

Effectiveness of transcranial direct current stimulation alone or preceding cognitive-behavioral management for chronic low back pain

Luedtke, Kerstin; Rushton, Alison; Wright, Christine; Jurgens, Tim; Polzer, Astrid; Muller, Gerd; May, Arne

DOI:
[10.1136/bmj.h1640](https://doi.org/10.1136/bmj.h1640)

License:
Creative Commons: Attribution-NonCommercial (CC BY-NC)

Document Version
Publisher's PDF, also known as Version of record

Citation for published version (Harvard):
Luedtke, K, Rushton, A, Wright, C, Jurgens, T, Polzer, A, Muller, G & May, A 2015, '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', *British Medical Journal*, vol. 350, h1640.
<https://doi.org/10.1136/bmj.h1640>

[Link to publication on Research at Birmingham portal](#)

Publisher Rights Statement:
Checked Jan 2016

General rights

Unless a licence is specified above, all rights (including copyright and moral rights) in this document are retained by the authors and/or the copyright holders. The express permission of the copyright holder must be obtained for any use of this material other than for purposes permitted by law.

- Users may freely distribute the URL that is used to identify this publication.
- Users may download and/or print one copy of the publication from the University of Birmingham research portal for the purpose of private study or non-commercial research.
- User may use extracts from the document in line with the concept of 'fair dealing' under the Copyright, Designs and Patents Act 1988 (?)
- Users may not further distribute the material nor use it for the purposes of commercial gain.

Where a licence is displayed above, please note the terms and conditions of the licence govern your use of this document.

When citing, please reference the published version.

Take down policy

While the University of Birmingham exercises care and attention in making items available there are rare occasions when an item has been uploaded in error or has been deemed to be commercially or otherwise sensitive.

If you believe that this is the case for this document, please contact UBIRA@lists.bham.ac.uk providing details and we will remove access to the work immediately and investigate.



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

¹Department of Systems Neuroscience, University Medical Centre Hamburg-Eppendorf, Martinistr. 52, 20246 Hamburg, Germany

²School of Sport, Exercise and Rehabilitation Sciences, College of Life and Environmental Sciences, University of Birmingham, Edgbaston, Birmingham, B15 2TT, UK

³Backpain Clinic "Am Michel", Ludwig-Erhard-Str.18, 20459 Hamburg, Germany

Correspondence to: A May a.may@uke.de

Additional material is published online only. To view please visit the journal online (<http://dx.doi.org/10.1136/bmj.h1618>)

Cite this as: *BMJ* 2015;350:h1640 doi: 10.1136/bmj.h1640

Accepted: 23 February 2015

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,^{7,8} 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 low^{26,27} 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 adjuvant 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 points³⁴⁻³⁷ 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 underneath the electrodes.⁴⁴ 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.^{45 46}

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 neurophysiology 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.⁴⁷⁻⁴⁹ 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.⁵⁰ 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),⁵¹ "bothersomeness,"⁵² RAND 36-item health survey,⁵³ fear avoidance beliefs questionnaire,⁵⁴ hospital anxiety and depression score,⁵⁵ and patient perceived satisfactory improvement.⁵⁶

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).^{57 58} Based on recommendations for a minimum clinically relevant change of 15 mm on a 0-100 mm visual analogue scale for pain⁵⁹ and 8 points on the Oswestry disability index,⁶⁰ and allowing for a dropout rate of 12% after transcranial direct current stimulation⁶¹ and a further 16% after the cognitive behavioural management,⁶² 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 large⁶³ (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.^{45 64} 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.⁶⁵ 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

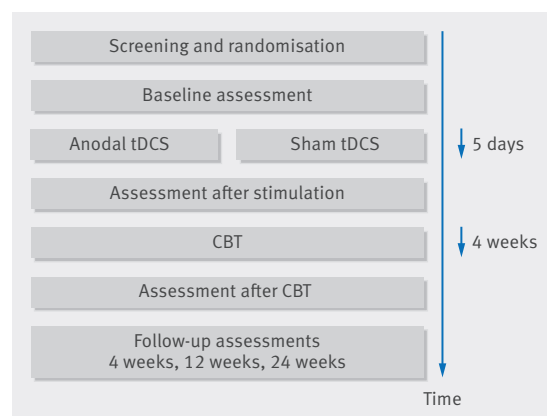


Fig 1 | Flowchart for trial of effectiveness of anodal or sham transcranial direct current stimulation (tDCS) alone and before cognitive behavioural management (CBT) for patients with chronic low back pain

(ANCOVA)).^{66,67} We reported results as *F* values (with degrees of freedom) and *P* values as well as 99% confidence intervals for differences between groups with Sidak adjustment for multiple comparisons.⁶⁸

We conducted secondary analyses at an exploratory level and did not require further adjustment of the α level for multiple testing.⁶⁵ 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.⁶⁹ These factors, as well as group (anodal, sham), were added to the model as fixed effect factors while time, time², and time³ were entered as random factors to model a non-linear trend over time.⁷⁰

