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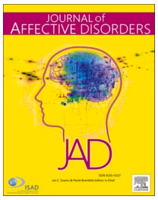

Research paper

Functional connectivity between right-lateralized ventrolateral prefrontal cortex and insula mediates reappraisal's link to memory control

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ABSTRACT

Background: : Memory control (MC) ability is critical for people's mental and physical health. Previous research had conceptually demonstrated that MC ability has close relationship with reappraisal. However, experimental evidence supporting the relationship was limited. Thus, in the present study, we investigated how MC and reappraisal are linked, both in behavior and in the brain.

Methods: : The habitual use of reappraisal was assessed by Emotion Regulation Questionnaire, and memory control ability was measured through directed forgetting task. Resting-state functional magnetic resonance imaging was used to test the seed-based functional connectivity in 181 healthy subjects.

Results: : Behavioral results revealed that more frequent reappraisal was associated with an enhanced ability to control negative memories. Resting-state seed-based functional connectivity showed that habitual use of reappraisal was positively related to the strength of functional connectivity between the right ventrolateral prefrontal cortex (VLPFC) and right insula. Most importantly, this functional connectivity mediated the effect of habitual use of reappraisal on control over negative memories.

Limitations: : Present results mainly showed the habitual use of reappraisal was related with MC ability in negative items. Future study could further explore the relationship between MC ability of different categories of negative emotional memories and other kinds of ER strategies.

Conclusions: : Our results support the notion that reappraisal provides opportunities for individuals to practice and enhance inhibitory control—a relationship underpinned by connectivity between the right VLPFC and right insula.

1. Introduction

Some memories remain elusive, despite seemingly salient reminders. Others have a habit of springing forth into awareness at the slightest provocation. Given that not all memories are helpful or desirable in a particular circumstance, the ability to regulate which memories occupy awareness, or memory control (MC), provides a boon to efficacy and well-being through forgetting (Fawcett and Hulbert, 2020). In contrast, a lack of control over unwanted memories is associated with—and may even contribute to—a number of psychopathologies (Banich et al., 2009; Nørby, 2018).

Recent research has begun to illuminate the mechanisms supporting MC abilities. Much of this work stems from two laboratory procedures designed to model real-world situations in which individuals are motivated to forget unwanted memories: the directed forgetting (DF) paradigm (Basden, 1996; Bjork, 1989) and the Think/No-think (TNT) task (Anderson, 2011; Anderson et al., 2004). While the former examines the consequences of instructions to forget issued shortly after an opportunity to study items or lists of items, the latter examines the lingering consequences of attempts to suppress automatic retrieval of unwanted

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memories in the face of previously learned memory associates. Despite their superficial differences, both procedures have revealed a partially overlapping network of brain regions engaged in (and suppressed by) MC (Anderson and Hanslmayr, 2014; Anderson and Hulbert, 2021; Banich and Depue, 2015). Numerous lines of evidence highlight the involvement of the prefrontal cortex in regulating memory representations, including their contextual and emotional features (Depue et al., 2007; Gagnepain et al., 2017).

Evidence suggests that successful MC requires sufficient attention and practice. Occupying working memory with a heavy cognitive load eliminates the inhibitory signature of memory suppression (Noreen and de Fockert, 2017), a finding that mirrors impaired suppression-induced forgetting in individuals who are sleep deprived (Harrington et al., 2020) or have been diagnosed with attention-deficit/hyperactivity disorder (Depue et al., 2010). Individuals with higher trait anxiety, dysphoria, or depression often show some impairment, as well (Hertel and Gerstle, 2003; Marzi et al., 2014; Stramaccia et al., 2019). Certain types of strategy training may, however, counteract the impairment seen in individuals with major depressive disorder (Joormann et al., 2009). Indeed, opportunities to prepare for and practice MC may be important for successful regulation more generally. Preparatory cues have been shown to enhance memory suppression in the general population (Hanslmayr et al., 2010), for instance, while extensive suppression practice is associated with reduced intrusions of unwanted memories (Levy and Anderson, 2012) and modulations of the brain regions and processes supporting the targeted memories (Depue et al., 2007; Hulbert and Anderson, 2018; Hulbert et al., 2016).

