Transcranial direct current stimulation of the dorsolateral prefrontal cortex increased pain empathy
TRANSCRANIAL DIRECT CURRENT STIMULATION OF THE DORSOLATERAL PREFRONTAL CORTEX INCREASED PAIN EMPATHY

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Abstract—Empathy for pain, a widely studied sub-form of empathy, is an ability to recognize and share the pain of others. It involves brain regions associated with the emotional component of pain. Recent studies found that emotional pain could be modulated by stimulating the dorsolateral prefrontal cortex (DLPFC) with transcranial direct current stimulation (tDCS). We hypothesized that tDCS of the DLPFC could modulate empathy for pain as well. In the present study, healthy subjects were asked to watch pictures depicting somebody under painful or non-painful conditions and to evaluate the pain intensity of others as well as their own pain-related unpleasantness before and after tDCS of the DLPFC. It was found that ratings for others’ pain increased in subjects with an anodal tDCS of the DLPFC in comparison to those with sham tDCS, indicating enhanced pain empathy with the anodal tDCS. Furthermore, the changes of ratings for others’ pain were positively correlated with the changes of pain-related self-unpleasantness. These findings indicate that tDCS could modulate pain empathy and be used as a potential tool for modulating diseases accompanied with empathy deficits.

Key words: transcranial direct current stimulation (tDCS), dorsolateral prefrontal cortex (DLPFC), pain empathy, pain-related emotion.

INTRODUCTION

Empathy for pain is the ability to recognize the pain perception of another person by imaging or observing other individuals in pain (Singer et al., 2004). It is measured by evaluating the severity of others’ pain by observers (Singer et al., 2004; Jackson et al., 2005). Empathy for pain is the most studied sub-form of empathy, which plays a key role in the prosocial behaviors of human beings and is involved in many psychopathological disorders characterized by empathy deficits (Decety and Moriguchi, 2007). Investigating the modulation of empathy for pain will help treat these disorders.

There is evidence that empathic pain involves brain regions responsible for emotional pain processing. Neuroimaging studies found that when one was watching somebody receiving painful stimuli (Singer et al., 2004; Lamm et al., 2011), the brain regions associated with the emotional component of pain were activated, including the anterior cingulate cortex (ACC), insular cortex and prefrontal cortex (Treede et al., 1999; Tracey, 2005). The ACC and insular cortex are positively related with empathic pain behaviors (Jackson et al., 2005). In contrast, lesions on these brain regions, for example, lesions of the anterior insular cortex, lead to pain empathy deficits (Gu et al., 2012). These findings support the ‘emotional-sharing’ theory of pain empathy (Singer et al., 2004; Jackson et al., 2005; Gu et al., 2012).

Evidence shows that emotional pain could be modulated by transcranial direct current stimulation (tDCS), a non-invasive brain stimulation technique that increases or decreases the excitability of brain regions (Nitsche and Paulus, 2000; Utz et al., 2010). A previous study reported that tDCS of the left dorsal lateral prefrontal cortex (DLPFC) with 2 mA for 5 min altered the emotional discomfort evoked by pictures depicting painful events in healthy subjects (Boggio et al., 2009). It is known that the DLPFC has extensive connections with the ACC and anterior insular (Singer et al., 2009). In addition, an functional magnetic resonance imaging (fMRI) neuroimaging study confirmed that tDCS of the DLPFC could activate the ACC and DLPFC (Keeser et al., 2011; Weber and Messing, 2014; Nelson et al., 2014). Thus, we hypothesized that tDCS of the DLPFC could modulate empathy for pain.

To test this hypothesis, the present study investigated the observer’s rating for other’s pain and the relationship with the observer’s pain-related emotion when viewing pictures of someone under painful and unpainful situations.
conditions after an anodal, cathodal or sham tDCS modality.

EXPERIMENTAL PROCEDURES

Subjects
Twenty-seven healthy right-handed subjects (mean age of 23.6 ± 2.9 years, 18 females) participated in the study. All the subjects had no history of epilepsy, psychiatric disease and were medication-free during the experiments. There were no metal implantations in their bodies as well. All the participants gave their written informed consent in accordance with the principles of the Declaration of the Helsinki. Subjects were blind to the purpose of the research. This experiment was approved by the Ethics Committee of the Beijing Normal University, China.

