

Critical role of the right VLPFC in emotional regulation of social exclusion: a tDCS study

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Abstract

There is abundant evidence suggesting that the right ventrolateral prefrontal cortex (rVLPFC) plays an important role in down-regulating the emotional response to social exclusion. However, a causal relationship between rVLPFC function and explicit emotional regulation is not clear in the context of social exclusion. This study employed anodal transcranial direct current stimulation (tDCS) to activate rVLPFC while participants used emotional regulation to reappraise pictures of social exclusion. Forty-four participants were randomly assigned to an active tDCS group or a sham group. Both groups viewed social exclusion images under two conditions: in the no-reappraisal condition, participants were instructed to passively view social exclusion images; in the reappraisal condition, they reappraised the images to down-regulate negative emotional responses. Compared to sham stimulation, anodal tDCS over the rVLPFC resulted in less negative emotion ratings, and produced significantly smaller pupil diameter in the reappraisal, compared to no-reappraisal block. The tDCS also led to longer fixation durations to *rejectees* and shorter fixation durations to *rejecters*. Taken together, these findings suggest a causal role for rVLPFC in down-regulation of negative emotions produced by social exclusion. This study has implications for clinical interventions targeting emotional regulation deficits.

Key words: transcranial direct current stimulation; right ventrolateral prefrontal cortex; emotional regulation; cognitive reappraisal; eye tracking

Introduction

Social exclusion leads to low self-esteem (Onoda *et al.*, 2010) and poses a strong threat to fundamental human needs, such as the need to belong and the need for control (Baumeister and Leary, 1995; Williams, 2007). Therefore, individuals who are socially excluded show increased negative emotional experiences and

hurt feelings (Eisenberger *et al.*, 2003). Such social pain can cause psychological responses similar to those resulting from physical pain (Riva *et al.*, 2011). In response to the negative and painful emotions elicited by social exclusion, effective emotional regulation potentially provides a coping strategy. Dysregulation of emotion is a core feature (Rive *et al.*, 2013) or plays a prominent role (Mazefsky *et al.*, 2013; Samson *et al.*, 2014)

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in disorders such as depression and autism spectrum disorder, and improving emotional regulation could therefore be a useful target for developing interventions.

Meta-analyses and systematic review of neuroimaging studies have indicated that both dorsolateral prefrontal cortex (DLPFC) and ventrolateral prefrontal cortex (VLPFC) are core regions involved in emotional regulation (Buhle *et al.*, 2014; Kohn *et al.*, 2014), especially in down-regulation of negative emotions (Zilverstand *et al.*, 2017). In the context of social exclusion, two brain regions, the ventral anterior cingulate cortex (VACC) and VLPFC, have been implicated in emotional regulation of social pain (Riva and Eck, 2016). VACC response has not been consistently reported to social exclusion; with studies variously suggesting either decreased, unchanged (Somerville *et al.*, 2006) or increased activity (Cristofori *et al.*, 2013). In contrast, neuroimaging studies have provided convergent evidence that the VLPFC, especially the right VLPFC (rVLPFC), shows increased activity in response to social exclusion and plays a regulatory or inhibitory role, thus reducing the social pain (Eisenberger *et al.*, 2003; Onoda *et al.*, 2010). For instance, rVLPFC activity has been found to be negatively correlated with self-reported distress when participants are faced with social exclusion, suggesting that this region plays a key role in reducing social pain (Eisenberger *et al.*, 2003; Masten *et al.*, 2009). Furthermore, studies investigating individual differences in response to social exclusion have found that (1) people with a higher level of general trust reported less social pain during a social exclusion task, and this correlation was mediated by rVLPFC activity (Yanagisawa *et al.*, 2011a), and (2) people with higher rejection sensitivity showed less rVLPFC activation when being socially excluded relative to people with lower rejection sensitivity (Kross *et al.*, 2007). In addition, some researchers explored the effect of temporal distance on the process of emotional regulation after social exclusion. They found that participants who were asked to imagine what they would do in the distant future, as compared to participants who imagined what they would do in the near future, showed increased rVLPFC activity and felt less social pain in a subsequent social exclusion task (Yanagisawa *et al.*, 2011b).

There is therefore a wealth of evidence implicating rVLPFC in the regulation of social exclusion (Eisenberger *et al.*, 2003; Masten *et al.*, 2009; Onoda *et al.*, 2010; Yanagisawa *et al.*, 2011a, b). In contrast, a previous study of repetitive transcranial magnetic stimulation on left DLPFC reported no effect on self-reported social pain (Fitzgibbon *et al.*, 2017). We therefore hypothesize that VLPFC activity specifically mediates the success of emotional reappraisal via connections to subcortical regions, such as amygdala and nucleus accumbens (Wager *et al.*, 2008). This hypothesis motivates our choice of rVLPFC as the target for stimulation in this study.

Previous transcranial direct current stimulation (tDCS) studies have supported a causal relationship between rVLPFC and the social pain regulation process: anodal stimulation of rVLPFC reduced negative emotional responses and behavioral aggression from social exclusion (Riva *et al.*, 2012, 2015a), while cathodal stimulation of rVLPFC boosted negative emotional responses to social exclusion (Riva *et al.*, 2015b). However, it should be noted that these tDCS studies did not use a voluntary emotional regulation task, so they explored the procedure of emotional regulation implicitly (i.e. no instruction was given for an explicit regulation of the participants' emotion). Thus, previous findings did not directly link the improvement or deterioration of emotional regulation abilities to tDCS-activated or deactivated rVLPFC. To address this question, this study used a standard emotional regulation task designed to examine the

influence of anodal tDCS over rVLPFC in explicit regulation of negative emotions arising from social exclusion.

