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Gray matter reduction associated with emotion regulation in female outpatients with major depressive disorder: A voxel-based morphometry study

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ABSTRACT

Objective: Though emotion dysregulation is the key feature in major depressive disorder, and structural changes in brain areas of depressed patients have been found, it is unknown how these regional volume alterations correlate with the ability to regulate emotion in the depressed population.
Method: We examined the gray matter concentration (GMC) and volume (GMV) in 17 depressed patients and 17 healthy volunteers using a voxel-based morphometry (VBM) study. Images were acquired using a 1.5 T MRI scanner, and were spatially normalized and segmented. Statistical comparisons were performed using the general linear model. The identified volumetric alterations in the depressed participants were correlated with their performance on an emotion regulation task that involved reduction of positive or negative emotions to emotional pictures that were selected according to their individual ratings.
Results: The depressed participants showed specific difficulty in regulating negative emotion, though not positive emotion, which was associated with reduced GMV and concentration in the anterior cingulate cortex (ACC) and the inferior orbitofrontal cortex (OFC). Decreased GMC in the superior temporal cortex was also found in people with major depressive disorder.
Conclusions: Abnormal structures in the ACC and OFC and the dysregulation of negative emotion may relate to the pathology of major depressive disorder.

1. Introduction

Structural differences in the regions of the brain have been found in people with major depressive disorder. It has been demonstrated that the gray matter volume (GMV) of patients with major depressive disorder was smaller than average in the subgenual region of the anterior cingulate gyrus (Drevets et al., 1997), the hippocampus (Bremner et al., 2004), and the orbitofrontal gyrus (Bremner et al., 2002). Successful treatment of major depressive episodes is associated with increased metabolism and blood flow within the dorsomedial and dorsolateral prefrontal cortices, and within the dorsal anterior cingulate gyrus (Mayberg et al., 1999, 2000), as well as with decreased metabolism within the subgenual cingulate gyrus (Drevets et al., 2002) and other limbic-related regions (Mayberg et al., 2000) post-intervention. Vasic et al. (2008) found that decreased gray matter concentration (GMC) of the right medial and inferior frontal gyri, and decreased GMV in the hippocampus, were associated with more depressive psychopathology and worse executive performance in people with depression. Decreased GMV of the cingulate cortex was associated with worse executive performance.

Mood-congruent processing biases have also been indicated by robust observation in the neuropsychological studies of depression (Leung et al., 2007): depressed participants tended to recall memories of negative emotional experiences (Bradley et al., 1995), and they showed a bias toward sad stimuli in an emotional go/no-go task (Murphy et al., 1999). Inability to regulate negative affect is the central characteristic of major depressive disorder (Davidson et al., 2002b). In a study of the self-regulation of sadness induced by negative emotional pictures, the degree of difficulty experienced while attempting to reduce sadness was significantly greater in depressed participants than in the control group (Beauregard et al., 2006). The same study also found that the more were the reported depressive symptoms, the higher was the reported degree of difficulty experienced during the regulation of sadness.

Abbreviations: ACC, anterior cingulate cortex; BDI, Beck Depression Inventory; GMC, gray matter concentration; GMV, gray matter volume; IAPS, International Emotion Picture System; ICD-10, International Classification of Diseases and Health-Related Problems — Tenth Revision; MRI, magnetic resonance imaging; OFC, orbitofrontal cortex; SSRIs, selective serotonin reuptake inhibitors; VBM, voxel-based morphometry.

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Numerous imaging studies on the neural correlates of regulating negative emotion have been carried out in the last few years (Levesque et al., 2003; Ochsner et al., 2002, 2004; Ohira et al., 2006; Phan et al., 2005). Participants were asked to voluntarily reduce their negative emotions evoked by emotional pictures. Data on down regulation of negative emotion consistently pointed to increased cortical activities, specifically in the frontal and anterior cingulate regions, and decreased limbic activities in the amygdala and insula during regulation (Levesque et al., 2003; Ochsner et al., 2002, 2004; Phan et al., 2005). Such top-down regulation by the cortical regions over the activity of the limbic-related regions (that had modulated the emotional significance of the stimuli) is purported to be the key mechanism underpinning emotion regulation (Ochsner and Gross, 2005; Phillips et al., 2003).