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, time² and time³ 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.⁶⁸ 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.⁷¹

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.^{62,72-74} 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.^{75,76}

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*time 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

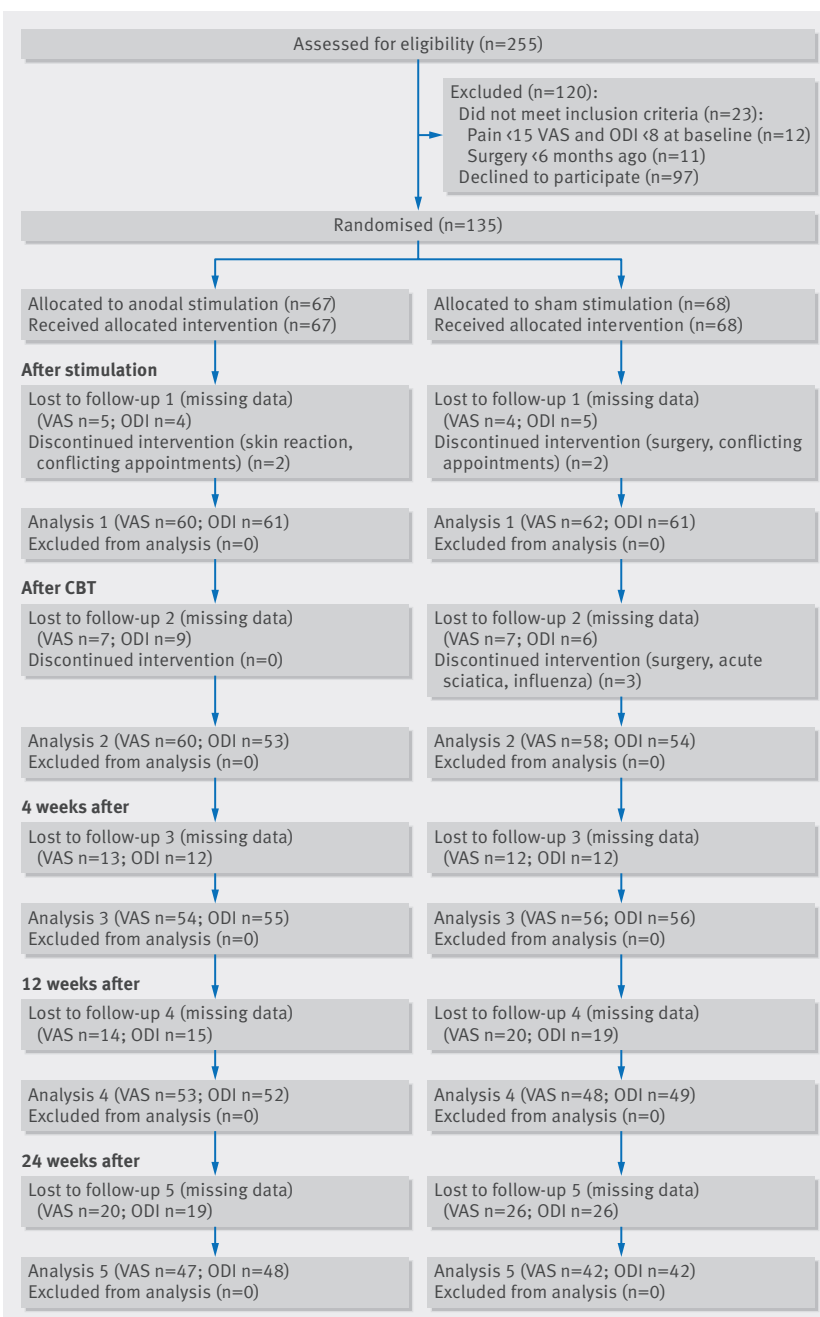


Fig 2 | Flow of patient inclusion and numbers of participants available for analysis at each prespecified time point for both primary outcome measures (Oswestry disability index (ODI) and visual analogue scale for pain (VAS)) in trial of effectiveness of anodal or sham transcranial direct current stimulation (tDCS) before cognitive behavioural management (CBT) for patients with chronic low back pain

Table 1 | Demographic and clinical characteristics of participants with back pain at baseline according to randomisation in trial of effectiveness of anodal or sham transcranial direct current stimulation (tDCS). Figures are numbers (percentage) of participants unless stated otherwise