In addition to subjective rating of negative emotion, this study also employed two measures of eye-tracker recording to objectively reflect physiological arousal and attention allocation during the task. First, pupil diameter was used as an index of emotional arousal in this study because it becomes larger in response to stimuli evoking greater emotional arousal (Bradley *et al.*, 2008). During emotional regulation processes, increasing subjective ratings of negative emotional experiences resulted in enlargement of pupil diameter (Kinner *et al.*, 2017). Second, gaze fixation was used to reflect attentional deployment since recent findings indicated attention is a core process involved in emotional regulation (van Reekum *et al.*, 2007).

This study used tDCS to investigate the causal role of the rVLPFC in the regulation of social exclusion. Cognitive reappraisal and expressive suppression are thought to be the two most common strategies of emotional regulation (Gross, 2001). Although both cognitive reappraisal (McRae *et al.*, 2010; Ochsner *et al.*, 2012; Dorfel *et al.*, 2014) and expressive suppression (Phillips *et al.*, 2008) strategies recruit VLPFC, the former strategy facilitates more positive emotion experience and expression, better interpersonal functioning, enhanced well-being (Gross and John, 2003) and more successful regulation to emotions (Webb *et al.*, 2012). Therefore, we employed cognitive reappraisal in our study, which involves reinterpreting and reframing the meaning of affective situation in ways that change its emotional impact (Gross and John, 2003). Two experiments were conducted in this study, with very similar procedures but different manipulations of reappraisal. The purpose of including two experiments was to test the replicability of the paradigm, i.e. to investigate whether changes of participants' perspective would influence the effect of tDCS. We hypothesized that anodal stimulation of the rVLPFC would increase excitability and thereby facilitate cognitive appraisal processes as compared to sham stimulation. This facilitation would result in lower rating of negative emotion experience and decreased pupil diameter in comparison with sham tDCS. We further hypothesized that the facilitation in cognitive appraisal induced by anodal stimulation of the rVLPFC would change attention deployment. However, no specific expectation was made regarding the attention change (from rejectee to rejecters, or a reverse direction) since there seems to be no previous literature focusing on social exclusion.

Materials and methods

Subjects

In Experiment 1, 50 college students with normal vision (all tDCS-naive) were recruited from Shenzhen University in China as paid participants. They were randomly assigned into active and sham tDCS groups. Six participants failed to complete the experiment due to technical problems or personal discomfort, so the data from 44 students were included in the following analyses (24 females; 21 ± 1.3 years old, mean \pm s.d.), with 23 individuals in the active group and 21 in the sham group (Table 1). Participants with any self-reported history of psychiatric or neurological disease were excluded from the study.

In Experiment 2, another 45 college students were recruited (with similar demographic characteristics as those in Experiment 1). Five participants failed to complete the experiment due to technical problems or personal discomfort, so the data from 40 students (22 females) were included (21 ± 1.3 years old), with 20 individuals in the active group and 20 in the sham group (Table 2).

Table 1. Demographical characteristics of active and sham stimulation groups in Experiment 1 (mean \pm s.d.)

Items	Active tDCS (n = 23)	Sham tDCS (n = 21)	t	P
Gender (male/female)	10/13	10/11		
Age (years)	20.87 \pm 1.4	21.1 \pm 1.3	-0.67	0.508
SDS	0.45 \pm 0.05	0.47 \pm 0.07	-0.94	0.354
STAI-T	39.4 \pm 6.5	39.2 \pm 7.2	0.05	0.958
ERQ				
Reappraisal	30.4 \pm 5.0	29.0 \pm 6.4	0.84	0.409
Suppression	15.0 \pm 4.4	15.5 \pm 3.9	-0.38	0.706
TAS-20				
Difficulty identifying feelings	18.4 \pm 4.6	17.5 \pm 4.0	0.63	0.532
Difficulty describing feelings	14.6 \pm 2.9	14.5 \pm 2.0	0.18	0.861
Externally oriented thinking	26.4 \pm 5.3	25.8 \pm 4.2	0.43	0.670
RSQ	10.4 \pm 1.8	11.1 \pm 1.8	-1.19	0.241
RSES	21.7 \pm 3.8	23.5 \pm 2.9	-1.72	0.093

SDS, Self-Rating Depression Scale; STAI-T, the Trait form of Spielberger's State-Trait Anxiety Inventory; ERQ, Emotional regulation Questionnaire; TAS-20, the 20-item Toronto Alexithymia Scale; RSQ, Rejection Sensitivity Questionnaire; RSES, Rosenberg self-esteem scale. Independent samples t-test was performed (two-tailed).

Written informed consent was obtained prior to the experiment. The experimental protocol was approved by the Ethics Committee of Shenzhen University.

Self-reported measures

The Self-Rating Depression Scale (SDS) is a widely used questionnaire to access depressive symptoms (Zung et al., 1965). It consists of 20 items that rate the levels of depressive symptoms during the past several days. SDS score ranges from 20 to 80, with high scores corresponding to high level of depression.

The Trait form of Spielberger's State-Trait Anxiety Inventory (STAI-T) is a commonly used measure of trait anxiety (Spielberger et al., 1983). It contains 20 items and scores from 20 to 80, with high scores corresponding to higher levels of anxiety.

The Emotion Regulation Questionnaire (ERQ) is designed to measure the habitual usage of two emotional regulation strategies: cognitive reappraisal and expressive suppression (Gross and John, 2003). It contains 10 items. The cognitive reappraisal subscale has 6 items and scores from 6 to 42 and the expressive suppression subscale has 4 items and scores from 4 to 28. Higher score on a subscale suggests that the strategy is more frequently used.

