Progress in Neuro-Psychopharmacology & Biological Psychiatry 33 (2009) 1184–1190

Contents lists available at ScienceDirect

Progress in Neuro-Psychopharmacology & Biological Psychiatry

journal homepage: www.elsevier.com/locate/pnp

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

Amanda K.Y. Mak [a,b,c], Michael M.C. Wong [d], Shi-hui Han [e], Tatia M.C. Lee [a,b,c,f,*]

[a] Lab a o of Ne o chology, The Uni e i of H ng K ng, H ng K ng, China
[b] Lab a o of Co gni i e Affec i e Ne o cience, The Uni e i of H ng K ng, H ng K ng, China
[c] In i e of Clinical Ne o chology, MacLeh e Medical Rehabili a i n Cen e and The Uni e i of H ng K ng, H ng K ng, China
[d] Q een Ma H i al, The Uni e i of H ng K ng, H ng K ng, China
[e] De a men of P chology and F nc inal Imaging Cen e, Academ for Ad anced In e di ci lina S die, Peking Uni e i , Beijing, China
[f] The S a e Ke Lab a o of B ain and Co gni i e Science, The Uni e i of H ng K ng, H ng K ng, China

T CLE FO

A icle hi o :
Received 8 May 2009
Received in revised form 2 June 2009
Accepted 29 June 2009
Available online 19 July 2009

Ke o d :
Anterior cingulate cortex
Depression
Emotion regulation
Orbitofrontal region
Vowel-based morphometry

B S T C T

Objec i e: 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.
Me h d: 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.
Re l : 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.
Co cl i n : Abnormal structures in the ACC and OFC and the dysregulation of negative emotion may relate to the pathology of major depressive disorder.

1.

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.

Abb e ia i n : 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.

* Corresponding author. K610, Laboratory of Neuropsychology, The University of Hong Kong, Pokfulam Road, Hong Kong, China. Tel.: +852 2857 8394; fax: +852 28190978.
E-mail add e : tmclee@hkusua.hku.hk (T.M.C. Lee).

0278-5846/$ – see front matter © 2009 Elsevier Inc. All rights reserved.
doi:10.1016/j.pnpbp.2009.06.025

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 regulatint0he-645.5(9)-23(thti)-15.8(p,/F1socTJ-8.7.1(i)06n)-64342.8Tf.61o., ctep0(e)-5-433.s1(i)01-260.7ethe5.45.5()15t3(la)-2i6(olesseTf.61s1(

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		-value	-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 da a finding

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).

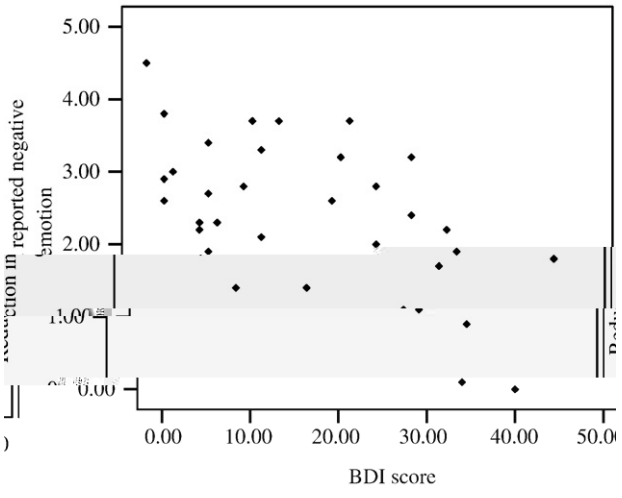
The clinical group showed reduced GMV in the right anterior cingulate gyrus (BA32), the right precentral gyrus (BA6), the right supplementary motor area (BA6), the right superior temporal pole gyrus (BA38), the left middle temporal gyrus (BA21), the left angular gyrus (BA39), and the left precuneous (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; =0.524, =0.001), the right inferior orbitofrontal gyrus (BA11; =0.374, =0.029), and the right superior temporal gyrus (BA22; =0.448, =0.008). The GMV in the right anterior cingulate gyrus (BA32) was positively correlated (=0.428, =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).

.

