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Research Submission

tDCS-Induced Analgesia and Electrical Fields in Pain-Related Neural Networks in Chronic Migraine

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Objective.—We investigated in a sham-controlled trial the analgesic effects of a 4-week treatment of transcranial direct current stimulation (tDCS) over the primary motor cortex in chronic migraine. In addition, using a high-resolution tDCS computational model, we analyzed the current flow (electric field) through brain regions associated with pain perception and modulation.

Methods.—Thirteen patients with chronic migraine were randomized to receive 10 sessions of active or sham tDCS for 20 minutes with 2 mA over 4 weeks. Data were collected during baseline, treatment and follow-up. For the tDCS computational analysis, we adapted a high-resolution individualized model incorporating accurate segmentation of cortical and subcortical structures of interest.

Results.—There was a significant interaction term (time vs group) for the main outcome (pain intensity) and for the length of migraine episodes (ANOVA, $P < .05$ for both analyses). Post-hoc analysis showed a significant improvement in the follow-up period for the active tDCS group only. Our computational modeling studies predicted electric current flow in multiple cortical and subcortical regions associated with migraine pathophysiology. Significant electric fields were generated, not only in targeted cortical regions but also in the insula, cingulate cortex, thalamus, and brainstem regions.

Conclusions.—Our findings give preliminary evidence that patients with chronic migraine have a positive, but delayed, response to anodal tDCS of the primary motor cortex. These effects may be related to electrical currents induced in pain-related cortical and subcortical regions.

Key words: transcranial direct current stimulation, chronic migraine, motor cortex, neuromodulation, brain stimulation, chronic pain

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Conflict of interest: The City University of New York has intellectual property on brain stimulation with Marom Bikson and Abhishek Datta as inventors.

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Abbreviations: CGI clinical global impression, CM chronic migraine, MMSE mini-mental state examination, PGA patient global assessment, tDCS transcranial direct current stimulation, VAS visual analogue scale

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Although migraine is a disorder characterized by episodic attacks, some patients can develop a progressive state of this disease with more than 15 attacks per month. This state is referred to as chronic migraine (CM). It has been shown that CM is not only a condition associated with more frequent attacks but also with changes in pain-related neural networks such as increased sensitivity to noxious stimuli (hyperalgesia) and even non-noxious stimuli (allodynia, a phenomenon that affects up to 63% of these patients).[1-5] Furthermore, neuroimaging studies have shown that development and perpetuation of migraine disorders have a similar neural basis as the pathophysiology of chronic pain.[6] For instance, these imaging studies on migraine found morphological and functional abnormalities in regions involved in central pain processing, such as the trigeminal somatosensory pathway, primary somatosensory cortex, and anterior cingulated cortex.[7] These results suggest that repeated attacks can lead to central sensitization.[6,8,9]

Given evidence that chronic migraine is also associated with central sensitization, one potential therapeutic approach for these patients is the use of a technique that can modulate pain-related neural networks such as transcranial direct current stimulation (tDCS). This robust method of brain modulation has demonstrated significant results in different types of chronic pain,[10-14] and has been shown to be more effective at increasing pain tolerance than other forms of transcranial stimulation.[15] tDCS has potential advantages for the treatment of chronic pain disorders, including its small portable size, low cost, and ability to provide a more reliable placebo condition.[16]

In order to preliminarily investigate the analgesic effects given our primary outcome of daily pain measured by the visual analogue scale (VAS) of an extensive 4-week tDCS treatment in chronic migraine, 13 patients with CM were randomized to receive active or sham stimulation of the primary motor cortex. In addition, we used high-resolution tDCS computational models to map the overall pattern of (sub)cortical current flow using our parameters of stimulation, which may influence tDCS pain treatment in a multimodal fashion.

METHODS

Study Subjects.—Our study consisted of a randomized, single-blinded with external blinded rater,[17,18] placebo-controlled, proof of principle clinical trial. The study conformed to the ethical standards of the Helsinki Declaration (1964) and was approved by the institutional ethics committee of Beth Israel Deaconess Medical Center. All patients provided written informed consent and the study took place at the Noninvasive Center for Noninvasive Brain Stimulation at Beth Israel Deaconess Medical Center. Patients were referred from chronic pain clinics from Boston such as the Arnold Pain Management Center at Beth Israel Deaconess Medical Center. The study included 13 participants between the ages of 18 and 60 years, diagnosed with chronic migraine by a pain specialist according to the revised International Headache Society Criteria (ICHD-II – appendix 1.5.1)[19] with an established headache history occurring on 15 or more days per month, however, for at least 1 year, instead of only 3 months as defined in the IHS guidelines. Patients with other neuropsychiatric or pain disorders were excluded, and they were instructed to maintain their regular preventive therapy during the trial.

