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Behavioral and neural correlates of memory suppression in subthreshold depression

Wenjing Yang[a,b], Peiduo Liu[a,b,*], Kaixiang Zhuang[a,b], Dongtao Wei[a,b], Michael C. Anderson[c,d], Jiang Qiu[a,b,*]

[a] Key Laboratory of Cognition and Personality (SWU), Ministry of Education, Chongqing 400715, PR China
[b] School of Psychology, Southwest University, No. 2 Tiansheng Road, BeiBei, Chongqing 400715, PR China
[c] MRC Cognition and Brain Sciences Unit, 15 Chaucer Road, Cambridge CB2 7EF, UK
[d] University of Cambridge, The Old Schools, Trinity Ln, Cambridge CB2 1TN, UK

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ABSTRACT

Many studies have demonstrated that healthy individuals can intentionally control memory. However, little is known about the behavioral and neural mechanisms of memory control in those with subthreshold depression (SD), a highly prevalent condition associated with severe impairments and a significant social burden. In this study, we used functional magnetic resonance imaging (fMRI) and a generalized form of task-dependent psychophysiological interaction (gPPI) analysis during the think/no-think task to examine the brain mechanism of memory suppression in SD participants. The behavioral results revealed that SD participants were unable to suppress negative memories. Neuroimaging data revealed that the SD group showed greater activation than the healthy control (HC) group in the prefrontal gyrus during memory processing. Moreover, gPPI analysis showed that the SD group had significantly lower right hippocampal functional coupling with the dorsolateral prefrontal cortex during negative memory suppression than the HC group. These results indicated that SD participants recruited more frontal control resources for memory suppression because of executive and prefrontal inhibitory dysfunction. However, the abnormal prefrontal–hippocampal inhibitory pathway resulted in a failure of the memory control process when the stimuli were negative. These findings provide some evidence for understanding why SD individuals have inefficient memory control of negative memories.

1. Introduction

Subthreshold depression (SD) is defined by the presence of clinically relevant depressive symptoms that do not meet the criteria for major depressive disorder (MDD) (Bertha and Balázs, 2013; Rodríguez et al., 2012). Although SD has somewhat milder symptoms than MDD, it is associated with severe impairments and a significant social burden. Negative cognitions are a symptom of depression and play a pivotal and causal role in the maintenance and recurrence of depression (Beck, 2008). Considerable evidence has shown that the frequent occurrence of negative memories not only occurs in individuals with MDD but also occurs in individuals at risk for depression (Disner et al., 2011; Gotlib et al., 2014). Thus, it is important to investigate the neural responses underlying intentional memory control in individuals affected by SD to develop effective interventions.

The think/no-think paradigm (TNT) and directed forgetting task are often used in laboratories to explore the capacity of memory control (Anderson and Green, 2001; Anderson and Hanslmayr, 2014). The TNT paradigm has often been used to explore how suppressing retrieval impairs people's ability to intentionally recall memories, whereas the directed forgetting paradigm focuses on inhibitory control at the encoding stage to limit and disrupt the consolidation of unwanted memories (Anderson and Hanslmayr, 2014). The conventional TNT paradigm consists of three phases: a training phase, the TNT phase, and a final test phase. Participants first learn some cue-target word pairs in the training phase. Then, participants perform a TNT task. During this phase, participants are told that some of the cue words will appear in green (think trials) and that their task is to recall the associated target words as soon as possible and keep them in mind for the duration of the trial. In contrast, other cue words will appear in red (no-think trials), and their task will be to prevent the associated target word from coming into awareness. Additional cue-target word pairs that are initially learned but not presented during the TNT phase serve as the baseline. After the TNT task, memory for all the word pairs is tested. The results

* Correspondence authors at: School of psychology, Southwest University, No. 2 Tiansheng Road, BeiBei, Chongqing, 400715, PR China.
E-mail addresses: liupeiduo@swu.edu.cn (P. Liu), qiuj318@swu.edu.cn (J. Qiu).

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have shown reduced recall for the no-think targets compared to the recall for the think or baseline targets. This effect has been termed suppression-induced forgetting (SIF) and arises from people's efforts to stop retrieval (Anderson and Hanslmayr, 2014; Anderson and Huddleston, 2012; Benoit et al., 2015; Depue et al., 2010). This effect has been replicated in many studies with neutral and emotional stimuli, including words, scenes, objects and even autobiographical memories (Anderson and Hanslmayr, 2014; Benoit and Anderson, 2012; Depue et al., 2006, 2007; Liu et al., 2016).

Many neuroimaging studies have shown that retrieval suppression activates multiple regions in the control network, including the dorsolateral prefrontal cortex (DLPFC) and the ventrolateral prefrontal cortex. Increased activity in these brain regions is accompanied by a reduction in activity in the bilateral hippocampus (Anderson et al., 2004; Benoit and Anderson, 2012; Depue et al., 2007, 2016; Levy and Anderson, 2012). Functional connectivity analyses have shown coupling between the DLPFC and the hippocampus during the suppression process (Benoit and Anderson, 2012; Benoit et al., 2015). These results suggest that during retrieval suppression, the lateral prefrontal control-related regions implement top-down control to suppress hippocampal mnemonic processing and prevent conscious recollection (Anderson and Hanslmayr, 2014; Depue, 2012; Levy and Anderson, 2008).

Accumulating evidence has shown that healthy individuals can successfully suppress emotional memories with repeated attempts (Anderson and Hanslmayr, 2014). However, some studies have found that depressed participants have difficulties in intentionally forgetting emotional memories within the TNT paradigm (Berman et al., 2011; Hertel and Gerstle, 2003; Joormann et al., 2009; Yang et al., 2016; Zhang et al., 2016). For example, one study Hertel et al. (2003) used the TNT paradigm and found that depressed participants showed less forgetting of negative material (Hertel and Gerstle, 2003). Moreover, Joormann et al. (2009) found that MDD participants could not intentionally forget negative stimuli unless they were aided with cognitive strategies. Some neuroimaging studies with the TNT task showed that depressed participants had stronger activity in the right middle frontal gyrus (MFG) during memory suppression than healthy controls (HCs) (Sacchet et al., 2017). Other studies using the directed forgetting paradigm also found that depressed participants were unable to intentionally forget negative stimuli and used different neural substrates than controls while forgetting negative stimuli (Berman et al., 2011; Yang et al., 2016).

