as educational sessions on the neuro-physiology of pain, pain coping strategies, and relaxation classes. Patients attended five hours daily for four weeks as outpatients. An interdisciplinary team of orthopaedic consultants, physiotherapists, psychologists, and sports scientists delivered the cognitive behavioural management programme.

Outcome measures
Transcranial direct current stimulation and cognitive behavioural management have different suggested roles within the management of non-specific chronic low back pain. Transcranial direct current stimulation directly targets pain processing areas within the brain, aiming to reduce pain intensity; this was therefore essential as a primary outcome measure. Cognitive behavioural management targets disability, cognitions, and beliefs associated with chronic pain and other psychosocial aspects of the pain experience and might not necessarily result in a reduction of pain intensity. To deal with the research objective of the combined effect of transcranial direct current stimulation and cognitive behavioural management, we therefore also selected disability (Oswestry disability index) as a primary outcome measure.

The initiative on methods, measurement, and pain assessment in clinical trials defined the following outcome domains as important for chronic pain trials: pain, physical functioning, emotional functioning, participants’ ratings of improvement and satisfaction, symptoms and adverse events, and participants’ disposition. We also selected the following secondary outcome measures according to their evidence base for evaluating non-specific chronic low back pain and their measurement properties: Funktionsfragebogen Hannover (Hannover functional ability questionnaire), “bothersomeness,” RAND 36-item health survey, fear avoidance beliefs questionnaire, hospital anxiety and depression score, and patient perceived satisfaction improvement.

Participants were assessed immediately before the first session of transcranial direct current stimulation (baseline), 24 hours after the final stimulation (primary endpoint 1), on the last day of cognitive behavioural management (primary endpoint 2), and four weeks, 12 weeks, and 24 weeks after cognitive behavioural management to observe longer term treatment effects (fig 1). Based on the two primary outcome measures and the two primary endpoints, we calculated the sample size at an α level of 0.0125 (90% power). Based on recommendations for a minimum clinically relevant change of 15 mm on a 0-100 mm visual analogue scale for pain and 8 points on the Oswestry disability index, and allowing for a dropout rate of 12% after transcranial direct current stimulation and a further 16% after the cognitive behavioural management, we required 135 participants. The calculated effect sizes were 0.79 for visual analogue scale and 0.75 for Oswestry disability index and were regarded as medium to large (G*Power Version 3.1.2).

To document any observed side effects, after each stimulation session participants were required to complete a standardised questionnaire routinely used for transcranial direct current stimulation trials. All procedures were tested in a feasibility trial conducted before the main data collection phase.

Data analysis
We collected participants’ characteristics and baseline values for primary and secondary outcome measures to allow comparisons between groups at baseline.

Primary analyses were conducted at an α level of P<0.0125 as described for the sample size calculation. To evaluate the effectiveness of transcranial direct current stimulation, we fitted a general linear model for each of the two primary outcome measures (visual analogue scale, Oswestry disability index) at each of the two primary endpoints (after stimulation and after cognitive behavioural management) using values after the intervention as the dependent variable and values before the intervention as covariates (analysis of covariance...
We conducted secondary analyses at an exploratory level and did not require further adjustment of the \( \alpha \) level for multiple testing.\(^6\) To evaluate the intervention effect on the primary outcome measures over time, we fitted a separate multilevel model for pain and disability, including all assessment time points. All secondary outcome measures were entered into the statistical model in a stepwise manner (forward approach) and removed if not significant.\(^6\) These factors, as well as group (anodal, sham), were added to the model as fixed effect factors while time, time\(^2\), and time\(^3\) were entered as random factors to model a non-linear trend over time.\(^7\)

To explore the effect of anodal stimulation compared with sham stimulation on each of the secondary outcome measures at the primary endpoints after stimulation and after cognitive behavioural management, we used analysis of covariance using baseline values as covariates. The secondary outcome measures were further evaluated by building a multilevel model with time, time\(^2\), and time\(^3\) as random factors and group (active, sham) as a fixed effect factor. We conducted Bonferroni corrected post hoc \( t \) tests if we identified a significant interaction of group by time for any secondary outcome measure.\(^6\) All analyses were performed with SPSS 18 for Apple Macintosh (SPSS, Chicago, IL).

