

Focal Modulation of the Primary Motor Cortex in Fibromyalgia Using 4×1-Ring High-Definition Transcranial Direct Current Stimulation (HD-tDCS): Immediate and Delayed Analgesic Effects of Cathodal and Anodal Stimulation

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Abstract: Fibromyalgia is a prevalent chronic pain syndrome characterized by altered pain and sensory processing in the central nervous system, which is often refractory to multiple therapeutic approaches. Given previous evidence supporting analgesic properties of noninvasive brain stimulation techniques in this condition, this study examined the effects of a novel, more focal method of transcranial direct current stimulation (tDCS), using the 4×1-ring configuration of high-definition (HD)-tDCS, on overall perceived pain in fibromyalgia patients. In this patient- and assessor-blind, sham-controlled, crossover trial, 18 patients were randomized to undergo single 20-minute sessions of anodal, cathodal, and sham HD-tDCS at 2.0 mA in a counterbalanced fashion. The center electrode was positioned over the left primary motor cortex. Pain scales and sensory testing were assessed before and after each intervention. A finite element method brain model was generated to predict electric field distribution. We found that both active stimulation conditions led to significant reduction in overall perceived pain as compared to sham. This effect occurred immediately after cathodal HD-tDCS and was evident for both anodal and cathodal HD-tDCS 30 minutes after stimulation. Furthermore, active anodal stimulation induced a significant bilateral increase in mechanical detection thresholds. These interventions proved well tolerated in our patient population.

Perspective: 4×1-ring HD-tDCS, a novel noninvasive brain stimulation technique capable of more focal and targeted stimulation, provides significant reduction in overall perceived pain in fibromyalgia patients as compared to sham stimulation, irrespective of current polarity. This technique may have other applications in research and clinical settings, which should be further explored.

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Key words: Fibromyalgia, chronic pain, transcranial direct current stimulation (tDCS), high-definition transcranial direct current stimulation (HD-tDCS), electrical brain stimulation, transcranial electrical stimulation (tES).

Fibromyalgia (FM) is a common cause of diffuse, chronic musculoskeletal pain in adults, with an estimated prevalence between 2 and 5% in the general popula-

tion.^{6,32,55} Even though its etiology and pathophysiology are not yet fully understood, current evidence strongly suggests that, similarly to other chronic pain syndromes,

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this is a disorder of pain regulation characterized by altered pain and sensory processing in the central nervous system (CNS), likely due to maladaptive plasticity in pain-related neural circuits.^{22,28,56} FM pain management is often challenging and many cases are refractory to current pharmacological and nonpharmacological approaches, including behavioral interventions and other alternative treatments, frequently leading to a considerable impairment in patients' quality of life (QOL). There is therefore an unmet clinical need to develop novel interventions for the treatment of FM.

Different neuromodulatory and neurostimulatory approaches, both invasive and noninvasive, have been successfully tested as potential therapeutic tools for chronic pain disorders given their ability to modify brain activity in neural networks in the area of stimulation as well as in distant, interconnected regions. Indeed, there has been a growing interest in 2 of these methods—transcranial direct current stimulation (tDCS) and repetitive transcranial magnetic stimulation (rTMS)—particularly due to their noninvasive nature and their ability to modify the excitability of cortical neural circuits. When delivered to the primary motor cortex (M1), these techniques are capable of modifying sensory aspects of pain via modulation of M1-thalamic inhibitory networks,⁴⁰ as well as of other cortico-cortical and cortico-subcortical projections involved in pain processing pathways.^{8,40} This is of particular relevance in FM, where pain can be characterized by a lack of inhibitory control over somatosensory processing.^{13,51} For this reason, modulation of the sensory aspects of pain via M1 stimulation, independent from modulation of affective components, may target one of the pathophysiological mechanisms of FM. Accordingly, an increasing body of evidence supports the analgesic effects of both tDCS^{4,17,43,44,51} and rTMS^{30,38} of the M1 in the setting of FM. tDCS may have some additional advantages due to its portability, ease of use, and low cost. However, this technique uses relatively large electrode pads (most commonly 35 cm²) that deliver direct current (DC) in rather diffuse areas of the brain,^{12,26,45} making focalized stimulation of target regions less feasible.

Increased focality would be desirable in tDCS for a number of reasons. First, it may help achieve beneficial clinical effects with larger effect sizes, as occurs with invasive interventions such as epidural M1 stimulation for chronic pain.²⁷ Second, it may also contribute to the understanding of the specific cortical regions implicated in therapeutic action, which is difficult to dissect with diffuse electrical stimulation. This would ultimately contribute to the rational development and optimization of therapy. Hence, a more focal approach may allow for tailoring of stimulation to individual indications and symptoms in a way not possible with diffuse stimulation. Finally, a more focal intervention may also be associated with increased safety. It could potentially reduce the likelihood of side effects due to decreased stimulation of adjacent regions, thus allowing for stimulation with increasing intensity or repetition to enhance efficacy.

High-definition (HD)-tDCS is a novel approach that uses arrays of smaller electrodes³¹ whose configuration

Focal M1 Modulation in Fibromyalgia Using HD-tDCS can be optimized for targeting.¹⁴ In particular, the 4×1-ring montage of HD-tDCS has been proposed for unidirectional and targeted stimulation, with the polarity (anode or cathode) set by a center electrode and the area of cortical modulation restricted by adjusting the radii of 4 return electrodes.¹² The targeting of 4×1-ring HD-tDCS may have important applications in research and eventually in clinical settings. Nevertheless, no studies have been published to date assessing its effects in a patient population.

In order to evaluate the analgesic effects of HD-tDCS in patients with FM, we performed a randomized, sham-controlled, crossover clinical trial where both participants and the assessor were blind to the assigned interventions. Specifically, we were interested in determining whether active anodal and cathodal HD-tDCS could induce a significant reduction in perceived pain as compared to sham stimulation, as evaluated using pain scales and sensory testing.

Methods

This trial is reported following 2010 CONSORT guidelines. A participant flow diagram is shown in Fig 1.