It has been proposed that decreased cortical regulation of limbic activation in response to negative stimuli might be associated with the prolonged and persistent sadness present in clinical depression (Anand et al., 2005). An fMRI study has demonstrated that the set of brain regions involved in down regulation of sad feelings was different between depressed and control participants (Beauregard et al., 2006). Specifically, the lack of significant activation in the orbitofrontal cortex (OFC) and the greater activation in the right amygdala, the right insula, and the right anterior temporal pole in the depressed group relative to the normal control group suggest a dysfunction in the neural circuitry of emotional self-regulation, resulting in a disinhibition of the limbic/paralimbic regions involved in emotional responses.

Though emotion dysregulation is the key characteristic in major depressive disorder, and structural changes in brain areas implicated in emotion regulation of depressed patients have been found, it is unknown how these regional volume alterations correlate with the ability to regulate emotion in the depressed population. In line with the findings on mood-congruent processing biases, it is expected that depressed participants would present with specific difficulties in regulating negative, but not positive, emotions. Since previous functional imaging studies have consistently shown that the frontal and anterior cingulate regions exert a top-down regulatory action over the limbic areas in response to emotional stimuli, it is hypothesized that the structural changes within the frontal and anterior cingulate regions would be associated with the ability to regulate negative emotion.

2. Method

2.1. Participants

Seventeen female patients with major depressive disorder (mean age = 45.5, S.D. = 8.5) and 17 healthy females (mean age = 45.8, S.D. = 9.8) participated in this study. All participants were right-handed. The clinical group was recruited from an outpatient psychiatric clinic in Hong Kong, while the control group was recruited from within the community. The participants' intellectual functioning was estimated by the abbreviated version of the Test of Nonverbal Intelligence — Third Edition (Brown et al., 1997). The two groups were matched on age and general intellectual functioning. Only female participants were recruited for this study to control for the confounding factor of sex-related differences in the volumetric brain structures and neural bases of emotion regulation that have been found in prior studies (De Vries, 2004; Lee et al., 2002, 2005). Patients received single depressive diagnostic labels from the psychiatrists based on the International Classification of Diseases and Health-Related Problems — Tenth Revision (ICD-10) criteria. The Chinese version of the Beck Depression Inventory — II (Chinese Behavioral Sciences Society, 2000) was administered on the day of scanning, and only those who got a score above the recommended clinical cutoff score for mild depression (Beck et al., 1996) were included. The mean BDI-II score of the depressed participants was 29.7 (S.D. = 8.5). All patients were on medication, including selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants, antipsychotics, benzodiazepine, and/or other hypnotics. Their medication was not withdrawn for ethical reasons.

The healthy controls also completed the BDI-II, and only those who had scores below the clinical cutoff were included. The mean BDI-II score of the healthy controls was 6.5 (S.D. = 3.3), which was significantly different ($p<0.001$) from that of clinical group. All participants were interviewed to exclude the possibility of their having a history of other co-morbid psychiatric disorders, or of other neurological diseases, mental retardation, or alcoholism.

2.2. Experimental stimuli

A total of 294 emotional pictures extracted from the International Emotion Picture System (IAPS) (Lang et al., 1999) and from the popular media were the potential stimuli for this study. The stimulus set was tailored for each participant according to their rating of the 294 emotional stimuli. Each participant viewed and rated all the emotional pictures on a 9-point Likert scale, according to her perceived emotional valence of the pictures (1 = very unpleasant, 5 = neutral, 9 = very pleasant). The pictures were shown for 3 s each in random order. Only those pictures rated by the participants as highly negative (i.e., equal to or lower than 3) and highly positive (i.e., equal to or higher than 7) were used in the subsequent fMRI study, so as to control the variation in intensity of stimuli. The protocol of this study contained 20 negative and 20 positive pictures, selected according to the participant's rating.

