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RESEARCH ARTICLE

# Functional specificity of the left ventrolateral prefrontal cortex in positive reappraisal: A single-pulse transcranial magnetic stimulation study

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## Abstract

Neuroimage studies have yielded evidence for a correlation between the left ventrolateral prefrontal cortex (VLPFC) and a specific type of cognitive reappraisal strategy, positive reappraisal. However, evidence is still lacking for a direct relation. We used single-pulse transcranial magnetic stimulation (TMS) over the left VLPFC at different time points to investigate the functional specificity of the left VLPFC in the success of positive reappraisal and the timing at which the left VLPC was involved in positive reappraisal. Fifteen participants engaged in a baseline experiment and in TMS experiments. All participants successfully reduced their negative emotional ratings using positive reappraisal in the baseline experiment. In the TMS experiments, participants performed the same task as in the baseline experiment but single-pulse TMS was applied over the left VLPFC at 300 ms or/and 3,300 ms after stimulus onset, as well as over the vertex as a control stimulation. Valence ratings of negative stimuli increased (unpleasantness reduction) when participants reappraised negative stimuli with TMS stimulation over the left VLPFC, regardless of the timing of the stimulation at 300 ms or/and at 3,300 ms after the stimulus onset, relative to the vertex stimulation and the baseline experiment. Our study provided evidence of the functional specificity of the left VLPFC in regulation of negative emotions using positive reappraisal. The left VLPFC was believed to be involved in different stages of positive reappraisal. The prominent facilitation effect of TMS over the left VLPFC makes it possible to consider potential applications in clinical practice for mood disorders.


**Keywords** Left ventrolateral prefrontal cortex · Functional specificity · Single-pulse TMS · Positive reappraisal

## Introduction

Cognitive reappraisal, one of the most important cognitive strategies of emotion regulation, aims to reinterpret the meaning of an emotional event or stimulus (Buhle et al., 2014; Foti & Hajcak, 2008; Gross & John, 2003; Hajcak & Nieuwenhuis, 2006; Ochsner & Gross, 2005). It encompasses a number of specific strategies that vary in how an individual reinterprets an emotional event (Shiota & Levenson, 2012). In most studies, detachment and positive reappraisal are commonly used to reappraise negative emotions (Ochsner & Gross, 2008; Ochsner et al., 2012). Detachment involves changing onepositive reappraisal are commonly used to reappraise negative emotions (event (he meaning of an emotional event or stimulus (sible ting negative situational aspects in a more positive light or on seeing potential positive outcomes of critical situations. Moreover, positive reappraisal was believed to be related to improved mental health and emotion

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regulation success (Nowlan et al., 2015). Both strategies are effective for emotion regulation, but they appear to depend on different neural correlates. For example, Ochsner et al. compasses (2012) found that positive reappraisal differentially called upon the ventral lateral prefrontal cortex implicated in response selection and inhibition while detachment recruited more regions in the right prefrontal and parietal cortex. Furthermore, D foun et al. (2014) directly compared the neural networks of the emotion regulation strategies of detachment, reinterpretation (which here refers to positive reappraisal), distraction, and expressive suppression, showing that, compared with the three other strategies, reinterpretation specifically recruited the left ventrolateral prefrontal cortex (VLPFC) and orbitofrontal gyrus in the downregulation of negative stimuli. A recent review conducted by Piction while detachment recruited more reg findings that greater activation in the left VLPFC and left superior temporal gyrus was associated with positive reappraisal in healthy controls. These studies yielded evidence that there was a special correlation between the left VLPFC and the deployment of positive reappraisal. However, evidence is still lacking that the left VLPFC contributes to functional specificity in positive reappraisal.

Until now, only a few studies have directly examined the link between the VLPFC and cognitive reappraisal using transcranial direct current stimulation (tDCS). For example, He et al. (2018) activated the right VLPFC with anodal tDCS while participants reappraised pictures of social exclusion and found they gave less negative emotion ratings than under sham stimulation. Marques et al. (2018) applied tDCS over the bilateral VLPFC and dorsolateral prefrontal cortex (DLPFC) in the downregulation and upregulation of negative emotions using cognitive reappraisal, finding that only the left VLPFC activated with anodal tDCS led to less negative valence of negative images, providing evidence that the left VLPFC was more associated with evaluation of negative stimuli relative to the DLPFC. These studies demonstrated that the VLPFC stimulation facilitated reduced negative emotion ratings via cognitive reappraisal, providing evidence for a direct link between the VLPFC and cognitive reappraisal. However, it was not clear which specific type of reappraisal strategy was used in their studies. Furthermore, tDCS has limited spatial focality resolution (Keeser et al., 2011), which prevents it from providing convincing causal links between the targeted brain region and specific psychological processes (Filmer et al., 2014). Therefore, it is hard to link the functional specificity of the left VLPFC with a specific type of reappraisal strategy (i.e., positive reappraisal). We need a more powerful technology to fill this gap.

More than tDCS, transcranial magnetic stimulation (TMS) has been demonstrated to be an effective method to test causal links between neural activity and cognitive function (see the review by Polanía, Nitsche, & Ruff, 2018). Importantly, it can assess the timing of engagement of the targeted brain region because of its excellent temporal resolution (Silvanto & Pascual-Leone, 2012). To our knowledge, there are no literature reports of the timing at which the left VLPFC is involved in positive reappraisal. Several event-related potential (ERP) studies measured how neural activity was modulated using the strategy of positive reappraisal. Their findings indicated that the process of positive reappraisal was temporally dynamic. For example, Moser et al. (2014) used this strategy to reappraise negative emotional stimuli and found that the frontal late positive potential (LPP) amplitudes from 750 ms were increased in the reappraisal condition relative to the maintain condition, and the parietal LPP amplitudes after 1,000 ms were reduced. Qi et al. (2017) found that this strategy modulated the frontal LPP from 700 ms and attenuated the central-parietal LPP from 1,300 ms. In our previous work (Cao, 2019), we also found that the central-parietal LPP amplitudes were reduced after 300 ms and after 3,300 ms poststimulus onset when participants used this strategy to reinterpret negative stimuli by predefined interpretations. These findings were in line with an implementation-maintenance model of cognitive reappraisal proposed by Kalisch (2009). This model suggested an early and late stage consisting of cognitive reappraisal. The early stage implemented the reappraisal strategy during the earlier time points of a reappraisal episode and the late stage maintained the strategy in working memory during later points, which indicated a recurrent process. Moreover, this meta-analysis indicated that frontal activation varied over a reappraisal episode. This leaves a question for us: whether the left VLPFC is involved in different stages of positive reappraisal?

