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Emotion regulation of social pain: double dissociation of lateral prefrontal cortices supporting reappraisal and distraction

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Abstract

The dorsolateral prefrontal cortex (DLPFC) and ventrolateral prefrontal cortex (VLPFC) are both crucial regions involved in voluntary emotion regulation. However, it remains unclear whether the two regions show functional specificity for reappraisal and distraction. This study employed transcranial magnetic stimulation (TMS) to explore, in a real social interactive scenario, whether different lateral prefrontal regions play relatively specific roles in downregulating social pain via reappraisal and distraction. Participants initially took part in a social interactive game, followed by receiving either active (the DLPFC- or VLPFC-activated group, $n = 100$ per group) or control (the vertex-activated group, $n = 100$) TMS session. They were then instructed to use both distraction and reappraisal strategies to downregulate any negative emotions evoked by the social evaluation given by their peers who interacted with them previously. Results demonstrated that the TMS-activated DLPFC has a greater beneficial effect during distraction, whereas the activated VLPFC has a greater beneficial effect during reappraisal. This result investigated the direct experience of social pain and extended previous findings on empathy-related responses to affective pictures while also controlling for confounding factors such as empathic concern. Therefore, we are now confident in the double dissociation proposal of the DLPFC and VLPFC in distraction and reappraisal.

Keywords: emotion regulation; social pain; ventrolateral prefrontal cortex; dorsolateral prefrontal cortex; reappraisal; distraction

Introduction

Social communication and interactions are critical aspects of people's daily lives. Impaired or destroyed social connection causes reduced prosocial behaviors (Twenge *et al.*, 2007), enhanced aggression (Richman and Leary, 2009) and poor mental health statuses such as post-traumatic stress, social anxiety and depression (Nolan *et al.*, 2003; Wang *et al.*, 2017; Durodié and Wainwright, 2019). Experiencing negative social events, such as interpersonal rejection and criticism, results in painful feelings similar to those of physical pain, thus being called as social pain (Eisenberger *et al.*, 2003; Eisenberger and Lieberman, 2004; Eisenberger, 2012). Studies have demonstrated that social support (Schmälzle *et al.*, 2017; Morese *et al.*, 2019) and emotion regulation (He *et al.*, 2018, 2020a,b; Zhao *et al.*, 2021; Li *et al.*, 2022) are both helpful in mitigating social pain. This study focuses on the latter approach, namely emotion regulation, as it is a self-supported and widely used method to reduce painful feelings (McRae and Gross, 2020).

Among various emotion regulation strategies, distraction and cognitive reappraisal (hereinafter abbreviated as reappraisal) are frequently employed and have been revealed to be more effective and adaptive in reducing negative emotions when compared to other strategies such as expressive suppression or rumination (Gross, 1998a; Ochsner *et al.*, 2012). According to the cognitive model of emotion regulation (Gross, 1998b), distraction is an early selection strategy at the attentional deployment stage, wherein individuals either focus their attention on a neutral aspect of a given situation or reallocate their attention to unrelated events/stimuli. Unlike distraction, reappraisal is a semantic selection strategy at a later stage of cognitive change, wherein individuals modify their interpretations of emotional situations from a more positive perspective (Ochsner *et al.*, 2012; Gross

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et al., 2019). Convergent evidence has demonstrated that both distraction and reappraisal can effectively reduce negative/distressing feelings, as well as weaken emotional neural responses observed in the amygdala, insula and ventral striatum (McRae et al., 2010; Kanske et al., 2011; Ochsner et al., 2012; Dörfel et al., 2014; Hermann et al., 2017).

While key brain regions for emotion regulation are primarily located in the prefrontal cortex (PFC; Ochsner et al., 2012; Dixon et al., 2017), some studies have revealed that distraction and reappraisal involve distinct neural substrates to some extent (Vrtička et al., 2011; Morawetz et al., 2017). Early functional magnetic resonance imaging (fMRI) studies found that, although both distraction and reappraisal utilize the PFC network, distraction additionally activates the dorsal anterior cingulate and parietal cortices, whereas reappraisal depends more on the orbitofrontal cortex and the anterior temporal region (McRae et al., 2010; Kanske et al., 2011). More recently, researchers rigorously defined emotion regulation tasks (e.g. excluding confusing factors such as memory encoding, language production and mental calculation and clearly differentiating reappraisal from distancing) and found that while the ventrolateral PFC (VLPFC) is more critical for reappraisal, the dorsolateral PFC (DLPFC) is more crucial for distraction (Dörfel et al., 2014; Marques et al., 2018; Moodie et al., 2020), although both the regions are largely involved in distraction and reappraisal (Rive et al., 2013; Kohn et al., 2014; Morawetz et al., 2017; Zilverstand et al., 2017).