2.3. Experimental task

The experimental paradigm was modified from our prior imaging studies on emotion regulation (Mak et al., 2009). There were two types of emotional stimuli (negative and positive) and two tasks for each emotion. The participants were asked to look at the emotional pictures without performing emotion regulation in the "view" condition, and then to reduce the emotional intensity with regard to those emotional pictures in the "regulate" condition. There were 10 emotional pictures in each condition, and the "view" condition always preceded the "regulate" condition. The sequence of emotion was counterbalanced across the participants.

Instructions for the experiment were given, and a practice trial was conducted immediately before each condition. In the "view" condition, the participants were asked to look at each emotional picture for 6 s. Immediately after the display of each picture, they were asked to rate their perceived emotional valence of the pictures on a 9-point Likert scale (1 = very unpleasant, 5 = neutral, 9 = very pleasant). After they had completed their viewing of the 10 emotional pictures, instructions were given and a practice trial was conducted for the "regulate" condition. During the "regulate" condition, the participants were asked to reduce the emotional intensity they experienced for each emotional picture. Although the pictures disappeared after being shown for 6 s, the participants were requested to continue their regulation and to rate their perceived emotional valence of the pictures until they had completed the regulation. During the practice trial, the participants were required to familiarize themselves with the experiment and to think of a strategy to regulate their emotion. The participants were asked if they were ready to start the experiment after the first practice trial. One additional practical trial would be given as per the participants' request. After they had finished regulating the 10 emotional pictures, a 10-minute break was given before they proceeded to the experiments. During the break, the participants were asked to explain the regulatory strategies they had used, elaborate on the method used to regulate their emotions with regard to three of the pictures, and report the perceived effectiveness of the emotion regulation.

2.4. Data analysis

2.4.1. Behavioral data analysis

The subjective mood ratings in the "view" and "regulate" conditions and the reaction time in the "regulate" condition were recorded. The magnitude of emotion regulation was measured by the change in subjective emotion ratings between the "regulate" and "view" conditions for each emotion. The subjective mood rating was analyzed by a repeated measures design that included within-participant factor tasks (i.e. to regulate and to maintain) and between-participant factor groups (the depressed and the control groups) for each emotion. The reaction time of regulation was analyzed by an independent t test, but no significant differences were found between the two groups for each emotion. Correlation analysis between the BDI score and the change in subjective mood ratings was performed to delineate the relationship between the depressive level and the magnitude of regulating negative and positive emotions.

2.4.2. MRI acquisition and preprocessing

The participants' brain structures were scanned by a Signa 1.5 T MRI scanner (General Electric Medical Systems, Milwaukee, WI, USA) with a standard head coil. Axial spin-echo T1-weighted images, fast spin-echo proton density and T2-weighted images, coronal fluid-attenuation inversion recovery sequences, three-dimensional spoiled gradient-recalled (3DSPGR) images with a slice thickness of 3 mm (no gap between slices), repetition time (TR) of 11.3 ms, echo time (TE) of 4.2 ms, inversion time (TI) of 600 ms, acquisition matrix of 256×256 flip angle of 15°, and field of view of 23 cm were selected.

The preprocessing and data analysis were performed using statistical parametric mapping (SPM2; Wellcome Department of Cognitive Neurology, London, UK; http://www.fil.ion.ucl.ac.uk/spm/) in the MATLAB 7.0.1 software package (The MathWorks Inc., Natick, MA) and the extension VBM toolbox (Gaser, http://dbm.neuro.uni-jena.de/vbm). The prior probability maps based on the Montreal Neurological Institute (MNI) template in SPM2 were employed to segment and normalize the images into gray matter, white matter, and cerebrospinal fluid. The resultant normalization parameters were then applied to the original whole-brain structural images. These images were then segmented and spatially normalized by means of the newly extracted individual brain mask to confiscate non-brain tissue. Spatial normalization of a 25 mm cutoff, medium regularization, and 16 non-linear iterations were applied. These segments were modulated to adjust for the volume changes during spatial normalization. The resultant gray matter values were referred to as "gray matter volume" (GMV), while the unmodulated values were described as "gray matter concentration (Eckert et al., 2006; Mechelli et al., 2005)" (GMC). The unmodulated and modulated images were smoothed using an isotropic Gaussian kernel of 12 mm full-width at half-maximum (FWHM) and 8 mm FWHM respectively. Since modulation had additionally smoothed the data (Gaser, http://dbm.neuro.uni-jena.de/vbm/vbm2-for-spm2/statistical-analysis/), a lower FWHM was used for the modulated images to achieve approximate smoothness to the unmodulated images. All images were resliced with $1\times1\times1$ mm^3 voxels.

