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Functional coupling of the orbitofrontal cortex and the basolateral amygdala mediates the association between spontaneous reappraisal and emotional response

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ABSTRACT

Emotional regulation is known to be associated with activity in the amygdala. The amygdala is an emotion-generative region that comprises of structurally and functionally distinct nuclei. However, little is known about the contributions of different frontal-amygdala sub-region pathways to emotion regulation. Here, we investigated how functional couplings between frontal regions and amygdala sub-regions are involved in different spontaneous emotion regulation processes by using an individual-difference approach and a generalized psycho-physiological interaction (gPPI) approach. Specifically, 50 healthy participants reported their dispositional use of spontaneous cognitive reappraisal and expressive suppression in daily life and their actual use of these two strategies during the performance of an emotional-picture watching task. Results showed that functional coupling between the orbitofrontal cortex (OFC) and the basolateral amygdala (BLA) was associated with higher scores of both dispositional and actual uses of reappraisal. Similarly, functional coupling between the dorsolateral prefrontal cortex (dlPFC) and the centromedial amygdala (CMA) was associated with higher scores of both dispositional and actual uses of suppression. Mediation analyses indicated that functional coupling of the right OFC-BLA partially mediated the association between reappraisal and emotional response, irrespective of whether reappraisal was measured by dispositional use (indirect effect(SE)=-0.2021 (0.0811), $95\%CI_{(BC)}$= [-0.3851, -0.0655]) or actual use (indirect effect(SE)=-0.1951 (0.0796), $95\%CI_{(BC)}$= [-0.3654, -0.0518])). These findings suggest that spontaneous reappraisal and suppression involve distinct frontal- amygdala functional couplings, and the modulation of BLA activity from OFC may be necessary for changing emotional response during spontaneous reappraisal.

1. Introduction

The amygdala is an important brain region for emotional processing, but different amygdala nuclei have different functions (Kim et al., 2011; Morris et al., 2001). Specifically, the nuclei of basolateral amygdala (BLA) and centromedial amygdala (CMA) play a vital role in the input processing of emotional information and the generation of behavioral responses, respectively (Danilo et al., 2013; Joseph, 2000). Similarly, the BLA evaluates sensory information (Brown et al., 2013) and adjusts the association between emotional stimulus and outcome value (Nasser et al., 2017; Parkes and Balleine, 2013). The BLA has also been implicated in memory processes for emotional experiences (Ferreira et al., 2005; Yoon et al., 2016). The CMA is involved in generating, coordinating and controlling emotion responses (Danilo et al., 2013; Ledoux, 1998), and deactivation of the CMA results in the impairment of emotional expression (Duvarci and Pare, 2014; Nicholson et al., 2015).

Functional couplings of different amygdala sub-regions and frontal regions have been implicated in different traits of affective disorder pathology (Aghajani et al., 2016; Hrybouski et al., 2016). For example, functional couplings of BLA and CMA with multiple distributed brain systems (e.g., sensory and perceptual system, frontoparietal attentional system, striatal reward system and saliency system) were found to be associated with anxiety severity and posttraumatic stress disorder (PTSD) (Herwig et al., 2007; Liu et al., 2015; Qin et al., 2014). Furthermore, recent studies have found that amygdala sub-regions (particularly the BLA and the CMA) and its functional couplings have different relationships with traits of emotion regulation (Hrybouski et al., 2016; Picó-Pérez et al., 2017). Specifically, functional coupling between the BLA

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and the supplementary motor area (SMA) is associated with the dispositional use of cognitive reappraisal, whereas functional coupling between the CMA and the SMA is associated with the dispositional use of expressive suppression (Picó-Pérez et al., 2017).

Cognitive reappraisal is a cognitive-linguistic strategy that alters the trajectory of emotional responses by reformulating the meaning of affective stimuli or events (Ochsner et al., 2004). Expressive suppression is a strategy directed towards inhibiting external behaviors associated with emotional responding (e.g., facial expressions, verbal utterances, gestures) (Goldin et al., 2008). According to the modal model of emotion (Gross and Thompson, 2007), the BLA and the CMA may play an important role in the early appraisal and late response stages of emotional processing, respectively. Consistent with this evidence, previous studies have identified cognitive reappraisal as an early-on, antecedent-focused strategy that works before the stimulus gives rise to full-fledged emotional response, whereas expressive suppression as a late, response-focused strategy that modulates emotional responses when they are fully blown (Goldin et al., 2008; Ochsner et al., 2012; Silvers et al., 2015). Therefore, it is reasonable to speculate that the BLA and its functional coupling may play a role in reappraising affective information, whereas the CMA and its functional coupling may play a role in inhibiting the output of emotional responses.

However, less work has directly examined the neural mechanisms underlying the relationship between different amygdala sub-regions and emotion regulation. Moreover, prior studies of amygdala sub-regions mostly focused on resting-state and did not involve emotion elicitation (Hrybouski et al., 2016; Picó-Pérez et al., 2017). There is a gap between resting-state and task-based spontaneous emotion regulation, which refers to a spontaneously arising emotion-regulatory process that is triggered by an emotional situation, in the absence of explicit instructions from another person (Baur et al., 2015; Ehring et al., 2010; Kanske et al., 2012; Scult et al., 2017). Furthermore, spontaneous emotion regulation is closely associated with mental health. Increased spontaneous reappraisal is associated with decreased symptoms of stress-related mood and anxiety (Scult et al., 2017), whereas reduced spontaneous reappraisal is related to higher depression vulnerability (Ehring et al., 2010). Therefore, clarifying how different amygdala sub-regions are involved in spontaneous emotion regulation would help to understand neural mechanisms of emotion-regulation dysfunction. Based on existing literature, we hypothesize functional couplings of the BLA and the CMA should be associated with spontaneous reappraisal and suppression, respectively.

In addition, the reduction of emotional response has been considered as the result of effective emotion regulation in previous studies. Although the activity and functional couplings of amygdala are closely associated with emotional response, few studies have investigated how amygdala sub-regions based functional couplings are implicated in emotional response and its association with spontaneous emotion regulation (Lee et al., 2012; Murphy et al., 2016). As mentioned above, emotional response could be associated with activity in both kinds of amygdala sub-regions pathways (Hrybouski et al., 2016). For example, some recent studies have found that resting-state functional couplings of the BLA and the CMA with the frontal cortex were both involved in fear response (Duvarci and Pare, 2014; Zhu et al., 2018). Thus, clarifying the neural mechanisms underlying decreased emotional response may help shed light on revealing the contributions of different frontal-amygdala sub-regions pathways to emotion regulation.

