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The right VLPFC and downregulation of social pain: A TMS study

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Abstract

Previous studies have demonstrated that the right ventrolateral prefrontal cortex (RVLPFC) is crucially involved in downregulating physical and social pain. However, it remains unclear whether the RVLPFC is more specific to either physical or social pain. The present study compares the role of RVLPFC in emotion regulation in physical- and social-pain conditions using repetitive transcranial magnetic stimulation (rTMS). A total of 60 healthy participants underwent active (n = 30) or sham (n = 30) rTMS over the RVLPFC. Following each TMS session, participants performed a non-reappraisal and then a reappraisal task to downregulate imagined physical or social pain evoked by pictures. Self-reported negative emotional ratings and electroencephalogram data were recorded during the emotion regulation task. Participants were then required to rate the valence and arousal of those pictures 30 min after the task. It is found that rTMS-activated RVLPFC led to reductions in subjective negative feelings and amplitudes of the late positive potential during reappraisal; however, these effects were found exclusively in the social-pain condition. Participants also reported higher positive valence for socially, compared to physically, painful pictures after 30 min of the task. Behavioral and electrophysiological evidence both supported the functional specificity of RVLPFC in regulation of social pain. The prominent delayed effect of rTMS makes it possible to consider the potential application of rTMS-VLPFC in clinical practice for social pain relief.

KEYWORDS

emotion regulation, event-related potential, physical pain, social pain, transcranial magnetic stimulation, ventrolateral prefrontal cortex

1 | INTRODUCTION

Social pain refers to a painful experience associated with actual or potential damage to desired social connections (Eisenberger, 2012, 2015). Social pain not only strongly threatens basic human needs such as belonging, control, and meaningful existence (Williams, 2007; Zadro, Williams, & Richardson, 2004), but also decreases prosocial behavior (Twenge, Baumeister, DeWall, Ciarocco, & Bartels, 2007) while increasing aggression (Richman & Leary, 2009; Twenge, Baumeister, Tice, & Stucke, 2001), thus leading to low self-esteem,

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depression or alienation (Onoda et al., 2010; Wang, Braun, & Enck, 2017; Williams, 2007). To mitigate the distressing feelings and negative effects elicited by social pain, effective emotion regulation is a helpful and easily feasible solution (Gross, 2002; He et al., 2018; He, Liu, Zhao, Elliott, & Zhang, 2019).

The emotion regulation of social pain crucially depends on the ventrolateral prefrontal cortex (VLPFC), especially its right portion (RVLPFC, Riva & Eck, 2016; Vijayakumar, Cheng, & Pfeifer, 2017). A wealth of evidence suggests that the RVLPFC could function via a self-regulatory mechanism by disrupting social pain distress (Eisenberger, Lieberman, & Williams, 2003; Masten et al., 2009; Onoda et al., 2010). This implicit function of RVLPFC in regulation of social pain has been causally demonstrated by studies using transcranial direct current stimulation (tDCS): anodal excitement of RVLPFC reduced social pain and behavioral aggression caused by social exclusion or romantic rejection (Hsu et al., 2015; Riva, Romero, Dewall, & Bushman, 2012; Riva, Romero, DeWall, Chester, & Bushman, 2015), while cathodal inhibition of RVLPFC increased social pain (Riva, Romero, Vergallito, DeWall, & Bushman, 2015). To address directly whether RVLPFC causally regulates social pain, our previous tDCS studies used an explicit emotion regulation task and provided direct evidence for the role of RVLPFC in emotion regulation of social pain (He et al., 2018, 2019).

However, the specificity of the RVLPFC in regulating social pain is still unclear, as this brain region is also involved in emotion regulation of physical pain (Lieberman et al., 2004; Wiech, Ploner, & Tracey, 2008). Physical pain and social pain induce similar psychological responses (Eisenberger, 2012). Previous studies have demonstrated that emotion experience of physical and social pains activates overlapping but also distinct brain regions (Eisenberger, 2012; Eisenberger & Lieberman, 2004; for a review, see Woo et al., 2014). For emotion regulation, however, very limited knowledge is available regarding shared or distinct regulatory networks for physical vs. social pain. In a recent study, Koban, Kross, Woo, Ruzic, and Wager (2017) compared placebo effects on physical and social pain, which found that the VLPFC was involved in mediating placebo effects in the condition of social pain and that enhanced activation of this brain region was predictive of positive affect ratings after social rejection. The main purpose of the current study is to directly test the functional specificity of RVLPFC, that is, whether the emotion regulation function of RVLPFC is more specific to social pain or equally applicable to both physical and social pain.

In addition, all the above-mentioned manipulation studies[1]employed tDCS to demonstrate the role of RVLPFC in regulating social pain. It is well known that tDCS has a limited spatial focality resolution (Keeser et al., 2011), which makes it difficult to provide convincing causal link between the targeted brain region and specific psychological processes (Filmer, Dux, & Mattingley, 2014). To overcome this drawback, the current study used repetitive transcranial magnetic stimulation (rTMS) to modulate the neural activation of RVLPFC. Compared to tDCS, rTMS offers more focused electric field and increased effectiveness, which makes it more widely used in clinical practice (Valero-Cabre, Amengual, Stengel, Pascual-Leone, & Coubard, 2017).