To the extent that laboratory procedures effectively models real-world MC, then real-world practice should provide a similar—if not more powerful—benefits to the development of effective control abilities. Many trauma survivors experience a strong motivation to limit the extent to which memory of the event(s) intrude in their everyday lives; not all are successful. A subset of survivors develop post-traumatic stress disorder (PTSD), a condition associated with impaired MC for both negative and neutral memories (Catarino et al., 2015; Sullivan et al., 2019; Waldhauser et al., 2018), as well as reduced intrusion-related negative coupling between the prefrontal cortex and the hippocampus (Mary et al., 2020). As ongoing work seeks to determine the causal connection between PTSD and MC impairments, correlational evidence from non-clinical samples has suggested that a relatively greater incidence of early-life trauma is actually associated with better control over neutral and negative memories (Hulbert and Anderson, 2018). This finding is consistent with the inhibition plasticity hypothesis, suggesting that exposure to certain types of trauma may provide natural opportunities to train inhibitory control so as to more effectively cope with reminders of unwelcome memories.

Unwanted memories may be more than simply distracting; oftentimes, they are associated with unpleasant emotions. Regulating negative emotions is crucial to good health (Eisenberg et al., 2000; John and Gross, 2004; Liliana and Nicoleta, 2014; Lopes et al., 2004). Emotion regulation (ER) refers to the way people evoke thoughts or behaviors which can influence the content of people's present emotions, the time they have them, and the way they express them (Gross, 1998). Reappraisal is one especially well-studied ER strategy that has been shown to reduce negative emotions while increasing positive emotions through the reinterpretation of originally emotion-inducing stimuli (Morawetz et al., 2017). This useful strategy targets both the potentially emotion-eliciting situation's meaning and the self-relevance of that situation (Gross, 2015; Haines et al., 2016; McRae and Gross, 2020; Morawetz et al., 2017). Previous work has suggested that successful ER relies, in large part, on inhibition (Bartholomew et al., 2019; Gross and Thompson, 2007; Ochsner and Gross, 2005), much as has been argued in the case of MC (Anderson and Hulbert, 2021). Does this seeming parallel between ER and MC go deeper?

Several studies have reviewed the relationship between people's MC ability and reappraisal at a conceptual level. Nørby (Nørby, 2018), for instance, considered how selective forgetting of negative memories might support healthy ER—one of the many virtues of forgetting named by Fawcett and Hulbert (Fawcett and Hulbert, 2020). The literature reviewed by Engen and Anderson (Engen and Anderson, 2018) led them to identify MC as a fundamental mechanism of ER. Their theoretical account holds that, because emotional experiences are frequently mediated by memories, controlling access to those memories is likely to provide important paths for ER. Engen and Anderson delineate a two-step process of reappraisal, which begins with the direct suppression of the original interpretation's memory representation and followed by the generation of a substitute interpretation. In so doing, the original interpretation should become less accessible and a new emotional interpretation elaborated, taking its place. In support of this view, Engen and Anderson (Engen and Anderson, 2018) discerned similar brain activations across studies examining the two forms of memory suppression (direct suppression and thought substitution) and reappraisal. More recently, Wei et al. (Wei et al., 2020) provided meta-analysis revealing shared neural and transcriptional correlates of control across memory and emotional domains.

A growing body of functional magnetic resonance imaging (fMRI) work has helped establish the neural correlates of DF, they have pointed out that inferior frontal gyrus (IFG), middle frontal gurus (MFG), cingulate gurus, hippocampus, inferior parietal lobule (IPL) are crucial during DF task. (Bastin et al., 2012; Nowicka et al., 2010; Wylie et al., 2007; Yang et al., 2016; Yang et al., 2013). For example, Nowicka et al. (Nowicka et al., 2010) found compared with unintentional forgetting, forgetting emotional images intentionally was associated with right MFG, right superior frontal gyrus and right IPL. Notably, the IFG are regularly associated with top-down MC during DF (Chao et al., 2013; Nee et al., 2007; Nowicka et al., 2009; Reber et al., 2002; Wylie et al., 2007). Bastin et al. (Bastin et al., 2012), for instance, reported that the IFG had increased activity in intentional forgetting. As part of IFG, ventrolateral prefrontal cortex (VLPFC), which is associated with the ability to suppress interference from useless information (Nee et al., 2007), has been identified as one key region engaged in DF (Badre et al., 2005; Nee et al., 2007; Nowicka et al., 2009; Wylie et al., 2007). Wylie et al. (Wylie et al., 2007) found right VLPFC showed increased activity during intentional forgetting contrasted with to-be-forgotten (TBF) - Remember condition. Additionally, several researches showed that emotion related areas showed decrease activation during intentional forgetting of negative emotional materials (Anderson and Hanslmayr, 2014; Depue et al., 2010; Depue et al., 2007; Marchewka et al., 2016). Marchewka (Marchewka et al., 2016) found that, intentional forgetting was associated with lower activation in amygdala compared with intentional remember in DF task. Therefore, emotion related regions are also recruited in intentional suppress of intrusive memories process.

