

Transcranial DC Stimulation in Fibromyalgia: Optimized Cortical Target Supported by High-Resolution Computational Models

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Abstract: In this study we aimed to determine current distribution and short-term analgesic effects of transcranial direct current stimulation (tDCS) in fibromyalgia using different electrode montages. For each electrode montage, clinical effects were correlated with predictions of induced cortical current flow using magnetic resonance imaging–derived finite element method head model. Thirty patients were randomized into 5 groups (Cathodal-M1 [primary motor cortex], Cathodal-SO [supra-orbital area], Anodal-M1, Anodal-SO, and Sham) to receive tDCS application (2 mA, 20 minutes) using an extracephalic montage. Pain was measured using a visual numerical scale (VNS), pressure pain threshold (PPT), and a body diagram (BD) evaluating pain area. There was significant pain reduction in cathodal-SO and anodal-SO groups indexed by VNS. For PPT there was a trend for a similar effect in anodal-SO group. Computer simulation indicated that the M1-extracerebral montage produced dominantly temporo-parietal current flow, consistent with lack of clinical effects with this montage. Conversely, the SO-extracerebral montage produced current flow across anterior prefrontal structures, thus supporting the observed analgesic effects. Our clinical and modeling findings suggest that electrode montage, considering both electrodes, is critical for the clinical effects of M1-tDCS as electric current needs to be induced in areas associated with the pain matrix. These results should be taken into consideration for the design of pain tDCS studies.

Perspective: Results in this article support that electrode montage is a critical factor to consider for the clinical application of tDCS for pain control, as there is an important correlation between the location of induced electrical current and tDCS-induced analgesic effects.

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Key words: Chronic pain, fibromyalgia, transcranial direct current stimulation, finite element modeling, MRI human head model, electrode montage.

Based on recent neuroimaging and neurophysiological studies showing significant brain activity dysfunction in fibromyalgia, noninvasive brain stimulation has been tested as a potential treatment strategy for this

condition. Trials using magnetic fields with transcranial magnetic stimulation (TMS) over the motor and prefrontal cortex have shown long-lasting effects for pain decrease in patients and in healthy volunteers.^{25,28,31} Studies with another technique of noninvasive brain stimulation—transcranial direct current stimulation (tDCS)—have also shown positive results for pain reduction,^{12,13,24,30} and might be more effective in increasing pain tolerance than other forms of transcranial stimulation.¹⁷ tDCS has further advantages as it can be combined with other behavioral interventions while being a relatively established, safe, low-cost, easy-to-apply technique that is therefore an attractive option for clinical research.^{16,17,26} Finally, recent tDCS research has shown its benefits in sleep and depression (symptoms usually manifested in fibromyalgia).^{2,30}

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tDCS electrode montage (the position and size of electrodes) determines the resulting brain current flow and hence neuro-physiological effect²⁷ and clinical outcomes. Indeed, the ability to customize tDCS treatment through electrode montage provides clinical flexibility and the potential to individualize therapies. At the same time, the need to understand and optimize electrode montages to treat specific diseases, such as fibromyalgia, remains a fundamental challenge in tDCS—inconsistent findings in the literature may reflect poor control of montage. In this context we aimed to address several critical questions in the planning of clinical trials for fibromyalgia including: 1) whether similar clinical effects can be induced with different electrode montages in fibromyalgia; and 2) whether the use of extracephalic reference electrode is an effective strategy.

In this study we determined whether extracephalic stimulation (placing 1 return electrode outside the scalp area and using different active electrode positions on the scalp) is an effective strategy in fibromyalgia as indexed by pain reduction and by intracranial current distribution using a magnetic resonance imaging (MRI)-derived finite element head model. The sites of the active electrode were the 2 most common cranial sites used for the treatment of chronic pain (primary motor cortex (M1) and fronto-polar area (SO–supraorbital)). Both the M1 and supraorbital region were stimulated with 2 poles (anode and cathode) in separate conditions. We used a computer head model to predict the location of current flow through the brain using the different electrode montages employed in this study. The significance of this approach lies in the combination of clinical evaluation and computer head-modeling data to investigate the effects of different electrode montages in reducing pain in fibromyalgia.

