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A Randomized, Sham-Controlled, Proof of Principle Study of Transcranial Direct Current Stimulation for the Treatment of Pain in Fibromyalgia

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Objective. **Recent evidence suggests that fibromyalgia is a disorder characterized by dysfunctional brain activity. Because transcranial direct current stimulation (tDCS) can modulate brain activity noninvasively and can decrease pain in patients with refractory central pain, we hypothesized that tDCS treatment would result in pain relief in patients with fibromyalgia.**

Methods. **Thirty-two patients were randomized to receive sham stimulation or real tDCS with the anode centered over the primary motor cortex (M1) or the dorsolateral prefrontal cortex (DLPFC) (2 mA for 20 minutes on 5 consecutive days). A blinded evaluator rated the patient's pain, using the visual analog scale for pain, the clinician's global impression, the patient's global assessment, and the number of tender points. Other symptoms of fibromyalgia were evaluated using the Fibromyalgia Impact Questionnaire and the Short Form 36 Health Survey. Safety was assessed with a battery of neuropsychological tests. To assess potential confounders, we measured mood and anxiety changes throughout the trial.**

Results. **Anodal tDCS of the primary motor cortex induced significantly greater pain improvement compared with sham stimulation and stimulation of the DLPFC ($P < 0.0001$). Although this effect decreased after treatment ended, it was still significant after 3 weeks of followup ($P = 0.004$). A small positive impact on quality of life was observed among patients who received anodal M1 stimulation. This treatment was associated with a few mild adverse events, but the frequency of these events in the active-treatment groups was similar to that in the sham group. Cognitive changes were similar in all 3 treatment groups.**

Conclusion. **Our findings provide initial evidence of a beneficial effect of tDCS in fibromyalgia, thus encouraging further trials.**

Recent evidence has shown that fibromyalgia is associated with specific changes in brain activity. In a recent single-photon–emission computed tomography study, patients with fibromyalgia (as compared with healthy controls) showed a decrease in regional cerebral blood flow in the thalamus, caudate nucleus, and pontine tegmentum (1). In addition, it has long been demonstrated that antidepressants, such as tricyclic agents, improve pain in fibromyalgia (2), and recent studies suggest that centrally acting drugs such as dopaminergic drugs are effective in alleviating the symptoms of fibromyalgia, as compared with placebo (3).

In this context of brain dysfunction, techniques for neuromodulation could be a beneficial approach for this group of patients. In fact, results of several studies have shown that motor cortex stimulation with epidural electrodes or with repetitive transcranial magnetic stim-

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ulation (rTMS) is effective in reducing pain in patients with central pain refractory to treatment (4–9), with response rates in the range of 40–80%.

We recently showed that another noninvasive technique for brain stimulation, transcranial direct current stimulation (tDCS), is effective in reducing pain that is refractory to medical treatment in patients with spinal cord injury (10). During tDCS, a weak DC current is injected into the brain for several minutes, resulting in a polarity-dependent modulation of brain activity. Studies in humans have demonstrated that stimulation of the motor cortex changes motor cortex excitability according to the stimulation polarity; whereas anodal stimulation increases cortical excitability, cathodal stimulation decreases it (11,12). Similar modulatory effects have also been described in the visual cortex (13). Stimulation of other cortical areas can result in clinical and behavioral changes (14). Transcranial DCS has some advantages, because it is easily applied and safe, and is reliably blinded by sham tDCS in the setting of clinical trials (15).

Taken together, all of this evidence suggests that tDCS might be a beneficial therapeutic tool for fibromyalgia, given the underlying pathophysiology of this condition. In addition, because many patients with fibromyalgia fail to respond to the available treatments, there is an enormous unmet clinical need for the development of new therapeutic approaches for this condition (16). Therefore, we conducted tests to determine whether active stimulation of the primary motor cortex or the dorsolateral prefrontal cortex (DLPFC) is associated with a clinical benefit (i.e., reduction of pain and other symptoms of fibromyalgia) as compared with sham stimulation. In addition, we collected preliminary data on safety. The primary motor cortex and the DLPFC were chosen as targets, because stimulation of the primary motor cortex induces a significant analgesic effect (10,17), and stimulation of the DLPFC is associated with a significant antidepressant effect (18).

PATIENTS AND METHODS

Patients. Thirty-two female patients (mean ± SD age 53.4 ± 8.9 years) participated in this study. Patients were selected from a specialized outpatient service. We selected only female patients who had an established diagnosis of fibromyalgia according to the 1990 criteria of the American College of Rheumatology (19). In addition, patients had to have a mean pain score ≥4 on a 10-point visual analog scale (VAS) during the 2 weeks preceding the clinical trial and a total tender point score of ≥20 (scale 0–72). We excluded patients with any uncontrolled clinical disease (as evaluated by each patient's clinician), such as thyroid, cardiovascular, pulmonary, hematologic, or renal disease, alcohol/substance abuse, pregnancy, lactation, and neuropsychiatric disorders. Patients were carefully evaluated by a licensed neurologist before the trial. Given the safety record of tDCS to date (20), no specific exclusion criteria needed to be applied.