Despite the attempts of some studies to explore the behavioral and neural mechanisms of memory control in depressed participants (Sacchet et al., 2017), whether individuals with SD can intentionally suppress unwanted memories and the neural mechanism of this process have not been elucidated. Considering that SD has been related to equally poor outcomes as MDD and has been regarded as the prodromal phase of MDD (Cuijpers et al., 2004), investigation of the neuropathology of SD is important for understanding the dynamic course of MDD and for developing preventative options for MDD. Thus, this study used functional magnetic resonance imaging (fMRI) to characterize how SD participants control negative memories and the neural mechanisms underlying this process. Previous studies have shown that subthreshold depressive symptoms are highly prevalent among 18- to 20-year-olds and that these symptoms correlate with significant health problems (Bertha and Balázs, 2013). Therefore, we selected late adolescent participants for this study. Previous studies have only focused on the contributions of specific brain regions involved in intentionally forgetting memories in individuals with MDD. However, the human brain is a complex network of interconnected regions, and no specific region can support the SIF process without interacting with other brain regions (Anderson et al., 2004; Sporns et al., 2004). Previous studies have demonstrated that prefrontal control regions coassociated with memory-related regions underlie the intentional forgetting process. However, how this connectivity is altered in SD individuals trying to intentionally forget the stimuli is unknown. In this study, we also conducted a generalized psychophysiological interaction analysis (gPPI) (Friston et al., 1997) to clarify different patterns of functional connectivity when individuals with SD intentionally suppress unwanted memories compared to these patterns in HC participants.

The aim of this study was to examine the neural mechanisms of memory suppression within the TNT paradigm among SD participants. We hypothesized that SD participants would be inefficient at intentionally forgetting negative stimuli because depressed individuals have deficits in controlling the processing of negative material (Gotlib and Joormann, 2010). On the neural level, we hypothesized that the frontal control brain regions [e.g., MFG, inferior frontal gyrus (IFG), superior frontal gyrus (SFG)], which underpin the memory-suppression process, would have stronger activation when SD participants tried to intentionally forget the negative stimuli because previous studies have shown that SD individuals suffer from executive and prefrontal inhibitory dysfunction. We also hypothesized that SD participants would exhibit aberrant connectivity between the DLPFC and the hippocampus during the suppression of negative stimuli.

2. Method

2.1. Participants

Four hundred and eighty participants from Southwest University, Chongqing, China, were recruited through advertisements. The potential participants were screened through two stages. First, all participants completed the Beck Depression Inventory-II (BDI) (Beck et al., 1996). Participants who scored 14 and above or 6 and below were invited to participate in the second session, which was conducted one week later. In the second session, participants completed an in-person screening session, which included the BDI and administration of the Structured Clinical Interview for the DSM-IV (SCID). SD participants were those who had a BDI score of $\geq$14 at both assessments. The healthy control (HC) participants were those who had a BDI score of $\leq$ 6 at the two stages of assessment and satisfied the same exclusion criteria as the SD participants. The exclusion criteria included the following: (1) major depressive episode, assessed by the SCID diagnostic criteria; (2) lifetime bipolar disorder, panic disorder or schizophrenia; (3) lifetime history of psychopharmacological or psychological treatment; (4) history of addictive disorders such as substance abuse or alcoholism; and (5) major medical, psychiatric or neurological disorder. Finally, 23 participants screened for SD, and 21 matched HCs participated in this study. All participants were right-handed and signed written informed consent forms prior to the study. The study was approved by the SWU Brain Imaging Center Institutional Ethics Review Board. After the experiment, participants were paid cash for their involvement in the study.

Two participants did not pass the first learning stages of the TNT task after three cycles of learning practice (50%), and four participants had excessive head motion in the scanner ($\geq$3 mm). Therefore, these participants were excluded from the data analyses. In all, the data from 20 participants in the HC group and 18 participants in the SD group were analyzed. The characteristics of the participants are presented in Table 1.

Table 1
. Demographic features of participants.

	Subthreshold depression		Healthy control		*P* value
	Mean	Standard deviation	Mean	Standard deviation	
Age	20.56	1.10	20.35	1.31	$p>0.05$
BDI	19.83	6.16	3.70	2.25	$p<0.001$

Note: BDI, Beck Depression Inventory-II.

2.2. Measures

Beck Depression Inventory-II: The BDI, which consists of 21 self-report items scored on a four-point scale (0–3), has widely been used to measure the severity of depressive symptoms for an individual during the previous week. The BDI is considered to be a reliable measure for assessing the severity of depressive symptoms in clinical and non-clinical samples (Beck et al., 1996).

2.3. Experimental design and materials

This study used a 2 (group: SD vs. HC) × 2 (emotion: neutral vs. negative) × 3 (memory condition: think/no-think/baseline) design. The emotion and memory condition were the within-group factors, and the group was the between-group factor. One hundred and sixty Chinese character words (80 neutral nouns and 80 adjectives) were selected from established pools of Chinese affective words (Wang et al., 2008). Using a self-report nine-point rating scale, we asked the participants to rate the emotional valence from very unpleasant to very pleasant and arousal from very calm to very excited. The negative and neutral adjectives differed in valence (mean: negative = 2.07 ± 0.19; neutral = 4.58 ± 0.63; t (158) = 33.568, $p < 0.001$) and arousal (mean: negative = 5.41 ± 0.52; neutral = 4.46 ± 0.39; t (158) = 12.951, $p < 0.001$). The familiarity of these neutral and negative words was not significantly different (t (158) = 0.932, $p > 0.05$). All 80 nouns were cue words, and the 80 adjectives were response words. To ensure that the cue and target words were weakly related to each other, words with low semantic relatedness, i.e., less than 2.5 (rated on a 5-point Likert scale), were used as materials. Five participants who did not participate in the following formal experiments assessed the semantic relatedness of all the word pairs. Eight word pairs were used as fillers in the practice phase. The other 72 word pairs were assigned into three subsets that were used in the baseline, think, and no-think conditions.

2.4. Procedure

2.4.1. Learning phase

We used the conventional TNT paradigm (Anderson et al., 2004) that consists of three phases: a training phase, the TNT phase, and a final test phase. In the training phase, participants were asked to learn 80 cue-target word pairs. In each trial, each of the 80 word pairs randomly and individually appeared in white font for 3 s, followed by a 500-ms fixation cross that separated the word pairs. After two cycles of direct learning, there was a test-feedback cycle in which at least 50% accuracy in recalling the associations needed to be achieved. The participants were presented with the cue word and asked to first think of the target word; then, the correct target word was presented for 1 s. The participants who recalled less than 50% of the word pairs correctly after three cycles did not continue to the next phase.