In order to address the above questions, the present study conducted an emotion elicitation task, in which we detected the alteration of functional coupling in amygdala sub-regions during spontaneous emotion regulation using an individual-difference approach (Drabant et al., 2009; Scult et al., 2017) and a generalized psycho-physiological interaction (gPPI) approach (Berger et al., 2017; Ginty et al., 2019; Masson et al., 2020). We measured the habitual use of two emotion regulation strategies (cognitive reappraisal and expressive suppression) in daily life using the Emotion Regulation Questionnaire (ERQ) (Gross and John, 2003). We also measured self-report scores of the actual use of these strategies in the picture- watching task, given that multiple emotional regulation strategies may be used during a natural emotion-evoking situation (Aldao and Nolen-Hoeksema, 2013; Opitz et al., 2015; Szasz et al., 2018). Subsequently, correlation analyses and mediation analyses were conducted to probe the associations between spontaneous emotion regulation, functional couplings of amygdala sub-regions and emotional response. Taken together, in the present study, we not only provide direct tests of whether functional couplings of the BLA and the CMA are associated with spontaneous emotion regulation, but also examined whether these functional couplings mediate the relationship between spontaneous emotion regulation and emotional responses.

2. Methods and materials

2.1. Participants

Fifty right-handed, healthy participants (24 females) were recruited for the current study. The participants were aged 18 to 25 years (M = 21.52 years, SD= 1.89) and reported no history of psychiatric or neurological illnesses. This study was approved by the local ethical committee of Sichuan Normal University and the Institutional Human Participants Review Board of the Southwest University Imaging Center for human brain research. All participants gave written informed consent and were paid a nominal amount for their participation.

2.2. Stimuli

Picture stimuli consisted of negative and neutral pictures taken from the International Affective Picture System (IAPS) and the Chinese Affective Picture System (CAPS). All of the presented stimuli were pretested for arousal and valence in a previous study, negative pictures (M = 6.84, SD= 0.59) were significantly more arousing than neutral pictures (M = 3.09, SD= 0.51), d = 3.75, t (29) = 29.35, p< 0.01, 95% CI [3.49, 4.01]; For valence ratings, negative pictures (M = 5.94, SD= 0.53) led to significantly higher scores of valence than neutral pictures (M = 4.06, SD= 0.59), d = 1.87, t (29) = 12.19, p< 0.01, 95% CI [1.56, 2.19]. Picture stimuli (both negative pictures and neutral pictures) were also selected to match for size (15×10 cm^2) and resolution (100 pixels/inch), luminance and complexity.

2.3. Behavioral assessment and experimental procedures

Prior to the start of fMRI scanning, participants were first administered the Chinese version of the Emotion Regulation Questionnaire (ERQ) on the same day of scanning. The ERQ was used to evaluate the dispositional use of emotion regulation strategies in daily life by measuring individual differences in suppression and reappraisal. (Gross and John, 2003). Previous studies have used the ERQ to assess the association between the dispositional use of emotion regulation and depressive tendencies (Abler et al., 2010), early life stress (Khawli et al., 2017), executive control processes (Scult et al., 2017; Vanderhasselt et al., 2013) or resting-state functional connectivity (Picó-Pérez et al., 2017). These prior studies have consistently shown the ERQ is a valid and reliable index of the dispositional use of emotion regulation. Given that emotional response might be impacted by individual difference in personality trait, we administered two control measures. First, we administered the Chinese version of the NEO Five-Factor Personality Inventory (Kurylo and Stevenson, 2011), a self-report questionnaire with five personality dimensions: Neuroticism, Extraversion, Openness to experience, Agreeableness, and Conscientiousness. Secondly, we administered the trait version of the State-Trait Anxiety Inventory (Shek, 1988) which assesses individual differences in trait anxiety.

We adopted a typical passive-viewing task by using an event-related design (Feng et al., 2014). In each trial, participants were first presented with a picture stimulus for 8 s. Participants were required to passively view the Negative or Neutral pictures and to let their emotional responses arise naturally. There were two experimental conditions: (1) Look Neutral: participants watched neutral pictures and were instructed to just naturally look at the screen. (2) Look Negative: Participants watched negative pictures and were also instructed to just naturally look at the screen. Following picture presentation, participants saw a jittered fixation interval (jitter range= 3–6 s; mean duration= 4 s) and subsequently rated their affective state on a 9-point Self-Assessment Scale (SAM) (1= Very good, 5= No feelings, 9= Very bad). Each trial concluded with a jittered fixation interval (on average, 4 s). Thirty negative and thirty neutral pictures were presented in a randomized order by 5 subsequent runs, which took approximately 20 min.

We provided a brief illustration of reappraisal and suppression after the experiment, to confirm participants knew which strategy they had used. The instructions of reappraisal and suppression are respectively as follows: *Reappraisal: "While watching pictures, you tried to reinterpret the content of the picture so that it no longer elicited a negative response"; Suppression: "While watching pictures, you tried to refrain from showing your expression so that no one can know your feelings"*. Participants were also told that they could ask the experimenter if they didn't understand these strategies. Then the experimenter will give a specific example (eg. Reappraisal: Assuming the perspective of a medical professional during watching an instructional picture or focusing on technical aspects of the picture; Suppression: Keeping their face still while viewing pictures so that someone watching their face would not be able to detect what was being experienced subjectively) to ensure correct understanding of these strategies. Then, the participants rated the extent to which they had used reappraisal and suppression during the whole task, that is Emotion Regulation in Tasking-state (ERT), using a 9-point scale ranging from 0 (not at all) to 9 (extremely). The ERT was used to measure the actual use of strategies during the current emotional task (Egloff et al., 2006). In summary, we collected emotion-related fMRI data, subjective emotional ratings, and self-report scores of both dispositional (Reappraisal$_{ERQ}$, Suppression$_{ERQ}$) and actual use (Reappraisal$_{ERT}$, Suppression$_{ERT}$) of two typical emotion regulation strategies.

2.4. FMRI data acquisition and preprocessing

Whole-brain fMRI data were acquired on a 3T General Electric Discovery MR750 (GE Healthcare, Milwaukee, Wisconsin) scanner. Structural images were acquired with a T_1-weighted protocol (128 sagittal sections, $1 \times 1 \times 1$ mm^3, 256×256 data acquisition matrix). Functional images were acquired with a $T_2{}^*$- weighted, gradient-echo planner imaging (EPI) pulse sequence recording 33 sections oriented roughly parallel to the anterior and posterior commissure at an in-plane resolution of $3.5 \times 3.5 \times 3.5$ mm^3 (inter-slice gap = 0; TE = 30 ms; TR = 2000 ms; FA = 90°; FoV = 224×224 mm^2; 64×64 data acquisition matrix). Slices were acquired in an interleaved ascending order. 221 whole-brain volumes were recorded. Stimuli were presented using E-Prime and were projected onto a flat screen mounted in the scanner bore. Participants viewed the screen using a mirror mounted on an 8-channel head coil.

