



A sham-controlled, phase II trial of transcranial direct current stimulation for the treatment of central pain in traumatic spinal cord injury

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Abstract

Past evidence has shown that motor cortical stimulation with invasive and non-invasive brain stimulation is effective to relieve central pain. Here we aimed to study the effects of another, very safe technique of non-invasive brain stimulation – transcranial direct current stimulation (tDCS) – on pain control in patients with central pain due to traumatic spinal cord injury. Patients were randomized to receive sham or active motor tDCS (2 mA, 20 min for 5 consecutive days). A blinded evaluator rated the pain using the visual analogue scale for pain, Clinician Global Impression and Patient Global Assessment. Safety was assessed with a neuropsychological battery and confounders with the evaluation of depression and anxiety changes. There was a significant pain improvement after active anodal stimulation of the motor cortex, but not after sham stimulation. These results were not confounded by depression or anxiety changes. Furthermore, cognitive performance was not significantly changed throughout the trial in both treatment groups. The results of our study suggest that this new approach of cortical stimulation can be effective to control pain in patients with spinal cord lesion. We discuss potential mechanisms for pain amelioration after tDCS, such as a secondary modulation of thalamic nuclei activity.

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1. Introduction

One of the most refractory types of pain is the one associated with lesions of the brain or spinal cord, such

as after stroke or traumatic spinal cord injury (Nicholson, 2004). It is not uncommon that patients, despite the availability of multiple pharmacologic approaches, fail to experience sufficient relief, thus establishing the need for new therapeutic approaches and prompting a renewed interest in neuromodulatory approaches with brain stimulation. Deep brain stimulation has shown promising results (Wallace et al., 2004), but less invasive forms of stimulation might also be effective. Studies of

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epidural motor cortex stimulation report response rates that vary between 50% (Carroll et al., 2000) and 70–80% (Tsubokawa et al., 1993; Herregodts et al., 1995; Ebel et al., 1996; Nguyen et al., 1999; Nuti et al., 2005) and mean pain relief that varies from 28% to 47% in the largest series (Nguyen et al., 1999; Nuti et al., 2005) and 50% to 70% in the smallest series (Herregodts et al., 1995; Ebel et al., 1996). Non-invasive brain stimulation using repetitive transcranial magnetic stimulation (rTMS) also appears to be effective with mean pain relief in the range of 20–45% (Lefaucheur et al., 2004; Pleger et al., 2004; Khedr et al., 2005).

Another technique of non-invasive brain stimulation – transcranial direct current stimulation (tDCS) – might have further advantages over rTMS as it may lead to longer-lasting modulatory effects of cortical function, and is easy to administer and perform, less expensive, and provides a reliable sham-stimulation condition to assess the specificity of the effects.

In tDCS, the cerebral cortex is stimulated through a weak DC current in a non-invasive and painless manner. Several studies have shown that this technique modulates cortical excitability in the human motor (Nitsche and Paulus, 2001) and visual cortex (Antal et al., 2001), that its modulatory effect remains after stimulation if tDCS is applied for several minutes, and that tDCS not only shifts activity of cortical areas situated directly under the electrodes, but also of distant areas, probably by interconnections of the primary stimulated area with these structures (Lang et al., 2005). Furthermore, recent research has demonstrated that tDCS can enhance some aspects of cognition (Nitsche et al., 2003b; Fregni et al., 2005b; Iyer et al., 2005) and promote the recovery of motor deficits in stroke patients (Fregni et al., 2005a; Hummel et al., 2005).

Therefore, here we aimed to study the effects of tDCS on pain reduction in patients with refractory central pain associated with spinal cord injury. We decided to study patients with spinal cord injury as pain develops in approximately 60–70% of these individuals, being severe in one-third of them (Bonica, 1991). In addition, because pain in these patients is associated with dysfunctional brain activity – a hyperexcitability of central nociceptors – rather than an overall increased input from peripheral pain receptors – a treatment that targets central structures might be the most adequate one in these patients.

2. Methods

2.1. Study design

Our study was a randomized, double-blinded, placebo-controlled, single-center, phase II parallel-group trial that was designed to evaluate the efficacy and safety of five daily sessions of transcranial direct current stimulation (tDCS) in

patients with chronic neuropathic central pain due to traumatic spinal cord injury. Evaluation of safety was an important aim of the trial as previous safety studies of tDCS evaluated the effects of only one session of 2 mA in healthy volunteers or several sessions of 1 mA tDCS in patients with major depression (Fregni et al., 2005a; Iyer et al., 2005). The study conformed to the ethical standards of the Helsinki declaration (1964) and was approved by the institutional ethics committee. All patients provided written, informed consent.

2.2. Subjects

Patients were prospectively and sequentially selected from a specialized pain clinic in the rehabilitation medical center of the Sao Paulo University. They were regarded as suitable to participate if they fulfilled the following criteria: (1) traumatic spinal cord injury – for instance, due to fall, car accident or gun shot; (2) stable chronic pain for at least the three preceding months; (3) score higher than or equal to 4 cm (0 cm = ‘no pain’ and 10 cm = ‘worst possible pain’) on the visual analogue scale (VAS) for pain perception at the baseline/start of the treatment; (4) refractoriness to drugs for pain relief – such as tricyclic antidepressants, antiepileptic drugs, and/or narcotics (pain resistant to at least two of these drugs supplied in adequate dosages for 6 months) and (5) pain was not attributable to other causes, such as peripheral inflammation.

We excluded patients with any clinically significant or unstable medical or psychiatric disorder, history of substance abuse, or neuropsychiatric comorbidity. In addition, we excluded patients with implanted devices for pain control, such as vagal or deep brain stimulators. Patients with clinical signs of syringomyelia were investigated with MRI and excluded if the MRI was positive for this condition. Only patients without significant alterations in head computed tomography and/or head MRI were included in the study. Seventeen patients (mean age 35.7 ± 13.3 years, mean \pm SD, 3 females) participated in the study. The general clinical characteristics of the patients are summarized in Table 1. Note that the low prevalence of females in the study is due to the low prevalence of females with spinal cord injury in our population (Sao Paulo, Brazil). Because a large number of spinal cord injuries occur in construction workers (work related – fall) or as a result of gun shots, prevalence of traumatic spinal cord injury is higher in men (Barros Filho et al., 1990).

2.3. Experimental design

The study had two phases: (1) baseline evaluation – that consisted in a 2-week period of observation to establish a baseline for pain and the other measures (such as mood, anxiety, and cognition) – this period of evaluation was necessary for habituation with daily measurements and to capture variability in the baseline pain scores; (2) 3-week double-blinded treatment – that consisted in daily treatment sessions with sham or active tDCS for 5 consecutive days and a follow-up period of 16 days.

During the baseline period, patients were randomized in a 1:2 ratio to receive sham or active tDCS, respectively. This randomization strategy (1:2) was chosen, given the relatively small sample size planned for this phase II trial and the lack of a priori information on the efficacy for a new treatment

Table 1
Clinical and demographic characteristics

	Active TDCS	Sham TDCS	<i>p</i> -value ^a
Number (<i>n</i>)	11	6	
Gender (males (%))	9 (82%)	5 (83.3%)	0.6
Age – years (SD)	36.6 (12.6)	34.2 (15.8)	0.47
Etiology of spinal cord injury			
Car/motorcycle accident	4	2	0.55
Fall	6	3	
Gun shot	1	1	
Duration of spinal cord injury – years (SD)	3.7 (1.8)	3.4 (1.5)	0.71
Location of the lesion			
Cervical	5	4	0.37
Below cervical (thoracic and lumbar)	6	2	
Spinal cord injury classification (Frankel)			
Complete (A)	8	3	0.56
Incomplete (B)	1	0	
Incomplete (C)	1	1	
Incomplete (D)	1	2	
Normal (E)	0	0	
Pain location			
Below lesion	9	4	0.44
Below lesion and in transition zone	2	2	
Duration of chronic pain (number of patients)			
More than 5 years	1	0	0.71
Between 2 and 5 years	8	4	
Less than 2 years	2	2	
Baseline scores			
VAS pain – baseline (SD)	6.2 (1.5)	6 (2)	0.73
BDI	8.9 (5.0)	12.6 (6.6)	0.2
MMSE	24.5 (2.1)	26.3 (3.6)	0.2

^a Student's *t*-test for the comparison of continuous variables and Fisher's exact test for the comparison of categorical variables.

