

Polarity-independent effects of transcranial direct current stimulation over the bilateral opercular somatosensory region: a magnetoencephalography study

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The opercular somatosensory region (OP) plays an indispensable role in pain perception. In the present study, we investigated the neurophysiological effects of transcranial direct current stimulation (tDCS) over the OP. Somatosensory-evoked magnetic fields following noxious intraepidermal electrical stimulation to the left index finger (pain-SEFs) were recorded before and after tDCS with a single-blind, sham-controlled, cross-over trial design. Three tDCS conditions of left anodal/right cathodal tDCS, left cathodal/right anodal tDCS (each, 2 mA, 12 min), and sham tDCS (2 mA, 15 s) were applied. Despite the subjective pain sensation being unaltered, the two anodal (real) interventions significantly decreased OP activity associated with pain-SEFs. In conclusion, tDCS over the OP with the present parameters did not have a significant impact on pain sensation, but modulated its cortical processing. *NeuroReport* 28:838–844 Copyright © 2017 The Author(s). Published by Wolters Kluwer Health, Inc.

Introduction

Pain, the occurrence of unpleasant somatic sensations, is an emotional and bodily experience associated with actual or probable tissue damage. The discomfort accompanying pain leads to markedly reduced activity and quality of daily life, resulting in altered mental states, encompassing negative emotionality, maladaptive stress responses, and depression [1]. Therefore, it is critically important to manage pain sensation in patients. Noninvasive brain stimulation techniques are often applied to manage pain sensation. Notably, transcranial direct current stimulation (tDCS) has a beneficial effect; it is portable, inexpensive, easy to use, and safe in the clinical setting [2].

Previous brain imaging studies have shown that the opercular somatosensory region (OP) plays an indispensable role in pain perception [3]. It has been shown that repetitive transcranial magnetic stimulation (rTMS) over the OP results in a reduction in chronic pain [4] and an increase in pain threshold [5]. However, tDCS studies

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have targeted the primary motor cortex (M1), the primary somatosensory cortex (S1), and the dorsolateral prefrontal cortex [6–8]. The tDCS effects of pain modulation were confirmed by measuring cortical excitability, which is suppressed through the indirect effects of pain-related neural networks as shown by the stimulation of M1 eliciting widespread modulation of cortical and sub-cortical areas [9]. However, the effects on the cortical processing of the stimulation over the OP have not been clarified. The primary aim of the present study was thus to examine the neurophysiological effects of tDCS over the OP by utilizing magnetoencephalography (MEG) and intraepidermal electrical stimulation (IES). IES relies on the fact that nociceptive fiber terminals are located mainly in the epidermis, whereas other fibers end deep in the dermis [10].

The secondary aim of the present study was to investigate the effect of tDCS over OP on pain sensation. In a previous report [11], we did not observe any significant analgesic effects on experimentally induced pain perception. However, a large interindividual variability in responses to tDCS has been reported recently [12–14]. Therefore, testing the robustness and replicability of the tDCS effects with another sample is important.

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We applied a bihemispheric tDCS protocol, which is a powerful strategy for controlling brain excitability and various neurological functions. Because of its greater impact on interhemispheric projections, bihemispheric tDCS applied simultaneously is more effective than unihemispheric tDCS for modulating motor performance and sensory perception [15,16]. Thus, bihemispheric tDCS potentiates the effects of anodal stimulation to one hemisphere through additional modulation of interhemispheric interactions by cathodal stimulation to the contralateral hemisphere. The bilateral OPs are reportedly linked, either directly by transcallosal connections or indirectly by thalamic and S1 circuitries [4,17].

Participants and methods

Participants

Twelve healthy male participants (28.2 ± 2.6 years; all right-handed) participated in the study. Participants were free from neurological diseases, psychiatric disorders, chronic pain disorders, or a family history of epilepsy. All experimental procedures were approved by the Human Research Ethics Committee of the National Institute for Physiological Sciences (Okazaki, Japan) and were conducted in accordance with the Declaration of Helsinki. All participants provided informed consent before participation.