This study employed two indices to measure emotion regulation effects. The first is the subjective rating of negative emotion levels (see also He et al., 2018, 2019; Ochsner et al., 2004). The second is an event-related potential (ERP) component. The late positive potential (LPP) provides an objective measure of the emotion regulation effect (Liu, Huang, McGinnis-Deweese, Keil, & Ding, 2012). It has been suggested that downregulating of negative emotional feelings reliably reduces LPP amplitudes (e.g., Schönfelder, Kanske, Heissler, et al., 2013; for a summary, see Hajcak, MacNamara, & Olvet, 2010). As this ERP component reflects facilitated perception of and attention to emotional stimuli (Liu et al., 2012; Schupp, Junghofer, Weike, & Hamm, 2004), the decreased LPP after emotion regulation may indicate reduced emotional responses due to cognitive control of prefrontal regulatory networks (Dennis & Hajcak, 2009; Ochsner & Gross, 2005).

It has been reported that Cognitive Behavioral Therapy increased pain-evoked neural activity in VLPFC, which may indicate that the effects of cognitive interventions originate in this region (Jensen et al., 2012). To probe the potential efficacy of TMS-RVLPFC to clinical practice, this study tested not only the immediate, but also the delayed effect of rTMS on emotion regulation. In line with our previous study (He et al., 2018, 2019), we chose cognitive reappraisal as the emotion regulation strategy due to its wide application (Buhle et al., 2014) and relatively long-lasting regulation effects compared with other emotion regulation strategies such as expressive suppression and distraction (Kross & Ayduk, 2008; Ochsner & Gross, 2005; Ochsner, Silvers, & Buhle, 2012; Webb, Miles, & Sheeran, 2012). According to previous findings (Koban et al., 2017), this study hypothesized that rTMS-activated RVLPFC would produce a larger beneficial effect of emotion regulation for social pain compared to physical pain. Considering that cognitive reappraisal could decrease the LPP amplitudes (Schönfelder et al., 2013; Wyczesany & Ligeza, 2017), we hypothesized that the rTMS effect would be associated with not only lower negative emotional ratings but also reduced LPP amplitudes when participants downregulate their negative emotions in the social pain compared to physical pain condition. Given the emerging research showing the prominent delayed effects of rTMS (Thut & Pascual-Leone, 2010; Valero-Cabre et al., 2017), we also hypothesized that the effect of VLPFC-enhanced emotion regulation would maintain for some period of time (e.g., 30 min).

2 | METHODS

2.1 | Participants

A total of 60 healthy college students (right handed) were recruited from Shenzhen University. They were randomly assigned into the active or sham TMS groups. None of them had any prior experience with TMS before the experiment. One subject failed to complete the experiment due to discomfort with the TMS. As a result, 29 (12 female, age = 21.5 ± 2.2 year) and 30 (13 female, age = 21.3 ± 1.8 year) were include in sham and active TMS groups respectively. There were no significant differences in age ($t[57] = 0.35$, $p = .723$) or gender

(χ^2 = 0.02, p = .879) between the two groups. The study was approved by the Ethics Committee of Shenzhen University. Informed consent was signed by participants before the experiment.

2.2 | Stimuli

Experimental materials were 120 pictures (60 for social pain and 60 for physical pain; Figure 1a). The social pain pictures were selected from the social exclusion pictures used in our previous studies (He et al., 2018, 2019). The physical pain pictures were downloaded from the internet using the searching word "physical pain". The valence and arousal of material were rated on a 9-point scale by another 20 college students who were not participants in the experiment (valence: 1 for the most negative and 9 for the most positive; arousal: 1 for the least arousing and 9 for the most arousing). Their ratings indicated that no significant difference in either valence (social pain = 2.4 ± 0.9, physical pain = 2.5 ± 1.3; t[19] = −0.7, p = .462) or arousal (social pain = 3.7 ± 1.4, physical pain = 4.0 ± 1.3; t[19] = −1.9, p = .078) between the two categories of pictures. In addition, number of people in the pictures was counterbalanced between conditions. During the experiment, the images were presented in the center of the LCD screen with a viewing angle of 3.0 × 3.5°.

2.3 | Experiment design and procedure

The study was a 2 (*regulation type*: no-reappraisal vs. reappraisal) × 2 (*picture type*: social pain vs. physical pain) × 2 (*TMS group*: sham vs. active) design. The *regulation type* and *picture type* were within-subject factors and the *TMS group* was the between-subject factor.

