tDCS modulates cortical nociceptive processing but has little to no impact on pain perception

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A B S T R A C T

Transcranial direct current stimulation (tDCS) effectively modulates cortical excitability. Several studies suggest clinical efficacy in chronic pain syndromes. However, little is known regarding its effects on cortical pain processing. In this double-blind, randomized, cross-over, sham controlled study, we examined the effects of anodal, cathodal, and sham stimulation of the left motor cortex in 16 healthy volunteers using functional imaging during an acute heat pain paradigm as well as pain thresholds, pain intensity ratings, and quantitative sensory testing. tDCS was applied at 1 mA for 15 minutes. Neither cathodal nor anodal tDCS significantly changed brain activation in response to nociceptive stimulation when compared with sham stimulation. However, contrasting the interaction of stimulation modes (anodal/cathodal) resulted in a significant decrease of activation in the hypothalamus, inferior parietal cortex, and both exclusively investigated the motor system [35,48]. Using arterial spin labelling, differential regional Cerebral Blood Flow (rCBF) after effects of anodal (increase in resting state rCBF) and cathodal (decrease in resting state rCBF) tDCS have been described [70]. In 2001, using functional magnetic resonance imaging (fMRI), it was shown that 5 minutes of cathodal tDCS caused a lasting decrease in the mean number of activated voxels in the supplementary motor area (SMA) [6]. In contrast, a very recent study reported that neither anodal nor cathodal tDCS over M1 for the (much shorter) stimulation period of 20 seconds induced a detectable blood oxygenation level dependent (BOLD) signal change [2]. However, in comparison to a voluntary finger-tapping task without stimulation, anodal tDCS during finger tapping resulted in a decrease of the BOLD response in the SMA. Cathodal stimulation did not result in significant changes in the BOLD response in the

1. Introduction

Invasive primary motor cortex stimulation (MCS) has emerged as a promising treatment option for specific chronic pain conditions [37]. Recent imaging studies showed an activation of the ventrolateral thalamus via corticothalamic projections induced by MCS, initiating a cascade of events involving the activation of medial thalamus, anterior cingulate/orbitofrontal cortex, and brainstem structures such as the periaqueductal gray matter (PAG) [21,22,50]. These findings facilitated the suggestion that the antinociceptive effects of MCS are mediated by a top-down activation of descending spinal inhibition. However, the use of epidural MCS is limited because of the risks associated with its invasive nature.

Alternatively, noninvasive methods of motor cortex modulation have been proposed recently. Transcranial direct current stimulation (tDCS) of the motor cortex has been reported to reduce chronic pain in small pilot studies [9,16–18,42] with an efficacy comparable to that of MCS.

Although the described working mechanisms of tDCS are dominantly intracortical [62], most studies investigating how tDCS exerts its effect have focused on clinical outcome measures and evoked potentials [11,62]. Only some studies so far have examined the effects of tDCS using modern brain imaging techniques. The majority focused on the effects of tDCS on resting state networks [1,30,49]. Only 2 trials investigated regional cerebral blood flow changes using (H2O-) positronen emissions tomographie (PET), and both exclusively investigated the motor system [35,48]. Using arterial spin labelling, differential regional Cerebral Blood Flow (rCBF) after effects of anodal (increase in resting state rCBF) and cathodal (decrease in resting state rCBF) tDCS have been described [70].
SMA. The authors concluded that the well-known polarity-dependent shifts in corticospinal excitability that have previously been demonstrated using measurements of motor evoked potentials (MEPs) after M1 stimulation are not paralleled by analogous changes in regional BOLD signal [2]. Another study showed conflicting results (anodal stimulation prompted an increase in activation) for the M1 leg area [31].

However, none of these studies investigated the influence of tDCS on BOLD effects as a marker of cortical activity after nociceptive input and none used a sham controlled randomized fashion. For this purpose, we applied a repetitive heat-pain paradigm that has been shown to activate key structures of the nociceptive system (the so-called pain matrix) during functional neuroimaging [8,56] before and after anodal, cathodal, and sham tDCS. Based on clinical findings in patients with pain discussed earlier, we additionally recorded the effects of cathodal and anodal tDCS of the motor cortex (M1) on painful somatosensory modalities as secondary outcome measures.