### Results

Recruitment took place from May 2011 to March 2013. All consecutive patients who were waiting for the cognitive Behavioural management programme (n=255) were contacted by telephone and assessed for eligibility to recruit the required 135 participants. Of 232 eligible patients, 97 declined to participate because of the additional time and travel required for the extra five visits to the back pain clinic for the stimulation. Figure 2 shows the numbers of participants analysed at each time point.\(^7\)

Table 1 shows the baseline characteristics by intervention group, which indicate representativeness of participants in comparison with internationally published trials evaluating cognitive behavioural management interventions in non-specific chronic low back pain.\(^6\)\(^7\)\(^2\)\(^4\) Table 2 presents baseline data on primary and secondary outcome measures.

None of the participants switched group. Missing data at the two primary endpoints were balanced across groups. The total amount of missing data was less than 10\% after stimulation and a further 3\% (pain) and 10\% (disability) after cognitive behavioural management. This amount was within the anticipated dropout rate for the sample size calculation. Reasons provided for discontinuing the trial were not based on clinical data but on additional time and travel. Data were therefore considered to be missing at random. Following published recommendations, data met the two main principles for intention to treat analysis.\(^5\)\(^7\)

There were no significant differences between groups for pain and Oswestry disability index at the two primary endpoints after stimulation and after cognitive behavioural management. Table 3 and figs 3 and 4 show mean values and results of statistical tests.

When we looked at the effects on pain and Oswestry disability index over time, we found no significant interactions between the factors group and time using a multilevel model analysis on visual analogue scale for pain (95\% confidence interval for the estimates of group \( t \)ime as a fixed effect was \(-0.84\) to \(0.20\); \(P=0.23\)) or Oswestry disability index (\(-0.16\) to \(0.11\); \(P=0.72\)) (table 4). Stepwise building of the multilevel models for pain
The analysis of secondary outcome measures at the primary endpoints (table 5) and throughout the trial showed results similar to pain and Oswestry disability index: both groups improved slightly during the stimulation period and significantly after the cognitive behavioural management (within group changes). Multilevel models for all secondary outcome measures showed that there were no significant differences between groups at any time point.

The success of blinding was based on ratings from 587 participants (one rating per participant per day of stimulation). Three quarters of ratings (n=442) indicated that participants believed they had received anodal stimulation. As agreement was poor to slight, participants were effectively blinded throughout the trial (table 6). The κ coefficient for correctly guessed treatment groups was κ=0.103. This result is translated as slight agreement and thereby indicating effective investigator blinding.

Discussion
Five days of anodal transcranial direct current stimulation compared with sham stimulation did not result in a reduction of the perceived intensity or level of disability and Oswestry disability index are reported in appendices 1 and 2.

Results in context
Furthermore, this is the first randomised controlled trial to exclusively investigate the effect of transcranial direct current stimulation on non-specific chronic low back pain. Two previous trials on transcranial direct current stimulation for the reduction of chronic pain included some participants with chronic low back pain. Antal and colleagues investigated a mixed population included some participants with chronic low back pain. Two previous trials on transcranial direct current stimulation for the reduction of chronic pain included eight with chronic low back pain. Results indicated a significant pain reducing effect in the group that received anodal stimulation. Only five patients with chronic low back pain, however, received both anodal and sham stimulation. As these patients were not analysed separately, we could not distinguish the effect of anodal transcranial direct current stimulation on chronic low back pain from the overall effect. A second exploratory study focused on the reduction of non-specific chronic low back pain and found no effect of transcranial direct current stimulation over sham stimulation. The study included eight participants and followed an interrupted time series design in which participants received sham stimulation until a randomly allocated day, when the stimulation changed to anodal mode. This method resulted in a minimum of three and a maximum of 15 stimulation sessions per patient. This design did not allow the evaluation of a specific stimulation paradigm.
especially as stimulation was applied with varying gaps between sessions of up to six days. The small sample size was a further limitation; hence the effectiveness of transcranial direct current stimulation on non-specific chronic low back pain could not be evaluated.