Additional questionnaires were also included: the Toronto Alexithymia Scale (TAS-20) (Parker et al., 2003), the Rejection Sensitivity Questionnaire (RSQ) (Downey and Feldman, 1996) and the Rosenberg Self-Esteem Scale (RSES) (Rosenberg, 1965).

Demographics of the two experimental groups are reported in Table 1. Basic psychometric variables did not differ between groups.

Stimuli

Experimental materials were social exclusion images, each including one rejectee and a group of rejecters. Stimuli selection was based on a prior validation study in which demographically

Table 2. Demographical characteristics of active and sham stimulation groups in Experiment 2

Items	Active tDCS (n = 20)	Sham tDCS (n = 20)	t	P
Gender (male/female)	9/11	9/11		
Age (years)	21.5 \pm 1.4	21.2 \pm 1.3	-0.35	0.725
SDS	0.45 \pm 0.05	0.46 \pm 0.07	-0.59	0.558
STAI-T	39.5 \pm 6.5	39.0 \pm 7.2	0.25	0.802
ERQ				
Reappraisal	30.2 \pm 5.3	29.0 \pm 6.5	0.66	0.511
Suppression	14.8 \pm 4.6	15.4 \pm 4.0	-0.44	0.663
TAS-20				
Difficulty identifying feelings	18.3 \pm 4.7	17.2 \pm 3.7	0.86	0.396
Difficulty describing feelings	14.8 \pm 2.9	14.3 \pm 1.9	0.71	0.485
Externally oriented thinking	26.2 \pm 5.5	26.0 \pm 4.2	0.13	0.899
RSQ	10.5 \pm 1.9	11.1 \pm 1.8	-0.98	0.335
RSES	21.5 \pm 4.0	23.2 \pm 2.8	-1.60	0.117

similar healthy volunteers (n = 20) rated 200 social exclusion images selected from the Internet. The 20 participants were required to judge, on a 9-point scale, the extent of social exclusion conveyed by the images (1 = no social exclusion at all; 9 = very apparent social exclusion). For the main study we selected the 72 pictures with the highest ratings for social exclusion (8.26 \pm 1.13).

In the main experiment, all pictures were presented on an LCD monitor (refresh rate = 60 Hz). Participants viewed the monitor at a distance of ~60 cm (3.0 \times 3.5° visual angle).

Emotional regulation task

The emotional regulation task (Ochsner et al., 2004) consisted of a 'no-reappraisal' block and a 'reappraisal' block. In order to avoid carry-over effects caused by the reappraisal instruction, the order of the blocks was fixed, with the no-reappraisal block followed by the reappraisal block. All 72 images were randomly assigned into these 2 blocks. Each block contained 36 trials. The assignment of pictures was random between participants.

As shown in Figure 1A, a trial started with a 2-s fixation followed by image presentation for 8 s. During this time, participants were instructed to passively view the picture or regulate their emotion via the reappraisal strategy. Afterwards, participants were asked to rate the strength of the negative emotion of the person alone in the picture (1 = no negative emotion, 9 = very strong negative emotion). This rating process was achieved by mouse clicking, so participants could keep their attention on the screen for the entire duration of the presentation without switching gaze to the keyboard.

In the no-reappraisal block, participants were instructed as follows: 'In this section, please think about how you would feel in a situation similar to that of the person alone in the picture' (i.e. first-person perspective). The instructions in the reappraise block were different in the two experiments. For Experiment 1, participants were required to freely use two strategies to establish effective cognitive reappraisal: one was to view the pictures objectively from the perspective of a third person who was not involved in the scene (i.e. third-person perspective); the other was to imagine a better outcome of the scene (i.e. first-person perspective). After the experiment, participants were asked to