	Intervention group	
	Anodal (n=67)	Sham (n=68)
Women	33 (49)	30 (44)
Age at study entry (years)*:		
Mean (SD)	45 (9)	44 (10)
Range	26-64	27-62
First onset of back pain (months ago)*:		
Mean (SD)	98 (106)	93 (125)
Range	6-600	6-384
This episode of back pain (months)*:		
Mean (SD)	23 (49)	19 (29)
Range	6-156	6-240
Drug treatment		
Drugs for pain:		
NSAIDs	43 (64)	34 (50)
Weak opioids	6 (9)	4 (6)
Strong opioids	7 (10)	6 (9)
Adjuvant drug treatments:		
Antidepressants	3 (4)	3 (4)
Muscle relaxants	1 (1)	1 (1)
Anticonvulsives	3 (4)	0 (0)
Glucocorticoids	1 (1)	0 (0)
Drug treatments taken for other conditions:		
Cardiovascular	9 (13)	9 (13)
Asthma	3 (4)	2 (3)
Thyroid	1 (1)	1 (1)
Restless legs	1 (1)	0 (0)
Hormone replacement	3 (4)	1 (1)
Malaria	1 (1)	0 (0)

NSAIDs=non-steroid anti-inflammatory drugs.

*No significant difference ($P<0.05$) between two groups at baseline.

and Oswestry disability index are reported in appendices 1 and 2.

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 $\kappa=0.103$. This result is translated as slight agreement and thereby indicating effective investigator blinding.⁷⁷

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

in non-specific chronic low back pain. Trial results did not support the pain reducing effect of transcranial direct current stimulation on chronic pain as reported by previously published trials or the small combined effect size identified in systematic reviews and meta-analyses.^{26 27} Furthermore, transcranial direct current stimulation preceding cognitive behavioural management did not influence the reduction of pain and disability levels after the behavioural management.

This trial was specifically designed to evaluate the effectiveness of transcranial direct current stimulation on pain and disability in non-specific chronic low back pain and the adjuvant effects of transcranial direct current stimulation on cognitive behavioural management. The study population was carefully selected with clear inclusion/exclusion criteria to achieve a level of homogeneity that reflected the typical participants of a cognitive behavioural management programme. This allows us to generalise our results to other cognitive behavioural management settings.

As critiqued in our systematic review,²⁷ all previous published trials have been limited by small sample sizes. Sample size calculations (if reported) were based on transcranial magnetic stimulation studies with large effect sizes and small standard deviations⁶¹ or on previous publications of equally underpowered studies.²⁹ Small sample sizes and risk of bias issues identified by systematic reviews^{26 27} reduce the confidence in such reported effect sizes for pain reduction after transcranial direct current stimulation. The current trial is the only trial to date on transcranial direct current stimulation that included a sufficient number of participants to show an effect on pain, based on a valid calculation of sample size.

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 of 23 patients with chronic pain that included eight with chronic low back pain.⁷⁸ 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.⁷⁸ 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.⁷⁹ 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,

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*

	Intervention group	
	Anodal (n=67)	Sham (n=68)
Primary outcome measures		
Mean (SD) VAS (0-100 mm)	48 (21)	48 (18)
Range	15-89	15-84
Mean (SD) ODI (0-50 points)	17 (6)	15 (5)
Range	8-32	8-29
Secondary outcome measures		
Mean (SD) FABQ physical activity (0-24 points)	14 (4)	15 (7)
Range	7-20	2-24
Mean (SD) FABQ work (0-42 points)	21 (11)	23 (10)
Range	2-42	9-40
Mean (SD) FFBH (12-36 points)	22 (4)	21 (4)
Range	12, 29	12, 33
Mean (SD) HADS anxiety (0-21 points)	7 (4)	6 (4)
Range	0-15	0-18
Mean (SD) HADS depression (0-21 points)	6 (4)	6 (4)
Range	0-15	0-14
RAND-36 (0-100%):		
Mean (SD) physical functioning	54 (19)	58 (23)
Range	0-90	10-100
Mean (SD) role limitations from physical health	19 (28)	15 (28)
Range	0-100	0-100
Mean (SD) pain	31 (16)	32 (12)
Range	0-74	0-52
Mean (SD) general health	50 (17)	54 (19)
Range	15-92	20-100
Mean (SD) energy / fatigue	38 (19)	44 (18)
Range	0-85	10-85
Mean (SD) social functioning	56 (26)	61 (26)
Range	0-100	0-100
Mean (SD) role limitations from emotional problems	51 (43)	49 (43)
Range	0-100	0-100
Mean (SD) emotional wellbeing	58 (19)	60 (18)
Range	20-96	24-92
Median (range) bothersomeness (0-4 points)	3 (2-4)	3 (2-4)
Interquartile range	3-4	3-4

FABQ=fear 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<0.05 there were no significant differences between groups at baseline.