Five days of anodal stimulation did not result in a significant reduction of the disability associated with non-specific chronic low back pain. Two trials on transcranial direct current stimulation for the reduction of fibromyalgia pain, 30 results were not analysed for significance between groups, and recommended minimum clinically relevant levels of change in the Roland Morris disability questionnaire of 4-5 points 80 90 were not met.

One previous trial applied transcranial direct current stimulation in combination with a multidisciplinary intervention for the reduction of fibromyalgia pain. 30 Twenty three patients were randomly assigned to intervention group in trial of effectiveness of anodal or sham transcranial direct current stimulation (tDCS) preceding cognitive behavioural management (CBT) for patients with chronic low back pain.

### Table 2 | Baseline data on primary and secondary outcome measures by intervention group in trial of effectiveness of anodal or sham transcranial direct current stimulation (tDCS) preceding cognitive behavioural management (CBT) for patients with chronic low back pain*

<table>
<thead>
<tr>
<th>Primary outcome measures</th>
<th>Intervention group</th>
<th>Mean (SD) VAS (0-100 mm)</th>
<th>Mean (SD) ODI (0-50 points)</th>
<th>Mean (SD) RAND 36 (0-100%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Anodal (n=67)</td>
<td>48 (21)</td>
<td>17 (6)</td>
<td>54 (19)</td>
</tr>
<tr>
<td></td>
<td>Sham (n=68)</td>
<td>48 (18)</td>
<td>15 (5)</td>
<td>58 (23)</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>15-89</td>
<td>8-32</td>
<td>10-100</td>
</tr>
<tr>
<td></td>
<td>Mean (SD) FABQ physical activity (0-24 points)</td>
<td>14 (4)</td>
<td>15 (7)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mean (SD) FABQ work (0-42 points)</td>
<td>21 (11)</td>
<td>23 (10)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mean (SD) FABQ physical activity (0-24 points)</td>
<td>14 (4)</td>
<td>15 (7)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mean (SD) FABQ work (0-42 points)</td>
<td>21 (11)</td>
<td>23 (10)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mean (SD) RAND 36 (0-100%)</td>
<td>54 (19)</td>
<td>58 (23)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mean (SD) physical functioning</td>
<td>50 (17)</td>
<td>54 (19)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mean (SD) role limitations from physical health</td>
<td>19 (38)</td>
<td>15 (20)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mean (SD) role limitations from physical health</td>
<td>19 (38)</td>
<td>15 (20)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mean (SD) pain</td>
<td>31 (16)</td>
<td>32 (12)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mean (SD) pain</td>
<td>31 (16)</td>
<td>32 (12)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mean (SD) general health</td>
<td>50 (17)</td>
<td>54 (19)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mean (SD) energy / fatigue</td>
<td>38 (19)</td>
<td>44 (18)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mean (SD) social functioning</td>
<td>56 (26)</td>
<td>61 (26)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mean (SD) social functioning</td>
<td>56 (26)</td>
<td>61 (26)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mean (SD) emotional wellbeing</td>
<td>58 (19)</td>
<td>60 (18)</td>
<td></td>
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<tr>
<td></td>
<td>Mean (SD) emotional wellbeing</td>
<td>58 (19)</td>
<td>60 (18)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Median (SD) bothersomeness (0-4 points)</td>
<td>3 (2-4)</td>
<td>3 (2-4)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Median (SD) bothersomeness (0-4 points)</td>
<td>3 (2-4)</td>
<td>3 (2-4)</td>
<td></td>
</tr>
</tbody>
</table>

FABQ=fei avoidance beliefs questionnaire; FFBH=Funktionsfragebogen Hannover; HADS=hospital anxiety and depression scale; ODI=Oswestry disability index; RAND 36=RAND 36-item health survey; VAS=visual analogue scale for pain.

*At P C0.05 there were no significant differences between groups at baseline.