This study used offline instead of online TMS procedure, that is, the rTMS sessions were performed at different time windows from the experimental tasks. This offline design was to reduce side effects (e.g., acoustic noise or muscle twitching) which might impact task performance. The experiment procedure is shown in Figure 1b. Each participant received two sessions of TMS. The first 15-min TMS session was given before the task. The second 15-min TMS session was given between passive view and reappraisal blocks. After the reappraisal stage, participants were allowed to relax for 30 min before rating the valence and arousal of the 120 pictures on a 9-point scale.

2.4 | Emotion regulation task

The task was divided into four blocks, corresponding to the four within-subject conditions. In order to avoid carry-over effects caused by the reappraisal instruction, the passive viewing task was always performed before the cognitive reappraisal task (see also He et al., 2018, 2019). The 60 physical pain images and 60 social pain images were randomly assigned to no-reappraisal and reappraisal blocks, that is, each block contained 30 images. The order of physical pain and social pain blocks was equal across the two TMS groups; and the order of the two kinds of blocks was counterbalanced within each TMS group. The four-block task took 28 min.

As is shown in Figure 1c, the trial began with a fixation (2 s) followed by image presentation for 8 s, during which participants were required to watch passively (no-reappraisal block) or downregulate

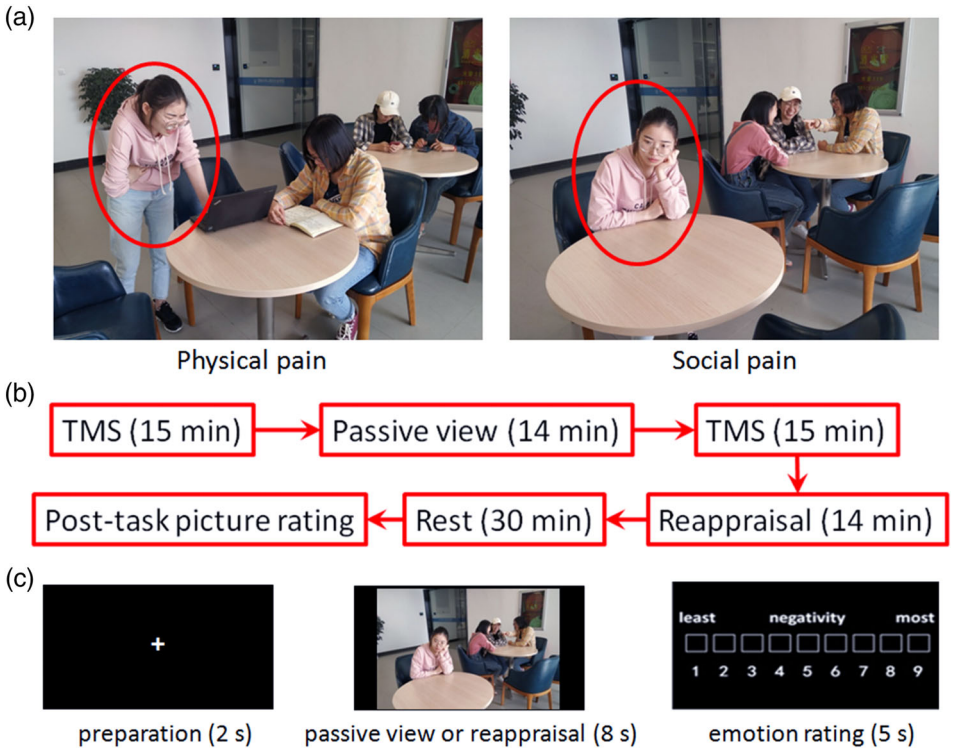

FIGURE 1 Experimental paradigm and sample images. (a) Sample images of physical pain and social pain. For the sake of copyright, the persons in the sample images are replaced by the graduate students in the research group. All the four persons in the picture gave their consent for the material to appear in academic journals. (b) Experiment procedure. (c) Stimulus presentation in one experiment trial

their negative emotions (reappraisal block). They were then asked to report their level of negative feeling on a 9-point scale (a high score indicated a high level of negativity) using a mouse.

When passively viewing physical pain images, participants were instructed as follows: "in this section, please think about how you would feel in a situation similar to that of the highlighted person in the picture." When reappraising physical pain images, participants were instructed as follows: "in this section, please imagine a better outcome or find a different explanation of the situation. For example, you could imagine that the wound is actually not as bad as you see or the doctor's help is on the way. After you re-interpret the nature of the scene, please think about how you would feel in this situation if you were the highlighted person in the picture."

When passively viewing social pain images, participants were instructed as follows: "in this section, please think about how you would feel in a situation similar to that of the highlighted person in the picture." When reappraising social pain images, participants were instructed as follows: "in this section, please image a better outcome or find a different explanation 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 re-interpret the nature of the scene, please think about how you would feel in this situation if you were the highlighted person in the picture."

