Journal of Pain Research

Dovepress
Taylor & Francis Group

Open Access Full Text Article

CLINICAL TRIAL REPORT

High-Definition Transcranial Direct Current Stimulation Improves Pain Empathy: A Randomized, Double-Blind, and Sham-Controlled Study Based on Event-Related Potentials (ERPs)

Zhengyu Hu[1,2,*], Yurong Wen[3,4,*], Beibei Feng[1,5,6,*], Yafei Wang[1,5,6], Yangyang Lin[1,5,6], Jian Shi[1], Chen Gong[1,5,6], Yuling Wang[1,5,6]

[1]Department of Rehabilitation Medicine, The Sixth Affiliated Hospital, Sun Yat-Sen University, Guangzhou, Guangdong, People's Republic of China; [2]Department of Rehabilitation and Traditional Chinese Medicine, The Second Affiliated Hospital of Zhejiang University School of Medicine, Hangzhou, Zhejiang, People's Republic of China; [3]Department of Rehabilitation, West China Second University Hospital, Sichuan University, Chengdu, Sichuan, People's Republic of China; [4]Key Laboratory of Birth Defects and Related Diseases of Women and Children (Sichuan University), Ministry of Education, Chengdu, Sichuan, People's Republic of China; [5]Biomedical Innovation Center, The Sixth Affiliated Hospital, Sun Yat-sen University, Guangzhou, Guangdong, People's Republic of China; [6]Guangdong Provincial Clinical Research Center for Rehabilitation Medicine, Guangzhou, Guangdong, People's Republic of China

*These authors contributed equally to this work

Correspondence: Yuling Wang, Department of Rehabilitation Medicine, The Sixth Affiliated Hospital, Sun Yat-sen University, No. 26, Yuancun 2nd Cross Road, Guangzhou, Guangdong, People's Republic of China, Tel +86-20-38476737, Email wangyul@mail.sysu.edu.cn; Chen Gong, Guangdong Provincial Clinical Research Center for Rehabilitation Medicine, Guangzhou, Guangdong, People's Republic of China, Email gongch33@mail.sysu.edu.cn

Abstract: The impact of transcranial direct current stimulation (tDCS) on pain empathy is a subject of debate and controversy. The variations in the results could be attributed to differences in the stimulus parameters. This study aimed to examine the impact of high-definition transcranial direct current stimulation (HD-tDCS) with different intensities on pain empathy through event-related potentials (ERPs). Thirty-nine participants were recruited for the experiment, and a parallel control design was used. The participants were randomly assigned to the sham group, 1 mA stimulation group, or 2 mA stimulation group. Before the experiment, all the participants provided basic information, completed relevant questionnaires and then wore an EEG cap for the first pain empathy task. After completing the task, each group received 20 minutes of HD-tDCS stimulation over the left DLPFC region at different intensities (2 mA, 1 mA, or sham), followed by a second pain empathy task. The findings from the pain-judgment and hands-counting tasks (task 1) demonstrated that both 1- and 2-mA stimulation increased Δ-N1 amplitudes, suggesting that anodal stimulation enhances early empathic responses. The results of the pain rating task (task 2) indicate that HD-tDCS stimulation did not improve the ratings of others' pain. However, the application of 2-mA tDCS significantly increased the Δ-intensity of unpleasantness compared with that of the other two groups. This suggests that 2-mA tDCS stimulation had a notable effect on the affective dimension of empathy, specifically the perception of unpleasantness. This finding indicates that 2mA stimulation primarily enhances affective empathy, whereas its influence on cognitive empathy appears to be limited. By employing different intensities of HD-tDCS, our findings build upon and extend previous findings in the field of pain empathy. These results have the potential to offer dose recommendations for future studies employing tDCS as an intervention to increase pain empathy.

Plain Language Summary:

Why was the study done?

Previous studies have shown inconsistent results concerning the impact of transcranial direct current stimulation (tDCS) on pain empathy, which might be due to differences in stimulation parameters. Therefore, Dr Wang's team explored how high-definition transcranial direct current stimulation (HD-tDCS) with different current intensities affects a human's ability to feel others' pain ("pain empathy").

What did the researchers do and find?

Received: 12 June 2025
Accepted: 12 September 2025
Published: 8 October 2025

Thirty-nine healthy adults were recruited and received either sham stimulation, lower-intensity (1 mA), or higher-intensity (2 mA) anodal HD-tDCS for 20 minutes over the brain area linked to empathy (the left DLPFC region). Dr Wang's team measured brain activity and responses to images of people in pain and reported that both the 1 mA and 2 mA doses increased very early brain signals linked to spontaneous feelings of others' pain; neither dose changed how much pain participants thought others were feeling; only the 2 mA dose made participants feel significantly more unpleasant when seeing others in pain.

What do these results mean?

The results show that the current intensity of anodal tDCS over the left DLPFC matters for modulating human pain empathy. Both lower-intensity (1 mA) and higher-intensity (2 mA) stimulation enhance spontaneous empathic responses at the early stage. However, only 2 mA HD-tDCS affects the emotional side of sharing others' pain. These results potentially indicate dose-dependent responses for future studies employing tDCS as an intervention to improve pain empathy.

Keywords: pain empathy, transcranial direct current stimulation, event-related potential, dorsolateral prefrontal cortex

Introduction

Empathy is defined as the ability to not only comprehend but also personally experience another individual's inner emotional state. This capacity enables us to care for, share knowledge with, and collaborate effectively with one another to achieve common objectives.[1] In the realm of daily social interactions, empathy assumes a pivotal role in our understanding of the cognitive and emotional processes of others.[2–4] Pain empathy is the most studied subform of empathy and plays a crucial role in the prosocial behaviors of humans.[5] Prior research has revealed the prevalence of empathy deficits among diverse groups, including healthcare professionals,[6] medical students,[7] violent offenders,[8] patients with chronic pain,[9,10] and people with mental illness[5] or sleep disorders.[11] Individuals who exhibit lower levels of pain empathy or who are overly sensitive to the suffering of others may encounter challenges in their social adaptation.[12]

An expanding body of evidence suggests that pain empathy is intricately linked to neural structures implicated in the actual experience of pain.[13] The dorsolateral prefrontal cortex (DLPFC), anterior insular cortex and medial/anterior cingulate cortex constitute the core neural network associated with pain empathy.[13,14] Remarkably, lesions affecting these brain regions have been shown to result in deficits in pain empathy.[15] Given the strong anatomical links between the DLPFC, anterior cingulate cortex and anterior insula[16] and the fact that stimulation over the DLPFC coactivates these regions along with itself,[17] the left dorsolateral prefrontal cortex (DLPFC) has emerged as a viable target for modulating pain empathy.[18]

Transcranial direct current stimulation (tDCS), a noninvasive neuromodulation technique, uses painless, relatively low-intensity current (usually 0.5–2 mA) through scalp electrodes to alter cortical excitability immediately, promotes lasting neuroplasticity[19,20] and is widely recommended for treating neurological and psychiatric disorders.[21] As mentioned, the DLPFC is closely connected with the central brain regions implicated in pain empathy and therefore holds promise as a potential therapeutic target. To date, two studies have evaluated the effects of applying tDCS to the DLPFC on pain empathy. One study reported that applying 2-mA anodal tDCS over the left DLPFC led to changes in perceived pain ratings for other healthy individuals.[22] In another study, tDCS targeting both the left and right DLPFC was found to reduce feelings of hostility, sadness, and self-perceived pain.[23] However, owing to the heterogeneity in design, it is still unclear whether the current intensity affects the stimulation effect, and further verification is needed. Moreover, the underlying neural mechanism remains unclear. In existing research on pain empathy, event-related potentials (ERPs) have been used to measure the process of pain empathy. Combining ERP indicators should be an alternative for understanding the potential mechanism by which tDCS improves pain empathy.[24]

Given the aforementioned, the present study aimed to investigate whether there are differential modulatory effects of various HD-tDCS intensities on pain empathy via ERPs. The participants took part in a pain empathy task before and after receiving 20 min of stimulation at different intensities (2 mA, 1 mA, or sham), and concurrent electroencephalographic signals were recorded. It is hypothesized that different stimulation intensities lead to discernible outcomes, which are reflected in neurophysiological findings.