Assessments.—Participants were randomized to 2 different groups – sham or active tDCS – using a simple randomization method. Baseline evaluation was performed 1 week before the study. Participants were assessed with self-report questionnaires and investigator-guided questionnaires. The primary outcome was perception of daily pain measured by the VAS. The other reported secondary outcomes included: length of migraine episodes, Patient Global Assessment (PGA), and Clinical Global Impression (CGI). In addition, safety was measured with an adverse effects checklist, Mini-Mental State Exami-

nation (MMSE) and Digit Span (forward and backward) (these last 2 instruments were used to index any detrimental effect on general cognitive function). For baseline data, we measured all outcomes for one full week immediately before the start of the trial in order to have a reliable baseline assessment. Measurements during treatment occurred at the midpoint (T15) and end of treatment (T30).

Finally, follow-up measurements were conducted at 60 (F60) and 120 (F120) days after the end of treatment. For the measurements, we collected daily data such as VAS pain, and averaged the periods of treatment (for instance, T15 indicates T1 to T15).

Transcranial Direct Current Stimulation.— Treatment was performed by an independent and trained investigator who had no knowledge of the subjects' group assignment. Subjects received a total of 10 sessions over a 4-week period (administered every other day during weekdays (Mo-Wed-Fri/Tue-Thu/Mo-Wed-Fri/Tue-Thu – over the course of 4 weeks) of either active or sham tDCS. The strategy of every other day treatment was chosen as to be able to give the treatment during a full month without being unfeasible (having patients coming daily would make the visits unfeasible for many patients). We have used this strategy successfully in other studies.[20]

During each session, the anode electrode (5 cm × 7 cm) was placed over the motor cortex (contralateral to the most [or predominant] painful side or the side where the symptoms begin) and the cathode electrode (5 cm × 7 cm) was placed over the contralateral supraorbital area. We chose this area based on previous results in tDCS trials in chronic pain.[10-14] In addition, the majority of studies do unilateral stimulation regardless whether pain is bilateral such as in fibromyalgia and spinal cord pain.[10,21-24] In fact, effects of unilateral stimulation on pain in these studies are observed bilaterally. In active tDCS subjects, 2 mA of tDCS (Magstim, UK) was applied for 20 minutes. For sham-controlled tDCS subjects, the same montage was used; however, current was applied only for 30 seconds, which successfully prevents subjects from distinguishing it from active tDCS.[16] The reason that tDCS offers a reliable sham method is that it uses a weak current (intensity of 2 mA) that is therefore usually below the skin threshold for perception – especially when applied continuously. Subjects often feel during current ramp up; for this reason, tDCS is offered during the first 30 seconds in the sham stimulation instead of no current. Thirty-second stimulation period is insufficient to produce meaningful changes[25,26] but mimics the initial sensation associated with active stimulation. This method of blinding is effective according to a recent study from the National Institutes of Health[16] and discussed in 3 recent reviews.[17,18,27] In addition, patients were naive to tDCS.

For further details about the tDCS protocol in this study, the method is visually explained in a stepwise manner by our scientific team in DaSilva et al.[28]

Statistical Analysis.—For statistical analysis, we assume that missing data were at random. We, therefore, performed the outcome investigation using intention-to-treat analysis with the method of last observation carried forward (for patients who started the treatment and received at least 1 session). We considered the average of values collected in the migraine diary (daily measurements) for baseline, T15 (middle of treatment), T30 (final day of treatment), F60 (first follow-up), and F120 (final follow-up) (see Fig. 1). Statistical analysis was conducted using STATA 11.0 (College Station, TX, USA). Initially, for continuous outcomes, as data are normally distributed (using Shapiro-Wilk test), we conducted a group analysis running a mixed ANOVA model in which the independent variables were time, condition of stimulation (sham vs active), the interaction term time vs the condition, and subject ID. If appropriate, we then performed post-hoc analysis using paired *t*-test to assess effects of each condition of stimulation. We did not correct for multiple comparisons as this was an exploratory proof-of-principle study. Finally, for ordinal outcomes (CGI and PGA), we performed the analysis using a Kruskal-Wallis test.

High-Resolution Computational Model.—Using a finite element (FE) model,[29,30] we further analyzed the effect of our electrode montage on the current flow in the brain, taking into consideration the electrical properties of cortical and subcortical structures. The human head model was derived from a high-spatial resolution (1 mm^3) 3T magnetic resonance imaging (MRI) of a male adult healthy subject, and segmented into compartments representing the scalp,