(see (Peto, 1978)). Randomization was performed using the order of entrance in the study and a previous randomization list generated by a computer using random blocks of six (for each six patients, two were randomized to sham and four to active tDCS) in order to minimize the risk of unbalanced group sizes.

To determine the sample size, we used the results of a previous study (Lefaucheur et al., 2004) that investigated rTMS for the treatment of central pain, because no studies are available for the treatment of pain with tDCS. In this study, a mean reduction of pain of 22.9% (± 3.6) in the active group and 7.8% (± 3.2) in the sham group was reported. Considering a power of 97.5% (this represents a power of 95% considering an unequal randomization – see (Pocock, 1979)) and a critical $\alpha = 0.01\%$, eight patients (four in each group) are needed to detect group differences. As we had no direct knowledge about the effect size of tDCS, we decided to increase the number of subjects studied to 14. To account for possible dropouts, we added three more subjects. Therefore, 17 patients were entered into the study.

2.4. Direct current stimulation

Direct current was transferred by a saline-soaked pair of surface sponge electrodes (35 cm²) and delivered by a specially developed, battery-driven, constant current stimulator (Schneider Electronic, Gleichen, Germany) with a maximum output of 10 mA. Patients received either anodal stimulation of primary motor cortex (M1) or sham stimulation of M1.

For anodal stimulation of M1, the anode electrode was placed over C3 or C4 (EEG 10/20 system) and the cathode electrode over the contralateral supraorbital area. This electrode position has been shown to be effective to enhance excitability of the primary motor cortex (Nitsche and Paulus, 2001). The hemisphere of stimulation was based on pain lateralization. For patients with an asymmetric pain, we stimulated the contralateral M1 – similar to the methodology of Lefaucheur's study (Lefaucheur et al., 2004) and for patients with symmetric pain, we stimulated the dominant, left (for right-handed patients) hemisphere. However, it should be noted that M1 stimulation with tDCS induces widespread changes in the activity of cortical areas and can indeed change the activity of the contralateral motor cortex (see Lang et al., 2005). This suggests that unilateral tDCS treatment might be sufficient for patients with bilateral pain. In addition, because the electrode for tDCS is large and the longer axis was aligned with the motor cortex strip, the stimulation encompassed a broad area of the motor cortex (upper limb and part of the lower limb and face) – see Fig. 1 in which we measured the brain location of the electrode using a frameless stereotactic system (Brainsight, Rogue Research, Montreal, Canada). A constant current of 2 mA intensity (subthreshold intensity) was applied for 20 min. Stimulation with 2 mA (for a single session) has been shown to be safe in healthy volunteers (Iyer et al., 2005). Subjects felt the current as an itching sensation at both electrodes at the beginning of the stimulation. For sham stimulation, the electrodes were placed in the same positions as for anodal M1 stimulation; however, the stimulator was turned off

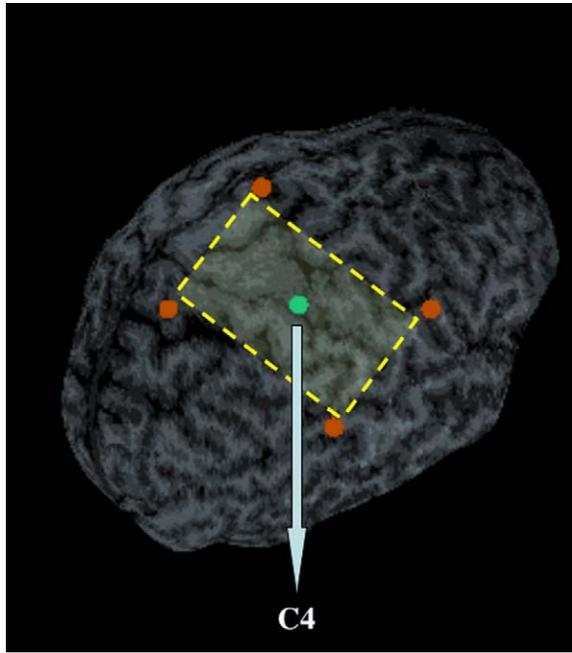


Fig. 1. Illustration showing the electrode area over the motor cortex. The position of the electrode was determined using a frameless stereotactic system (Brainsight software, Rogue Research, Canada). Note that the electrode covers almost the entire motor cortex strip.

after 10 s of stimulation as previously described (Fregni et al., 2005a) and also assessed as a reliable method of sham stimulation (Fregni et al., in press-b). Therefore, the subjects felt the initial itching sensation, but received no current for the rest of the stimulation period.

2.5. Evaluations and endpoints

All evaluations were performed by a blinded rater twice at baseline, daily during treatment period (except BDI, MMSE, and cognitive tests, that were conducted on day 1 and day 5, and CGI and PGA that were measured on day 2, 3, 4, and 5), and once in the follow-up visit. Except for VAS pain and VAS anxiety (that were carried out before and after stimulation), all evaluations were carried out immediately after the stimulation.

2.5.1. Pain measurement

Visual analogue scale (VAS) for pain. This self-evaluation scale ranges from 0 to 10 as visually described in centimeter units: 0 cm indicates no pain and 10 cm means the worst pain possible. Participants were asked to rate their pain during the previous 24 h. This scale has been widely used in studies that evaluate pain as an outcome: both validity and reproducibility have been demonstrated (Bolton and Wilkinson, 1998). As we expected daily variability in pain levels, pain was self-assessed frequently during baseline (once a day for 2 weeks) and then twice a day during the treatment phase (before and after the treatment) and once at the follow-up period.

Analgesic use. We instructed the participants to continue their routine medication regimen. All changes in dosing were recorded in the patient's medication use diary.

Herbal remedies and alternative therapies such as massage or acupuncture were allowed if they had been used for at least 4 weeks before randomization, and the regimen was maintained constant throughout the study.

Clinical Global Assessment (CGI). CGI is a two-item scale that encompasses: (1) Severity of Illness and (2) Global Improvement. Item 1 is rated on a seven-point scale (1 = normal to 7 = extremely ill); item 2 on a seven-point scale (1 = very much improved to 7 = very much worse). The severity of illness item requires the clinician to rate the severity of the participants' illness at the time of assessment as relative to the clinician's past experience with participants who have the same diagnosis. The Global Improvement item requires the clinician to rate how much the participants' illness has improved or worsened relative to a baseline state.

Patient Global Assessment (PGA). The Global Assessment asks each participant to rate the change in his/her overall pain status relative to their personal baseline on a seven-point scale ranging from much worse to much improved. Although the PGA provides a retrospective recording that may overestimate improvement as a result of recall or motivational bias, we consider this scale to be important as it is easy for the participants to understand and yields data that correspond to the main treatment target (pain symptom severity).

2.5.2. Confounders measurement

Because depression and anxiety can be important confounders for pain improvement, we measured these two domains using the following instruments:

Beck Depression Inventory (BDI). The Beck Depression Inventory (BDI) is a 21-item test presented in multiple-choice format, which measures the presence and the degree of depression in adults.

VAS for anxiety. The VAS for anxiety is a self-evaluation scale that ranges from 0 to 10 cm, where 0 means no anxiety and 10 cm means the worst anxiety ever.

2.5.3. Cognitive function and safety

Although the electric current induced by tDCS is weak (2 mA – well below the pain threshold), it is applied continuously for several minutes in this protocol. Since potential adverse effects of this technique might include cognitive changes, we completed the following tests:

Mini-mental state examination. This is a brief, quantitative measure of cognitive status that is widely used to examine cognition at a given point of time and to follow the course of cognitive changes in an individual over time (van Belle et al., 1990).

Stroop test. This instrument is a test of selective attention and interference susceptibility. This test might measure cognitive domains that involve focused attention and decision-making, and thus provide a measure of executive (frontal) function.