Trial Design and Overview

This study was a patient- and assessor-blind, randomized, sham-controlled, crossover clinical trial with equal allocation ratio (1:1). The protocol consisted of a total of 5 study visits. After undergoing a telephone screening, patients were scheduled for their first visit, where we further screened them using the 2010 American College of Rheumatology Preliminary Diagnostic Criteria for FM,⁵⁴ obtained written informed consent, and did a baseline evaluation, as detailed below. On visits 2, 3, and 4, each participant underwent single sessions of anodal, cathodal and sham HD-tDCS delivered to the left M1, which were preceded and followed by pain scales and sensory testing. The order of stimulation was counterbalanced and randomly assigned for each individual. Finally, a follow-up evaluation was conducted on visit 5. All visits were separated by a washout period of at least 7 days to prevent any carryover effects or contamination of the sham stimulation by a preceding active session. Although patients were scheduled for participation at different times of the day based on their availability, each individual patient was scheduled for all of his/her visits at approximately the same time of day. Fig 2 provides an overview of our study design.

All study procedures were conducted in the Laboratory of Neuromodulation at Spaulding Rehabilitation Hospital, Harvard Medical School, Boston, MA. The study was approved by the local Institutional Review Board (Protocol # 2010-p-000990) and registered in ClinicalTrials.gov (NCT01402960). This randomized controlled trial was conducted in accordance with the Declaration of Helsinki.

Participants

We included patients 1) who were between 18 and 64 years of age; 2) who had a formal diagnosis of FM made by a rheumatologist (FM was chosen as a type of diffuse

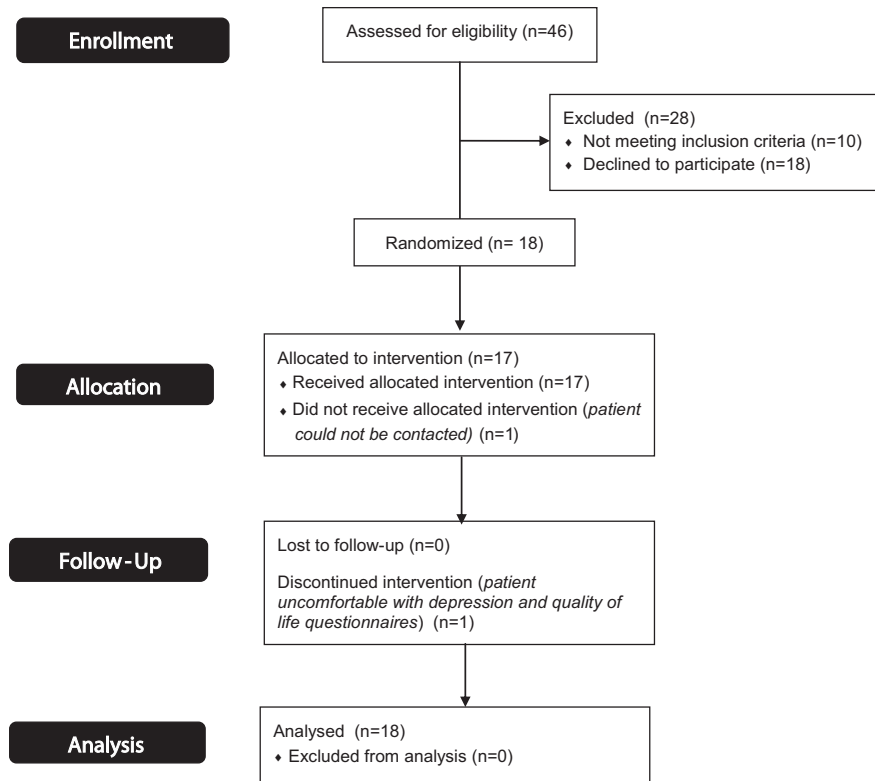


Figure 1. CONSORT 2010 patient flow diagram.

musculoskeletal pain disorder) for a duration greater than 6 months at the time of enrollment, with an average overall pain intensity of at least 3/10 on a visual numerical scale (VNS); and 3) whose pain was refractory to common analgesics and muscle relaxants. Patients taking analgesics or CNS-active medication were allowed to enroll if dosages had been stable for at least 2 months prior to their screening. Given ethical concerns, they were encouraged to keep taking their usual medication at stable doses for the duration of the trial. A list of CNS-active drug use among study participants is provided as a [Supplementary Table](#).

As a safety measure and in order to eliminate variables that could interfere with the effects of the stimulation, our exclusion criteria were as follows: 1) current pregnancy; 2) presence of metallic implants in the head; 3) history of substance abuse within the past 6 months; 4) use of carbamazepine within the past 6 months; 5) severe depression, as defined by a baseline score ≥ 29 in the Beck Depression Inventory-II (BDI-II)⁷; and 6) any history of epilepsy, stroke, moderate-to-severe traumatic brain injury, severe migraines, or brain surgery.

A total of 18 patients fulfilled the above-mentioned inclusion criteria and provided written informed consent to participate in our trial. Population characteristics are summarized in [Table 1](#). Participants were recruited through local support groups and online listings over a period of 6 months (see [Fig 1](#)).