Study design

A single-blind, sham-controlled, cross-over trial design was used. Participants underwent three tDCS conditions with different stimulation protocols: (a) anodal and cathodal tDCS over the left and right OP, respectively (LA/RC); (b) cathodal and anodal tDCS over the left and right OP, respectively (LC/RA); and (c) sham tDCS. To avoid carry-over effects, sessions were separated by at least 1 week. The order of conditions was counter-balanced across participants. Primary outcome measures included MEG activities in the OP contralateral to the stimulated side (cOP) and ipsilateral to the stimulated side (iOP), and the visual analog scale (VAS) score for the assessment of subjective pain sensation. The secondary outcome measures included S1 activity following innocuous median nerve (MN) stimulation.

Experimental procedures

At the beginning of the study, the stimulus intensity was set at a level sufficient to evoke a pain sensation in each participant with a VAS score of 5. This intensity level was maintained throughout the experimental procedures. One set of measurements under a tDCS condition consisted of five blocks (a) measurement of S1 activity by MN stimulation; (b) measurement of OP activity by IES; (c) tDCS intervention; (d) measurement of OP activity; and (e) measurement of S1 activity. The tDCS intervention was administered outside the magnetically shielded room. Following all interventions, the subjective states (attention, fatigue, pain, sleepiness, and

discomfort) of each participant during tDCS were assessed using a questionnaire based on a four-point scale [2].

tDCS protocol

A DC Stimulator Plus (NeuroConn, Ilmenau, Germany) was used to deliver a direct current over the OP through two sponge surface electrodes (surface area = $5 \times 5 \text{ cm}^2$) soaked with sodium chloride. These experiments were conducted according to a bihemispheric protocol in which the center of each of two stimulation electrodes was placed over one of the two bilateral OPs. Stimulation points were determined through anatomical brain images obtained using a Magnetom Verio 3 T MRI System (Siemens Ltd, Bavaria, Germany) and aBrainsight2 frameless stereotaxic navigation system (Rogue Research Inc., Montreal, Quebec, Canada). The OP is part of the parietal lobe and includes the secondary somatosensory cortex. Here, it was defined as the cortical area adjacent to the junction of the rostral end of the postcentral gyrus and the upper bank of the sylvian fissure [5]. Under the real tDCS conditions (LA/RC and LC/RA), the current was ramped up over the first 15 s to a maximum of 2 mA, held constant for 690 s, and then ramped down over the last 15 s. For the sham condition, the same procedure was used, but the constant current was delivered for only 15 s.

MEG recording

MEG measurements were carried out in magnetically shielded room using a whole-head MEG system (Vektorview; Elekta Neuromag, Helsinki, Finland). The signals were recorded with a bandpass filter of 0.1–200 Hz and digitized at a sampling rate of 1000 Hz. Epochs of somatosensory-evoked fields following noxious IES (pain-SEFs) and innocuous MN stimulation (MN-SEFs) were averaged at least 60 and 200 times, respectively. Trials with noise of more than 2.7 pT/cm were rejected automatically from the averaging.

Noxious stimulation for pain-SEFs

An IES electrode and a portable peripheral nerve stimulator (PNS-7000, Nihon; Koden, Tokyo, Japan) were used. The electrode consisted of an outer ring with a diameter of 1.3 mm and an inner needle protruding 0.02 mm from the outer ring. Parameters of stimulation were as follows: the inner needle served as the cathode and the outer ring served as the anode; the electric pulse corresponded to a triangular wave with a rise and fall time of 0.5 ms; and the pulse train corresponded to four pulses with an interstimulus interval of 5 ms [18]. Participants received pain stimulation to the dorsum of the left index finger, restricted to the first metacarpal bone. The stimulus interval was set at 10 s to avoid habituation to the stimulus.