More relevant to our focus on downregulating social pain, previous fMRI studies have demonstrated that both the VLPFC and the DLPFC (especially their right hemispheric parts) are closely associated with the reduction of social pain (Vijayakumar et al., 2017; Wang et al., 2017). Using neural modulation techniques such as transcranial direct current stimulation and transcranial magnetic stimulation (TMS), multiple studies have causally demonstrated that activating the right VLPFC (rVLPFC) could effectively reduce experienced social pain (Riva et al., 2012; Hsu et al., 2015), as well as any aggressive behaviors caused by social pain (Riva et al., 2015). Meanwhile, the DLPFC has been found to play a causal role in improving affective feelings when participants perceive and evaluate social feedback (Allaert et al., 2022). While the above-mentioned studies demonstrated the involvement of the DLPFC and VLPFC in automatic (or implicit) emotion regulation of social pain, our recent study employed an explicit emotion regulation task and provided direct evidence for the role of these two PFC areas in voluntary emotion regulation following social exclusion events (Zhao et al., 2021). Thus, we provided the first evidence based on a single study that these two brain regions show functional specificity to some extent for reappraisal and distraction: while the VLPFC-facilitated participants showed a better regulation effect during reappraisal, the DLPFC-facilitated participants showed a better regulation effect when using the distraction strategy (Zhao et al., 2021).

However, there was a non-negligible problem in the study of Zhao et al. (2021) as well as our other related studies (He et al., 2018, 2020a,b): we previously examined imagined, rather than actually experienced, social pain; that is, participants were required to imagine themselves as the person who was excluded by a group of peers as shown in social exclusion pictures (refer to Zheng et al. (2022) for the details of these social exclusion pictures; see Figure 1C for an example). This imagining paradigm relies upon an empathy-based process that might introduce confounding factors. For example, Masten et al. (2011b) required participants to observe one person being excluded by others and found that participants' trait empathy positively predicted their neural activation of the bilateral anterior insula, suggesting that the experienced social pain via observation and imagination is influenced by individuals' empathy ability. In addition, the severity of social pain often differs between direct experience of pain and indirect observing others in pain due to an empathy gap (Nordgren et al., 2011); thus, these two kinds of social pain might need dissociable brain networks for emotion regulation.

This study was implemented to overcome the disadvantage of the study by Zhao et al. (2021); that is, we used a novel paradigm to evoke 'first-hand' social pain, followed by investigating whether the VLPFC and the DLPFC show double dissociation during explicitly downregulating social pain via reappraisal and distraction strategies. To verify the double dissociation hypothesis, we included a large sample of participants ($n = 300$) as compared to the small sample ($n = 90$) in Zhao et al. (2021). With such a large sample size, we could also examine the effect of individual differences on emotion regulation, as previous studies have demonstrated that depression (Rive et al., 2013; Liu and Thompson, 2017), trait anxiety (Zilverstand et al., 2017), social anxiety (Jazaieri et al., 2015; Dryman and Heimberg, 2018; Dixon et al., 2020) and the frequency of using emotion regulation strategies (Kanske et al., 2012; Vanderhasselt et al., 2013) might significantly affect emotion regulation. In line with our previous studies (He et al., 2018, 2020a,b; Zhao et al., 2021; Li et al., 2022), we used subjective ratings of experienced emotions as the main index to measure the effect of emotion regulation. In addition, this study tested both the immediate and delayed TMS effect to provide empirical evidence for translational research in psychiatry.

Methods

Participants

There were three TMS groups in this study: the VLPFC-activated group, the DLPFC-activated group and the vertex-activated (control) group. During the experiment design, we conducted a priori power analysis using G*Power 3.1.7 [F-tests, analysis of variance (ANOVA): repeated measures, within-between interaction] based on the effect size ($\eta_p^2 = 0.083$) reported in our previous TMS study (Zhao et al., 2021). According to the result of this power analysis, 51 participants in total (i.e. 17 ones per group) would ensure 99% statistical power. Since the purpose of this study was to re-examine the double dissociation issue (i.e. the roles of the DLPFC and VLPFC during distraction and reappraisal) in a large sample size and investigate the influence of individual differences on emotion regulation, we therefore decided to include 100 participants per TMS group. A total of 300 healthy college students (all right-handed) were recruited from Shenzhen University. Unfortunately, we missed data of two, four and seven participants due to technique problems in the three groups. As a result, the sample size was 98, 96 and 93 in the VLPFC-activated group, the DLPFC-activated group and the control group, respectively.

On the day of the experiment, participants were required to complete four questionnaires before their group assignment, including the Beck Depression Inventory Second Edition (BDI-II; Beck et al., 1996), the Trait form of Spielberger's State-Trait Anxiety Inventory (STAI-T; Spielberger et al., 1983), the Liebowitz Social Anxiety Scale (LSAS; Liebowitz, 1987) and the Thought Control Questionnaire (TCQ; Wells and Davies, 1994). Among them, the BDI-II, STAI-T and LSAS measure participants' levels of depression, trait anxiety and social anxiety; the TCQ is used to assess