Materials and Methods

Study Design

This randomized, double-blind, sham-controlled, three-arm parallel study (sham, 1-mA, 2-mA tDCS) was conducted at the Sixth Affiliated Hospital of Sun Yat-Sen University. It included two phases: baseline and poststimulation empathy assessments. To maintain blinding, participants were not allowed to communicate, and both participants and evaluators were unaware of group assignments. Only the HD-tDCS operators handling randomization knew the group details. The first participant was randomized on September 25, 2022. The study was approved by the ethics committee of the Sixth Affiliated Hospital, Sun Yat-Sen University (2022ZSLYEC-397), and followed the Declaration of Helsinki. Informed consent was obtained from all participants.

Participants

Forty participants aged 18–35 years were recruited through community and online platforms. The inclusion criteria included a) right-handedness; b) absence of neurological disease, neurosurgery, epilepsy, brain injury, or cerebral metal implants; and c) self-rating anxiety scale (SAS) scores < 50 and self-rating depression scale (SDS) scores < 53. The exclusion criteria were as follows: 1) prior to participation in psychological experiments; 2) severe cardiovascular diseases; 3) indications of neurological impairments; 4) brain tissue injury-related conditions; 5) psychiatric disorders; 6) malignant tumors and rheumatoid arthritis; 7) pregnancy or lactation; and 8) severe insomnia. Among the study participants, one participant did not meet the inclusion criteria (SDS = 57). The participants were stratified by age and sex for randomization. Ultimately, 39 eligible individuals were randomly assigned to one of three experimental groups.

Procedure

The subjects were asked to complete demographic (age, sex, education, and sleep duration) and psychological questionnaires, including the Chinese version of the Interpersonal Reactivity Index (IRI-C), SAS, and SDS. The subjects sat comfortably on stools in a quiet, soundproof room with soft light. The investigator measured the head circumference of the subjects and wore an electroencephalogram (EEG) cap of appropriate size. The EEG paste was then injected between the scalp and the electrodes to ensure that the electrode–skin impedance of all electrodes remained below 10 kΩ. The subjects were instructed to focus on the screen and decrease the rate of eye blinking. The participants were subsequently asked to complete two tasks: Task 1 (pain judgment, hand counting) and Task 2 (pain rating). After the two tasks, the subjects received HD-tDCS stimulation with the NG Pistim electrode filled with conductive glue (sham, 1 mA, or 2 mA) for 20 min. The investigator then checked the impedance of all of the EEG electrodes. The subjects were asked to repeat the two tasks with EEG data recorded for the pain-judgment and hand-counting tasks. Following device removal, participants completed an adverse effects questionnaire. Blinding efficacy was assessed on the basis of accuracy in identifying the type of stimulation received (active/sham). The overall process is illustrated in Figure 1.

Empathy Task

Sixty color photographs depicting hands in painful or nonpainful daily scenarios served as stimuli.[25] No-pain images mirrored pain images in contextual content but excluded nociceptive elements. All the images were luminance-, contrast-, and color-matched and were centrally presented against a black background.

Task 1: Pain Judgment and Hand-Counting Tasks

As shown in Figure 2a, each trial started with a 500-ms fixation in the center of the screen, followed by a blank screen (randomly lasting 1000–2000 ms) and then a pain or no-pain image (lasting 1000 ms). During the pain-judgment task, the participants rapidly classified images as painful/nonpainful via keyboard keys (7/9). In the hands-counting task, they indicated hand count (1/2). Each 60-trial task included 30 pain images. Trial intervals were randomly jittered between 2000–4000 ms. Behavioral data, including reaction time (RT) and accuracy, and EEGs were continuously recorded. Researchers believe that the stimulus material of other people's pain initiates an empathic response in individuals and interferes with the performance of hands-counting tasks, resulting in increased RT and decreased accuracy with respect to

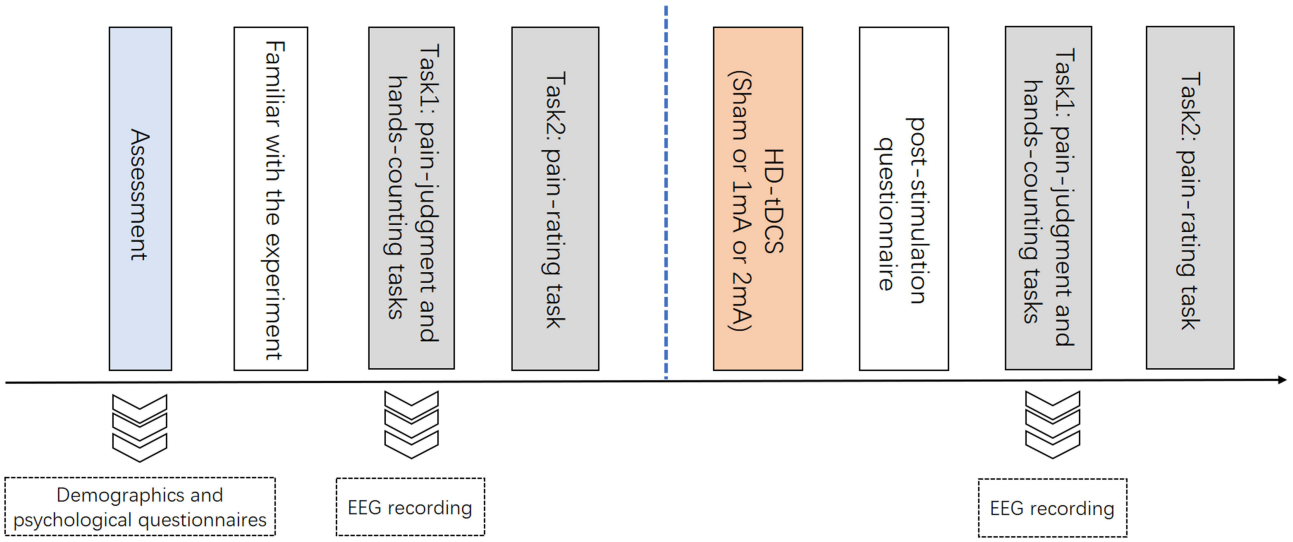

Figure 1 Experimental protocol for assessing the effects of HD-tDCS on pain empathy. The participants completed tasks within the classical pain empathy paradigm: pain-judgment, hands-counting, and pain-rating tasks. After completing the tasks, the participants underwent HD-tDCS stimulation (2 mA, 1 mA, sham) for 20 min before completing a poststimulation questionnaire. The participants subsequently performed the tasks again. EEG data were collected during task 1, whereas task 2 did not involve EEG signal acquisition.