Methods

Study Population

This study consisted of a randomized, double-blind clinical trial conducted at the Advanced Physical Therapy Clinic (CAFIS) of the Bahiana School of Medicine and Public Health (EBMSP) in the period from September, 2008 to November, 2009 and a computer head-modeling study conducted at the Neural Engineering Laboratory at The City College of New York of CUNY, and also in collaboration with the Laboratory of Neuro-modulation (Spaulding Rehabilitation Hospital–Harvard Medical School). The study included 30 participants diagnosed with fibromyalgia by the criteria of the American College of Rheumatology (ACR), literate, and in the age group between 18 and 60 years. We excluded individuals on medication for pain control or undergoing physical treatment for less than 2 months; individuals with epilepsy and malignant diseases; pregnant women and infants; patients with metal implants in the encephalon or skull; and patients using illicit drugs.

All the participants were submitted to 4 stages of the study: 1) assessment for compatibility with the inclusion/exclusion criteria (the patients selected by the crite-

ria signed a term of free and informed consent, and were provided with all the information with reference to the research); 2) pain assessment by an examiner blinded to the treatment; 3) treatment with transcranial direct current stimulation or sham; and 4) reassessment by the same examiner in stage 2 using the same outcomes.

This study was approved by the Research Ethics Committee of the Bahiana School of Medicine and Public Health (EBMSP), No. 59/2008, and in agreement with Resolution 196/96 of the National Health Council (BRA).

Assessment Methods

Because we were interested in the short-term effects of tDCS in pain, we chose the appropriate following assessments: 1) a Visual Numerical Scale (VNS) of pain, zero being no pain and 10 the worst possible pain; 2) the marking of areas of pain on a body map, and the total area (pixels/cm²) of pain was assessed for each patient by an image editing program (Java Image, NIH); 3) the measurement of pressure pain threshold (PPT) with the use of a pressure algometer (Pain Diagnostics & Thermographics Corporation, Great Neck, NY) to establish minimum pressure that triggers pain in the 18 pre-established points for the diagnosis of fibromyalgia.³³ For statistical analysis, we used a single value (sum of 18 points). All patients were submitted to the assessment before and immediately after a single session of tDCS.

Transcranial Direct Current Stimulation (tDCS)

Treatment was performed by a therapist with no knowledge of the measurements assessed and our hypotheses. As aforementioned, 2 stimulation sites that have been extensively employed in recent research, in accordance with the International 10/20 System of Electrode Placement,¹⁵ were used: position C3, corresponding to the region of the left primary motor cortex (M1) and the right supra-orbital area, corresponding to the anterior prefrontal cortex region (PFC). The location of electrodes was determined through individual measurement.

Patients were randomly divided into 5 groups named according to the transcranial electrode: 1) Group cat-M1–cathodal stimulation of the left M1 region; 2) Group cat-SO–cathodal of the right supra-orbital region; 3) Group ano-M1–anodal stimulation of the left M1; 4) Group ano-SO–anodal stimulation of the right supra-orbital region; and 5) sham stimulation group. The peripheral electrode was placed over the transition of the cervical and thoracic spine (between the scapulas) in all the groups. We chose the left M1 and right SO positions as this has been used in several of our previous studies.^{12,13}

tDCS was performed using a universal pulse generator (941 NEMESYS, Quark Medical Products, Brazil) previously calibrated for the study. The treatment method involved a single application of a direct current at an intensity of 2 mA for 20 minutes through pairs of aluminum-sponge surface electrodes of 2 sizes: 80 × 100 mm when used on the extracephalic position, and 40 × 40 mm when used cranially. For sham stimulation, current was turned ON only for the initial 30 seconds.

FEM Model of Induced Brain Current Flow

To consider the role of different electrode montages on induced brain current flow during tDCS, we developed finite element (FE) models. All models were based on a single MRI-derived head model from a healthy adult subject. We considered 3 electrode montages (M1-extracerebral; SO-extracerebral; and also M1-SO; although this last montage was not used in the present clinical study, this montage was used previously by our group in other studies and served as a means to compare clinical and modeling results). The head model was created at the same resolution ($1 \times 1 \times 1$ mm) as the MRI data used to derive it. The entire workflow, including segmentation of data, mesh creation, and the eventual export to a finite element method solver (Simpleware Ltd., Exeter, UK), was detailed previously.⁸ Since the FEM model was directly derived from the subject's anatomical data and in order to approximate the exact clinical montage used, a dummy neck and shoulder region was fused onto the existing segmented head. For the model used in this paper (Fig 1) the electrical properties of the tissues are assigned representative isotropic average values (in S/m): gray matter, .276; white matter, .126; CSF, 1.65; skull, .01; scalp, .465; muscle, .334; air, $1e-15$; eye region, .4; and dummy region, .17. The blood vessel compartment was assigned the same tissue property as that of scalp.