2. Subjects and methods

2.1. Study design

The study was conducted in a double-blind and placebo-controlled design to ensure that neither subjects nor researchers were aware of the stimulation condition. All subjects underwent 3 tDCS sessions (cathodal, anodal, and sham tDCS) in a random order and counterbalanced across subjects on 3 separate days. A 1-week interval between stimulations avoided carry-over effects, based on published data that indicated a return to baseline levels [19]. The pain thresholds of our subjects were within the normal range of an age- and gender-matched sample of normative values, and in accordance with those provided by the thermode manufacturer [68,69], as well as with a previous study on normative data of various sensory tests including heat pain thresholds [57]. Only after the subjects had taken part in the introductory session and fulfilled all inclusion criteria (see Subjects section) did they participate in the actual study phase.

2.2. Subjects

Sixteen healthy subjects (mean age 27 years [SD 6.6]; 10 female; range 23 to 41 years) participated. All volunteers gave written informed consent, all methods and procedures were clearly explained, and volunteers were free to withdraw from the experiment at any time. The study was conducted in accordance with the Declaration of Helsinki and approved by the local ethics committee (Ärztekammer Hamburg PV2922). All volunteers were right-handed, had normal pain thresholds, and had no history of any neurological or psychiatric disease. Particularly, none of them had any history of chronic pain whatsoever or acute pain in the 3 months before and during the study period. We also assessed any occurrence of minor pain events (toothache, etc.) 4 weeks before and during the study period, and the participants were further instructed to take no medication 24 hours before and after the experiment.

2.3. Introductory session

A separate introductory session was provided to all subjects before the actual experimental phase. During this session, all subjects were made familiar with the pain stimulation and rating procedures, and pain thresholds were determined using the method of limits [19]. The pain thresholds of our subjects were within the normal range of an age- and gender-matched sample of normative values, and in accordance with those provided by the thermode manufacturer [68,69], as well as with a previous study on normative data of various sensory tests including heat pain thresholds [57]. Only after the subjects had taken part in the introductory session and fulfilled all inclusion criteria (see Subjects section) did they participate in the actual study phase.

2.4. Quantitative sensory testing

According to a standardized QST procedure [57], we assessed the heat pain thresholds using the method of limits and calculated the arithmetic mean of 3 repetitions. We further assessed the mechanical pain sensitivity and dynamic mechanical allodynia using a set of 7 pinprick stimulators that exerted forces of 8, 16, 32, 64, 128, 256, and 512 mN and 3 tactile innocuous stimuli. These stimuli were applied 3 times in a standardized order, and the participants were asked to give a pain rating for each stimulus on a numerical rating scale from 0 (no pain) to 100 (worst imaginable pain). Mechanical allodynia may occur as a physiological response to thermal pain [29]. To detect any potential influence of tDCS on pain processing, the modulation of mechanical allodynia was chosen as an additional secondary outcome measure.

![Timeline of assessments in each session consisting of 3 sequences: preintervention, intervention, postintervention. All subjects underwent 3 tDCS sessions (cathodal, anodal, and sham tDCS) in a random order and counterbalanced across subjects on 3 separate days. A 1-week interval between stimulations avoided carry-over effects. tDCS = transcranial direct current stimulation.](image-url)
2.5. Interventions: single-pulse TMS

The stimulation target was M1 because current evidence is strongest for this target to exert effects on experimental and clinical pain [2,10,18] and it can safely be located by single-pulse TMS. The motor cortical representational field of the right ADM was identified by single-pulse TMS of the left M1 using a figure-of-8–shaped magnetic coil with an outer diameter of 70 mm and a Magstim 200 magnetic stimulator (The Magstim Company, Dyfed, UK).

2.6. Nociceptive session

The heat pain stimulation equipment and design used in the present study is described in detail elsewhere [8,56,65]. Briefly, we used a repetitive stimulation with a 48°C thermode-induced heat stimulus, which inevitably activates peripheral heat nociceptors and evokes a moderate to intense painful sensation. Each stimulation session consisted of 10 blocks of heat stimuli with each block containing a series of six 48°C stimuli (each lasting 6 seconds with 4 seconds rest between stimuli), resulting in a total number of 60 thermal stimuli. The rest period between blocks was 30 seconds. Thermal stimuli were applied to the right volar forearm and delivered by a 30 × 30-mm Peltier device (TSAl1, Medoc, Israel). Five seconds after the 6th thermal stimulus of each pain block, the subject was prompted to rate the average sensation for the last 6 painful stimuli on a 0-to-100–mm visual analogue scale (VAS). The bottom anchor of the VAS reflected no pain (VAS 0), and the upper anchor reflected maximum pain imaginable (VAS 100). The VAS was programmed using Presentation (http://www.neurobehavioralsystems.com) and was presented on a computer screen during the sessions.