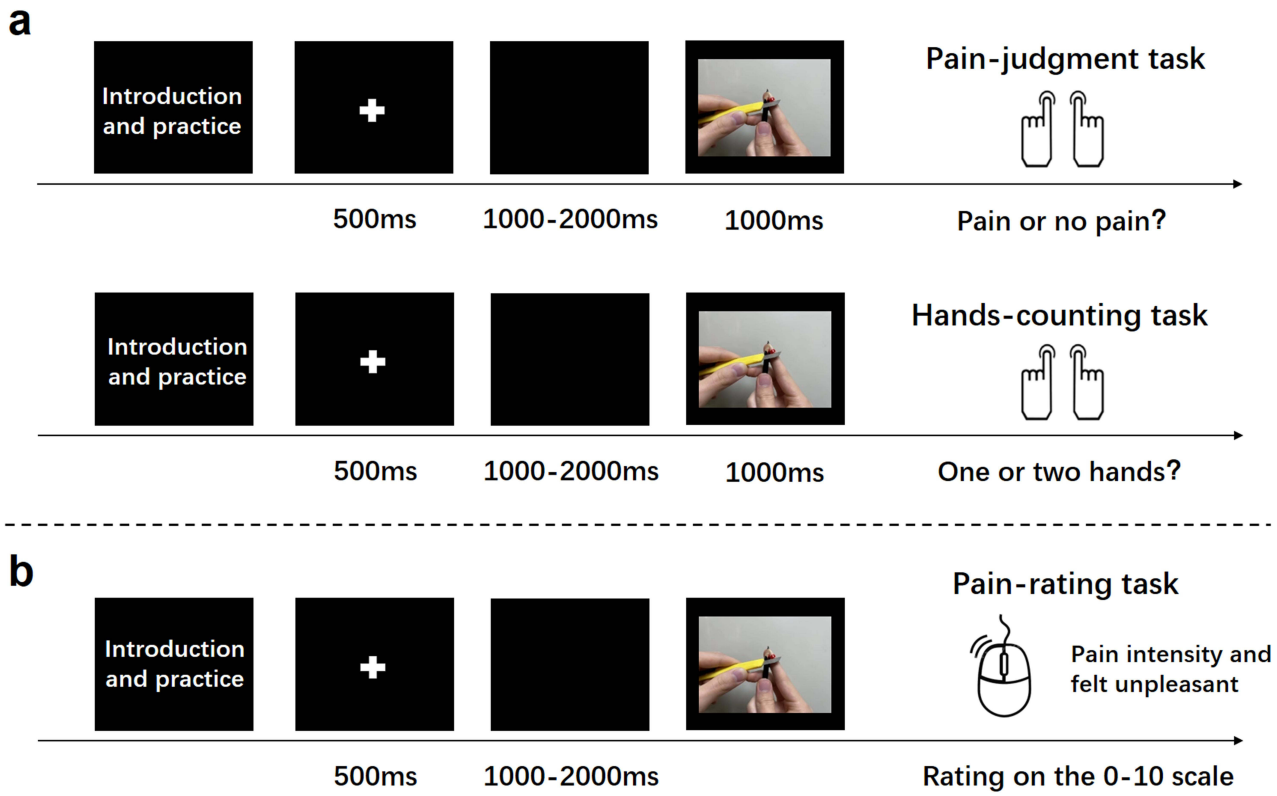

Figure 2 Experimental paradigms for pain empathy. (**a**) Pain-judgment and hand-counting tasks. The participants will encounter instructional prompts on the screen before engaging in practice or formal experiments. Initially, a fixation cross ("+") appears at the center of the screen for 500 ms, followed by a blank screen lasting 1000–2000 ms. Subsequently, images, randomly selected from either painful or neutral categories, are presented, with a duration of 1000 ms. Participants are required to rapidly and accurately determine whether the hand in the displayed image is experiencing pain, pressing "7" and "9" for pain and no-pain images, respectively. In the hands-counting task, participants were required to assess the number of hands presented in the displayed images. (**b**) Pain-rating task. The experimental procedure begins with a central fixation cross ("+") displayed for 500 ms, followed by a blank screen lasting 1000–2000 ms. Subsequently, images are presented continuously until the participant makes a judgment. The participants are required to rate the perceived pain intensity of the individuals in the images and their level of unpleasantness via a numeric rating scale (NRS) with 11 levels, where a score of 0 indicates no pain or no unpleasantness, whereas a score of 10 represents extreme pain or extreme unpleasantness.

pain pictures. The stronger the emotional empathy ability of individuals is, the more susceptible they are to interference from pain information in the hands-counting task, and the worse the performance of the task.[26]

Task 2: Pain Rating Task

As shown in Figure 2b, pain and no-pain images were presented on the screen. Using an 11-point numeric rating scale (NRS), participants assessed other-pain intensity (0 = no pain, 10 = unbearable pain) for depicted individuals and self-experienced unpleasantness (0 = none, 10 = extreme). Researchers generally assume that ratings of the intensity of others' pain in stimulus material involve reasoning about the somatic sensation of others' pain and reflect cognitive empathy. The emotional changes (self-unpleasantness score) caused by the pain of the characters in the stimulus material involve alternative emotional experiences and reflect emotional empathy.[27]

High-Definition Transcranial Direct Current Stimulation (HD-tDCS)

High-definition tDCS employs 3.14 cm^2 NG PiStim electrodes (Neuroelectrics) integrated within a 64-channel EEG cap. Electrode configurations were optimized via SimNIBS-generated computational models of cortical electric field distributions.[28] HD-tDCS was administered via Starstim 8 (Neuroelectrics, Spain) using a 4×1 ring configuration: an anode at F3 (targeting the left DLPFC) with four return electrodes (Fp1, Fz, C3, F7). The active stimulation groups received 20-min left DLPFC stimulation at 1 mA or 2 mA, including 30-s ramp-up/down phases.[29] For the sham group, participants received stimulation on the left DLPFC at an intensity of 2 mA with the same montage, but the stimulation was only given during the first and last 30s.

Cortical electric fields induced by HD-tDCS were simulated via SimNIBS.[28] The electrodes were modeled as 1-mm-thick, 2-cm-diameter discs with embedded 12-mm Ag/AgCl pellets and 2.0-mm gel layers. The resulting electric fields (normEs) were postprocessed and visualized in Gmsh.[30]

EEG Data Collection and Analysis

EEG data were acquired via a 64-channel SynAmpsRT amplifier (Compumedics Neuroscan) in DC mode at 1000 Hz. Electrode impedances were maintained below 5 kΩ (all channels <10 kΩ). The reference electrode (REF) was used for online recording, while ocular artifacts were monitored with simultaneous electrooculogram (EOG) surface electrodes. The EEG data were preprocessed in EEGLAB[31] on MATLAB: 0.1–30 Hz filtering; segmentation into 2000-ms epochs (−1000 to 1000 ms) with prestimulus baseline correction; manual artifact rejection; ICA ocular artifact removal;[32] and mastoid referencing.[33] ERPs were analyzed from −200 to 800 ms post-stimulus. Group-level waveforms were generated by averaging participant-level ERPs per tDCS condition. On the basis of grand average ERP scalp topographies and prior pain empathy research,[25,34] we identified key ERP components: N1, N2, P3, and LPP. Electrode selection and time windows were determined through visual inspection of grand average ERP waveforms and topographies, which is consistent with methodologies from previous studies in which identical pictorial stimuli were used.[25,33,35]

Statistical Analysis

Data analysis was conducted via SPSS 24.0. Sociodemographic and psychological data were summarized descriptively, with group differences analyzed via ANOVA. Baseline-to-poststimulation changes were first examined, and Δ-scores ([post]–[baseline]) were used for intergroup comparisons. A three-factor mixed-design ANOVA (group × picture × task) was applied to the behavioral (Δ-RT, Δ-accuracy) and EEG data (ΔN1, ΔN2, ΔP3, ΔLPP), with group as a between-subjects factor and image/task as a within-subjects factor. If the results were not significant, two-factor ANOVAs (group × picture) were conducted separately for each task. For the pain rating task, another two-way ANOVA was used to analyze differences in the other-pain and self-emotion scores. Significance was set at $p < 0.05$.