Digit span forward and backward. These two tests are relatively simple to apply and provide valuable information about attention, information storage, working memory, and mental double-tracking and reversing operations.

Simple reaction time. Because our stimulation was targeted to motor cortex, assessing a possible detrimental effect of anodal tDCS on motor function was important. We used a simple reaction time task in which patients were seated in front of a computer screen placed at eye level. A circle of 4 cm diameter was presented in the center of the screen following

a warning sign (small cross in the center of the screen) after a randomly variable interval of 2–5 s. The patients were asked to push a response key as soon as they saw the circle on the screen using only the right index finger (afterwards the test was repeated with the left index finger), which was rested on the key. The time between the appearance of the circle and the push of the response key was defined as simple reaction time (sRT). The experiment consisted of blocks of 30 trials. Patients were allowed to practice for 60 trials prior to the test in order to familiarize themselves with the procedure. The stimuli were generated and response times recorded using Superlab pro v2.0 software (Cedrus Corporation, San Pedro, CA).

Finally we monitored adverse events, asking patients after each session of stimulation and in the follow-up if they have experienced any adverse event and the relationship of these events to the treatment with tDCS.

2.5.4. Statistical analysis

Initially we compared baseline results for both groups of patients in order to rule out that differences between sham and active stimulation might have been due to a priori differences between these two groups. For this analysis, continuous variables were compared using Student's *t*-test and categorical variables using Fisher's exact test. Analyses were done with Stata statistical software (version 8.0, College Station, Texas).

Dropouts in our study might indicate a treatment failure as these patients depend on special transportation to come to the hospital to receive the treatment and have a low socio-economic status so that no improvement would discourage their continuation in this trial. Therefore, we analyzed the primary and secondary endpoints using the intention-to-treat method including patients who received at least one dose of the randomized treatment and had at least one post-baseline efficacy evaluation. We used the last evaluation carried out to the session before the missed session, assuming no further improvement after the dropout, for this calculation.

For the analyses with continuous variables, we used a repeated-measures analysis of variance in which the dependent variable was the endpoint (for instance VAS scores) and the factors were: group (sham and active tDCS) and time of treatment (baseline, day 1, day 2, day 3, day 4, day 5, and follow-up or baseline, day 5 and follow-up). In addition, for some endpoints, we also ran a one-way ANOVA of the active tDCS group including only the time factor as a repeated measurement. When appropriate, post hoc comparisons (between sham and active group and between post-treatment evaluations and baseline evaluations) were carried out using Bonferroni correction for multiple comparisons.

For categorical variables, we constructed a 2×2 table with group of treatment (sham or active) as a row and time of treatment (before and after 5 days) as column and performed a measure of association using Fisher's exact test.

To evaluate if depression and anxiety were confounding our results, we built a model of regression. Pain improvement was taken as dependent variable. We included the independent variables time, group, and time \times group. The variables *depression* (as defined by BDI score changes) and *anxiety* (as defined by VAS anxiety score changes) were added individually to the model. Confounding was defined by changes of $\pm 20\%$ or higher in the beta coefficient of the interaction term of the original (reduced) model.

Finally, we correlated pain change (as indexed by change in VAS score) with some disease characteristics, such as disease duration, baseline VAS pain scores, site of spinal cord lesion (lumbar, thoracic or cervical), Frankel classification (complete versus incomplete lesion), type of pain (paroxysmal, continuous or both), and location of pain (lower limbs, upper limbs or both). Pearson correlation coefficient was used to analyze the relationships between continuous variables. For categorical variables we dichotomized the mean pain changes in two groups and compared them using a Student's *t*-test.

Unless stated otherwise, all results are presented as means and standard deviation, and statistical significance refers to a two-tailed *p* value < 0.05 .

3. Results

Table 1 summarizes demographic and clinical characteristics at baseline and Table 2, medication characteristics at baseline. There were no significant differences in clinical and demographic characteristics between the sham and active tDCS groups. All patients tolerated the tDCS well without experiencing any adverse effects. When explicitly asked, none of the patients could tell whether the stimulation was active or sham. There were two dropouts – one in each group – and the main reason that prevented both patients to complete the experiment was the difficulty in transportation. Additionally, both patients had no or small improvement that could have contributed to their decision of abandoning the treatment.

Patients described their pain as: a burning (76.5%), stabbing (58.9%) or tingling sensation (35.3%). The most common site of pain were the lower limbs

Table 2
Medication characteristics

Drugs	Active TDCS			Sham TDCS		
	Number	Mean dosage (mg)	Mean duration (months)	Number	Mean dosage (mg)	Mean duration (months)
Amytriptiline (<i>n</i>)	7	33.1 (± 20.4)	33.9 (± 13.9)	3	41.7 (± 28.9)	31.0 (± 11.3)
Carbamazepine	2	400.0 (± 282.8)	23.5 (± 20.5)	1	400.0	18
Gabapentin	2	1200 (± 848.5)	25.5 (± 19.1)	3	300 (± 0)	24.7 (± 14.2)
Baclofen	4	24.0 (± 8.9)	29.8 (± 16.9)	3	36.7 (± 5.7)	20.0 (± 8.5)
Chlorpromazine	3	37.5 (± 33.1)	12.7 (± 3.1)	1	25	18
Diazepam	2	20 (± 14.1)	27.5 (± 2.1)	3	15 (± 5.8)	28.5 (± 13.1)
Morphine	0			1	40	18

(64.7%), followed by back pain (29.4%), and pain in the upper limbs (17.6%). Only one patient reported also pain in the face (5.8%). Pain was described as continuous (41.2%) or continuous with paroxysms (41.2%), or only paroxysmal (17.6%).

Routine medical treatment of the patients was performed according to the guidelines of our pain clinic. They therefore were using the following medications: amitriptyline (low dosage – 25 to 75 mg/day – 58.8% of patients); antiepileptic drugs (carbamazepine or gabapentin – 41.2%); baclofen (41.2%); neuroleptic (chlorpromazine – 23.5%); benzodiazepines (diazepam and clonazepam – 29.4%); one patient only was taking morphine (5.8%).

3.1. Pain control – VAS

To analyze whether tDCS treatment was associated with pain improvement, we performed a repeated-measures analysis of variance in which the dependent variable was change of VAS pain scores from the baseline and the independent variable was time of evaluation

(baseline, day 1, day 2, day 3, day 4, day 5, and follow-up) and group of treatment (active versus sham tDCS). This analysis revealed a significant main effect of group of treatment ($F_{(1,105)} = 61.1$; $p < 0.0001$) and interaction term (group versus time; $F_{(1,105)} = 3.03$; $p = 0.009$) (Fig. 2A). We therefore performed additionally a one-way ANOVA to examine the main effect of time in the active group only. Because this effect was significant ($F_{(6,30)} = 11.95$; $p < 0.0001$), we performed post hoc comparisons using Bonferroni correction (comparing baseline VAS scores with the subsequent sessions). This analysis showed a significant difference after the third session that remained significant until the last session for the active tDCS group (Baseline comparison with: first session – $p = 0.95$; second session – $p = 0.1$; third session – $p = 0.015$; fourth session – $p = 0.001$; fifth session – $p = 0.001$, corrected for multiple comparisons). In the follow-up, however, there was only a trend toward a significant difference between baseline versus follow-up ($p = 0.1$). The largest pain reduction was achieved after the fifth session of stimulation (mean VAS pain scores – 2.6; 95% confidence interval (CI),