### Table 3 | Mean (SD) values and results from analysis of covariance (ANCOVA) for visual analogue scale (VAS) pain at baseline and primary endpoints (after anodal or sham transcranial direct current stimulation (tDCS) and after cognitive behavioural management (CBT)) for patients with chronic low back pain

<table>
<thead>
<tr>
<th>Outcome measure</th>
<th>After stimulation</th>
<th>After CBT</th>
</tr>
</thead>
<tbody>
<tr>
<td>VAS (mm)</td>
<td>Mean (SD) anodal</td>
<td>42 (24), n=60</td>
</tr>
<tr>
<td></td>
<td>Mean (SD) sham</td>
<td>41 (23), n=62</td>
</tr>
<tr>
<td></td>
<td>Mean difference between groups (99% CI)</td>
<td>1 (−6.13 to 6.3)</td>
</tr>
<tr>
<td></td>
<td>P value</td>
<td>0.68</td>
</tr>
</tbody>
</table>

| ODI (points)    | Mean (SD) anodal  | 15 (7), n=61 | 7 (6), n=53 |
|                 | Mean (SD) sham    | 14 (6), n=61 | 7 (5), n=54 |
|                 | Mean difference between groups (99% CI) | 1 (−7.37 to 1.98) | 0 (−2.45 to 2.62) |
|                 | P value | 0.86 | 0.92 |
Table 4 | Primary outcome measures at 4, 12, and 24 weeks’ follow-up after cognitive behavioural management (CBT) and results of multilevel model analysis

<table>
<thead>
<tr>
<th>Outcome measure and group</th>
<th>Mean (SD) score by time after CBT</th>
<th>95% CI for estimates of group*time interaction</th>
<th>P value for group*time interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4 weeks</td>
<td>12 weeks</td>
<td>24 weeks</td>
</tr>
<tr>
<td>Visual analogue scale for pain</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sham</td>
<td>23 (23), n=56</td>
<td>22 (22), n=48</td>
<td>22 (21), n=42</td>
</tr>
<tr>
<td>Anodal</td>
<td>26 (26), n=54</td>
<td>27 (26), n=53</td>
<td>29 (26), n=47</td>
</tr>
<tr>
<td>Oswestry disability index</td>
<td>7 (6), n=56</td>
<td>6 (6), n=49</td>
<td>7 (6), n=42</td>
</tr>
<tr>
<td>Anodal</td>
<td>8 (7), n=56</td>
<td>9 (7), n=52</td>
<td>9 (7), n=48</td>
</tr>
</tbody>
</table>

Table 5 | (Mean SD) values and results from analysis of covariance (ANCOVA) for all secondary outcome measures after stimulation and after cognitive behavioural management (CBT)