Results

Demographic Characteristics

Among the 39 initially screened participants, three were excluded because of technical issues (equipment failure or excessive EEG noise), resulting in a final sample of 36 individuals (12 per group). Table 1 summarizes the participants' demographic and psychological characteristics, which showed no significant baseline differences across the groups. In terms of tDCS side effects, itching severity differed marginally among the groups (p = 0.05), although most adverse events were mild. No severe reactions necessitating medical intervention occurred (Table 2). Blinding effectiveness varied: while only 33.3% of the patients accurately detected sham stimulation, the correct identification rates increased to 66.7% (1-mA group) and 75% (2-mA group) for active stimulation. However, Fisher's exact test comparing correct and incorrect responses was not significant ($p = 0.166$), indicating successful blinding.

Task 1: Pain-Judgment and Hands-Counting Tasks

The Δ-reaction time (Δ-RT) and Δ-accuracy (Δ-ACC) are presented in Figure 3. The group × picture × task mixed model ANOVA conducted on Δ-RT revealed no significant main or interaction effects. Analysis of the Δ-ACC revealed significant main effects ($F = 4.032$, $p = 0.047$, $\eta_p^2 = 0.030$), which manifested as a lower Δ-ACC for the hands-counting task than for the pain-judgment task (−0.006 ± 0.06 vs 0.016 ± 0.074). No other significant main effects or

Table 1 Demographic and Psychological Features of the Participants

	Sham (Group 1) (n=12)	1-mA (Group 2) (n=12)	2-mA (Group 3) (n=12)	*P* Value
Demographics				
Age > years, mean (SD)	22.92 (1.98)	23.42 (3.45)	23.08 (2.43)	0.898
Education, years, mean (SD)	16.33 (1.37)	16.50 (1.83)	16.75 (2.01)	0.843
Sleep time, h, mean (SD)	7.33 (0.49)	7.38 (0.93)	7.29 (0.81)	0.965
Female, n (%)	10 (83.3%)	8 (66.7%)	9 (75.0%)	0.641
Psychological factors				
IRI-C, mean (SD)	102 (7.41)	97.08 (12.41)	97.67 (8.63)	0.409
PT, mean (SD)	26.33 (3.23)	26.17 (2.86)	24.33 (2.83)	0.204
FS, mean (SD)	24.67 (5.02)	21.50 (5.16)	21.33 (4.39)	0.183
EC, mean (SD)	27.17 (4.28)	26.17 (5.37)	28.58 (3.50)	0.419
PD, mean (SD)	24.83 (2.44)	23.25 (4.65)	23.41 (3.06)	0.486
SAS, mean (SD)	35.58 (5.35)	32.17 (6.01)	39.42 (8.89)	0.06
SDS, mean (SD)	39.42 (7.61)	34.08 (8.45)	39.17 (7.84)	0.196

Abbreviations: IRI-C, Interpersonal Reactivity Index-C; PT, Perspective-taking; FS, Fantasy scale; EC, Empathetic concern; PD, Personal distress; SAS, Self-rating Anxiety Scale; SDS, Self-rating Depression Scale.

Table 2 tDCS-Related Adverse Events Until the End of Follow-up

	Sham (Group 1) (n=12)	1-mA (Group 2) (n=12)	2-mA (Group 3) (n=12)	*P* value
Headache, n (%)	1 (8.3%)	3 (25%)	4 (33.3%)	0.324
Trouble concentrating, n (%)	2 (16.7%)	4 (33.3%)	7 (58.3%)	0.102
Nervousness/anxiety, n (%)	2 (16.7%)	3 (25%)	3 (25%)	0.852
Problems with vision, n (%)	4 (33.3%)	3 (25%)	5 (41.7%)	0.687
Fatigue, n (%)	4 (33.3%)	4 (33.3%)	5 (41.7%)	0.887
Nausea, n (%)	0 (0%)	0 (0%)	0 (0%)	/
Scalp pain, n (%)	5 (41.7%)	4 (33.3%)	5 (41.7%)	0.89
Tingling, n (%)	3 (25%)	6 (50%)	9 (75%)	0.05
Itching, n (%)	4 (33.3%)	4 (33.3%)	3 (25%)	0.877
Burning sensation, n (%)	1 (8.3%)	2 (16.7%)	2 (16.7%)	0.793

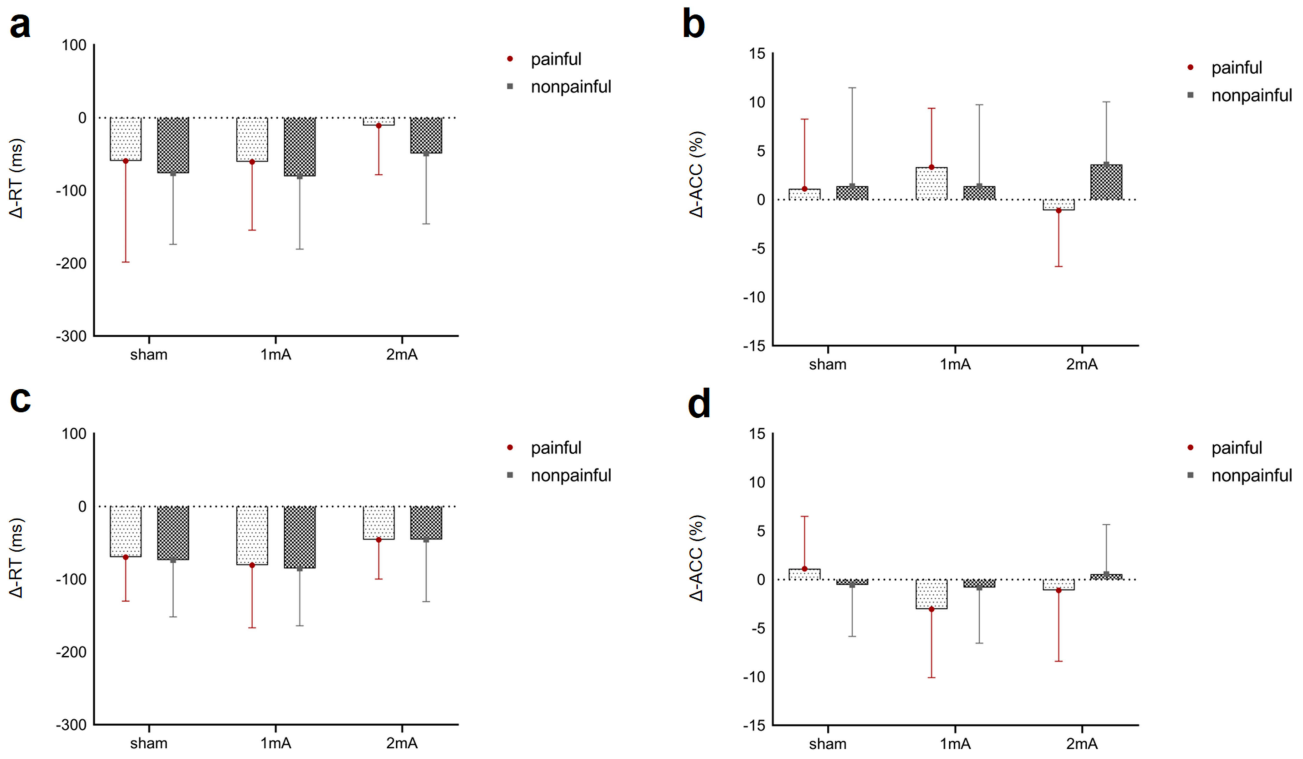

Figure 3 Behavioral results in the pain-judgment and hands-counting tasks. (**a**) Δ-RT in the pain-judgment task; (**b**) Δ-ACC in the pain-judgment task; (**c**) Δ-RT in the hands-counting task; and (**d**) Δ-ACC in the hands-counting task.