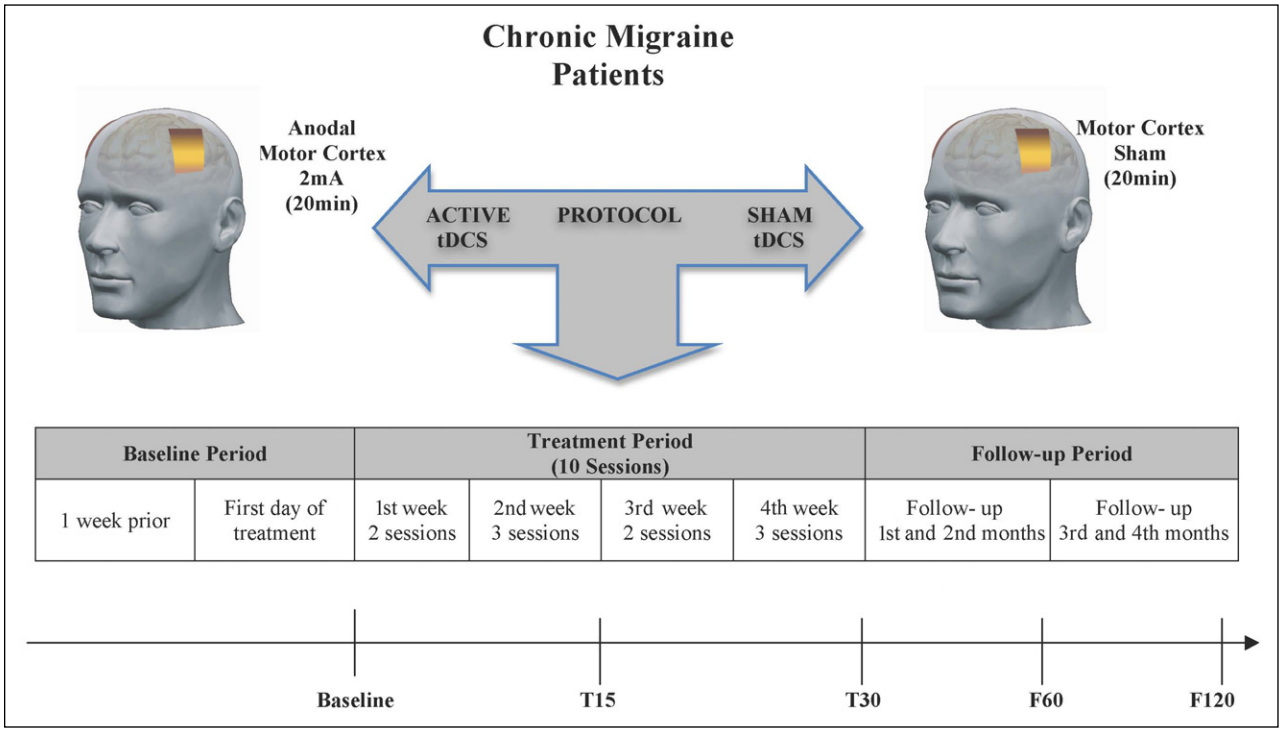

Fig 1.—Protocol design and method of time-points assessed during the protocol.

skull, cerebrospinal fluid, eye region, muscle, gray matter, white matter, and air, respectively. In addition to analyzing current flow patterns through structures implicated in pain matrix processing, subcortical and brain stem structures like insula, cingulate, thalamus, midbrain, pons, medulla oblongata were also segmented (Custom Segmentation, Soterix Medical, New York, NY, USA). Since the head model was directly derived from the MRI acquisition volume, it was limited by the anatomical sections collected. Thus, a synthetic dummy neck and shoulder region was fused onto the existing segmented head.[22,29] Sponge-based electrode stimulation pads (5 cm × 7 cm) were imported as computer-aided design (CAD) models and placed onto the segmented head to mimic the clinically used montage: anode electrode over the motor cortex and the cathode electrode at the forehead above the contralateral orbita. From the segmented data, volumetric mesh was generated and exported to an FE solver (COMSOL Multiphysics 3.5a, COMSOL Inc., Burlington, MA, USA). The following isotropic electrical conductivities (in S/m) were assigned: scalp – 0.465; skull – 0.01; cerebrospinal fluid – 1.65; eye region – 0.4; muscle – 0.334; gray matter – 0.276; white matter – 0.126; air – 1e-15; synthetic region – 0.17; sponge – 1.4; electrode – 5.8e7. The cingulate cortex, insula, and the thalamus were assigned gray matter conductivity while the midbrain, pons, and the medulla oblongata were assigned white matter conductivity. The Laplace equation was solved, and current density corresponding to 2 mA total current was applied. Induced cortical surface electric field (EF) magnitude and directional surface (showing inward and outward cortical currents) were determined (Fig. 3). In addition, cross-section magnitude plots were generated by plotting EF magnitude on axial slices through the different subcortical and brain stem regions (Fig. 4). Finally, it is important to note that the head model does not capture functional changes (unlike functional [f]MRI) and is based on simple physical assumptions such as Ohm's law. Nevertheless, we expect that the novel and intriguing prediction of current flow through deep brain structures is robust across subjects, and this general finding must be taken into account in future work on tDCS as well.

Table 1.—Clinical and Demographic Characteristics at Baseline

	Active tDCS	Sham tDCS
Number of subjects	8	5
Age (years, mean ± SD)	45.2 (±6.9)	45 (±4.2)
Gender (number of females)	5	3
Duration of disease (years, mean ± SD)	27.8 (±11.7)	31 (±4.2)
Number of days in migraine (per month, mean ± SD)	28.4 (±2)	29.5 (±0.7)
Pain intensity (VAS, mean ± SD)	4.6 (±2.1)	4.4 (±1.9)
Length of migraine episodes (hours, mean ± SD)	8 (±8.5)	12 (±10.7)

There were no differences between active and sham tDCS group ($P > .05$ for all the comparisons).
SD = standard deviation; tDCS = transcranial direct current stimulation; VAS = visual analogue scale.