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

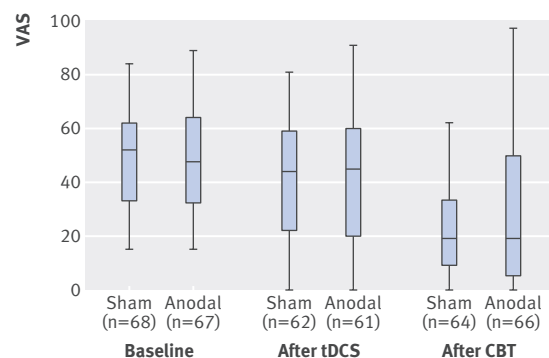


Fig 3 | Box plot of visual analogue scale (VAS) pain values at baseline and primary endpoints (after anodal or sham transcranial direct current stimulation (tDCS) and after cognitive behavioural management (CBT)) for patients with chronic low back pain

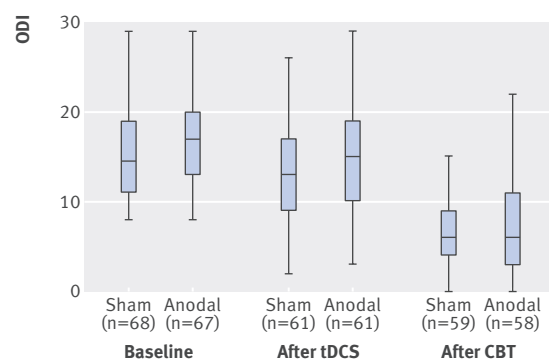


Fig 4 | Box plot of Oswestry disability index (ODI) values at baseline and primary endpoints (after anodal or sham transcranial direct current stimulation (tDCS) and after cognitive behavioural management (CBT)) for patients with chronic low back pain

pain evaluated disability with the Roland Morris disability questionnaire as a secondary outcome. In a crossover trial in seven participants with chronic pelvic pain, Fenton and colleagues found a reduction of 0.83 out of 24 points that was significant but not clinically relevant.⁸⁰ A second trial in eight participants resulted in a reduction of 0.5 points in the sham group and 1.7 points in the anodal stimulation group.⁷⁹ 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^{59 60} 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

Table 3 | Mean (SD) values and results from analysis of covariance (ANCOVA) for visual analogue scale (VAS) for pain and Oswestry disability index (ODI) after stimulation and after cognitive behavioural management with 99% confidence intervals for differences between groups

Outcome measure	After stimulation				After CBT			
	Mean (SD) anodal	Mean (SD) sham	Mean difference between groups (99% CI)	P value	Mean (SD) anodal	Mean (SD) sham	Mean difference between groups (99% CI)	P value
VAS (mm)	42 (24), n=60	41 (23), n=62	1 (-8.69 to 6.3)	0.68	26 (23), n=60	23 (18), n=58	3 (-10.32 to 6.73)	0.58
ODI (points)	15 (7), n=61	14 (6), n=61	1 (-1.73 to 1.98)	0.86	7 (6), n=53	7 (5), n=54	0 (-2.45 to 2.62)	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

Outcome measure and group	Mean (SD) score by time after CBT			95% CI for estimates of group*time	P value for group*time interaction
	4 weeks	12 weeks	24 weeks		
Visual analogue scale for pain					
Sham	23 (23), n=56	22 (22), n=48	22 (21), n=42	−0.84 to 0.20	0.23
Anodal	26 (26), n=54	27 (26), n=53	29 (26), n=47		
Oswestry disability index					
Sham	7 (6), n=56	6 (6), n=49	7 (6), n=42	−0.16 to 0.11	0.72
Anodal	8 (7), n=56	9 (7), n=52	9 (7), n=48		

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)

	After stimulation				After CBT			
	Mean (SD) anodal	Mean (SD) sham	95% CI for differences between groups	P values	Mean (SD) anodal	Mean (SD) sham	95% CI for differences between groups	P values
FABQ:								
Physical activity	15 (4), n=62	15 (4), n=61	-3.24 to 3.14	0.98	9 (4), n=54	10 (7), n=55	-4.75 to 5.32	0.91
Work	21 (12), n=62	21 (12), n=61	-5.92 to 4.74	0.82	16 (9), n=54	14 (11), n=55	-8.47 to 5.96	0.72
FfBH	21 (4), n=62	20 (5), n=61	-0.70 to 1.39	0.51	16 (4), n=54	16 (4), n=55	-1.58 to 1.11	0.73
HADS:								
Anxiety	7 (4), n=59	6 (4), n=58	-0.95 to 0.51	0.56	5 (4), n=52	4 (3), n=52	-1.10 to 0.88	0.83
Depression	6 (4), n=59	6 (4), n=57	-1.10 to 0.69	0.65	4 (4), n=52	4 (3), n=51	-0.85 to 1.15	0.77
Bothersomeness	3 (1), n=61	3 (1), n=61	-0.18 to 0.30	0.63	2 (1), n=54	2 (1), n=55	-0.47 to 0.30	0.67
PPSI	1 (1), n=61	2 (1), n=61	-0.29 to 0.55	0.54	3 (1), n=54	3 (1), n=55	-0.57 to 0.21	0.36
RAND-36:								
Physical activity	57 (19), n=62	62 (21), n=61	-2.64 to 8.45	0.30	81 (19), n=58	85 (18), n=59	-3.51 to 8.64	0.41
Role limitations from physical health	23 (32), n=61	21 (32), n=61	-5.90 to 11.53	0.52	53 (46), n=53	59 (44), n=54	-7.09 to 23.71	0.29
Pain	33 (13), n=61	33 (14), n=61	-3.12 to 4.35	0.77	49 (18), n=53	53 (17), n=55	-1.44 to 11.31	0.13
General health	52 (19), n=58	55 (19), n=61	-5.52 to 4.37	0.82	60 (20), n=53	63 (21), n=55	-5.36 to 5.54	0.97
Energy/fatigue	43 (20), n=59	47 (18), n=61	-7.02 to 2.87	0.41	56 (16), n=54	58 (19), n=54	-4.59 to 6.87	0.69
Social functioning	59 (26), n=62	64 (28), n=59	-3.82 to 7.24	0.54	77 (22), n=54	75 (22), n=53	-13.25 to 0.88	0.09
Role limitations from emotional problems	47 (45), n=62	52 (46), n=61	-3.62 to 21.13	0.16	70 (42), n=54	78 (37), n=54	-5.78 to 19.53	0.28
Emotional wellbeing	60 (19), n=60	63 (17), n=60	-1.83 to 5.83	0.30	73 (18), n=53	73 (16), n=53	-7.89 to 2.03	0.24