2.5 | Repetitive transcranial magnetic stimulation (rTMS)

A figure-eight-shaped coil was connected to the magnetic stimulator (Yingchi, Shenzhen, China). The location of the coil was determined by the International 10/20 electroencephalogram system and the rVLPFC is at the F8 site. The subject's resting motor threshold (rMT) was measured at the motor cortex (the C4 site on the EEG cap) and the intensity was defined as 50% of the pulses reliably producing thumb twitches. The rTMS was applied at 10 Hz at 90% of the subject's rMT (see also Ahn, Kim, & Kim, 2013; Dlabac-de Lange et al., 2015; Pripfl, Tomova, Riecansky, & Lamm, 2014). Each 15-min session contained 30 trains (a total of 1,170 pulses); each train lasted for 3.9 s, separated by inter-train intervals of 26.1 s (De Raedt et al., 2010). For the sham TMS group, the coil was placed at a 90° angle to the head so that it did not induce any measurable electrical currents (Zwanzger et al., 2014). The TMS simulated electric field is illustrated on an adult brain model in Figure 2 (SimNIBS software, www.simnibs.org).

2.6 | EEG recording and analysis

EEG data were recorded using a 32-channel amplifier (Brain Products, Munich, Germany) with a sampling frequency of 250 Hz. Electrode impedances were kept below 5kΩ. The reference electrode was at FCz.

Data analysis was performed using Matlab R2011a (MathWorks, Natick, MA). Data were re-referenced to the average of the left and right mastoids. Ocular artifacts were eliminated using the independent component analysis. Then, the EEG data were filtered using a 0.01–30 Hz band-pass filter. The filtered data were segmented beginning 200 ms prior to the onset of the picture and lasting for 1,000 ms. The baseline-correction was based on the 200 ms prestimulus time window. Since this study was interested in emotion regulation, the ERP analysis focused on the LPP component, which was measured as the average amplitudes across the electrode sites of P3, P4, Pz, CP1, and CP2 within a time window of 400–1,000 ms post stimulus onset.

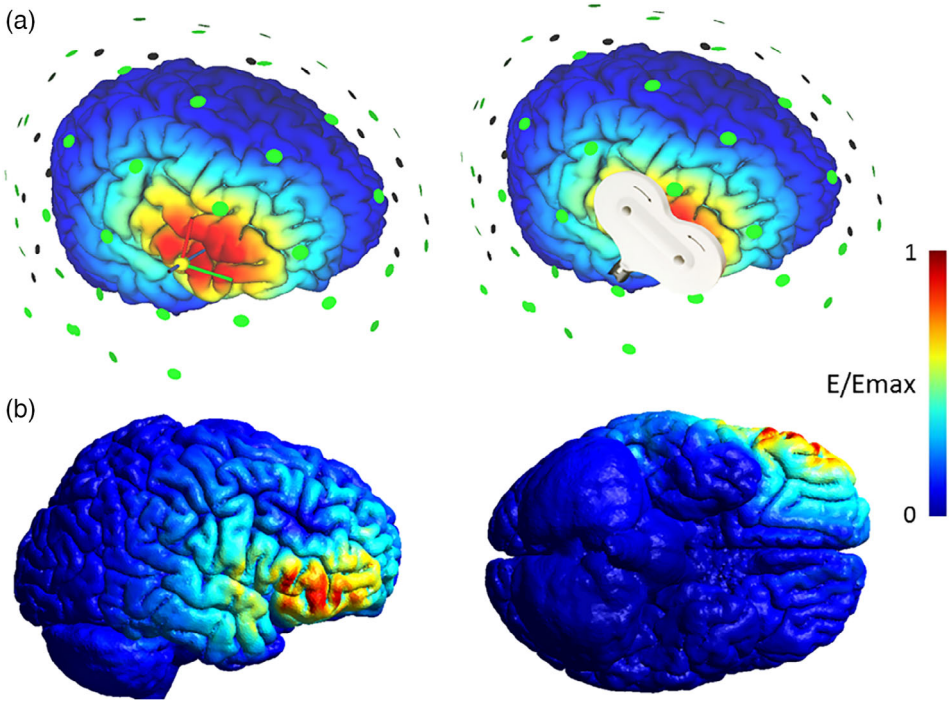

FIGURE 2 An illustration of TMS electric field using the SimNIBS. (a) The stimulation site and preview of the magnetic vector potential on the brain gray matter surface. The rTMS stimulation was delivered by a figure-of-eight coil at the F8 site of the International 10/20 EEG system. (b) Simulated electric field for the rTMS coil. The color represents electric field strength scaled from 0 (blue) to the individual maximum (red)

2.7 | Statistics

Statistical analysis was performed using SPSS Statistics 20.0 (IBM, Somers, USA). Descriptive data were presented as mean ± *SD*, unless otherwise mentioned. Repeated-measures ANOVA was performed on subjective ratings and LPP amplitudes, with *regulation type* and *picture type* as within-subject factors, and *TMS group* as a between-subject factor.