Meta-analysis have similarly identified the involvement of the prefrontal cortex during reappraisal (Badre et al., 2005; Buhle et al., 2013; Deak et al., 2017; Kohn et al., 2014). Indeed, evidence suggests that reappraisal depends on interactions between prefrontal areas involved in cognitive control and areas implicated in emotional responding (Ochsner and Gross, 2008). In accordance with this perspective, researchers have observed decreased activity in emotion related regions, such as the amygdala and insula, when people used reappraisal strategy (Kalisch, 2009; Kim and Hamann, 2007; McRae et al., 2010; Ochsner and Gross, 2008; Ochsner et al., 2004). Prominent among these reappraisal-associated prefrontal cortex is the VLPFC (Silvers et al., 2017). Powers (Powers and LaBar, 2019) pointed out that the VLPFC is associated with cognitive control during reappraisal. Importantly, the right VLPFC is notable for its connection to the successful reduction of negative affect through reappraisal, through a variety of subcortical pathways (Wager et al., 2008). Besides, several Transcranial Direct Current Stimulation (tDCS) researches emphasized VLPFC's role in ER (He et al., 2018; Marques et al., 2018; Riva et al., 2012; Riva et al., 2015). For instance, Marques (Marques et al., 2018) found that tDCS induced effects on the VLPFC had a better effect on increasing emotional valence of negative images during reappraisal compared with the DLPFC. Overall, right VLPFC played an important part during cognitive control (Anderson and Weaver, 2009; Falconer et al., 2008), which are related with reappraisal (Hooker and Knight, 2006) and MC (Anderson et al., 2016) mental processes. It may be helpful to focuse on these areas in the relationship between reappraisal and MC.

Our brief review of the existing literature highlights numerous neurobehavioral commonalities linking MC and reappraisal-based ER. However, to the best of our knowledge, no empirical studies have yet been reported that examine the neural relationship between item-method directed forgetting task (IM-DF) and reappraisal. The present study attempts to fill this gap. We hypothesized that: (1) Individuals who use reappraisal more often would have relatively better MC abilities owing to the MC practice that strategy is theorized to entail; (2) Resting-state functional connectivity (FC) between VLPFC and certain emotion-processing regions of the brain (e.g., the amygdala or insula) would mediate the relationship between reappraisal and MC ability in emotional items.

2. Method

2.1. Participants

The data from 181 right-handed, healthy (free of current or previous psychiatric disorders and indications of drug/smoking/alcohol abuse) college students (of whom, 105 were female) with ages ranging from 17-25 (mean = 19.88 ± 1.19) were obtained from the Southwest University Longitudinal Image Multimodal (SLIM) Dataset (INDI, http://fcon_1000.projects.nitrc.org/). This dataset represents a large sample multi-modal (sMRI, rsMRI, DWI and behavioral) investigation of the neural underpinnings and development of creativity and emotion (Liu et al., 2017). This study was approved by the Academic Committees of Southwest University and Chongqing Medical University in China and all the participants provided an informed consent before the experiment.

2.2. Behavioral Materials and Procedures

2.2.1. Emotion Regulation Questionnaire (ERQ)

Participants' tendency to utilize reappraisal for the purpose of ER was assessed by 10-item ERQ (Gross and John, 2003). This questionnaire was designed to measure individual differences in the habitual use of two kinds of ER strategies: reappraisal and expressive suppression. Items 1, 3, 5, 7, 8, and 10 capture reappraisal, while the remaining items capture expressive suppression. Participants rate each item on a 7-point intensity scale, from 1 (totally disagree) to 7 (totally agree). Cronbach's alpha coefficient for the ERQ's internal consistency in our sample was determined to be acceptable (Cronbach's alpha = *0.706*).