Experimental procedure
After measuring trait empathy, the subjects were randomly assigned into three experimental groups: the anodal stimulation group (eight subjects), the cathodal stimulation group (nine subjects) and the sham stimulation group (10 subjects). The subjects were blind to the grouping. The other-pain rating and pain-related self-unpleasantness rating tests were performed before and after the tDCS (Fig. 1).

Trait empathy. The Interpersonal Reactivity Index (IRI) was applied to estimate trait empathy (Davis, 1996). The Chinese version of the IRI has been evaluated by Siu and Shek (2005). This survey consists of 28 items, including empathic concern (EC), personal distress (PD), perspective taking (PT) and fantasy scale (FS) subscales. Each item was rated by a five-point Likert scale, ranging from 0 (does not describe me well) to 4 (describes me well). The subjects gave their scores for each item (Table. 1).

Other-pain rating. The subjects sat in front of a screen at a distance of one meter. Pictures depicting right hands being injured and matched pictures showing intact hands (20 of each) were presented on the computer screen with the E-prime software version 2 (Psychology Software Tools, Inc., Pittsburgh, Pennsylvania, USA). Each picture lasted for 1 s and was followed by a question assessing how painful the person in this picture felt. The subjects were instructed to evaluate the pain intensity of the person in the picture on a scale of 0–9 (0: no pain at all, 9: extreme pain). These pictures appeared randomly.

Pain-related self-unpleasantness rating. After evaluating pain in others, the subjects were asked to estimate their own comfortableness when shown a scale showing six self-assessment manikin (SAMs), from smiling (0: pleasant) to crying (5: most unpleasant).

tDCS. Direct current was delivered by a battery-driven, constant current stimulator (DC-STIMULATOR, NeuroConn GmbH, Ilmenau, Germany) and applied to the scalp through a saline-soaked pair of surface sponge electrodes (35 cm²). During the stimulation, a constant current of 2 mA was applied for 5 min (including 15 s ramped up and 15 s ramped down). For the anodal stimulation, an anode electrode (positive current input) was placed over the left DLPFC, the F3 according to the international 10–20 system for Electroencephalography (EEG) electrode placement, which was validated by a previous neuronavigational study (Herwig et al., 2003) and a cathodal electrode was placed on the FP2. For the cathodal stimulation, the cathodal electrode was placed on the F3, while the anodal on the FP2. The placement of sham stimulation was equal to anodal stimulation but with a 2-mA current for 30 s.

Statistical analysis
One-way analysis of variance (one-way ANOVA), with group as the independent variable, was used for the comparison of the differences among the three groups. Bonferroni Post hoc analysis was used if the ANOVA findings were significant. The eta squared ($\eta^2$) was calculated for estimating the effect sizes. The significance level was set at $p < 0.05$.

RESULTS
Anodal tDCS increased pain empathy
The effect of tDCS on pain empathy was evaluated by the difference of ratings for others’ pain before and after tDCS. The tDCS modulated the rating for others’ pain when subjects were viewing others under painful conditions ($F_{(2,26)} = 3.824, p = 0.036, \eta^2_{(group)} = 0.242$). After the anodal stimulation of the left DLPFC, the rating
for others’ pain increased in comparison with sham stimulation \((p = 0.033, \text{Bonferroni post hoc test})\). However, the cathodal stimulation reduced the rating for others’ pain, but showed no significant differences with the sham stimulation. In contrast, the rating was not changed by tDCS when the subjects were watching the non-painful pictures. There was no significant difference among the three tDCS modalities \((F_{(2,26)} = 2.480, p = 0.105)\) (Fig. 2A). These results indicate that anodal tDCS of the DLPFC could enhance pain empathy.