FABQ=fear avoidance beliefs questionnaire; FfBH=Funktionsfragebogen Hannover; HADS=hospital anxiety and depression scale; PPSI=patient perceived satisfactory improvement.

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 α level of 0.05 and a power of 80%. No adjustments for multiple testing were made.

Neurophysiological 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.^{45 64 88-92} In summary, there is sufficient

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

	Day 1 (n=112)	Day 2 (n=120)	Day 3 (n=124)	Day 4 (n=118)	Day 5 (n=120)
Agreement between guessed and received stimulation	$\kappa=0.111$	$\kappa=0.000$	$\kappa=-0.014$	$\kappa=-0.007$	$\kappa=-0.120$
Interpretation (Landis and Koch ⁷⁷)	Slight agreement	Slight agreement	Poor agreement	Poor agreement	Poor agreement

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.^{62 72 73 74} A 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.³⁰

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.

Funding: This study was funded by the Deutsche Forschungsgemeinschaft DFG (MA 1862/10-1).

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: AM, TJ, KL, and AP had financial support from DFG (MA 1862/10-1) and NeuroImageNord for the submitted work.

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 honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies are disclosed.

This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

- 1 Becker A, Held H, Redaelli M, et al. Low back pain in primary care: costs of care and prediction of future health care utilization. *Spine* 2010;35:1714-20.
- 2 Henschke N, Maher CG, Refshauge KM, et al. Prevalence of and screening for serious spinal pathology in patients presenting to primary care settings with acute low back pain. *Arthritis Rheum* 2009;60:3072-80.
- 3 Chou R, Shekelle P. Will this patient develop persistent disabling low back pain? *JAMA* 2010;303:1295-02.
- 4 Grotle M, Brox JJ, Veierod MB, et al. Clinical course and prognostic factors in acute low back pain: patients consulting primary care for the first time. *Spine* 2005;30:976-82.