Innocuous stimulation for MN-SEFs

The left MN at the wrist was stimulated percutaneously at a frequency of 1 Hz using a conventional felt-tip

bipolar electrode. The stimulus pulse corresponded to a square monophasic waveform with a plus width of 0.3 ms and the intensity was maintained just above the motor threshold.

Subjective pain measurement

Participants were asked to rate the magnitude of their subjective pain intensity during MEG recording. After each pain stimulation, a horizontal bar moved from the left (VAS=0; no pain) to the right (VAS=10; worst imaginable pain) on a screen. They manipulated a push-type button with their right hand and stopped the movement of the horizontal line at the optimal location for the perceived sensation.

Data analysis

MEG activities were analyzed by a multiple dipole analysis to detect temporally overlapping equivalent current dipoles (ECDs) using the Brain Electric Source Analysis software package (NeuroScan, Mclean, Virginia, USA). The averaged waveform was filtered offline with a bandpass of 0.5–100 Hz and the pre-stimulus 100 ms period was used as the baseline.

A multiple dipole model was obtained, with a focus on IES-evoked activity in the cOP and iOP. Two ECDs (one in each bilateral OP) were first determined. If necessary, one or more sources were determined to explain the residual data. However, the contribution of these sources toward the overall recorded fields was small, and therefore, these responses were not included in the present analysis. ECD location and orientation were averaged before and after tDCS applications and among tDCS conditions, and the averaged model was applied to all data. Peak-to-peak amplitude was calculated as the magnitude of OP activities. The ECDs for the S1 activities induced by MN-SEFs were also estimated. To confirm the location of the obtained ECDs, they were superimposed on individual MRIs using the head position indicator system and the Brain Voyager QX 1.4 (Brain Innovation, Maastricht, The Netherlands) software.

Statistical analysis

MEG activities and VAS scores were subjected to a two-way repeated-measures analysis of variance (ANOVA) with three tDCS conditions (LA/RC, LC/RA, and sham tDCS) and two time points (before and after the tDCS intervention) as within-subject factors. Questionnaire scores were analyzed using the Kruskal–Wallis test because of the nonparametric nature of the distribution. The SPSS software (version 21; SPSS Inc., Chicago, Illinois, USA) was used for statistical analysis. Quantifiable data are reported as mean \pm SD. Statistical significance was set at *P*-value less than 0.05. Post-hoc analyses were carried out using paired *t*-tests with Bonferroni's correction (*P* < 0.017 for the post-hoc tests).

Results

Two participants were excluded from the analysis because pain-SEFs could not be recorded clearly. Accordingly, the data included in the final analysis were obtained from 10 participants (28.4 \pm 2.7 years).

IES-evoked OP activity

As shown in Fig. 1, the ECDs were obtained around the bilateral OP and the source strength was reduced after the tDCS intervention. For the cOP, the results of two-way repeated-measures ANOVA showed significant interactions between the conditions and time ($F_{2,18}=9.425$, $P < 0.05$, and $\eta_p^2=0.51$) and a significant main effect of time ($F_{1,9}=28.70$, $P < 0.05$, and $\eta_p^2=0.76$). In contrast, the main effect of tDCS intervention was not significant ($F_{2,18}=0.74$, $P=0.49$, and $\eta_p^2=0.08$). Post-hoc analysis showed that the amplitude was significantly reduced after LA/RC and LC/RA ($P < 0.017$) (Fig. 2a).

For the iOP, significant interactions among the conditions and time ($F_{2,18}=4.76$, $P < 0.05$, and $\eta_p^2=0.35$) and a significant main effect of time ($F_{1,9}=10.92$, $P < 0.05$, and $\eta_p^2=0.55$) were found. In contrast, the main effect of tDCS was not significant ($F_{2,18}=0.86$, $P=0.44$, and $\eta_p^2=0.08$). The post-hoc test showed that the amplitude was significantly reduced after LA/RC and LC/RA ($P < 0.017$) (Fig. 2b).