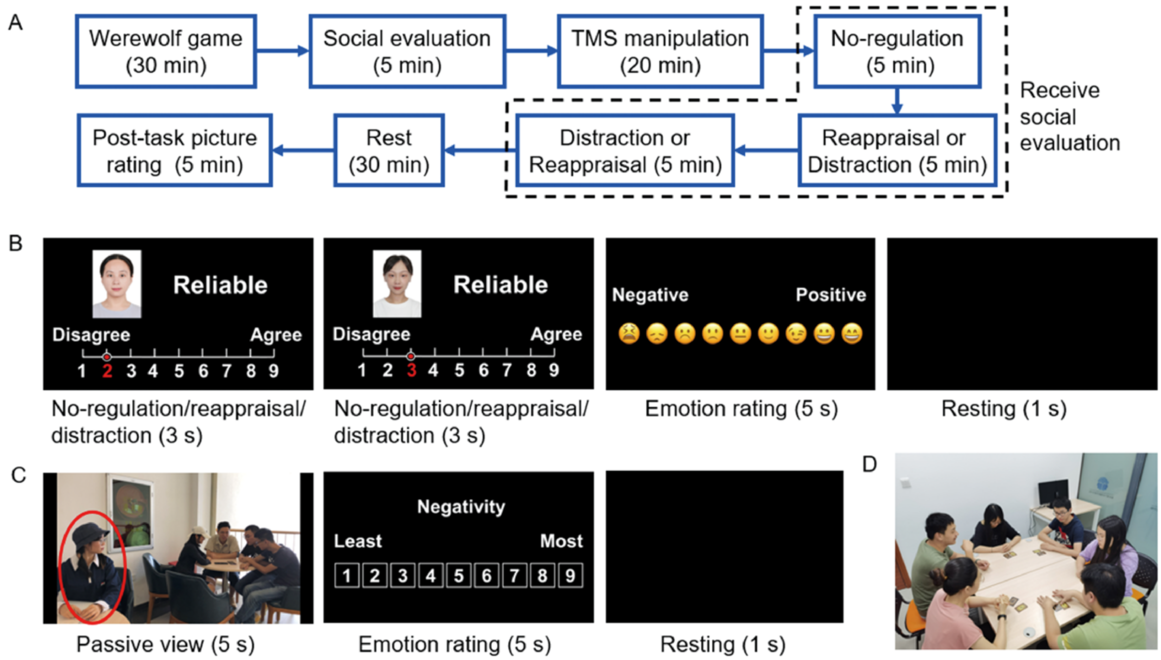

Fig. 1. Illustrations of experimental methods. (A) A flow chart of the task procedure. (B) One trial of the main task. (C) One trial of the post-task rating. (D) A picture of the Werewolf game. Due to copyright, the people in the images presented here are all replaced by the graduate students from the research group. All the persons in these pictures gave their consent for the materials to appear in academic journals.

Table 1. Demographic characteristics of the three groups (mean ± s.d.)

Items	DLPFC ($n = 98$)	VLPFC ($n = 96$)	Control ($n = 93$)	Statistics[a]	
				F/χ^2	P
Gender (M/F)	45/53	43/53	49/44	1.38	0.502
Age (years)	19.7 ± 1.7	19.6 ± 1.8	19.4 ± 1.3	1.13	0.325
BDI-II	7.4 ± 5.2	7.4 ± 5.9	6.9 ± 5.1	2.37	0.095
STAI-T	40.3 ± 8.3	40.6 ± 7.4	39.1 ± 6.0	1.18	0.307
LSAS	37.9 ± 16.7	38.0 ± 21.3	34.3 ± 14.6	1.35	0.262
TCQ-D	17.7 ± 3.2	17.0 ± 2.8	17.0 ± 2.9	1.88	0.154
TCQ-R	15.5 ± 2.8	15.3 ± 3.5	16.0 ± 3.6	1.35	0.260

[a]One-way ANOVA or chi-squared test across the three groups.

the frequency of using distraction (distraction subscale) and reappraisal (reappraisal subscale) when regulating unpleasant and unwanted thoughts. Participants were randomly assigned to the three TMS groups. No difference was found in the scores of these questionnaires across the groups. No participant had any prior experiences with TMS before this experiment. No significant differences were found in participants' gender or ages across the three groups (Table 1). The study protocol was approved by the Ethics Committee of Sichuan Normal University. Informed consent was signed by the participants prior to their engagement in the experiment.

Experimental design and materials

The study was a 3 × 3 mixed design. The within-subject factor was the 'regulation type' (no-regulation, reappraisal and distraction), and the between-subject factor was the 'TMS group' (VLPFC-activated, DLPFC-activated and control).

The main task used 42 personality trait words (21 positive and 21 negative words), which were assigned equally into three blocks. The familiarity and emotional valence of the words were rated on a 1-to-9-point scale by another 30 individuals whose demographic characteristics were comparable with the participants of this study. One-way ANOVA showed that no significant difference was found in familiarity (positive: $F < 1$; no-regulation, reappraisal and distraction = 7.1 ± 0.4, 7.1 ± 0.2 and 7.1 ± 0.3; negative: $F < 1$; 6.1 ± 0.3, 6.2 ± 0.5 and 6.2 ± 0.5) or valence (positive: $F < 1$; 7.3 ± 0.3, 7.2 ± 0.3 and 7.3 ± 0.3; negative: $F < 1$; 3.6 ± 0.5, 3.6 ± 0.5 and 3.7 ± 0.6) across the three sets of materials. Besides words, the main task also employed identity photos of all the participants (refer to the subsection of Experimental procedure). Photos were taken in the laboratory after a social interactive game, and participants were required to show neutral facial expressions during photo taking. Photos were then standardized in size, luminance and background color before they were used in the main task.

In the post-task rating task, we used 20 social exclusion pictures to present negative social situations. The people in the pictures were undergraduate or graduate students. Each picture included one rejectee and a group of rejecters (three to four students). These pictures were selected from the image database of social inclusion/exclusion in young Asian adults (ISIEA), which were produced by our laboratory to induce social pleasure/pain for research purposes (Zheng et al., 2022). During the task, the 20 pictures were sequentially presented in the center of the screen.