3 | RESULTS

3.1 | Rating of negative emotion

The main effect of *regulation type* was significant ($F(1,57) = 228.3$, $p < .001$, $\eta_p^2 = 0.800$): participants reported less negative feeling in the reappraisal (3.6 ± 1.3) compared to no-reappraisal block (5.5 ± 1.5). Also, there was significant two-way interactions between *TMS group* and *regulation type* ($F(1,57) = 8.5$, $p = .005$, $\eta_p^2 = 0.130$) as well as between *regulation type* and *picture type* ($F(1,57) = 5.0$, $p = .029$, $\eta_p^2 = 0.081$).

More importantly, we observed a three-way interaction of *TMS group* × *regulation type* × *picture type* ($F(1,57) = 4.2$, $p = .045$, $\eta_p^2 = 0.069$; Figure 3a). To interpret the three-way interaction, we defined a measure called *reappraisal advantage* as the differential rating between no-reappraisal and reappraisal blocks (see also He et al., 2019). As a result, the three-way interaction was simplified to a two-way interaction between *TMS group* and *picture type* ($F(1,57) = 4.2$, $p = .045$, $\eta_p^2 = 0.069$). Further simple effects analysis indicated that while the active TMS group showed a larger *reappraisal advantage* (2.7 ± 1.4) compared to the sham TMS group (1.6 ± 1.1) for the social pain pictures ($F(1,57) = 12.1$, $p = .001$, $\eta_p^2 = 0.176$), no significant group difference was observed for the physical pain pictures ($F < 1$; active vs. sham = 1.8 ± 1.1 vs.1.5 ± 1.4).