- 5 Gurcay E, Bal A, Eksioğlu E, et al. Acute low back pain: clinical course and prognostic factors. *Disabil Rehabil* 2009;31:840-5.
- 6 Henschke N, Maher CG, Refshauge KM, et al. Prognosis in patients with recent onset low back pain in Australian primary care: inception cohort study. *BMJ* 2008;337:a171.
- 7 Balague F, Mannion AF, Pellise F, et al. Non-specific low back pain. *Lancet* 2011;379:482-91.
- 8 Airaksinen O, Brox JJ, Cedraschi C, et al. Chapter 4. European guidelines for the management of chronic nonspecific low back pain. *Eur Spine J* 2006;S192-300.
- 9 Latremoliere A, Woolf CJ. Central sensitization: a generator of pain hypersensitivity by central neural plasticity. *J Pain* 2009;10:895-926.
- 10 Woolf CJ. Central sensitization: implications for the diagnosis and treatment of pain. *Pain* 2011;152:S2-15.
- 11 Apkarian AV, Baliki MN, Geha PY. Towards a theory of chronic pain. *Prog Neurobiol* 2009;87:81-97.
- 12 Zhang L, Zhang Y, Zhao ZQ. Anterior cingulate cortex contributes to the descending facilitatory modulation of pain via dorsal reticular nucleus. *Eur J Neurosci* 2005;22:1141-8.
- 13 Beck JS. Cognitive behavior therapy: basics and beyond. 2nd ed. Guilford Press, 2011:19-20.
- 14 Koes BW, van Tulder M, Lin CW, et al. An updated overview of clinical guidelines for the management of non-specific low back pain in primary care. *Eur Spine J* 2010;19:2075-94.
- 15 Lambert M. ICSI releases guideline on chronic pain assessment and management. *Am Fam Physician* 2010;82:434-9.
- 16 Savigny P, Watson P, Underwood M. Early management of persistent non-specific low back pain: summary of NICE guidance. *BMJ* 2009;338:b1805.
- 17 Van Middelkoop M, Rubinstein SM, Kuijpers T, et al. A systematic review on the effectiveness of physical and rehabilitation interventions for chronic non-specific low back pain. *Eur Spine J* 2011;20:19-39.
- 18 Moseley GL, Flor H. Targeting cortical representations in the treatment of chronic pain: a review. *Neurorehabil Neural Repair* 2012;26:646-52.
- 19 Wand BM, O'Connell NE. Chronic non-specific low back pain—subgroups or a single mechanism? *BMC Musculoskelet Disord* 2008;9:11.
- 20 Wand BM, Parkitny L, O'Connell NE, et al. Cortical changes in chronic low back pain: current state of the art and implications for clinical practice. *Man Ther* 2011;16:15-20.
- 21 Nitsche MA, Cohen LG, Wassermann EM, et al. Transcranial direct current stimulation: state of the art 2008. *Brain Stimul Brain Stimul* 2008;1:206-23.
- 22 Holsheimer J, Nguyen JP, Lefaucheur JP, et al. Cathodal, anodal or bifocal stimulation of the motor cortex in the management of chronic pain? *Acta Neurochir Suppl* 2007;97:57-66.
- 23 DosSantos MF, Love TM, Martikainen IK, et al. Immediate effects of tDCS on the mu-opioid system of a chronic pain patient. *Front Psychiatry* 2012;3:93.
- 24 Garcia-Larrea L, Peyron R. Motor cortex stimulation for neuropathic pain: From phenomenology to mechanisms. *Neuroimage* 2007;37:S71-9.
- 25 Pagano RL, Assis DV, Clara JA, et al. Transdural motor cortex stimulation reverses neuropathic pain in rats: a profile of neuronal activation. *Eur J Pain* 2011;15:268.e1-14.
- 26 O'Connell NE, Wand BM, Marston L, et al. Non-invasive brain stimulation techniques for chronic pain. *Cochrane Database Syst Rev* 2014;4:CD008208.
- 27 Luedtke K, Rushton A, Wright C, et al. Transcranial direct current stimulation for the reduction of clinical and experimentally induced pain: a systematic review and meta-analysis. *Clin J Pain* 2012;28:452-61.
- 28 Cosentino G, Fierro B, Paladino P, et al. Transcranial direct current stimulation preconditioning modulates the effect of high-frequency repetitive transcranial magnetic stimulation in the human motor cortex. *Eur J Neurosci* 2012;35:119-24.
- 29 Boggio PS, Amancio EJ, Correa CF, et al. Transcranial DC stimulation coupled with TENS for the treatment of chronic pain: a preliminary study. *Clin J Pain* 2009;25:691-5.
- 30 Riberto M, Marcon Alfieri F, Monteiro de Benedetto Pacheco K, et al. Efficacy of transcranial direct current stimulation coupled with a multidisciplinary rehabilitation program for the treatment of fibromyalgia. *Open Rheumatol J* 2011;5:45-50.
- 31 Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *Int J Surg* 2010;9:672-7.
- 32 International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. Guideline for good clinical practice www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf.
- 33 World Medical Association. Declaration of Helsinki. www.wma.net/e/ethicsunit/helsinki.htm.
- 34 Altman DG, Bland JM. How to randomise. *BMJ* 1999;319:703-4.
- 35 Herbert RD. Randomisation in clinical trials. *Aust J Physiother* 2005;51:58-60.