RESULTS

Demographic Data and Adverse Effects.— Thirteen individuals were included in this study (9 women; mean age of 45.8 years [±6.3]), with 8 patients randomized to the active group and 5 patients to the placebo group as we used a simple randomization method. Demographic characteristics are described in Table 1 (there were no significant differences between sham and active tDCS groups). There were no severe adverse effects. We reported adverse effects in Table 2. Frequency of adverse effects was not significantly different between the 2 groups of stimulation. Also, there was no significant difference in the general cognitive assessment (MMSE and digit span) comparing the 2 groups of stimulation.

Table 2.—Adverse Effects Frequency

	Active tDCS	Sham tDCS	Total
Headache	7	5	12
Neck pain	5	2	7
Tingling	4	2	6
Skin redness	2	4	6
Sleepiness	1	4	5
Scalp pain	1	1	2
Total	20	18	38

There were no differences in adverse effects frequency between sham and active group ($P = .46$). Statistical analysis for total adverse effects in each group.
tDCS = transcranial direct current stimulation.

Clinical Effects of tDCS Over the Motor Cortex.— Mixed ANOVA revealed a significant interaction effect (between time and condition) for both VAS pain and length of migraine episodes ($F(8,44) = 2.46$, $P = .02$ for pain intensity and $F(8,44) = 2.49$, $P = .02$ for length of migraine episodes) but no significant changes for level of anxiety. We then conducted post hoc testing initially for VAS pain comparing baseline vs other time-points. This analysis for the active tDCS group revealed no significant change in pain intensity at the first time-point T15 (*t*-test, $P = .9$) and a trend for significance at the second time-point T30 (*t*-test, $P = .12$) and F60 (*t*-test, $P = .06$). We then found a significant decrease in pain levels at the last follow-up – after 4 months (*t*-test, $P = .03$). In fact, pain levels continued to decrease after the end of treatment (Baseline = 4.6 (±2.1); T15 = 4.7 (±2.7); T30 = 3.7 (±2); F60 = 3.1 (±2.7); F120 = 2.9 (±2.9) – see Fig. 2). There was a similar result for length of migraine episodes showing a trend for significant improvement at the T30, F60, and F120 (*t*-test, $P = .2$ for T30; $P = .17$ for F60; and $P = .05$ for F120), and also a decrease in the absolute values for this variable across time (length of migraine attacks (in hours) = baseline = 8 (±8.5); T15 = 4.7 (±7.9); T30 = 5 (±7.9); F60 = 4.3 (±6.4); F120 = 0.9 (±1.1)). For the analysis of CGI efficacy and improvement, statistical results revealed no differences at T15 but a significant difference at T30 for both CGI efficacy and improvement (Kruskal-Wallis, $P < .01$ for both CGI improvement and efficacy). For PGA, there was only a trend of significance at T30 ($P = .14$). Indeed, for CGI, we observed that 75% of patients had moderate improvement with partial remission of symptoms in the active group, while in the sham group 80% of patients had only slight improvement at the end of treatment.

tDCS-Induced Electric Current Fields: High-Resolution Computational Models.—Brain current flow (electric fields) though cortical and subcortical structures was predicted using a high-resolution

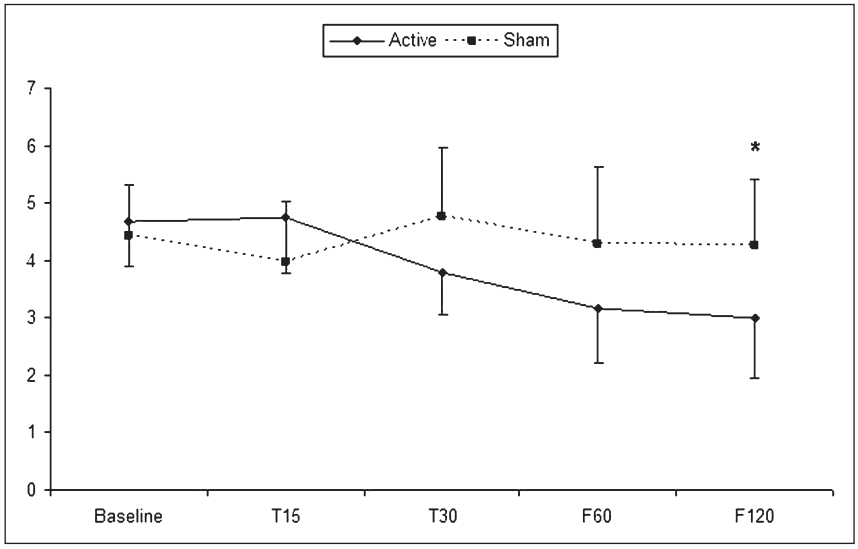

Fig 2.—Mean pain levels (as assessed by visual analogue scale) at baseline, T15, T30, F60, and F120 in the 2 groups of stimulation (active and sham tDCS). Error bars indicate standard error of the mean.

FE model of a representative adult male head (see methods).