Patients who were receiving medication for pain were not excluded. We selected patients with moderate to severe pain and thought that it would be unethical to ask them to discontinue taking analgesics and maintain them without pharmacologic treatment for several weeks. However, we required that the patients received stable doses of analgesics for at least 2 months prior to the beginning of the study, and we analyzed whether medications confounded the effects of this treatment. The inclusion of the sham group also controlled for this potential confounder.

This study was performed according the principles of the Declaration of Helsinki (see World Medical Association Declaration of Helsinki; online at http://www.wma.net/e/policy/b3.htm) and was approved by the internal review board as part of a large study to evaluate the effects of tDCS in chronic pain. Written informed consent was obtained from all participants prior to entering the study. This study was performed at the Institute of Psychiatry, University of Sao Paulo.

Study design. The study had 3 phases, as follows: 1) a 2-week observation period during which baseline levels of pain were established, 2) a period of double-blinded treatment, during which patients received daily treatment with sham tDCS, tDCS of the primary motor cortex, or tDCS of the DLPFC for 5 consecutive days, and 3) a 21-day followup period.

During the baseline period, patients were randomized at a ratio of 1:1:1 to receive sham tDCS (sham group), active tDCS of the primary motor cortex (M1 group), or active tDCS of the left DLPFC (DLPFC group). The primary motor cortex was chosen because extensive literature shows that stimulation (either invasive or noninvasive) of this area is associated with pain improvement (7–9,17,21,22). The left DLPFC was chosen because several studies of rTMS, as well as studies of tDCS, have shown that stimulation of this area is associated with improvement of depression (18,23) and, thus, might have similar mechanisms of action as compared with antidepressants (particularly tricyclic antidepressants), which also induce an analgesic effect in fibromyalgia. Randomization was performed using the order of entry into the study and a previous computer-generated randomization list, using random blocks of 6 patients (for each 6 patients, 2 were randomized to each group) in order to minimize the risk of unbalanced group sizes.

Furthermore, at baseline, we evaluated demographic and clinical characteristics such as baseline pain, sleep characteristics, and body mass index (BMI). We used these data to provide descriptive characteristics of our population and also to analyze whether the patients' characteristics could be predictive of the outcome. All of the assessments were conducted by raters who were blinded to the treatment arm.

Clinical assessments. Pain was measured with a VAS for pain (17), a VAS for analgesic use (17), clinician global impression (CGI) and patient global assessment (PGA) (17), and the number of tender points (24). Although both the CGI and the PGA measure the effects of treatment on a 7-point scale ranging from "much worse" to "much improved," the

CGI is scored by a clinician after a clinical interview and thus is based on the clinician's past experience, while the PGA is scored directly by the patient based on his or her subjective perception of pain.

Quality-of-life and other domains of fibromyalgia were measured using the Fibromyalgia Impact Questionnaire (FIQ) (online at http://www.myalgia.com/FIQ/FIQ.htm) and the acute form of the Short Form 36 Health Survey (SF-36) (online at http://www.sf-36.org). Psychiatric symptoms were assessed with the Beck Depression Inventory (BDI) and a VAS for anxiety (17). Cognition and safety were evaluated by the Mini-Mental State Examination, the Stroop test, digit span forward and backward, and simple reaction time (for review, see ref. 17).

Finally, we monitored adverse events by asking patients, after each session of stimulation and during the followup period, whether they had experienced any adverse event and the relationship of these events to treatment with tDCS.

Direct current stimulation. Direct current was transferred by a pair of saline-soaked surface sponge electrodes (35 cm^2) and delivered by a specially developed battery-driven constant current stimulator (for details, contact Sergio A. Boggio at sboggio@colband.com.br) with a maximum output of 10 mA. This device has a special feature that makes it particularly reliable for double-blind trials and was developed by our group, because we noted in our previous trials that patients try to look at the tDCS display during stimulation and encountered situations in which we had to hide the device from patients receiving sham treatment. We therefore incorporated a switch in the back of the tDCS device that could be activated by the researcher to interrupt the electrical current while maintaining the display "on" and displaying the parameters of stimulation throughout the procedure.

As previously mentioned, patients were randomized to receive 1 of 3 different types of treatment. Patients in the M1 group underwent anodal stimulation of the primary motor cortex. The anode electrode was placed over the C3 position (using the 10/20 system of electrode placement), and the cathode electrode was placed over the contralateral supraorbital area, similar to the montage of our recent study of tDCS in neuropathic pain (17). Patients in the DLPFC group underwent anodal stimulation of the left DLPFC. The anode electrode was placed over the F3 position (using the 10/20 system). This method of DLPFC localization was used previously in TMS studies (25) and has been confirmed by neuronavigation techniques as a relatively accurate method of localization (26). The cathode was placed over the contralateral supraorbital area, similar to the montage of our recent study of tDCS in depression (18). Patients in the sham group received sham stimulation of the primary motor cortex. The electrodes were placed in the same positions as for anodal M1 stimulation, but the stimulator was turned off after 30 seconds of stimulation. Therefore, patients in the sham group felt the initial itching sensation but received no current for the rest of the stimulation period. A recent study showed that this method of sham stimulation is reliable (14).

A constant current of 2-mA intensity was applied for 20 minutes. Stimulation with 2 mA (for a single session) has been shown to be safe in healthy volunteers (27). In addition, we previously observed that these parameters were safe and effective in patients with neuropathic pain (17).