Taken together, in the current study, we applied single-pulse TMS over the left VLPFC at different time points when individuals reappraised negative emotional stimuli using the strategy of positive reappraisal. We hypothesized that TMS stimulation over the left VLPFC would facilitate unpleasantness reduction in the down-regulation of negative emotions using the strategy of positive reappraisal based on previous tDCS studies (He et al., 2018; Marques et al., 2018).

## Materials and methods

### Participants

Fifteen healthy right-handed individuals participated in the study (male/female = 9/6; mean age = 23.53 ± 4.44; mean years of education = 15.93 ± 2.12). All participants were recruited from Shanghai University. Based on self-report, they had no history of neurological or psychiatric illness; none of them used psychoactive medication, and they had no history of substance or alcohol abuse. Each participant had normal or corrected-to-normal vision. All participants filled out the self-rating anxiety scale (SAS) and the self-rating depression scale (SDS). Based on their scores (SAS = 41.73 ± 2.57; SDS =

39.09 ± 1.85), they were not anxious or depressed. All of them were fully informed of potential risks of TMS experiments, and they then signed an informed consent form before the experiment and were paid for participation. The experimental protocol was approved by the Ethics Committee at Shanghai Mental Health Center. The study was conducted in accordance with the Declaration of Helsinki.

## Materials

We used the stimuli materials[1] described in Foti and Hajcak (2008). Seventy-five color images (50 negative, 25 neutral), size 260 x 195 pixels, were chosen from the International Affective Picture System (IAPS; Lang et al., 2005). The images were controlled for arousal and valence. The valence scale ranged from 1 to 9 with 1 = most negative and 9 = most positive. The arousal scale ranged from 1 to 9 with 1 = calm and 9 = aroused. The two image categories differed in valence (M = 5.05, SD = 1.21 for neutral; M = 2.82, SD = 1.64 for negative), $t(73) = 18.899$, $p < 0.001$, and arousal (M = 2.91, SD = 1.93 for neutral; M = 5.71, SD = 2.16 for negative), $t(73) = -17.071$, $p < 0.001$. Before each image, a brief description of the upcoming image was presented on an LCD-screen (17-inch), which aimed to help participants interpret the meaning of the stimulus. For the 25 neutral images, the description depicted the contents of the images in a neutral way. For the 50 negative images, two types of descriptions were presented: one type described the image in a negative way, whereas the others described the image in more neutral/positive terms. The complete lists of associated descriptions of all stimuli were described in Foti and Hajcak (2008).

The stimuli were presented on a color monitor using E-prime 2.0 stimulus presentation software (Psychology software tools, USA), at a viewing distance of approximately 70 cm, on the LCD-screen, with each image presented at a visual angle of approximately 400others described the image in more neuing was conducted in a sound-attenuated chamber.

## Procedure

At first, participants took part in a baseline experiment. They were instructed to perform a cognitive reappraisal task. Before the formal task, they were trained through several practice trials to ensure that they understood what they would do in the sequence of the task before the reappraisal task. After the training, they performed the cognitive reappraisal task. Next, participants who reappraised successfully in the baseline experiment (the definition of reappraisal success is described below in Section 2.3.2) participated in the following TMS experiments. The time interval between experiments was set to at least 1 week to reduce the familiarity of the task.

### Cognitive reappraisal task

The cognitive reappraisal task consisted of five blocks of 15 trials each. For all trials, participants were required to keep their eyes on the screen. Each block included three types of stimuli with five trials each: a neutral image depicted with a neutral description (neutral stimuli), and a negative image depicted with either a negative description (negative stimuli) or with a description framed in a neutral/positive way (reappraisal stimuli). For all trials, participants were instructed to interpret the image according to the description.

A complete experimental trial (as in Figure 1a) started with a black fixation cross in the center of a gray screen for 1 second, followed by a brief description of the upcoming image for 4 seconds. Following the description, a black fixation cross appeared again in the center of a gray screen for 1 second. An image was then displayed for 5 seconds against a gray background. After the offset of each image, participants rated the image on the dimensions of valence and arousal separately, with the range of the rating scale of 1-9. For valence, the rating of 1 stood for h a black fixation cross in the center of a gray screen for 1 second, followed by a brief description of the upcoming image for 4 seconds. Followin." The next trial began after participants completed the ratings. The sequence of the trials and the description that preceded each negative image within each block was randomized for each participant, and the order of the blocks was counterbalanced. Participants took a break of one minute between the blocks.

### Definition of reappraisal success

Previous research indicated that reappraisal success was defined as the decrease in the ratings of emotional experience (i.e., valence and arousal) when reappraisal was applied to negative images relative to when the negative images were watched only (Wager et al., 2008; Shiota and Levenson, 2009). In this study, we defined reappraisal success as the decrease in ratings of negative valence (valence ratings increase) and in ratings of arousal to reappraisal stimuli. For each participant engaged in the baseline experiment, we conducted paired *t*-tests of valence and arousal ratings between 25 negative trials and 25 reappraisal trials. If the valence ratings to reappraisal trials were significantly higher than valence ratings for negative trials ($p < 0.05$), and arousal ratings for reappraisal trials were significantly lower than arousal ratings

[1] The codes of the IAPS images used are as follows:

Negative - 1050, 1201, 1302, 1930, 2120, 2130, 2141, 2205, 2399, 2661, 2683, 2688, 2691, 2700, 2710, 2716, 2750, 2810, 3168, 3220, 3301, 6020, 6190, 6212, 6250, 6312, 6313, 6570.1, 6571, 6830, 6831, 8230, 9042, 9050, 9250, 9400, 9421, 9425, 9470, 9490, 9520, 9584, 9600, 9611, 9635.1, 9800, 9901, 9911, 9920, 9921.
Neutral - 2102, 2393, 2575, 2580, 2593, 5530, 5740, 7002, 7004, 7010, 7056, 7090, 7130, 7140, 7150, 7175, 7211, 7217, 7491, 7500, 7550, 7595, 7700, 7705, 7950.