Outer Cortical Regions.—In the present study, we identified clusters of electric current in regions located anterior to the central sulcus. This increased current flow was particularly intense in the dorsolateral prefrontal cortex (DLPFC) (putative Brodmann areas 8, 9, 9/46, and 46), with the highest current density in the middle frontal gyri (putative Brodmann area 46). In addition, significant peaks were also shown in other areas, such as: non-primary motor cortex (putative Brodmann area 6) and ventrolateral prefrontal cortex (putative Brodmann areas 44, 45, and 47/12), bilaterally. Elevated current density was as well identified in the orbital frontal cortex on both sides. Another noteworthy prediction is the increased current density along the lateral (Sylvian) fissure, especially on the right hemisphere (Fig. 3).

Inner (Sub)Cortical Regions.—*Insula.*—The analysis of the current flow during tDCS showed a peak of current density in the anterior insula, especially in the anterior and middle short insular gyri, bilaterally. There was another cluster of current in the posterior insula, mostly in the anterior long insular gyrus on the right side (Fig. 4).

Cingulate Cortex.—In the anterior regions of the cingulate cortex, the current flow pattern displayed increased density, including parts of the pregenual anterior cingulate cortex (pACC) (putative Brodmann areas 32 and 24) and anterior mid-cingulate cortex (aMCC) (putative Brodmann areas 32 and 24) bilaterally. Furthermore, the peak of current density was found on the right aMCC (putative Brodmann area 32). Low current densities were demonstrated along the posterior regions of the cingulate cortex, and clusters with peaks of current flow could also be seen in the PCC, particularly on the right side (putative Brodmann area 23) (Fig. 4).

Thalamus.—Our stimulations predicted current flow in several regions of the thalamus associated with pain. However, in the superior view, it was possible to observe that the highest density occurred in the posterior medial regions of the thalamus on the left side, presumably affecting the ventral posteromedial nucleus (VPM), the lateral posterior (LP), the pulvinar (Pu) nuclei, and in the anterior medial and regions on the right side, including dorsal medial (DM) and the ventral anterior (VA) nuclei. Moreover, the inferior view showed a peak current flow in both medial and lateral areas of the thalamus, including areas of the nucleus previously cited and other nuclei, such as the centromedian (CMe), the parafascicular (PF), the ventrolateral (VL), and the LP (Fig. 4).

Brainstem.—Peaks of activation could be observed in the cerebral peduncles, bilaterally. These peaks of current extended medially to the