2.4.2. Think/no-think phase

The TNT phase was conducted in the MRI scanner. Prior to the study, the participants were instructed that all the cue words would be presented in one of two colors, that is, green or red. If the cue word was green, they needed to recall the associated target word as soon as possible and keep it in mind for the duration of the trial. If the cue word was red, their task was to prevent the associated target word from coming into awareness by blocking out all thoughts about it without replacing it with any other thoughts (no-think condition). Every word was repeated twice in each block. For each trial, a cue word was presented for 4 s, and the interstimulus interval (ISI) (2 s, 4 s, 6 s, 8 s) was jittered to optimize the efficiency of the event-related fMRI design. The participants viewed a fixation cross during the ISI. Each run began with a 10-s blank period to allow the scanner signal to stabilize and ended with an 8-s blank period to allow for the time lag in the hemodynamic response. A training session was carried out with filler word pairs before the formal TNT phase to ensure that all the participants understood the instructions.

2.4.3. Test phase

The participants completed the test phase out of the scanner. In this phase, the cue words were presented on the screen for 4 s, and participants needed to recall the target words aloud.

2.5. fMRI data acquisition

Whole-brain imaging data were acquired on a Siemens 3T scanner (Siemens Magnetom Trio TIM, Erlangen, Germany) using an 8-channel head coil. T2*-weighted functional images were acquired using a single-shot gradient echo-planar imaging (EPI) pulse sequence (32 slices, repetition time (TR) = 2000 ms, echo time (TE) = 30 ms; flip angle = 90°; field of view (FoV) = 220 mm × 220 mm; matrix size = 64 × 64; voxel size = 3.4 × 3.4 × 4 mm^3). In addition, T1-weighted high-resolution anatomical images were also recorded (slices = 176, TR = 1900 ms; TE = 2.52 ms; FoV = 256 × 256; voxel size = 1 × 1 × 1 mm^3).

2.6. fMRI data preprocessing and general linear model (GLM) analysis

The functional images were preprocessed with SPM8 (Welcome Department of Cognitive Neurology, London, UK, http://www.fil.ion.ucl.ac.uk/spm/spm8). Slice timing was used to correct the differences in image acquisition time between slices, and realignment was performed to correct for head motion. Then, images were normalized to the Montreal Neurological Institute (MNI) EPI template (3 × 3 × 3 mm^3). The normalized data were spatially smoothed with a Gaussian kernel with a full-width at half-maximum of 8 × 8 × 8 mm^3. Low-frequency drifts were removed by applying a highpass filter set at 128 s. The first 5 volumes of each run were discarded to allow for equilibration effects.

Statistical analysis for each individual participant was conducted using the GLM. For each group, two factors (memory condition and emotion) yielded four conditions, namely, think negative (T-NG), think neutral (T-NE), no-think negative (NT-NG), and no-think neutral (NT-NE). The onset of each of these four conditions was modeled, and each trial was modeled as an event. Six realignment parameters for each participant were also modeled as confounding factors. All six runs were modeled in a GLM.

Contrast coefficients were calculated at the individual level with t-tests and then entered into a group-level random-effects analysis to estimate the error variance across individuals. The contrasts of interest were NT-NG > T-NG and NT-NE > T-NE, reflecting brain activation when participants attempted to suppress the negative and neutral stimuli, respectively. To explore the different activation patterns between the SD group and HC group when participants attempted to suppress the negative and neutral materials, two-sample t-tests were conducted to compare contrast images induced by NT-NG > T-NG and NT-NE > T-NE between these two groups. All analyses were conducted at the whole-brain level, and the threshold was set to $p < 0.05$ [false discovery rate (FDR) corrected] for multiple comparisons with a minimum spatial extent of 10 contiguous voxels. For the two-sample t-test results, we also used a lenient threshold of $p < 0.001$ uncorrected for multiple comparisons with a threshold for minimum spatial extent of 10 contiguous voxels for exploratory analyses.

2.7. Task-dependent functional connectivity analysis

A generalized form of task-dependent PPI (gPPI) was conducted to explore functional connectivity in SD participants when suppressing unwanted memories. Previous studies have shown that the hippocampus and the lateral prefrontal regions coordinate to suppress

unwanted memories (Benoit and Anderson, 2012; Benoit et al., 2015). The PPI analysis focused on the no-think versus think conditions with the hippocampus as the seed region to explore functional connectivity of the hippocampus with other voxels of the brain, particularly in the prefrontal control systems. The hippocampus seeds were defined as a 4-mm sphere centered at the local peak of corresponding clusters showing significant interaction effects between memory instruction, emotion and group in the univariate GLM analysis [MNI coordinates 24, −15, −12 (*x, y, z*) (right hippocampus), −24, 12, 12 (left hippocampus)]. Separate PPI analyses were conducted for each index area. The time series from this seed were extracted for each participant and deconvolved to obtain an estimate of the physiological activity. Next, four PPI regressors (no-think negative vs. think negative; no-think neutral vs. think neutral) were obtained by multiplying the estimated neuronal activity of the seed region with a vector representing the effects of each condition. These four psychophysiological interaction vectors were further reconvolved with the hemodynamic response function (HRF) and entered into a GLM. Task-related activations were also included in the GLM to exclude the effects of common driving inputs on brain connectivity.

The contrast images corresponding to the PPI effects from the first-level analysis in each participant were then entered into a second-level random-effect model, in which task-dependent PPI effects were investigated with one-sample t-tests to separately explore the functional coupling during suppression of the negative and neutral memories for the SD and HC groups. To explore the different functional coupling between the HC and the SD groups, we entered the contrast images from the SD and HC groups that showed a greater influence during the no-think than the think condition into a two-sample *t*-test model to compare the PPI results between the groups. We report the results with a threshold of uncorrected $p < 0.001$ with at least 20 contiguous voxels. The PPI beta value of the significant functional connectivity, a measure of the strength of functional connectivity between the hippocampus and each coupled region, was then extracted for the subsequent correlation and mediation analysis.

2.8. Mediation analysis

To test whether the functional connectivity between the right hippocampus and right DLPFC can explain the relationship between memory control abilities for the negative memories and depression, we performed an exploratory mediation analysis using an indirect macro implemented in SPSS (Preacher and Hayes, 2008).

3. Results

3.1. Behavioral results

3.1.1. Demographic characteristics

The demographic characteristics of the participants are shown in Table 1. There was no significant difference between the HC and SD group in terms of age. However, the BDI scores in the SD group were significantly higher than those in the HC group ($p < 0.001$).

3.1.2. Learning performance

The recall accuracy after the learning phase was not significantly different [$T(36) = 1.026, p > 0.05, \eta 2\ p = 0.028$] between the SD and HC groups. Moreover, the interaction between group and emotion was not significant [$F(1, 36) = 0.714, p > 0.05, \eta 2\ p = 0.019$].