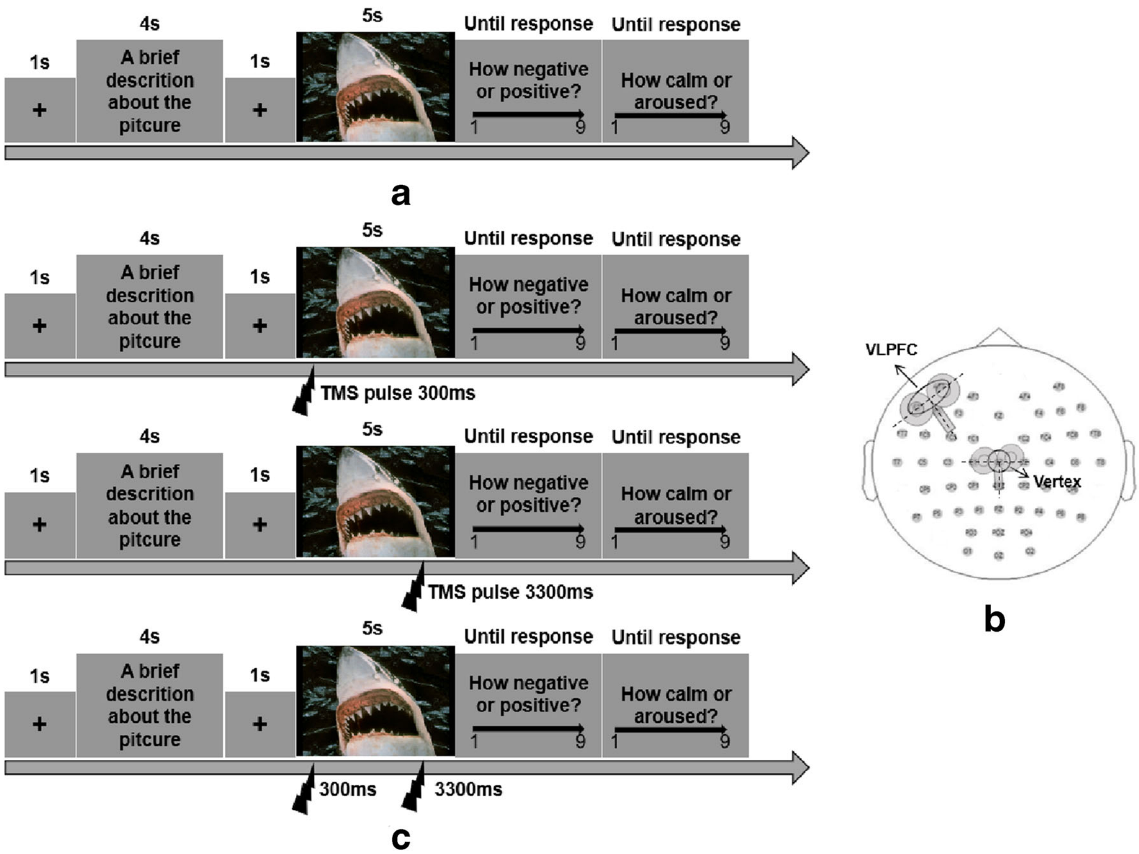


**Fig. 1** Example trials of the baseline experiment and the TMS experiments. **a** One example of the trial sequence in the cognitive reappraisal task in the baseline experiment. **b** Locations of the TMS coil for the targeted stimulation and the vertex stimulation. The targeted stimulation was applied between electrodes AF7 and F7. The vertex stimulation was applied on the Cz electrode. The TMS coil was tangential to the skull with the handle perpendicular to the gyrus. The dotted lines denote the orientations of the coil and the handle. **c** Example trials of the TMS experiments with different timing stimulations at 300 ms (top), 3,300 ms (middle), and double timing (middle). The TMS pulse was applied at 300 ms or/and at 3,300 ms.

for negative trials ($p < 0.05$), the strategy of using positive reappraisal was considered a success. This approach was validated in our previous work (Cao et al., 2020). All 15 participants reappraised successfully. They went on to perform the following TMS experiments.

### TMS experiment

Single-pulse TMS was delivered by a Magpro aisal was considered a success. This apprMN), using a hand-held figure-8 coil (MCF-DB80). Participantsand-held figure-8 coil (M (RMT) was measured using electromyography. Ag/AgCl surface electrodes were placed over the right abductor pollicis brevis. The optimal coil position was determined by moving the coil in 0.5-cm steps around the left motor cortex where the stimulation produced the largest motor-evoked potential (MEP) from the abductor pollicis brevis and reliable thumb twitches. The RMT was defined as minimum stimulus intensity that could elicit a MEP of at least 50 µb in 50% of pulses. Single-pulse TMS was applied at 90% of the individual RMT and the grand average of RMT was 36.8% ± 4.9%.

The TMS pulse was delivered over the left VLPFC when the participants performed the cognitive reappraisal task. The coil was positioned between electrodes AF7 and F7 (Weintraub-Brevda, 2017) since using the 10-20 system of electroencephalogram (EEG) electrodes for TMS positioning was applicable at low cost and could reach desired cortex regions reliably on a larger scale level (Herwig et al., 2003). In addition, we selected the vertex as a control stimulation site and the coil was positioned on electrode Cz (Jung et al., 2016; Olk et al., 2015). For both TMS sites, the TMS coil was located tangentially to the skull with the handle perpendicular to the gyrus, to direct the electric field perpendicularly to the gyrus shape. The location of the TMS coil is shown in Figure 1b. As in previous studies (Ferrari et al., 2018; Ku et al., 2015), participants wore earplugs during the TMS tasks to attenuate the influence of sounds evoked by the coil discharge.

Our previous work measured how neural activity was modulated using the same cognitive reappraisal task (Cao, 2019). Results showed that the central-parietal LPP amplitudes were attenuated from 300 ms and from 3,300 ms poststimulus in positive reappraisal. Based on our findings, we selected these two time points as the timing of TMS stimulation. All participants performed 6 TMS sessions (shown in Fig. 1c): 1) TMS stimulation over the left VLPFC at 300 ms (abbreviated as T300); 2) TMS stimulation over the left VLPFC at 3,300 ms (abbreviated as T3300); 3) TMS stimulation over the left VLPFC at sequence 300 ms + 3,300 ms (abbreviated as Tdouble); 4) TMS stimulation over the vertex at 300 ms (abbreviated as C300); 5) TMS stimulation over the vertex at 3,300 ms (abbreviated as C3300); and 6) TMS stimulation over the vertex at sequence 300 ms + 3,300 ms (abbreviated as Cdouble). Hereinafter, TMS stimulation over the left VLPFC is abbreviated as targeted stimulation and TMS stimulation over the vertex as vertex stimulation. The order of TMS sessions was counterbalanced across participants and the interval time between the sessions was at least one week.