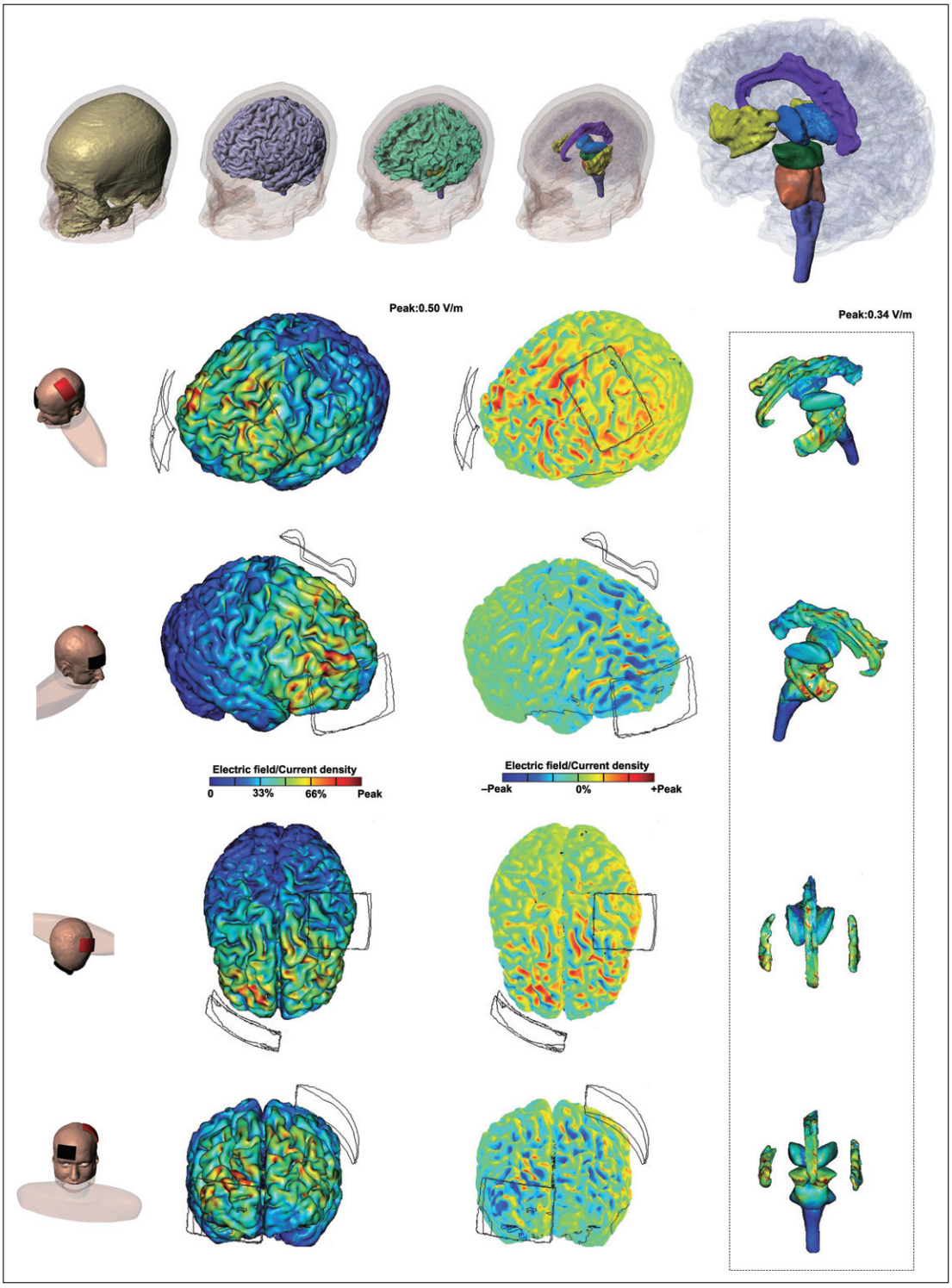

Fig 3.—tDCS current flow (electric field) through superficial brain structures. The top image illustrates tissue masks from the most superficial areas (eg, skin, scalp, and outer cortical areas) to the inner structures (eg, insula, thalamus, cingulate gyrus, and brainstem). The following sequence shows the electrodes montage, with the anode placed over the primary motor cortex (M1) and the cathode over the supra-orbital cortex in different views. Current flow across outer cortex is represented by both electric field magnitude (second column) and electric field component normal to the cortical surface (with direction; third column). The color map depicts the current density, with red indicating high-current density and blue indicating low-current density. The peak of current density is 0.25 V/m for outer cortical regions and 0.17 V/m for inner brain regions.