Preprocessing was performed using statistical parametric mapping (SPM12) tools (www.fil.ion.ucl.ac.uk) implemented in DPARSF (DPARSFA v3.2, http://rfmri.org/DPARSF) (Yan et al., 2016). Preprocessing comprised adjusting for variable acquisition time over slices (slice-timing), head motion correction (realignment). Two steps were adopted in this study to control for the effects of head motion on the signals. First, if Power frame displacement was found to be greater than 0.5, then that time point was deemed a "bad" time point, and the time points before and after that bad time point were scrubbed using each of the bad time points as a regressor (Power et al., 2012). Second, only the subjects whose data satisfied our criteria for head motion, displacement of $<$ 3 mm in any plane and rotation of $< 3^\circ$ in any direction were included in final analysis. We performed these steps by using DPARSF and no participants were excluded because of motion artifacts according to our criteria. A total of 50 subjects were entered into the final data analysis. Then, normalization was conducted by applying DPARSF, which leads to an improved registration between subjects (Fastenrath et al., 2014; Tian et al., 2020; Zheng et al., 2019). Normalization incorporated the following steps: (1) anatomical images of each subject were segmented using the "New Segment" procedure in SPM12; (2) the resulting gray and white matter images were used to derive a study-specific group template; (3) an affine transformation was applied to map the group template to the Montreal Neurological Institute (MNI) space; (4) subject-to-template and template-to-MNI transformations were combined to create a single normalization transformation for each subject; and (5) the normalization transformation for each subject was then applied to map. Finally, spatial smoothing using an 8 mm Gaussian kernel to increase signal-to-noise ratio.

2.5. Whole-brain analyses

Whole brain image analysis was completed with SPM12, and custom written programs in Matlab (R2017a, processing MathWorks, Inc., USA). Stimulus-viewing and response portions of each trial were modeled as boxcar regressors convolved with a canonical hemodynamic response function. Separate regressors were made for each task condition and robust regression analyses were performed for each participant (i.e., a robust first-level GLM was created for each participant). For the first-level analyses, we compared the brain activity associated with the conditions of interest (e.g., negative>neutral; neutral>negative). Pairwise t statistics for the contrasts of interest were calculated for each subject. The first-level analyses produced whole-brain average and activation t maps for each condition, contrast of interest, and TR/time point. The outputs of first-level analyses were used as inputs for second-level random-effects within-group analyses. By using subjective emotion ratings of each picture as a parameter on a single subject level, we ran a random effect group analysis (one-sample *t*-test) to assess the activation associated with a subjective increase in the degree of emotion for negative pictures. To correct for multiple comparisons within a volume, we applied a height threshold of a family-wise error rate (FWE) of $p< 0.05$ and a cluster threshold of $k> 10$ voxels (Li et al., 2020; Snook et al., 2007; Torta et al., 2016). Recent studies suggest that the FWE correction method is an acceptable correction method for studies in the field of social neuroscience (Han and Glenn, 2018; Han et al., 2019), despite the issue of inflated FWE-rates indicated by Eklund and colleagues (Eklund et al., 2016). The FWE correction method provides a more appropriate balance between false positives and false negatives than other correction methods. Moreover, several studies argued that cluster tests failed in Eklund and colleagues' study (2016) because they violated the assumptions underlying analytic (random field theory) approximations to null distributions (Flandin and Friston, 2019), in particular, violated the assumption that clusters are defined by a reasonably high threshold. Therefore, the threshold values in the current study should be acceptable, non-problematic for cluster-level inference (Loose et al., 2017).

2.6. Regions-of-interest (ROI) analyses

To examine the association between spontaneous emotion regulation and regional brain activation, we used a similar approach as performed in previous studies investigating the correlation of brain activation with ERQ/ERT scores (Drabant et al., 2009; Vanderhasselt et al., 2013). In this approach, ERQ/ERT scores were correlated with Percent signal change (PSC), which was extracted as estimates for BOLD response in the identified activation clusters generated at the whole-brain level. To correct for multiple comparisons in our study, we used Holm-Bonferroni correction for multiple testing (α= 0.05, two-tailed) (Holm, 1979).

2.7. Connectivity analysis

We employed a seed-to-voxel connectivity analysis using the BLA and the CMA as seed regions, then we conducted a gPPI contrast of Negative > Neutral. Maps of voxel-wise connectivity analysis were thresholded at the voxel-level $p < 0.005$ (uncorrected) for cluster formation, with cluster-based FWE correction ($p < 0.05$). Subsequently, we extracted Negative > Neutral gPPI values for each ROI (regions showing significant cluster values change in the contrast of Negative > Neutral). Finally, we separately calculated correlations between the gPPI values and ERQ&ERT scores, Holm-Bonferroni correction was used in our correlation analyses for multiple comparisons. The steps of current analyses were consistent with several previous studies of functional connectivity (Li et al., 2014; Murphy et al., 2016; Späti et al., 2015). The selection of the seed regions of interest was based in previous studies, and corresponded to amygdala subdivisions shown to have distinct whole-brain functional connectivity patterns (Baur et al., 2013; Picó-Pérez et al., 2017). Signal extraction was performed using MarsBaR region-of-interest toolbox (Brett et al., 2002) in MNI stereotaxic space. As in previous studies with these same regions of interest (Cano et al., 2016; Picó-Pérez et al., 2017), seeds were defined in both hemispheres as 3.5 mm radial spheres centered at: left BLA (x=−26, y=−5, z=−23), right BLA (x = 29, y=−3, z=−23), left CMA (x=−19, y=−5, z=−15) and right CMA (x = 23, y=−5, z=−13) (Fig. 2A). Importantly, all these coordinates were spatially separated between each other by at least 8 mm (1 FWHM), according to the formula:

$$\sqrt{\left((x1-x2)^2+(y1-y2)^2+(z1-z2)^2\right)}$$

Where (x1 y1 z1 & x2 y2 z2) refer to the coordinates of any two voxels in MNI space. This ensured we were obtaining specific functional connectivity maps for each seed region of interest. Moreover, since signal artifacts have been typically described in the amygdala region, we ensured both at the group and the individual level that our images provided an adequate coverage of this region.