interactions were observed. The results suggest that HD-tDCS stimulation did not seem to have a notable effect on the differences in Δ-RT and Δ-ACC across the tasks.

Grand average ERP waveforms for pain and no-pain images during both experimental tasks are displayed in Figure S1. Visual inspection revealed that both image types elicited maximal N1 and N2 amplitudes over frontocentral regions, whereas the P3 and LPP components peaked over centroparietal regions. Figure 4 presents the Δ amplitudes for all four ERP components during the pain judgment task. Analysis of the Δ-N2, Δ-P300, and Δ-LPP amplitudes revealed no significant main effects or interactions ($p > 0.05$ for all comparisons). The main effect of group was significant for frontal-central Δ-N1 amplitudes ($F = 3.265$, $p = 0.044$, $\eta_p^2 = 0.09$), which manifested as greater Δ-N1 amplitudes for the 2-mA group than for the sham group (1.245 ± 4.657 μV vs −1.753 ± 4.034 μV) and for the 1-mA group than for the sham group (1.086 ± 4.748 μV vs −1.753 ± 4.034 μV). In contrast, there was no significant difference in the Δ-amplitude between the 1-mA and 2-mA groups (1.245 ± 4.657 μV vs 1.086 ± 4.748 μV). No other significant main effects or interactions were observed.

Task 2: Pain Rating Task

In Task 2, the Δ-intensity of the pain and the unpleasantness felt by the participants when viewing images are shown in Figure 5. The group × picture mixed model ANOVA conducted on the Δ-intensity of the pain revealed no significant main or interaction effects. These results suggest that HD-tDCS stimulation does not lead to significant intergroup differences in pain ratings in the other-pain rating task.

Analysis of the Δ-intensity of the unpleasantness showed significant main effects of group ($F = 6.190$, $p = 0.003$, $\eta_p^2 = 0.158$), which manifested as a greater Δ-intensity of the unpleasantness for the 2-mA group than for the 1-mA group (11.333 ± 27.132 vs −3.792 ± 9.496) and for the 2-mA group than for the sham group (11.333 ± 27.132 vs −5.875 ± 17.578). The interaction between group × picture was also significant ($F = 4.862$, $P = 0.011$, $\eta_p^2 = 0.128$). Post hoc comparisons revealed that when pain images were viewed, the Δ-intensity of the unpleasantness was greater in the 2-mA group than in the 1-mA group (22.667 ± 35.206 vs −6.833 ± 12.590) and the sham group (22.667 ± 35.206 vs −9 ± 22.964). In contrast, when images of no pain were viewed, no significant effects were observed. In the 2-mA group, the Δ-intensity of the unpleasantness for pain images was significantly

https://doi.org/10.2147/JPR.S540255

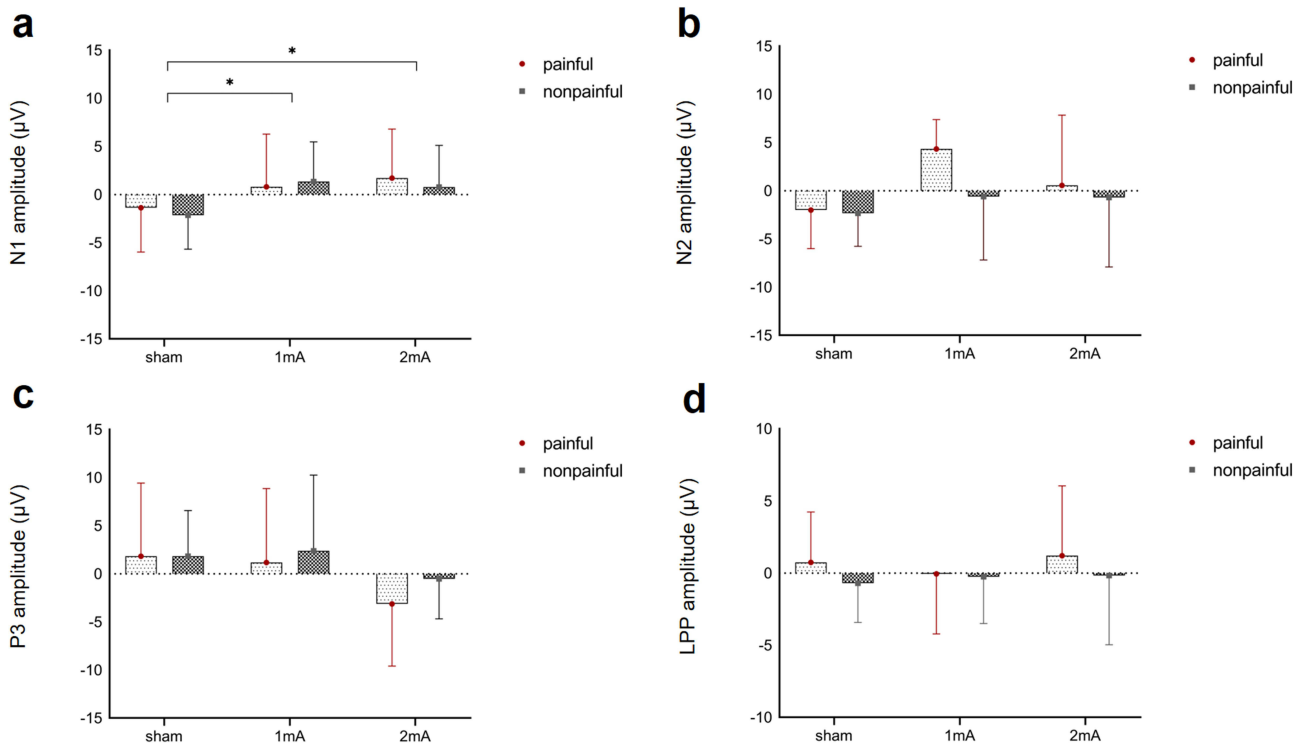

Figure 4 Δ-Amplitudes of the four ERP responses in the pain judgment tasks. (**a**) Δ-N1 amplitude in the pain-judgment task; (**b**) Δ-N2 amplitude in the pain-judgment task; (**c**) Δ-P3 amplitude in the pain-judgment task; and (**d**) Δ-LPP amplitude in the pain-judgment task. **P*<0.05.