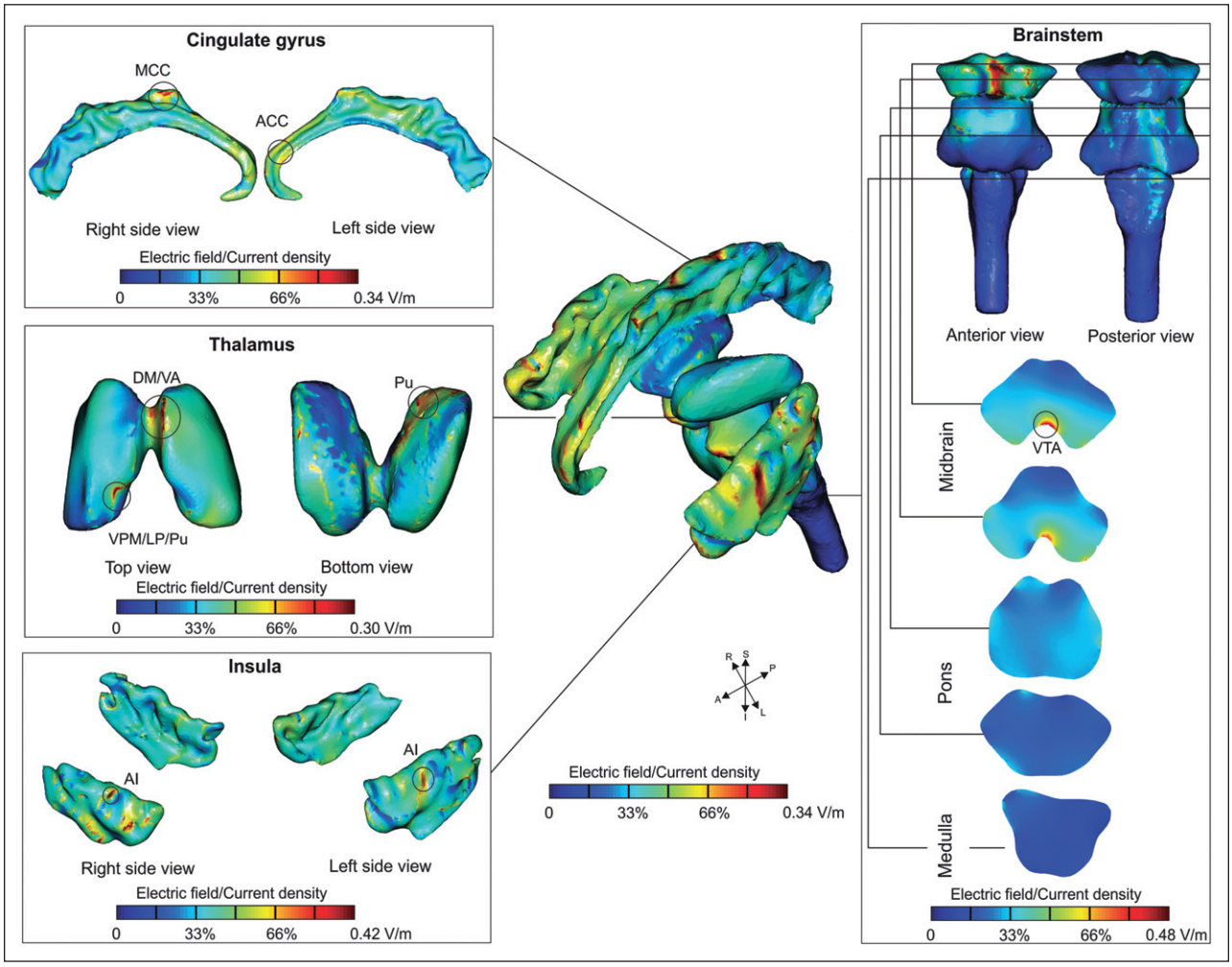

Fig 4.—tDCS current flow (electric field) is represented in 4 different deep brain structures (cingulate gyrus, thalamus, insula, and brainstem). The color coding depicts the current density, with red indicating high-current density and blue indicating low-current density. Specific areas with peaks of current density (eg, ACC, MCC, dorsal medial, ventral anterior, ventral posteromedial nucleus, lateral posterior, AI, and ventral tegmental area) are also identified. ACC = anterior cingulate cortex; MCC = mid-cingulate cortex; AI = anterior insula.

interpeduncular fossa. The horizontal slices of the midbrain revealed that the current flow reaches the ventral tegmental area (VTA), mainly in the rostral midbrain. In fact, it seems that this region received the highest current flow in the midbrain. The current flow also extended inferiorly to the pons but at reduced levels. Nonetheless, the midbrain concentrated most parts of the brainstem activity (Fig. 4).

DISCUSSION

Our results demonstrate that tDCS applied over motor (anodal) and orbitofrontal (cathode) cortices, with sessions spread over the course of 1 month, can decrease gradually the intensity of pain, length of the chronic migraine episodes, and patients' clinical impression. Derived from our tDCS forward analysis, these therapeutic effects may be associated with the direct modulation of the pain neuromatrix. Previous imaging and modeling studies have suggested tDCS induces subcortical current flow;[31-33] we illustrate that significant current flow is induced across the brain by our stimulation protocol, which extends from the immediate target cortical regions to the even deeper regions, including cingulate, insula, thalamus, and brainstem.

The analgesic effect we observed with the tDCS montage targeting primary motor cortex (M1) cortex supports the notion that the mechanisms of chronic migraine are associated with plastic changes of central structures, ie, central sensitization. This may also be associated with a deficient inhibitory process, as noticed with other chronic disorders with a similar response to tDCS therapy.[15,34,35] In this context, excitability enhancing anodal tDCS of the primary motor cortex might have as equivalent an effect as high-frequency repetitive transcranial magnetic stimulation (TMS) of normalizing the defective inhibitory mechanisms in chronic pain.[36] In addition, potentially independent of M1 modulation, cathodal stimulation over anterior prefrontal regions (supraorbital electrode [SO]) also has analgesic effects via pain neuromatrix structures.[22] For example, prominent current peaks are predicted in the DLPFC and orbitofrontal cortices. According to neuroimaging studies, these areas play a relevant role in the mechanism of mood disorders and chronic pain,[37-39] including chronic analgesic-overuse headache developing from episodic migraine.[40] Based on those studies, it is possible to suggest that our particular M1-SO tDCS electrode montage may additionally alter the cortical excitability in the anterior regions of the cerebral cortex related to pain. Thus, the effects of tDCS need to be seen as the combination of both electrodes as they will determine where currents will be induced, as investigated in this study.

Modeling predicated significant electric current in neighboring inner cortical structures linked to CM pathophysiology, as revealed in our results. For instance, we demonstrated peak of current flow in the anterior insula, bilaterally, especially in its rostral parts (anterior and middle short gyri). Such effect of tDCS stimulation in the rostral anterior insula might help to explain the significant improvement of pain intensity, length of migraine episodes, and CGI in patients with chronic migraine, since the aforementioned area has a crucial importance in clinical and emotional aspects of pain perception. Likewise, the results of the current investigation suggest that tDCS could potentially induce changes in the cortical excitability of the anterior cingulate cortex, especially in its anterior areas (pACC and aMCC). Indeed, previous functional (using positron emission tomography [PET] and functional MRI) and structural (voxel-based morphometry) studies demonstrated changes in the cingulate cortex of migraine patients, mostly in the anterior and midcingulate cortex (ACC and MCC)[41-45] but also in the posterior cingulate cortex (pCC).[41]