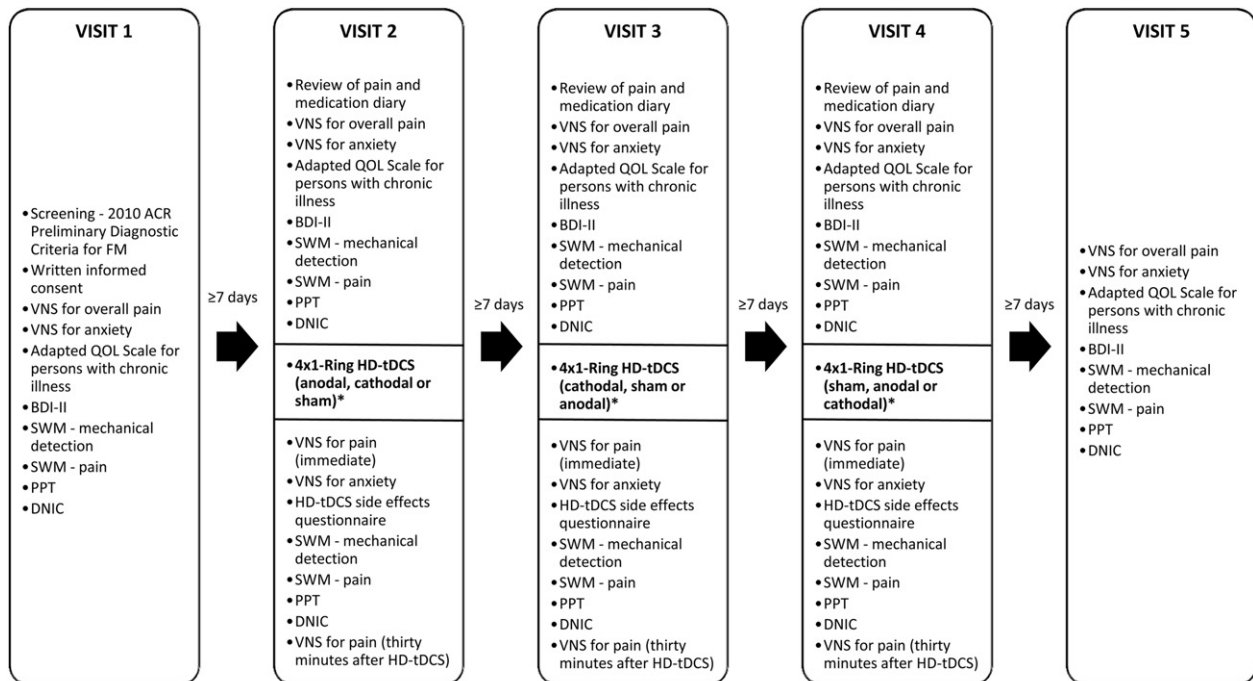
Intervention: 4×1-Ring HD-tDCS

We employed a 4×1 Multichannel Stimulation Adaptor (Model 4×1-C2; Soterix Medical Inc, New York, NY)

connected to a conventional tDCS device (Model 1224-B; Soterix Medical Inc) to deliver DC to the scalp via Ag/AgCl sintered ring electrodes (EL-TP-RNG Sintered; Stens Biofeedback Inc, San Rafael, CA), as described by Minhas et al.³¹ Electrodes were held in place by specially designed plastic casings embedded in a modular electroencephalography (EEG) recording cap.

We positioned the center electrode (anode or cathode) over C3 based on the International 10/20 EEG System,⁴² which corresponds approximately to the location of the left M1. Four return electrodes (cathode or anode, respectively) were placed in a radius of approximately 7.5 cm from the center electrode. Their locations corresponded roughly to Cz, F3, T7, and P3, as depicted in [Fig 3](#). The decision to use this radius aimed at collecting data supporting different possible montages. By changing the position of the return electrodes while keeping the radius constant, the outcomes would not be expected to differ markedly.

The hair underlying each electrode was separated in order to expose the scalp, and approximately 1.5 mL of highly conductive gel (Signa Gel; Parker Laboratories, Fairfield, NJ) was placed beneath each electrode to improve conductance. Given that electrode resistance is nonlinear to electrode-interface electrochemical processes,²⁹ electrode resistance (impedance) can be misleading. For example, the resistance apparently measured fully depends on test current.²⁰ Therefore, based on prior experience in set-up and stimulation using HD electrodes, contact quality is normalized to “quality units” by the 4×1-C2 Adapter test circuit. Impedance values were verified to be ≤ 1.50 “quality units” for



ACR = American College of Rheumatology; FM = Fibromyalgia; VNS = Visual Numerical Scale; QOL = Quality of Life; BDI = Beck Depression Inventory; SWM = Semmes-Weinstein Monofilaments; PPT = Pressure Pain Thresholds; DNIC = Diffuse Noxious Inhibitory Controls; HD-tDCS = High-Definition Transcranial Direct Current Stimulation.
* Delivered in random and counterbalanced order.

Figure 2. Overview of study design.

each of the 5 electrodes before the beginning of each stimulation session.

During each active 4×1-ring HD-tDCS session, DC was gradually ramped up over a period of 30 seconds until reaching an intensity of 2.0 milliamperes (mA), which were delivered for 20 minutes. These parameters had previously been shown to be well tolerated in healthy subjects.⁹ The same montage was used for the sham procedure; however, current was applied for 30 seconds only. This duration has been reported to be a reliable method for blinding participants in conventional tDCS trials,¹⁹ which induces no effects on cortical excitability.^{33,35} Borckardt et al⁹ also reported this blinding strategy to be successful in their HD-tDCS trial.

Table 1. Demographic Characteristics of Study Participants

CHARACTERISTICS	VALUES
Mean age, years (SD)	50.3 (8.5)
Mean time since FM diagnosis, years (SD)	10.7 (6.8)
Gender, n (%)	
Female	15 (83.3)
Male	3 (16.7)
Self-reported ethnicity, n (%)	
Caucasian	15 (83.3)
African American	2 (11.1)
Hispanic	1 (5.6)
Education, n (%)	
Some college	12 (66.7)
Undergraduate degree	2 (11.1)
Graduate degree	4 (22.2)

Outcomes

Participants sat in a chair with back and arm support during all stages of data collection. The following assessments were performed, in order, at the beginning of every visit: 1) baseline VNS for overall pain; 2) VNS for anxiety; 3) Adapted QOL Scale for persons with chronic illness¹⁰; 4) BDI-II⁷; 5) Semmes-Weinstein monofilaments (SWMs) for pain and mechanical detection thresholds; 6) pressure pain thresholds (PPTs); and 7) diffuse noxious inhibitory controls (DNICs). Additionally, patients were asked to keep a pain and medication diary for the duration of the study.

On visits 2, 3, and 4, these assessments were followed by the assigned HD-tDCS sessions, as described above. Patients were again asked to rate their overall level of pain using the VNS immediately and 30 minutes after active or sham HD-tDCS. The VNS for anxiety, SWMs, PPTs, and DNICs were also evaluated immediately after the intervention, and a questionnaire was used to inquire about potential adverse effects related to the stimulation. Changes in VNS for pain constituted our primary outcome measure. All other outcome measures were considered secondary.

VNS for Pain

Patients were asked to rate their current overall level of pain on a visual scale from 0 to 10 divided at .5-point intervals, with 0 being "complete absence of pain" and 10 "the worst pain imaginable."

VNS for Anxiety

Since anxiety levels might act as a confounder for changes in pain perception, we evaluated them using

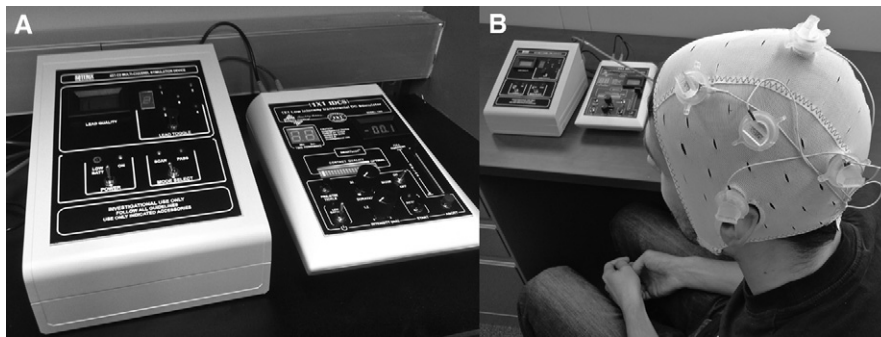


Figure 3. Equipment for 4×1-ring HD-tDCS. (A) Multichannel Stimulation Adaptor (left) connected to conventional tDCS device (right). (B) Electrode positioning used for left primary motor cortex stimulation.

a similar visual scale, where 0 corresponded to “completely calm” and 10 to “extremely anxious.”