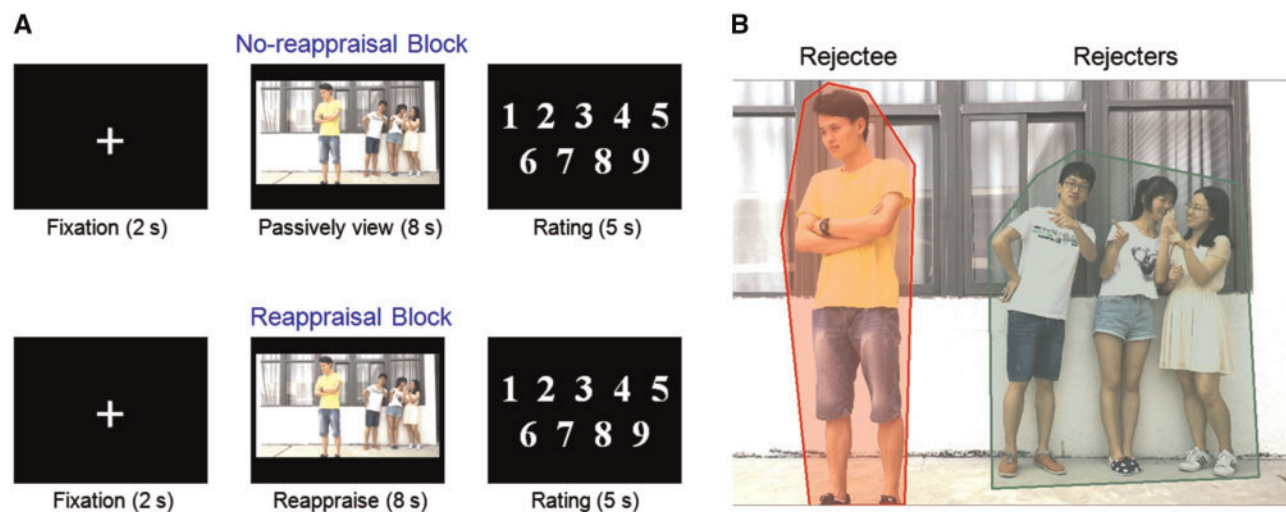


Fig. 1. Experimental paradigm and example of an AOI template. (A) Schematic of the emotional regulation task. On the no-reappraisal block, participants were asked to image him/herself as the rejectee in the images. On the reappraisal block, participants were instructed to down-regulate their negative emotional response. (B) A picture similar to those employed in the study. The polygonal areas represent the AOIs drawn for data analysis, including the rejectee (red) and the rejecters (green). For the sake of copyright, the persons in the picture are replaced by the graduate students in the authors' lab. All the four persons in the picture gave their consent for the material to appear in academic journals.

report which strategy they mainly used. A Chi-square test showed that the use of third-/first-person strategies did not differ between groups ($\chi^2 = 0.322$, $P = 0.570$; active stimulation group = 14/9, sham stimulation group = 11/10). In Experiment 2, participants were required to down-regulate their negative emotion only using the 'first-person perspective' strategy. In particular, participants were instructed as follows: 'In this section, please imagine a better outcome of the situation. For example, you could imagine that the group of people who are interacting with each other are talking about something that the person alone is not interested in, or the person alone could make some change and join the group very soon. After you reinterpret the nature of the scene, please think about how you would feel in this situation if you are the person alone in the picture.'

tDCS manipulation

The tDCS was delivered using a constant current stimulator via saline-soaked surface sponge electrodes with a size of 5×5 cm (Brainstim, EMS, Bologna, Italy). For anodal stimulation of the rVLPFC, the anode electrode was placed over F6 according to the international 10/20 EEG system (Riva et al., 2015a; Cai et al., 2016). The cathodal electrode was placed above the contralateral supra-orbital area (Fp1) ~ 5 cm from the anode (Miranda et al., 2006; Feeser et al., 2014; Riva et al., 2015a). In the condition of active stimulation, a constant current of 2.5 mA (0.1 mA/cm^2) was started 4 min before the task onset and prolonged for the entire task (Feeser et al., 2014) (a total of 24 min). Stimulation with 2.5 mA has been shown to be safe in healthy adult volunteers (Koenigs et al., 2009; Cogiamanian et al., 2011; Fregni et al., 2015; Seibt et al., 2015). In the sham stimulation, constant current with the same current intensity was started 4 min before the task onset but lasted for only 30 s, which mimicked the itching sensation of the active stimulation condition while showing negligible effects on neural activity (Feeser et al., 2014; Riva et al., 2015a). All the 44 participants reported skin itching at the beginning of tDCS but no other sensation or adverse effect and all believed they received an electrical stimulation during the whole task.

Eye-tracker recording and data analysis

The experimental room was illuminated using an LED ceiling lamp with constant brightness (25 lx). Gaze fixations and pupil diameter were recorded with a sampling frequency of 60 Hz using a desk-mounted eye tracker [D6, Applied Science Laboratories (ASL), Bedford, USA].

This study used two indexes provided by ASL Result Plus (Applied Science Laboratories, Bedford, MA). The first was fixation duration. Fixations were defined as a minimal time of 50 ms spent within a 50-pixel diameter region (van Reekum et al., 2007). In stimulus images of this study, individuals are depicted as falling into one of two roles, i.e. the 'rejectee' (the individual being excluded) and the 'rejecters' (a group of people who are interacting with each other and excluding the rejectee) (Gaertner et al., 2008). Accordingly, we defined two areas of interest (AOIs) in this study. Polygons were manually drawn on each picture to create two AOIs (Figure 1B). Then the percentage of fixation duration was calculated by dividing the fixation duration on the pre-defined AOIs by the total fixation duration (Manera et al., 2014). We used a relative measure of fixation duration instead of an absolute value because the former reflects the amount of time spent on the AOIs after controlling for the total fixation time (Manera et al., 2014).

The second index was pupil diameter. Blinks and missing data points were linearly interpolated by the program (19 ± 6.7 and $15 \pm 4.2\%$ data were missing per dataset in Experiment 1 and 2). The baseline for pupil diameter was assessed by averaging the data during the first 167 ms (the first 10 time samples) after the onset of the picture (Silk et al., 2012). Then the change in pupil diameter was calculated by subtracting baseline pupil diameter from diameter during a trial. This manipulation was used to control individual difference in baseline pupil diameter.

Statistics

Descriptive data are presented as mean \pm s.d., unless otherwise mentioned. Negative emotion ratings and the two eye-tracker measures were analyzed using repeated-measures analyses of variance (ANOVAs) to test for main effects and interactions. The