3.1.3. Final recall performance

Repeated-measures ANOVA was performed over the recall data, with memory instruction (baseline vs. think vs. no-think) and emotion (negative vs. neutral) as the within-subject factors and group (SD vs. HC) as the between-subject factor. The results showed a main effect of memory instruction [$F(2, 72) = 12.377, p < 0.001, \eta 2\ p = 0.256$], in which the recall accuracy of the no-think condition items was lower than that of the baseline condition items and the think condition items, thereby replicating the SIF effect (Anderson and Green, 2001; Benoit et al., 2015; Catarino et al., 2015). There was no main effect of emotion [$F(1, 36) = 0.238, p > 0.05, \eta 2\ p = 0.007$] or group [$F(1, 36) = 0.703, p > 0.05, \eta 2\ p = 0.019$]. Interestingly, a marginal significant three-way interaction of emotion × memory instruction × group was found [$F(2, 72) = 3.105, p = 0.05, \eta 2\ p = 0.079$]. Simple effect analyses showed that the SIF effect was significant both with the negative stimuli [$F(2, 35) = 6.321, p < 0.01, \eta 2\ p = 0.265$] and the neutral stimuli [$F(2, 35) = 4.604, p < 0.05, \eta 2\ p = 0.208$] in the HC group. Meanwhile, the SIF effect was found in the SD group with the neutral stimuli [$F(2, 35) = 3.459, p < 0.05, \eta 2\ p = 0.165$]. However, this effect was reversed in the negative stimuli [$F(2, 35) = 3.949, p < 0.05, \eta 2\ p = 0.184$]. These results suggest that the SIF effect was modulated by group and valence.

The priori interest of this study aimed to explore the difference of SIF between the HC and SD groups. Therefore, we assessed individual SIF by subtracting the recall percentage of the no-think items from that of baseline items. A repeated-measures ANOVA was performed over the SIF effect, with emotion (negative vs. neutral) as the within-subject factor and group (SD vs. HC) as the between-subject factor. This analysis aimed to determine whether group and emotion influenced SIF. The results showed that the main effect of emotion, [$F(1, 36) = 2.390, p > 0.05, \eta 2\ p = 0.062$], and group [$F(1, 36) = 2.262, p > 0.05, \eta 2\ p = 0.059$] were not significant. However, the interaction between emotion and group was significant [$F(1, 36) = 4.734, p < 0.05, \eta 2\ p = 0.116$]. The simple effect showed that the SIF effect for neutral memories was not significantly different between the SD and HC groups [$F(1, 36) = 0.164, p > 0.05, \eta 2\ p = 0.005$]. However, the SIF effect for negative memories was significantly different between these two groups [$F(1, 36) = 4.961, p < 0.05, \eta 2\ p = 0.121$], with the SD group exhibiting a lower SIF effect than the HC group.

An exploratory analysis showed that SIF of negative memories was significantly and negatively correlated with BDI scores ($r = -0.371$, $p = 0.022$) (Fig. 1).

3.2. GLM analysis results

To compare the results with previous TNT studies, we first compared the brain activity on the contrast of no-think and think conditions (Table 2 and Fig. 2). When HC participants suppressed neutral and negative stimuli, the MFG, medial frontal gyrus, middle temporal gyrus (MTG) and parietal lobe were activated. The hippocampus, cuneus and lingual gyrus were deactivated during the NT > *T* contrast. This result was consistent with previous studies (Anderson and Hanslmayr, 2014; Anderson et al., 2004; Depue et al., 2007). When the SD group suppressed memories, the MFG, medial frontal gyrus, SFG, IFG, MTG, superior parietal gyrus, inferior parietal gyrus, and fusiform gyrus were activated.

A between-group analysis was performed to explore the differences in activation between the SD and HC groups (Table 3 and Fig. 3) and revealed that brain activation during suppression of the negative and neutral stimuli was significantly different. When suppressing neutral stimuli, the SD group had greater activation in the MFG, motor area and occipital lobe than the HC group. However, when suppressing negative stimuli, the SD group had greater activation in the bilateral MFG, SFG, IFG, lingual gyrus and precentral gyrus than the HC group.

3.3. PPI analysis results

The comparison of the HC and SD groups (HC > SD) revealed significantly higher hippocampal functional coupling with the DLPFC when suppressing negative stimuli. One-sample *t*-test results showed that activity in the right hippocampus showed a positive correlation with the DLPFC in the HC group, consistent with previous studies

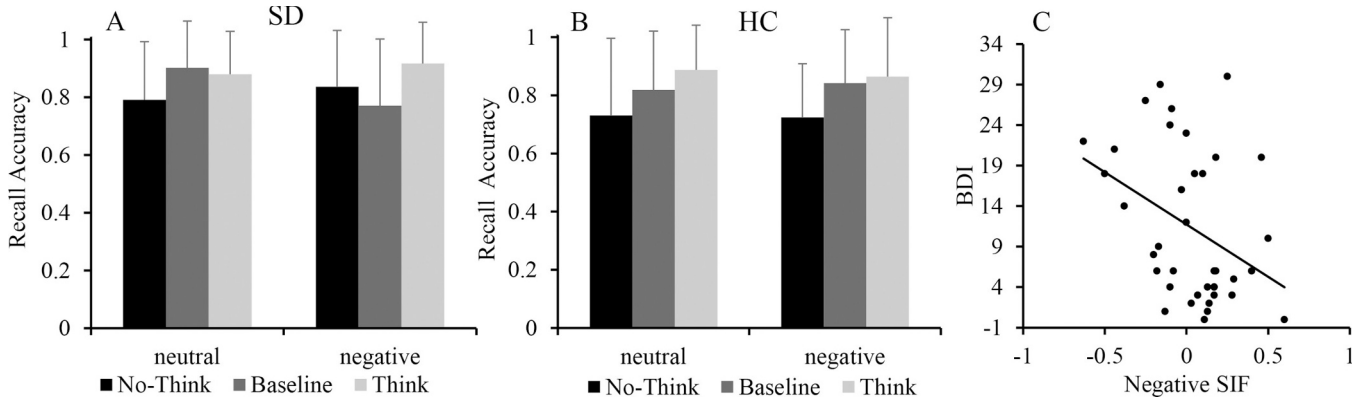

Fig. 1. A and B: The recall accuracy in each condition for the subthreshold depression participants and healthy controls. Error bars represent standard deviation of the recall accuracy. C: The correlation between the Beck Depression Inventory-II (BDI) scores and memory control with the negative memories (Negative SIF). HC, healthy control; SD, subthreshold depression.