The functional seed-to-voxel analysis was conducted with the CONN toolbox (v18; https://www.nitrc.org/projects/conn/) (Whitfield-Gabrieli and Nieto-Castanon, 2012). The CONN toolbox is suited for the analysis of functional connectivity in event-related designs (Berger et al., 2017; Ginty et al., 2019), by conducting a generalized psycho-physiological interaction (gPPI) approach (see CONN manual v18; https://www.nitrc.org/projects/conn/). To correct for confounds of motion and physiological noise (Chai et al., 2012; Murphy et al., 2009), the CONN toolbox implemented the anatomical component-based noise correction method (Behzadi et al., 2007), extracting principal components related to the segmented cerebrospinal fluid (CSF) and white matter. This approach has been shown to increase the validity, sensitivity and specificity of functional connectivity analyses (Chai et al., 2012). Therefore, white matter and CSF noise components were used as confound regressors in the subject-level GLM. In addition, estimates of global signal and motion parameters were included as confound regressors. To control for simple condition-related activation effects, we also included the main task effects (negative, neutral) as confound regressors in our functional connectivity analysis. Low-frequency drifts were removed via a high pass filter (128 s). The mean time-series were averaged across all voxels within each seed and were used as a regression parameter, and correlated with all other voxels in the brain in a seed-to-voxel connectivity analysis. For the analysis, the CONN toolbox conducted a gPPI approach with connectivity measures calculated as bivariate correlations. This approach results in group-level statistics representing Fisher-z transformed correlation coefficient values.

To test the hypotheses that individual differences in spontaneous emotion regulation are related to specific functional connectivity patterns, we examined the correlation between functional couplings of amygdala sub-regions and individual scores on ERQ/ERT scores (reappraisal, suppression). The results of seed-to-voxel connectivity analysis in the contrast of Negative > Neutral were thresholded at cluster-based FWE correction ($p < 0.05$) for multiple comparisons at the whole-brain level in CONN. To examine whether the functional connectivity change of Negative > Neutral covaried with the ERQ- and ERT, we extracted Negative > Neutral gPPI values for each ROI (regions showing significant cluster values change in the contrast of Negative > Neutral) and separately calculated correlations between the gPPI values and ERQ&ERT scores. To correct for multiple comparisons, Holm-Bonferroni correction was conducted by SPSS script outside CONN in our correlation analysis.

Table 1
The correlation between emotion ratings, the bilateral amygdala activation and ERQ/ERT scores ($^{*}p < 0.05$, $^{**}p < 0.01$).

	ERQ		ERT	
	Reappraisal	Suppression	Reappraisal	Suppression
Emotion Response	−0.448**	−0.308*	−0.447**	−0.365**
Right Amygdala	−0.345*	−0.257	−0.363*	−0.275
Left Amygdala	−0.311*	−0.240	−0.322*	−0.240

2.8. Mediation analyses

Mediation analyses were conducted using a bootstrapping method (MacKinnon et al., 2004). Models were tested using the SPSS macro PROCESS (Hayes, 2012), which calculates a bootstrap estimate of the indirect effect between the independent variable and dependent variable, an estimated standard error, and 95% confidence intervals (CI) for the population value of the indirect effect. The indirect effects of functional couplings of the BLA and the CMA on emotional response were bootstrapped using 5000 samples. Prior to conducting analyses, all variables were z-scored to produce standardized β weights.

3. Results

3.1. Emotional responding

We conducted a paired sample t-test with picture type (Negative and Neutral) as a within-participants factor to examine whether the task elicited emotion successfully. As in earlier study, participants reported significantly higher negative affect for negative stimuli ($M = 6.84$, SD= 0.84, $d = 2.63$, $t\ (49) = 16.57$, $p < 0.01$, 95% CI [2.32, 2.96]) than neutral stimuli ($M = 4.21$, SD= 0.49) (Fig. 1B). Emotional response scores were calculated by the differences in emotional rating between Negative and Neutral conditions. Moreover, the results of whole-brain analyses showed that the Negative versus Neutral contrast led to significant activation of the bilateral amygdala (Fig. 1A).

3.2. Spontaneous emotion regulation

Means and standard deviations for the self-report scores of participants: ERQ-Reappraisal ($M = 26.70$, $SD = 4.21$) and ERQ-Suppression ($M = 15.74$, $SD = 4.49$); ERT-Reappraisal ($M = 5.78$, $SD = 0.72$) and ERT-Suppression ($M = 5.62$, $SD = 0.77$). Emotional response scores and PSCs of the bilateral amygdala were negatively correlated with both types of measures of spontaneous reappraisal and suppression (i.e., ERQ & ERT, Table 1). These results are consistent with the findings of previous studies, which reflect that participants with higher ERQ & ERT scores have less unpleasantness and decreased amygdala activation (Drabant et al., 2009). Additionally, we found spontaneous emotion regulation—as measured by the ERQ — showed high convergent validity with our ERT scores, $r = 0.71$ (reappraisal) and $r = 0.69$ (suppression). This showed consistency between the dispositional use and actual use of emotion regulation strategies (Egloff et al., 2006).

We also conducted a correlation analysis between PSCs of the bilateral BLA/CMA and ERQ/ERT scores. Results showed that PSCs of the bilateral BLA were negatively associated with both ERQ- and ERT-reappraisal scores (Fig. 2B&C). In contrast, PSC of left but not right CMA

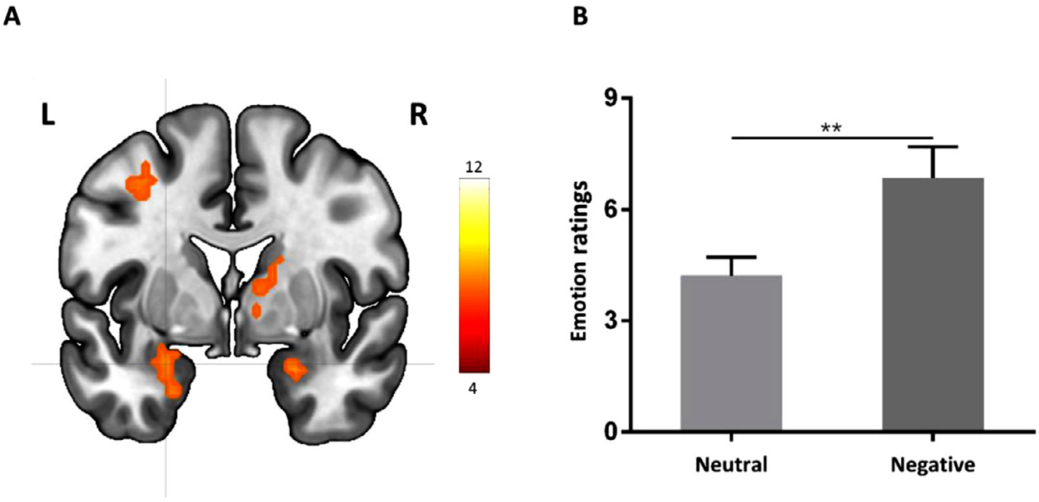

Fig. 1. **(A)** From the one-sample *t*-test across all 50 subjects for the contrast (Negative>Neutral). The display threshold was a cluster-wise threshold of $p < 0.05$, FWE corrected, based on a voxel-wise threshold of $p < 0.005$. **(B)** The emotion ratings of picture type (Negative>Neutral).