Adapted QOL Scale for Persons With Chronic Illness¹⁰

This tool uses a 7-point scale (1 = terrible; 7 = delighted) to assess 16 QOL-related domains among chronic illness populations.

BDI-II⁷

This questionnaire consists of 21 multiple-choice questions for evaluating the presence and severity of depression in adults.

SWMs

Calibrated esthesiometers (Touch-Test Sensory Evaluators; North Coast Medical Inc, Morgan Hill, CA) were used for assessing mechanical detection and pain thresholds. While patients kept their eyes closed, filaments of increasing thicknesses were sequentially applied to the thenar region of both hands. For each hand, we registered the values at which patients first perceived the stimulus touching their skin (mechanical detection threshold) and reported it as painful (pain threshold).

PPTs

PPTs were evaluated by delivering blunt pressure in 4 paired points of the body using the standard 1-cm² hard-rubber nozzle of a Commander Algometer (JTECH Medical, Salt Lake City, UT). Pressure was gradually increased at a rate of approximately 2 lb/second, and patients were instructed to inform the assessor as soon as they experienced a sensory transition from pressure to pain. When this occurred, the device was immediately removed and the value recorded. If no pain was reported, we recorded the threshold maximum of 25 lb. This procedure was performed 3 times in each point of interest, and their average was used for statistical analyses.

Petzke et al³⁹ reported that examination of tenderness by dolorimetry at only 3 paired sites is a reliable and clinically useful assessment that highly predicts overall pain threshold in FM patients and healthy subjects. Therefore, we measured PPTs in 1) the area of the

forearm 2 cm distal to the lateral epicondyle; 2) the supraspinatus muscle, above the medial border of the scapular spine; and 3) the occiput, at the suboccipital muscle insertions. These are the sites that showed the highest correlation with overall pain threshold in the above-mentioned study and have also been documented by Tastekin et al⁴⁸ as having high discriminative ability for FM syndrome. In addition, we measured PPTs in the thenar area as a control site. In all cases, assessments in the right side of the body preceded the left.

DNICs

Participants were asked to immerse their left hand in cold water (10–12°C) for the duration of the test (1 minute total). Once the initial 20 seconds had elapsed, patients rated their local level of pain on a VNS, which had to be ≥4.0 in order to proceed. If pain levels were lower, ice was added until this threshold was reached. During the last 30 seconds, PPT assessments were performed in the right thenar area as previously described. After allowing for normalization of cutaneous temperature, the same procedure was performed in the opposite hand.

Pain and Medication Diary

Patients were given preformatted forms where they were asked to rate their average levels of overall pain on a daily basis using a VNS. They were encouraged to do so at approximately the same time each day. An average of each week's values was used for statistical analyses. Additionally, any changes in their medication (analgesics in particular) were recorded.

Randomization

Participants were consecutively assigned to a randomization scheme generated on the website [Randomization.com](http://www.randomization.com) (Dallal GE, <http://www.randomization.com>, 2008). We used the second generator, with random permutations for a 3-group trial. The randomization sequence was concealed until interventions were assigned. Generation of the random allocation sequence and assignment of participants were performed by a research coordinator not involved with any other aspect of the trial.

Blinding

In order to prevent introduction of bias,⁵² all participants and the trained physiatrist (P.W.) who performed the assessments were blind to the type of stimulation. Once baseline assessments had been performed on each visit, a different researcher (M.F.V.) was allowed to check the randomization code for that patient. He then set up the montage, operated the device, and delivered the stimulation accordingly. The assessor (P.W.) was not present in the room during delivery of the stimulation. Once the HD-tDCS session had ended and the operator (M.F.V.) removed the equipment, the assessor came back to the room and finished the assessments. Blinding of participants was discussed as part of the Intervention section.

Statistical Analyses

Patients' characteristics were summarized using descriptive statistics. Differences in baseline values between the 3 stimulation conditions were analyzed by 1-way analysis of variance.

A multilevel regression model was used to analyze global differences in changes over time in VNS for pain across stimulation conditions, allowing for random individual patient responses (the intercepts) and autocorrelation of repeated responses within patients, while simultaneously adjusting for baseline values. Significant global differences (2-tailed $P < .05$) were further analyzed with Wald tests under the multilevel regression model to detect any significant differences between the 3 possible pairs of stimulation conditions (sham versus anodal, sham versus cathodal, and anodal versus cathodal). P values were corrected for multiple comparisons (Bonferroni) and then converted in order to maintain a level of significance of .05. Effect sizes of the active interventions were calculated. A similar model was conducted for each of our secondary outcomes.

Sample size was estimated based on results from a previous study on patients with refractory chronic pain.¹⁵ In this trial, active anodal tDCS induced a significant reduction ($P < .05$) in perceived pain of .797 points (SD .5) in a visual analog scale, as compared to sham stimulation. Given a power of 80% and an alpha of 5%, 16 patients would be needed. We increased the sample to 18 patients to account for potential dropouts.

All statistical analyses were performed using STATA (StataCorp 2009. Stata Statistical Software: Release 11. StataCorp LP, College Station, TX). Two-tailed P values $< .05$ were considered statistically significant in all cases.

Finite Element Method (FEM) Brain Model of Induced Current Flow

A FEM model simulating 4×1 stimulation over C3 was generated based on previously described protocols^{49,50} to predict electric field distribution. A 3-dimensional 1-mm isotropic T1 magnetic resonance image of an adult male was segmented into 20 different head regions using a combination of automated and manual techniques. These 20 regions were then assigned 1 of 7

Focal M1 Modulation in Fibromyalgia Using HD-tDCS possible conductivities: skin, fat, skull, cerebrospinal fluid, gray matter, white matter, or air. Electrodes with conductive gel were modeled to resemble a 4×1 montage with a radius of approximately 75 mm. This corresponded to a center electrode at C3, and surround electrodes at F3, Cz, P3, and T3. An inward current density of $1A/m^2$ was applied to the surface of the center electrode; ground was applied to the surrounds. Cortical electric field magnitude and radial electric field were then calculated and scaled for 2.0 mA and -2.0 mA of stimulation.