Experimental procedure

The whole experimental procedure is shown in Figure 1A. In each experiment, two invited participants (a man and a woman) first played a social interactive game (i.e. Werewolf; Braverman et al., 2008; Osawa et al., 2021) with the same four pseudo-participants (two men and two women), during which the six persons communicated freely under the rules of the game and finally formed first impressions with each other (Figure 1D). After this interactive game, the experimenter took identity photographs of each of the six participants, which were then used in the following task.

In the social evaluation task, photos of the other five participants were presented sequentially and each participant was required to assess how well the 42 personality trait words matched the person in the photo, using a 1-to-9-point scale (1 for very disagree and 9 for very agree). Unknown to the participants, their evaluation scores were actually replaced by another set of scores designed ahead of time and used in the upcoming main task.

To evoke social pain during the emotion regulation task (i.e. the main task), the 42 evaluation outcomes were set to 30 negative (valid stimuli) and 12 positive ones (fillers). The negative outcome was reflected by 'disagreement' (rating score 1–4) of the positive personality trait words or 'agreement' (rating score 6–9) of the negative trait words. In contrast, the positive outcome was reflected by 'disagreement' of the negative trait words or 'agreement' of the positive trait words. After the above cover story, the two real participants were guided into two separate experimental rooms and performed the following two tasks.

The main task of emotion regulation began with a 20 min TMS session, and participants assigned to the three TMS groups received the magnetic stimuli in different brain regions. Then, they were presented with a social evaluation given by the other five players, during which they were required to regulate their emotions according to instructions. This task was divided into three blocks, i.e. no-regulation, distraction and reappraisal. The no-regulation (i.e. passive viewing) block was always performed first to avoid any carry-over effects by the reappraisal/distraction instructions (see also He et al., 2018, 2020a,b; Zhao et al., 2021; Li et al., 2022; Yuan et al., 2023). The order of the two emotion regulation blocks (reappraisal and distraction) was counterbalanced across participants within each TMS group. Each block used 14 personality trait words (seven positive and seven negative words associated with 10 negative and four positive evaluation outcomes). As shown in Figure 1B, in each trial, one personality trait word was associated with two social evaluation scores from two players; the two scores indicated consistent evaluation, i.e. both the players gave positive or negative social evaluations to the participant. During the presentation of evaluation outcomes (6 s), participants were required to either watch passively (during the no-regulation block) or downregulate their negative feelings using reappraisal (during the reappraisal block) or distraction strategies (during the distraction block). They were then required to report their affective feelings by clicking the mouse on one of the cartoon faces within 5 s. Here we used the 1-to-9-point valence scale to measure the self-report affective feelings (1 for very negative and 9 for very positive).

The instruction of the no-regulation block was as follows: 'In this section, please experience and report your emotional feelings when you receive the social evaluations from the other participants.' The instruction of the reappraisal block was as follows: 'In this section, please find a more positive explanation or interpretation regarding the unpleasant social evaluations. For example, you could think that these participants are unfamiliar with you and a brief interactive game is not enough for them to know your good qualities. Or you accidentally performed poorly in the game so your ratings could not accurately represent your abilities and traits. Please report your affective feelings after you reinterpret the social evaluations.' The instruction of the distraction block was as follows: 'In this section, please do not focus on the unpleasant evaluations when you watch them. For example, you could transfer your attention to the facial characteristics of the player on the photo or to the rhythms of your breathing and heartbeat. Report your affective feelings after you distract yourself from the unpleasant social evaluations.'

After the main task, participants have a rest for 30 min. Then they performed the post-task rating, during which 20 social exclusion pictures were shown sequentially. Participants were required to image how they would feel in a situation like that of the highlighted person in the picture and report their negative feelings using the mouse on a 9-point scale (1 representing the least and 9 representing the most negative). This task was designed to examine whether the TMS effect could still be valid 45 min post magnetic stimuli (He et al., 2020b; Zhao et al., 2021; Li et al., 2022).

Participants were interviewed at the end of the experiment. All of them reported that they were seriously involved in the game and believed that the feedback during the task was real.

Repetitive TMS

This study used offline TMS to reduce any side effects (e.g. acoustic noise or scalp unpleasant feeling) that may impact participants' task performances. The TMS targets were the rVLPFC and right DLPFC (rDLPFC) for the two experimental groups. For the control group, the TMS was targeted at the vertex to provide a similar scalp sensation as it did in the experimental groups (Hartwright et al., 2016; Zhao et al., 2021; Li et al., 2022). A figure-eight-shaped coil was connected to the magnetic stimulator (M-100 Ultimate; Yingchi, Shenzhen, China). The location of the coil was determined with reference to the International 10/20 electroencephalogram system. During the TMS sessions, participants wore the EEG cap for coil location. The rVLPFC is at the F8 (coil was placed parallel to the nasion-inion line), the rDLPFC is at the F4 (coil parallel to the nasion-inion line) and the vertex is at the Cz (90° from the nasion-inion line). The coil was placed tangentially on the scalp so that most of the magnetic field lines could go through the scalp and reach the targeted region. Each participant's resting motor threshold (rMT) was measured from their motor cortex (C3), with the intensity being defined as 50% of the pulses that reliably produced thumb twitches. The repetitive TMS (rTMS) was applied at 10 Hz at 90% of each participant's rMT (Xu et al., 2023). The mean stimulation intensity was $48.60 \pm 3.61\%$, $48.55 \pm 3.16\%$ and $48.80 \pm 3.09\%$ of the maximum TMS output in the DLPFC group, the VLPFC group and the control group, respectively. The 20 min rTMS session contained 40 trains, with each train lasting for 3.9 s (a total of 1560 pulses; Zhao et al., 2021). The inter-train interval was 26.1 s.