Table 2

Results of the functional seed-to-voxel connectivity analysis (Negative>Neutral) for the subregions of amygdala as seed region. Results are thresholded at the voxel-level $p< 0.005$ (uncorrected) for cluster formation,with cluster-based FWE correction ($p< 0.05$).

Seed	Anatomical Region	Lat.	Coordinates			T	p	k
			x	y	z			
right BLA	orbitofrontal cortex	R	34	44	−12	4.12	0.01	21
	dorsolateral prefrontal cortex	L	−2	54	30	3.74	0.02	20
	dorsal anterior cingulate	R	6	48	14	3.52	0.04	18
left BLA	insula	L	−36	2	6	3.49	0.04	16
left CMA	dorsolateral prefrontal cortex	L	−38	52	14	4.47	0.01	24
	inferior parietal lobule	L	−56	−64	36	3.71	0.03	20
	angular gyrus	L	−50	−64	50	3.31	0.03	16

was negatively correlated with both ERQ- and ERT-suppression scores (Fig. 2D). In addition, regression analyses showed that our results were not due to individual differences in emotional reactivity (eg. neuroticism and anxiety) (For more details, see supplementary material).

3.3. Functional connectivity

For connectivity analysis, we conducted a seed-to-voxel connectivity analysis using the bilateral BLA and the left CMA as seed regions. We have reported the functional connectivity cluster values change in the contrast of Negative > Neutral (cluster-based FWE correction ($p< 0.05$)). These results were shown in Table 2 and Fig. 3A&B. To examine whether the functional connectivity change of Negative > Neutral covaried with the ERQ or ERT, we extracted Negative > Neutral gPPI values for each ROI (regions showing significant cluster value change in the contrast of Negative > Neutral) and separately calculated correlations between the gPPI values and ERQ&ERT scores. These results were shown in Fig. 3C&D. To correct for multiple comparisons, Holm-Bonferroni correction was conducted by SPSS script outside CONN. Our results showed that both ERQ- and ERT-reappraisal scores positively correlated with increased functional coupling of the right OFC-BLA (r_{ERQ}= 0.383, p = 0.006; r_{ERT}= 0.369, p = 0.008) (Fig. 3C), and both ERQ- and ERT-suppression scores positively correlated with increased functional coupling of the left dlPFC–CMA (r_{ERQ}= 0.416, p = 0.003; r_{ERT}= 0.398, p = 0.004) (Fig. 3D). No significant results were found between ERQ-(or ERT-) reappraisal scores and increased functional coupling of the left dlPFC–CMA (r_{ERQ}= 0.001, p = 0.993; r_{ERT}= −0.102, p = 0.482). Similarly, there was no significant ERQ- (or ERT-) suppression scores and increased functional coupling of the right OFC-BLA (r_{ERQ}= −0.034, p = 0.812; r_{ERT}= 0.002, p = 0.990). To correct for multiple comparisons in our study, we used Holm-Bonferroni multiple comparison to correct significance threshold for seven tests (α= 0.05, p = 0.007) (Holm, 1979). Given the conservative nature of the Bonferroni correction, our current results are still reliable though one of them is a marginal significant correlation (r_{ERT}= 0.369, p = 0.008). These results indicated that spontaneous reappraisal is associated with the functional coupling of BLA and spontaneous suppression is associated with the functional coupling of CMA.

3.4. Functional coupling of the right OFC-BLA mediates the association between reappraisal and emotional response

The mediation analysis is based on a standard three-variable path model and with a bootstrap test for the statistical significance of the indirect effect, as diagrammed in Fig. 4. As illustrated in Fig. 4, the results showed that indirect effects of ERQ- and ERT-reappraisal scores on emotional response scores were significant. However, we did not find significant indirect effects of ERQ- and ERT-suppression scores on emotional response scores. These results, shown in Table 3, indicate that functional coupling of the right OFC-BLA partially accounts for the association between reappraisal and emotional response (For more details on our mediation analysis, see supplementary material). A confidence interval (CI) that does not contain zero indicates that there is a significant mediation effect for the proposed mediating factor. The significant mediation effects reported in Table 3 should be considered reliable, given that several functional neuroimaging studies with small CI lower values also showed convincing mediation effects (Menatti et al., 2015; Wager et al., 2008; Wang et al., 2020).