2.4.3. Imaging data analysis

Processed images were analyzed with SPM2 using the framework of the general linear model (Friston et al., 1995). In the primary analysis, the brain regions showing GMV and GMC reduction in patients with depression relative to the healthy controls were identified by analyses of covariance (ANCOVAs). The global GMVs were used as nuisance covariates to identify disproportionate regional volume changes between the two groups relative to the overall gray matter (GM) size. These analyses produced statistical parametric maps based on a voxel-level height threshold of $p<0.001$ (uncorrelated) and a cluster-extent threshold of eight voxels in the primary analyses. Coordinates are maxima in a given cluster according to the standard MNI template.

In the secondary analysis, each patient's GMV and GMC values were extracted for each cluster of volume/concentration difference obtained from the primary analysis. The "volume of interest" (VOI) function in SPM2 was used to obtain the predicted GMV and GMC values (y adjusted) for the percentage of total GMV in the regions of GMV and GMC reduction found in the primary analysis. Correlation analysis was used to investigate the relationship between the reduction in GMV or GMC and the strength of emotion regulation as measured by the change in mood rating during the regulation condition in the regions with gray matter reduction. The correlation was considered to be significant at $p<0.05$.

3. Results

3.1. Behavioral findings

The subjective mood rating was analyzed by a repeated measures design involving within-participant factor tasks (to regulate and to maintain) and between-participant factor groups (the depressed and control groups) for each emotion. The mean subjective mood ratings are displayed in Fig. 1. A significant main effect of condition was found in both negative ($F(1, 32)=211.072$, $p<0.001$, partial $\eta^2=0.868$) and positive ($F(1, 32)=144.572$, $p<0.001$, partial $\eta^2=0.819$) emotions, and further paired t tests showed that there was a significant difference in the subjective mood ratings between the "regulate" and "view" conditions in both groups and for both types of emotion (see Table 1). For the negative emotion, there was a significant interaction effect ($F(1, 32)=4.85$, $p=0.035$, partial $\eta^2=0.132$) between tasks and groups, suggesting that the change in subjective mood rating between the "regulate" and "view" conditions varies as a function of groups, and that the reduction in reported negative emotion was significantly smaller in the depressed group (mean = 2.04) than in the control group (mean = 2.77). Such an interaction effect was not found for the positive emotion, suggesting that the reduction in reported positive emotion was comparable between the two groups (Depressed: mean = 2.7, Control: mean = 2.88). The reaction time of regulation was analyzed by an independent t test, but no significant difference was found between the two groups for each emotion.

Correlation analysis (see Fig. 2) was performed to delineate the relationship between the BDI score and the change in participants' mood ratings for each emotion. The results showed that the BDI score was negatively correlated with the change in reported negative emotion ($r=-0.558$, $p=0.001$) but not with the change in reported positive emotion, suggesting that the higher reported depressive level was associated with a weaker regulation of negative emotion, but that there was no relationship between the reported depressive level and the regulation of positive emotion.

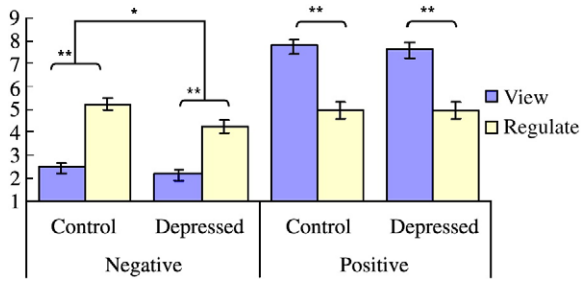

Fig. 1. The mean subjective mood ratings in each group and condition. Note. Control = control group; Depressed = depressed group; View = view condition; Regulate = regulate condition; *$p<0.05$; **$p<0.01$.