(Benoit and Anderson, 2012; Benoit et al., 2015). However, the opposite pattern was observed when the SD participants suppressed the negative stimuli (Table 4). A correlation analysis between the memory control index for the negative unwanted memories and the PPI beta estimate of the significant functional connectivity revealed that the connectivity between the right hippocampus and right DLPFC was positively correlated with individual differences in memory control of negative memories ($r = 0.353$, $p = 0.030$) (Fig. 4).

3.4. Mediation analysis

Exploratory mediation analysis showed that the functional coupling between the right DLPFC and right HC mediated the association between memory control and BDI scores (indirect effect = 2.13; 95% confidence interval: lower limit = −10.79; upper limit = −1.75) (Fig. 4).

4. Discussion

The aim of this study was to characterize the different behavioral and neural mechanisms exhibited by SD participants to intentionally suppress unwanted memories. The behavioral results showed that it was difficult for SD participants to suppress negative unwanted memories, although their ability to suppress neutral stimuli was similar to that of HCs. Brain activation analysis showed that the SD group had stronger activation in the bilateral MFG, right SFG, right IFG, lingual gyrus and precentral gyrus when they intentionally suppressed unwanted memories than in the HC group. Moreover, functional connectivity analysis with gPPI showed that the SD group had significantly lower right hippocampal functional coupling with the DLPFC during suppression of the negative memories than the HCs. The results suggested that distinct patterns of brain activation and hippocampal-prefrontal functional connectivity were involved in the suppression of negative memories in the HC and SD groups.

The behavioral results showed that the SD participants could not suppress the negative memories in a manner similar to the HCs. This finding was consistent with clinical observations that depression is characterized by the frequent occurrence of unintentional and uncontrollable negative thoughts and memories (Beck, 2008; Gotlib and Joormann, 2010). We also found that individual differences in memory control of negative memories were significantly negatively correlated with BDI scores, potentially indicating that retrieval suppression was more compromised in individuals with more severe symptoms. The executive control hypothesis of memory control holds that individual differences in the regulation of unwanted memories are mediated by executive control abilities (Levy and Anderson, 2008). Accumulating evidence has found that depressed individuals suffer from executive and prefrontal inhibitory dysfunction (Langenecker et al., 2007; Müller et al., 2017; Pizzagalli, 2011; Rogers et al., 2004) and rumination on negative thinking and events (Beck, 2008; Gotlib et al., 2014). Therefore, suppressing negative memories is difficult for depressed individuals. The current results are similar to those of previous studies that found that MDD participants were unable to intentionally forget negative memories but able to intentionally forget neutral memories (Hertel and Gerstle, 2003; Zhang et al., 2016). The dimensional view argues that depression is a continuous rather than discrete disorder and that adolescent SD is a precursor to MDD (Angst et al., 2000; Ayuso-Mateos et al., 2010; Cuijpers et al., 2004; Rapaport et al., 2002). Our results indicated that SD participants and those with MDD exhibit similar patterns of memory control processes. Future research can directly explore whether there are subtle differences in memory control between individuals with SD and MDD.

Both the SD and HC groups consistently showed activation of the lateral prefrontal gyrus (e.g., MFG and SFG) in the suppression process. Previous studies using the TNT task have demonstrated that the lateral prefrontal gyrus, which includes the IFG and MFG, is important in the memory-suppression process (Anderson et al., 2004; Benoit and Anderson, 2012; Depue et al., 2007, 2016; Levy and Anderson, 2012; Paz-Alonso et al., 2013). Functional connectivity analyses have demonstrated that the DLPFC implements a top-down inhibitory regulation of hippocampal activity that supports retrieval (Benoit and Anderson, 2012; Benoit et al., 2015). In addition to the activation of the PFC during the memory control process, we also observed hippocampal deactivation during the memory-suppression process in both the SD and HC groups. The gPPI results showed that the functional connectivity between the hippocampus and the DLPFC was increased when HCs suppressed negative memories. Moreover, the correlation analysis showed that functional connectivity between the right hippocampus and the right DLPFC was positively correlated with individual differences in memory control of negative memories. This result was consistent with previous studies (Anderson and Hanslmayr, 2014; Benoit and Anderson, 2012; Benoit et al., 2015), suggesting that our experiment was effective and confirming that the prefrontal–hippocampal inhibitory pathway plays an important role in the memory-suppression process. Our results also showed deactivation of the amygdala when participants suppressed negative memories, consistent with previous studies (Depue et al., 2010, 2007), suggesting cognitive control over memory representations by the lateral prefrontal gyrus via modulation of the hippocampus and the amygdala during intentional suppression of emotional content.

Interestingly, the SD participants exhibited a significantly greater activation in the bilateral MFG upon memory suppression than the HC group. These results were consistent with a previous study that found that MDD individuals exhibited greater activity in the right MFG during

Table 2.
Brain regions with significant activations while suppressing the neutral and negative stimuli. The results are shown separately for each group (healthy controls and subthreshold depression participants) and valence (negative and neutral).