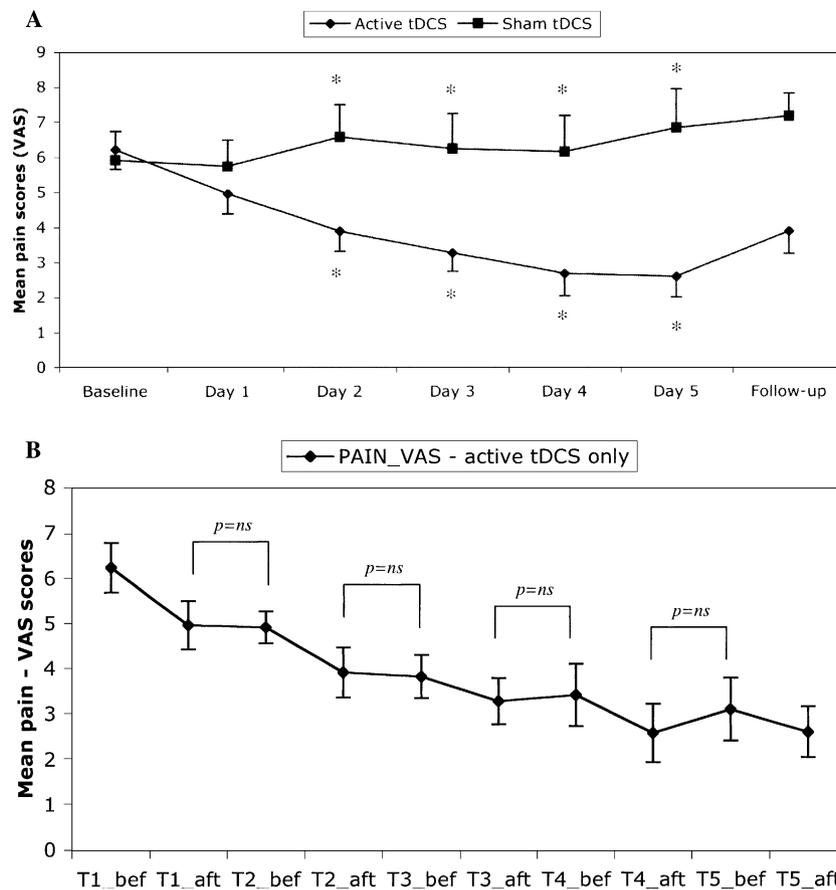


Fig. 2. Pain scores as indexed by visual analogue scale (VAS) throughout the experiment. (A) The VAS scores for each time point in the two groups of treatment (sham and active tDCS). (B) shows VAS scores (pre- and post-treatment) for each day of evaluation for the active tDCS group only – there was no significant difference between the post-treatment and pre-treatment of consecutive days. * Indicates statistically significant ($p < 0.05$). Each point represents mean VAS scores for pain \pm SEM (standard error of mean).

1.44–3.74). The magnitude of this effect decreased during the follow-up period (mean VAS pain scores – 3.9; 95% CI, 2.6, 5.1), however, pain rating was still diminished compared to baseline scores (mean VAS pain scores – 6.2; 95% confidence interval (CI), 5.1–7.3). Because for the sham tDCS group, the one-way ANOVA showed no time effect ($F_{(6,30)} = 1.12$; $p = 0.37$), we did not perform post hoc comparisons for the different time points. And it is worthy of note that the magnitude of the placebo effect was indeed low compared to other studies (varied from –18.9% to +9.8% during treatment). Such low placebo response may indicate the clinical refractoriness of our population, since it has been shown that the severity and therapeutic refractoriness of symptoms do correlate negatively with placebo response (Ruck and Sylven, 2006).

Interestingly, not only the effects of consecutive sessions were cumulative, but they also lasted for at least 24 h as the pain VAS scores for the post-treatment were not significantly different from those of the pre-treatment on the following day (see Fig. 2B) ($p = 0.93$, $p = 0.80$, $p = 0.76$, $p = 0.25$, for the comparisons T1 after/T2 before; T2 after/T3 before; T3 after/T4 before and T4 after/T5 before, respectively) (Fig. 2B).

We compared VAS changes at each time point between sham tDCS and active tDCS. This analysis showed similar results as the comparison of the active tDCS group relative to baseline. The difference between active and sham tDCS treatment became significant after the second session (first session – $p = 0.18$; second session – $p = 0.047$; third session – $p = 0.039$; fourth session – $p = 0.028$; fifth session – $p = 0.004$, corrected for multiple comparisons) and the effects decreased in the last session as there was only a trend for a difference between the two groups at this time ($p = 0.063$).

There were seven responders (reduction of 50% or more in the VAS) in the active tDCS group (63% of patients) and only 1 responder in the sham tDCS group (16%). This difference was marginally significant ($\chi^2 = 3.68$; $p = 0.055$). Interestingly, in the follow-up evaluation; four patients in the active tDCS group were still considered as responders and the only responder in the sham tDCS group reported no longer pain improvement, there was a trend for a significant difference between these two groups at this time point ($\chi^2 = 2.85$; $p = 0.09$).

3.2. Pain control – CGI and PGA

We initially performed repeated-measures ANOVA in which we included two factors: group of treatment (active or sham tDCS) and time of evaluation (day 2, day 3, day 4, day 5, and follow-up). This analysis revealed an effect of group ($F_{(1,75)} = 54.1$; $p < 0.0001$), but not time ($F_{(4,75)} = 0.65$; $p = 0.65$), or interaction

time \times group ($F_{(4,75)} = 1.11$; $p = 0.35$), suggesting that the treatment-related difference in both groups was stable throughout the study (i.e., independent of time). Because these tests do not contemplate baseline values as they measure clinical improvement over time, this might have decreased the power to detect a significant interaction. Thus, we performed an individual repeated-measures ANOVA for the active group only and found a trend toward a significant effect of time ($F_{(4,40)} = 2.38$; $p = 0.068$).

We performed a similar analysis for PGA and obtained similar results. The overall ANOVA for this analysis revealed an effect for group ($F_{(1,75)} = 42.28$; $p < 0.0001$), but not for time ($F_{(4,75)} = 0.88$; $p = 0.48$), or interaction time \times group ($F_{(4,75)} = 0.80$; $p = 0.53$). An individual repeated-measures ANOVA for the active group only revealed a significant effect of time ($F_{(4,40)} = 3.31$; $p = 0.02$), suggesting that there was a significant trend of greater pain reduction (as indexed by PGA) over time in the active tDCS group.

Finally, we performed a post hoc analysis comparing the sham and active tDCS groups at the different time-points. For the CGI, there was a significant difference between active and sham tDCS groups on day 2 ($p = 0.042$), day 3 ($p = 0.017$), day 4 ($p = 0.013$), day 5 ($p = 0.012$), but not in the follow-up ($p = 0.22$). For the PGA, a significant difference was observed only on day 3 ($p = 0.033$) and day 4 ($p = 0.013$); there was a trend for a significant difference on day 5 ($p = 0.07$) and follow-up ($p = 0.1$); but not for day 2 ($p = 0.57$) (see Figs. 3A and B). Note that these tests were not performed for day 1 as they measure the clinical improvement over a period of time.

3.3. Anxiety and depression

For anxiety, we initially performed a repeated-measures ANOVA with two factors: time (day 1, day 2, day 3, day 4, day 5 and follow-up) and group (active and sham tDCS). This analysis revealed a significant effect of time ($F_{(6,105)} = 3.95$; $p = 0.001$), but not of group ($F_{(1,105)} = 0.63$; $p = 0.42$) or the interaction time \times group ($F_{(6,105)} = 0.14$; $p = 0.99$). This result suggests that there was a change of anxiety levels throughout the trial that was similar in both groups (see Fig. 4).

We performed a similar analysis for depression evaluation – BDI scale scores. This analysis showed no significant effect of time ($F_{(2,45)} = 0.20$; $p = 0.82$), group of treatment ($F_{(1,45)} = 0.63$; $p = 0.43$) or interaction term time \times group ($F_{(2,45)} = 0.06$; $p = 0.94$). The mean BDI scores at baseline were 9.3 (± 6.7) in the active tDCS group and 11.3 (± 5.4) in the sham tDCS group and after 5 sessions of treatment they were 8.8 (± 5.4) and 9.5 (± 4.1), respectively.