We modeled the conventional sponge-based electrodes using in this study: 80 mm \times 100 mm when used outside the head, and 40 mm \times 40 mm when used over the scalp, and calculated the induced currents in the cortex resulting from application of 2 mA total current (corresponding to an average electrode surface current density of .28 A/m² in the cranial electrode). We modeled 3 electrode montages (Fig 1): 1) M1-extracerebral—One electrode was placed over the primary motor cortex (corresponding to C3 according to the 10/20 EEG system) and the other electrode was placed over the cervical/thoracic transition dorsal midline; 2) Supraorbital (SO)-extracerebral—One electrode was placed over the supraorbital area and the other electrode was placed in the same extracerebral position as montage A; and 3) We performed a third modeling using the position of electrodes most used in studies to modulate chronic pain (M1-SO) as to have a comparison (this is the montage we used in our previous study with the same methodology and similar patient population as the current study).^{12,13,30} During conventional tDCS, rectangular sponges are typically soaked in saline and the abutting electrode is energized. The sponge was thus assigned the electrical conductivity of saline ($\sigma = 1.4$ S/m) and the stimulation electrodes were modeled as conductors ($\sigma = 5.8 \times 10e7$ S/m). The electrodes had a thickness of 1 mm and the thickness of the sponge varied from 1 to 2.5 mm.⁸

The Laplace equation was solved and current densities corresponding to 2 mA total current were applied (Datta et al⁸). Surface-magnitude plots were generated for each of the montages by plotting the magnitude of electric fields (EF) on the cortical surface. All false color map plots

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were plotted between 0 and the peak EF magnitude induced in Montage A.

Importantly, researchers acquiring modeling data were blinded to the clinical results.

Statistical Analysis

Statistical analysis was conducted using STATA v.11.0 (College Station, TX). Initially we conducted a group analysis running an ANOVA model in which the main outcome was change in pain intensity and the independent variables were time (before versus after) and condition of stimulation (groups of treatment) and the interaction term between these two variables (time \times condition). If appropriate, we then performed post hoc analysis using paired t-test to assess effects of each condition of stimulation. We tested data normality using a Shapiro-Wilk test and if not normal we used nonparametric tests (Kruskal-Wallis and Mann-Whitney). Finally we conducted exploratory correlation analysis between demographic characteristics and VNS changes.

Results

Thirty individuals were included in this study (28 females, mean age of 43.2 years [± 9.8]). The clinical and demographic characteristics of the patients are shown in Table 1. Patients reported stimulation as mild tingling at the beginning of sham and active stimulation (initial seconds) and most of the subjects reported no further sensation at the rest of stimulation period. There were no adverse reactions and no dropouts.

All patients were either on medication and physical therapy to treat pain for more than 2 months or not taking medications or physical therapy for at least 2 months and were similar across treatment groups. The most used medications were: codeine phosphate and paracetamol (33%), amitriptyline (26.6%), fluoxetine (16.6%), clonazepam (16.6%), dipyrone (10%), and ketoprofen (10%).

Pain Intensity (VNS) and Pain Threshold (PPT)

We initially conducted a group analysis using an ANOVA in which the dependent outcome was pain intensity (as indexed by VNS) and pain threshold (as indexed by PPT). This analysis revealed a significant interaction (between time and group) for both VNS and PPT ($F_{(9,28)} = 5.63$, $P = .0002$ for VNS and $F_{(9,28)} = 2.23$, $P = .05$ for PPT). We then conducted post hoc testing that revealed significant pain decrease in the cat-SO (t-test, $P = .0104$) and ano-SO groups (t-test, $P = .015$) for VNS, showing that fronto-polar (supra-orbital) tDCS is associated with a significant analgesic effect, irrespective of the pole used (Fig 2). There was a trend for a similar effect using PPT as the outcome but only in the ano-SO group (t-test $P = .059$) (Fig 2).