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 i* 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



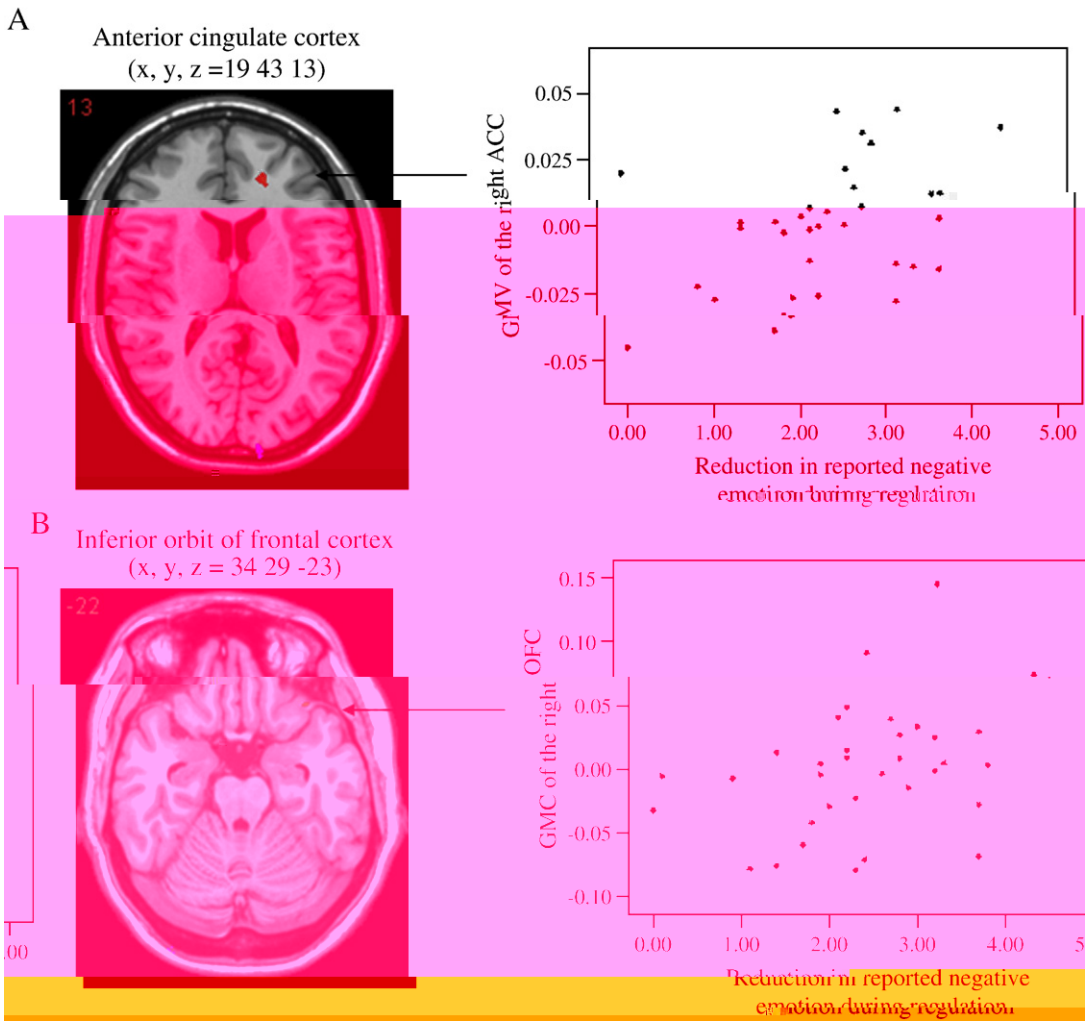
. 2. Scatterplot showing the relationship between the score on the Beck Depression Inventory — II (BDI) and the reduction in reported negative emotion during regulation of negative emotion.

2

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

Brain regions	Side	BA			z	F	Cluster size
Gray matter concentration							
Cn ol>De e ed							
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							
Cn ol>De e ed							
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; , 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 <0.001 uncorrected, the cluster-extent threshold of eight voxels for all contrasts.



. 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.

This project was supported by the Research Output Prize of The University of Hong Kong and the National Natural Science Foundation of China (#30828012).