<table>
<thead>
<tr>
<th>After stimulation</th>
<th>Mean (SD)</th>
<th>Mean (SD)</th>
<th>95% CI for differences between groups</th>
<th>P values</th>
<th>After CBT</th>
<th>Mean (SD)</th>
<th>Mean (SD)</th>
<th>95% CI for differences between groups</th>
<th>P values</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>anodal</td>
<td>sham</td>
<td></td>
<td></td>
<td></td>
<td>anodal</td>
<td>sham</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FABQ</td>
<td>15 (4), n=62</td>
<td>15 (4), n=61</td>
<td>-3.24 to 3.14</td>
<td>0.98</td>
<td>9 (4), n=54</td>
<td>10 (7), n=55</td>
<td>-4.75 to 5.32</td>
<td>0.91</td>
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<tr>
<td></td>
<td>21 (12), n=62</td>
<td>21 (12), n=61</td>
<td>-5.92 to 4.74</td>
<td>0.82</td>
<td>16 (9), n=54</td>
<td>14 (11), n=55</td>
<td>-8.47 to 5.96</td>
<td>0.72</td>
<td></td>
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<tr>
<td></td>
<td>21 (4), n=62</td>
<td>20 (5), n=61</td>
<td>-0.70 to 1.39</td>
<td>0.51</td>
<td>16 (4), n=54</td>
<td>16 (4), n=55</td>
<td>-1.58 to 1.11</td>
<td>0.73</td>
<td></td>
</tr>
<tr>
<td>HADS</td>
<td>7 (4), n=59</td>
<td>6 (4), n=58</td>
<td>-0.95 to 0.51</td>
<td>0.56</td>
<td>5 (4), n=52</td>
<td>4 (3), n=52</td>
<td>-1.10 to 0.88</td>
<td>0.83</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6 (4), n=59</td>
<td>6 (4), n=57</td>
<td>-1.10 to 0.69</td>
<td>0.65</td>
<td>4 (3), n=52</td>
<td>4 (3), n=51</td>
<td>-0.85 to 1.15</td>
<td>0.77</td>
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<td>3 (1), n=61</td>
<td>3 (1), n=61</td>
<td>-0.18 to 0.30</td>
<td>0.63</td>
<td>2 (1), n=54</td>
<td>2 (1), n=55</td>
<td>-0.47 to 0.30</td>
<td>0.67</td>
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<tr>
<td></td>
<td>1 (1), n=61</td>
<td>2 (1), n=61</td>
<td>-0.29 to 0.55</td>
<td>0.54</td>
<td>3 (1), n=54</td>
<td>3 (1), n=55</td>
<td>-0.57 to 0.21</td>
<td>0.36</td>
<td></td>
</tr>
<tr>
<td>RAND-36</td>
<td>57 (19), n=62</td>
<td>62 (21), n=61</td>
<td>-2.64 to 8.45</td>
<td>0.30</td>
<td>81 (19), n=58</td>
<td>85 (18), n=59</td>
<td>-3.51 to 8.64</td>
<td>0.41</td>
<td></td>
</tr>
<tr>
<td></td>
<td>23 (32), n=61</td>
<td>21 (32), n=61</td>
<td>-5.90 to 11.53</td>
<td>0.52</td>
<td>53 (46), n=53</td>
<td>59 (44), n=54</td>
<td>-7.09 to 23.71</td>
<td>0.29</td>
<td></td>
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<tr>
<td></td>
<td>33 (13), n=61</td>
<td>33 (14), n=61</td>
<td>-3.12 to 4.35</td>
<td>0.77</td>
<td>49 (18), n=53</td>
<td>53 (17), n=55</td>
<td>-1.46 to 11.31</td>
<td>0.13</td>
<td></td>
</tr>
<tr>
<td></td>
<td>52 (19), n=58</td>
<td>55 (19), n=59</td>
<td>-5.52 to 4.37</td>
<td>0.82</td>
<td>60 (20), n=53</td>
<td>63 (21), n=59</td>
<td>-5.36 to 5.54</td>
<td>0.97</td>
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<tr>
<td></td>
<td>43 (20), n=59</td>
<td>47 (18), n=61</td>
<td>-7.02 to 2.87</td>
<td>0.41</td>
<td>56 (16), n=54</td>
<td>58 (19), n=54</td>
<td>-4.59 to 6.87</td>
<td>0.69</td>
<td></td>
</tr>
<tr>
<td></td>
<td>59 (26), n=62</td>
<td>64 (28), n=59</td>
<td>-3.82 to 7.24</td>
<td>0.54</td>
<td>77 (22), n=54</td>
<td>75 (22), n=53</td>
<td>-13.25 to 0.88</td>
<td>0.09</td>
<td></td>
</tr>
<tr>
<td></td>
<td>47 (45), n=62</td>
<td>52 (46), n=60</td>
<td>-3.62 to 2.113</td>
<td>0.16</td>
<td>70 (42), n=54</td>
<td>78 (37), n=54</td>
<td>-5.78 to 19.53</td>
<td>0.28</td>
<td></td>
</tr>
<tr>
<td>Emotional wellbeing</td>
<td>60 (19), n=60</td>
<td>63 (17), n=60</td>
<td>-1.83 to 5.83</td>
<td>0.30</td>
<td>73 (18), n=53</td>
<td>73 (16), n=53</td>
<td>-7.89 to 2.03</td>
<td>0.24</td>
<td></td>
</tr>
</tbody>
</table>

Table 6 | Effectiveness of blinding of participants in trial of effectiveness of anodal or sham transcranial direct current stimulation preceding cognitive behavioural management for patients with chronic low back pain