Table 1
The mean subjective mood ratings reported by the control and clinical groups performing the view condition and the regulate condition when stimuli portraying negative or positive emotion were presented.

		View		Regulate		*t*-value	*p*-value
		Mean	S.D.	Mean	S.D.		
Negative	Control	2.453	0.797	5.224	1.119	−14.541	<0.001
	Depressed	2.176	0.740	4.218	1.188	−7.535	<0.001
Positive	Control	7.829	0.765	4.947	1.610	0.193	<0.001
	Depressed	7.629	1.172	4.929	1.575	−0.134	<0.001

Note. View = view condition; Regulate = regulate condition; Negative = negative emotion; Positive = positive emotion; Control = control group; Depressed = clinical group.

3.2. Imaging data findings

The clinical group showed reduced GMC in the right anterior cingulate gyrus (BA32), the right superior frontal gyrus (BA8/9), the right medial superior frontal gyrus (BA8), the left middle frontal gyrus (BA46), the right inferior orbitofrontal gyrus (BA11), the right precentral gyrus (BA6), the right superior temporal gyrus (BA22), the left middle temporal gyrus (BA21), the right fusiform gyrus (BA30), and the left precuneous (BA7).

The clinical group showed reduced GMV in the right anterior cingulate gyrus (BA32), the right precentral gyrus (BA6), the right supplementary motor area (BA6), the right superior temporal pole gyrus (BA38), the left middle temporal gyrus (BA21), the left angular gyrus (BA39), and the left precuneous (BA7) (see Table 2).

Significant positive correlations were observed between GMC and the magnitude of negative mood reduction during regulation in the right anterior cingulate gyrus (BA32; $r=0.524$, $p=0.001$), the right inferior orbitofrontal gyrus (BA11; $r=0.374$, $p=0.029$), and the right superior temporal gyrus (BA22; $r=0.448$, $p=0.008$). The GMV in the right anterior cingulate gyrus (BA32) was positively correlated ($r=0.428$, $p=0.012$) with the magnitude of negative mood reduction during the regulation. There were no significant correlations between both GMC and GMV and the magnitude of positive mood reduction during such regulation in any brain regions (see Fig. 3).

4. Discussion

The behavioral findings of this study clearly indicate that the depressed participants had specific difficulty in regulating negative emotion, as they performed significantly poorer than the normal controls in the regulation of negative emotion. Such difficulty was not observed when regulation of positive emotion was requested. The imaging data support our *a priori* hypothesis that the structural changes in the anterior cingulate gyrus and the orbitofrontal gyrus were associated with dysregulation of negative emotion in the depressed participants. A recent review study (Konarski et al., 2008) has reported that regional deficits in the frontal lobe, particularly in the anterior cingulate and the orbitofrontal cortices, appear to consistently differentiate participants with mood disorders from the general population. These findings provide further evidence supporting the correlation of these structures with the ability to regulate negative emotion.

The anterior cingulate cortex (ACC) is extensively connected with the limbic-related regions (Bush et al., 2000). It is important for the integration of salient affective and cognitive information that subsequently modulates the cognitive processes within the dorsal anterior cingulate and prefrontal regions (Mayberg et al., 1999). In our previous neuroimaging studies on emotion regulation (Mak et al., 2009), the bilateral ACC was strongly associated with the regulation of negative emotion. Leppänen (2006) found that people with major depressive episodes show a decreased connectivity between the anterior cingulate and the limbic regions during emotional stimulation, resulting in disruption of emotional regulation. Hypoactivities in the ACC have consistently been reported in previous studies of depressed participants, and an opposite pattern was observed for depressed participants after treatment (Davidson et al., 2002a,b; Taylor and Liberzon, 2007), highlighting the role of the ACC in the pathogenesis of depression and in the manifestation of its symptomatology. Davidson et al. (2002b) postulated that the hypoactivation in the ACC may be associated with impaired monitoring of competition among various response options and blunted conscious experience of affect, hypoarousal, anhedonia, and reduced coping potential in situations characterized by uncertainty, conflict, and expectancy violation between the environment and one's affective state. Mayberg (1997) reported that patients with hyperactivation of the rostral ACC