Results

Participants

Most patients in our sample were females of Caucasian ethnicity. Mean age was 50.3 (SD 8.5) years, and mean time since FM diagnosis was 10.7 (SD 6.8) years (see Table 1). Eighteen patients were originally recruited. One of them dropped out after visit 1, without having undergone any brain stimulation and could not be contacted for further visits. Another patient withdrew from the study after the first 2 visits, explaining that having to fill in depression and QOL questionnaires on every study visit forced her to focus more on her symptoms and made her uncomfortable. In order to comply with intention-to-treat analysis, a multiple imputation technique was used to handle missing observations.

Primary Outcome: Changes in VNS for Overall Pain

Baseline comparisons between stimulation conditions showed no significant a priori differences. A decrease in mean overall pain scores assessed before, immediately after, and 30 minutes after each stimulation was observed over time, as depicted in Fig 4, and significant pain improvement across interventions was detected (P for global test = .004). When evaluating changes in perceived pain immediately after stimulation, only cathodal HD-tDCS led to significant improvement as compared to sham ($P = .012$). However, both active conditions induced significant mean pain reduction 30 minutes after the end of the stimulation (anodal versus sham, $P = .031$; cathodal versus sham, $P = .001$), as shown in Table 2. Overall effect sizes of active anodal and cathodal stimulation were .36 and .30, respectively.

Secondary Outcomes

Significant increases in mechanical detection thresholds were found for the active intervention in both the left ($P = .003$) and right ($P = .004$) hands (Fig 5). After detailed comparisons, only anodal stimulation led to significantly increased thresholds in both sides of the body as compared to sham (sham versus anodal on the left, $P = .003$; sham versus anodal on the right, $P < .001$). No significant changes were detected for other secondary outcomes, such as VNS for anxiety, SWMs for pain thresholds, PPTs, or DNICs, as reported in Table 3.

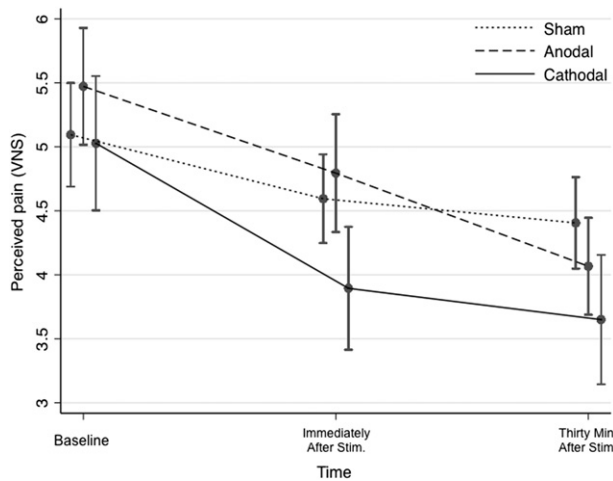


Figure 4. Change in visual numerical scale for pain under each stimulation condition measured at baseline, immediately after and 30 minutes after HD-tDCS. Whiskers represent standard deviation.

QOL Measures

No significant changes between visits were found for the Adapted QOL Scale for persons with chronic illness, BDI-II, or the pain and medication diary.

Safety

All study participants tolerated the 4x1-ring HD-tDCS sessions satisfactorily. The vast majority reported a mild-to-moderate tingling or itching sensation during both active and sham stimulation, which typically faded out over a few minutes. No unexpected adverse effects were observed.

FEM Model Findings

Consistent with previous models,¹² peak cortical electric field was restricted to cortical regions circumscribed by the ring electrodes, with local clustering based on brain idiosyncratic anatomy (Fig 6A). The polarity of stimulation was nominally set by the center electrode, and modeling of current flow in and out of the cortex confirms that, qualitatively, anode center stimulation produces dominantly inward current inside

the ring, while cathode center stimulation produces dominantly outward current inside the ring (Fig 6C). However, the biophysics dictates that current flowing into the cortex needs to flow out. Because anode-center and cathode-center produce symmetrical current flow, we simply consider current flow “associated with” the center electrode (radial inward for anode-center and radial outward for cathode-center) versus current flow associated with the outer electrode (Fig 6D). Using this representation, qualitatively, inside the ring current is consistent with the center polarity while, especially on the outer banks of gyri walls and under the ring electrodes, some current flow consistent with the outer polarity is evident. Comparing the percentage of outer-electrode polarity nodes to center-electrode polarity nodes over the range of radial electric field values reveals a quantitative difference in the intensity distribution. There are more outer-polarity nodes with a low electric field, whereas nodes at peak intensity are close to 100% center polarity. Thus, while the total inward/outward cortical current must be balanced, using the 4x1 HD-tDCS montage produces a concentration of center-dominated current flow under this electrode, and distributes the outer-electrode current flow. This FEM model suggests there is a degree of both spatial and polarity focality afforded by the HD-tDCS 4x1 montage.

Discussion

In our sample of 18 middle-aged patients with an established diagnosis of FM, a single 20-minute session of active 4x1-ring HD-tDCS of the left M1 provided significant reduction in overall perceived pain as compared to sham stimulation, regardless of the polarity used. This effect was seen immediately after cathodal HD-tDCS and was evident for both anodal and cathodal HD-tDCS 30 minutes after stimulation. Thus, the effects of both active conditions lasted for at least 30 minutes after the end of the stimulation. In addition, active anodal stimulation induced a significant bilateral increase in mechanical detection thresholds. The protocol used in this study proved well tolerated in our patient population and showed no carryover effects.

Table 2. Visual Numerical Scale for Pain Before and After Each Type of Intervention, and Change From Baseline

POINT IN TIME	TYPE OF INTERVENTION						P VALUE
	SHAM		ANODAL		CATHODAL		
	MEAN (SD)	CHANGE FROM BASELINE (MEAN [SD])	MEAN (SD)	CHANGE FROM BASELINE (MEAN [SD])	MEAN (SD)	CHANGE FROM BASELINE (MEAN [SD])	
Before stimulation (baseline)	5.09 (1.72)	N/A	5.47 (1.94)	N/A	5.03 (2.23)	N/A	.767
Immediately after stimulation	4.59 (1.47)	-.50 (1.38)	4.79 (1.96)	-.68 (.86)	3.89 (2.04)	-1.13 (1.19)	.029*
Thirty minutes after stimulation	4.41 (1.52)	-.69 (1.48)	4.07 (1.61)	-1.41 (.81)	3.65 (2.14)	-1.38 (1.33)	.004†

Abbreviation: N/A, does not apply.