Pain Representation

Here we used a nonparametric test, because we found a skewed distribution of values; thus, we used Kruskal-Wallis. This analysis showed no significant

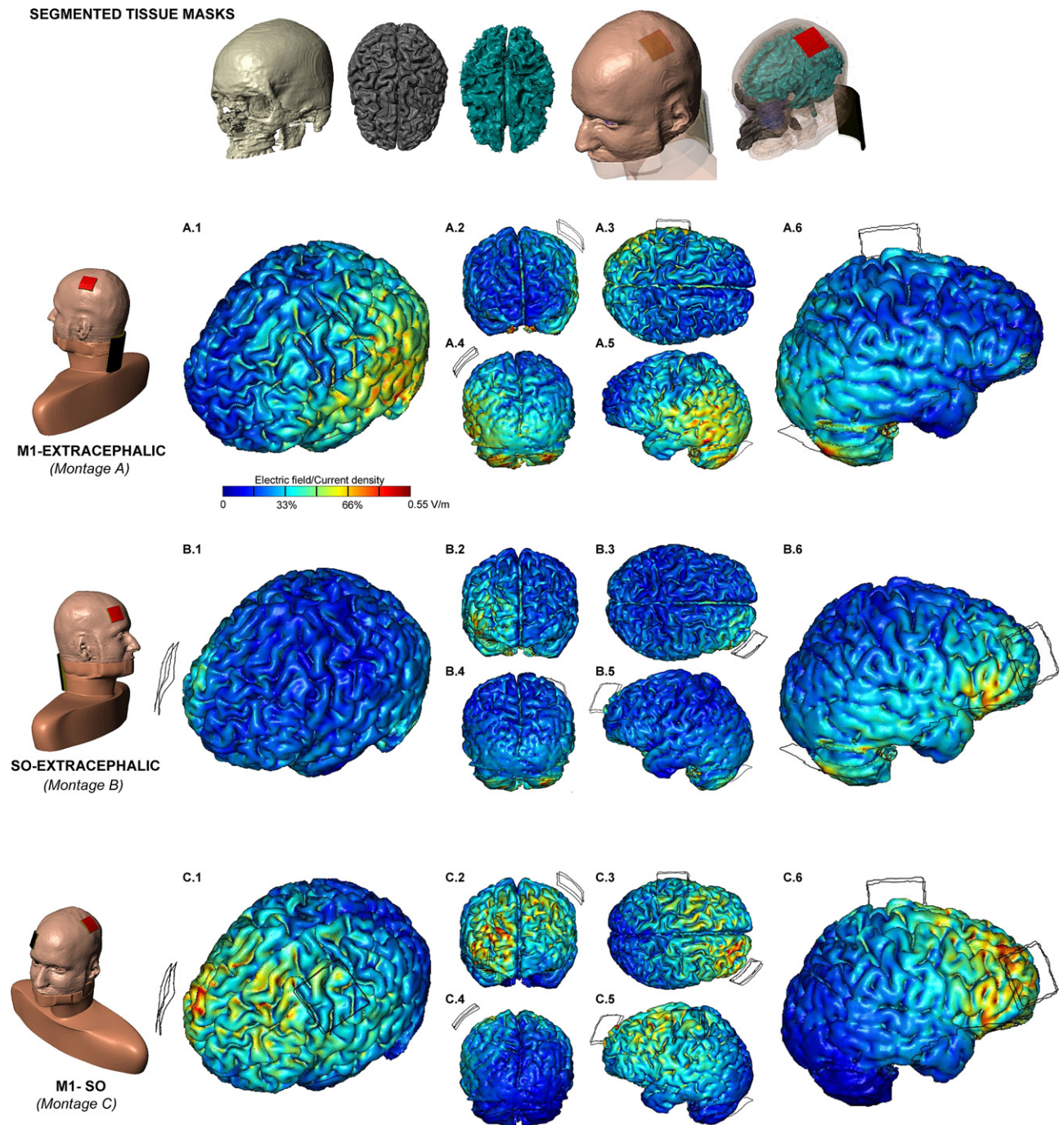


Figure 1. Computational results of induced cortical currents during tDCS in Fibromyalgia using a $1 \times 1 \times 1$ mm resolution head model. Montage A, M1-extracerephalic; Montage B, SO-extracerephalic; Montage C, M1-SO (see Methods). For each montage, we calculated the induced cortical electric field (EF) magnitude. All false color maps were generated between 0 and .55 V/m, the peak cortical EF magnitude induced for Montage A. Surface magnitude plots of EF were generated with different views. Top row: Sample segmentation masks. A. 1 and A.6; B. 1 and B.6; C.1 and C.6 were generated at a higher zoom level to highlight current flow in the M1 region and the right side regions respectively. A.2, B.2, C.2 show the frontal view while A.4, B.4, C.4 show the posterior view. A.3, B.3, C.3 show current flow in the top view and A.5, B.5, C.5 show current flow in the left side regions. (Please see www.jpain.org for adequate visualization of this figure.)

differences across groups ($P = .21$). We therefore did not conduct post hoc analysis for this outcome.

Correlations

We performed an analysis to search for correlation between demographic characteristics and pain reduction,

and we did not find any significant correlations for the active conditions.

Baseline Comparisons

Because there was a small but not significant difference between baseline values (although this was not a crossover study) we adjusted our findings to baseline

Table 1. Clinical and Demographic Characteristics

	CAT-M1	CAT-SO	ANO-M1	ANO-SO	SHAM	P-VALUE*
Number (n)	6	6	6	6	6	
Age (years)	41.8 (±12.9)	43.5 (±8.5)	44.5 (±10.5)	42.6 (±9.2)	43.5 (±10.4)	.9
Gender (female (%))	83.4%	100%	83.4%	100%	100%	
VNS pain–baseline	6 (±2.8)	6.5 (±1.8)	5.5 (±2.4)	8.3 (±2.7)	8.6 (±1.5)	.09
PPT–baseline	27.6 (±10.4)	19.6 (±19.4)	30.5 (±15)	22.2 (±15.8)	30.2 (±12.5)	.6
Pain location (pixels/cm)	4.2 (±4.3)	8.2 (±8.8)	3.3 (±1.4)	6.5 (±5)	6.8 (±6.3)	.5