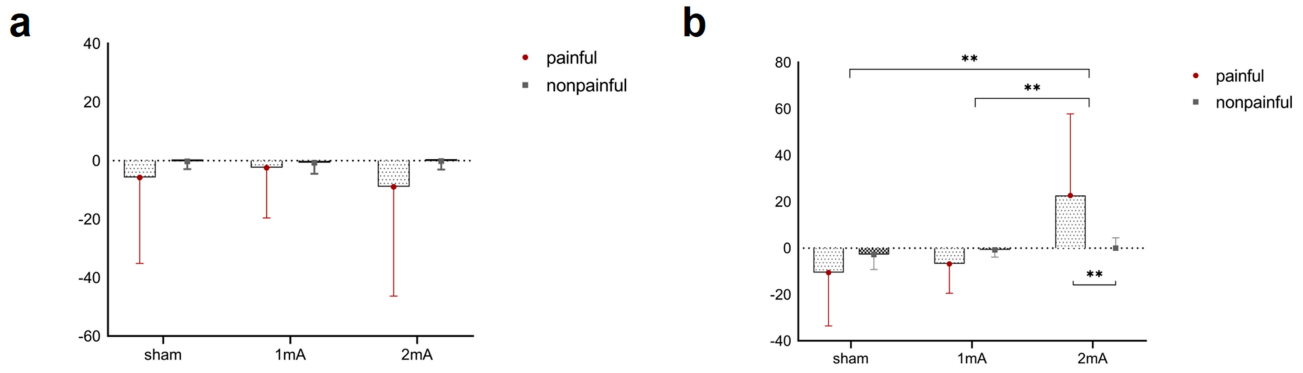

Figure 5 Behavioral results in the pain-judgment and hands-counting tasks. (**a**) Δ-intensity ratings of pain and (**b**) Δ-intensity ratings of unpleasantness. ** *P*<0.01.

greater than that for no-pain images (22.667 ± 35.207 vs 0 ± 4.411). However, for the other two groups, there was no significant difference between the Δ intensity of the unpleasantness for the pain images and the no-pain images. These results indicate that in the self-emotion rating task, 2-mA HD-tDCS stimulation enhances participants' ratings of the unpleasantness of pain images.

Discussion

This study aimed to explore how different HD-tDCS intensities modulate pain empathy via ERPs. Both 1- and 2-mA stimulation increased the Δ-N1 amplitude, suggesting that stimulation enhances early empathic responses. However, only 2-mA tDCS significantly increased the Δ-intensity of unpleasantness compared with the other two groups, which indicated that 2-mA tDCS stimulation had a notable effect on the affective dimension of empathy, specifically the perception of unpleasantness, but had a limited effect on cognitive empathy. Our results provide additional insights into

the field of pain empathy through the use of varying intensities of HD-tDCS. These findings may provide dosage indications for future research using tDCS as a pain empathy-boosting intervention.

In Task 1 pain-judgment and hands-counting tasks, a dual-choice paradigm using identical visual stimuli for both the pain-judgment and hands-counting tasks was used to assess top-down attentional modulation in pain empathy. RTs and ACCs served as indirect empathy indicators. In the pain-judgment task, higher accuracy and faster responses reflected stronger empathy. In contrast, the hands-counting task triggered empathic interference, leading to slower responses and lower accuracy when viewing pain-related images. Individuals with greater empathy showed greater sensitivity to this interference, with a more pronounced performance decline for painful stimuli.[26] In this study, the pain-judgment task resulted in longer average RTs and lower accuracy than did the hands-counting task, indicating greater cognitive complexity. The participants had significantly longer RTs for pain-related images in the pain-judgment task, but no such difference was found in the hands-counting task. Our findings suggest that pain-related content disrupts image processing, which is consistent with previous research.[25,36] RTs decreased after stimulation in both tasks, although the differences between groups were not statistically significant, unlike the results of earlier studies.[37–40] While prior research often used within-subject designs with varied stimulation conditions, this study used a between-subjects approach with uniform stimulation. The short interval between the pre- and posttests may have introduced practice effects. Future studies should consider longer gaps between tasks to reduce these effects.

Previous investigations into pain empathy using ERPs have provided insights into the temporal dynamics of neural responses when individuals witness others experiencing pain.[25,34] ERP studies on pain empathy have shown that early components, such as N1 and N2, reflect emotional sharing and spontaneous bottom-up processing,[41] whereas later components, such as P3 and LPP, are linked to emotion regulation and cognitive evaluation.[42,43] N1, occurring at approximately 125–155 ms in the frontocentral cortex, is associated with early automatic emotional processing and is typically greater in response to painful stimuli.[44] The N1 component is chiefly associated with the early stages of automatic emotional processing.[34] In this study, both 1- and 2-mA HD-tDCS increased N1 amplitudes compared with those in the sham group, suggesting enhanced early affective empathy via left DLPFC stimulation. However, no significant effects were observed for later components, implying a limited impact on cognitive empathy. This may be due to the short time interval between assessments or single-session stimulation.[18]

In Task 2, the participants rated their own negative feelings (affective empathy) and assessed the pain of others (cognitive empathy) to directly measure pain empathy. Consistent with prior studies, 2-mA HD-tDCS significantly increased unpleasantness ratings, indicating increased affective empathy.[22,45] Similarly, Wang et al reported that 2 mA stimulation of the left DLPFC improved emotional and cognitive empathy,[22] whereas Xu et al reported increased self-unpleasantness after 1.5 mA stimulation.[45] Interestingly, compared with sham HD-tDCS, 1 mA HD-tDCS did not enhance affective empathy. The neuroplastic effects of tDCS depend on parameters such as current intensity and duration. Previous neurophysiological[46,47] and behavioral[48,49] studies have shown that higher intensity increases cortical excitability and performance. In the present study, with respect to the findings of Task 1 and Task 2, 1 mA may increase early empathic response but may be insufficient for enhancing emotional empathy.

Empathy deficits are common in psychiatric[5,50,51] and chronic pain disorders[9,10,52–54;] however, studies using tDCS to address impaired pain empathy in these groups are still limited. The findings of this study suggest that the optimal stimulation current intensity for different diseases is crucial and may encourage targeted and personalized interventions. In addition, future research should further explore the relationships between changes in pain empathy and disease progression, which could inform new treatment approaches. Given its noninvasive, efficient, and cost-effective nature, tDCS holds strong potential for clinical use. The high-definition method used in this study outperforms traditional sponge-based tDCS designs in terms of precision in targeting specific brain regions.[55,56]

Despite its strengths, this study has several limitations. First, the short interval between the pre- and postintervention assessments may have introduced learning effects; future studies should consider a longer interval to mitigate this issue. Second, the use of static images may have restricted emotional engagement, whereas dynamic video stimuli could elicit stronger empathic responses. Third, the study involved only a single stimulation session. Given that previous research indicates cumulative effects with repeated sessions, future investigations should explore multisession protocols. Moreover,

this was a single-center study with a relatively small sample size, which may constrain the generalizability of the findings, and future research is warranted to include a large sample size with various stimulation conditions.

Conclusion

The present study revealed that anodal HD-tDCS enhances early empathic responses, with 2-mA stimulation being more effective than 1-mA stimulation in improving affective empathy. These findings provide useful guidance for future tDCS dosage recommendations, especially for individuals with empathy deficits.

Abbreviations

ACCs, accuracies; DLPFC, dorsolateral prefrontal cortex; EEG, electroencephalogram; ERPs, event-related potentials; Fmri, functional magnetic resonance imaging; HD-tDCS, high-definition transcranial direct current stimulation; NRS, numerical rating scale; RTs, reaction times; REF, reference electrode; SAS, self-rating anxiety scale; SDS, self-rating depression scale; tDCS, transcranial direct current stimulation.