### Statistical analysis

Valence and arousal ratings were examined as a function of the stimulus type. For the baseline experiment, we examined whether positive reappraisal successfully reduced the negative emotions elicited by negative stimuli. We performed repeated measures analysis of variance (RMANOVA) with a within-subject factor of Condition (neutral/negative/reappraisal) on both the valence and arousal ratings. For the TMS experiments, we examined how TMS stimulation over the left VLPFC at different time points affected both the valence and arousal ratings. RMANOVA was performed with three within-subject factors: Site (vertex/target), Time (300 ms/3,300 ms/double), and Condition (neutral/negative/reappraisal).

Simple effects analysis was performed if any interaction between factors was found. All analyses were conducted at the 0.05 level of significance. Multiple comparisons were corrected with Bonferroni correction. All statistical analyses were performed with SPSS 22.0.

## Results

### Positive reappraisal successfully reduced negative emotions

For the valence ratings in the baseline experiment (shown in Figure 2a), a significant effect of Condition, $F(2, 28) = 82.020$, $p < 0.001$, $\eta^2 = 0.854$, showed that reappraisal of negative stimuli increased the valence ratings relative to negative stimuli (reappraisal: 4.36 ± 0.79; negative: 2.58 ± 0.44; $p < 0.001$), whereas ratings of reappraisal stimuli were less positive than those of neutral stimuli (neutral: 5.30 ± 0.37; $p = 0.005$). The ratings of negative stimuli were more negative than those of neutral stimuli ($p < 0.001$).

For the arousal ratings (Figure 2b), a significant effect of Condition also was found, $F(2, 28) = 51.080$, $p < 0.001$, $\eta^2 = 0.785$). Reappraisal of negative stimuli attenuated the ratings relative to negative stimuli (reappraisal: 5.76 ± 0.84; negative: 6.96 ± 0.75; $p < 0.001$). The ratings of neutral stimuli (3.72 ± 1.58) were less arousing than those of negative stimuli ($p < 0.001$) and of reappraisal stimuli ($p < 0.001$). Taken together, participants successfully applied the strategy of positive reappraisal to negative stimuli.

### TMS over the left VLPFC facilitated reduction of negative emotions in positive reappraisal

(1) **Valence ratings**

A main effect of Condition, $F(2, 28) = 115.566$, $p < 0.001$, $\eta^2 = 0.892$, showed that reappraisal stimuli were rated as more positive than negative stimuli ($p < 0.001$) while reappraisal stimuli were rated as less positive than neutral stimuli ($p = 0.015$); the ratings of negative stimuli were more negative than those of neutral stimuli ($p < 0.001$). An interaction of Site*Condition was found, $F(2, 28) = 12.432$, $p < 0.001$, $\eta^2 = 0.47$. Importantly, a three-way interaction effect of Site*Time*Condition also was significant, $F(2, 28) = 4.285$, $p = 0.017$, $^2 = 0.234$. No other effects were found ($p > 0.05$). Figure 3a-c presents the valence ratings to neutral, negative, and reappraisal stimuli from the targeted and vertex stimulation across subjects and conditions.

To follow-up on the three-way interaction of Site*Time*Condition, RMANOVA was conducted with two within factors in the left factor.

- RMANOVA with two factors of Site*Time in each condition

The effect of Site in reappraisal condition showed that the ratings for the reappraisal of negative stimuli increased from the targeted stimulation relative to the vertex stimulation, $F(1, 14) = 12.305$, $p = 0.003$, $^2 = 0.468$. Moreover, the interaction effect of Site*Time was found, $F(2, 28) = 5.119$, $p = .026$, $^2 = 0.268$, while the simple effect analyses did not reach significance ($p > .05$). No Time effect was found ($p = .085$). For negative stimuli, the ratings from the vertex stimulation were less negative relative to those from the targeted stimulation, $F(1, 14) = 5.043$, $p = .041$, $^2 = 0.265$. No Time effect as well as the interaction effect was found ($p > .05$). For neutral stimuli, any effect of Site and Time was not significant ($p > .05$).

- RMANOVA with two factors of Time*Condition for each site

For the vertex stimulation, the main effect of Condition, $F(2, 28) = 93.362$, $p < 0.001$, $\eta^2 = 0.87$, showed that the

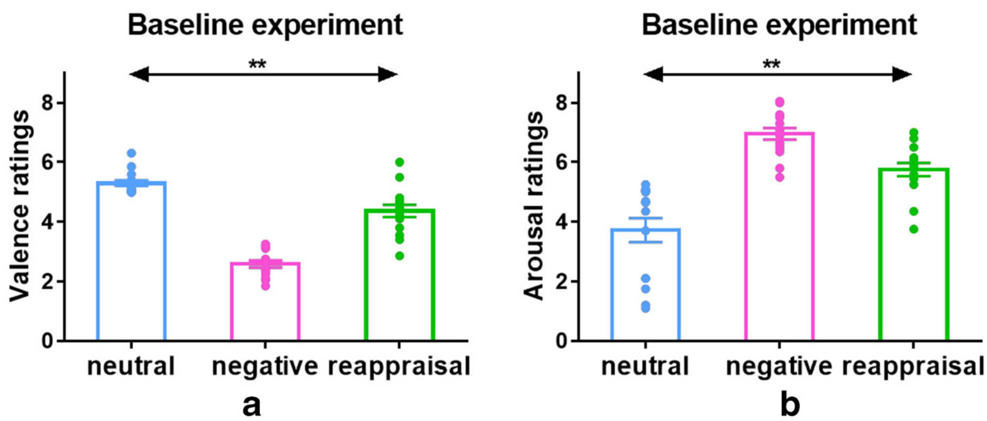


**Fig. 2** Ratings of valence and arousal to the negative (pink), neutral (blue), and reappraisal (green) stimuli from the baseline experiment. Each solid circle represents one subject's rating. $^{**}p < 0.01$ means any two conditions showed significance. **a** Valence ratings to the negative, neutral, and reappraisal stimuli from the baseline experiment. Reappraisal of negative stimuli successfully increased the valence ratings relative to the negative stimuli ratings and it was less positive than the ratings to neutral stimuli. **b** Arousal ratings to the negative, neutral, and reappraisal stimuli from the baseline experiment. Reappraisal of negative stimuli successfully dropped the arousal ratings relative to the negative stimuli ratings, and it was more arousing than the ratings to neutral stimuli.