Statistics

Statistical analysis was performed using SPSS Statistics 20.0 (IBM, Somers, NY, USA). Descriptive data are presented as mean ± s.d., unless otherwise mentioned.

A repeated-measures two-way ANOVA was performed on self-ratings of emotional valence, with the 'regulation type' as the within-subject factor and the 'TMS group' as the between-subject factor. Meanwhile, a repeated-measures one-way ANOVA was

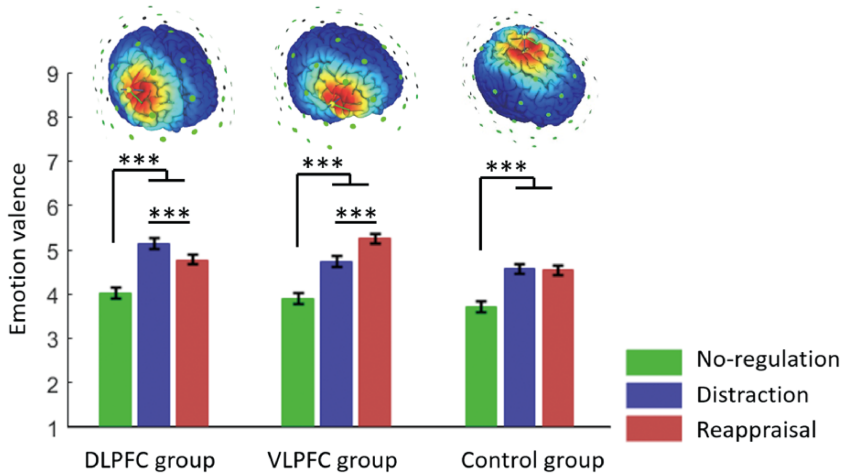

Fig. 2. Subjective ratings of negative emotions. A 1-to-9-point scale was used, with higher scores indicating more positive feelings toward the social evaluation (1 for the most negative and 9 for the most positive). Bars represent the SEM. ***$P < 0.001$. The TMS-simulated electric fields are illustrated on top of the plot (SimNIBS, www.simnibs.org, Thielscher *et al.*, 2015).

performed on post-task self-ratings of negative emotions, with the 'TMS group' as the between-subject factor. The Greenhouse–Geisser correction for the ANOVA tests was used whenever appropriate. Multiple comparisons were corrected using the Bonferroni method.

To investigate the influential factors of emotion regulation using the distraction strategy, we performed a multiple linear regression (enter method) on the rating of emotional valence in the distraction block. The variables selected as predictors included: 'gender' (man: 1 and woman: 0), 'TMS manipulation' (DLPFC activated: 1 and VLPFC/vertex activated: 0), 'depression' (measured by BDI-II), 'trait anxiety' (measured by the STAI-T), 'social anxiety' (measured by the LSAS) and the 'frequency of using distraction' [measured by the distraction subscale of TCQ (TCQ-D)]. Similarly, to investigate the influential factors of emotion regulation using the reappraisal strategy, we performed another multiple linear regression on the rating of emotional valence in the reappraisal block. The following variables were selected as predictors: 'gender', 'TMS manipulation' (VLPFC activated: 1 and DLPFC/vertex activated: 0), 'depression', 'trait anxiety', 'social anxiety' and the 'frequency of using reappraisal' [measured by the reappraisal subscale of the TCQ (TCQ-R)].

Table 2. Linear regression for the rating of emotional valence during distraction

Predictor	β[a]	t	P
Gender	0.030	0.502	0.616
TMS manipulation	0.195	3.361	0.001
Depression	0.085	1.031	0.304
Trait anxiety	−0.081	−0.977	0.329
Social anxiety	−0.093	−1.349	0.178
Frequency of using distraction	0.139	2.370	0.018

[a] β is the standardized coefficient.
Bold *P* value indicates significant result.

Results

Rating of emotional valence

The main effect of the 'regulation type' was found to be highly significant ($F(2174) = 157.5$, $P < 0.001$, $\eta_p^2 = 0.357$): participants rated their emotions more positively in the distraction (4.82 ± 1.12) and reappraisal blocks (4.86 ± 1.10) when compared to the no-regulation block (3.88 ± 1.16, $P < 0.001$), whereas the emotion valence between the reappraisal and distraction blocks did not differ ($P = 1.000$). Additionally, there was a significant main effect of the 'TMS group' ($F(2284) = 5.0$, $P = 0.007$, $\eta_p^2 = 0.034$): participants rated their emotions more positively in the DLPFC (4.64 ± 1.01, $P = 0.017$) and VLPFC groups (4.63 ± 1.45, $P = 0.021$) when compared to the control TMS group (4.27 ± 1.10), whereas the emotion valence between the two active TMS groups did not differ ($P = 1.000$).