Data Statement

The datasets used and analyzed during the current study are available from the corresponding author (Yuling Wang, wangyul@mail.sysu.edu.cn) upon reasonable request for academic purposes.

Acknowledgments

Chen Gong and Yuling Wang are co-senior authors for this study. We thank LetPub (www.letpub.com.cn) for its linguistic assistance during the preparation of this manuscript. The authors would like to thank all the participants in this study for their contributions.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This work was supported by the National Natural Science Foundation of China (grant number 82503056), the Guangdong Provincial Clinical Research Center for Rehabilitation Medicine (grant number 2023B110003), the Research Foundation of Traditional Chinese Medicine Bureau of Guangdong Province (grant number 20251065), the Guangdong Hopson-Pearl River Education Development Foundation (grant number H20190116202012724) and the Traditional Chinese Medicine Science and Technology Project of Zhejiang Province (grant number 2025ZR148).

Disclosure

The authors declare that they have no competing interests, financial or otherwise, related to the research presented in this manuscript.

References

1. Preston SD, de Waal FBM. Only the PAM explains the personalized nature of empathy. *Nat Rev Neurosci*. 2017;18(12):769. doi:10.1038/nrn.2017.140
2. Keuken MC, Hardie A, Dorn BT, et al. The role of the left inferior frontal gyrus in social perception: an rTMS study. *Brain Res*. 2011;1383:196–205. doi:10.1016/j.brainres.2011.01.073
3. Krall SC, Volz LJ, Oberwelland E, Grefkes C, Fink GR, Konrad K. The right temporoparietal junction in attention and social interaction: a transcranial magnetic stimulation study. *Human Brain Mapp*. 2016;37(2):796–807. doi:10.1002/hbm.23068
4. Yang CC, Khalifa N, Völlm B. The effects of repetitive transcranial magnetic stimulation on empathy: a systematic review and meta-analysis. *Psychol Med*. 2018;48(5):737–750. doi:10.1017/s003329171700232x

5. Decety J, Moriguchi Y. The empathic brain and its dysfunction in psychiatric populations: implications for intervention across different clinical conditions. *BioPsychoSoc Med*. 2007;1:22. doi:10.1186/1751-0759-1-22
6. Fernandez AV, Zahavi D. Basic empathy: developing the concept of empathy from the ground up. *Int J Nurs Stud*. 2020;110:103695. doi:10.1016/j.ijnurstu.2020.103695
7. Smith CK, Peterson DF, Degenhardt BF, Johnson JC. Depression, anxiety, and perceived hassles among entering medical students. *Psychol Health Med*. 2007;12(1):31–39. doi:10.1080/13548500500429387
8. Sergiou CS, Santarnecchi E, Franken I, Dongen JJA, Behavior V. The effectiveness of Transcranial Direct Current Stimulation as an intervention to improve empathic abilities and reduce violent behavior: a literature review. *Aggression Violent Behav*. 2020;55:101463.
9. de Tommaso M, Ricci K, Conca G, Vecchio E, Delussi M, Invitto S. Empathy for pain in fibromyalgia patients: an EEG study. *Int J Psychophysiol*. 2019;146:43–53. doi:10.1016/j.ijpsycho.2019.09.007
10. Ma J, Wang X, Qiu Q, Zhan H, Wu W. Changes in empathy in patients with chronic low back pain: a structural-functional magnetic resonance imaging Study. *Front Hum Neurosci*. 2020;14:326. doi:10.3389/fnhum.2020.00326
11. Duan H, Wang YJ, Lei X. The effect of sleep deprivation on empathy for pain: an ERP study. *Neuropsychologia*. 2021;163:108084. doi:10.1016/j.neuropsychologia.2021.108084
12. Li Y, Li W, Zhang T, Zhang J, Jin Z, Li L. Probing the role of the right inferior frontal gyrus during Pain-Related empathy processing: evidence from fMRI and TMS. *Human Brain Mapp*. 2021;42(5):1518–1531. doi:10.1002/hbm.25310
13. Lamm C, Decety J, Singer T. Meta-analytic evidence for common and distinct neural networks associated with directly experienced pain and empathy for pain. *NeuroImage*. 2011;54(3):2492–2502. doi:10.1016/j.neuroimage.2010.10.014
14. Ellingsen DM, Isenburg K, Jung C, et al. Brain-to-brain mechanisms underlying pain empathy and social modulation of pain in the patient-clinician interaction. *Proc Natl Acad Sci U S A*. 2023;120(26):e2212910120. doi:10.1073/pnas.2212910120
15. Gu X, Gao Z, Wang X, et al. Anterior insular cortex is necessary for empathetic pain perception. *Brain*. 2012;135(Pt 9):2726–2735. doi:10.1093/brain/aws199
16. Singer T, Critchley HD, Preuschoff K. A common role of insula in feelings, empathy and uncertainty. *Trends Cognitive Sci*. 2009;13(8):334–340. doi:10.1016/j.tics.2009.05.001
17. Nelson JT, McKinley RA, Golob EJ, Warm JS, Parasuraman R. Enhancing vigilance in operators with prefrontal cortex transcranial direct current stimulation (tDCS). *NeuroImage*. 2014;85 Pt 3:909–917. doi:10.1016/j.neuroimage.2012.11.061
18. Bahji A, Forth E, Yang CC, Khalifa N. Transcranial direct current stimulation for empathy: a systematic review and meta-analysis. *Soc Neurosci*. 2021;16(3):232–255. doi:10.1080/17470919.2021.1889657
19. Nitsche MA, Doemkes S, Karaköse T, et al. Shaping the effects of transcranial direct current stimulation of the human motor cortex. *J Neurophysiol*. 2007;97(4):3109–3117. doi:10.1152/jn.01312.2006
20. Nitsche MA, Paulus W. Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. *J Physiol*. 2000;527 Pt 3(Pt 3):633–639. doi:10.1111/j.1469-7793.2000.t01-1-00633.x
21. Fregni F, El-Hagrassy MM, Pacheco-Barrios K, et al. Evidence-based guidelines and secondary meta-analysis for the use of transcranial direct current stimulation in neurological and psychiatric disorders. *Int J Neuropsychopharmacol*. 2021;24(4):256–313. doi:10.1093/ijnp/pyaa051
22. Wang J, Wang Y, Hu Z, Li X. Transcranial direct current stimulation of the dorsolateral prefrontal cortex increased pain empathy. *Neuroscience*. 2014;281:202–207. doi:10.1016/j.neuroscience.2014.09.044
23. Rêgo GG, Lapenta OM, Marques LM, et al. Hemispheric dorsolateral prefrontal cortex lateralization in the regulation of empathy for pain. *Neurosci Lett*. 2015;594:12–16. doi:10.1016/j.neulet.2015.03.042
24. Coll MP. Meta-analysis of ERP investigations of pain empathy underlines methodological issues in ERP research. *Soc Cognit Affective Neurosci*. 2018;13(10):1003–1017. doi:10.1093/scan/nsy072
25. Meng J, Jackson T, Chen H, et al. Pain perception in the self and observation of others: an ERP investigation. *NeuroImage*. 2013;72:164–173. doi:10.1016/j.neuroimage.2013.01.024
26. Coll MP, Viding E, Rütgen M, et al. Are we really measuring empathy? Proposal for a new measurement framework. *Neurosci Biobehav Rev*. 2017;83:132–139. doi:10.1016/j.neubiorev.2017.10.009
27. Mischkowski D, Crocker J, Way BM. From painkiller to empathy killer: acetaminophen (paracetamol) reduces empathy for pain. *Soc Cognit Affective Neurosci*. 2016;11(9):1345–1353. doi:10.1093/scan/nsw057
28. Windhoff M, Opitz A, Thielscher A. Electric field calculations in brain stimulation based on finite elements: an optimized processing pipeline for the generation and usage of accurate individual head models. *Hum Brain Mapp*. 2013;34(4):923–935. doi:10.1002/hbm.21479
29. Beltran Serrano G, Rodrigues LP, Schein B, et al. Comparison of hypnotic suggestion and transcranial direct-current stimulation effects on pain perception and the descending pain modulating system: a crossover randomized clinical trial. *Front Neurosci*. 2019;13:662. doi:10.3389/fnins.2019.00662
30. Geuzaine C, JFJIjfnmie R. Gmsh: a 3-D finite element mesh generator with built-in pre-and post-processing facilities. *Int J Num Meth Eng*. 2009;79(11):1309–1331.
31. Delorme A, Makeig S. EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. *J Neurosci Meth*. 2004;134(1):9–21. doi:10.1016/j.jneumeth.2003.10.009
32. Jung TP, Makeig S, McKeown MJ, Bell AJ, Lee TW, Sejnowski TJ. Imaging brain dynamics using independent component analysis. *Proceedings IEEE Institute Electrical Electronics Engineers*. 2001;89(7):1107–1122. doi:10.1109/5.939827
33. Cui F, Ma N, Luo YJ. Moral judgment modulates neural responses to the perception of other's pain: an ERP study. *Sci Rep*. 2016;6:20851. doi:10.1038/srep20851
34. Decety J, Yang CY, Cheng Y. Physicians down-regulate their pain empathy response: an event-related brain potential study. *NeuroImage*. 2010;50(4):1676–1682. doi:10.1016/j.neuroimage.2010.01.025
35. Zheng P, Lyu Z, Jackson T. Fear of pain and event-related potentials during exposure to image-cued somatosensory stimulation. *Brain Res*. 2018;1695:91–101. doi:10.1016/j.brainres.2018.05.042
36. Cheng Y, Chen C, Decety J. An EEG/ERP investigation of the development of empathy in early and middle childhood. *Dev Cognitive Neurosci*. 2014;10:160–169. doi:10.1016/j.dcn.2014.08.012