Statistical analysis. Analyses were performed with SAS statistical software, version 9.1 (Cary, NC). We used a mixed linear model to analyze changes in pain throughout the trial. The advantage of use of linear models rather than analysis of variance (ANOVA) is that time can be analyzed as a continuous (rather than a categorical) variable in the linear models. We modeled change in pain on a VAS using the covariates of time, group, and interaction between group and time. Because in longitudinal data the variability of within-individual differences is always smaller than the variability of between-individual differences, the correlation (covariance) of the repeated measures within each patient was also modeled. Using Akaike's information criterion ([–2] $\times$ natural log of the likelihood + 2 $\times$ number of parameters tested under the model) to compare models with different covariance matrices, we chose the compound symmetry matrix.

For the other end points measuring pain (number of tender points, the CGI, and the PGA), quality of life (the FIQ and the SF-36), safety (the Stroop test, the Mini-Mental State Examination, digit span), and psychiatric symptoms (the BDI and the VAS for anxiety), we used a repeated-measures ANOVA in which the dependent variable was one of the variables listed previously and the independent variables were group (sham and active tDCS), time of treatment (baseline, day 5, and followup), and interaction group versus time. We used ANOVA for these other end points because there were fewer time points (baseline, day 5, and followup) for these variables, and therefore the use of time as a categorical variable was not problematic. When appropriate, post hoc comparisons were performed using Bonferroni adjustments.

Using Pearson's correlation coefficient, we tested, in a exploratory manner, whether there was a correlation between changes in pain (as measured on a VAS) and the variables age, medications (selective serotonin reuptake inhibitors [SSRIs], tricyclic antidepressants, nonsteroidal antiinflammatory drugs [NSAIDs], benzodiazepines, and neuroleptics), duration of pain, sleep (as measured on a VAS), fatigue (as measured on a VAS), BMI, and baseline scores of depression (the BDI), pain (as measured on a VAS), anxiety (as measured on a VAS), tender points, and the FIQ.

One patient (in the M1 group) withdrew, and the few missing data were considered to be missing at random. We analyzed data using the intent-to-treat method and the conservative last observation carried forward approach. *P* values (2-tailed) less than 0.05 were considered significant.

RESULTS

Eleven patients were randomized to each group receiving active tDCS (M1 or DLPFC), and 10 patients were assigned to the group receiving sham tDCS. The patients were not significantly different in terms of baseline demographic, clinical, and pain characteristics (Table 1).

Only 1 patient withdrew from the study. This patient, who was in the M1 group, withdrew after the second session of stimulation, because of the development of mild, transient (only a couple of minutes)

Table 1. Baseline characteristics of patients randomized to receive tDCS*

	DLPFC	M1	Sham
Age, years	54.2 ± 7.4	54.8 ± 9.3	50.8 ± 10.2
BMI, kg/m^2	28.9 ± 7.4	27.3 ± 6.5	26.3 ± 4.4
Pain VAS score (0–10 scale)	8.0 ± 1.6	8.5 ± 1.4	7.5 ± 1.9
Pain duration, years	8.4 ± 9.3	10.0 ± 7.8	8.1 ± 7.5
Tender points (0–72 scale), total	46.0 ± 10.6	48.9 ± 8.9	47.7 ± 8.3
BDI score (0–63 scale)	17.8 ± 8.7	19.9 ± 8.2	20.7 ± 8.1
MMSE score (0–30 scale)	24.6 ± 2.5	27.1 ± 2.4	26.3 ± 2.6
Fatigue VAS score (0–10 scale)	7.8 ± 1.6	8.8 ± 1.6	8.4 ± 1.8

* Values are the mean ± SD. P not significant for all comparisons. tDCS = transcranial direct current stimulation; DLPFC = dorsolateral prefrontal cortex; M1 = primary motor cortex; BMI = body mass index; VAS = visual analog scale, BDI = Beck Depression Inventory; MMSE = Mini-Mental State Examination.

redness and itching at the site of stimulation. Despite our reassurance, the patient was concerned that this reaction could worsen. Aside from this episode, patients tolerated the tDCS treatments well, and few adverse effects occurred. The most frequent adverse effects were sleepiness (1 patient in the DLPFC group [9%], 3 patients in the M1 group [27%], and 1 patient in the sham group [10%]) and headache (1 patient in the DLPFC group [9%], 3 patients in the M1 group [27%], and 2 patients in the sham group [20%]).

Patients were treated according to the guidelines of the local outpatient service. Seventy-two percent of the patients received NSAIDs, 28% received benzodiazepines, 25% received SSRIs, and 22% received tricyclic antidepressants. There were no significant differences across treatment groups regarding medication use. Importantly, medication intake remained constant throughout the trial.

Assessment of pain. In order to assess pain (as indexed by the VAS), we initially ran a mixed linear model (using empirical variance) considering time as a categorical variable. The type 3 fixed-effects test revealed a significant effect of time ($F[2,290] = 15.35$, $P < 0.0001$), group ($F[2,29] = 5.98$, $P = 0.007$), and the interaction term time versus group ($F[20,290] = 4.10$, $P < 0.0001$). Although the nonparametric model is better for explaining our data (because the Akaike's information criterion is smaller in this model as compared with the model using time as a continuous variable [1,344.7 and 1,465.3, respectively]), we used the parametric model to compare the slopes for the 3 groups, i.e., to evaluate whether the slopes (pain changes over time) were different across the 3 groups (M1, DLPFC, and sham). Compared with the slope for the sham group, the slope for the DLPFC group was not significantly different ($t_{317} = 1.14$, $P = 0.25$); for the M1 group, however, this difference reached significance ($t_{317} = 2.22$, $P = 0.027$), indicating that change in pain over time in the M1 group was significantly different from that in the sham group.