2.2.2. Directed forgetting task

In present study, the IM-DF paradigm was adopted to determine participants' MC ability. We followed a conventional design, consisting of two phases: a study phase and test phase (Bjork, 1989). The task was performed outside of the fMRI scanner. For this purpose, 244 words (80 in positive, negative and neutral valence each, plus 4 words used for avoiding primacy effects and recency effects) selected from established Chinese Affective Words pools (Wang et al., 2008). In order to validate this selection, we recruited a separate sample of 30 participants to rate the words' valence and arousal on 9-point intensity scale. Participants were asked to rate the emotional valence from 1 ("very unpleasant") to 9 ("very pleasant"), and the arousal from 1 ("very calm") to 9 ("very excited"). The three-category materials differed in valence (mean: negative = 2.79 ± 0.36, neutral = 5.63 ± 0.48, positive = 5.78 ± 0.52; Chi square = 212.48, df = 2, $p < 0.001$) and arousal (mean: negative = 5.63 ± 0.49, neutral = 4.62 ± 0.47, positive = 4.89 ± 0.49; $F(2, 237) = 94.58$, $p < 0.001$). However, the difference in familiarity between these two groups was not significant ($F(2, 237) = 0.978$, $p > 0.05$).The sequence of these two kinds of words was counterbalanced across participants. After validating the distinction between positive, negative and neutral words, we randomly divided these words into two sets of 120 words, each with an equal number of positive, negative and neutral words. One set served as the learning items, whereas the other was used as distractions in the recognition task. The study and distraction items matched in valence, arousal, and familiarity. The study items were randomly separated into the TBF and to-be-remember (TBR) conditions.

Prior to the study phase, participants received practice on the IM-DF task using filler words until they demonstrated that they understood the procedure.

The study phase included 120 critical trials. At the beginning of each trial, a fixation cross "+" appeared at the center of the screen for 500ms. Subsequently, a word from the study set replaced the cross and remained for 2s. The presentation order was pseudorandomized. Immediately following this study period, a memory instruction (i.e., "$\surd$" means remember the previously presented words and " × " means forget it) was displayed on the screen for 1.5s in accordance with the pseudorandomized condition assignment for the word that just disappeared. After the study phase, the participants performed a three-minute calculation test as a distracter task.

In the test phase, participants were asked to judge whether the word presented on the screen had been studied or not in the previous phase, regardless of the instruction with which it had been associated (this latter point was emphasized in the instructions to participants). The 120 studied words were mixed with an equal number of distractor words. Each test word was showed for 2s following a 500ms fixation cross. Participants were asked to press "1" on the keyboard during the word presentation if they thought the word had been studied ; otherwise, they were asked to press "2". All participants completed the behavior test from 28 February 2012 to 24 December 2012.

2.3. Image acquisition

The resting-state functional image was collected between 19 November 2011 and 1 October 2012, using a Siemens 3.0-T Trio MRI scanner (Siemens Medical Systems, Erlangen, Germany). All participants were instructed to lie down, keep their eyes open, and rest without thinking specific things but stay awake during scanning. Whole-brain rs-fMRI images (242 volumes) were acquired using a gradient-echo type echo-planar imaging (GRE-EPI) sequence with the following parameters: repetition time (TR)/echo time (TE) = 2000/30ms; slices = 32; flip angle = 90; field of view (FOV) = 220 mm × 220mm^2; matrix = 64 × 64; thickness/slice gap = 3/1mm; and acquisition voxel size= 3.4 × 3.4 × 4mm^3.

2.4. Data preprocessing

The resting-state fMRI data were preprocessed by the Data Processing Assistant for Resting-State fMRI (DPARSF V3.1, http://rfmri.org/DPARSF) (Yan and Zang, 2010) run in MATLAB 2008a (MathWorks, Natick, MA, USA). The first 10 volumes of each participant's were discarded for the purposes of signal equilibrium. The remaining 232 scans were slice-time corrected and realigned to the middle volume to correct for head motion. After that, realigned images were spatially normalized to the standard Montreal Neurological Institute (MNI152) template and resampled into 3 × 3 × 3 mm and were spatial smoothed with an isotropic 8 mm full-width half maximum Gaussian kernel. Then, the smoothed images were linearly detrended and had a band-pass filter (0.01-0.08 Hz) applied to eliminate low-frequency fluctuations. Nuisance signals, such as white matter, cerebrospinal fluid, global signal and head-movement profiles, were regressed out in order to minimize the influence of physiological artifacts.

2.5. Functional connectivity analysis

The FC was investigated by using a region of interest (ROI) based method performed in the DPARSF_V3.1. According to previous research emphasizing the importance of right VLPFC in reappraisal/ER (Ochsner and Gross, 2005; Phillips et al., 2008), we created a 6 mm radius sphere around a seed region at the right VLPFC (*x, y, z=48, 15, 6* in MNI space), a region which is proved to be consistently recruited during reappraisal by meta-analysis of contrasts comparing reappraisal to a baseline condition (Buhle et al., 2013). To get the FC map, each participant's mean time series across all voxels contained in the seed region was first extracted. Then, we performed a correlation analysis between the seed region's activity and the time course of each voxel in the whole brain, to obtain the FC map. A Fisher r-to-z transformation was applied to improve the normality of the resulting correlation coefficients (Fox and Raichle, 2007).