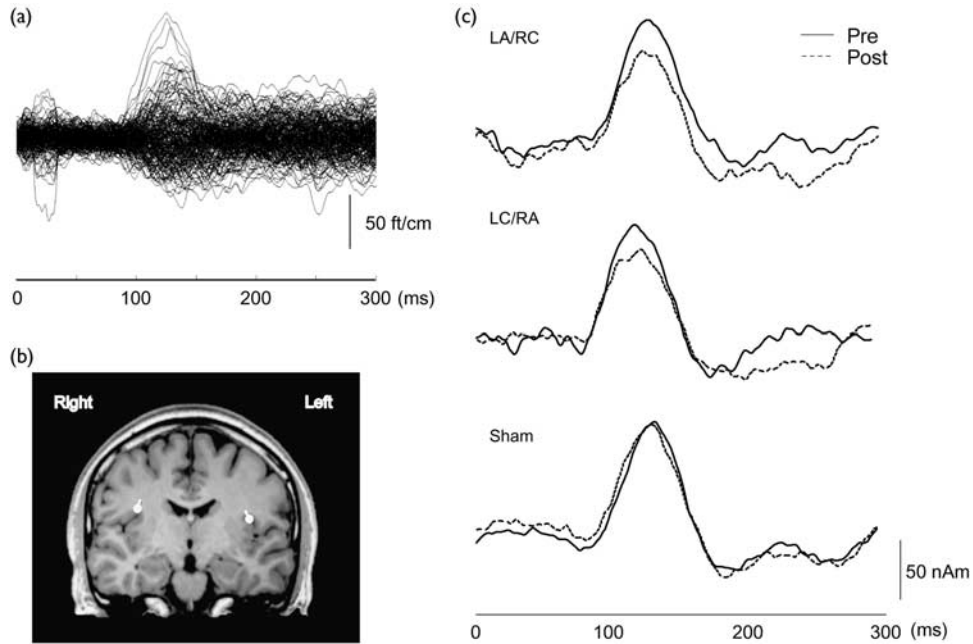
MN-evoked S1 activity

The ECD location for MN-SEFs was present around the postcentral gyrus. The source strength waveform showed several peaks with different polarities at 20, 35, and 60 ms (N20, P35, and N60). The results of two-way repeated-measures ANOVA indicated no significant interactions among the conditions and time (N20: $F_{2,18}=1.68$, $P=0.22$, and $\eta_p^2=0.16$; P35: $F_{2,18}=0.96$, $P=0.40$, and $\eta_p^2=0.10$; and P60: $F_{2,18}=0.11$, $P=0.90$, and $\eta_p^2=0.01$) and no significant main effect of time (N20: $F_{1,9}=0.05$, $P=0.82$, and $\eta_p^2=0.006$; P35: $F_{1,9}=0.98$, $P=0.35$, and $\eta_p^2=0.10$; and P60: $F_{1,9}=0.80$, $P=0.40$, and $\eta_p^2=0.08$) or tDCS condition (N20: $F_{2,18}=0.40$, $P=0.67$, and partial $\eta^2=0.43$; P35: $F_{2,18}=3.10$, $P=0.07$, and $\eta_p^2=0.25$; and P60: $F_{2,18}=3.32$, $P=0.06$, and $\eta_p^2=0.27$) (Fig. 3). These results indicate that S1 excitability is not modulated by tDCS intervention.