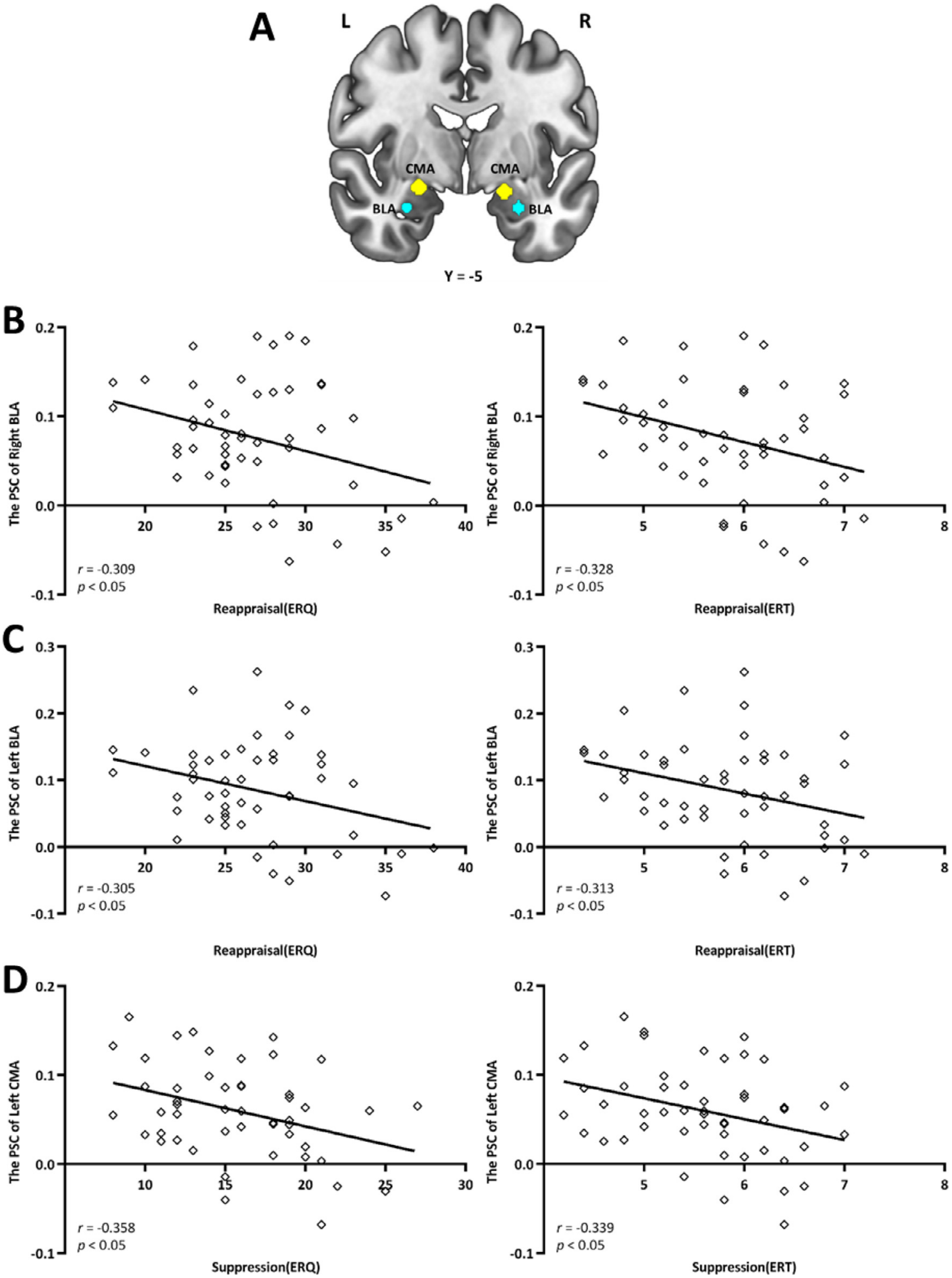

Fig. 2. **(A)** The location of Amygdala sub-regions. **(B)** Scatter plot between reappraisal scores (ERQ/ERF) and the PSC extracted from right BLA. **(C)** Scatterplots between reappraisal scores (ERQ/ERF) and the PSC extracted from left BLA. **(D)** Scatterplots between suppression scores (ERQ/ERF) and the PSC extracted from left CMA. (PSC, percent signal change).

4. Discussion

This study aimed to explore the contributions of different frontal-amygdala sub-regions pathways during spontaneous emotion regulation. We detected the alteration of functional coupling in amygdala sub-regions by using an individual-difference approach and a gPPI approach. We also examined the mediation effects of different functional couplings on the relationship between spontaneous emotion regulation and emotional response. We demonstrated that amygdala sub-regions were associated with those cerebral regions that were involved in the emotion regulation process. Specifically, correlation analysis used in this study suggests that reappraisal score (ERQ/ERT) is positively correlated with increased functional coupling between right OFC and right BLA, and suppression score (ERQ/ERT) is positively correlated with increased

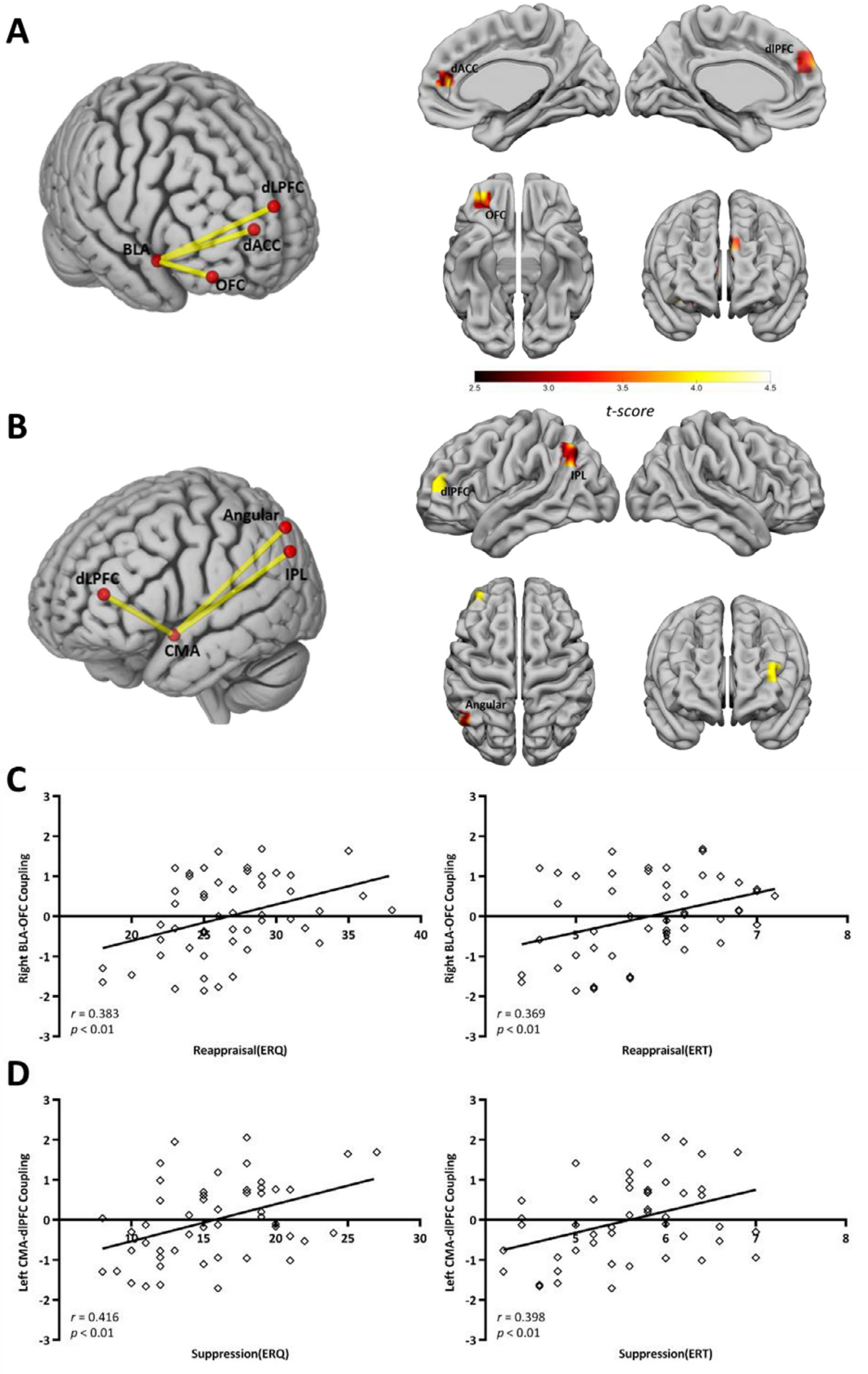

Fig. 3. **(A)** Nodes and links & Increased functional couplings of right BLA from neutral to negative trials (negative > neutral). **(B)** Nodes and links & Increased functional couplings of left CMA from neutral to negative trials (negative> neutral). **(C)** Scatterplots between reappraisal scores (ERQ/ERF) and functional coupling of the right OFC-BLA (Z score). **(D)** Scatterplots between suppression scores (ERQ/ERF) and functional coupling of the left dlPFC–CMA (Z score).