More importantly, we observed a two-way interaction between 'TMS group' × 'regulation type' ($F(4568) = 9.5$, $P < 0.001$, $\eta_p^2 = 0.063$; Figure 2). A simple effects analysis indicated that, while participants in the three TMS groups rated their emotions more positively in the distraction and reappraisal blocks when compared to the no-regulation block ($P < 0.001$), the two emotion regulation blocks showed different patterns of results. Participants in the DLPFC-activated group reported more positive emotion in the distraction than in the reappraisal block ($F(2283) = 46.1$, $P < 0.001$, $\eta_p^2 = 0.246$; distraction *vs* reappraisal $= 5.14 \pm 0.83$ *vs* 4.77 ± 0.85, $P < 0.001$). In contrast, participants in the VLPFC-activated group reported more positive emotions during the reappraisal block than during the distraction block ($F(2283) = 72.5$, $P < 0.001$, $\eta_p^2 = 0.339$; distraction *vs* reappraisal $= 4.74 \pm 1.42$ *vs* 5.26 ± 1.23, $P < 0.001$). However, no significant difference was observed between the reappraisal and distraction blocks in the control group ($F(2283) = 30.9$, $P < 0.001$, $\eta_p^2 = 0.179$; distraction *vs* reappraisal $= 4.57 \pm 0.95$ *vs* 4.54 ± 1.07, $P = 1.000$).

In the distraction block, the linear regression on the rating of emotional valence revealed that two variables are associated with the emotion regulation during distraction ($R = 0.276$, $F(6280) = 3.8$, $P = 0.001$; Table 2): (i) the TMS-activated DLPFC resulted in more positive emotional ratings and (II) individuals using distraction more frequently rated their emotions more positively. In the reappraisal block, the linear regression on the rating of emotional valence revealed that three variables are associated with the emotion regulation during reappraisal ($R = 0.372$, $F(6280) = 7.5$, $P < 0.001$; Table 3): (i) the TMS-activated VLPFC resulted in more positive emotional ratings, (II) individuals using reappraisal more frequently rated their emotions more positively

Table 3. Linear regression for the rating of emotional valence during reappraisal

Predictor	β	t	P
Gender	0.002	0.029	0.977
TMS manipulation	0.270	4.800	<0.001
Depression	0.091	1.150	0.251
Trait anxiety	−0.076	−0.950	0.343
Social anxiety	−0.185	−2.833	0.005
Frequency of using reappraisal	0.155	2.716	0.007

Bold *P* value indicates significant result.

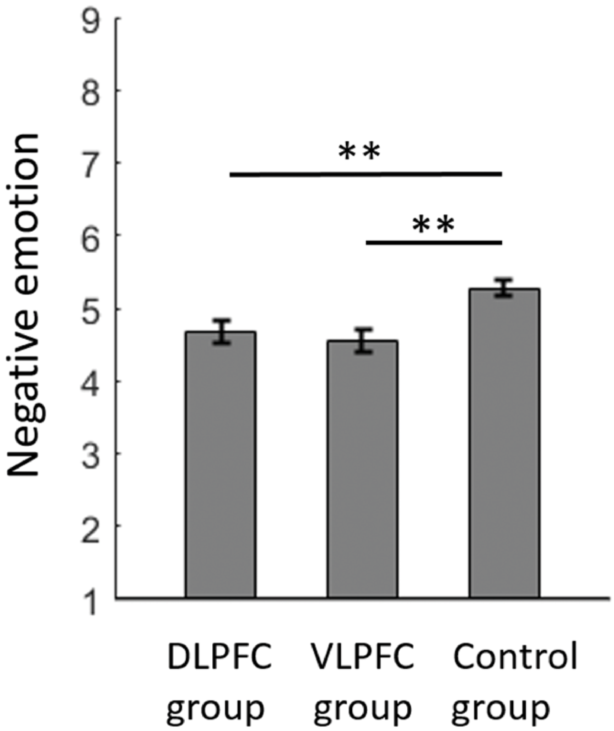

Fig. 3. Post-task ratings of negative emotions. A 1-to-9-point scale was used, with higher scores indicating more negative feelings toward the social exclusion pictures (1 for the least negative and 9 for the most negative). Bars represent the SEM. **$P < 0.010$.

and (III) individuals with a high level of social anxiety tended to report more negative emotions after reappraisal.

Post-task rating of negative emotions

Half an hour after the main task, the effect of the 'TMS group' was found to be significant ($F(2284) = 7.4$, $P = 0.001$, $\eta_p^2 = 0.049$): the negative feelings reported by both the DLPFC-activated group (4.67 ± 1.55, $P = 0.009$) and the VLPFC-activated group (4.54 ± 1.44, $P = 0.001$) were weaker than those reported by the control TMS group (5.28 ± 1.17, Figure 3).

Discussion

This study employed a large sample to explore, in a real social interactive scenario, whether different lateral prefrontal cortical regions play relatively specific roles in explicit downregulation of social pain via reappraisal and distraction strategies. Our results confirmed the hypothesis: while facilitating both the VLPFC and DLPFC effectively relieved social pain, the TMS-activated DLPFC group had a better regulation effect in the distraction condition, whereas the TMS-activated VLPFC group had a better regulation effect in the reappraisal condition. In addition, the linear regression model revealed that the effect of emotion regulation was also associated with individual habitual use of distraction and reappraisal.