Anatomical region	MNI coordinates			Number of voxels	Peak *t*-value
	X	*Y*	*Z*		
HC group					
NG_NT > *T*					
Middle temporal gyrus	60	−57	12	749	6.20
Middle temporal gyrus	−60	0	−27	177	5.36
Medial frontal gyrus	3	18	−12	81	4.53
Angular gyrus	−51	−69	36	90	4.55
Middle frontal gyrus	45	12	30	120	5.79
Parietal lobe	−27	−81	48	36	4.39
Middle frontal gyrus	30	−3	48	189	6.09
NG_*T*>NT					
Cuneus/Precuneus	−9	−87	0	2160	−6.23
Hippocampus	27	−30	−6	104	−4.69
Hippocampus	−24	−24	−9	74	−4.75
Caudate	−12	21	12	44	−4.05
Postcingulate	9	−39	21	25	−4.37
Precentral gyrus	48	−6	12	23	−3.44
Cingulate gyrus	3	−27	33	38	−4.34
NE_NT > *T*					
Middle temporal gyrus	−54	−12	−18	235	6.90
Middle temporal gyrus	63	−57	9	146	6.85
Middle frontal gyrus	48	0	33	120	6.00
Middle occipital gyrus	−36	−87	30	15	4.65
NE_*T*>NT					
Lingual gyrus	18	−96	−15	557	−9.37
Hippocampus	−24	−36	3	53	−5.76
Hippocampus	30	−39	6	32	−5.53
Thalamus	−3	−12	9	49	−4.59
Caudate	−9	18	9	19	−5.24
Inferior frontal gyrus	−48	45	15	15	−5.47
Parietal lobe	−57	−15	18	13	−4.26
Precuneus	−12	−69	33	54	−6.94
SD group					
NG_NT > *T*					
Superior frontal gyrus	15	12	66	2958	6.89
Middle temporal gyrus	−51	9	−24	510	4.86
Fusiform	−30	−48	−15	32	3.54
Medial frontal gyrus	−3	33	−21	51	3.30
Middle occipital gyrus	39	−84	27	1995	7.13
Middle Occipital gyrus	−48	−78	18	979	5.46
Middle frontal gyrus	−36	27	42	1131	4.50
Postcentral gyrus	57	−18	33	27	3.14
Superior parietal	−18	−63	54	123	3.75
NG_*T*>NT					
Cuneus	15	−93	6	2024	−8.36
Hippocampus	27	−27	−9	147	−6.05
Hippocampus	−27	−27	−6	158	−4.54
Amygdala	27	9	−15	13	−2.74
Caudate	9	9	18	52	−4.26
Thalamus	−3	−9	3	59	−4.17
Insula	39	−15	21	36	−3.39
Precuneus	15	−63	30	90	−4.46
Cingulate gyrus	−3	−36	27	28	−3.16
Inferior parietal	−33	−54	39	27	−3.94
NE_NT > *T*					
Middle frontal gyrus	18	15	60	706	7.05
Middle temporal gyrus	−48	−75	21	567	5.79
Inferior frontal gyrus	51	36	−9	237	3.94
Supramarginal gyrus	63	−48	30	1175	5.92
Middle frontal gyrus	30	33	33	259	5.07
Superior frontal gyrus	−12	57	27	385	5.16
Middle temporal gyrus	−27	27	15	26	−5.33
Inferior parietal lobe	33	−45	51	39	3.48
Precuneus	−9	−63	60	35	3.38
NE_*T*>NT					
Middle occipital gyrus	18	−93	6	1890	−7.72
Middle occipital gyrus	−33	−93	−6	31	−3.33
Hippocampus	−27	−36	0	167	−4.73
Hippocampus	27	−30	−6	46	−4.51
Frontal lobe	−39	−6	21	113	−4.04
Caudate	6	18	3	45	−4.36
Frontal lobe	−63	0	33	49	−3.61
Superior frontal gyrus	33	63	−3	23	−4.75
Cingulate gyrus	−3	−36	27	101	−4.57
Precuneus	15	−66	33	45	−3.86

Note: A positive t-value indicates increased activity. A negative t-value indicates decreased activity. All the results survived FDR correction, $p < 0.05$, K > 20. MNI, Montreal Neurological Institute coordinate system; HC, healthy control; SD, subthreshold depression; NG, negative; NE, neutral; NT, no-think; T, think.

memory suppression than HCs (Sacchet et al., 2017). The lateral prefrontal gyrus is important in the inhibitory regulation of hippocampal activity that supports memory retrieval (Anderson and Hanslmayr, 2014; Benoit and Anderson, 2012; Benoit et al., 2015). The present results suggested that the SD participants recruited more frontal resources than the HCs to intentionally suppress memory retrieval, especially for the negative stimuli. Some previous studies also showed that participants with depression had stronger PFC gyrus activation than HCs during tasks that required executive function (Bär et al., 2007; Diener et al., 2012; Wagner et al., 2006). For example, Harvey et al., 2005 found that MDD participants had stronger activation in the lateral PFC than HCs during the n-back task. The authors interpreted the results as an indication that the MDD participants needed to recruit greater activation of the same neural network as the HCs to maintain a similar level of performance during the working memory task. Some studies also found that depressed individuals had stronger activation in the frontal regions than HCs during these processes in the behavior inhibition task (Langenecker et al., 2007) and emotion regulation task (Johnstone et al., 2007). During retrieval suppression, the lateral prefrontal control regions implement top-down control that suppresses the hippocampus to prevent conscious recollection of memory (Anderson et al., 2004; Benoit and Anderson, 2012; Depue et al., 2007, 2016 Levy and Anderson, 2012). However, evidence has shown that individuals with SD suffer from executive and prefrontal inhibitory dysfunction (Alexopoulos, 2002; Goodwin, 1997; Langenecker et al., 2007; Rogers et al., 2004) and would therefore need to recruit more frontal inhibitory control to suppress unwanted memories. However, when the suppressed memories are negative, the biased processing of negative stimuli results in a failure of the suppression process (Beck, 2008; Gotlib et al., 2014). The current results suggested that SD participants recruit greater activation in the prefrontal regions (e.g., MFG, IFG) than HCs to suppress memory retrieval. When the suppressed memory is negative, an even stronger level of prefrontal gyrus activation is unable to efficiently suppress the negative memories.

The gPPI results showed that the SD participants had significantly lower hippocampal functional coupling with the DLPFC during the suppression of negative memories than the HCs. When the SD participants suppressed negative memories, decreased functional connectivity between the right hippocampus and right DLPFC was observed, whereas the opposite pattern of connectivity results was observed in the HC group. During the TNT task, the DLPFC implements a top-down inhibitory modulation of hippocampal activity that supports memory retrieval (Benoit and Anderson, 2012; Benoit et al., 2015; Paz-Alonso et al., 2013). However, SD participants have been shown to suffer from executive and prefrontal inhibitory dysfunction and negative bias processing (Alexopoulos, 2002; Goodwin, 1997; Langenecker et al., 2007; Rogers et al., 2004). Therefore, the prefrontal-hippocampus connectivity underlying memory control processes is abnormal, and this abnormal functional coupling between the right hippocampus and the right DLPFC results in an inefficient suppression of negative memories by SD participants. Notably, the functional connectivity between the right hippocampus and the right DLPFC mediated the correlation