Magnitude of subjective pain sensation

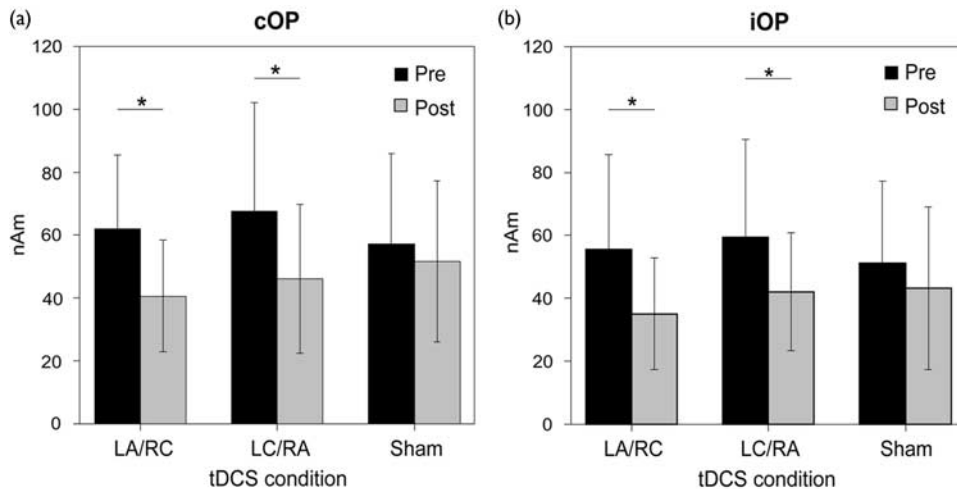
Two-way repeated-measures ANOVA showed no significant interactions among the conditions and time ($F_{2,18}=0.78$, $P=0.47$, and $\eta_p^2=0.08$) and no significant main effect of time ($F_{1,9}=0.81$, $P=0.39$, and partial $\eta^2=0.08$) or tDCS condition ($F_{2,18}=0.13$, $P=0.88$, and $\eta_p^2=0.014$) (Table 1). These results were consistent with our previous report [11].

Fig. 1



Representative data. Data from a representative participant. (a) Superimposed magnetoencephalography waveforms following intraepidermal electrical stimulation. (b) Source locations of the estimated equivalent current dipoles overlaid on MRIs. (c) Time courses of opercular somatosensory region activity following intraepidermal electrical stimulation under three conditions (LA/RC, LC/RA, and sham). Solid and dashed lines indicate waveforms before and after the transcranial direct current stimulation intervention, respectively. LA/RC, left anodal/right cathodal transcranial direct current stimulation; LC/RA, left cathodal/right anodal transcranial direct current stimulation.

Fig. 2



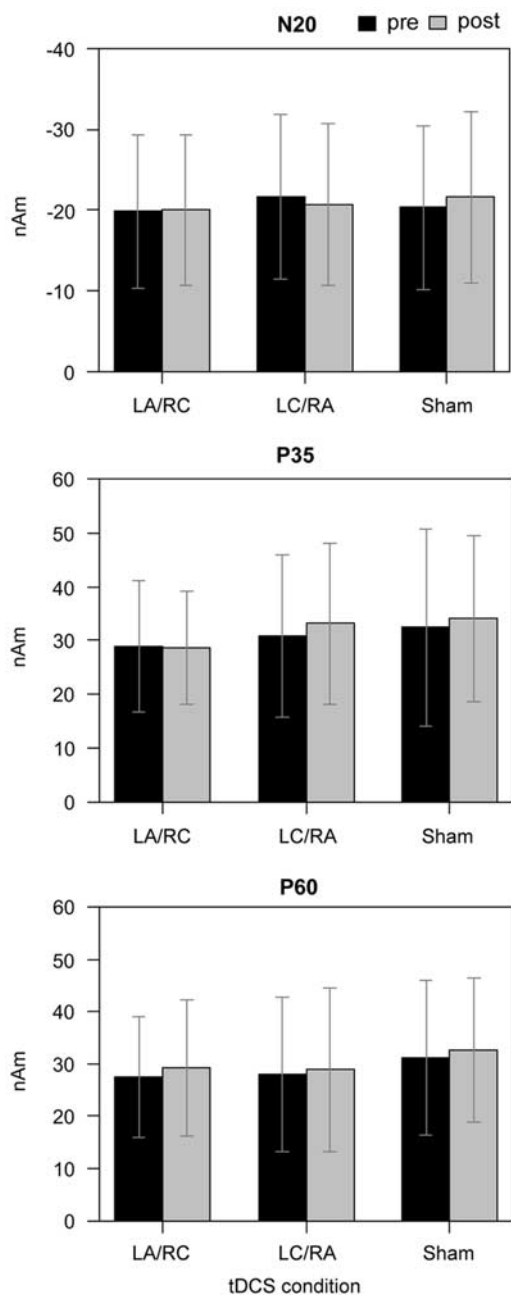
Mean amplitude of intraepidermal electrical stimulation-evoked activity. Pre-transcranial direct current stimulation (tDCS) (black columns) and post-tDCS (gray columns) comparison of the mean source strength amplitude of the equivalent current dipoles in the (a) cOP and (b) iOP. Data are given as mean \pm SD (* $P < 0.017$). cOP, opercular somatosensory region in the hemisphere contralateral to the stimulated side; iOP, opercular somatosensory region in the hemisphere ipsilateral to the stimulated side; LA/RC, left anodal/right cathodal transcranial direct current stimulation; LC/RA, left cathodal/right anodal transcranial direct current stimulation.