*Overall change adjusted for baseline; sham versus anodal, P = .612; sham versus cathodal, P = .012; anodal versus cathodal, P = .045.

†Overall change adjusted for baseline; sham versus anodal, P = .031; sham versus cathodal, P = .001; anodal versus cathodal, P = .287.

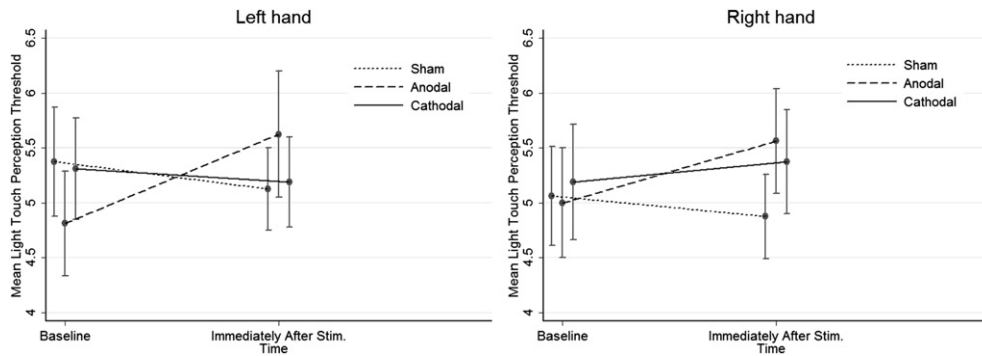


Figure 5. Change in sensory perception under each stimulation condition, assessed through SWMs (measured in units). Whiskers represent standard deviation.

In accordance with previous brain-modeling studies,^{9,12,25} our findings suggest that 4×1-ring HD-tDCS is an effective noninvasive brain stimulation technique capable of combining the advantages of conventional tDCS with an increased focality, allowing for a more accurate stimulation of cortical targets. This could have important applications in research and eventually in clinical settings and may provide further details on the mechanisms that underlie the effects of noninvasive brain stimulation. In this regard, the fact that focal M1 stimulation led to a significant reduction in overall perceived pain in our trial, as well as in studies using rTMS,^{30,38} supports the theory that tDCS-induced modulatory effects on pain-related neural circuitry are dependent on modulation of M1 activity. Still, modification of behavioral symptoms after M1 HD-tDCS may be dependent on

secondary modulation of other areas such as thalamic nuclei, cingulate cortex, and insular cortex.^{11,40} Based on the findings of our FEM model, it cannot be ruled out that the protocol used in this study may have resulted in modulation of the cingulate and insular cortices. Approaches consisting of stimulation of other cortical targets, such as the dorsolateral prefrontal cortex, can also lead to analgesic effects in FM patients,⁴⁷ possibly by modulating affective-emotional networks associated with pain.^{8,47}

Although the changes in overall perceived pain showed a relatively large variability, as evidenced by the standard deviation values, this goes in accordance with the large variability in baseline pain levels among participants in our trial. This can be expected in FM patients given the substantial between-subject

Table 3. Changes in Secondary Outcome Measures Immediately After Each Type of Intervention, as Compared to Baseline

OUTCOME MEASURE	TYPE OF INTERVENTION									
	SHAM			ANODAL			CATHODAL			P VALUE†
	SIDE	POINT IN TIME*	MEAN (SD)	SIDE	POINT IN TIME	MEAN (SD)	SIDE	POINT IN TIME	MEAN (SD)	
PPTs (lb)	Right	Before	4.16 (.74)	Right	Before	4.66 (.79)	Right	Before	4.68 (.90)	.961
		After	4.70 (.84)		After	5.27 (.96)		After	5.21 (1.04)	
	Left	Before	4.16 (.78)	Left	Before	4.86 (.79)	Left	Before	4.65 (.88)	.560
		After	4.63 (.78)		After	5.32 (1.02)		After	5.34 (1.03)	
DNICs (lb)	Right	Before	6.25 (.92)	Right	Before	7.10 (.99)	Right	Before	6.94 (.83)	.164
		After	6.86 (.98)		After	7.21 (1.04)		After	6.91 (.90)	
	Left	Before	5.85 (.85)	Left	Before	6.67 (.97)	Left	Before	7.14 (1.11)	.342
		After	6.89 (.97)		After	6.99 (.95)		After	7.81 (1.17)	
SWMs-Mechanical detection (units)	Right	Before	5.06 (.45)	Right	Before	5.00 (.50)	Right	Before	5.19 (.53)	.004‡
		After	4.88 (.39)		After	5.56 (.47)		After	5.38 (.47)	
	Left	Before	5.38 (.50)	Left	Before	4.81 (.48)	Left	Before	5.31 (.46)	.003§
		After	5.13 (.38)		After	5.63 (.58)		After	5.19 (.41)	
SWMs-Pain (units)	Right	Before	17.1 (.38)	Right	Before	16.9 (.48)	Right	Before	16.4 (.64)	.574
		After	17.0 (.35)		After	17.1 (.43)		After	16.6 (.55)	
	Left	Before	16.9 (.30)	Left	Before	16.5 (.52)	Left	Before	16.5 (.58)	.133
		After	16.9 (.34)		After	16.9 (.52)		After	16.5 (.58)	

*Before versus immediately after stimulation.

†All P values are for overall change adjusted for baseline.

‡Sham versus anodal, $P < .001$; sham versus cathodal, $P = .084$; anodal versus cathodal, $P = .114$.

§Sham versus anodal, $P = .003$; sham versus cathodal, $P = .982$; anodal versus cathodal, $P = .004$.