Positive relationship between pain empathy and emotional pain

To further illustrate the relationship of other-pain evaluation and pain-related self-unpleasantness under tDCS conditions, we measured the effect of tDCS on the observer’s pain-related unpleasantness rating and its correlation with other-pain rating. As shown in Fig. 2B, the effect of tDCS on the rating of self-unpleasantness evoked by painful pictures had the same trend as the rating of others’ pain, although no significant difference among the unpleasant rating was observed between the three groups for both painful \((F_{(2,26)} = 0.327, p = 0.724)\) and non-painful pictures \((F_{(2,26)} = 0.873, p = 0.430)\). The correlation between other-pain rating and self-unpleasantness evoked by painful pictures was further tested. Fig. 3 showed that the change of other-pain rating was positively correlated with the change of pain-related self-unpleasantness rating \((r^2 = 0.38, p < 0.001)\).

DISCUSSION

In the present study, we demonstrated that with anodal tDCS of the DLPFC, the ratings for others’ pain was enhanced, indicating increased pain empathy. Additionally, other-pain rating was positively correlated with pain-related self-unpleasantness.

The effect of anodal tDCS of the left DLPFC on empathic pain

Consistent results indicated that empathy for pain involved the brain regions of emotional pain. The activity of the emotional pain matrix, especially the ACC and the anterior insula, showed positive correlation with the intensity of empathy for pain when healthy subjects

Table 1. Interpersonal Reactivity Index scores

<table>
<thead>
<tr>
<th>Group</th>
<th>FS</th>
<th>EC</th>
<th>PT</th>
<th>PD</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sham</td>
<td>2.20 ± 0.36</td>
<td>2.24 ± 0.31</td>
<td>2.57 ± 0.41</td>
<td>2.33 ± 0.47</td>
<td>9.34 ± 1.17</td>
</tr>
<tr>
<td>Anodal</td>
<td>2.14 ± 0.47</td>
<td>2.23 ± 0.43</td>
<td>2.43 ± 0.40</td>
<td>2.26 ± 0.43</td>
<td>8.59 ± 1.39</td>
</tr>
<tr>
<td>Cathodal</td>
<td>2.20 ± 0.83</td>
<td>2.21 ± 0.27</td>
<td>2.40 ± 0.53</td>
<td>2.30 ± 0.71</td>
<td>9.09 ± 1.79</td>
</tr>
</tbody>
</table>

FS, fantasy scale; EC, empathic concern; PT, perspective taking; PD, personal distress.

Fig. 2. Effects of tDCS on ratings for others’ pain intensity and self-emotion. (A) The change of ratings for others’ pain intensity before and after tDCS when the viewer watched somebody under painful (left) and non-painful conditions (right). Observers’ ratings for others’ pain increased after anodal tDCS of the DLPFC. (B) The change of ratings for self-emotion before and after tDCS when the viewer watched somebody under painful (left) and non-painful conditions (right). *\(p < 0.05\).
The effect of anodal tDCS of the left DLPFC on observers' emotional pain

A prior study found that during the 2-mA anodal tDCS of the left DLPFC for 5 min, the subject's emotional rating reduced in comparison with sham stimulation when watching painful pictures (Boggio et al., 2009; Maeoka et al., 2012). However, in our experiment, the subject's self-emotional rating did not decrease, but showed an increased tendency from anodal tDCS of the left DLPFC.

In our experimental design, the effect of tDCS on pain-related self-unpleasantness was estimated by comparing the ratings before and after tDCS for each stimulation montage. It should be noted that these ratings were obtained on the same day. This was different from previous studies which estimated the effect of tDCS by comparing the ratings after sham tDCS with ratings after active tDCS obtained on two separate days. Because an emotional rating is influenced by daily varied mood or motivation (Schmid and Mast, 2010), it seems that the changes of emotional rating obtained on the same day reflected more specific effects of tDCS than that obtained on two separate days. Besides, the state of brain activity when tDCS was applied differed between previous studies (active state) and our study (resting state). It was reported that working memory was enhanced when tDCS was applied during but not before the task, indicating the activity-dependence of tDCS (Teo et al., 2011). Thus, it is possible that different tDCS applications lead to opposite results between previous researches and our study. In addition, we used a between-subject design instead of the within-subject design as previous studies did. In the within-subject design we used, subjects were under the same condition (after the first viewing) when they received the same tDCS stimulation montage. In contrast, in the within-subject design, the conditions of subjects varied (the first or second or third viewing) when they received the same tDCS stimulation montage. Because the first and following views evoked different brain activities due to habituation effects, a shortage of limited comparability arises in the within-subject design but was overcome by the between-subject design.