ratings of negative stimuli were more negative than those of neutral stimuli ($p < 0.001$) and reappraisal stimuli ($p < 0.001$). The ratings of reappraisal stimuli were less positive than those of neutral stimuli ($p = 0.008$). The interaction effect of Time*Condition, $F(4, 56) = 3.296$, $p = 0.037$, $\eta^2 = 0.191$, showed that the effect of Time was significant for reappraisal stimuli, $F(1, 14) = 4.782$, $p = 0.046$, $\eta^2 = 0.255$. However, the post-hoc analyses did not reach significance ($p > 0.05$). No Time effect was found for other two stimuli ($p > 0.05$). Regarding the targeted stimulation, the main effect of Condition, $F(2, 28) = 119.116$, $p < 0.001$, $\eta^2 = 0.895$, indicated that the ratings of negative stimuli were more negative than those of neutral stimuli ($p < 0.001$) and reappraisal stimuli ($p < 0.001$), whereas no difference was found between the ratings of neutral stimuli and reappraisal stimuli ($p = 0.12$). No effect of Time as well as the interaction effect was found ($p > 0.05$).

- RMANOVA with two factors of Time*Condition at each timing

For TMS applied at 300 ms after the stimulus onset (Figure 3a), the interaction effect of Site*Condition, $F(2, 28) = 10.541$, $p < 0.001$, $\eta^2 = 0.43$, indicated the effect of Site for reappraisal stimuli in which the ratings for the reappraisal of negative stimuli increased from the targeted stimulation relative to the vertex stimulation, $F(1, 14) = 15.404$, $p = 0.002$, $\eta^2 = 0.524$. No effect of Site was found for other two stimuli ($p > 0.05$). For TMS applied at 3,300 ms (Figure 3b), the interaction effect of Site*Condition was found as well, $F(2, 28) = 9.845$, $p = 0.001$, $\eta^2 = 0.413$. The ratings for the reappraisal of negative stimuli increased from the targeted stimulation relative to the vertex stimulation, $F(1, 14) = 6.123$, $p = 0.027$, $\eta^2 = 0.304$, while the ratings for negative stimuli were less negative from the vertex stimulation relative to the targeted stimulation, $F(1, 14) = 9.233$, $p = 0.009$, $\eta^2 = 0.397$. No effect of Site was found for neutral stimuli ($p > 0.05$). For TMS applied at double timing (Figure 3c), the interaction effect of Site*Condition, $F(2, 28) = 8.222$, $p = 0.003$, $\eta^2 = 0.37$, noted that the ratings for the reappraisal of negative stimuli increased from the targeted stimulation relative to the vertex stimulation, $F(1, 14) = 7.651$, $p = 0.015$, $\eta^2 = 0.353$, while no effect of Site was found for negative and neutral stimuli ($p > 0.05$).

(2) **Arousal ratings**

A main effect of Condition, $F(2, 28) = 33.969$, $p < 0.001$, $\eta^2 = 0.708$, indicated that the ratings of negative stimuli were more arousing than those of neutral stimuli ($p < 0.001$) and of reappraisal stimuli ($p < 0.001$); the ratings of reappraisal stimuli were more arousing than those of neutral stimuli as well ($p = 0.003$). In addition, a two-way interaction effect of Site*Condition was found, $F(2, 28) = 12.556$, $p < 0.001$, $\eta^2 = 0.473$). No Site/Time effects as well as other interaction effects were found ($p > 0.05$).

To follow-up on the interaction of Site*Condition, RMANOVA with a within-subjects factor of Site was performed in each condition. This analysis showed that the arousal to reappraisal of negative stimuli decreased from the targeted stimulation relative to the vertex stimulation, $F(1, 14) = 8.474$, $p = 0.011$, $\eta^2 = 0.377$. For negative stimuli, the arousal from the vertex stimulation were less arousing than those from the targeted stimulation, $F(1, 14) = 12.773$, $p = 0.003$, $\eta^2 = 0.477$. For neutral stimuli, no effect of Site was found ($p > 0.05$).

Next, RMANOVA with a within factor of Condition was performed for each site. For the vertex stimulation, a main effect of Condition, $F(2, 28) = 32.021$, $p < 0.001$, $\eta^2 = 0.696$, showed that the ratings of negative stimuli were more