Subsequently, we explored this output to identify regions whose FC with the right VLPFC significantly related to individual differences in the frequency of reappraisal use by correlation analysis. Age, gender, and head movement parameters were included as covariates in the model. This was carried out using the "statistical analysis" command in DPABI V3.1 (Yang et al., 2016). We adopted small-volume correlation (SVC) for the multiple comparison correction across the regions of interest (ROIs). The ROIs was defined based on the noted role of the insula (Carlson and Mujica-Parodi, 2010; Goldin et al., 2008; Grecucci et al., 2013; Hermann et al., 2014; Schulze et al., 2011; Zhang et al., 2020) and amygdala (Banks et al., 2007; Denny et al., 2015; Drabant et al., 2009; Sarkheil et al., 2015; Wu et al., 2020) during reappraisal. Wake Forest University (WFU) Pick Atlas (Maldjian et al., 2003) was used to define the areas of the insula (contains 4256 voxels) and amygdala (contains 468 voxels). Specific ROIs were examined at a corrected threshold of $p < .05$ using the false discovery rate (FDR) for multiple comparison correction in the "viewer" command in DPABI.

2.6. Mediation analysis

We investigated the neural basis of the relationship between MC and reappraisal through a mediation analysis supported by the PROCESS macro in SPSS (Preacher and Hayes, 2008). Several paths among variables are estimated in typical mediation analysis, including the total effect of the independent variable X on the dependent variable Y (path c), which reflects the combination of the direct effect of X on Y (path c') after controlling the mediator variable M and the indirect effect of X on Y through M (the product of the effect of X on M [path a] and the effect of M on Y [path b]). In the present study, X was defined as the habitual use of reappraisal measured by ERQ, Y was defined as MC ability measured by the IM-DF task (see below for calculation), and M was defined as the FC strength between ROI and related region. During the analysis, age, gender and interval time between behavior test and resting-state fMRI collection were considered covariates. To generate 95% confidence intervals (CI), 5,000 bootstrapped samples were drawn. If the CI does not contain zero, this indicates a significant indirect effect of the independent variable (X) on the dependent variable (Y) through the mediators (M) (Preacher and Hayes, 2008).

3. Results

3.1. Behavioral results

Each participant's ability to control memories was defined as the Remember - Forget accuracy difference score obtained on the final old/new recognition test, higher difference scores reflect relatively better MC ability (Fawcett et al., 2013). The results were reported in Table 1. Repeated measures ANOVA was performed over the hit rates of TBR and TBF, with the types of valence (positive, neutral, negative) and instruction (Remember, Forget) as factors. The result showed significant main effect of both the instruction [F (1, 180) = 381.551, $p < 0.001$], meaning the hit rate of the TBR items (67.5% ± 0.166) was greater than that of the TBF items (52.1% ± 0.179), and the valence [F (2, 179) = 6.259, $p = 0.002$]. Also, the interaction between these two factors was significant [F (2, 179) = 35.545, $p < 0.001$].

Table 1
Means and standard errors (Mean ± SE) of recognition bias.

	TBR	TBF
Positive item	0.935±0.322	0.997±0.263
Neural item	1.310±1.063	1.346±0.757
Negative item	1.019±0.613	1.065±0.355

[a]TBR, to-be-remembered; TBF, to-be-forgotten

In order to consider the recognition biases when only the hit rate was calculated, we performed another repeated measures ANOVAs over participants' discriminate accuracy and recognition biases (Macmillan and Creelman, 2004; Stanislaw and Todorov, 1999). The mean recognition biases and discriminate accuracies are presented in Table 1 and Table 2. The results indicated main effect of both the instruction for discriminate accuracy [$F(1, 165) = 363.091, p < .001$], and the valance for discriminate accuracy [F (2, 164) = 79.336, $p < .001$]. Also, the interaction between instruction and valance was significant [F (2, 330) = 20.514, $p < 0.001$].

Taken age, gender as covariates, the Pearson correlation analysis revealed that participants' habitual use of reappraisal was positively correlated with their MC ability of negative memories ($r_{177} = .233$, $p = .002$), meaning that participants who chose to use reappraisal as their ER strategy more often exhibited greater DF effects—they were better able to control unwanted negative memories.