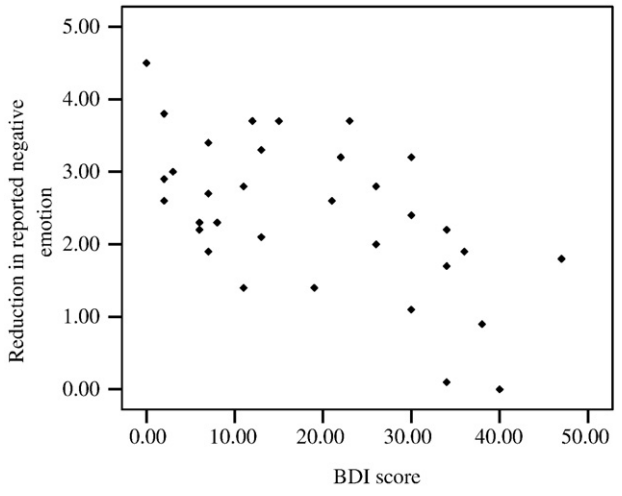

Fig. 2. Scatterplot showing the relationship between the score on the Beck Depression Inventory — II (BDI) and the reduction in reported negative emotion during regulation of negative emotion.

Table 2
Areas of differential gray matter concentration and gray matter volume between the clinical and the control groups.

Brain regions	Side	BA	*x*	*y*	*z*	*F*	Cluster size
Gray matter concentration							
Control>Depressed							
Anterior cingulate gyrus	R	32	18	42	15	5.59	1205
Superior frontal gyrus	R	6	20	5	56	4.4	367
Superior medial frontal gyrus	R	8	7	28	41	3.54	16
Middle frontal gyrus	L	46	−23	54	15	3.79	80
Inferior orbitofrontal gyrus	R	11	34	29	−23	3.45	230
Precentral gyrus	R	6	70	9	45	4.95	549
Superior temporal pole gyrus	R	38	31	21	−31	3.91	230
Superior Temporal gyrus	R	22	57	−15	−8	4.34	336
Middle temporal gyrus	L	21	−52	−45	−5	3.7	55
Fusiform gyrus	R	30	24	−41	−16	3.65	18
Precuneous	L	7	−1	−71	61	3.48	8
Gray matter volume							
Control>Depressed							
Anterior cingulate gyrus	R	32	19	43	13	4.45	207
Precentral gyrus	R	6	66	11	44	5.09	418
Supplementary motor area	R	6	13	−18	59	3.81	23
Superior temporal pole gyrus	R	38	31	21	−31	3.83	60
Middle temporal gyrus	L	21	−51	−46	−4	3.16	8
Angular gyrus	L	39	−50	−60	36	3.92	41
Precuneous	L	7	−1	−67	60	3.78	83

Note. L = left hemisphere; R = right hemisphere; BA = approximate Brodmann's area; *x*, *y*, *z* are in MNI coordinates; Control = control group; Depressed = clinical group; Cluster size is in mm^3; the threshold for between-group comparison (control>depressed) was set to $p<0.001$ uncorrected, the cluster-extent threshold of eight voxels for all contrasts.