We then used the nonparametric model to analyze differences in the pain response across these 3 groups at each time point. This analysis showed that all 10 interaction terms between time point and group were not significant when the DLPFC group was compared with the sham group (day 1 posttreatment [post], $P = 0.40$; day 2 pretreatment [pre], $P = 0.99$; day 2 post, $P = 0.49$; day 3 pre, $P = 0.87$; day 3 post, $P = 0.83$; day 4 pre, $P = 0.59$; day 4 post, $P = 0.41$; day 5 pre, $P = 0.22$; day 5 post, $P = 0.18$; followup, $P = 0.65$). In the M1 group, however, the interaction term was significant (or there was a statistical trend) compared with the sham group for all time points (day 1 post, $P = 0.07$; day 2 pre, $P = 0.009$; day 2 post, $P = 0.08$; day 3 pre, $P = 0.02$; day 3 post, $P = 0.03$; day 4 pre, $P = 0.01$; day 4 post, $P = 0.02$; day 5 pre, $P = 0.002$; day 5 post, $P = 0.01$; followup, $P = 0.004$), indicating a significant change in pain for the M1 group throughout the experiment.

When analyzing the parametric model and setting the M1 group as the reference in order to obtain the slope for this group (i.e., the "time" effect), this slope had a significant effect ($P < 0.0001$), and the mean ± SD beta coefficient was 0.31 ± 0.78, indicating that after each evaluation the mean decrease in pain was 0.31, as indexed by the VAS (Figure 1).

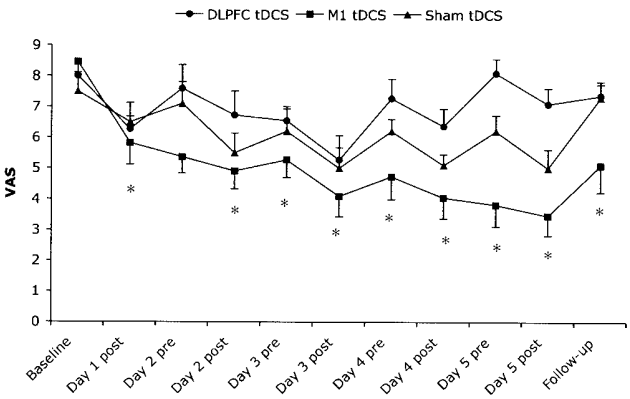

Figure 1. Changes in motor function performance over time in the 3 treatment groups. Visual analog scale (VAS) scores were assessed at baseline (day 1), on days 2, 3, 4, and 5 before (pre) and after (post) treatment, and at followup (after 3 weeks of treatment). Values are the mean and SEM. DLPFC = dorsolateral prefrontal cortex; tDCS = transcranial direct current stimulation; M1 = primary motor cortex. * = statistically significant versus sham stimulation.

For the CGI and PGA, we were interested in group differences, because these instruments measure improvement in pain compared with baseline. A repeated-measures ANOVA showed a significant group effect for CGI improvement ($F[2,116] = 10.99$, $P = 0.0003$). The time effect approached significance ($F[4,116] = 2.17$, $P = 0.07$), and there was no effect for the interaction term group versus time ($F[8,116] = 0.74$, $P = 0.66$). These results indicate that there was an overall difference across groups for all time points. Taken as a whole, the mean ± SD CGI scores were 2.51 ± 0.72 for the M1 group, indicating that the score for improvement was between 2 (much improvement) and 3 (minimal improvement), 3.11 ± 0.99 for the DLPFC group, indicating that the improvement was between 3 (minimal improvement) and 4 (no change), and 3.62 ± 0.83 for the sham group, indicating that the improvement was between 3 (minimal improvement) and 4 (no change). Post hoc comparisons showed a significant difference between M1 and DLPFC stimulation ($P = 0.001$), M1 and sham stimulation ($P < 0.0001$), and DLPFC and sham stimulation ($P = 0.008$). When each group was analyzed individually, there was no time effect for any of the groups, indicating that pain improvement was constant throughout the trial ($P = 0.39$ for the DLPFC group, $P = 0.87$ for the M1 group, and $P = 0.32$ for the sham group) (Figure 2A).

For the PGA, a significant group effect ($F[2,116] = 8.24$, $P = 0.0015$) and a significant time effect ($F[4,116] = 7.90$, $P < 0.001$) were observed, but there was no significant effect of the interaction term group versus time ($F[8,116] = 1.10$, $P = 0.36$). These results demonstrate that the mean rate of subjective improvement was different across the 3 treatment groups (group effect), and there was also a significant change in this rating for all 3 groups over time (time effect). Considering all time points, the mean ± SD changes in PGA scores were 2.29 ± 0.74 for the M1 group, indicating a change in pain between 2 (much improvement) and 3 (minimal improvement), 3.1 ± 1.01 for the DLPFC group, indicating a change between 3 (minimal improvement) and 4 (no change), and 3.2 ± 0.98 for the sham group, indicating a change between 3 (minimal improvement) and 4 (no change) (Figure 2B).