Although there was no significant effect of the treatment on depression and the effects of tDCS on anxiety

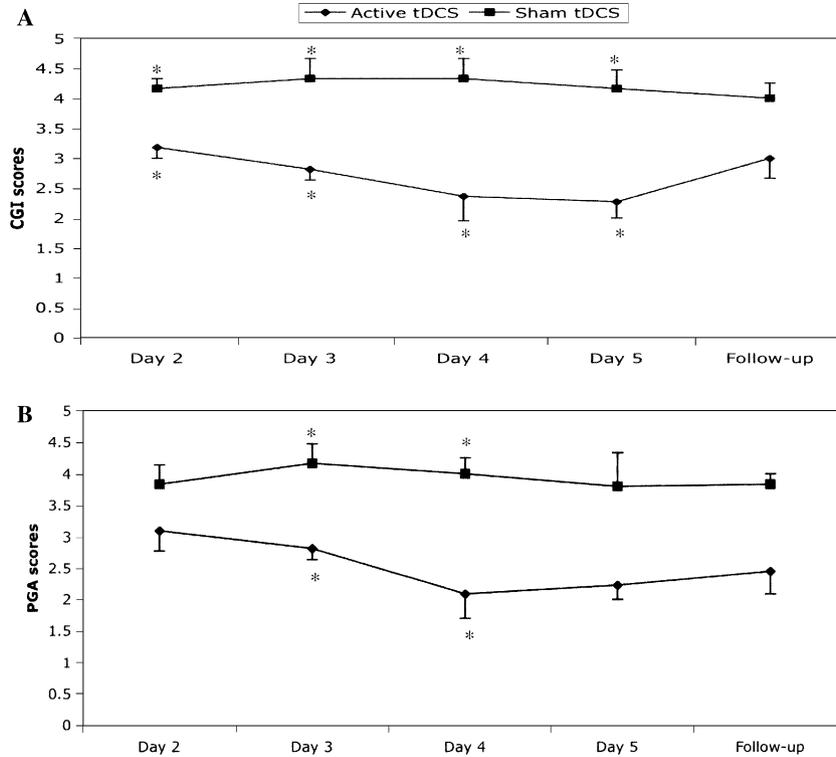


Fig. 3. Pain scores as indexed by Clinician Global Assessment (CGI) and Patient Global Assessment (PGA) throughout the experiment. (A) Shows CGI scores for sham and active treatment groups for each time point and (B) Shows PGA scores for sham and active treatment groups for each time point. * Indicates statistically significant ($p < 0.05$) (sham versus active tDCS group comparison). Each point represents mean CGI or PGA scores \pm SEM (standard error of mean).

were similar in both groups, we calculated two regression models in which pain improvement was the dependent variable in order to further rule out changes in anxiety and mood as confounders for the measured pain improvement. In the first model, we included the following variables: time, group, time \times group, and anxiety (or depression). In the second model (reduced model), we included only time, group, and time \times group. For anxiety this analysis showed that the beta coefficient for the interaction term in the reduced model was 0.69

($p < 0.001$) and the inclusion of the term anxiety did not change it by more than 20% (0.65, $p < 0.001$), showing that anxiety was not confounding our results. For depression, the same analysis showed that the beta coefficient for the interaction term in the reduced model was 0.65 ($p = 0.01$) and the inclusion of the term depression did not change it by more than 20% (0.66, $p = 0.008$), showing that depression was not confounding our results.

Finally it should be noted that the lack of effects of tDCS on depression and anxiety symptoms might be

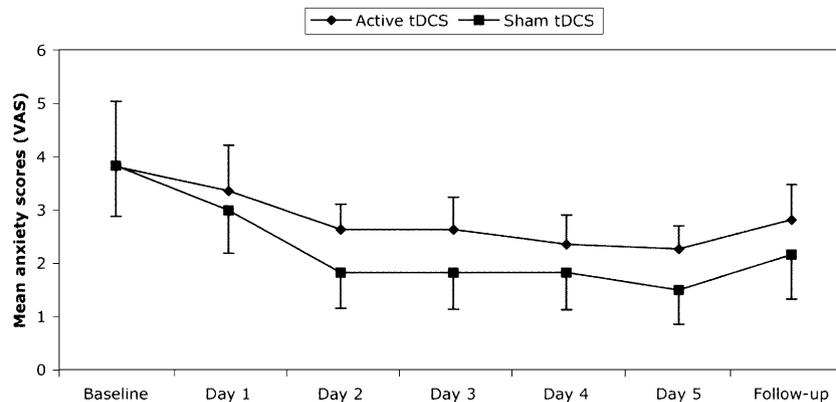


Fig. 4. Anxiety scores (as indexed by visual analogue scale) for sham and active tDCS groups throughout the experiment. Although there was a significant time effect, there was no interaction effect, suggesting a similar improvement in these two groups over time. Each point represents mean VAS scores for anxiety \pm SEM (standard error of mean).

due to the stimulated area (motor cortex) and mild symptoms of both depression and anxiety in this patient group.

3.4. Safety – cognitive and motor evaluation

The analysis for the MMSE showed that there was no significant effect for the main effect of time ($F_{(2,45)} = 0.27$; $p = 0.76$), group of treatment ($F_{(1,45)} = 0.59$; $p = 0.44$) or interaction term time \times group ($F_{(2,45)} = 0.92$; $p = 0.40$), therefore MMSE scores did not change significantly throughout the trial. The mean MMSE scores at baseline were 24.5 (± 2.2) in the active tDCS group and 25.5 (± 3.7) in the sham tDCS group and after five sessions of treatment they were 24.8 (± 2.7) and 26.3 (± 3.6), respectively.

For the Stroop test, we collapsed and averaged the results of performance of the Stroop colors, words, and interference task, as these were similar. A repeated-measures ANOVA with two factors: group (active and sham tDCS) and time (baseline, day 5 and follow-up) showed no significant main effect of group ($F_{(1,45)} = 2.34$; $p = 0.13$), time ($F_{(2,45)} = 0.25$; $p = 0.78$), and the interaction group \times time ($F_{(2,45)} = 0.001$; $p = 0.99$). Interestingly, although there was no significant time effect, both groups showed a negative slope (Fig. 5A) (i.e., a decrease of the execution time over these three time points) indicating a possible learning effect.

For the analysis of the digit span forward and backward (DSF and DSB) performance, we performed a similar analysis. The effects for group of treatment ($F_{(1,45)} = 0.01$; $p = 0.90$ for DSF and $F_{(1,45)} = 1.60$; $p = 0.21$ for DSB), time ($F_{(1,45)} = 0.29$; $p = 0.75$ for DSF and $F_{(1,45)} = 0.26$; $p = 0.77$ for DSB), and the interaction time \times treatment ($F_{(1,45)} = 0.001$; $p = 0.99$ for DSF and $F_{(1,45)} = 0.35$; $p = 0.71$ for DSB) (see Figs. 5B and C) were not significant.

Finally, for the simple reaction time test, we initially performed a repeated-measures ANOVA that showed no significant effect for group of treatment ($F_{(1,30)} = 1.60$; $p = 0.22$), time ($F_{(2,30)} = 0.37$; $p = 0.69$), and the interaction time \times treatment ($F_{(2,30)} = 0.27$; $p = 0.76$) for the right hand, and similar results for the left hand ($F < 1$ for the group, time, and interaction effect) (see Table 3 for the summary results at each time point). Although we did not show a significant difference in motor performance after treatment between the two treatment groups, a respective trend can be seen: whereas there was a motor improvement of 23.6% in the active group, patients in the sham group had a worsening of 2.3% of motor function. The lack of significance may be a result of the small sample size (aggravated by the fact that some patients could not perform this task) and the variance of the baseline motor function across patients.