*ANOVA 1-way for the comparison of variables.

values. This analysis revealed that baseline values did not influence the results.

Computer Head Modeling

We modeled the current distribution in the head during tDCS with 2 mA using the 2 electrode montages evaluated here, and 1 additional montage used in a previous treatment study. We considered the electric field magnitude distribution and the peak electric field induced along the cortical surface. The M1-extracerebral montage stimulation resulted in .55 V/m peak cortical electric field magnitude. Importantly (differently than the traditional M1-SO montage) (see Fig 1A and C), current was localized in the temporo-parietal cortex and not over the motor cortex. The SO-extracerebral electrode config-

uration resulted in peak EF being more localized under the frontal electrode (Fig 1B). The M1-SO configuration also resulted in peak cortical electric field in the frontal regions (Fig 1C) but with significant electric field/current flow in the cortical regions between electrodes (comparable to Datta et al⁸). (Note that all figures in Fig 1 were plotted to the same peak, as observed in Montage A; therefore the main difference observed was in the location, rather than peak, of electric field). In summary, there was a significant difference in current distribution when comparing the most used montage (M1-SO) with the extracerebral montages (M1-extracerebral and SO-extracerebral).

Discussion

Our results suggest for the first time in a clinical setting the important notion that current distribution is critical for the effects of tDCS in reducing pain in fibromyalgia. Specifically our findings support that using the cortical sites associated with positive effects (montage M1-SO) but in an isolated manner with a different current distribution (using extracerebral electrodes) resulted in a lack of effects for primary motor cortex stimulation and in positive effects for supraorbital electrodes. Importantly there was a strong association between the clinical and modeling results such that only electrode montages producing significant current flow through relevant brain structures produced positive clinical effects.