2.7. tDCS

Bipolar tDCS was administered using 2 saline-soaked sponge electrodes sized 5 × 7 cm (35 cm²) and delivered using a DC-Stimulator (NeuroConn, Ilmenau, Germany). For anodal stimulation, the anode was placed over M1, and the cathode was positioned over the contralateral supraorbital region (vice versa for cathodal stimulation). DC stimulation was delivered for a duration of 15 minutes at 1-mA intensity (8 seconds ramp in and 8 seconds ramp out). For sham tDCS, the DC stimulator has a built-in placebo mode that is activated by a 5-digit number code and includes ramp periods at the beginning (8 seconds) and at the end (5 seconds) to mimic the somatosensory perception (paresthesia) of real tDCS. The sham condition could be identified neither by the examiner nor by the participants in a previous study [20], and the effectiveness of blinding was evaluated using a questionnaire at the end of the experiment.

2.8. Image acquisition

Echo-planar images were collected on a 3-T scanner (Siemens-Trio, Erlangen, Germany) using a 12-channel head coil. Functional scans used these parameters: 42 axial slices were acquired; voxel size = 3 mm³; time to echo = 30 ms; repetition time = 2620 ms, flip angle 80°, field of view 192 mm². Additionally, high-resolution T1-weighted structural images (voxel size = 1 mm³) were acquired using a magnetization prepared rapid gradient echo (MPRAGE) sequence.

2.9. Analysis of behavioral data

To test for differences of mean heat pain ratings at baseline across all stimulation modalities, a 1-way ANOVA with the within-subject factor “stimulation mode” (STIM; anodal, cathodal, sham) was performed. Changes of mean heat pain ratings after the intervention as well as the slope of the heat pain increase were analyzed by 2-way repeated-measures ANOVA with the factors “stimulation mode” (STIM; anodal, cathodal, sham) and “time” (PREPOST; pre vs. post intervention). Post-hoc tests with Fisher’s least significant difference tests were performed when appropriate. Paired t tests were used for comparing heat pain ratings at the first block with pain ratings at the 10th block across all test sessions at baseline.

In all tests, P values < .05 were considered significant. No adjustment for multiple testing was made because behavioral data were treated as secondary outcome measures and interpreted at an exploratory level [66]. Behavioral data analysis was performed using SPSS (Statistical Program for Social Sciences, version 17.0).

2.10. Preprocessing and statistical analysis of the functional imaging data

fMRI data were statistically analyzed using SPM 5 (Statistical Parametric Mapping; Welcome Department for Imaging Neuroscience, London, UK). Preprocessing included slice time correction, realignment (to the first volume), and spatial normalization into the Montreal Neurological Institute stereotactic space [41]. Finally, images were smoothed. We used a 10 mm³ full-width at half-maximum isotropic Gaussian kernel that is appropriate for cortical regions.

Statistical data analyses were performed using the general linear model. The following types of events were modeled as delta functions convolved with a canonical hemodynamic response function with its time derivative as implemented in SPM5: 1) nociceptive stimuli, 2) rating procedure (onset of presenting the VAS and duration until rating was completed). Additionally all 6 movement regressors have been implemented as additional regressors in the first-level analysis.

Because we were interested in correlating the brain activity in response to pain stimulation and individual pain ratings, we additionally modeled a parametric regressor (a vector consisting of 10 VAS values) including the pain ratings from each individual in the first-level models.

Data then were analyzed for each subject individually, and contrast images were entered into a random-effects second-level model to analyze group effects. Based on known mechanisms and thus anticipated activation pattern [34], and based on published data pointing toward an analgesic effect of anodal tDCS [3,9,16–18,42,59,67], we tested whether there were functional correlates underlying the rating patterns in these groups. Using a null conjunction analysis [43] including contrast images resulting from the parametric regressor, we aimed to explore whether there were brain areas where the height of the activity level directly corresponded to the rating behavior (=intensity of pain perception). Thus, we focused on brain areas where the BOLD response decreased after anodal stimulation and increased after cathodal stimulation with no effect in the sham condition. Four major contrasts were used:

Contrast I: Main effect analysis (conjunction) over all groups (pain vs no pain)
Contrast II: Effects of anodal stimulation vs sham stimulation
Contrast III: Effects of cathodal stimulation vs sham stimulation
Contrast IV: Interaction analysis: decrease after anodal stimulation compared with sham stimulation and increase after cathodal stimulation compared with sham stimulation

For the conjunction we used a significance threshold of P < .05 corrected, and for all other analyses a threshold of P < .001 uncorrected for whole-brain comparisons.
3. Results

3.1. Functional imaging data

3.1.1. Contrast I: main effect analysis

The group analysis for the repetitive painful thermal stimulation showed a significant activation in brain regions associated with pain processing in all groups for all 3 days ($P < .05$, familywise error-corrected). These areas included the insular cortex, midcingulate cortex, parietal operculum, dorsolateral prefrontal cortex, thalamus, cerebellum, and brainstem. No significant changes were found in the pre-post conjunction analysis across groups (anodal, cathodal, sham), indicating that there was no global time effect before vs after stimulation.

3.1.2. Contrasts II-IV: differential effects

First we performed a group comparison on day 1 to see if differences between groups were already evident on day 1, and found no significant differences between groups ($P < .001$ uncorrected). In contrast II, no significant changes were found in the contrast decrease of BOLD signal after anodal stimulation. The reverse contrast, searching for increase in BOLD signal after anodal stimulation, also showed no significant changes. In contrast III, no significant changes were found in the contrast assessing a decrease of BOLD signal after cathodal stimulation. The reverse contrast, searching for an increase in BOLD signal after cathodal stimulation, also showed no significant changes. In contrast IV, finally, we tested for between-group (anodal/cathodal) differences of cortical activation during painful stimulation. Contrasting the interaction of stimulation modes (anodal/cathodal), we found a decrease in rCBF after anodal stimulation and an increase in rCBF after cathodal stimulation in the hypothalamus, inferior parietal cortex, inferior parietal lobule, anterior insula, and precentral gyrus contralateral to the stimulation site ($P < .001$ uncorrected whole-brain approach) (Fig. 4, Table 1).

3.2. Behavioral data

On evaluation of tDCS blinding, overall no side effects nor relevant discomfort were observed during the experiment, and tDCS generally was well tolerated. The Spearman's rho correlation test yielded a coefficient of 0.037, indicating that the participants could not discriminate between verum and sham stimulation. Heat pain thresholds were within normal limits before [mean (SEM), 46.3°C (0.13)]; and after [mean (SEM), 46.0°C (0.08)] the stimulation and showed no significant differences between stimulation modes neither before nor after the stimulation (Fig. 2). The pain paradigm resulted in a moderate pain perception that was not significantly altered after tDCS irrespective of stimulation mode. Some individual trends could be observed, but group effects were not statistically significant (anodal vs sham $P = .15$; cathodal vs sham $P = .80$) (Fig. 3). Moreover, the observed trend that anodal stimulation seemed to prompt less painful ratings (mean pain reduction 3 mm on 0 to 100 VAS), whereas cathodal stimulation prompted slightly higher pain ratings (mean pain increase 1 mm on 0 to 100 VAS) was not within a clinically meaningful range. On QST testing, there was a significant increase in mean pinprick pain ratings from baseline [mean (SEM), 1.12 (0.19)] to postintervention assessment [mean (SEM), 3.53 (0.67)] ($P = .01$). Because QST parameters were assessed after the first heat pain paradigm and before tDCS intervention (Fig. 1), the finding indicated a sensitization provoked by the heat pain paradigm. There was no significant difference in mean pinprick pain ratings between second (prestimulation) and third QST (poststimulation) assessment over all groups or between groups.

4. Discussion

The aim of this study was to explore the underpinnings of the previously suggested antinociceptive effects of tDCS over the motor cortex [21,22,50]. We found that neither cathodal nor anodal tDCS over the left M1 (1 mA, 15 minutes) significantly changed cortical nociceptive processing as a response to a heat pain paradigm when compared with sham stimulation. Only contrasting the interaction between responses to anodal and cathodal stimulation, we found substantial polarity-specific differences of regional brain activation after painful stimulation: anodal stimulation provoked a decrease of rCBF, whereas cathodal stimulation resulted in an increase of rCBF in the hypothalamus, inferior parietal cortex, inferior parietal lobule, anterior insula, and precentral gyrus contralateral to the stimulation site.