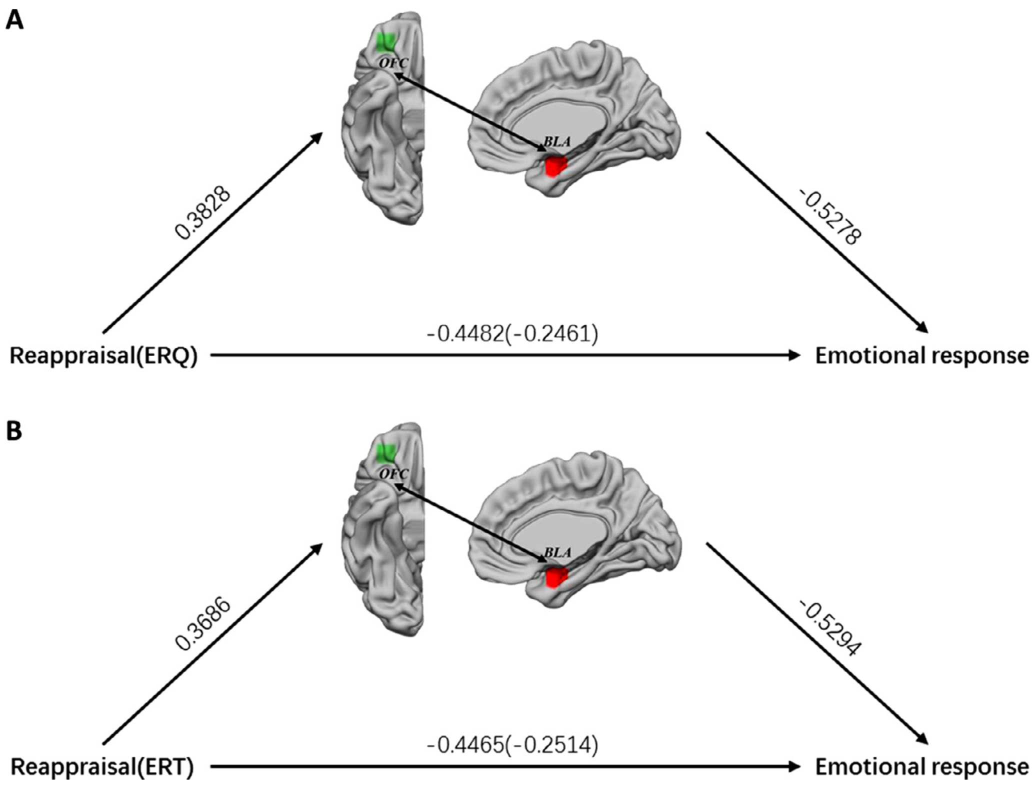

Fig. 4. The mediating effect of functional coupling of the right OFC-BLA. Indirect path $a = 0.3828$(ERQ)/0.3686(ERT); indirect path b=−0.5278(ERQ)/−0.5294(ERT); total relationship c=−0.4482(ERQ)/−0.4465(ERT) and direct path c'=−0.2461(ERQ)/−0.2514(ERT).

Table 3
The indirect effects of ERQ/ERT on emotional response through functional couplings of the right OFC-BLA and the left dlPFC–CMA.

Predictor Variables		Mediator	Indirect Effect	SE	95%CI(BC)	
					Lower	Upper
ERQ						
	reappraisal	Right BLA—OFC	−0.2021	0.0811	−0.3851	−0.0655
	suppression	Left CMA—dlPFC	−0.0732	0.0688	−0.2122,	0.0631
ERT						
	reappraisal	Right BLA—OFC	−0.1951	0.0796	−0.3654	−0.0518
	suppression	Left CMA—dlPFC	−0.0607	0.0701	−0.2342	0.0537

Note: Number of Bootstrap Resamples = 5000. CI(BC) = bias corrected confidence interval.

functional coupling between left dlPFC and left CMA. Additionally, mediation analyses indicate that functional coupling of the right OFC-BLA partially mediates the association between reappraisal and emotional response. Our findings extend the understanding of the function in amygdala sub-regions during spontaneous emotion regulation, in that spontaneous reappraisal and suppression involve different frontal-amygdala functional couplings. Importantly, our mediation results emphasize that the regulation of BLA from OFC may be necessary for changing emotional response during spontaneous reappraisal.

The BLA has been shown to be involved in processing high-level sensory input and stimulus-value associations, while the CMA is involved in generating attentional, vegetative and motor responses (Danilo et al., 2013; Hrybouski et al., 2016). A recent study suggested that the resting-state functional connectivity of different amygdala sub-regions was associated with the dispositional use of emotion regulation strategies (Picó-Pérez et al., 2017). Specifically, functional coupling between the SMA and the BLA was associated with the use of cognitive reappraisal; and the functional coupling between the SMA and the CMA is associated with the use of expressive suppression. Therefore, our current results suggest that the neurobiological differences between spontaneous regulation strategies probably depend on the specific amygdala region being inhibited, with downregulation of the BLA activity associated with spontaneous reappraisal, and downregulation of the CMA activity associated with spontaneous suppression.

The amygdala has direct connections with the dorsal anterior cingulate (dACC) and the insula, which are both considered to be nodes of the salience network (Ghashghaei et al., 2007; Livneh and Paz, 2012). The dACC is considered as an integration cortex to detect external events and internal states and to adjust behavioral responses accordingly. The BLA is involved in fear learning, by integrating information from the sensory cortex, thalamus and dACC in people with anxiety (Hakamata et al., 2020). The insula could receive signals of discomfort from the body, and then integrate the signals and send the discomfort information to the amygdala (Nasser et al., 2017; Uematsu et al., 2015). Ferreira et al. (2005) found that the connection between the BLA and insula is important during the formation of disgust feelings. Taken together, the current results showed that increased BLA functional couplings with the dACC and insula may be due to the formation of negative feelings before emotion regulation.

Prior neuroimaging studies have suggested that the inferior parietal lobule (IPL) is associated with emotion recognition and emotional contagion (Engelen et al., 2015; Shamay-Tsoory, 2011). For instance, individuals with schizophrenia showed functional abnormalities in the IPL during imaging studies of emotion recognition (Radua et al., 2010; Venkatasubramanian et al., 2010). Mukherjee and colleagues also found that the effective connectivity from the amygdala to the IPL corresponds to fearful facial expression processing in schizophrenia (Mukherjee et al., 2012). For the angular gyrus, it has a function in supporting subjective memory vividness and is associated with a subjective feeling of recollection, as indicated by prior studies (Kensinger et al., 2011; Slotnick, 2010). Therefore, one possible explanation of increased functional couplings between the CMA and left IPL/angular gyrus is that these CMA-based functional connections may be implicated in negative emotion recognition and processing.