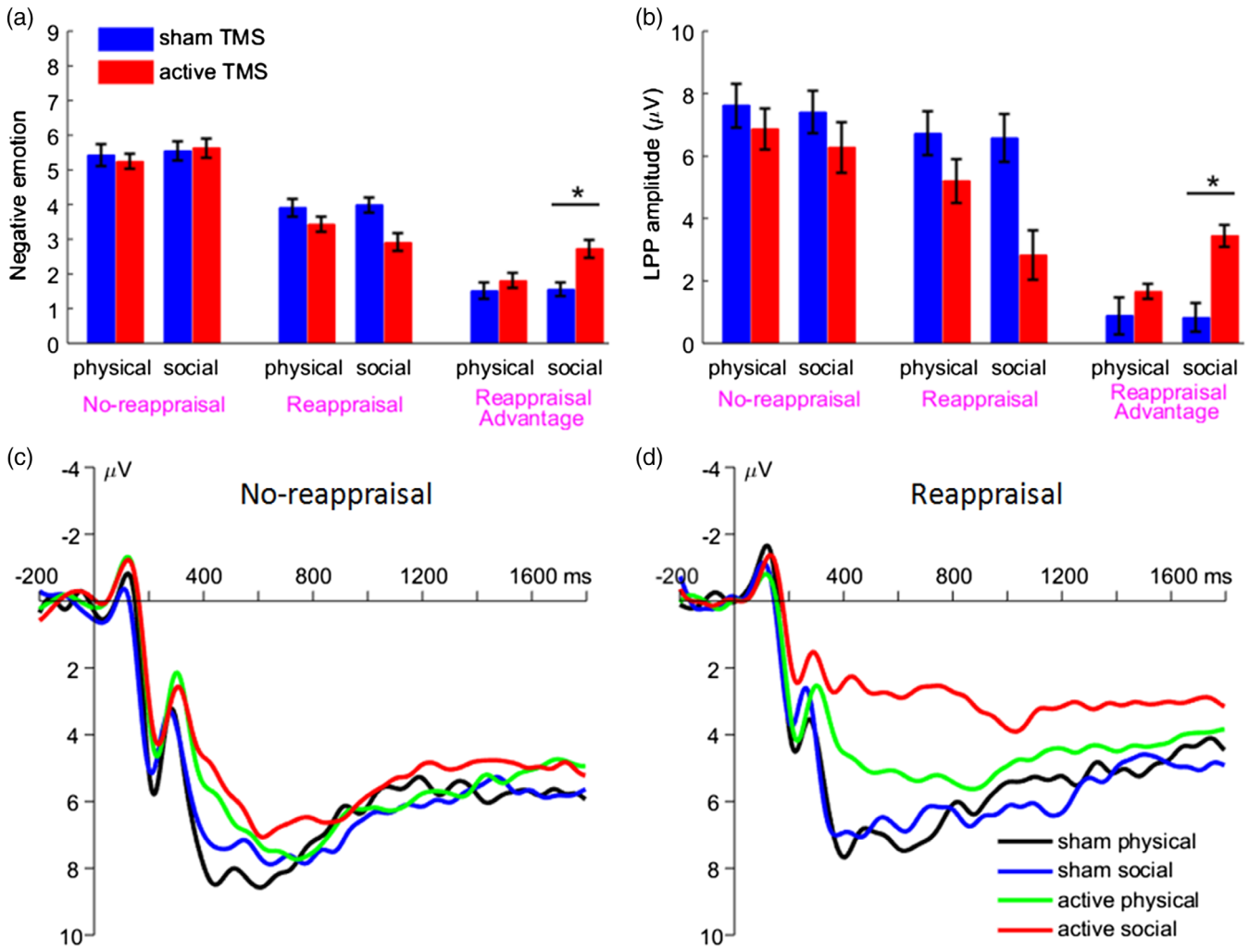

FIGURE 3 Negative emotion rating and LPP results. (a) The three-way interaction on ratings of negative emotion. A 9-point scale was used, with higher scores indicating higher levels of negative emotions. The "reappraisal advantage" denotes the rating difference between no-reappraisal and reappraisal blocks. (b) The bar diagram of LPP amplitudes (time window = 400 to 1,000 ms). (c) The grand-mean ERP waveforms across different conditions. The data were averaged from P3, P4, Pz, CP1, and CP2

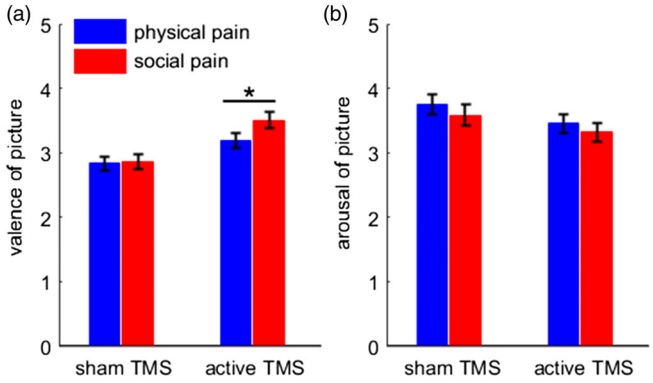

FIGURE 4 Post-task picture ratings using a 9-point scale. (a) The valence of pictures with higher scores indicating more positive of pictures (1 for the most negative and 9 for the most positive). (b) The arousal of pictures with higher scores indicating higher levels of arousal (1 for the least arousing and 9 for the most arousing)

3.2 | LPP amplitudes

The main effect of *regulation type* was significant ($F(1,57) = 64.5$, $p < .001$, $\eta_p^2 = 0.531$): the reappraisal block (3.8 ± 4.3 μV) evoked smaller LPP amplitudes than no-reappraisal block (4.7 ± 4.6 μV). The main effect of *picture type* was significant ($F(1,57) = 7.6$, $p = .008$, $\eta_p^2 = .118$): the LPP evoked by physical pain pictures (4.9 ± 4.6 μV) was larger than that evoked by social pain pictures (3.5 ± 4.2 μV). Also, we observed significant two-way interactions between *TMS group* and *regulation type* ($F(1,57) = 15.8$, $p < 0.001$, $\eta_p^2 = 0.217$) and between *TMS group* and *picture type* ($F(1,57) = 4.6$, $p = .036$, $\eta_p^2 = 0.075$).

More importantly, there was a three-way interaction of *TMS group* × *regulation type* × *picture type* ($F(1,57) = 4.5$, $p = .038$, $\eta_p^2 = 0.073$; Figure 3b,c). To interpret the three-way interaction, we calculated the measure *reappraisal advantage* as the differential LPP amplitudes between no-reappraisal and reappraisal blocks. As a result, the three-way interaction was simplified to a two-way interaction between *TMS group* and *picture type* ($F(1,57) = 4.5$, $p = .038$, $\eta_p^2 = 0.073$). Further simple effects analysis indicated that while the active TMS group showed a larger *reappraisal advantage* (3.4 ± 2.0 μV) compared to the sham TMS group (0.8 ± 2.5 μV) for the social pain pictures ($F(1,57) = 20.0$, $p < .001$, $\eta_p^2 = 0.260$), no significant group difference was observed for the physical pain pictures ($F(1,57) = 1.5$, $p = .231$; active vs. sham = 0.9 ± 3.2 vs. 1.6 ± 1.3 μV).

Significant correlations were found between LPP amplitude and rating of negative emotion (two-tailed Pearson correlations in four conditions of *regulation type* × *picture type*; $r = .350$ to $.439$, $p \leq .007$; $n = 59$).

3.3 | Post-task picture ratings

For the valence of pictures, the main effect of *TMS group* was significant ($F(1,57) = 11.2$, $p = .001$, $\eta_p^2 = 0.164$: the valence reported by the active TMS group (3.3 ± 0.7) was higher than that reported by the sham TMS group (2.8 ± 0.6). The main effect of *picture type* was also significant ($F(1,57) = 11.3$, $p = 0.001$, $\eta_p^2 = 0.165$): the valence of social pain pictures (3.2 ± 0.7) were reported higher than that of physical pain pictures (3.0 ± 0.6). More importantly, there was a significant interaction between *TMS group* and *picture type* ($F(1,57) = 8.4$, $p = .005$, $\eta_p^2 = 0.128$; Figure 4a): the valence of social pain pictures (3.5 ± 0.6) was rated higher than that of physical pain pictures (3.2 ± 0.6; $F(1,57) = 19.9$, $p < .001$, $\eta_p^2 = 0.259$) in the active but not in the sham TMS group (social vs. physical = 2.8 ± 0.6 vs. 2.8 ± 0.5; $F < 1$).