Another variable that was used to measure pain was the tender point assessment. Analysis of this variable showed that there was no difference between the mean discomfort at each tender point between the left and right sides, before and after treatment, for each point in each group. Furthermore there was no significant difference in the rate of improvement across tender points (for the M1 group, $P = 0.87$ by one-way ANOVA; for the DLPFC group, $P = 0.50$ by one-way ANOVA). This result suggests that stimulation effects were not somatotopically guided. Analysis of the total tender point scores showed that only the time effect was significant ($F[2,58] = 4.68$, $P = 0.01$). Although the magnitude of improvement in the M1 group was larger on day 5, the lack of a significant interaction effect might be explained by the fact that at followup, scores returned to values similar to those at baseline. Indeed, when analyzing the percent change in the tender point scores after 5 days of treatment, a significant difference across the 3 groups was observed ($F[2,29] = 5.43$, $P = 0.009$), and post hoc tests revealed a significant difference

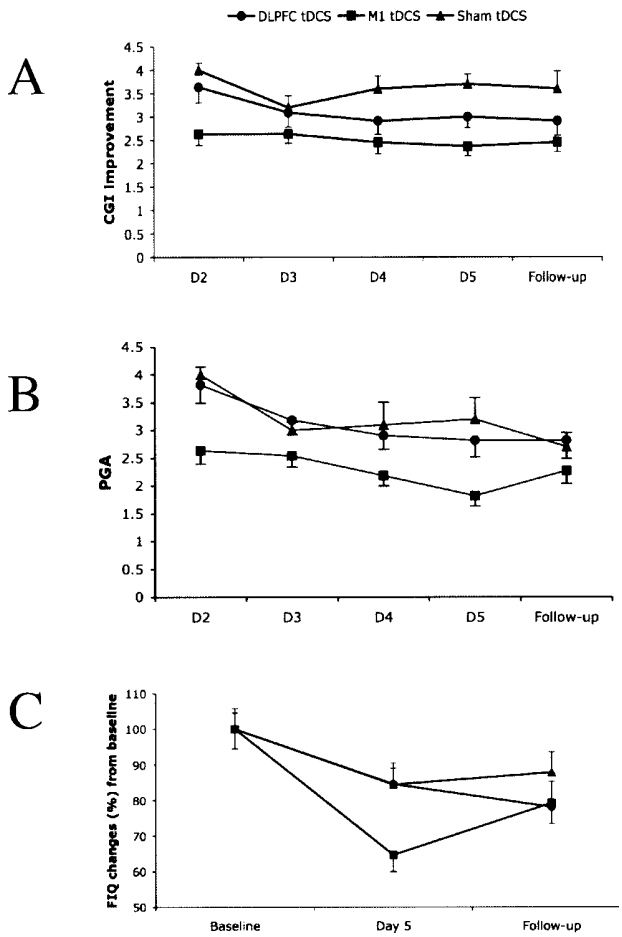

Figure 2. Changes in pain scores over time in the 3 treatment groups. **A,** Clinician global impression (CGI) scores on day 2 (D2), day 3 (D3), day 4 (D4), day 5 (D5), and at followup. **B,** Patient global assessment (PGA) scores on days 2, 3, 4, 5, and at followup. **C,** Total Fibromyalgia Impact Questionnaire (FIQ) scores at baseline, day 5, and followup. Values are the mean and SEM. See Figure 1 for other definitions.

Table 2. Results of the Short Form 36 Health Survey in the 3 groups receiving tDCS*

	DLPFC	M1	Sham	F[1,29]	P†
Physical functioning (0–57.1)					
Baseline	30.4 ± 10.1	32.1 ± 7.9	30.3 ± 8.1		
Day 5	0.11 ± 0.22	0.14 ± 0.22	0.07 ± 0.10	4.44	0.02
Followup	0.06 ± 0.27	0.22 ± 0.26	0.01 ± 0.11		
Role–physical (0–56.2)					
Baseline	33.1 ± 6.4	33.4 ± 9.8	34.4 ± 9.7		
Day 5	0.04 ± 0.35	0.17 ± 0.35	0.14 ± 0.35	0.27	0.76
Followup	0.05 ± 0.24	0.06 ± 0.23	0.08 ± 0.13		
Bodily pain (0–62.7)					
Baseline	37.2 ± 5.9	38.9 ± 4.8	37.5 ± 5.6		
Day 5	0.06 ± 0.12	0.17 ± 0.21	0.07 ± 0.21	3.3	0.05
Followup	0.02 ± 0.14	0.06 ± 0.28	0.12 ± 0.20		
General health (0–64)					
Baseline	43.3 ± 8.0	44.1 ± 8.1	43.5 ± 10.8		
Day 5	0.03 ± 0.14	0.11 ± 0.23	0.04 ± 0.26	1.25	0.3
Followup	0.00 ± 0.13	−0.05 ± 0.22	−0.08 ± 0.26		
Vitality (0–70.4)					
Baseline	40.0 ± 8.1	42.2 ± 7.6	42.9 ± 12.4		
Day 5	0.07 ± 0.13	0.15 ± 0.22	0.14 ± 0.20	0.77	0.47
Followup	0.10 ± 0.22	0.06 ± 0.26	0.14 ± 0.27		
Social functioning (0–57.1)					
Baseline	40.9 ± 8.1	43.3 ± 11.9	42.8 ± 12.4		
Day 5	0.05 ± 0.19	0.16 ± 0.28	0.06 ± 0.35	0.52	0.6
Followup	0.05 ± 0.22	0.07 ± 0.32	0.09 ± 0.35		
Role–emotional (0–55.3)					
Baseline	32.3 ± 12.3	34.2 ± 12.4	34.2 ± 12.5		
Day 5	0.11 ± 0.32	0.17 ± 0.26	0.37 ± 0.44	0.22	0.8
Followup	0.13 ± 0.39	0.21 ± 0.35	0.28 ± 0.29		
Mental health (0–64.1)					
Baseline	39.3 ± 9.5	39.1 ± 10.9	39.3 ± 10.9		
Day 5	−0.01 ± 0.13	0.32 ± 0.43	0.18 ± 0.41	0.23	0.79
Followup	0.00 ± 0.20	0.21 ± 0.36	0.13 ± 0.59		