<table>
<thead>
<tr>
<th>Agreement between guessed and received stimulation</th>
<th>Day 1 (n=112)</th>
<th>Day 2 (n=120)</th>
<th>Day 3 (n=124)</th>
<th>Day 4 (n=118)</th>
<th>Day 5 (n=120)</th>
</tr>
</thead>
<tbody>
<tr>
<td>κ=0.111</td>
<td>κ=0.000</td>
<td>κ=0.014</td>
<td>κ=0.007</td>
<td>κ=0.120</td>
<td></td>
</tr>
<tr>
<td>Interpretation (Landis and Koch)</td>
<td>Slight agreement</td>
<td>Slight agreement</td>
<td>Poor agreement</td>
<td>Poor agreement</td>
<td>Poor agreement</td>
</tr>
</tbody>
</table>

weekly active and sham stimulation sessions for 10 weeks during a multidisciplinary intervention. No effect for pain was found, and disability was not measured.

Compared with sham stimulation, however, anodal stimulation was associated with a significant effect on the SF-36 subscale for pain. This effect should be interpreted with caution as the sample size calculation was based on a large effect size of 3 cm on a 0-10 cm visual analogue scale and standard deviations of 2.5. Furthermore, two outcome measures were presented (but not defined a priori) in the results section at an level of 0.05 and a power of 80%. No adjustments for multiple testing were made.

Neuropsychological explanations for the lack of a treatment effect can only be hypothesised. Top down pain inhibition is the most described working mechanism for transcranial direct current stimulation.81,82 It is also known as central pain modulation and relies on the concept that altered cortical activity leads to a descending cascade of events consequently resulting in pain relief.83 The primary motor cortex is the origin of the descending corticothalamic pathway. Polania and colleagues found an increased functional coupling of the motor cortex and the thalamus after anodal transcranial direct current stimulation over the primary motor cortex84 and further evidence suggested a spreading of electrical currents to subcortical areas distant from the stimulation site.85,86 Modulation of the H reflex in the quadriceps muscle indicated that the effects of transcranial direct current stimulation descended as far down as the leg via the spinal pathway in healthy participants.87 But evidence that these remote effects lead to pain reduction relied on studies with controversial results using experimental pain or pain thresholds.85,88,89 In summary, there is sufficient
evidence to support a reliable cortical and subcortical neurophysiological response to transcranial direct current stimulation but alterations in pain perception were absent or inconsistent.

Limitations
A limitation of this trial is that it was conducted at one study centre. The sample of patients with non-specific chronic low back pain, however, is representative for international cognitive behavioural management settings regarding baseline demographic data and baseline clinical variables. Further limitation could be that transcranial direct current stimulation was applied before cognitive behavioural management. We cannot exclude a beneficial effect of transcranial direct current stimulation on non-specific chronic low back pain applied during cognitive behavioural management, although Riberto and colleagues evaluated transcranial direct current stimulation applied during a multidisciplinary intervention and found no effect on pain in patients with fibromyalgia.

In conclusion, we have shown that transcranial direct current stimulation alone or in combination with cognitive behavioural management is inefficient for the reduction of pain and disability in patients with non-specific chronic low back pain.

Contributors: All authors substantially contributed to the trial and its reporting, approved of the final version of the manuscript and agree to be accountable for all aspects of the work. KL contributed to the literature search, study design, data collection, data analysis, data interpretation, figures, and writing. AR contributed to the overview methodological quality, study design, data interpretation, and writing. CW contributed to the study design, data interpretation, data analysis, and writing. TJ contributed to the literature search and study design. AP helped with data collection. GM contributed to the study design. AM contributed to the literature search, study design, data interpretation, writing, and financing and was guarantor.

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Ethical approval: This study was approved by the German ethics authorities (PV 3297) and the University of Birmingham research ethics committee (ERN, 10-0863).

Data sharing: Statistical code and dataset (anonymised patient data) are available from the corresponding author.

Transparency: The lead author affirms that the manuscript is an original work, the data have not been previously published, and the manuscript is an accurate representation of the study. The authors have no competing interests and disclose no financial or personal relationships that could inappropriately influence their work.

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Appendix 1: Stepwise building of mixed model for visual analogue scale over all time points

Appendix 2: Stepwise building of mixed model for Oswestry disability index over all time points