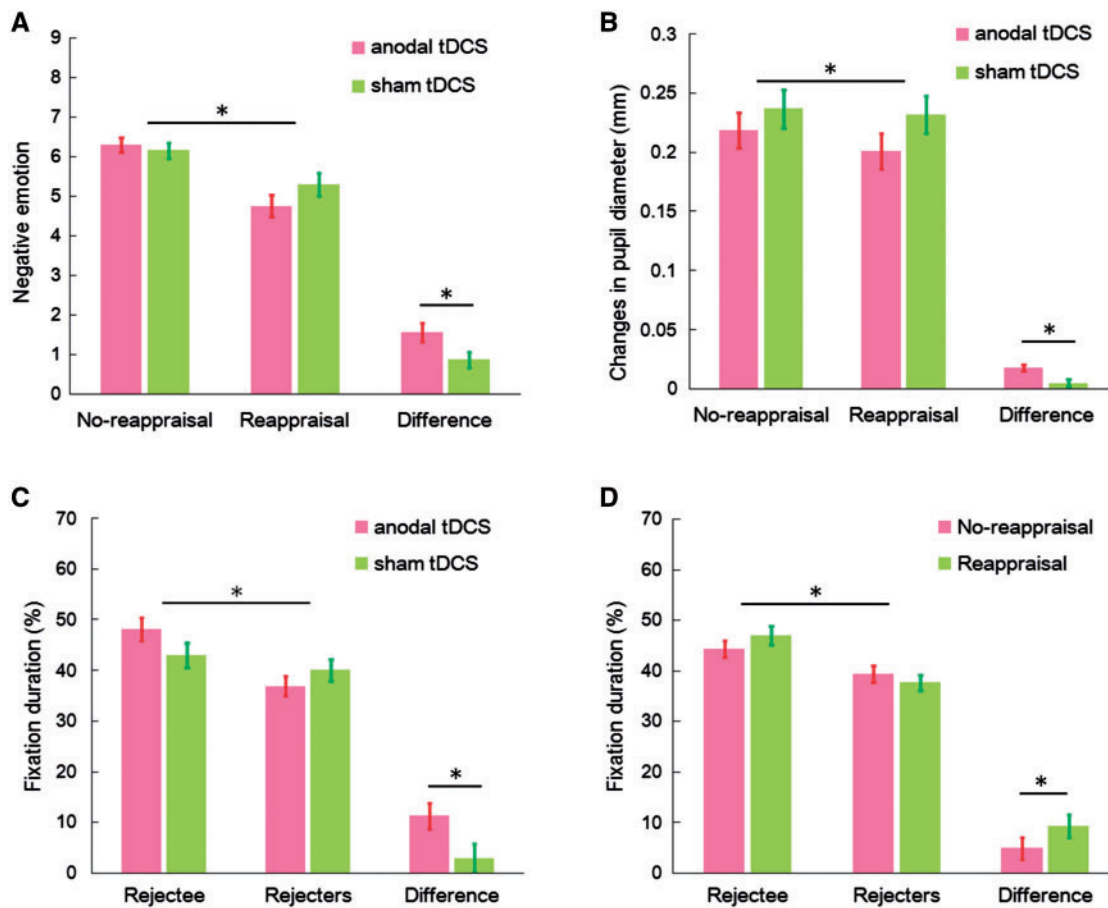


Fig. 2. Results of Experiment 1. (A) Mean ratings of negative emotion experience in both groups (anodal vs sham tDCS) and the two tasks (no-reappraisal vs reappraisal). (B) Mean changes of pupil diameter (relative to baseline) in both groups and the two tasks. (C) Mean percentage of fixation duration in both groups (anodal vs sham tDCS) and the two AOIs (rejectee vs rejecters). (D) Mean percentage of fixation duration in the two task blocks (no-reappraisal vs reappraisal) and the two AOIs. * $P < 0.05$. Error bars represent \pm SEM.

between-subject factor was group (active vs sham) while the within-subject factors were task (no-reappraisal vs reappraisal) and AOIs (rejectee vs rejecters). All tests were two-tailed and significance level was set at a probability of $P < 0.05$. Statistical analyses were carried out using SPSS Statistics 20.0 (IBM, Somers, USA).

Results

Experiment 1

Rating of negative emotion. There was a significant interaction between group and task [$F(1, 42) = 4.71, P = 0.036, \eta_p^2 = 0.101$]. Although both the active stimulation group [$F(1, 42) = 49.2, P < 0.001$; no-reappraisal = 6.30 ± 0.83 ; reappraisal = 4.75 ± 1.32] and the sham stimulation group [$F(1, 42) = 13.7, P = 0.001$; no-reappraisal = 6.16 ± 0.93 ; reappraisal = 5.30 ± 1.30] reported lower ratings of negative emotion in the reappraisal block than in the no-reappraisal block, this emotional regulation effect was greater in the active stimulation group (Figure 2A).

There was also a significant main effect of task [$F(1, 42) = 56.5, P < 0.001, \eta_p^2 = 0.574$]. The rating of negative emotion was lower in the reappraisal block (5.01 ± 1.33) as compared to that in the no-reappraisal block (6.23 ± 0.87). This result verified the validity of emotional regulation (Ochsner et al., 2004).

In this study, the order of two blocks was fixed. To exclude a possible effect of habituation, an additional temporal analysis was performed in each block, with the rating of negative emotion in the first half of trials compared to that in the second half of trials. Paired-samples t-test shows that the rating of negative emotion was not significantly different between two halves of the no-reappraisal block [$t(43) = -1.66, P = 0.104$; first half = 6.14 ± 0.98 , second half = 6.34 ± 0.95] as well as the reappraisal block [$t(43) = 0.32, P = 0.750$; first half = 5.04 ± 1.50 , second half = 4.99 ± 1.37]. This result indicates that the decrease in reported negative emotion in the second block (reappraisal block) is not due to habituation.

Changes in pupil diameter. A significant interaction was found between group and task [$F(1, 42) = 10.5, P = 0.002, \eta_p^2 = 0.200$]. While the active stimulation group had smaller pupil diameter in the reappraisal block (0.201 ± 0.070 mm) than that in the no-reappraisal block [0.219 ± 0.071 mm; $F(1, 42) = 40.8, P < 0.001$], the sham stimulation group did not show significant difference in pupil diameter between the two blocks [$F(1, 42) = 2.66, P = 0.110$; no-reappraisal = 0.237 ± 0.073 mm, reappraisal = 0.232 ± 0.073 mm; Figure 2B]. A significant main effect of task was also observed [$F(1, 42) = 31.3, P < 0.001, \eta_p^2 = 0.427$]. Pupil diameter was smaller in the reappraisal block (0.216 ± 0.073 mm) compared to the no-reappraisal block (0.228 ± 0.071 mm).