3.2. Functional connectivity analyses

After regressing out age, gender, interval time, and head movement, our correlation analysis revealed that reappraisal use (quantified as reappraisal scores) was significantly and positively correlated with the strength of FC between the right VLPFC and the right insula (SVC, $p_{\text{corrected}} < .05$, peak coordinates in MNI: *45,3,12*; see Fig. 1A; $r_{176} = .302$, $p < .001$; see Fig. 1B). However, we didn't find any area with which there was significant relationship between reappraisal scores and the FC of right VLPFC in the bilateral amygdala.

To explore whether the FC between the right VLPFC and other brain regions was related to reappraisal scores, we also performed a whole-brain analysis. We used a lenient, uncorrected threshold of clusters > 10 voxels for exploratory purposes. However, we did not obtain any significant results except for the right insula.

3.3. Mediation analysis

As mentioned above, we observed a significant correlation between reappraisal scores and the ability to control negative memories on an IM-DF task. Furthermore, we found evidence that the strength of the FC between the right VLPFC and the right insula was associated with the use of reappraisal. Then, we analyzed whether the FC between underlying habitual use of reappraisal was associated with control ability of negative memories. The Pearson correlation analyses revealed that the FC strength between the right VLPFC and the right insula was positively associated with the control ability of negative memories ($r_{176} = .211$, p

Table 2
Means and standard errors (Mean ± SE) of discriminate accuracies.

	TBR	TBF
Positive item	0.644±0.523	0.277±0.433
Neural item	1.199±0.554	0.587±0.471
Negative item	0.864±0.486	0.498±0.411

[a]TBR, to-be-remembered; TBF, to-be-forgotten

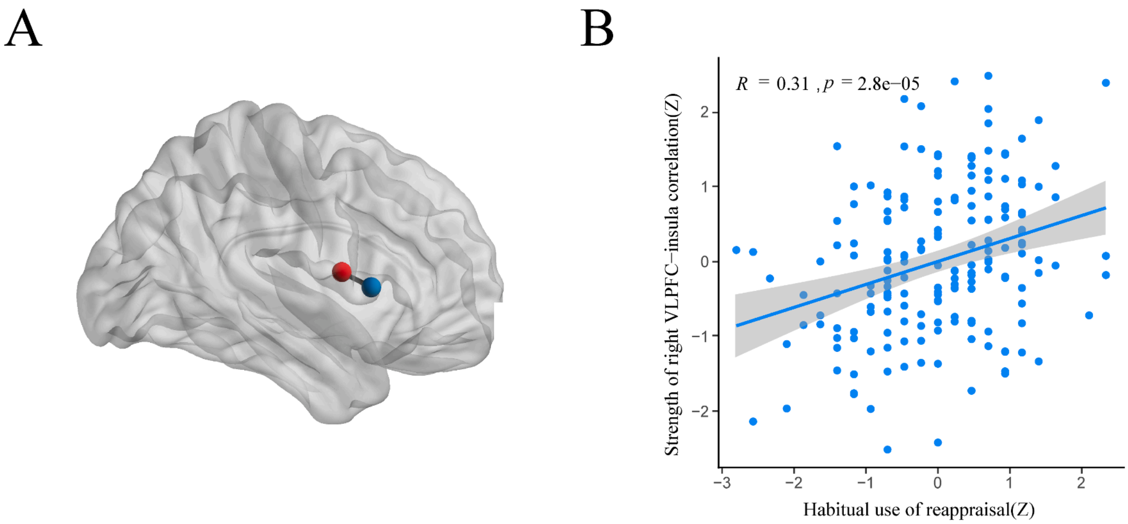

Fig. 1. Results of the resting state functional connectivity analysis. (A) Regions of interest are depicted as nodes, with the right ventrolateral prefrontal cortex in blue and the right insula in red. (B) Scatter plot of the correlation between reappraisal score and strength of resting-state functional connectivity between the right ventrolateral prefrontal cortex and the right insula after regressing out age and gender. Both dimensions have been Fisher Z-transformed for analysis and display.

= .005). Based on proposals in the literature (Engen and Anderson, 2018), we further hypothesized a mediating role of this FC in the relationship between reappraisal and control over negative memories. The first step of the mediation model showed the regression of habitual use of reappraisal on control ability over negative memories, ignoring the mediator, was significant, $b = .234$, $t_{176} = 3.148$, $p = .002$. The second step showed that the regression of habitual use of reappraisal on the mediator, strength of FC between the right VLPFC and the right insula, was also significant, $b = .303$, $t_{176} = 4.198$, $p < .001$. The third step of the mediation analysis showed that the mediator (the strength of FC between the right VLPFC and the right insula), controlling for the habitual use of reappraisal, was significant, $b = .157$, $t_{175} = 2.045$, $p = .042$. The last Step of this analysis revealed that, controlling for the mediator (the strength of FC between the right VLPFC and the right insula), the habitual use of reappraisal was a significant predictor of the ability to control negative memories $b = .186$, $t_{175} = 2.411$, $p = .017$ The indirect effect of habitual use of reappraisal on MC ability of negative memories was found to be statistically significant [Effect = 0.048, 95% CI, (0.0065, 0.1097)]. These results demonstrate that the positive relationship between reappraisal and MC ability of negative memories is partially accounted for by the FC between the right VLPFC and the right insula (see Fig. 2).