One interesting aspect is that cathodal or anodal stimulation of the supraorbital region had an important influence on the pain variables studied, pointing to the fact that the prefrontal cortex (in addition to the M1) is a critical region in the modulation of pain in patients with fibromyalgia. This region has many connections with the other brain structures that are highly involved in pain modulation such as the medial dorsal nucleus of the thalamus, the limbic association cortex, hypothalamus, and the periaqueductal gray substance.^{10,21} These connections are associated with an important role in the modulation of emotions, particularly anxiety and fear,^{9,23,32} and behavioral characteristics of attention and perception.^{1,7,29} In fact, studies using neuromodulation techniques over the prefrontal cortex showed positive results in decreasing pain threshold in healthy volunteers using tDCS and TMS.^{4,6,25} The stimulation of this region also shows positive results for patients with chronic pain using TMS,^{5,31} supporting that the prefrontal cortex is a possible target for

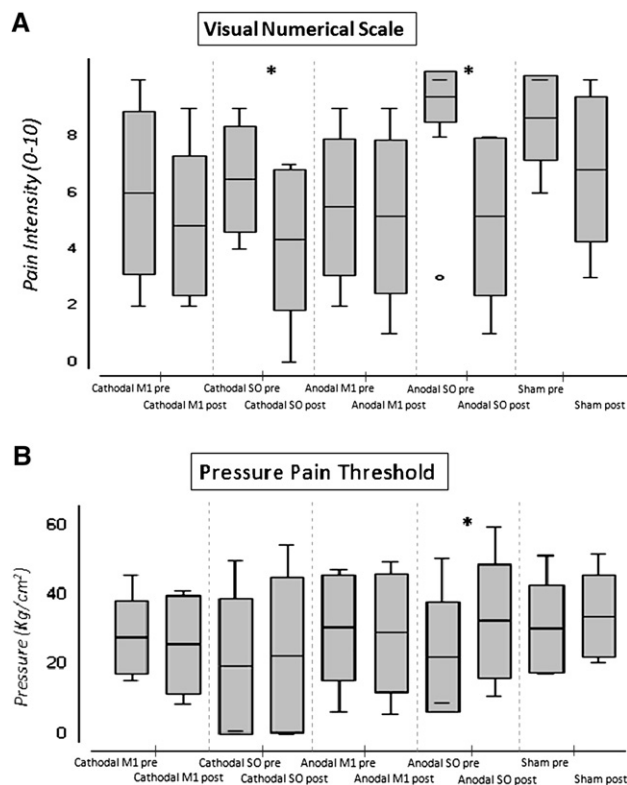


Figure 2. (A) Demonstrates the scores of pain intensity before and after treatment in each group. There was a significant reduction in pain intensity in the CSO and ASO groups. (B) Scores of pain pressure threshold before and after treatment in each group. There was an improvement in the pain threshold in the ASO group. *Indicates significantly different values (t-test, $P < .05$). The measures are represented by mean and standard deviation.

treatment of patients with chronic pain with other brain stimulation methods such as tDCS. One important point is that we observed a similar effect for anodal and cathodal stimulation over the SO area and therefore it raises the question of whether modulation of different inhibitory and excitatory circuits within the anterior prefrontal cortex leads to modulation of pain-related neural circuits. Although most of the studies targeted dorsolateral prefrontal cortex (DLPFC) and not frontopolar areas as we did in our study, it is possible that this area is as effective as DLPFC for the modulation of pain-related circuits. Finally, the observation that presumed anterior prefrontal cortex stimulation with a SO electrode has clinical significant effects raises interesting questions about numerous studies where an SO-electrode was used as a (nominally inactive) reference electrode in pain studies.

On the other hand, electrode montages with cathodal or anodal stimulation over regions of the M1 with an extracephalic return did not produce significant analgesic effect. At first glance, without accurate consideration of induced cortical current flow (eg, with models), this result would appear to contrast with extensive invasive and noninvasive brain stimulation data showing that primary motor cortex is an excellent target for the treatment of chronic pain (see review, Lima and Fregni²⁰). Indeed, previous tDCS studies have shown that positioning the anode in M1 and the cathode in the supraorbital region (M1-SO) had analgesic effects under several conditions.^{12,13,24,30} The main rationale for motor cortex stimulation is that M1 modulation activates superficial layers of the motor cortex (intercortical interneurons, rather than corticospinal axons) that leads to a cascade of synaptic events resulting in modulation in an extensive neural network that includes thalamic nuclei, limbic system, brainstem nuclei and spinal cord—critical areas of the pain matrix.²⁰ However, in this study, computer modeling results indicate that the M1-extracephalic montage produces a dominant current flow pattern that largely avoids M1—consistent with this montage producing insignificant analgesic effects.