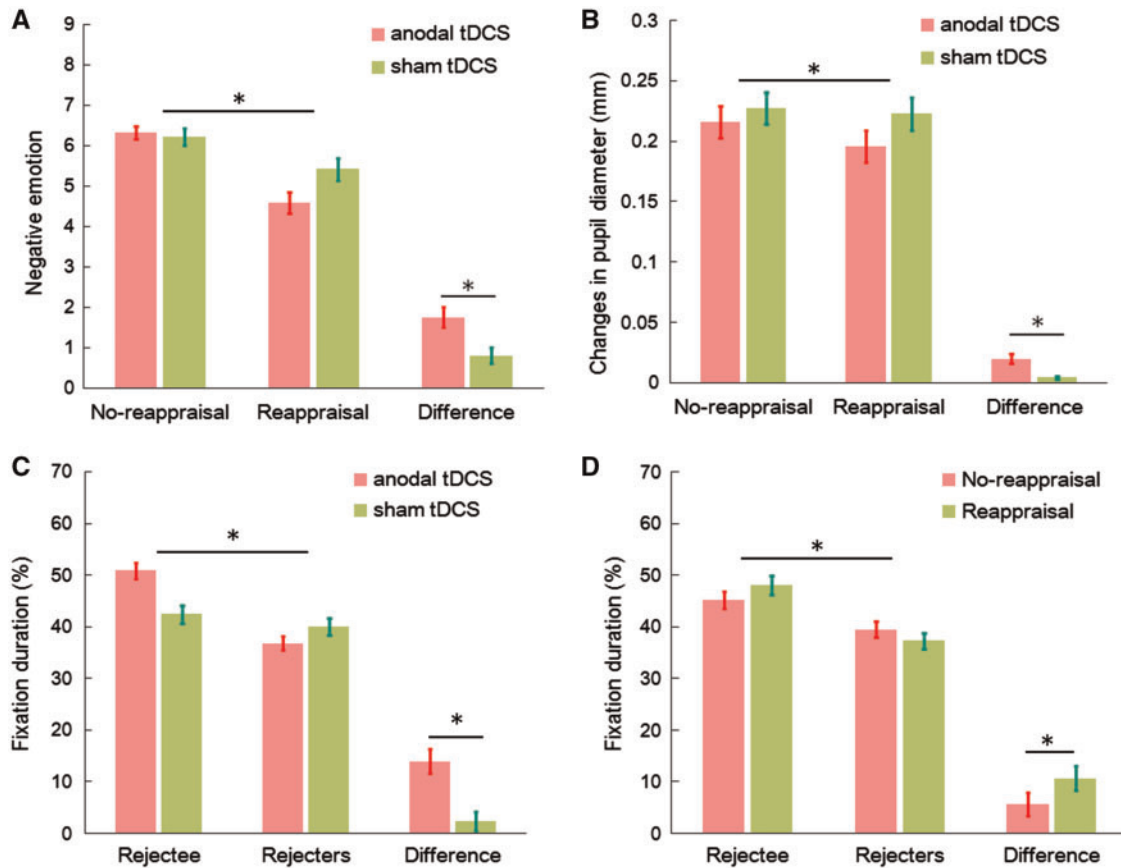


Fig. 3. Results of Experiment 2. (A) Mean ratings of negative emotion experience. (B) Mean changes of pupil diameter. (C, D) Mean percentage of fixation duration.

Fixation duration. A significant interaction was observed between group and AOIs [$F(1, 42) = 4.70, P = 0.036, \eta_p^2 = 0.101$]. While the active stimulation group had a longer fixation duration for the AOI of rejectee ($48.2 \pm 12.0\%$) compared to the AOI of rejecters [$37.0 \pm 10.2\%$; $F(1, 42) = 18.3, P < 0.001$], the sham stimulation group did not show a significant difference in fixation durations between the two AOIs [$F(1, 42) = 1.17, P = 0.284$; rejectee = $43.1 \pm 11.3\%$, rejecters = $40.1 \pm 10.4\%$; Figure 2C].

The interaction of task and AOIs was also significant [$F(1, 42) = 4.41, P = 0.042, \eta_p^2 = 0.095$]. Although the fixation duration was longer for the AOI of rejectee than for the AOI of rejecters in both the no-reappraisal block [$F(1, 42) = 5.62, P = 0.022$; rejectee = $44.4 \pm 11.2\%$; rejecters = $39.4 \pm 10.6\%$] and the reappraisal block [$F(1, 42) = 17.5, P < 0.001$; rejectee = $47.0 \pm 12.5\%$; rejecters = $37.7 \pm 10.2\%$], this AOI effect was more significant in the reappraisal block (Figure 2D).

The main effect of AOIs was also significant [$F(1, 42) = 14.0, P = 0.001, \eta_p^2 = 0.249$]. Participants had longer fixation duration to the AOI of rejectee ($45.7 \pm 11.9\%$) than the AOI of rejecters ($38.5 \pm 10.4\%$).

Experiment 2

In general, the statistical result of Experiment 2 is very similar with that in Experiment 1.