For the arousal rating, neither main effects nor interaction effects were significant ($F(1,57) \leq 2.7$, $p \geq .106$; Figure 4b).

Descriptive statistics of all the above-mentioned measures are listed in Table 1.

4 | DISCUSSION

The RVLPFC has been regarded as a key region involved in regulation of physical and social pain (Eisenberger & Lieberman, 2004; Lieberman et al., 2004). This study employed rTMS to examine the functional specificity of RVLPFC by directly comparing physical and social pain regulation. The immediate and delayed effects of rTMS on emotion regulation has been assessed. Beyond our previous study (He et al., 2018, 2019), we added the LPP as a neural index to

TABLE 1 Descriptive statistics of picture ratings and the amplitude of LPP component (mean ± *SD*)

		No-reappraisal task		Reappraisal task	
Measure	TMS group	Physical pain	Social pain	Physical pain	Social pain
Negative emotion	Sham	5.4 ± 1.7	5.5 ± 1.5	3.9 ± 1.4	4.0 ± 1.1
	Active	5.2 ± 1.2	5.6 ± 1.5	3.4 ± 1.2	2.9 ± 1.4
LPP amplitude (μV)	Sham	7.6 ± 3.8	7.4 ± 3.8	6.7 ± 3.8	6.6 ± 4.0
	Active	6.9 ± 3.6	6.3 ± 4.4	5.2 ± 3.9	2.8 ± 4.4
Post-task valence	Sham	2.8 ± 0.5		2.8 ± 0.6	
	Active	3.2 ± 0.6		3.5 ± 0.6	
Post-task arousal	Sham	3.7 ± 0.8		3.6 ± 0.9	
	Active	3.4 ± 0.8		3.3 ± 0.8	

objectively measure the emotion regulation effect. Results showed that rTMS-activated RVLPFC induced a successful emotion downregulation of social but not physical pain (lower negative emotional ratings and reduced LPP amplitudes); and this RVLPFC-enhanced effect on social pain regulation persisted 30 min following the reappraisal task. These findings support our hypotheses that participants with enhanced RVLPFC activity due to rTMS were more capable of reappraising social pain (compared to sham rTMS group) rather than physical pain.

The main finding that the self-reported social but not physical pain was effectively downregulated after RVLPFC rTMS procedure highlights the functional specificity of RVLPFC in emotion regulation of social compared to physical pain experiences. Results support and extend our earlier tDCS studies (He et al., 2018, 2019) which demonstrated that the RVLPFC is critical and shows functional specificity in social pain regulation without using physical pain as a baseline. The current finding is in accordance with previous literature, which found that the exclusive involvement of VLPFC in mediating the placebo effect of social pain, as compared to physical pain (Koban et al., 2017). Similar results have been obtained in another study showing that VLPFC was preferentially activated in processing social meaning in contrast to physical features of the objects (Tylen, Philipsen, Roepstorff, & Fusaroli, 2016). The functional specificity of VLPFC for social context has also been reported in nonhuman primates (Sliwa & Freiwald, 2017). In that study, the VLPFC was exclusively active during recognition of social interactions as opposed to physical interactions; this region was therefore indicated as part of the "exclusively social interaction network" (Sliwa & Freiwald, 2017). We reason that the rTMS-induced regulation effect on social pain rather than physical pain observed in our study might be driven by this "social stimuli preference" of RVLPFC. Previous neuroimaging studies found that there is a negative functional connectivity between the VLPFC and dorsal ACC (dACC) (Eisenberger et al., 2003) and that enhanced activation of the VLPFC is associated with more reduced experience of social pain compared with physical pain (Woo et al., 2014). Thus, we speculate that the rTMS-induced RVLPFC excitability in this study may strengthen the connectivity of dACC-VLPFC and facilitate the emotion reappraisal of social pain. However, verification of this idea needs further experiment employing rTMS coupled with neuroimaging techniques.

Unlike social pain regulation, however, physical pain regulation was not significantly improved by rTMS, probably because the RVLPFC is not the most important region of physical pain regulation. Instead, ventromedial PFC (VMPFC) has been highlighted as a critical prefrontal region in modulation of physical pain (Woo, Roy, Buhle, & Wager, 2015). Furthermore, the VMPFC has been proposed as one of the neurologic signatures of physical pain discriminating from social pain (Wager et al., 2013). A similar role has been also reported in DLPFC: tDCS and TMS studies demonstrated the causal role of DLPFC in physical pain regulation (Boggio, Zaghi, & Fregni, 2009; Graff-Guerrero et al., 2005); and the DLPFC, rather than VLPFC, activity was negatively correlated with physical pain (Lorenz, Minoshima, & Casey, 2003). In contrast, applying TMS on the left DLPFC showed no effect on self-reported social pain (Fitzgibbon et al., 2017). These studies together provide evidence that modulation of physical and social pain may recruit partially separated prefrontal networks while both types of pain might share overlapping affect-related pain regions such as dACC and anterior insula (Eisenberger, 2012, 2015; Eisenberger & Lieberman, 2004; Peyron, Laurent, & Garcia-Larrea, 2000).