- 36 Meinert CL. Clinical trials: design, conduct, and analysis. Oxford University Press, 1986.
- 37 Schulz KF, Grimes DA. Generation of allocation sequences in randomised trials: chance, not choice. *Lancet* 2002;359:515-9.
- 38 Zelman DC, Hoffman DL, Seifeldin R, et al. Development of a metric for a day of manageable pain control: derivation of pain severity cut-points for low back pain and osteoarthritis. *Pain* 2003;106:35-42.
- 39 Gandiga PC, Hummel FC, Cohen LG. Transcranial DC stimulation (tDCS): a tool for double-blind sham-controlled clinical studies in brain stimulation. *Clin Neurophysiol* 2006;117:845-50.
- 40 Loo CK, Sachdev P, Martin D, et al. A double-blind, sham-controlled trial of transcranial direct current stimulation for the treatment of depression. *Int J Neuropsychopharmacol* 2010;13:61-9.
- 41 Priori A, Hallett M, Rothwell JC. Repetitive transcranial magnetic stimulation or transcranial direct current stimulation. *Brain Stimulation* 2009;2:241-5.
- 42 O'Connell NE, Cossar J, Marston L, et al. Rethinking clinical trials of transcranial direct current stimulation: participant and assessor blinding is inadequate at intensities of 2 mA. *PLoS One* 2012;7:e47514.
- 43 Landis JR, Koch GG. An application of hierarchical kappa-type statistics in the assessment of majority agreement among multiple observers. *Biometrics* 1977;33:363-74.
- 44 Ambrus GG, Al-Moyed H, Chaieb L, et al. The fade-in—short stimulation—fade out approach to sham tDCS—reliable at 1 mA for naive and experienced subjects, but not investigators. *Brain Stimul* 2012;5:499-504.
- 45 Jurgens TP, Schulze A, Klein T, et al. Transcranial direct current stimulation does neither modulate results of a quantitative sensory testing protocol nor ratings of suprathreshold heat stimuli in healthy volunteers. *Eur J Pain* 2012;16:1251-63.
- 46 Ihle K, Rodriguez-Raecke R, Luedtke K, et al. tDCS modulates cortical nociceptive processing but has little impact on pain perception. *Pain* 2014;155:2080-7.
- 47 McCracken LM, Turk DC. Behavioral and cognitive-behavioral treatment for chronic pain: outcome, predictors of outcome, and treatment process. *Spine* 2002;27:2564-73.
- 48 Scascighini L, Toma V, Dober-Spielmann S, et al. Multidisciplinary treatment for chronic pain: a systematic review of interventions and outcomes. *Rheumatology* 2008;47:670-8.
- 49 Turk DC. Clinical effectiveness and cost-effectiveness of treatments for patients with chronic pain. *Clin J Pain* 2002;18:355-65.
- 50 Turk DC, Dworkin RH, Allen RR, et al. Core outcome domains for chronic pain clinical trials: IMMPACT recommendations. *Pain* 2003;106:337-45.
- 51 Kohlmann T, Raspe H. [Hannover functional questionnaire in ambulatory diagnosis of functional disability caused by backache]. *Rehabilitation (Stuttg)* 1996;35:I-VIII.
- 52 Dunn KM, Croft PR. Classification of low back pain in primary care: using "bothersomeness" to identify the most severe cases. *Spine* 2005;30:1887-92.
- 53 Hays RD, Sherbourne CD, Mazel RM. The RAND 36-item health Survey 1.0. *Health Econ* 1993;2:217-27.
- 54 Pfingsten M, Kroner-Herwig B, Leibing E, et al. Validation of the German version of the fear-avoidance beliefs questionnaire (FABQ). *Eur J Pain* 2000;4:259-66.
- 55 Hinz A, Zeynert U, Kittel J, et al. [Measurement of change with the Hospital Anxiety and Depression Scale (HADS): sensitivity and reliability of change]. *Psychother Psychosom Med Psychol* 2009;59:394-400.
- 56 Ten Klooster PM, Drossaers-Bakker KW, Taal E, et al. Patient-perceived satisfactory improvement (PPSI): interpreting meaningful change in pain from the patient's perspective. *Pain* 2006;121:151-7.
- 57 Cleophas TJ, Zwinderman AH. Clinical trials are often false positive: a review of simple methods to control this problem. *Curr Clin Pharmacol* 2006;1:1-4.
- 58 Neuhauser M. How to deal with multiple endpoints in clinical trials. *Fundam Clin Pharmacol* 2006;20:515-23.
- 59 Ostelo RW, Deyo RA, Stratford P, et al. Interpreting change scores for pain and functional status in low back pain: towards international consensus regarding minimal important change. *Spine* 2008;33:90-4.
- 60 Maughan EF, Lewis JS. Outcome measures in chronic low back pain. *Eur Spine J* 2010;19:1484-94.
- 61 Fregni F, Boggio PS, Lima MC, et al. A sham-controlled, phase II trial of transcranial direct current stimulation for the treatment of central pain in traumatic spinal cord injury. *Pain* 2006;122:197-209.
- 62 Lamb SE, Hansen Z, Lall R, et al. Group cognitive behavioural treatment for low-back pain in primary care: a randomised controlled trial and cost-effectiveness analysis. *Lancet* 2010;375:916-23.
- 63 Cohen J. A power primer. *Psychol Bull.* 1992;112:155-9.
- 64 Luedtke K, May A, Jurgens TP. No effect of a single session of transcranial direct current stimulation on experimentally induced pain in patients with chronic low back pain—an exploratory study. *PLoS One* 2012;7:e48857.