Rating of negative emotion. There was a significant interaction between group and task [$F(1, 38) = 8.55, P = 0.006, \eta_p^2 = 0.184$]. Although both the active stimulation group [$F(1, 38) = 58.0, P < 0.001$; no-reappraisal = 6.33 ± 0.71 ; reappraisal = 4.58 ± 1.19]

and the sham stimulation group [$F(1, 38) = 12.1, P = 0.001$; no-reappraisal = 6.22 ± 0.90 ; reappraisal = 5.42 ± 1.20] reported lower ratings of negative emotion in the reappraisal block than in the no-reappraisal block, this emotional regulation effect was greater in the active stimulation group (Figure 3A). There was also a significant main effect of task [$F(1, 38) = 61.6, P < 0.001, \eta_p^2 = 0.619$; reappraisal block = 5.00 ± 1.26 , no-reappraisal block = 6.28 ± 0.80].

Changes in pupil diameter. A significant interaction was found between group and task [$F(1, 38) = 14.5, P < 0.001, \eta_p^2 = 0.276$]. While the active stimulation group had smaller pupil diameter in the reappraisal block (0.196 ± 0.060 mm) than that in the no-reappraisal block [0.216 ± 0.058 mm; $F(1, 38) = 48.3, P < 0.001$], the sham stimulation group did not show significant difference in pupil diameter between the two blocks [$F(1, 38) = 2.44, P = 0.126$; no-reappraisal = 0.228 ± 0.059 mm, reappraisal = 0.223 ± 0.062 mm; Figure 3B]. A significant main effect of task was also observed [$F(1, 38) = 36.2, P < 0.001, \eta_p^2 = 0.488$; reappraisal block = 0.210 ± 0.061 mm, no-reappraisal block = 0.222 ± 0.058 mm].

Fixation duration. A significant interaction was observed between group and AOIs [$F(1, 38) = 9.98, P = 0.003, \eta_p^2 = 0.208$]. While the active stimulation group had a longer fixation duration for the AOI of rejectee ($50.9 \pm 9.89\%$) compared to the AOI of rejecters [$36.9 \pm 8.59\%$; $F(1, 38) = 29.2, P < 0.001$], the sham stimulation group did not show a significant difference in fixation durations between the two AOIs [$F(1, 38) < 1$; rejectee = $42.5 \pm 11.2\%$, rejecters = $40.0 \pm 10.6\%$; Figure 3C]. The interaction of task and AOIs was significant [$F(1, 38) = 5.12,$

$P=0.02$, $\eta_p^2=0.119$]. Although the fixation duration was longer for the AOI of rejectee than for the AOI of rejecters in both the no-reappraisal block [$F(1, 38)=7.43$, $P=0.010$; rejectee = $45.3 \pm 10.6\%$; rejecters = $39.5 \pm 9.8\%$] and the reappraisal block [$F(1, 38)=24.5$, $P<0.001$; rejectee = $48.1 \pm 12.0\%$; rejecters = $37.4 \pm 9.7\%$], this AOI effect was more significant in the reappraisal block (Figure 3D). The main effect of AOIs was significant [$F(1, 38)=20.1$, $P<0.001$, $\eta_p^2=0.346$; AOI of rejectee = $46.7 \pm 11.3\%$, AOI of rejecters = $38.5 \pm 9.7\%$].

Discussion

Using tDCS and a standardized cognitive reappraisal instruction, this study investigated the causal effects of rVLPFC stimulation on emotional regulation of social exclusion. The two experiments consistently demonstrated that anodal tDCS over rVLPFC facilitated emotional regulation abilities. Consistent with our first hypothesis, tDCS caused a greater decrease of negative emotion rating and pupil diameter associated with active emotional regulation. These findings provide direct causal evidence to support the critical role of rVLPFC in reappraising negative emotions elicited by social exclusion.

The central finding of this study was that anodal stimulation of rVLPFC led to lower ratings of negative emotions elicited by social exclusion and thereby confirmed the notion that this area plays an important role in reducing the impact of social exclusion (Eisenberger et al., 2003). This result is consistent with previous tDCS studies on social pain regulation that did not use an explicit instruction to regulate emotion (Riva et al., 2012, 2015a). The novel contribution of this study is that, by using a standardized emotion reappraisal task, we directly demonstrated a causal role for rVLPFC in actively reappraising social exclusion emotions. That is, social pain can be ameliorated through emotional regulation by directly activating rVLPFC using tDCS.

This result is also in line with recent fMRI meta-analyses showing that the rVLPFC is a critical region involved in various kinds of emotional regulation (Buhle et al., 2014; Kohn et al., 2014). Studies focused on the down-regulation of emotions have identified a negative correlation between rVLPFC activation and self-reported negative emotion (Ochsner et al., 2004; Wager et al., 2008). In the context of social exclusion, the rVLPFC might inhibit dorsal ACC (dACC) activity to down-regulate social pain (Eisenberger et al., 2003). Although we did not measure activity in dACC or its connectivity with rVLPFC, it is very possible that the increased cortical excitability of rVLPFC induced by tDCS may strengthen prefrontal modulation of dACC and thus result in greater emotion reappraisal success. We suggest further studies combining brain stimulation and neuroimaging to investigate the issue in the future (Riva et al., 2015b).

The facilitating effect of tDCS on emotional regulation of social exclusion was further supported by our pupil data, which demonstrated significantly decreased pupil diameter in the active tDCS group when reappraising pictures. This result was in accordance with the negative emotion rating finding. Pupil diameter represents an objective measure of emotional arousal (Bradley et al., 2008), and therefore this result indicated that decrease in tDCS-induced subjective negative emotion (ratings) is accompanied by decrease in emotional arousal (pupil diameter). Thus, our finding provides peripheral physiological evidence for the tDCS induced changes in emotional regulation ability.