37. Adenzato M, Brambilla M, Manenti R, et al. Gender differences in cognitive theory of mind revealed by transcranial direct current stimulation on medial prefrontal cortex. *Sci Rep*. 2017;7:41219. doi:10.1038/srep41219
38. Conson M, Errico D, Mazzarella E, Giordano M, Grossi D, Trojano L. Transcranial electrical stimulation over dorsolateral prefrontal cortex modulates processing of social cognitive and affective information. *PLoS One*. 2015;10(5):e0126448. doi:10.1371/journal.pone.0126448
39. Cotelli M, Adenzato M, Cantoni V, et al. Enhancing theory of mind in behavioural variant frontotemporal dementia with transcranial direct current stimulation. *Cognit Affective Behav Neurosci*. 2018;18(6):1065–1075. doi:10.3758/s13415-018-0622-4
40. Snowdon ME, Cathcart S. tDCS potentiation provides no evidence for a link between right dorsal-lateral prefrontal cortical activity and empathic responding. *Soc Neurosci*. 2018;13(2):190–201. doi:10.1080/17470919.2016.1273133
41. Tamietto M, de Gelder B. Neural bases of the non-conscious perception of emotional signals. *Nat Rev Neurosci*. 2010;11(10):697–709. doi:10.1038/nrn2889
42. Dennis TA, Hajcak G. The late positive potential: a neurophysiological marker for emotion regulation in children. *J Child Psychol Psychiat Allied Discipline*. 2009;50(11):1373–1383. doi:10.1111/j.1469-7610.2009.02168.x
43. Fan Y, Han S. Temporal dynamic of neural mechanisms involved in empathy for pain: an event-related brain potential study. *Neuropsychologia*. 2008;46(1):160–173. doi:10.1016/j.neuropsychologia.2007.07.023
44. Vogel EK, Luck SJ. The visual N1 component as an index of a discrimination process. *Psychophysiology*. 2000;37(2):190–203. doi:10.1111/1469-8986.3720190
45. Xu Y, Chen S, Kong Q, Luo S. The residential stability mindset increases racial in-group bias in empathy. *Biol psychol*. 2021;165:108194. doi:10.1016/j.biopsycho.2021.108194
46. Ammann C, Lindquist MA, Celnik PA. Response variability of different anodal transcranial direct current stimulation intensities across multiple sessions. *Brain Stimulation*. 2017;10(4):757–763. doi:10.1016/j.brs.2017.04.003
47. Esmaeilpour Z, Marangolo P, Hampstead BM, et al. Incomplete evidence that increasing current intensity of tDCS boosts outcomes. *Brain Stimulation*. 2018;11(2):310–321. doi:10.1016/j.brs.2017.12.002
48. Iyer MB, Mattu U, Grafman J, Lomarev M, Sato S, Wassermann EM. Safety and cognitive effect of frontal DC brain polarization in healthy individuals. *Neurology*. 2005;64(5):872–875. doi:10.1212/01.Wnl.0000152986.07469.E9
49. Shekhawat GS, Sundram F, Bikson M, et al. Intensity, duration, and location of high-definition transcranial direct current stimulation for tinnitus relief. *Neurorehabil Neural Repair*. 2016;30(4):349–359. doi:10.1177/1545968315595286
50. Bragado-Jimenez MD, Taylor PJ. Empathy, schizophrenia and violence: a systematic review. *Schizophr Res*. 2012;141(1):83–90. doi:10.1016/j.schres.2012.07.019
51. Schreiter S, Pijnenborg GH, Aan Het Rot M. Empathy in adults with clinical or subclinical depressive symptoms. *J Affective Disorders*. 2013;150(1):1–16. doi:10.1016/j.jad.2013.03.009
52. Sohn HS, Lee DH, Lee KJ, et al. Impaired empathic abilities among patients with complex regional pain syndrome (Type I). *Psychiatry Invest*. 2016;13(1):34–42. doi:10.4306/pi.2016.13.1.34
53. Mu J, Wang Q, Dun W, et al. The effects of long-term menstrual pain on pain empathy in women with primary dysmenorrhea. *Pain*. 2021;162(7):2051–2059. doi:10.1097/j.pain.0000000000002205
54. Zhang HB, Ou H, Meng DH, et al. Impaired cognitive empathy in outpatients with chronic musculoskeletal pain: a cross-sectional study. *Neural Plast*. 2021;2021:4430594. doi:10.1155/2021/4430594
55. Verveer I, Hill AT, Franken IHA, Yücel M, van Dongen JDM, Segrave R. Modulation of control: can HD-tDCS targeting the dACC reduce impulsivity? *Brain Res*. 2021;1756:147282. doi:10.1016/j.brainres.2021.147282
56. Xu H, Zhou Y, Wang J, et al. Effect of HD-tDCS on white matter integrity and associated cognitive function in chronic schizophrenia: a double-blind, sham-controlled randomized trial. *Psychiatry Res*. 2023;324:115183. doi:10.1016/j.psychres.2023.115183