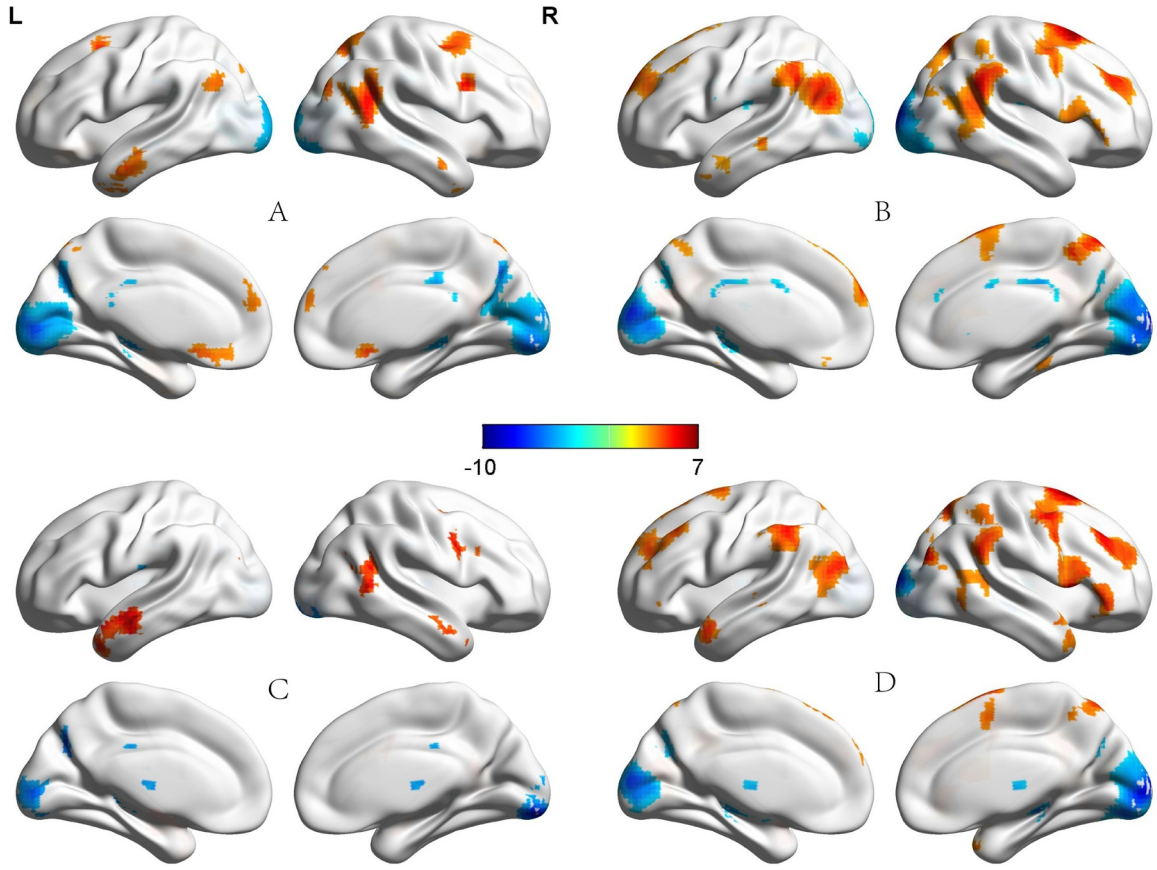

Fig. 2. Brain activity for the contrast of no-think and think conditions when subthreshold depression participants and healthy controls intentionally suppressed the negative and the neutral stimuli. A depicts the brain activity when the healthy controls suppressed the negative stimuli (no-think > think conditions). B depicts the brain activity when the subthreshold depression participants suppressed the negative stimuli. C depicts significant brain activation when the healthy controls suppressed the neutral stimuli. D depicts significant brain activation when the subthreshold depression participants suppressed the neutral stimuli. All the results survived FDR correction, $p < 0.05$, K > 20.

Table 3
. Brain regions which showed significantly different activation on the contrast of no-think and think for the negative and the neutral stimuli between the subthreshold depression participants and healthy controls (subthreshold depression > healthy controls).

Anatomical region	MNI coordinates			Number of voxels	*t*-value
NE_NT > *T*	x	y	z		
Middle frontal gyrus	−39	51	18	37	4.02
Middle frontal gyrus	33	36	30	11	3.56
Supp_Motor_Area	9	15	72	11	3.66
Occipital lobe	0	−96	−9	17	3.44
NG_NT > *T*					
Middle frontal gyrus	36	39	27	170	4.68*
Superior frontal gyrus	21	−3	78	61	4.83*
Middle frontal gyrus	−36	45	18	65	4.63*
Inferior frontal gyrus	42	12	12	61	3.68
Lingual gyrus	−12	−90	0	19	3.68
Precentral	60	9	18	17	3.70

Note: All the results were threshold $p < 0.001$ uncorrected. $K > 10$. The results with * survived after FDR correction, $p < 0.05$. No significant differences were found on the contrast of control > subthreshold depression. MNI, Montreal Neurological Institute coordinate system; HC, healthy control; SD, subthreshold depression; NG, negative; NE, neutral; NT, no-think; T, think.

between the SIF of negative stimuli and the BDI scores. Clinical observations suggest that depression is characterized by the frequent occurrence of unintentional and uncontrollable negative thoughts and memories (Beck, 2008; Disner et al., 2011). Our results suggest that alterations in the prefrontal–hippocampal inhibitory pathway may be the mechanism for this dysfunction. Moreover, MDD is characterized by impaired regulation of negative affect (Beck and Bredemeier, 2016; Mathews and MacLeod, 2005). Some studies have found that MDD participants demonstrate abnormal frontal-limbic interactions during cognitive emotion regulation (Davis et al., 2018; Doré et al., 2018; Ochsner et al., 2012; Rive et al., 2013). One recent article presented a theoretical account of how the mechanism of memory control constitutes core component processes of cognitive emotion regulation (Engen and Anderson, 2018). Future studies should explore to what degree the neural mechanisms supporting affective control overlap with those supporting memory control for MDD individuals. A recent meta-analysis study showed that individuals with SD were approximately two times more likely than non-depressed individuals to develop MDD (Lee et al., 2019). Many studies have called for better identification of and effective interventions for SD (Cuijpers et al., 2007). Recent studies have shown that repeatedly practicing memory control can improve one's memory control ability (Hulbert and Anderson, 2018), which may have some implications for preventative interventions for the transition from SD to MDD.