4. Discussion

The present research explored the neurobehavioral relationship between the use of reappraisal in ER and the ability to forget negative memories. As predicted, the results affirmed that: 1) self-reported tendency to use reappraisal to regulate emotions was positively associated with DF of negative memories; 2) that relationship appears to be mediated by the FC strength between the right VLPFC and right insula. Taken together, these results are consistent with the possibility that the use of reappraisal may offer natural opportunities to train MC abilities through strengthening the connection between a region thought to exert control and an area involved in emotional responses.

Our behavioral results showed that people who used reappraisal to regulate their emotion will have stronger MC abilities on negative memories. Previous studies have confirmed that MC ability could be improved through practicing (Anderson, 2001; Hulbert and Anderson, 2018; Mary et al., 2020). Based on present findings, we suggest that training people to choose reappraisal as their ER strategy more often may be a potential way to develop their MC capacity on negative events. Also, we noticed that participants' habitual use of reappraisal were only positively related with their MC ability in negative items, but not with positive and neural materials. According to previous studies, we found

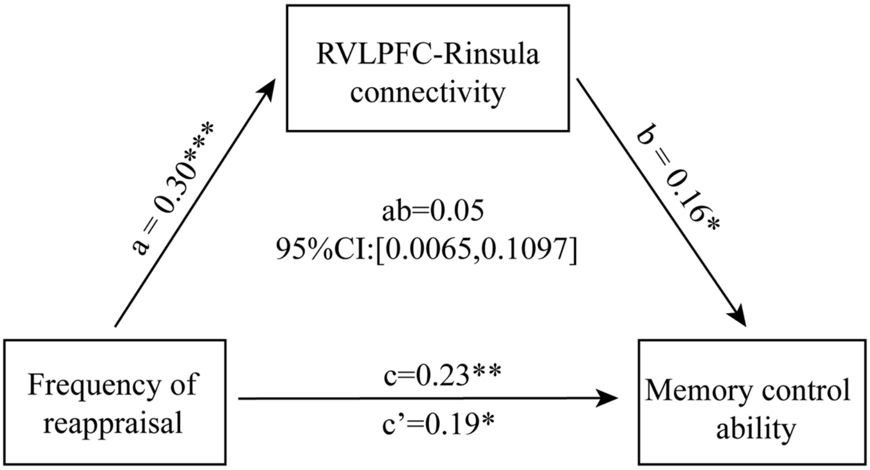

Fig. 2. The mediation model. The association between memory control ability and frequency of reappraisal was partially mediated by the strength of resting-state functional connectivity between the right ventrolateral prefrontal cortex and the right insula. *$p < .05$. **$p < .01$. ***$p < .001$.

that people use regulation strategies on negative rather than positive stimuli more frequently (Volokhov and Demaree, 2010), and when focus on regulating positive emotions, people prefer to maintain and increase their positive states and tend to choose response-focused strategies, such as savoring rather than reappraisal (Carl et al., 2013). However, reappraisal is considered as a more effective strategy of decreasing self-reported negative emotional experience (Gross, 2002) and have prolong effect on reducing negative feelings (Hermann et al., 2016). Therefore, present results are with previous studies and further support the view that reappraisal is link with control ability of negative items.

We also provided evidence that the habitual use of reappraisal is positively correlated with the strength of the right VLPFC-insula connection. Previous researches have certified the important roles of VLPFC (Nelson et al., 2015; Opialla et al., 2015; Zilverstand et al., 2017) and insula (Giuliani et al., 2011; Goldin et al., 2009) during reappraisal. What we found was consistent with previous studies about the function of VLPFC and insula. The VLPFC has been proved to be implicated during inhibitory control (Eich et al., 2014; Hooker and Knight, 2006; Levy and Wagner, 2011). And the insula have been proposed to be one crucial area which involved in the processes of emotion generation (Gasquoine, 2014), such as the conscious representation of emotional bodily states (i.e., interoception), awareness of body movement, emotional awareness and so on (Craig and Craig, 2009). Some studies showed the PFC could impact on the activity in regions associated with negative affect, such as the insula to decrease negative emotion (Etkin and Wager, 2007; Wager et al., 2008), and present results has proved the connection of these two areas played an important role during reappraisal.