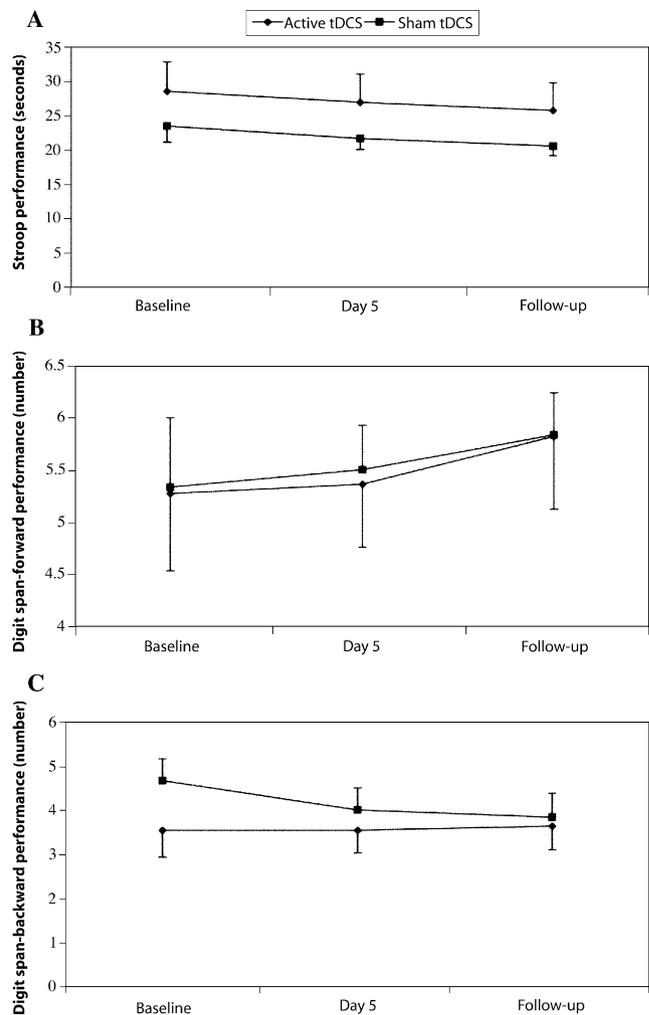


Fig. 5. Cognitive function assessment. (A) Stroop test performance (execution time in seconds) for sham and active tDCS groups throughout the experiment. (B) Digit span forward performance (number of correct sequences) for sham and active tDCS groups throughout the experiment. (C) Digit span backward performance (number of correct sequences) for sham and active tDCS groups throughout the experiment. Each point represents mean test performance \pm SEM (standard error of mean).

3.5. Adverse effects

There was a low incidence of adverse events in both groups of treatment. These adverse events were all mild and consisted of mild headache (three in the active group and one in the sham group) and itching under the electrodes (two in the active group and three in the sham group). Importantly, active tDCS did not worsen pain in any of the patients that received this treatment.

3.6. Correlations – pain improvement and disease characteristics

Although the small sample size of this study limits the investigation of potential predictors associated with a good outcome (for the active tDCS group only), we

Table 3
Cognitive and motor tests performance

	Active TDCS			Sham TDCS		
	Baseline	Day 5	Follow-up	Baseline	Day 5	Follow-up
Stroop ^a	28.5 (14.2)	26.9 (13.6)	25.6 (13.9)	23.4 (5.7)	21.6 (3.9)	20.5 (3.4)
Digits span – forward ^b	5.3 (2.5)	5.4 (2.0)	5.8 (2.3)	5.3 (1.6)	5.5 (1.0)	5.8 (1.0)
Digits span – backward ^b	3.5 (1.6)	3.5 (1.7)	3.6 (1.8)	4.6 (1.5)	4 (1.3)	3.8 (1.3)
sRT right hand ^c	605.9 (250.1)	463.1 (191.5)	459.1 (169.2)	405 (45.7)	414.4 (26.2)	375.4 (61.7)
sRT left hand ^c	529.3 (175.5)	424.5 (144.2)	445.9 (197.9)	419.5 (56.6)	412.8 (38.5)	395.7 (89.6)

^a Stroop (mean of Stroop colors, words and interference – in seconds).

^b Number of correct sequences.

^c sRT – simple reaction time (ms).

performed correlation analysis for some characteristics of the disease. This analysis revealed a significant negative correlation between pain improvement and duration of disease ($r = -0.66$, $p = 0.025$) – which suggests that the shorter the disease duration, the larger is the pain improvement. Pain improvement and baseline VAS scores did not correlate significantly ($r = -0.11$, $p = 0.74$) (Fig. 6). To compare the categorical variables with pain improvement, we dichotomized patients in two groups and compared whether the mean pain reduction was different between both groups. This analysis revealed that patients with pain paroxysms (compared to continuous pain only) had a significantly greater reduction in their pain scores ($\Delta = 4.74 \pm 0.95$ versus $\Delta = 1.12 \pm 1.54$, respectively, $p = 0.005$). In addition, pain in the lower limbs and thoracic and lumbar lesions were significantly associated with better outcome compared to pain in the upper limbs/back pain and cervical lesions ($\Delta = 4.79 \pm 0.83$ versus $\Delta = 1.1 \pm 1.3$, respectively, $p = 0.0006$, for the comparison of pain location and $\Delta = 4.99 \pm 1.00$ versus $\Delta = 1.16 \pm 1.09$, respectively, $p = 0.024$ for the comparison of lesion site). More-

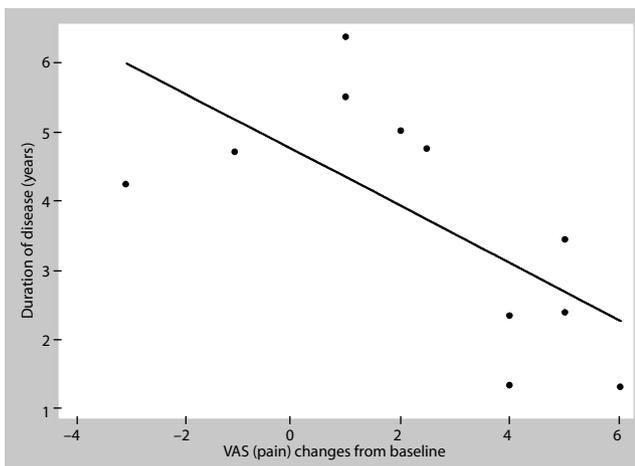


Fig. 6. Correlation between pain changes (as indexed by VAS) scores and duration of spinal cord injury. Note that there was a negative correlation between these variables, such as that patients with shorter duration of disease had a better outcome (more pain reduction).

over, there was no significant difference in pain improvement between the groups of patients with complete lesion versus patients with incomplete lesion (Frankel classification, $p = 0.27$).

Because carbamazepine might decrease the effects of anodal stimulation after a single session of tDCS (Liebetanz et al., 2002), we did a subanalysis in which we divided patients by use of antiepileptic drugs (carbamazepine (two patients); gabapentine (two patients) and no antiepileptic drugs (seven patients)). Although there was a difference in the magnitude of the effects across the three groups (mean pain reduction of 36.7%, 62.9%, and 74.1%, respectively), they were not significantly different (perhaps due to the small sample size of the subgroups). However, this result might suggest that patients with carbamazepine may respond less to this treatment.

4. Discussion

4.1. Pain improvement

Previous studies showed that high-frequency rTMS – another technique of non-invasive brain stimulation – is also associated with a significant pain improvement compared to sham stimulation (Lefaucheur et al., 2001, 2004; Pleger et al., 2004; Khedr et al., 2005). Interestingly the attempt of the use of inhibitory low-frequency motor cortex rTMS (1 Hz) for pain control in these patients did not result in pain alleviation (Lefaucheur et al., 2004). Based on these studies, it has been proposed that an increase of the local excitability of the motor cortex might be associated with pain control in patients with central pain. The mechanism of tDCS to reduce pain in our patients might be similar, because anodal tDCS is also associated with an increase of cortical excitability that lasts beyond the stimulation period (Nitsche and Paulus, 2001; Nitsche et al., 2003a). However, the mechanisms responsible to increase cortical excitability might be different between tDCS and rTMS as tDCS induces a weak continuous electric current and rTMS (and also epidural stimulation) induces repetitive pulses of electrical current at near threshold intensities. It has been proposed that tDCS induces a change in

the electrical properties of the neuronal membrane that can result in a hyperpolarization or depolarization of the stimulated area (Nitsche et al., 2005); while repetitive stimulation induced by rTMS induces a change in the synaptic strengthening efficacy through mechanisms of long-term potentiation and depression (Huang et al., 2005). The main difference with regard to the after-effects of both techniques might be that tDCS induces a more widespread and long-lasting effect compared to rTMS (Nitsche and Paulus, 2001; Romero et al., 2002; Lang et al., 2005). However, both techniques might lead to a similar indirect change of activity of connected areas and thus result in similar effects on pain.