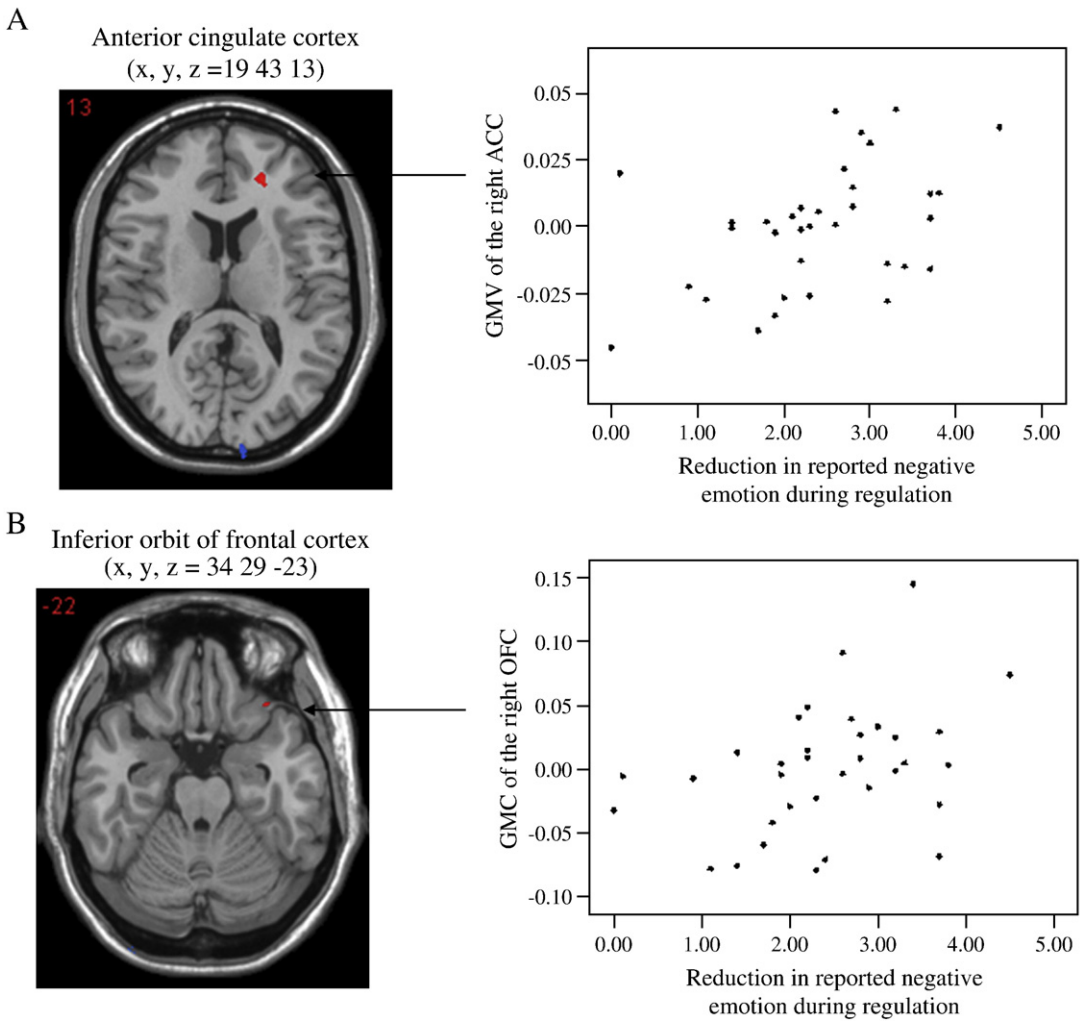

Fig. 3. Scatterplots showing the relationship between the (A) gray matter volume of the anterior cingulate cortex (ACC) and (B) the gray matter concentration of the right orbitofrontal cortex (OFC) with the reduction in reported negative emotion during regulation of negative emotion.

at the baseline can be predicted to have a better treatment outcome, which suggested that the sensitivity to affective conflict could influence the treatment response.

Davidson et al. (2002b) further proposed that there may exist subtypes of depression that take the form of a primary ACC-based depression subtype and a primary PFC-based depression subtype. They hypothesized that the ACC subtype may be reflected phenomenologically in a deficit in the "will-to-change" as such patients may fail to experience the conflict between their current state and the demands of the context, while the PFC subtype may involve the capacity to experience the conflict but is sufficient to activate the PFC-based mechanisms needed to organize and guide behavior toward the resolution of the conflict. In this study, structural abnormalities were observed in both the ACC and the prefrontal cortex, while only the structural changes in the ACC were associated with the ability to regulate negative emotion, which may suggest the crucial role of ACC in emotion regulation. This may have clinical implications in that it might be equally important to not only guide the depressed patients toward resolving the conflict, but also to help them to be sensitive to conflict and to enhance their "will-to-change" so as to call upon other brain regions to execute the cognitive function to resolve the conflict.