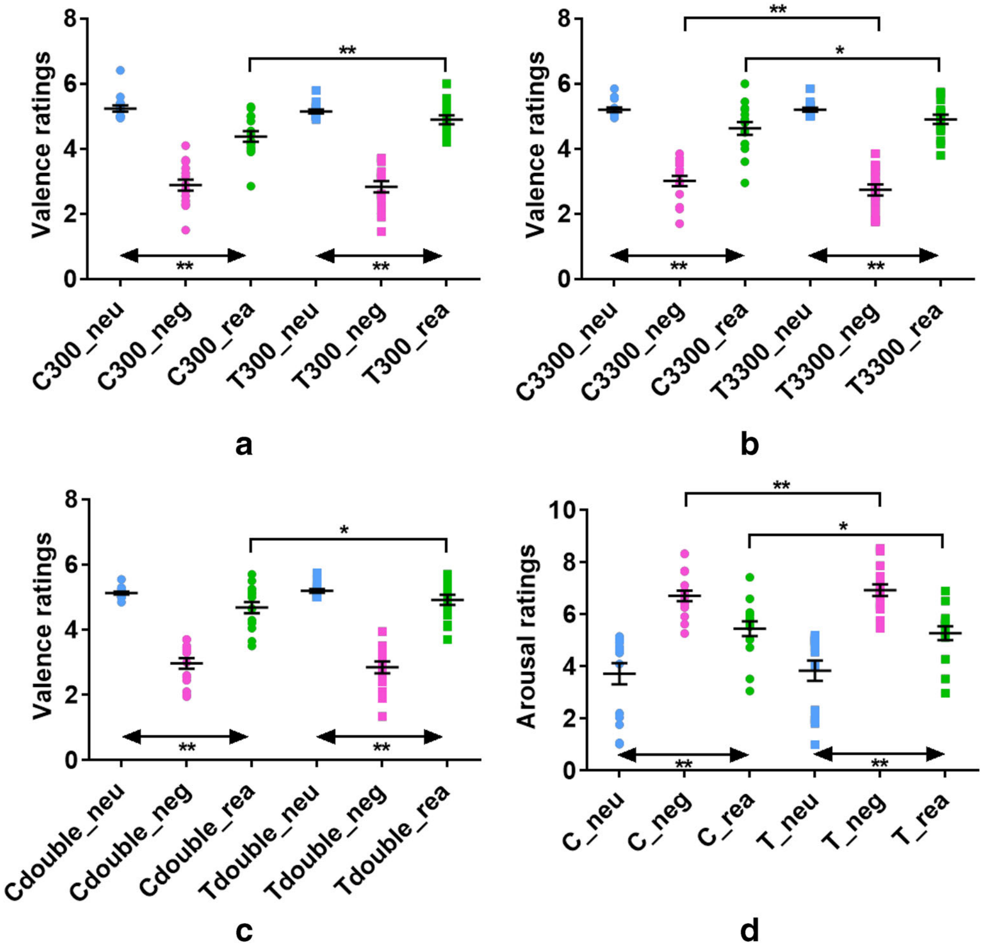


**Fig. 3** Ratings of valence and arousal to the negative (pink), neutral (blue), and reappraisal (green) stimuli from the targeted and the vertex stimulation. Each solid circle represents one subject's rating from the vertex stimulation, and each solid square represents one subject's rating from the targeted stimulation. $^{**}p < 0.01$; $^{*}p < 0.05$. **a** Valence ratings from the targeted and the vertex stimulation at 300 ms. Valence ratings to the reappraisal stimuli were significantly increased from the targeted stimulation relative to the vertex stimulation. Moreover, the ratings to the three stimuli significantly differed among each other from the targeted/vertex stimulation. **b** Valence ratings from the targeted and the vertex stimulation at 3,300 ms. Valence ratings to the reappraisal stimuli were significantly increased from the targeted stimulation relative to the vertex stimulation, while the valence ratings to the negative stimuli were less negative from the vertex stimulation relative to the targeted stimulation. Moreover, the ratings to the three stimuli significantly differed among each other from the targeted/vertex stimulation. **c** Valence ratings from the targeted and the vertex stimulation at double stimulations. The results were similar with those from (**a**). **d** Combined arousal ratings with three timing stimulations from the targeted/vertex stimulation. The arousal ratings to the reappraisal stimuli were significantly less arousing from the targeted stimulation relative to those from the vertex stimulation. In addition, the arousal ratings to the negative stimuli were less arousing from the vertex stimulation than those from the targeted stimulation. Arousal ratings to the three stimuli significantly differed among each other from the targeted/vertex stimulation.

arousing than those of neutral stimuli ($p < 0.001$) and reappraisal stimuli ($p < 0.001$); the ratings of reappraisal stimuli were more arousing than those of neutral stimuli as well ($p = 0.002$). For the targeted stimulation, the effect of Condition, $F(2, 28) = 35.464$, $p < 0.001$, $\eta^2 = 0.717$, also showed that the ratings of negative stimuli were more arousing than those of neutral stimuli ($p < 0.001$) and of reappraisal stimuli ($p < 0.001$); the ratings of reappraisal stimuli were more arousing than those of neutral stimuli as well ($p = 0.004$). Figure 3d presents the combined arousal ratings with different timing stimulations to neutral, negative and reappraisal stimuli from the targeted and vertex stimulation across subjects.

In summary, TMS over the left VLPFC facilitated the reappraisal of negative stimuli shifting to a positive direction while the timing of stimulation pulse did not affect the outcomes on the reappraisal stimuli (valence and arousal ratings). Unexpectedly, the effect of TMS over the vertex affected the valence and arousal ratings of negative stimuli, especially when the vertex stimulation applied at 3,300 ms after the stimulus onset. Table 1 presents the grand averaged ratings (±SD) of

**Table 1** Ratings (mean±SD) of valence and arousal to neutral, negative, reappraisal stimuli from C300, C3300, Cdouble, T300, T3300 and Tdouble sessions.

| Ratings | Sessions | Neutral | Negative | Reappraisal |
|---|---|---|---|---|
| Valence | C300 | 5.24 ± 0.38 | 2.88 ± 0.66 | 4.38 ± 0.64 |
| | C3300 | 5.20 ± 0.26 | 3.01 ± 0.62 | 4.63 ± 0.77 |
| | Cdouble | 5.13 ± 0.17 | 2.97 ± 0.63 | 4.68 ± 0.67 |
| | T300 | 5.15 ± 0.23 | 2.83 ± 0.68 | 4.89 ± 0.52 |
| | T3300 | 5.20 ± 0.23 | 2.73 ± 0.66 | 4.91 ± 0.56 |
| | Tdouble | 5.19 ± 0.22 | 2.85 ± 0.70 | 4.92 ± 0.61 |
| Arousal | C300 | 3.69 ± 1.57 | 6.63 ± 0.85 | 5.46 ± 1.19 |
| | C3300 | 3.71 ± 1.56 | 6.76 ± 0.82 | 5.47 ± 0.99 |
| | Cdouble | 3.76 ± 1.66 | 6.76 ± 0.79 | 5.44 ± 1.22 |
| | T300 | 3.89 ± 1.49 | 6.84 ± 0.95 | 5.27 ± 0.73 |
| | T3300 | 3.79 ± 1.62 | 6.99 ± 0.82 | 5.29 ± 1.14 |
| | Tdouble | 3.83 ± 1.51 | 6.98 ± 0.91 | 5.28 ± 1.25 |

the valence and arousal to neutral, negative, and reappraisal stimuli from all TMS sessions.

## Ratings from the TMS experiments compared with the baseline experiment

To further validate the fact that the above findings were generated by the TMS pluses, we compared the ratings from the baseline experiment with those from the vertex stimulation or from the targeted stimulation. For arousal ratings, we combined the ratings from different timing stimulations for the vertex and the targeted stimulation respectively since the timing effect did not affect the performance. Therefore, we performed RMANOVA with two within-subject factors: TMS (baseline/vertex or targeted stimulation) and Condition (neutral/negative/reappraisal) on the arousal ratings. Due to the Time effect involved in the three-way interaction effect on valence ratings above, we performed similar RMANOVA with the arousal ratings but at each timing stimulation (300 ms, 3,300 ms, or double) on valence ratings.