Up-regulation of motor cortex excitability might modulate pain perception through indirect effects on pain-modulating areas, such as thalamic nuclei. Indeed, a change of the thalamic and subthalamic nuclei activity is associated with epidural stimulation of the motor cortex (Peyron et al., 1995; Garcia-Larrea et al., 1997, 1999), TMS (Strafella, 2004) and tDCS (Lang et al., 2005). Garcia-Larrea et al. (1997) proposed a model in which thalamic nuclei activation would lead to several events in other pain-related structures, such as the anterior cingulate, periaqueductal gray, and spinal cord that could ultimately modulate the affective-emotional component of pain and also inhibit pain impulses from spinal cord (Garcia-Larrea et al., 1997, 1999).

An important consideration is the functional reorganization of the motor cortex after spinal cord injury. Two studies showed a significant correlation between changes in the motor cortical representation and phantom limb pain (Flor et al., 1998; Karl et al., 2001). If such plastic changes following deafferentation are causally involved with chronic pain, then somatotopic stimulation would be advantageous. However, the current clinical data are paradoxical. Whereas the best stimulation site using rTMS for pain control is not the area corresponding to the painful zone (but the adjacent one) (Lefaucheur et al., 2004), for epidural stimulation, a study with 32 patients showed the most efficacious position of the stimulating electrodes was the one corresponding to the cortical somatotopic representation of pain perception (Nguyen et al., 1999). For tDCS, due to the large electrode size, it is likely that it induced a modulation over a large area of the motor cortex that encompassed both the area corresponding to the pain and the adjacent area (see Fig. 1). Further studies are needed to explore whether smaller electrodes with somatotopically guided stimulation might optimize the analgesic effect of tDCS.

Compared to previous studies that used brain stimulation for the treatment of chronic pain, the magnitude of our results (mean pain response of 58%) is superior to that of other similar rTMS studies that report mean pain relief that ranges from 20 to 45% (Lefaucheur et al., 2001; Khedr et al., 2005); however, when analyz-

ing the response rate, it is a little inferior than Khedr's study (63% versus 75%) – that had the largest response rate. Regarding the long-lasting effect, only one study investigated the effects of five consecutive sessions of rTMS – Khedr's study. The comparison of long-lasting effects between Khedr's and our study showed similar results: our study reports a mean pain reduction of 37% in the follow-up evaluation – that is similar to the 40% decrease in Khedr's study. Although there is a difference in the percentage of pain responders (36% versus 61%, ours and Khedr's study, respectively), this might be a result of the different criteria of pain responders between these studies (i.e., whereas the threshold for responders was set at 50% in our study, this was 40% in Khedr's study). Finally, compared to epidural stimulation, tDCS may result in a smaller treatment effect (our study showed 58% mean pain decrease and 63% of responders versus surgical approach that showed 28–70% of mean pain reduction and 50–80% of responders). The main reason for this difference is that the effects of five sessions of tDCS are likely to have a shorter impact on brain activity than what is achieved using direct motor cortex stimulation with epidural electrodes for several months. Although there is a difference in the magnitude of the pain improvement across these different techniques of brain stimulation, previous data suggest that patients that respond to epidural stimulation also respond to noninvasive brain stimulation with rTMS (Migita et al., 1995; Canavero et al., 2002). Further studies should also test whether tDCS treatment can be a predictor to the effects of epidural stimulation for the treatment of pain.

One interesting finding of previous studies is the relationship between sensory changes and therapeutic improvement after motor cortex stimulation (Drouot et al., 2002; Brown and Pilitsis, 2005), however, we did not find a significant relationship between pain improvement and sensory deficits (as defined by Frankel classification) – one of the reasons might be because of the small sample size of this study and low number of patients with some degree of intact sensory function (three in the active and three in the sham tDCS group).

4.2. Safety – cognitive and motor evaluation

Because tDCS has been only recently tested for clinical applications, such as stroke (Fregni et al., 2005a; Hummel et al., 2005) and depression (Fregni et al., *in press-a*), the impact of consecutive sessions of motor cortex tDCS (at the intensity of 2 mA) on cognition and specifically on the motor function is not yet fully known. Our findings show no significant cognitive and motor performance change in either group after the treatment with sham or active tDCS.

These results are in line with the study by Iyer et al. (2005) on the safety of tDCS. In this study, the authors

tested the safety of tDCS using a neurocognitive battery and motor tests (simple reaction test and Pegboard Grooved test). The authors did not find any significant cognitive or motor deterioration with tDCS application, on the contrary, they found a significant improvement of verbal fluency after stimulation with anodal tDCS over the prefrontal cortex. They are also in accordance with other safety studies using related stimulation protocols, where no change of serum neurone specific enolase concentration – a sensitive marker of neuronal damage, no disturbances of the blood–brain-barrier and no cerebral edemas were found (Nitsche and Paulus, 2001; Nitsche et al., 2003a, 2004). The results of our study, therefore, add more safety information as we showed that there was no cognitive or motor function worsening after five consecutive days of 2 mA motor cortex anodal stimulation. To our knowledge, this parameter of stimulation (2 mA for 5 consecutive days) is the highest dose of tDCS applied in clinical trials thus far (higher than our depression study that used 1 mA of tDCS over 5 consecutive days) (Fregni et al., in press-a). However, we did not measure other safety parameters such as brain activity using electroencephalogram and therefore our safety data should be interpreted as a preliminary safety evidence.

4.3. Limitations

This study has some limitations that should be discussed. Although we selected patients with central pain due to traumatic spinal injuries only, the localization of the lesion and etiology of trauma differed across patients and our sample size might not have been large enough to detect characteristics associated with a positive outcome. Second, a potential limitation was the fact that patients were allowed to change their medication regimen throughout the trial; however, we did not detect a significant change in the use of these medications, perhaps due to the fact that most of the patients were taking drugs with chronic effects such as antidepressants. Therefore, medication change did not confound our results.