Relationship between emotional pain and empathy for pain

Previous studies report that perceiving others’ pain activates brain regions implementing the emotional component of pain, suggesting that the neural mechanisms of the emotional component of pain are involved in the observer's empathy for pain (Singer et al., 2004; Jackson et al., 2005; Gu et al., 2012). Here, we investigated both pain empathy and pain-related discomfort with cortical modulation of the left DLPFC by tDCS. Interestingly, it was found that the rating for pain in others was positively correlated with self-unpleasant ratings, indicating consistent modulation of pain empathy.

The effect of anodal tDCS of the left DLPFC on empathy for pain

The modulating effect of tDCS on the rating for others' pain correlated with the effect on the rating for self-discomfort when subjects watched somebody under painful conditions. There was a positive correlation between the modulation of pain empathy and that of pain affection.
and pain-related discomfort. This finding provides evidence for the theory of ‘affective sharing’ from a cortical modulation perspective. When explaining the results, it should be kept in mind that the subjects in our study were asked to respond to one picture by a sequence of two questions assessing pain empathy and self-discomfort to avoid over-exposure to the same picture. Although we have used different scales for rating pain empathy (0–9 numbering scale) and for rating emotional responses (0–5 SAM scale), it cannot rule out the possibility that the subjects were inclined to make similar ratings, which may result in the correlation between them.

Potential clinical applications of tDCS

tDCS of the left DLPFC has been shown to alleviate chronic pain in fibromyalgia patients (Valle et al., 2009). Our results showed that tDCS of the left DLPFC could increase pain empathy. Thus, empathy for pain may be limited in chronic pain patients. This hypothesis is consistent with the finding that the neural processing of empathy for pain was reduced in patients with chronic pain (Lee et al., 2013).

As a non-invasive and effective neural modulation tool, the advantages of tDCS, such as its simple procedure and inexpensive cost, make it suitable for clinical applications. The modulating effect of tDCS on empathy demonstrated in our study, together with a previous study indicating the role of DLPFC on empathy (Santiesteban et al., 2012), suggests that tDCS of the left DLPFC is a potential tool in controlling diseases that are accompanied with empathy deficits such as alexithymia and autism (Baron-Cohen and Wheelwright, 2004; Moriguchi et al., 2007). Indeed, dysfunction of the left DLPFC has been suggested to contribute to autism (Fujii et al., 2010).

Limitation of this study

This study was a pilot study on empathy and tDCS. The underlying mechanism remains unclear. Further studies combined with neuroimaging tools and a detailed questionnaire concerning empathy should be performed in the future.

Besides, the possibility of socially desirable responding when subjects were answering the IRI questionnaire could not be excluded. It could lead to the potential influence of the unbalanced group. But, according to the review finding (van de Mortel, 2008), studies on pain rating have fewer socially desirable responses.

In addition, we applied a between-subjects design in this study to avoid the confounding factor of repeated over-exposure to the same painful pictures, which could lead to possible habituation effects and change the emotional response (Mu et al., 2008; Decety et al., 2010). However, such experimental design has the possible issue of big individual differences and unbalanced distribution among groups. A within-subjects design with several picture sets should be further tested.

CONCLUSIONS

We found that anodal tDCS of the left DLPFC enhanced pain empathy. The modulation of pain empathy was correlated with that of pain-related emotion by tDCS. Our findings not only extend the potential application of tDCS for patients with empathy deficits, but also provide evidence of the modulatory effects for the ‘emotion-sharing’ theory of pain empathy.

CONFLICT OF INTEREST

All the authors declare no conflicts of interest.

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