(1) **Baseline versus Targeted stimulation**

- **Valence ratings**

Significant interaction effects of TMS*Condition were found, regardless of the timing stimulation at 300 ms ($F(2, 28) = 7.332$, $p = 0.005$, $\eta^2 = 0.344$), at 3,300 ms ($F(2, 28) = 4.535$, $p = 0.021$, $\eta^2 = 0.245$), or double ($F(2, 28) = 4.234$, $p = 0.036$, $\eta^2 = 0.232$). RMANOVA with a within-subjects factor of TMS was performed in each condition. We only found a main effect of TMS for reappraisal stimuli (300 ms: $F(1, 14) = 6.279$, $p = 0.025$, $\eta^2 = 0.310$; 3,300 ms: $F(1, 14) = 5.216$, $p = 0.039$, $\eta^2 = 0.271$; double: $F(1, 14) = 4.853$, $p = 0.045$, $\eta^2 = 0.257$), in which the ratings from the targeted stimulation were more positive than from the baseline experiment. No effect was found for neutral stimuli as well as negative stimuli ($p > 0.05$).

- **Arousal ratings**

A significant interaction effect of TMS*Condition was found, $F(2, 28) = 6.175$, $p = 0.006$, $\eta^2 = 0.306$. RMANOVA with a within-subjects factor of TMS was performed in each condition. We only found a main effect of TMS for reappraisal stimuli, $F(1, 14) = 8.685$, $p = 0.011$, $\eta^2 = 0.383$, in which the ratings from the targeted stimulation were less arousing than those from the baseline experiment. No effect was found for neutral or negative stimuli ($p > 0.05$).

(2) **Baseline versus Vertex stimulation**

- **Valence ratings**

For TMS at 3,300 ms, we found a significant interaction effect of TMS*Condition, $F(2, 28) = 4.396$, $p = 0.022$, $\eta^2 = 0.239$. RMANOVA with a within-subjects factor of TMS was performed in each condition. We only found a main effect of TMS for negative stimuli, $F(1, 14) = 8.693$, $p = 0.011$, $\eta^2 = 0.383$, in which the ratings from the vertex stimulation were less negative than those from the baseline experiment. No effect was found for neutral stimuli as well as reappraisal stimuli ($p > 0.05$). The significant interaction effect of TMS*Condition was also found when TMS was applied at double timing, $F(2, 28) = 4.573$, $p = 0.034$, $\eta^2 = 0.246$. The TMS effect for negative stimuli also indicated that the ratings from the vertex stimulation were less negative than those from the baseline experiment, $F(1, 14) = 6.875$, $p = 0.020$, $\eta^2 = 0.329$. No effect was found for neutral stimuli as well as reappraisal stimuli ($p > 0.05$). No interaction effect of TMS*Condition was found at timing 300 ms.

- **Arousal ratings**

No interaction effect of TMS*Condition was found ($p = 0.193$).

Taken together, the comparisons between the baseline experiment and the TMS experiments validated the findings derived from Section 3.2. TMS stimulation over the left VLPFC facilitated reduction of negative emotion using positive reappraisal. In addition, TMS stimulation over the vertex disrupted self-reported evaluations of negative stimuli, especially when the timing stimulation was applied at 3,300 ms after the stimulus onset.

## Discussion

Our results provide evidence for the functional specificity of the left VLPFC in positive reappraisal. TMS stimulation over the left VLPFC facilitated reduction of negative emotions using the strategy of positive reappraisal of negative stimuli, regardless of whether the stimulating time point was at 300 ms or/and at 3,300 ms. This implies that the left VLPFC is involved in both the early and late stages of the process of positive interpretation.

### Functional specificity of the left VLPFC in positive reappraisal

Positive reappraisal as a specific cognitive strategy aims to reinterpret negative emotional stimuli in a more positive light, which has commonly been used in previous studies (Ochsner & Gross, 2008; Ochsner et al., 2012). In the current study, participants were instructed to reinterpret the negative emotional stimulus using a predefined description in a neutral/positive way. This approach allowed participants to successfully reduce the self-reported negative emotions, indicating the effectiveness of this strategy in the down-regulation of negative emotions. Our findings were in line with previous studies using a similar strategy (Foti & Hajcak, 2008; MacNamara et al., 2009).

The left VLPFC is regarded as a critical region involved in regulation of negative emotions using positive reappraisal. Previously, fMRI studies demonstrated that deployment of positive reappraisal specifically recruited the left VLPFC, yielding evidence for a correlation between the left VLPFC and this specific strategy (Dörfel et al., 2014; Picó-Pérez et al., 2017). Recent tDCS studies provided further evidence that VLPFC stimulation led to reductions in self-reported negative emotions in cognitive reappraisal, indicating a direct link between the VLPFC and cognitive reappraisal (He et al., 2018; Marques et al., 2018). However, these findings cannot be treated as indicating a direct relation between the left VLPFC and deployment of positive reappraisal. Beyond previous studies, we adopted single-pulse TMS stimulation over the left VLPFC at different time points after the image onset when participants performed a cognitive reappraisal task with deployment of positive reappraisal. Results showed that TMS stimulation over the left VLPFC reduced negative emotional ratings in the reappraisal of negative stimuli, relative to TMS stimulation over the vertex and the baseline experiment. These findings support our hypothesis that TMS stimulation over the left VLPFC facilitated unpleasantness reduction in positive reappraisal, providing evidence for the functional specificity of the left VLPFC involved in positive reappraisal.

The modulation effect of TMS on behavior could be facilitatory when single-pulse TMS induces an increase in cortical excitability in the stimulated region (Silvanto & Muggleton, 2008). Moliadze et al. (2003) found that firing rates in neural populations increased when single-pulse TMS was applied shortly before the onset of a perceptual process; moreover, this stimulation before the onset of a perceptual process increased sensitivity to subsequent sensory stimulation. Silvanto and Muggleton (2008) provided an explanation in terms of behavioral facilitation that TMS was most effective in increasing neural activity at its baseline level when TMS is applied before the onset of a cognitive process, and there were no differences in the activation states of neural populations of different tunings. Therefore, in the current study, participants were more capable of reappraising negative emotional stimuli using positive reappraisal, probably because of the increase in cortical excitability of the left VLPFC induced by TMS.