Direct current stimulation of the motor cortex leads to local and referred excitability changes [34]. Cortical excitability increases during anodal stimulation (positive electrode over motor cortex) and is reduced during cathodal stimulation, as confirmed by changes of magneto-electric evoked potentials [36] and activation of the motor cortex in fMRI [32]. Using this directivity, we focused on contrast IV and thus report the outcome of this interaction analysis independent of ipsilateral or contralateral location.

Small but consistently altered BOLD responses after tDCS also were reported in a recent systematic review [5] and in previous publications investigating altered cortical response to motor tasks after tDCS [6,26,71]. Whereas anodal stimulation is generally reported to enhance performance (represented by an increased BOLD response) in studies that investigated motor performance [eg, [26]], our results indicated a decreased rCBF after anodal stimulation that can be interpreted as reduced cortical pain processing. A recent study supported this theory using an animal model that showed effects of tDCS on stress-induced hyperalgesia and allodynia as well as stress-associated mediators [60]. This decreased cortical response to a nociceptive input after anodal tDCS confirms previous findings in chronic clinical pain populations that consistently reported a pain reduction after anodal stimulation [3,9,16-18,42,59,67].

However, our behavioral data did not indicate a pain-reducing effect of anodal stimulation. tDCS exerted subclinical antinociceptive effects, and these occurred in the predicted direction, but these were neither statistically significant nor within a clinically meaningful range. Interestingly, previous studies on experimental pain using the same stimulation paradigm also showed inconclusive effects on psychophysical variables [24,27,38], whereas neurophysiological outcomes (such as evoked potentials) were altered in the majority of trials after tDCS [5,14,40]. One potential explanation could be that psychophysical variables depend on a range of different pathways because evaluation of pain is a more complex process than mere somatosensory processing in evoked potentials. Higher stimulation intensities, a longer stimulation duration, or repeated stimulation sessions may be required to produce a statistically significant experimental pain reduction that matches the effect observed in chronic clinical pain studies. fMRI findings in our study, although present bilaterally at lower thresholds, were only statistically significant on the side contralateral to tDCS.

This result challenges the result of a report by Kwon et al. [32], who reported altered cortical activity only on the stimulated side after repeated tDCS. However, Stagg et al. and Kim et al. [31,63] observed BOLD signal changes in contralateral brain regions in addition to changes on the ipsilateral side. It seems likely that tDCS induces a significant intrahemispheric and interhemispheric connectivity change with consequences on brain synchronization and topological functional organization [52].
The observed activations of the inferior parietal cortex, anterior insula, and hypothalamus identify these areas as potential targets for analgesic properties using tDCS. The activation of the right inferior parietal cortex in pain processing has been reported in other imaging studies [35,49,63] and can be interpreted as co-innervation of the stimulated left M1. The insular cortex is part of the paralimbic circuit and has integrative functions for somatosensory and visceral information. In pain processing, it is responsible for the affective aspects, the linking of sensorial signals to emotion, and recognition of former pain experiences [4,23]. Furthermore, it plays a role in empathy [58] and anticipation of pain [51]. Aside from these affective functions, caudal parts of the insula encode pain intensity [13].

The hypothalamus projects to other regions of the descending antinociceptive system, such as the amygdala, the periaqueductal gray, and the rostral ventromedial medulla. Aside from the

### Table 1

Results of the different analyses (contrasts I to VI) tabulated after peak voxels with coordinates in Montreal Neurological Institute space, and the corresponding \( P \) and \( t \) values.