Our finding supported the causal role of both the DLPFC and VLPFC in downregulating negative emotions, irrespective of either the distraction or reappraisal strategy. The cognitive neuroscientific model of emotion processing (Etkin *et al.*, 2015) proposed that while automatic or implicit emotion regulation depends mainly on the medial (especially the ventral medial) PFC, voluntary and explicit emotion regulation recruits the lateral PFC to a large extent (i.e. the VLPFC and DLPFC). Numerous studies have suggested that both the VLPFC and DLPFC are key cortical regions involved in voluntary emotion regulation (Ochsner *et al.*, 2012; Dörfel *et al.*, 2014; Kohn *et al.*, 2014; Morawetz *et al.*, 2017). In the specific scenario of social pain (i.e. the interest of this study), Eisenberger *et al.* (2003) first found using fMRI that the rVLPFC activation was negatively correlated with the intensity of experienced social pain. Thereafter, this finding has been replicated in several fMRI studies (Onoda *et al.*, 2010; Masten *et al.*, 2011a). Similar to the VLPFC, increased DLPFC activation has been associated with decreased social pain (Nishiyama *et al.*, 2015; Morese *et al.*, 2019). For example, Koban *et al.* (2017) found in a placebo study that the activations of both the VLPFC and DLPFC could predict positive emotion after social exclusion. While these fMRI studies consistently correlated both the VLPFC and DLPFC with automatic/implicit emotion regulation, the current study gives direct causal evidence for the participation of the VLPFC and DLPFC in voluntary, explicit emotion regulation.

The most essential finding of this study was the relatively specific functions of the DLPFC and VLPFC in facilitating distraction and reappraisal, respectively. In particular, we found that the TMS-activated DLPFC has a greater beneficial effect during distraction, while the activated VLPFC has a greater beneficial effect during reappraisal. This finding is consistent with previous fMRI studies, showing that reappraisal and distraction, specifically and separately, recruit the VLPFC and DLPFC, respectively (Dörfel *et al.*, 2014; Moodie *et al.*, 2020). It is noteworthy that the current result generalizes our previous empathy-dependent finding (Zhao *et al.*, 2021) into situations where first-hand social pain was directly experienced. This direct emotion-inducing method excluded confounding factors such as empathic concern, picture interpretation and imagination abilities. Although many studies found overlapped affective experience system (including the anterior cingulate cortex, anterior insula and amygdala) and emotion regulation system (mainly located in the prefrontal cortices) when participants either experience actual social pain themselves or observe the experience of social pain in other people (Beeney *et al.*, 2011; Novembre *et al.*, 2015; Zaki *et al.*, 2016), some neuroimaging studies revealed that the experiences of 'first-hand' and 'second-hand' negative feeling or pain involve different brain regions: while the direct experience of pain evoked stronger activation of the medial cingulate cortex, dorsal medial PFC, supplementary motor area and somatosensory cortex, seeing another person in pain involved stronger activation of the pars opercularis of inferior frontal gyrus (located in the VLPFC) (Lamm *et al.*, 2011). For instance, the study of Novembre *et al.* (2015) not only supported overlapped neural substrates for directly experienced social pain and empathy for social pain but also revealed that seeing another person being socially excluded additionally recruited superior orbitofrontal gyrus and supramarginal gyrus. In this study, we let participants experience direct social pain and found the same separative functions of the DLPFC and VLPFC for distraction and reappraisal, as observed in the social pain empathy study of Zhao *et al.* (2021). Furthermore, the large sample size enhanced the reliability of this finding. Therefore, we are now confident in the double dissociation proposal of the lateral PFC in emotion regulation: the DLPFC engages more during distraction and the VLPFC engages more during reappraisal, irrespective of first- or second-hand negative experiences.

Distraction relies on attentional control to shift attention from emotional stimuli to irrelevant neutral events (Kanske *et al.*, 2011). The DLPFC is associated with cognitive control (Dolcos and McCarthy, 2006; Dolcos *et al.*, 2011; Rosero Pahi *et al.*, 2020) and is widely recognized as a key brain region involved in the attentional network (Hauer *et al.*, 2019). During distraction, the DLPFC disengages attention from negative information and maintains attention to appropriate aspects of the current scenario according to the goal of emotion regulation (De Raedt *et al.*, 2010). In addition, reallocating attention during distraction requires the DLPFC together with the anterior cingulate cortex and parietal lobe to monitor and resolve conflicts between regulation goals and existing emotional responses (Dörfel *et al.*, 2014; Comte *et al.*, 2016). Unlike distraction, cognitive reappraisal modulates subcortical emotional responses by altering semantic representations of emotional situations (Buhle *et al.*, 2014; Messina *et al.*, 2015). The VLPFC is related to semantic memory and evaluation during emotion regulation to generate a goal-consistent interpretation of the current scenario (Ochsner *et al.*, 2012; Messina *et al.*, 2015; Morawetz *et al.*, 2016, 2017, 2020). Additionally, the implementation of reappraisal demands inhibitory control associated with the VLPFC to suppress inappropriate interpretation that is contradictory to the emotion regulation goal (Dörfel *et al.*, 2014; Kohn *et al.*, 2014; Helion *et al.*, 2019). Therefore, while the DLPFC plays a more pivotal role in distraction, the VLPFC plays a more critical role in cognitive reappraisal.