The orbitofrontal cortex (OFC) has also been implicated in the pathophysiology of major depression (Drevets, 2007). The severity of the depression correlates inversely with the physiological activity in the parts of the posterolateral and medial OFC, and the dysfunction of the OFC is associated with cerebrovascular lesions, which increases the vulnerability for developing the major depressive syndrome. This region of the brain regulates the endocrine and autonomic systems, neurotransmitters, and behavioral responses to emotional stimuli by directly modulating neuronal activity within the limbic structures that mediate and organize the expression of emotion (Ongur et al., 2003). A previous neuroimaging study (Beauregard et al., 2006) found that the OFC was recruited by the normal participants, but not by the depressed participants, in down regulation of sadness, suggesting a dysfunction in the neural circuitry underlying emotion regulation. Our findings further show that abnormalities in the OFC are associated with dysregulation of negative emotion in depression.

Given the roles in the top-down regulation of emotion played by the ACC and the OFC, our speculation is that the dysfunctional ACC and OFC of the depressed patients might be associated with a weakened ability to regulate or suppress the mood-congruent information of negative emotional pictures, resulting in sustained negative emotion in the experiment. This supports the imbalance of cortical-limbic circuitry underpinning emotion regulation that decreases GMC and GMV in the ACC and the OFC, impairing their modulatory role over the limbic-related regions and resulting in disinhibiting or dysregulating limbic responses to the negative emotional stimuli, and giving rise to the clinical signs and symptoms of depression.

The overall structural differences between the clinical group and the healthy controls were consistent with previous neuroimaging and post-mortem studies showing that people with depression have structural or activity changes in the ACC and OFC (Bremner et al., 2002; Caetano et al., 2004; Davidson et al., 2002a,b; Drevets et al., 1997; Harrison, 2002; Marshall and Fox, 2000). However, we did not find significant structural differences in the limbic-related regions, such as the amygdala and hippocampus. Nonetheless, it should be noted that the findings on the amygdala volume of depressed patients were inconsistent with a review by Drevets (2007), and it has been argued that hippocampal atrophy only occurs in patients with recurrent or treatment-resistant depressive disorder (MacQueen et al., 2003; Posener et al., 2003). Since half of our depressed participants had only suffered from a single depressive episode, this might be a reason for the failure to identify any structural change in the hippocampus.

Some previous studies have found that depressed participants were more sensitive to negative emotional stimuli and had a less intense response to positive stimuli (Forbes and Dahl, 2005; Leppänen, 2006), but the reported negative and positive emotions of the depressed participants during the "view" condition in this study were comparable with those of the normal controls. Results suggested that the major problem underlying major depressive disorder is the dysregulation of negative emotions, specifically the inability to disengage from the negative emotional state, rather than the ability to appraise either negative or positive emotions.

It has been found that different emotional regulatory strategies involve different patterns of neural activity (Goldin et al., 2008; Ochsner et al., 2004), and examining the use of different regulatory strategies may enrich the findings of the present study. Furthermore, due to the resource constraints, we only used the participants' mood rating to reflect the emotional experience of our participants. Though it is a reliable measure, previous studies have also included the physiological responses to emotion as an objective emotional measure (Ohira et al., 2006), which may be worth considering for future studies.

Findings of this study may have been confounded by the effect of the medications prescribed for the depressed patients because they were not withdrawn from these medications due to ethical reasons. To control for the noise contributed by the medication, future studies may consider acquiring data shortly after the diagnosis of first episode of major depressive disorders was established and before the patients were put on the pharmacotherapy regime. The sample size of this study was small, but the findings are well aligned with previous studies on emotion regulation (Levesque et al., 2003; Ochsner et al., 2002, 2004). Nonetheless, the findings in this study can serve as a basis for further investigation with a larger sample size and stronger statistical power. It is interesting to note that there were differences in the results from the analysis of GMC and GMV: since they are considered to have the ability to detect different aspects of gray matter abnormalities (Good et al., 2001), further investigation into the differences is warranted.

As far as we are aware, this is the first study that confirms the relationship between structural differences in the brains of depressed patients and the ability to regulate negative emotion. Both this study and our previous imaging studies on emotion regulation show a robust relationship between the OFC and ACC on the one hand and the ability to regulate negative emotion on the other, leading to an increased vulnerability for developing major depressive disorder. This helps to provide a better understanding of the nature of emotion dysregulation in major depressive disorder.

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