Questionnaire results

The subjective state during the tDCS intervention could potentially impact participants' performance. However,

no intervention-evoked alterations of subjective state were noted that might have affected the overall results of the present investigation (Table 2).

Fig. 3



Mean amplitude of MN-SEFs in the primary somatosensory cortex. Pre-transcranial direct current stimulation (tDCS) (black columns) and post-tDCS (gray columns) comparison of the mean source strength amplitude of the equivalent current dipoles for three latency components (N20, P35, and P60). Data are given as mean \pm SD. LA/RC, left anodal/right cathodal transcranial direct current stimulation; LC/RA, left cathodal/right anodal transcranial direct current stimulation; MN-SEF, somatosensory-evoked magnetic field following innocuous left median nerve stimulation.

Discussion

This study used a single-blind, sham-controlled, cross-over trial design to evaluate the effects of bihemispheric tDCS on the OP. Our results provide the first evidence

Table 1 Effects of tDCS on the magnitude of subjective pain sensation

	LA/RC		LC/RA		Sham	
	Pre	Post	Pre	Post	Pre	Post
VAS	1.8 \pm 0.9	1.7 \pm 1.1	1.7 \pm 0.7	1.8 \pm 0.8	1.9 \pm 0.9	1.7 \pm 0.9

Data are represented as mean \pm SD.

LA/RC, left anodal/right cathodal transcranial direct current stimulation; LC/RA, left cathodal/right anodal transcranial direct current stimulation; VAS, visual analog scale.

Table 2 Questionnaire results for the tDCS intervention

	LA/RC	LC/RA	Sham	χ^2	P-value
Attention	1.0 \pm 0	1.0 \pm 0	1.0 \pm 0	–	–
Fatigue	1.0 \pm 0	1.0 \pm 0	1.0 \pm 0	–	–
Pain	1.3 \pm 0.5	1.4 \pm 0.5	1.3 \pm 0.5	0.5	0.79
Sleepiness	1.1 \pm 0.3	1.0 \pm 0	1.1 \pm 0.3	1	0.61
Discomfort	1.3 \pm 0.5	1.1 \pm 0.3	1.1 \pm 0.3	2	0.37

Data are represented as mean \pm SD.

All parameters were scored on a scale of 1–4 (1 = no distraction of attention, fatigue, pain, sleepiness, or discomfort; 4 = highest level of distraction of attention, fatigue, pain, sleepiness, or discomfort).

LA/RC, left anodal/right cathodal transcranial direct current stimulation; LC/RA, left cathodal/right anodal transcranial direct current stimulation.

that bihemispheric tDCS can decrease IES-evoked OP activity in a polarity-independent manner in healthy adults. This finding suggests that tDCS could modulate the cortical activity in a deeper-located region such as OP [19]. In contrast, subjective pain sensation and MN-evoked S1 activity were similar before and after the tDCS intervention, as found in a previous report [11].