Fixation duration was also measured and our prior hypothesis was that there would be a three-way interaction between group, task and AOIs. However, only two-way interactions were

discovered. Participants spent more time looking at rejectees than rejecters in the reappraisal condition, to a greater extent than in the no-reappraisal condition. The result is consistent with previous reports that regulation goals influence the attention deployment (van Reekum et al., 2007; Manera et al., 2014). Our finding indicates that individuals are more likely to look at 'self' (the rejectee) relative to 'others' (the rejecters) when reappraising social exclusion. A previous study showed that self-focused attention combined with reappraisal resulted in greater recovery from social exclusion (Sethi et al., 2013). The authors argued that reappraisal can resolve the discrepancy between the actual self (i.e. target of social exclusion) and the ideal self (i.e. being accepted by others) when people are self-focused, thereby reducing the negative effect of social exclusion (Sethi et al., 2013). In this study, we suggest that the decrease of negative emotion rating may due to reappraisal in combination with self-focused attention. We had also hypothesized that tDCS-activated rVLPFC would boost reappraisal ability and thus strengthen self-focused attention. However, we observed only a significant interaction between group and AOIs, i.e. the active tDCS group paid more attention to rejectees than rejecters while the sham group had similar attention to both AOIs. Here, the effect did not differ between the two tasks (no-reappraisal and reappraisal) and was therefore not associated with active emotional regulation. One possible reason is that when the rVLPFC is activated by tDCS, individuals tend to automatically down-regulate social exclusion, even when explicit emotional regulation instructions are not given (DeWall et al., 2011).

One reason why we did not find the expected three-way interaction might be due to cultural effects; our participants were Chinese but the individuals in the social exclusion pictures were from other ethnic backgrounds. There is evidence that the negative emotion elicited by social exclusion is stronger when the rejecters are from a similar ethnic/social background (Krill and Platek, 2009). However, all participants viewed the same pictures and this study focused on between-subject differences. Therefore, it is unlikely that our positive findings are affected by such effects.

An additional limitation is that although this study proposed that anodal tDCS facilitates emotional regulation in rVLPFC, there may be other possible mechanisms underlying the current finding due to non-specific effect of tDCS. First, the brain function modulated by tDCS is not specific, i.e. tDCS stimulation focusing on VLPFC can influence various cognitive processes such as memory control (Badre et al., 2005), regulation of vocal production (Loh et al., 2017) and response inhibition (Jacobson et al., 2011). Second, the brain region targeted by tDCS is not focal, i.e. the neural changes induced by tDCS usually extend to a broad network of structurally and functionally connected regions (Keeser et al., 2011; Polanía et al., 2012; Miranda et al., 2013). Therefore, it should be cautious when linking a specific process (i.e. emotional regulation) to a specific brain region (i.e. rVLPFC) on the basis of tDCS results (Filmer et al., 2014). Here, we give some suggestions to improve the specificity of tDCS: (1) conduct control experiments with alternative reference locations to exclude the effect of tDCS at the reference electrode (i.e. Fp1 in this study; see also Filmer et al., 2013); (2) examine the spatial specificity using a more focused technique (e.g. transcranial magnetic stimulation) or by testing whether the same effect would be produced by stimulating another brain region not involved in emotional regulation (see also Riva et al., 2015b); (3) perform a follow-up study including non-social negative pictures to investigate whether the tDCS effect is different between non-social and social events (see also Elliott et al., 2012); and (4) use small-size target electrode and employ 3D position tracking systems to guarantee stable placement of electrodes on the scalp.

Also, it should be pointed out that this study used a tDCS current intensity of 2.5 mA while relevant studies (Riva et al., 2012, 2015a, 2015b) used a current intensity of 1.5 mA. This is because Chinese subjects usually have thicker hair than Caucasians (who were the subjects of Riva et al.), and thicker hair produces larger resistance for electric current. Actually, we performed a preliminary study on 40 subjects (20 in active and 20 in sham group) using 1.5 mA (without eye-tracker recording). However, the effect of tDCS was only marginally significant ($P = 0.078$). Therefore in this study, we decided to select a higher current intensity.

Our results have potential clinical implications. The finding that anodal tDCS-rVLPFC facilitated the ability to regulate emotional responses to social exclusion could be used to improve treatments for patients with deficits in emotional regulation and social function (e.g. depression; Rive et al., 2013; Kupferberg et al., 2016) and autism spectrum disorder (APA, 2013; Mazefsky et al., 2013). In particular, the poor social functioning in depression is characterized by impaired social affiliation and attachment, including social anhedonia and hypersensitivity to social rejection (Kupferberg et al., 2016). Reduced recruitment of VLPFC in reappraisal of negative emotion (Zilverstand et al., 2017) might lead to inefficient emotion regulation of social distress in depressed patients. As suggested by our findings, anodal tDCS focused on the rVLPFC could be beneficial for cognitive behavioral therapies targeting emotional dysregulation and aiming to improve the prefrontal emotion control in depression (DeRubeis et al., 2008) and autism spectrum disorder (Scarpa and Reyes, 2011; Pitskel et al., 2014).

Conclusion

This tDCS study demonstrated that anodal tDCS stimulation of rVLPFC improved the ability to down-regulate negative emotion responses associated with social exclusion. We interpreted our findings as suggesting that the effect of tDCS was, at least partly, mediated by attention re-allocation from rejecters to rejectees. Findings from this study support the use of tDCS in clinical interventions targeting poor social functioning in depression and autism spectrum disorder.

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