Acknowledgments

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References

- Antal A, Nitsche MA, Paulus W. External modulation of visual perception in humans. *Neuroreport* 2001;12:3553–5.
- Barros Filho TE, Taricco MA, Oliveira RP, Greve JM, Santos LC, Napoli MM. Epidemiological study of patients with spinal cord injuries and neurologic deficit, admitted to the Institute of Orthopedics and Traumatology at the Hospital das Clinicas of the School of Medicine of the University of Sao Paulo. *Rev Hosp Clin Fac Med Sao Paulo* 1990;45:123–6.
- Bolton JE, Wilkinson RC. Responsiveness of pain scales: a comparison of three pain intensity measures in chiropractic patients. *J Manipulative Physiol Ther* 1998;21:1–7.
- Bonica JJ. Introduction: semantic, epidemiologic, and educational issuers. In: Casey KL, editor. *Pain and central nervous system disease: the central pain syndromes*. New York: Raven Press; 1991.
- Brown JA, Pilitis JG. Motor cortex stimulation for central and neuropathic facial pain: a prospective study of 10 patients and observations of enhanced sensory and motor function during stimulation. *Neurosurgery* 2005;56:290–7. discussion 290–7.
- Canavero S, Bonicalzi V, Dotta M, Vighetti S, Asteggiano G, Cocito D. Transcranial magnetic cortical stimulation relieves central pain. *Stereotact Funct Neurosurg* 2002;78:192–6.
- Carroll D, Joint C, Maartens N, Shlugman D, Stein J, Aziz TZ. Motor cortex stimulation for chronic neuropathic pain: a preliminary study of 10 cases. *Pain* 2000;84:431–7.
- Drouot X, Nguyen JP, Peschanski M, Lefaucheur JP. The antalgic efficacy of chronic motor cortex stimulation is related to sensory changes in the painful zone. *Brain* 2002;125:1660–4.
- Ebel H, Rust D, Tronnier V, Boker D, Kunze S. Chronic precentral stimulation in trigeminal neuropathic pain. *Acta Neurochir (Wien)* 1996;138:1300–6.
- Flor H, Elbert T, Muhlnickel W, Pantev C, Wienbruch C, Taub E. Cortical reorganization and phantom phenomena in congenital and traumatic upper-extremity amputees. *Exp Brain Res* 1998;119:205–12.
- Fregni F, Boggio PS, Mansur CG, Wagner T, Ferreira MJ, Lima MC, et al. Transcranial direct current stimulation of the unaffected hemisphere in stroke patients. *Neuroreport* 2005a;16:1551–5.
- Fregni F, Boggio PS, Nitsche M, Berman F, Antal A, Feredoes E, et al. Anodal transcranial direct current stimulation of prefrontal cortex enhances working memory. *Exp Brain Res* 2005b;166:23–30.
- Fregni F, Boggio PS, Nitsche M, Marcolin MA, Rigonatti SP, Pascual-Leone A. Treatment of major depression with transcranial direct current stimulation. *Bipolar Disord*, in press.
- Fregni F, Thome-Souza S, Nitsche M, Freedman SD, Valente KD, Pascual-Leone A. A controlled clinical trial of cathodal DC polarization in patients with refractory epilepsy. *Epilepsia* 2006;47:335–42.
- Garcia-Larrea L, Peyron R, Mertens P, Gregoire MC, Lavenne F, Bonnefoi F, et al. Positron emission tomography during motor cortex stimulation for pain control. *Stereotact Funct Neurosurg* 1997;68:141–8.
- Garcia-Larrea L, Peyron R, Mertens P, Gregoire MC, Lavenne F, Le Bars D, et al. Electrical stimulation of motor cortex for pain control: a combined PET-scan and electrophysiological study. *Pain* 1999;83:259–73.
- Helsinki, 1964. <http://www.wma.net/e/policy/b3.htm>.
- Herregodts P, Stadnik T, De Ridder F, D'Haens J. Cortical stimulation for central neuropathic pain: 3-D surface MRI for easy determination of the motor cortex. *Acta Neurochir Suppl* 1995;64:132–5.
- Huang YZ, Edwards MJ, Rounis E, Bhatia KP, Rothwell JC. Theta burst stimulation of the human motor cortex. *Neuron* 2005;45:201–6.

- Hummel F, Celnik P, Giraux P, Floel A, Wu WH, Gerloff C, et al. Effects of non-invasive cortical stimulation on skilled motor function in chronic stroke. *Brain* 2005;128:490–9.
- Iyer MB, Mattu U, Grafman J, Lomarev M, Sato S, Wassermann EM. Safety and cognitive effect of frontal DC brain polarization in healthy individuals. *Neurology* 2005;64:872–5.
- Karl A, Birbaumer N, Lutzenberger W, Cohen LG, Flor H. Reorganization of motor and somatosensory cortex in upper extremity amputees with phantom limb pain. *J Neurosci* 2001;21:3609–18.
- Khedr EM, Kotb H, Kamel NF, Ahmed MA, Sadek R, Rothwell JC. Long lasting antalgic effects of daily sessions of repetitive transcranial magnetic stimulation in central and peripheral neuropathic pain. *J Neurol Neurosurg Psychiatr* 2005;76:833–8.
- Lang N, Siebner HR, Ward NS, Lee L, Nitsche MA, Paulus W, et al. How does transcranial DC stimulation of the primary motor cortex alter regional neuronal activity in the human brain? *Eur J Neurosci* 2005;22:495–504.
- Lefaucheur JP, Drouot X, Keravel Y, Nguyen JP. Pain relief induced by repetitive transcranial magnetic stimulation of precentral cortex. *Neuroreport* 2001;12:2963–5.
- Lefaucheur JP, Drouot X, Menard-Lefaucheur I, Zerah F, Bendib B, Cesaro P, et al. Neurogenic pain relief by repetitive transcranial magnetic cortical stimulation depends on the origin and the site of pain. *J Neurol Neurosurg Psychiatr* 2004;75:612–6.
- Liebetanz D, Nitsche MA, Tergau F, Paulus W. Pharmacological approach to the mechanisms of transcranial DC-stimulation-induced after-effects of human motor cortex excitability. *Brain* 2002;125:2238–47.
- Migita K, Uozumi T, Arita K, Monden S. Transcranial magnetic coil stimulation of motor cortex in patients with central pain. *Neurosurgery* 1995;36:1037–9. discussion 1039–40.
- Nguyen JP, Lefaucheur JP, Decq P, Uchiyama T, Carpentier A, Fontaine D, et al. Chronic motor cortex stimulation in the treatment of central and neuropathic pain. Correlations between clinical, electrophysiological and anatomical data. *Pain* 1999;82:245–51.
- Nicholson BD. Evaluation and treatment of central pain syndromes. *Neurology* 2004;62:S30–6.
- Nitsche MA, Paulus W. Sustained excitability elevations induced by transcranial DC motor cortex stimulation in humans. *Neurology* 2001;57:1899–901.
- Nitsche MA, Liebetanz D, Antal A, Lang N, Tergau F, Paulus W. Modulation of cortical excitability by weak direct current stimulation—technical, safety and functional aspects. *Suppl Clin Neurophysiol* 2003a;56:255–76.
- Nitsche MA, Schauenburg A, Lang N, Liebetanz D, Exner C, Paulus W, et al. Facilitation of implicit motor learning by weak transcranial direct current stimulation of the primary motor cortex in the human. *J Cogn Neurosci* 2003b;15:619–26.
- Nitsche MA, Niehaus L, Hoffmann KT, Hengst S, Liebetanz D, Paulus W, et al. MRI study of human brain exposed to weak direct current stimulation of the frontal cortex. *Clin Neurophysiol* 2004;115:2419–23.
- Nitsche MA, Seeber A, Frommann K, Klein CC, Rochford C, Nitsche MS, et al. Modulating parameters of excitability during and after transcranial direct current stimulation of the human motor cortex. *J Physiol* 2005;568:291–303.
- Nuti C, Peyron R, Garcia-Larrea L, Brunon J, Laurent B, Sindou M, et al. Motor cortex stimulation for refractory neuropathic pain: four year outcome and predictors of efficacy. *Pain* 2005;118:43–52.
- Peto R. Clinical trial methodology. *Biomedicine* 1978;28:24–36.
- Peyron R, Garcia-Larrea L, Deiber MP, Cinotti L, Convers P, Sindou M, et al. Electrical stimulation of precentral cortical area in the treatment of central pain: electrophysiological and PET study. *Pain* 1995;62:275–86.
- Pleger B, Janssen F, Schwenkreis P, Volker B, Maier C, Tegenthoff M. Repetitive transcranial magnetic stimulation of the motor cortex attenuates pain perception in complex regional pain syndrome type I. *Neurosci Lett* 2004;356:87–90.
- Pocock SJ. Allocation of patients to treatment in clinical trials. *Biometrics* 1979;35:183–97.
- Romero JR, Anshel D, Sparing R, Gangitano M, Pascual-Leone A. Subthreshold low frequency repetitive transcranial magnetic stimulation selectively decreases facilitation in the motor cortex. *Clin Neurophysiol* 2002;113:101–7.
- Ruck A, Sylven C. “Improvement” in the placebo group could be due to regression to the mean as well as to sociobiologic factors. *Am J Cardiol* 2006;97:152–3.
- Strafella AP, Vanderwerf Y, Sadikot AF. Transcranial magnetic stimulation of the human motor cortex influences the neuronal activity of subthalamic nucleus. *Eur J Neurosci* 2004;20(8):2245–9.
- Tsubokawa T, Katayama Y, Yamamoto T, Hirayama T, Koyama S. Chronic motor cortex stimulation in patients with thalamic pain. *J Neurosurg* 1993;78:393–401.
- van Belle G, Uhlmann RF, Hughes JP, Larson EB. Reliability of estimates of changes in mental status test performance in senile dementia of the Alzheimer type. *J Clin Epidemiol* 1990;43:589–95.
- Wallace BA, Ashkan K, Benabid AL. Deep brain stimulation for the treatment of chronic, intractable pain. *Neurosurg Clin N Am* 2004;15:343–57. vii.