* Values are the mean ± SD for absolute values (baseline) and mean ± SEM for the percent differences from baseline (day 5 and followup). Numbers inside the parentheses are the score ranges for each domain. Positive change indicates improvement from baseline. Scoring for the Short Form 36 Health Survey was based on algorithms published in the Short Form 36 Health Survey Manual and Interpretation Guide. See Table 1 for definitions.

† By two-way analysis of variance, with the factors group and time (day 5 and followup).

between the M1 group and the sham group ($P = 0.008$) but not between the sham group and the DLPFC group ($P = 0.13$). On day 5, tender point scores decreased by 17.1 ± 11.8% in the M1 group, by 11.8 ± 8.3% in the DLPFC group, and by 2.3 ± 10.9% in the sham group.

Assessment of quality of life. Changes in domains other than pain were assessed using the FIQ and the SF-36 (acute version). Repeated-measures analysis for the FIQ showed a significant effect for time ($F[2,58] = 23.72$, $P < 0.0001$) and for the interaction term time versus group ($F[4,58] = 2.92$, $P = 0.028$). There was no significant group effect ($F[2,58] = 2.26$, $P = 0.12$). Although the results showed that the 3 groups had a decrease in FIQ scores over the course of the trial, the decrease in the M1 group (36.2 ± 15.6%) was significantly different from that seen in the sham group ($P = 0.023$) and the DLPFC group ($P = 0.018$) (Figure 2C). Although the items "pain" and "number of days you feel good" were associated with the largest changes (49.2 ± 24.4% and 43.4 ± 19.6%, respectively), there was no significant difference across all items ($P = 0.24$), suggesting a uniform improvement in the domains evaluated by this instrument. For the SF-36, although the absolute values suggest an improvement in all domains after stimulation of the primary motor cortex (except for the domain role–emotional), the only domains that showed a significant difference across groups were physical functioning ($F[1,29] = 4.44$, $P = 0.02$) and bodily pain ($F[1,29] = 3.3$, $P = 0.05$) (Table 2).

Assessment of depression and anxiety. For the assessment of depression, although there was no significant difference in BDI scores across the 3 groups of treatment (for the interaction term group versus time, $F[4,58] = 0.53$, $P = 0.71$), the absolute values suggest

Table 3. Results of cognitive assessments in the 3 groups receiving tDCS*

	DLPFC	M1	Sham	P†
MMSE total score (0–30 scale)				
Baseline	24.6 ± 2.5	27.1 ± 2.4	26.3 ± 2.6	
Day 5	25.8 ± 3.0	26.4 ± 2.0	25.2 ± 3.6	0.07
Followup	26.1 ± 2.6	26.3 ± 1.8	25.0 ± 3.5	
Stroop test, seconds				
Baseline	28.0 ± 8.4	26.3 ± 5.1	28.5 ± 8.7	
Day 5	27.8 ± 9.7	24.7 ± 5.4	28.1 ± 10.6	0.09
Followup	24.5 ± 5.7	23.9 ± 5.1	29.1 ± 13.9	
Simple reaction time, right hand, msec				
Baseline	702.4 ± 392.1	559.4 ± 317.0	632.7 ± 325.3	
Day 5	466.6 ± 276.1	402.4 ± 206.6	604.0 ± 294.7	0.03
Followup	463.5 ± 246.4	400.8 ± 203.9	624.7 ± 373.1	

* Values are the mean ± SD. Values for the Stroop test are the average scores for words, colors, and interference. MMSE = Mini-Mental State Examination (see Table 1 for other definitions).
† For the interaction term (group × time), by two-way analysis of variance.

that stimulation of the DLPFC was the only treatment that could induce a long-lasting mood improvement (mean ± SD baseline BDI score 17.8 ± 8.7; followup BDI score 14.6 ± 5.7). For the M1 and sham groups, BDI scores returned to baseline levels (for the M1 group, 19.9 ± 8.2 at baseline and 18.6 ± 9.1 at followup; for the sham group, 20.7 ± 8.1 and 18.0 ± 7.7, respectively).