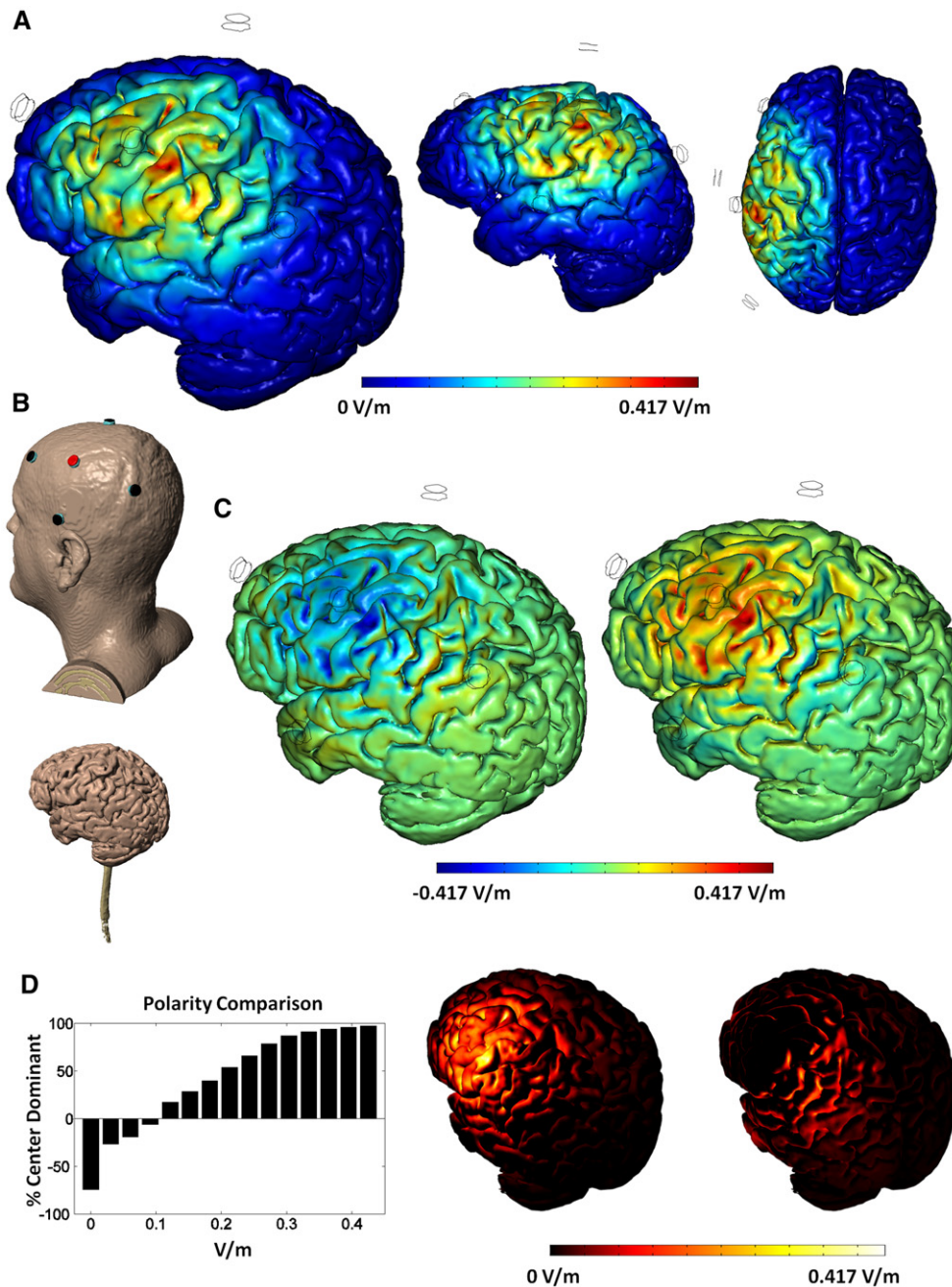


Figure 6. Results from finite element method model. Values are given for a 4×1 HD-tDCS montage with a 75-mm radius and intensity of 2.0 mA. Peak cortical electric field is circumscribed within the ring electrodes. Anodal and cathodal stimulation have symmetric spatial distributions with reversed polarity. Further analysis shows stimulation due to both the center (active) and outer (return) electrodes; however, there are 70% more outer-polarity nodes at low intensity while peak intensity is nearly 100% center polarity. **(A)** Electric field magnitude; **(B)** position of HD electrodes; **(C)** radial electric field: cathodal (left) and anodal (right); **(D)** radial polarity magnitude: distribution comparison (left), active component (middle), return component (right).

differences in pain variability typical of this disorder.²¹ Therefore, any decrement in pain scores would likely follow a similar pattern. The significant results in our study, despite the large variability, strengthen our findings.

A novel finding of this trial that needs to be carefully discussed is that of the effects of DC polarity, since both cathodal and anodal HD-tDCS induced significant pain relief. This contrasts with rTMS data showing that excitability enhancement with high-frequency M1

rTMS leads to pain improvement, while reduction of excitability using low-frequency M1 rTMS leads to worsening of pain.^{1,16,37} However, the mechanisms of action of tDCS differ from those of rTMS.⁵³ Although studies show that M1 anodal tDCS is associated with significant pain reduction,³⁷ M1 cathodal stimulation has not been widely tested in chronic pain syndromes. In fact, in the only published studies that we could find where M1 cathodal tDCS was used with analgesic purposes in chronic pain disorders, Antal and Paulus³

found significant pain reduction in a patient with refractory orofacial pain, while Knotkova et al²⁴ reported neuropathic pain relief in a patient with complex regional pain syndrome. Additionally, cathodal tDCS has been described to exert analgesic effects in healthy subjects.² In this context, there are 2 possibilities: 1) cathodal M1 tDCS also leads to pain reduction; and/or 2) cathodal M1 tDCS, when applied focally, leads to pain reduction. Because of the preliminary testing of cathodal M1 tDCS using conventional pads, it is not possible to reject the first hypothesis.

Broader issues may limit inferences about polarity-specific mechanisms. Although, simplistically, anodal and cathodal stimulation are often assumed to increase and inhibit cortical excitability, respectively, emerging evidence shows that 1) modulation is not monotonic with stimulation intensity, such that increasing duration and/or amplitude can reverse the direction of modulation (personal communication, Nitsche et al, 2012); 2) the direction of modulation is dependent on the state of the underlying network^{18,34} and pain networks may be altered^{22,28,53}; and 3) the relationship between the direction of changes in excitability and changes in task performance by a given brain region are not direct,²³ and this can also occur in relation to pain control, as previously discussed. Future research is needed to clarify and understand the role of polarity, if any, when using HD-tDCS therapeutically in FM and other chronic pain syndromes.