An intriguing prediction of the present study is that electric current produced by tDCS modulates subcortical structures, including those of the pain neuromatrix. Bilateral thalamic activation has been frequently demonstrated in PET and fMRI studies of pain.[38,39,46-53] In addition, it has been described that the effects of both invasive motor cortex stimulation (MCS) and noninvasive (tDCS; TMS) motor cortex stimulations on pain relief depend on the projection of fibers from the motor cortex to other structures involved in pain processing, such as the thalamus and brainstem nuclei.[36,54] Our montage, placing the electrode over the primary motor cortex, resulted in a decrease of chronic migraine pain, and the results of the current flow analysis showed a significant amount of current reaching the VPM nucleus of the thalamus. An interesting question here is whether pain modulation induced by tDCS is due to direct effects of currents reaching the thalamus through indirect modulation, as shown by neuroimaging studies.[55] Thus, one important point is that effects of tDCS would lack specificity, as a broad neural area is affected simultaneously during stimulation. It is therefore not possible to make homotopic claims when using tDCS, as recently discussed and shown in a study using another technique of brain stimulation – TMS.[36]

Structural and functional changes have been described in the brainstem of patients with migraine. Most changes were reported in the ventral and dorsal midbrain, periaqueductal gray (PAG) area, dorsolateral and dorsomedial pons,[7,42,45,56] and also in the locus coeruleus and raphe nuclei.[57,58] Interestingly, a study using PET scans to investigate changes in the regional blood flow in the human brain during spontaneous migraine attacks demonstrated increased blood flow in several areas of the brain, including regions of the cerebral hemispheres, cingulate, visual association cortex, and brainstem. However, the brainstem was

the only neural structure that still showed activation even after a sumatriptan injection, which reduced headache, phonophobia, and photophobia.[45] Notwithstanding changes in the inner parts of the brainstem that could not be detected in this study, the strong current activity seen in the cerebral peduncles, with extension to the interpeduncular fossa and VTA, suggests that the positive effect of tDCS in chronic pain could be, at least in part, due to modulation of the midbrain, which could include PAG, locus coeruleus, and the raphe nuclei and VTA. The last region contains dopaminergic neurons that project to amygdala nucleus accumbens (NAcc), modulating their activities. Among the functions of the NAcc are reward, placebo response, and pain.[59,60]

Although we show similar tDCS-induced analgesic effects in this study (when analyzing the follow-up) as compared to other tDCS studies, there are some important differences. First, we were not able to demonstrate an immediate effect on the main clinical outcome during treatment, but we showed a significant improvement in the long-term evaluation (starting after the period of stimulation up to 4 months after treatment). Some reasons to explain this finding should be considered here. For example, data variability of pain scores might have decreased the power for the analysis during stimulation; however, the data variability of follow-up is similar to the data variability during treatment. The alternative explanation might be due to our strategy of stimulation. The difference with other pain studies is that we used a protocol for tDCS in which it was applied every other day. This might have reduced the initial efficacy of tDCS as compared to daily tDCS sessions (as shown in a depression study[61]), and therefore cumulative changes developed more gradually. Finally, long-lasting changes in plasticity, as observed in this study, have been seen before in other conditions using tDCS.[10,14,62]

Even considering the potential delayed effects observed in this study, it needs to be underscored that repeated exposure may be needed in order to induce lasting plastic changes promoting synaptic strengthening of the structures targeted. Actually, previous studies have already demonstrated cumulative effects of tDCS for diseases with different mechanisms such as craving and motor recovery after stroke.[63,64] In agreement with these findings, the subjects in our study had a long duration of disease (mean duration of 28.6 years); therefore, it is conceivable that these subjects have strong plastic changes in pain-related neural networks. Hence, this might explain not only the reduced effects during stimulation but also the delayed effects after the end of stimulation. This study has some limitations. We did not measure neurophysiological data as to assess the mechanisms underlying the effects of tDCS as the main study goal was to collect preliminary data on the behavioral effects of tDCS in CM. Further studies collecting neurophysiological data can provide mechanistic insights on the effects of tDCS in CM. Because our study was a proof of principle study, thus the goal was to detect a signal that the tDCS has an effect on pain in migraine, and also to assess feasibility of this intervention and the effects over time. Although our sample size of 13 patients could detect an effect size F of 0.67 (given 4 measurements and a correlation of 0.5 among measurements), our study has a small sample size, and therefore, we might have been underpowered to detect changes in pain during treatment, and how other variables influenced our results, for instance, gender or medication effects on the outcome.

Finally, our tDCS computer modeling is based on a single MRI-derived head model and is not patient specific. We used this representative head model to simulate our clinically used tDCS montage. Although the precise distribution of current flow would be effected by individual idiosyncratic anatomy and electrode montage, significant current flow through inner cortical and deep brain structures is expected using most conventional tDCS montages, as supported by other modeling efforts[32,33] and consistent with imaging studies. Future studies may not only consider the role of deeper structures in tDCS but even optimize electrode montage to target one or more regions of interest.[65]

This is a preliminary study aimed to evaluate in an exploratory manner the clinical effects and neuromodulatory mechanisms of tDCS on CM patients. Here, we demonstrated that tDCS has a delayed effect on CM patients as they showed improvement during the follow-up period as compared to sham stimulation. In addition, this beneficial effect is asso-

ciated with direct neuromodulation of cortical and subcortical areas associated with the pain neuromatrix, and CM pathophysiology. Future research needs to further explore other parameters of stimulation, maintenance treatment, and the mechanisms associated with clinical improvements.

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