A decrease in anxiety levels throughout the trial was observed in the 3 treatment groups (for the effect of time, $F[10,290] = 10.55$, $P < 0.0001$). This decrease was similar across groups (for the interaction term, $F[20,290] = 1.22$, $P = 0.24$), indicating that the decrease in the anxiety may have been a result of increased anxiety at the beginning of the trial due to participation in a new research protocol.

Safety/cognitive evaluation. *MMSE.* Although the repeated-measures ANOVA showed no significant time effect ($F[2,58] = 0.12$, $P = 0.88$) or group effect ($F[2,58] = 0.79$, $P = 0.46$), there was a trend toward a significant effect for the interaction term group versus time ($F[4,58] = 2.33$, $P = 0.07$). This might be the result of the slight improvement in MMSE scores in the DLPFC group (Table 3).

Stroop test. We averaged the results of the 3 subtests (colors, words, and interference), because they had similar changes throughout the study. The repeated-measures ANOVA showed that there was no significant group effect ($F[2,58] = 0.12$, $P = 0.59$) or interaction term effect ($F[4,58] = 1.69$, $P = 0.16$), but there was a trend toward a significant time effect ($F[2,58] = 2.51$, $P = 0.09$). Such a trend might reflect improved performance of this test in the M1 and DLPFC groups over the course of the trial (Table 3).

Digit span, forward and backward. We summed the scores for both forward and backward digit span and performed the analysis with the total digit scores. The results of the repeated-measures ANOVA showed no significant effect for group, time, or the interaction term group versus time ($F < 2$ for all tests, $P > 0.14$).

Simple reaction time. Our results revealed that there was a significant change in simple reaction time performance across groups for the right hand (contralateral to the stimulated hemisphere) (for the interaction term time versus group, $F[4,58] = 2.85$, $P = 0.03$) but not for the left hand (for the interaction term time versus group, $F[4,58] = 1.75$, $P = 0.15$). Post hoc tests for the right hand revealed that, as compared with sham stimulation, stimulation of the primary motor cortex and the DLPFC resulted in improved performance ($P = 0.0006$ [mean ± SEM improvement 28 ± 3.3%] and $P = 0.02$ [mean ± SEM improvement 26 ± 9.3%]) (Table 3).

Correlations. In an exploratory manner, we performed correlation tests between pain improvement after stimulation of the primary motor cortex, as indicated by changes in the VAS (between baseline and day 5 after treatment), and the following variables: age, medications (SSRIs, tricyclic antidepressants, NSAIDs, benzodiazepines, and neuroleptics), duration of pain, sleep (as measured on a VAS), fatigue (VAS), BMI, and baseline scores of depression (as measured on the BDI), pain (VAS), anxiety (VAS), tender points, and the FIQ. The results showed that the only significant correlations were between pain improvement and BMI ($r = -0.76$, $P = 0.007$), indicating that the greater the BMI, the lesser the pain improvement, and between pain improvement and the number of tender points ($r = -0.78$, $P =$

0.005), indicating that the greater the number of tender points, the lesser the pain improvement.

DISCUSSION

Our results show that anodal tDCS of the primary motor cortex in patients with fibromyalgia induces a larger, significant improvement of pain compared with sham stimulation. This effect is specific to the site of stimulation and can last for several weeks after treatment with stimulation has ended. Although small, a positive impact on other domains of the quality of life of these patients (e.g., physical functioning) was observed after anodal stimulation of the primary motor cortex. Active tDCS is associated with mild adverse events that are not different from those induced by sham treatment and does not result in cognitive impairment. Finally, results of the correlation analyses suggest that patients with a low BMI and a low score for tender points tend to have a better outcome.

We hypothesized that a therapy that can modulate brain activity could induce pain relief in patients with fibromyalgia. Several facts support the relationship between fibromyalgia-associated pain and central nervous system dysfunction. First, non–rapid eye movement (non-REM) sleep is altered in patients with fibromyalgia (28) and is associated with symptom severity (29). The association between the lack of non-REM sleep and symptoms of fibromyalgia might be linked to an abnormality in serotoninergic transmission. Indeed, it has been shown that *p*-chlorophenylalanine, a centrally acting serotonin synthesis inhibitor, can induce symptoms similar to those associated with fibromyalgia (30). Second, the association of depression and fibromyalgia is well described (31), and some investigators hypothesize that a similar pathophysiologic phenomenon might underlie both conditions (2). Third, several studies have shown that tricyclic antidepressants and other antidepressants are associated with an improvement in the symptoms of fibromyalgia, including pain (2). In fact, tricyclic antidepressants have also been demonstrated to be efficacious in promoting pain relief in patients with other pain syndromes (32). Finally, neuroimaging studies have shown that regional cerebral flow in some pain-related brain areas (e.g., thalamic nuclei) in patients with fibromyalgia is different from that in healthy control subjects (1,33), and a TMS study showed motor cortex excitability changes in the excitatory and inhibitory system in patients with fibromyalgia compared with healthy controls that are also similar to those observed in patients with another chronic pain disorder (rheumatoid arthritis) (34).

If fibromyalgia is a manifestation of dysfunctional brain activity, then neuromodulatory techniques might be suitable for modifying this activity and alleviating symptoms. To our knowledge, no published study has investigated the use of brain stimulation in patients with fibromyalgia. We initially decided to test tDCS, a noninvasive technique of brain stimulation, for several reasons: this technique is a powerful method to modulate brain activity (for review, see refs. 10 and 35), it has a reliable sham condition (14) that is particularly important for fibromyalgia, and it is easy to apply.