Another important finding was that, although their maximum duration is yet to be determined, the analgesic effects of 4×1-ring HD-tDCS lasted for at least 30 minutes and in fact, for anodal stimulation, the peak of behavioral effects was observed 30 minutes after the intervention. Using TMS assessments of motor-evoked potentials, Kuo et al²⁵ recently showed that motor cortex excitability is modulated in a polarity-specific manner following a 10-minute session of 4×1-ring HD-tDCS at 2.0 mA with a radius of 3.5 cm between electrodes. In their study, anodal and cathodal HD-tDCS led to maximal excitation or inhibition, respectively, 30 minutes after delivery of each intervention, with aftereffects as long as 2 hours. The magnitude and duration of these neuromodulatory effects were more prominent than those induced by conventional tDCS. This “delayed” effect is supported by our findings. However, it differs from that of tDCS using conventional electrode pads, as a single 13-minute session of conventional anodal tDCS can modify cortical excitability for approximately 90 minutes but the peak of effects occurs immediately after stimulation.³⁶ The timing of the peak effects of conventional tDCS was also corroborated by Kuo et al.²⁵ Due to the complex time-dependent effects observed in our trial and in the above-mentioned study, it appears that the effects of 4×1 HD-tDCS may be diminished immediately after stimulation and therefore need to be interpreted carefully.

Given the transient nature of the effects of a single session of DC stimulation, our stimulation paradigm expectedly did not translate into a significant change in patients’ QOL, depression scores, or analgesic drugs

Focal M1 Modulation in Fibromyalgia Using HD-tDCS intake. This implies that 1) the washout period between visits was adequate; and 2) there were no long-lasting effects of the stimulation capable of making a significant impact on patients’ QOL. These results are nevertheless encouraging, and future studies using HD-tDCS may choose to deliver more prolonged protocols in order to achieve greater effect sizes, as has been done for conventional tDCS. Using this intervention, delivery of daily stimulation sessions for 2,¹⁵ 5,^{4,17} and 10⁵¹ consecutive days all led to cumulative and longer-lasting effects. Nonetheless, it must be noted that the effect size of a single session of 4×1-ring HD-tDCS for perceived pain in our study (.36 for anodal and .30 for cathodal center electrode) was comparable to that of a single session of high-frequency rTMS to the M1 in the setting of chronic pain syndromes (.40).³⁷ Unfortunately, no meta-analytical data are available regarding the effect size of a single session of conventional tDCS on chronic pain, and therefore we could not compare it directly with that of HD-tDCS in our study. Delivery of multiple HD-tDCS sessions may be critical in helping define optimal stimulation protocols. In fact, given the long-lasting aftereffects reported by Kuo et al,²⁵ multiple stimulation sessions may translate into a more effective, cumulative integration of HD-tDCS treatment across days.

With respect to our secondary outcomes, only mechanical detection thresholds (SWMs) showed a significant change in relation to the intervention. This effect was seen, bilaterally, only after anodal HD-tDCS. We did not observe any significant changes in pain thresholds (SWMs, PPTs, or DNICs). A study in which FM patients underwent weekly 20-minute sessions of conventional anodal tDCS to the left M1 also did not find any significant changes in PPT assessments.⁴³ Similarly, Borckardt et al⁹ did not find any changes in mechanical pain or heat pain thresholds in healthy subjects immediately after delivery of 2.0 mA of anodal 4×1-ring HD-tDCS for 20 minutes, and reported only a marginal analgesic effect for cold pain thresholds. The latter finding may be related to the absence of significant pain reduction immediately after anodal HD-tDCS in our study.

Conversely, a previous study assessing the effects of conventional tDCS on thermal and mechanical perception thresholds in healthy volunteers showed a temporary reduction in sensitivity to A-fiber-mediated and nonpainful somatosensory inputs only after cathodal stimulation,⁵ while other trials report an increase in both sensory and pain perception thresholds after anodal tDCS of the left M1.^{8,41} However, all these studies were performed in healthy subjects, in whom conventional tDCS may have distinct effects due to the absence of anomalous central pain processing. In this population, anodal tDCS has been proposed to modulate perception via corticothalamic inhibition of epicritic and nociceptive sensation at the ventral posterolateral and ventral posteromedial nuclei of the thalamus, respectively.⁸ Additionally, these differences may be explained by the fact that conventional tDCS stimulates rather diffuse cortical areas, which may include the somatosensory cortex.

Finally, all of our 4×1-ring HD-tDCS sessions proceeded uneventfully and were not associated with any adverse effects other than a mild-to-moderate tingling or itching sensation. In most cases it faded out after the first few minutes of stimulation and was reported during both active and sham HD-tDCS. This supports the tolerability of this intervention in both healthy subjects⁹ and patients when 2.0 mA are delivered for 20 minutes.

Limitations

Our study has some limitations. First, there is an issue of variability in the data given that our primary outcome was a subjective, patient-reported variable, which could potentially lead to biased results from measurements. Even semiobjective measurements such as quantitative sensory testing still rely on patient's report. However, we attempted to reduce this bias by employing a patient- and assessor-blind, single-rater design for all data collection.

Secondly, there is a potential for low power due to the small sample size of 18 patients. For this reason, we employed a crossover design to increase the power of this trial, which was intended to be a small, proof-of-principle study providing early evidence on the potential analgesic role of 4×1-ring HD-tDCS in a chronic pain patient population. Nevertheless, post hoc power analyses showed that it was greater than 90%. In the future, we plan to carry out a larger trial to test the efficacy of HD-tDCS with a greater number of participants and multiple consecutive days of stimulation.

Twelve of the 18 patients who participated in our study were taking 1 or more CNS-acting drugs at the time of their enrollment. However, dosages were kept stable throughout their participation in all cases to ensure that the effects of HD-tDCS were not affected by changes in drug dosages. Because of the small sample in our study and the heterogeneous use of CNS-acting medication, it would not be possible to conduct subgroup analyses based on the dosages of these drugs. However, it is

important to underscore that our crossover design addressed the issue of potential differences in medications across groups.

Lastly, due to difficulties in its interpretation, CONSORT 2010 guidelines no longer encourage testing for and reporting the success of blinding.^{46,52} For this reason, this parameter was not formally evaluated in our study. However, we followed a rigorous methodology, as previously described, in order to minimize the possibility of bias.

Conclusion

A single 20-minute session of active 4×1-ring HD-tDCS, with a radius of approximately 7.5 cm between electrodes and delivering 2.0 mA to the left M1, provided significant overall pain relief in FM patients as compared to sham stimulation, regardless of current polarity. This protocol was well tolerated in this patient population, in whom it induced no moderate or serious adverse effects. Although these findings are not sufficient to definitely establish 4×1-ring HD-tDCS as a therapy for FM, this trial represents an initial step toward the study of a potentially effective intervention.

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Supplementary Data

Supplementary data related to this article can be found online at <http://dx.doi.org/10.1016/j.jpain.2012.12.007>

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