The left VLPFC was demonstrated to be correlated with emotional enhancement of memory (EEM) for negative stimuli through its role in elaborative encoding and controlled processing (Rygula et al., 2010). One study applied inhibitory continuous theta burst stimulation (cTBS) over the left VLPFC before participants encoded “neutral,” “negative nonarousing,” and “negative arousing” words (Weintraub-Brevda & Chua, 2018). Results showed that after inhibition of the left VLPFC, the EEM effect for “negative nonarousing” stimuli was reduced relative to “negative arousing” stimuli, suggesting a specific role of the left VLPFC in the EEM effect through controlled processing for “negative nonarousing” stimuli rather than arousing stimuli. In our study, TMS stimulation over the left VLPFC facilitated unpleasantness reduction in the process of positive reappraisal, which might be explained by the specific role of the left VLPFC for “negative nonarousing” stimuli found in the study by Weintraub-Brevda and Chua (2018). The approach of positive reappraisal we used was demonstrated to be effective at reducing the negative valence and arousal of negative stimuli based on the findings from a pre-TMS experiment. We infer that the TMS-activated left VLPFC might improve the elaborative encoding of the memory about the pre-defined descriptions through controlled processing, resulting in a better reappraisal of negative stimuli. In the current study, we used pre-defined descriptions to interpret the stimuli, which were more likely to represent the process of interpretation. To study the process of reappraisal strictly, future studies should first show a certain type of initial interpretation, and then investigate how the initial interpretation changes when the individual reappraises the stimulus.

It is worth mentioning that relative to the decrease of arousal ratings using positive reappraisal, TMS stimulation over the left VLPFC reduced more on negative valence, shifting to a more positive direction. Previous research suggested that two routes were involved in reducing negative emotions successfully: one route was to up-regulate positive emotion and the other was to down-regulate negative emotion (Wager et al., 2008). Increasing positive affect showed small decreases in arousal and a qualitative shift in valence while decreasing negativity appeared to produce a decrease in both valence and arousal (McRae et al., 2012). Furthermore, positive reappraisal tends to shift one's emotional experience toward positive affect (Shiota & Levenson, 2012). Therefore, positive reappraisal is mainly effective at regulating the emotional valence of negative stimuli. In addition, some research found an association between the left VLPFC and emotional valence. For instance, Kensinger and Corkin (2004) showed that the left inferior PFC (BA 47) activated more during encoding of negative nonarousing words (valence-only words) than arousing or neutral words. Wager et al. (2008) found a positive correlation between activation of the left VLPFC and reduction of negativeness when participants were instructed to apply the strategy of positive reappraisal to negative emotional stimuli. Regarding our study, we believe that the increase in cortical excitability of the left VLPFC induced by TMS led to greater reduction of negativeness in positive reappraisal, providing evidence for the role of the left VLPFC in the evaluation of negative emotion in terms of the valence dimension.

## Timing of left VLPFC involved in positive reappraisal

Another question we considered was the timing at which the left VLPC was involved in positive reappraisal. Our results revealed that single-pulse TMS over the left VLPFC at 300 ms or/and at 3,300 ms facilitated the reduction of negative emotions with the deployment of positive reappraisal. A previous review noted that behavioral facilitation could be observed when single-pulse TMS was applied *shortly before* the onset of a cognitive process, and behavioral inhibition could be found when the TMS was applied *during* the cognitive process (Silvanto & Muggleton, 2008). Both the stimulation times we applied facilitated behavioral performance in our study. Therefore, we could infer that TMS stimulation at 300 ms/3,300 ms occurred *shortly before* the onset of the process of reappraisal, rather than the process of reappraisal lasting until 3,300 ms. This speculation is in line with the idea that cognitive reappraisal is recurrent, as proposed in the model of Kalisch (2009). This model suggests that cognitive reappraisal consists of early and late stages and shifts between the stages should occur in seconds. The stimulation timing in our study may imply these two stages of reappraisal: the time point of 300 ms may suggest the approach of the early stage and 3,300 ms may indicate the approach of the late stage. However, more evidence is necessary to provide the precise time points regarding the onset of the two stages of reappraisal in future studies.

In addition, our results also showed that the left VLPFC was involved in both stages of positive reappraisal. Activation of the same brain area may be observed during both the early and late stages of reappraisal, probably because of the readjustment of reappraisal (Kalisch, 2009). Although several LPP studies showed that the LPP amplitudes from different regions were modulated by positive reappraisal (Moser et al., 2014; Qi et al., 2017), it is hard to say that modulation of the LPP amplitudes by positive reappraisal was due to the involvement of the left VLPFC. Future studies should apply a combination of TMS with other techniques to investigate further how the involvement of the left VLPFC in different stages of reappraisal modulates cortical activity, to provide evidence for the precise timing of engagement of the left VLPFC.

## TMS stimulation on the vertex disrupted the evaluation of negative emotions

Recently, Jung et al. (2016), using a TMS-fMRI paradigm to investigate how fMRI blood-oxygenation-level-dependent (BOLD) signal changed when TMS was applied on the vertex in the resting state, found that TMS applied on the vertex deactivated the BOLD signal in brain regions related to the default mode network but did not influence the functional connectivity of this network. They provided evidence in support of the use of vertex simulation as a control condition in TMS, which supported the selection of the control stimulation site in our work. However, an unexpected result was found for the vertex stimulation: TMS stimulation over the vertex mainly attenuated the valence ratings to negative stimuli compared with those from the baseline experiment and the targeted stimulation. This finding indicated that the vertex stimulation disrupted the evaluation of negative stimuli. Disruptions in behavior were generally obtained when single-pulse TMS was applied during the cognitive process (Silvanto & Muggleton, 2008). However, we did not find any research indicating an association between negative emotion and the vertex. This might imply that the vertex was not always inert in the cognitive process. We need more tests to explain this unexpected finding.

## Conclusions and limitations

Our study provided evidence for the functional specificity of the left VLPFC in positive reappraisal. Single-pulse TMS on the left VLPFC facilitated reduction of negativeness in ratings of negative emotions using positive reappraisal, revealing the left VLPFC as a promising new target for therapeutic brain stimulation in mood disorders. Moreover, the left VLPFC was involved in both early and late stages of positive reappraisal, which supported the idea that reappraisal is recurrent, as proposed by Kalisch (2009). In addition, the vertex was not always inert in the cognitive process according to the unexpected finding that the vertex stimulation by TMS disrupted the evaluation of negative emotions.

Potential limitations of the current study should be mentioned. The first limitation is that the location of the TMS coil was relatively rough, based on the 10-20 EEG system. Image-guided neuronavigation is highly recommended to determine the location of the coil in future studies. The second limitation is that our study included a small sample size, which limited the current study to being exploratory research. We suggest future studies recruit more participants to retest the findings of this study. Finally, to examine further the precise timing of engagement of the left VLPFC in positive reappraisal, more combinations of TMS with other electrophysiological techniques or direct recordings of the neutral activity of the left VLPFC are necessary.

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## Declarations

**Conflict of Interest** None of the authors have potential conflicts of interest to disclose.

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