The present results also indicate that the relationship between MC and reappraisal was partly mediated by the strength of the right VLPFC-insula connection, revealing a potential neural mechanism behind this association. Early research has pointed the important role of VLPFC during the procedure of both controlling retrieval and selecting the replacements of unwanted memory (Benoit and Anderson, 2012) though MC task, meanwhile, these two cognitive processes were thought as parts of reappraisal (Ochsner and Gross, 2008). Therefore, the VLPFC could be considered as a crucial part of mechanism that link reappraisal and MC, which was further confirmed in present study. Also, research has showed that the abnormal functional integration of VLPFC and insula during Stroop task may be a critical feature of bipolar disorder (Pompei et al., 2011), indicated that functional integration of VLPFC-insula was important in inhibitory control process. Based on that, our results are aligned with several studies that have previously demonstrated that inhibitory control plays an important role in reappraisal (Ochsner and Gross, 2005; Prakash et al., 2015) and also in IM-DF (Conway et al., 2000; Fawcett and Taylor, 2008; Wilson and Kipp, 1998; Zacks et al., 1996). Further more, we confirmed that inhibitory control ability was the basic cognitive process linked reappraisal frequency and MC ability. Additionally, previous research has demonstrated that frequent adaptive reappraisal tends to improve inhibitory control function (Bartholomew et al., 2019; Cohen et al., 2012), and a positive correlation consistent with a practice effect in people's MC ability was found (Hulbert and Anderson, 2018). Our results provides another opportunities to improve MC abilities—as it pertains to reappraisal in real life.

There were several limitations to the present study. First, this study only explored MC ability of negative memories during memory encoding phase by employing IM-DF task. Previous research has shown that MC ability can be either during the encoding or retrieval of TBF items to limit retention of unwanted memories (Anderson et al., 2004; Wylie et al., 2007). Therefore, it might be worthwhile for future studies to examine the relationship between reappraisal and MC that occurs memory retrieval (e.g., in the context of the TNT task). Second, present results showed the habitual use of reappraisal was related with MC ability in negative items. However, negative items comprise different kinds of emotions, such as angry and sad, research has pointed out that people prefer to use reappraisal for sad ER and distraction for regulating angry (Rivers et al., 2007). Therefore, it may be worth to explore the relationship between MC ability of different categories of emotional memories and ER strategies in feature study. Third, the sample in this study only consisted of healthy, young undergraduates, so the generalizability of the results to the broader population remains unknown. As we mentioned before, several mental diseases, such as PTSD, depression, were associated with MC defects (Anderson, 2011). Based on our results, future studies could explore whether training these patients to use reappraisal when facing negative stimulus could help to improve their MC abilities. In addition, present study only explored the relationship between habitual use of reappraisal estimated through ERQ and MC, several studies have investigated the relationship between habitual use of reappraisal and reappraisal ability, and indicated that they were related but not exactly the same (Bîlc et al., 2015; McRae et al., 2012). In that case, based on hypothesis which inferred that reappraisal involves MC processes (Engen and Anderson, 2018), future researchers could detect the association of MC and reappraisal ability and explore neural mechanism behind them adopting reappraisal task.

Conclusion

In summary, this is (to the best of our knowledge) the first study to experimentally identify a positive correlation between the frequency of reappraisal in everyday life and an objective measure of control over negative memories. We observed that participants who commonly rely on reappraisal as their ER strategy have better MC abilities. More importantly, the results from our mediation analysis indicate that the strength of FC between the right VLPFC and right insula might account for this relationship. These findings suggest that practicing reappraisal may train the brain to more effectively control access to negative memories.

Compliance with Ethical Standards

The procedure used here are in accordance with institutional guidelines of the local ethics committee as well as the declaration of Helsinki.

CRediT authorship contribution statement

Wenjing Yang: Conceptualization, Methodology, Writing - review & editing, Resources, Project administration. **Hui Jia:** Conceptualization, Investigation, Data curation, Methodology, Formal analysis, Visualization, Writing - original draft. **Qiuyang Feng:** Conceptualization, Investigation, Writing - review & editing. **Dongtao Wei:** Conceptualization, Methodology, Writing - review & editing. **Jiang Qiu:** Conceptualization, Investigation, Resources, Project administration. **Justin C. Hulbert:** Conceptualization, Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no financial disclosures or potential conflicts of interests.

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