Anand A, Li Y, Wang Y, Wu J, Gao S, Bukhari L, et al. Activity and connectivity of brain mood regulating circuit in depression: a functional magnetic resonance study. Biol Psychiatry 2005;57(10):1079–88.
Beauregard M, Paquette V, Levesque J. Dysfunction in the neural circuitry of emotional self regulation in major depressive disorder. Learn Memory 2006;17:843–6.
Beck AT, Steer RA, Brown GK, editors. Manual for the Beck Depression Inventory — II. Psychological Corporation, San Antonio; 1996.
Bradley BP, Mogg K, Williams R. Implicit and explicit memory for emotion-congruent information in clinical depression and anxiety. Behav Res Ther 1995;33(7):755–70.
Bremner JD, Vythilingam M, Vermetten E, Nazeer A, Adil J, Khan S, et al. Reduced volume of orbitofrontal cortex in major depression. Biol Psychiatry 2002;51(4):273–9.
Bremner JD, Vythilingam M, Vermetten E, Vaccarino V, Charney DS. Deficits in hippocampal and anterior cingulate functioning during verbal declarative memory encoding in midlife major depression. Am J Psychiatry 2004;161(4):637–45.
Brown L, Sherbenou RJ, Johnsen SK, editors. Test of nonverbal intelligence, 3rd ed. 1997.
Bush G, Luu P, Posner MI. Cognitive and emotional influences in anterior cingulate cortex. Trends Cogn Sci 2000;4(6):215–22.
Caetano SC, Hatch JP, Brambilla P, Sassi RB, Nicoletti M, Mallinger M, et al. Anatomical MRI study of hippocampus and amygdala in patients with current and remitted major depression. Psychiatry Research. Neuroimaging 2004;132(2):141–7.
Chinese Behavioral Sciences Society, ed. The Chinese version of the Beck Depression Inventory Licensed Chinese translation, 2nd ed. The Psychological Corporation. Hacourt Brace: New York; 2000.
Davidson RJ, Lewis DA, Alloy LB, Amaral DG, Bush G, Cohen JD, et al. Neural and behavioral substrates of mood and mood regulation. Biol Psychiatry 2002a;52(6):478–502.
Davidson RJ, Pizzagalli D, Nitschke JB, Putnam K. Depression: perspectives from affective neuroscience. Annu Rev Psychol 2002b;53:545–74.
De Vries GJ. Minireview: sex differences in adults and developing brains: compensation, compensation, compensation. Endocrinology 2004;145:1063–8.
Drevets WC. Orbitofrontal cortex function and structure in depression. Ann N Y Acad Sci 2007;1121:499–527.
Drevets WC, Price JL, Simpson Jr JR, Todd RD, Reich T, Vannier M, et al. Subgenual prefrontal cortex abnormalities in mood disorders. Nature 1997;386(6627):824–7.
Drevets WC, Bogers W, Raichle ME. Functional anatomical correlates of antidepressant drug treatment assessed using PET measures of regional glucose metabolism. Eur Neuropsychopharmacol 2002;12(6):527–44.
Eckert MA, Tenforde A, Galaburda AM, Bellugi U, Korenberg JR, Mills D, et al. To modulate or not to modulate: differing results in uniquely shaped Williams syndrome brains.

Murphy FC, Sahakian BJ, Rubinsztein JS, Michael A, Rogers RD, Robbins TW, et al. Emotional bias and inhibitory control processes in mania and depression. Psychol Med 1999;29(6):1307–21.
Ochsner KN, Gross JJ. The cognitive control of emotion. Trends Cogn Sci 2005;9:243–9.
Ochsner KN, Bunge SA, Gross JJ, Gabrieli JD. Rethinking feelings: an FMRI study of the cognitive regulation of emotion. J Cogn Neurosci 2002;14(8):1215–29.
Ochsner KN, Ray RD, Cooper JC, Robertson ER, Chopra S, Gabrieli JD, et al. For better or for worse: neural systems supporting the cognitive down- and up-regulation of negative emotion. Neuroimage 2004;23(2):483–99.
Ohira H, Nomura M, Ichikawa N, Isowa T, Iidaka T, Sato A, et al. Association of neural and physiological responses during voluntary emotion suppression. Neuroimage 2006;29(3):721–33.
Ongur D, Ferry AT, Price JL. Architectonic subdivision of the human orbital and medial prefrontal cortex. J Comp Neurol 2003;460:425–49.
Phan KL, Fitzgerald DA, Nathan PJ, Moore GJ, Uhde TW, Tancer ME. Neural substrates for voluntary suppression of negative affect: a functional magnetic resonance imaging study. Biol Psychiatry 2005;57(3):210–9.
Phillips ML, Drevets WC, Rauch SL, Lane R. Neurobiology of emotion perception I: the neural basis of normal emotion perception. Biol Psychiatry 2003;54(5):504–14.
Posener JA, Wang L, Price JL, Gado MH, Province MA, Miller MI, et al. High-dimensional mapping of the hippocampus in depression. Am J Psychiatry 2003;160(1):83–9.
Taylor SF, Liberzon I. Neural correlates of emotion regulation in psychopathology. Trends Cogn Sci 2007;11(10):413–8.
Vasic N, Walter H, Hose A, Wolf RC. Gray matter reduction associated with psychopathology and cognitive dysfunction in unipolar depression: a voxel-based morphometry study. J Affect Disord 2008;109(1–2):107–16.