Similar to the results of self-reported social pain, we also found a concomitant reduction of LPP amplitudes derived from rTMS-activated RVLPFC in the social but not physical pain condition. The LPP could be enhanced by social (Baddam et al., 2016; Crowley, Wu, Molfese, & Mayes, 2010) or physical (Fan & Han, 2008) painful stimuli and reduced by emotion downregulation (Hajcak et al., 2010). Thus, the LPP amplitude is usually used as an index of reduced emotional responses due to the recruitment of prefrontal resources associated with cognitive control (Dennis & Hajcak, 2009; Ochsner & Gross, 2005). In this study, it was found that the reduction of LPP magnitudes was more prominent in active compared to sham TMS group during reappraisal of social exclusion pictures, demonstrating that rTMS facilitated the emotion regulation of VLPFC and thus decreased the level of social pain. Therefore, the ERP finding provides electrophysiological evidence for the rTMS-induced improvement of social but not physical pain regulation.

Another important finding of the current study is that the rTMS-induced effect of social pain regulation persisted 30 min after the reappraisal task, as revealed by a more positive valance reported for social vs. physical pain pictures in the active TMS group. This result is consistent with evidence described in previous TMS reviews that the delayed effects of one or two sessions of rTMS last for an average period of 30 min and can extend up to 60 min post stimulation (Thut & Pascual-Leone, 2010; Valero-Cabre et al., 2017). Further studies will be needed to explore whether the effect persists for longer than 30 minutes, however the current study suggests potential feasibility of applying the rTMS on RVLPFC to relieve social pain in clinical practice.

Potential limitations of the current study should be mentioned when interpreting the results. First, we focused on imagined, rather than actual, pain. It is therefore possible that the selective effect of rTMS on social, but not physical, emotion regulation will be due to the fact that the imagining paradigm is less sufficient in eliciting physical pain, or that our findings might be explained more by empathy rather than emotion regulation. We argue that (a) empathy was involved in all conditions so the observed differences across conditions were less likely to be produced by empathy; (b) it was found that empathy for physical and social pain evoked very similar psychological responses (e.g., distress, anxiety, feeling of discomfort) and neural activation patterns as those evoked by directly experienced physical/social pain (Godinho, Magnin, Frot, Perchet, & Garcia-Larrea, 2006; Novembre, Zanon, & Silani, 2015); (c) a meta-analysis for physical pain studies demonstrated that the VLPFC is one of common brain regions associated with processing of both actually experienced pain and empathy for pain (Lamm, Decety, & Singer, 2011); and (d) the imagining paradigm used here has been proved to be an efficient way of assessing

the influence of emotion regulation (Ochsner et al., 2004; Wager, Davidson, Hughes, Lindquist, & Ochsner, 2008). However, since imagined pain involves only affective but not sensory components of pain (Singer et al., 2004), we acknowledge that the imagined physical and social pain could not produce exactly the same negative experience and brain response (e.g., activation of somatosensory cortices; Moisset & Bouhassira, 2007) as "first-hand" pain. We thus strongly encourage future studies to verify the findings of this study using designs evoking real-time pain experience (e.g., electrical shock for physical pain and Cyberball task for social pain). The second limitation of this study is that the location of TMS coil was relatively rough based on the 10–20 EEG system. An image-guided neuronavigation is highly recommended to location the coil in future studies. The third limitation is that we used a sham-stimulation method as the control group, participants in the active vs. sham groups may felt differently during the stimulation phase. We suggest future studies employ an alternative control method (e.g., target on a task-irrelevant brain region) and retest the findings of this study.

In sum, behavioral and electrophysiological evidence of this study highlights a more specific causal relationship between RVLPFC rTMS and reappraisal success of social pain compared to physical pain. This RVLPFC-enhanced effect on social pain regulation was sustainable even 30 min later. Our findings of the functional specificity of RVLPFC in social pain regulation and the durable delayed effect may open up the possibility of treating this brain region as a therapeutic target for social pain relief.

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CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest in relation to the subject of this study

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ENDNOTE

[1] Here we define "manipulation studies" as the studies using manipulation techniques (lesion, TMS, tDCS, etc). The other category is measurement study which employs measurement techniques such as single-unit recording, electroencephalogram (EEG) and functional magnetic resonance imaging.

DATA AVAILABILITY STATEMENT

The data and code of this study would be available upon reasonable request and with approvals of School of Psychology, Shenzhen University. More information on making this request can be obtained from the corresponding author.

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