One important aspect to notice is that previous studies used 2 electrodes over the head (bilateral montage). Although our results suggest that M1-extracephalic is not an effective montage, it is important to underscore that the return extracephalic electrode position is critical since different placements of this electrode will change current direction—for instance, some other extracephalic positions for M1 stimulation might induce significant currents in M1—therefore testing different extracephalic montages is warranted. The role of return electrode position (and size) in modulating neurophysiological effects under the active electrode is established.^{22,27} Our findings here using extracephalic electrodes, taken together with the aforementioned M1-SO results, provide the clearest evidence to date of the importance of total electrode montage (active and return) design in determining clinical outcome; moreover, our clinical findings substantiate the need and utility of accurate computer modeling of cortical current flow. More generally, our results provide specific insights

into the use of extracephalic electrodes, including how the use of an extracephalic electrode may profoundly affect cortical currents under and around active electrodes and, hence, account in part for variability across studies.

One interesting and unexpected finding was that supra-orbital tDCS was associated with analgesic effects irrespective of polarity (anodal and cathodal SO were associated with significant analgesic effects). Although if we compare this result with the other technique of non-invasive brain stimulation (repetitive TMS), we would expect that excitability enhancing anodal-tDCS would be the only condition associated with analgesic effects; however, the mechanisms of tDCS are different. In fact, we showed in 3 previous tDCS studies that prefrontal tDCS induces cognitive and behavioral modulation that is independent of polarity (ie, anodal and cathodal tDCS are associated with significant effects).^{3,11,14} A potential explanation here is because of the large electrical fields induced by tDCS; thus, it is possible that inhibitory and also excitatory activity are beneficial as different neural networks are simultaneously activated. It is also important to mention that cephalic electrode placed in SO could have influenced more areas than when the electrode was positioned in M1 due to the direction of created fields.

This trial gives some insights on the cortical mechanisms of pain modulation as we showed with modeling and clinical data cortical areas associated with pain modulation. In addition, our results suggest that extracephalic montage might not induce significant currents in the area under the electrode and therefore current distribution needs to be carefully addressed in studies using this montage. There are some limitations in our trial. First, the small sample of the subgroups might have resulted in false negative results; however, there was not even a trend for significant results when analyzing data from M1 stimulation. Another potential limitation is that we only conducted 1 session of tDCS and measured the short-term effects. However, extensive work by Lefaucheur et al^{18,19} showed that 1 session of noninvasive brain stimulation is effective to induce pain relief. We also showed similar results with no significant or positive effects for M1-extracephalic tDCS, using the same montage for 5 days of stimulation in patients with fibromyalgia (unpublished data).

We did not measure neurophysiological data in this study; however, because we decided to study also prefrontal cortex as an isolated area, TMS-cortical excitability would not be helpful in this case. Also, we wanted to show clinical changes associated with location of stimulation (from modeling studies). Here it needs to be underscored also that we did not measure other pain-related cognitive and behavioral changes as well as investigation of other pain characteristics (for instance, such as those indexed by the McGill questionnaire); therefore, it is possible that these domains were also affected by changes in current distribution using alternative electrode montages and they need to be explored in future studies. Finally, it is important to note that our computational results were based on a single individualized MRI derived head model. Interindividual

variability⁸ may have some influence in the magnitude and the spatial extent of induced cortical fields predicted in this study, although this influence would be expected to be small.

In conclusion, it was observed that the stimulation of the prefrontal cortex with tDCS, irrespective of the polarity of the electrode, resulted in short-term pain decrease in patients with fibromyalgia, and that the stimulation of the M1 area using the extracephalic electrode had no immediate analgesic effect. Our study supports the notion that the electrodes montage is fundamental to achieving a positive result in pain decrease. The usage of extracephalic electrodes with motor cortex or prefrontal cortex electrodes activates different cortical areas compared

tDCS Clinical-Modeling Study in Fibromyalgia with the use of 2 electrodes over the scalp; therefore, we showed a match between currents induced in areas associated with pain matrix and pain reduction. These findings should be taken into consideration in future tDCS studies.

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