Functional brain imaging studies have shown that specific frontal brain regions, such as the OFC, dlPFC, are engaged in emotion regulation of reappraisal or suppression (Beauregard et al., 2006; Ochsner et al., 2012; Silvers et al., 2015). Interestingly, we found the dlPFC was both associated with the BLA and the CMA. However, the OFC was only associated with the BLA. Previous studies suggested that both reappraisal and suppression strategies activated the dlPFC, but the OFC activation was specific to the use of reappraisal (Armita et al., 2012; Nicholson et al., 2016; Rolls, 2019). A possible interpretation of current results might be that the OFC was engaged in cognitive reappraisal of negative emotion, whereas the dlPFC was more generally recruited for cognitive control, regardless of regulatory strategies. Moreover, previous studies have demonstrated that the OFC was associated with in-depth regulation of emotional meaning, e.g. cognitive reappraisal of emotional stimuli in healthy people (Armita et al., 2012; Kanske et al., 2010; Petrovic et al., 2016). And the BLA plays an important role in evaluating and integrating sensory information (Danilo et al., 2013), especially encoding changes in the meaning of outcome value (Parkes and Balleine, 2013). Thus, the covariation between the right OFC and the BLA may be crucial to the reformulation of emotional stimulus meanings during spontaneous reappraisal. Prior studies in major depressive disorder indicate that the dlPFC is linked with emotional and cognitive information processing and inhibits emotional responses through efferent connections to limbic–paralimbic targets (Harvey et al., 2005; Lu et al., 2012). The children anxiety research showed that the CMA has a role in the generation of endocrine, autonomic and somatomotor outputs and is essential for controlling automatic expressions of negative emotion (Qin et al., 2014). Therefore, our results suggest that functional coupling of the left dlPFC–CMA may be associated with the control of external behavioral reactions to emotional events during spontaneous suppression.

More importantly, the mediation analysis showed that only functional coupling of the right OFC-BLA mediated the association between spontaneous reappraisal and emotion response. It is worth noting that the left dlPFC–CMA connectivity did not mediate the association between spontaneous suppression and emotion response. These results are consistent with previous findings that the BLA is critical for emotion acquisition whereas the CMA play an important role in emotion expression (Hrybouski et al., 2016; Kim et al., 2011; Zu et al., 2019). For example, several studies argued that the prefrontal cortex impacts fear acquisition by regulating the BLA, but influences fear expression and fear response execution by regulating the CMA (Duvarci and Pare, 2014). Our current results suggest that decreasing emotional information inputs by effective modulation of BLA may be necessary to the reduction of emotional response. Moreover, prior evidence on primate brain anatomy and human brain imaging reveals large variability concerning direct projections between the amygdalae and regions of the frontal lobes (Gur et al., 2002; Ray and Zald, 2012). The OFC receives direct input from the amygdala (Barbas et al., 2003; Zikopoulos and Barbas, 2006), whereas the dlPFC receives less, and mostly indirectly, input via the cingulate or OFC (Ray and Zald, 2012). Therefore, an alternative explanation is that the dlPFC does not have direct connections to the amygdala, it may modulate amygdala activity through connections via the OFC (Domes et al., 2010). Additionally, results from different samples suggested that the OFC and its connectivity with amygdala might serve as a compensatory mechanism to promote effective emotion regulation (García-Cabezas and Barbas, 2017; Kong et al., 2019; Mao et al., 2020; Perry et al., 2016). Together, our mediation results suggest that although both the role of dlPFC and that of OFC are important in emotion regulation, the regulation of BLA activity from OFC may be specific and necessary for changing emotional response during reappraisal.

4.1. Implication and limitation

The current findings have several implications for research on emotion regulation. First, in line with previous studies (Picó-Pérez et al., 2017), the current study demonstrates that spontaneous reappraisal is associated with the functional coupling of BLA and spontaneous suppression is associated with the functional coupling of CMA. Second, our correlation findings indicate that reappraisal is related to functional coupling of the right OFC-BLA while suppression is associated with functional coupling of the left dlPFC–CMA, which suggests the two frontal-amygdala pathways contribute to distinct types of spontaneous emotion regulation. Third, only functional coupling of the right OFC-BLA mediates the association between reappraisal and emotional response, which suggests the regulation of BLA is necessary for changing emotional response, and the OFC may play an important role during spontaneous reappraisal. Future studies might examine the effects of transcranial direct current stimulation (tDCS) over the right OFC in patients with impaired emotion processing or regulation as a part of treatment protocols, in isolation or accompanying traditional psychotherapeutic interventions.

Several limitations of our study should also be noted. First, in this study, we did not include positive emotional stimuli (i.e., pleasant pictures) because the current study focused on negative emotion. In this regard, these findings may not be generalizable to other forms of emotional experience. Second, our task specifically involved cognitive reappraisal and expressive suppression, and thus the findings may not be applicable to other strategies of emotion regulation (i.e., distraction). Third, this study relied on self-report measures to infer effective emotion regulation, future studies can employ corroborative objective measures (i.e., skin conductance) to index regulatory success. Fourth, further work is needed to examine whether our conclusions can generalize to other age groups, given that our sample was comprised of age range of 18–25. Fifth, we employed the seed ROIs based on recent studies of emotion regulation strategies (Picó-Pérez et al., 2017), which are appropriate to the purpose of our current study. Given that anatomical ROIs are more convincing, future studies can define the BLA and CMA based on high quality anatomical atlases to examine the current results. Finally, although prior studies have suggested the validity of post hoc ratings of emotion regulation (Egloff et al., 2006), we also need to acknowledge potential individual understanding biases of these strategies which might influence the validity of subjective ratings. In this regard, future studies should employ objective physiological index to confirm the current results.

Conclusion

Using multiple approaches, this study extends the emotion regulation research by showing that different frontal-amygdala pathways subserve distinct forms of spontaneous emotion regulation. Specifically, spontaneous reappraisal is associated with functional coupling of the right OFC-BLA, while spontaneous suppression is associated with functional coupling of the left dlPFC–CMA. These results could be explained by that functional coupling between the OFC and the BLA is associated with reformulating emotional stimulus meanings during spontaneous reappraisal. By contrast, functional coupling between the dlPFC and the

CMA is associated with the control of external behavioral reactions to emotional events during spontaneous suppression. Furthermore, functional coupling of the right OFC-BLA partially mediates the association between reappraisal and emotional response. These findings underscore that the regulation of BLA activity from OFC may be necessary for changing emotional response during reappraisal.

Declaration of Competing Interest

All authors declared no conflicts of interest with respect to the authorship or the publication of this article.

Credit authorship contribution statement

Wei Gao: Investigation, Formal analysis, Writing – original draft. **Bharat Biswal:** Methodology, Writing – review & editing. **ShengDong Chen:** Formal analysis, Data curation. **XinRan Wu:** Formal analysis, Visualization. **JiaJin Yuan:** Conceptualization, Resources, Writing – review & editing, Supervision, Funding acquisition.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.neuroimage.2021.117918.

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