- 65 Turk DC, Dworkin RH, McDermott MP, et al. Analyzing multiple endpoints in clinical trials of pain treatments: IMMPACT recommendations. Initiative on methods, measurement, and pain assessment in clinical trials. *Pain* 2008;139:485-93.
- 66 Twisk J, Proper K. Evaluation of the results of a randomized controlled trial: how to define changes between baseline and follow-up. *J Clin Epidemiol* 2004;57:223-8.
- 67 Vickers AJ, Altman DG. Statistics notes: analysing controlled trials with baseline and follow up measurements. *BMJ* 2001;323:1123-4.
- 68 Field A. Discovering statistics using SPSS. 3rd ed. Sage Publications, 2009.
- 69 Draper N, Smith H. Applied regression analysis. 2nd ed. John Wiley, 1981.
- 70 Twisk J, de Boer M, de Vente W, et al. Multiple imputation of missing values was not necessary before performing a longitudinal mixed-model analysis. *J Clin Epidemiol* 2013;66:1022-8.
- 71 Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol* 2009;62:1006-12.
- 72 Vibe Fersum K, O'Sullivan P, Skouen J, et al. Efficacy of classification-based cognitive functional therapy in patients with non-specific chronic low back pain: a randomized controlled trial. *Eur J Pain* 2013;17:916-28.
- 73 Lang E, Liebig K, Kastner S, v. Multidisciplinary rehabilitation versus usual care for chronic low back pain in the community: effects on quality of life. *Spine J* 2003;3:270-6.
- 74 Kääpä EF, Sarna K, Malmivaara S. Multidisciplinary group rehabilitation versus individual physiotherapy for chronic nonspecific low back pain. *Spine* 2008;31:371-6.
- 75 Polit DF, Gillespie BM. The use of the intention-to-treat principle in nursing clinical trials. *Nurs Res* 2009;58:391-9.
- 76 Polit DF, Gillespie BM. Intention-to-treat in randomized controlled trials: recommendations for a total trial strategy. *Res Nurs Health* 2010;33:355-68.
- 77 Landis JR, Koch GG. The measurement of observer agreement for categorical data. *Biometrics* 1977;33:159-74.
- 78 Antal A, Terney D, Kuhn S, et al. Anodal transcranial direct current stimulation of the motor cortex ameliorates chronic pain and reduces short intracortical inhibition. *J Pain Symptom Manage* 2010;39:890-903.
- 79 O'Connell NE, Cossar J, Marston L, et al. Transcranial direct current stimulation of the motor cortex in the treatment of chronic nonspecific low back pain: a randomized, double-blind exploratory study. *Clin J Pain* 2013;29:26-34.
- 80 Fenton BW, Palmieri PA, Boggio P, et al. A preliminary study of transcranial direct current stimulation for the treatment of refractory chronic pelvic pain. *Brain Stimulation* 2009;2:103-7.
- 81 Knotkova H, Nitsche MA, Cruciani RA. Putative physiological mechanisms underlying tDCS analgesic effects. *Front Hum Neurosci* 2013;7:628.
- 82 Medeiros LF, de Souza IC, Vidor LP, et al. Neurobiological effects of transcranial direct current stimulation: a review. *Front Psychiatry* 2012;3:110.
- 83 Ossipov MH, Dussor GO, Porreca F. Central modulation of pain. *J Clin Invest* 2010;120:3779-87.
- 84 Polania R, Paulus W, Nitsche MA. Modulating cortico-striatal and thalamo-cortical functional connectivity with transcranial direct current stimulation. *Hum Brain Mapp* 2011;33:2499-508.
- 85 Lang N, Nitsche MA, Paulus W, et al. Effects of transcranial direct current stimulation over the human motor cortex on corticospinal and thalamocortical excitability. *Exp Brain Res* 2004;156:439-43.
- 86 Reidler JS, Mendonca ME, Santana MB, et al. Effects of motor cortex modulation and descending inhibitory systems on pain thresholds in healthy subjects. *J Pain* 2012;13:450-8.
- 87 Roche N, Lackmy A, Achache V, et al. Effects of anodal tDCS on lumbar proprioceptive system in healthy subjects. *Clin Neurophysiol* 2011;123:1027-34.
- 88 Antal A, Brepohl N, Poreisz C, et al. Transcranial direct current stimulation over somatosensory cortex decreases experimentally induced acute pain perception. *Clin J Pain* 2008;24:56-63.
- 89 Boggio PS, Zaghi S, Lopes M, et al. Modulatory effects of anodal transcranial direct current stimulation on perception and pain thresholds in healthy volunteers. *Eur J Neurol* 2008;15:1124-30.
- 90 Csifcsak G, Antal A, Hillers F, et al. Modulatory effects of transcranial direct current stimulation on laser-evoked potentials. *Pain Med* 2009;10:122-32.
- 91 Bachmann CG, Muschinsky S, Nitsche MA, et al. Transcranial direct current stimulation of the motor cortex induces distinct changes in thermal and mechanical sensory percepts. *Clin Neurophysiol* 2011;121:2083-9.
- 92 Grundmann L, Rolke R, Nitsche MA, et al. Effects of transcranial direct current stimulation of the primary sensory cortex on somatosensory perception. *Brain Stimul* 2011;4:253-60.

© BMJ Publishing Group Ltd 2015

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