The powerful modulatory effects of this technique on brain activity have been extensively reported in the literature. Animal studies on the effects of tDCS were performed in the 1950s and 1960s. Those studies showed that polarizing currents applied to the surface of the brain resulted in modulation of cortical activity. Surface anodal polarization of the cortex increases spontaneous unit discharges (36,37) and initiates paroxysmal activity (38), whereas cathodal polarization generally depresses these events. These results were later confirmed by human studies in which tDCS changed motor cortex excitability according to the stimulation polarity: whereas anodal stimulation increases cortical excitability, cathodal stimulation decreases it (11,39). Similar modulatory effects have also been described in the visual cortex (12,40). Indeed, the modulatory effects of the tDCS technique have been shown to induce clinical effects in patients with stroke (41), those with epilepsy (42), and patients with chronic pain (17).

Because tDCS induces a weak, constant electric current, it has been proposed that tDCS would cause behavioral effects by changing the membrane resting potential; that is, tDCS would induce hyperpolarization or depolarization of the stimulated area (43). In terms of the after-effects of stimulation, other mechanisms such as the modulation of synaptic transmission via modulation of the N-methyl-D-aspartate receptors have been proposed and demonstrated experimentally (44). Because tDCS seems to be able to change the state of local cortical excitability, this method might revert the dysfunctional brain activity changes associated with fibromyalgia. Because anodal stimulation increases cortical excitability, the improvement in pain after this treatment might have been related to an up-regulation of motor cortex activity.

Up-regulation of motor cortex excitability might modulate pain perception through indirect effects of neural networks on pain-modulating areas, such as tha-

lamic nuclei. Past neuroimaging research has shown that stimulation of the motor cortex with epidural electrodes changes activity in thalamic and subthalamic nuclei (45–47). A model has been proposed in which thalamic nuclei activation would lead to several events in other pain-related structures, such as the anterior cingulate, the periaqueductal gray, and the spinal cord, that could ultimately modulate the affective–emotional component of pain and also inhibit pain impulses from the spinal cord (46).

The findings of this study are similar to those of our previous study, in which we showed that tDCS is effective for improving pain in patients with chronic spinal cord injury. In that trial, 17 patients were randomized to receive active or sham tDCS over the primary motor cortex, and the results showed significant pain improvement in the group that received active tDCS as compared with the group receiving sham stimulation (17). Interestingly, we showed a linear effect of pain improvement that was similar to the findings in the present study. Although the mechanisms of pain in fibromyalgia and chronic spinal cord injury are likely quite different (one is presumably caused by a chronic deafferentation and the other by an overall brain dysfunction that is not yet elucidated), both conditions share pathophysiologic similarities, e.g., dysfunction in thalamic nuclei activity (1,47).

One finding that should be discussed is the lack of antidepressant effects associated with tDCS as compared with sham stimulation (patients in the 3 groups had a similar, mild antidepressant response). This result is discordant, at least partially, from our previous research, which showed that tDCS to the DLPFC is associated with mood improvement (18). However, those results were obtained in patients with severe major depression, and it should be noted that the pathophysiologic mechanisms of depression in patients with fibromyalgia are presumed to be different from that in patients with major depression (48,49). Furthermore, the severity of the depressive symptoms in the patients with fibromyalgia was relatively mild (mean BDI score 19.4), in contrast to our previous major depression study in which the mean BDI score was 40.3 (18). In addition, whereas it has been shown that patients with major depression have decreased activity over the prefrontal cortex (50) that is correlated to the degree of depression and can be reversed by successful antidepressant treatment (50), the prefrontal cortex in patients with fibromyalgia does not show any change in its perfusion (1). Therefore, DLPFC might not be the best target for the treatment of depression in patients with fibromyalgia.

In order to identify clinical features that might be associated with a treatment response, we performed correlation tests with several demographic and clinical variables. Although these tests were not adequately powered, we obtained 2 significant correlations (pain improvement versus BMI, and pain improvement versus the tender point scores). The negative relationship with BMI is intriguing. One possible cause for this association is that BMI is a surrogate for the clinical symptoms of fibromyalgia. In other words, patients with a higher BMI would have disease that is more refractory to treatment (24). This hypothesis is also consistent with the negative correlation between pain improvement and tender point severity. Therefore, patients with disease that is more refractory and severe might have a worse outcome or may simply need more sessions of tDCS to get the same level of pain relief.

Finally, our study showed that active tDCS is associated with mild and benign adverse effects, such as mild headache; these effects were observed at a similar frequency in the group of patients who received sham stimulation. In addition, we demonstrated that tDCS is not associated with significant changes in cognitive function as compared with sham stimulation. These findings are important in terms of providing initial safety data. However, it should be noted that other safety parameters were not evaluated. This is in accordance with our previous data showing that 5 consecutive sessions of tDCS are not associated with adverse effects on cognition in patients with major depression (51) or those with chronic pain (17).

The findings of the current study support the need for future investigations of novel neuromodulatory approaches for the treatment of fibromyalgia. Such studies should explore the duration of tDCS effects by performing longer-term followup evaluations and also by using different parameters of stimulation.

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