The current study had several limitations. First, the sample size was relatively small. Therefore, a study with a larger sample size is required to replicate these results. Second, because this study mainly focused on the different neural mechanisms underlying the suppression of memories by individuals with SD, the independent cue test (IP test), which uses a novel cue that is semantically related to the target, was not used during the test phase to assess participants' memories. The IP test is a purer index for the inhibitory process on the target itself, and the same probe test (SP test) mixes the inhibition with associative interference

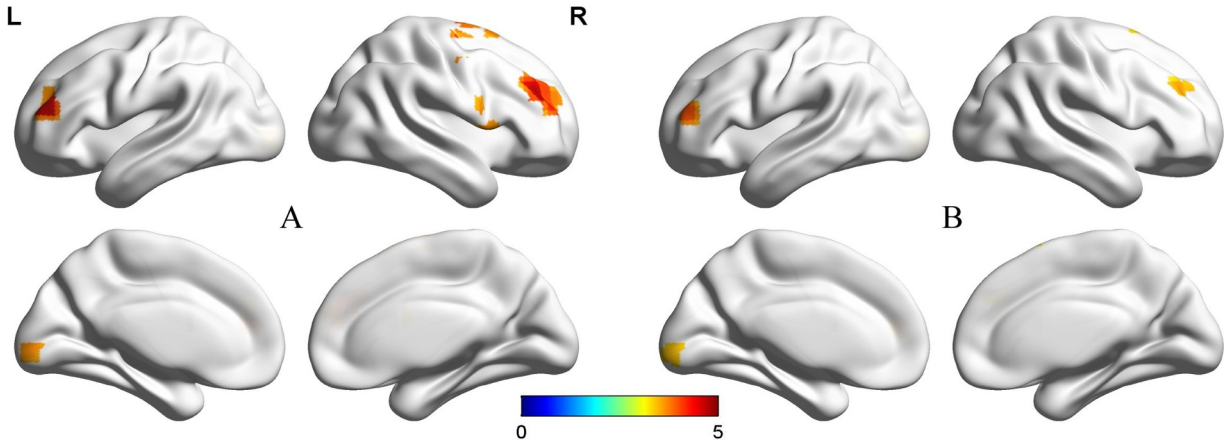

Fig. 3. Differences in brain regions between the subthreshold depression participants and healthy controls (subthreshold depression > healthy controls) when intentionally suppressing the neutral and negative stimuli. A depicts differential brain activation between the subthreshold depression participants and healthy controls during suppression of the negative stimuli. B depicts differential brain activation between the subthreshold depression participants and healthy controls during suppression of the neutral stimuli. All the results were thresholded at an uncorrected $p< 0.001$, $K > 10$, for display only.

Table 4.
The different gPPI results between the subthreshold depression participants and healthy controls during suppression of the neutral and the negative stimuli.

Anatomical region	MNI coordinates			Number of voxels	*t*-value
Right hippocampus as seed	x	y	z		
Superior frontal gyrus	21	39	57	32	4.24
Left hippocampus as seed					
Frontal lobe	−9	30	3	80	4.71
Superior frontal gyrus	−15	48	42	36	3.68
Superior frontal gyrus	18	36	57	165	4.82

Note: MNI, Montreal Neurological Institute coordinate system.

(Anderson and Levy, 2007). Therefore, future studies may use the IP test to differentiate failed memory suppression in SD participants that was related to inhibition that weakened the association between the cue and the target or the target itself.

In conclusion, the current study showed that suppression of negative unwanted memories is difficult for SD participants. The SD group recruited more frontal and parietal inhibitory control resources during suppression of unwanted memories than the HC group because of deficits in inhibitory control. However, when the suppressed stimuli were negative, the lower hippocampal functional coupling with the DLPFC resulted in a failure of the memory control. The results showed that the prefrontal–hippocampal inhibitory pathway was the mechanism of the negative association between memory control of negative memories

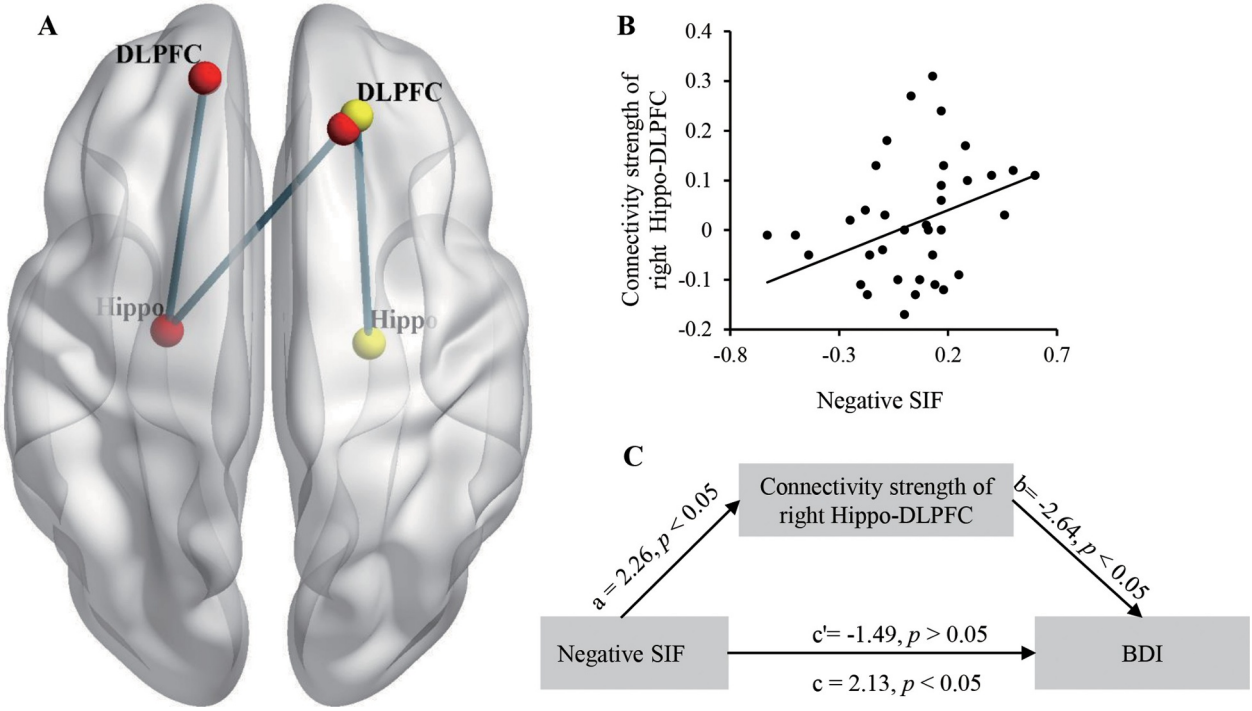

Fig. 4. A: Different brain connectivity between the subthreshold depression participants and healthy controls during suppressing the negative stimuli. The results were thresholded at an uncorrected $p< 0.001$, $K > 10$. B: The connectivity strength of the right hippocampus and dorsolateral prefrontal cortex (DLPFC) was positively correlated with memory control with the negative stimuli (negative SIF). C: The connectivity strength of the right hippocampus and DLPFC mediated the correlation between the BDI scores and memory control with the negative stimuli in the subthreshold depression. Hippo: Hippocampus.

and the severity of depressive symptoms in individuals. These results might have some implications for preventative interventions for individuals with SD.

Declaration of Competing Interest

The authors declare no conflicts of interest.

Acknowledgments

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