We targeted the OP because the medial parietal operculum and the posterior insula are considered areas where electrical stimulation can trigger activation of the pain cortical network [3]. In addition, some studies have shown that rTMS intervention over the OP reduced chronic and experimentally induced pain [4,5].

Bilateral OPs are considered to be connected either directly by transcallosal connections or indirectly by the thalamic and S1 circuitry [17]. We therefore propose that the inhibitory effects of one hemisphere receiving cathodal tDCS might be further augmented by simultaneously enhanced interhemispheric inhibitory inputs to the other hemisphere receiving anodal tDCS. However, polarity-independent effects were not observed, as was also the case in several previous studies [20,21]. Because cathodal stimulation is generally inhibitory, whereas anodal stimulation is excitatory, it remains unclear why bihemispheric tDCS might elicit polarity-independent effects. There are two possible explanations for this result.

First, OP excitability might be decreased by both stimulations. In support of this hypothesis, rTMS studies found that both facilitatory (high frequency) [5] and inhibitory (low frequency) [4] stimulation over the OP

suppressed the pain perception. Hence, our application of anodal tDCS over the bilateral OP might have inhibited, rather than facilitated, OP excitability. Further studies using monopolar stimulation are required to elucidate the influence of tDCS with respect to polarity differences.

Second, the function of the connections must be considered. Earlier work on pain-SEFs showed that peak latency was shorter for the cOP than the iOP by ~5–15 ms [22], which is consistent with the present study. The difference has been interpreted to reflect the time required to transmit signals through the corpus callosum. This implies that when OP activity following IES in the contralateral hemisphere is suppressed by cathodal stimulation, ipsilateral activation by the callosal transmission is consequently reduced. However, in this case, the iOP receives anodal stimulation, presumably increasing excitation in the region. Therefore, the final output in both hemispheres depends on the balance between excitatory and inhibitory influences.

Despite the inhibitory tDCS effects on IES-evoked cortical responses, modest effects on the magnitude of subjective pain sensation were found as with our previous report [11]. This discrepancy indicates that cortical pain processing does not impact on subjective pain sensation, which leads us to speculate that subjective pain sensation is more complex than mere pain-related somatosensory processing.

Although anodal tDCS over the S1 or M1 facilitated the MN-evoked S1 activities [23], we observed no change in MN-evoked S1 activity. Therefore, the ability of bihemispheric tDCS over the OP cannot be explained by changes in S1 excitability. Because the effectiveness of tDCS on the excitability of the stimulated cortex depends on the current density [24], reduced IES-evoked cortical responses might be attributed to the modulation of OP excitability, but not S1 excitability.

This study has certain limitations. First, the small number of participants undoubtedly restricts the strength of our conclusions. Second, we did not separate temporally overlapping OP sources, potentially affecting our results, given that there are multiple sources in the OP (e.g. the secondary somatosensory cortex, anterior, and posterior insula). Third, our study carried out bihemispheric tDCS only; thus, we did not address whether unihemispheric tDCS is also effective for the suppression. Finally, we tested the effects in healthy participants. The data obtained might not be directly transferable to the treatment of chronic pain patients because they show functional and structural changes in the central nervous system [25]. Future investigations should be designed to compare the efficacy of tDCS in healthy individuals and pain patients.

Conclusion

This study used a single-blind, cross-over, sham-controlled trial design to investigate whether bihemispheric tDCS can modulate OP activity and the magnitude of subjective pain sensation in healthy individuals. The main finding was that OP activity was reduced by bihemispheric tDCS in a polarity-independent manner.

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K. Nakagawa and S. Koyama designed and performed the research, analyzed the data, and wrote the manuscript; K. Inui, S. Tanaka, R. Kakigi, and N. Sadato designed the research, analyzed the data, and wrote the manuscript.

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Conflicts of interest

There are no conflicts of interest.

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