<table>
<thead>
<tr>
<th>Region</th>
<th>Coordinates of the peak voxels (x, y, z, in mm)</th>
<th>Peak level</th>
<th>( t )</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hippocampus</td>
<td>−39, −18, −15</td>
<td>12.08</td>
<td>.001</td>
<td></td>
</tr>
<tr>
<td>Left rolandic operculum</td>
<td>−54, 0, 3</td>
<td>9.85</td>
<td>.001</td>
<td></td>
</tr>
<tr>
<td>Left insula</td>
<td>−36, 3, 9</td>
<td>9.65</td>
<td>.001</td>
<td></td>
</tr>
<tr>
<td>Right rolandic operculum</td>
<td>57, 12, 3</td>
<td>10.52</td>
<td>.001</td>
<td></td>
</tr>
<tr>
<td>Right insula</td>
<td>36, 12, 6</td>
<td>9.35</td>
<td>.001</td>
<td></td>
</tr>
<tr>
<td>Left cerebellum lobule 8a</td>
<td>−18, −69, −48</td>
<td>6.79</td>
<td>.001</td>
<td></td>
</tr>
<tr>
<td>Left cerebellum lobule 7a crus 1</td>
<td>−36, −69, −30</td>
<td>6.31</td>
<td>.001</td>
<td></td>
</tr>
<tr>
<td>Right cerebellum lobule 7a crus 1</td>
<td>36, −72, −27</td>
<td>6.12</td>
<td>.001</td>
<td></td>
</tr>
<tr>
<td>Right cerebellum lobule 7b</td>
<td>18, −69, −48</td>
<td>6.71</td>
<td>.001</td>
<td></td>
</tr>
<tr>
<td>Right cerebellum lobule 5</td>
<td>12, −48, −21</td>
<td>5.81</td>
<td>.001</td>
<td></td>
</tr>
<tr>
<td>Right middle frontal gyrus</td>
<td>45, 45, 15</td>
<td>6.55</td>
<td>.001</td>
<td></td>
</tr>
<tr>
<td>Left area 4a</td>
<td>−21, −24, 54</td>
<td>5.67</td>
<td>.001</td>
<td></td>
</tr>
</tbody>
</table>

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**Fig. 2.** Pain thresholds averaged over all participants and presented for type of stimulation. There were no significant changes between pre-post ratings on each session or between sessions. Pre = basic value; post = after intervention.
influence on endogenous analgesia, it plays a role in the placebo effect [15]. In contrast, activation of the hypothalamus also can aggravate pain and lead to hyperalgesia and allodynia [39], a phenomenon also observed in anxiety induced hyperalgesia [7].

This study was neither designed nor powered to investigate pain perception as a primary outcome measure. Pain ratings showed some interindividual variation, resulting in a high standard deviation.

Based on our previous work [27], we chose a current strength of 1 mA, applied over an area of 35 cm². These parameters lead to reliable effects without risks for the participants [53]. Higher current densities, which were used in later studies [3,16,25], are accompanied by stronger side effects and diminish the sham function of the tDCS stimulator [47]. However, a higher-stimulation intensity, a longer duration, or repeated stimulations might have resulted in a more convincing pain reduction. We found that heat pain ratings increased during the duration of the paradigm indicating primary heat hyperalgesia [54], which probably depends on peripheral sensitization of nociceptive afferents [33]. This phenomenon could theoretically impede the presumed analgesic effect of tDCS.

As recently shown, effects of tDCS on nociception persisted for at least 40 minutes after cathodal tDCS [64]. As the interval was approximately 20 minutes between stimulation and second pain.
application in the scanner, a wearing-off effect was unlikely. tDCS conveys its effects by induction of a static electric field underneath the electrode, which leads to a polarity-dependent shift in resting membrane potentials. Anodal stimulation is generally considered to be facilitatory by depolarizing and cathodal stimulation to be inhibitory by hyperpolarizing the membrane potential [44]. However, the net effect of motor cortex stimulation may be a mixed effect, as cathodal tDCS may also exert a facilitatory effect by deactivating inhibitory interneurons [46]. Moreover, the excitatory net effect also depends on the current intensity, electrode size, and the spatial orientation of the neurons, as well as the cortical layer activated [28]. This may partly explain the inconclusive outcomes in tDCS studies of experimentally evoked pain in humans. One study showed that laser-evoked potentials in healthy volunteers were reduced by cathodal tDCS of the contralateral primary motor cortex (M1), whereas anodal stimulation had no effect [14]. Another study reported beneficial effects of tDCS on electrically evoked pain and nonpainful sensations only after anodal stimulation of the M1 [10]. Additionally, although experimental pain research plays an important role in pain research because experimental pain is easier to standardize and pain perception is less influenced by factors associated with chronic pain such as psychological comorbidities [12, 61], results might not be directly transferable to chronic pain populations [55]. There is a quest to further studies in patients with chronic pain using higher-stimulation intensities and repetitive stimulation sessions to fully assess the therapeutic potential of tDCS.

Finally, we only found statistically significant cortical responses in the interaction between the (nonsignificant) change in BOLD after anodal tDCS and the (nonsignificant) change after cathodal tDCS. Neither of these individual changes was significant in absolute terms when compared with sham, only their interaction was. Significant interactions in the absence of significant main effects are difficult to interpret, and although the findings occurred in the predicted direction, these data have to be interpreted with caution.

Conflict of interest statement

None of the authors has a conflict of interest.

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