Someone might doubt that we used a fixed order of blocks in the emotion regulation task, i.e. the no-regulation block always ran before the reappraisal/distraction blocks. This design could avoid carry-over effects of emotion regulation instructions and has been employed by many previous studies (e.g. Krompinger *et al.*, 2008; Troy *et al.*, 2013; He *et al.*, 2018, 2020a,b; Zhao *et al.*, 2021; Li *et al.*, 2022). However, it may introduce a time confound for the TMS effect, given that the TMS effect attenuated over time (accompanied by the frequency and fatigue effects increased over time). Thus, the impact of the TMS may be stronger for the no-regulation block than the reappraisal/distraction blocks; that is, the TMS effect on reappraisal and distraction might be underestimated in this study. Nevertheless, we want to argue that the main finding of this study (i.e. the double dissociation of the lateral PFC in reappraisal and distraction) could not be driven by the time confound due to the fixed order of the no-regulation block because we well counterbalanced the order of the reappraisal and distraction blocks across the participants. Moreover, one recent study in our laboratory (Yuan *et al.*, 2023) used both a fixed and random order of the no-regulation and regulation blocks, which did not find significant differences in the results between the two designs.

Our findings have therapeutic implications for emotional dysregulation since we provide a clear empirical rationale for improving emotion regulation capabilities by activating either the DLPFC (combined with distraction training) or the VLPFC (combined with reappraisal training). Furthermore, we observed the correlation between individual characteristics and emotion regulation; that is, participants who used reappraisal or distraction more frequently in daily life showed more beneficial regulation outcomes when employing the corresponding strategies. The result is consistent with previous behavioral (Mauersberger *et al.*, 2018; Roos and Bennett, 2023) and neuroimaging studies (Kanske *et al.*, 2012; Brudner *et al.*, 2018), showing that habitual use of reappraisal or distraction strategies is associated with reduced negative mood and decreased activation of the amygdala. Our result suggests that it is helpful to train patients with different disorders to habitually employ proper emotion regulation strategies in their daily lives. For instance, reappraisal is considered a suitable strategy to help patients with post-traumatic stress disorder to eliminate unwanted invasive flashbacks (Bryant *et al.*, 2021), whereas distraction is usually suggested to serve as a first-aid tool for depressed patients to rapidly attenuate downcast moods (Smoski *et al.*, 2014). In addition, we found that an individual's social anxiety score correlated with emotion regulation outcome in the reappraisal condition, which is in line with clinical studies showing that symptom severity of social anxiety disorder (SAD) correlated with both elevated negative feelings during reappraisal (Goldin *et al.*, 2009; Dixon *et al.*, 2020) and reduced activation of the prefrontal emotion control network (Jacob *et al.*, 2019). Our finding indicates that the deteriorative reappraisal ability might be a characteristic of SAD (see Dryman and Heimberg (2018) for a review) and that it is promising to improve the emotion regulation ability of SAD patients by activating the VLPFC combined with reappraisal training. Finally, our result showed a delayed TMS effect that lasted for at least 45 min after the single TMS session. Beyond this finding, we suggest future studies explore multiple-session TMS protocols to obtain long-term benefits in clinical people.

Two limitations should be noticed when interpreting the current findings. First, this study used the International 10/20 electroencephalogram system to locate the TMS coil. We suggest future studies employ an image-guided neuronavigational system to identify individualized stimulation sites so as to increase the precision of coil location (e.g. Douw *et al.*, 2020; Cash *et al.*, 2021; Feng *et al.*, 2022). Typically, a meta-analysis (Beynel *et al.*, 2019) showed that individualized fMRI guidance increased targeting efficacy by a factor of 10 over scalp-based targeting methods. Second, it is worth noting that this study focused on the right hemisphere of the DLPFC and VLPFC during emotion regulation in healthy individuals, while those diagnosed with certain psychiatric disorders such as depression show hypoactivation in their left prefrontal cortices (see Rive *et al.* (2013) for a review). Clinically, using TMS to activate the left DLPFC has been proved to be effective for treating depression (see Perera *et al.* (2016) for a review). Future studies are suggested to examine and compare the benefits in emotion regulation by modulating the left (e.g. our recent study of Li *et al.*, 2023), right or bilateral prefrontal cortices of psychiatric patients using TMS.

In summary, this study evoked directed experienced social pain in participants and successfully provided solid evidence for the double dissociation of the DLPFC and VLPFC in distraction and reappraisal. A final note is that the dissociable neural representation model is a relative frame; that is, the DLPFC contributes relatively more than the VLPFC to distraction, whereas the VLPFC contributes relatively more than the DLPFC to reappraisal. We should keep in mind that both the lateral PFC regions are important for the two regulation strategies. Furthermore, considering the complexity of the emotion regulation network, future work needs to investigate other brain regions besides the DLPFC/VLPFC so as to build a sophisticated neural model of emotion regulation, including the lateral and medial PFCs, supplementary motor areas and parietal and temporal regions.

Data availability

The data and code of this study would be available upon reasonable request and with the approvals of the Institute of Brain and Psychological Sciences, Sichuan Normal University. More information on making this request can be obtained from the corresponding author.

Author contributions

D.Z., L.M. and S.L. designed research; L.M., S.L., S.C., Y.L. and F.X. performed the experiment; D.Z. and L.M. analyzed the data and D.Z., L.M. and S.L. wrote the paper.

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Conflict of interest

The authors declared that they had no conflict of interest with respect to their authorship or the publication of this article.

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