Dysfunction in the neural circuitry of emotional self-regulation in major depressive disorder

Mario Beauregard[a,b,c,d,e], Vincent Paquette[a,c,e] and Johanne Lévesque[a,c,e]

Département de [a]Psychologie, [b]Radiologie, [c]Centre de Recherche en Neuropsychologie et Cognition (CERNEC), [d]Centre de Recherche en Sciences Neurologiques (CRSN), Université de Montréal, [e]Centre de Recherche, Institut Universitaire de Gériatrie de Montréal (CRIUGM), Montréal, Québec, Canada

Correspondence and requests for reprints to Mario Beauregard, Département de Psychologie, Université de Montréal, C.P. 6128, succursale Centre-Ville, Montréal, Québec, Canada H3C 3J7
Tel: + 1 514 343 7651; fax: + 1 514 340 3548; e-mail: mario.beauregard@umontreal.ca

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An inability to self-regulate negative emotions appears to play a pivotal role in the genesis of major depressive disorder. This inability may be related to a dysfunction of the neural circuitry underlying emotional self-regulation. This functional magnetic resonance imaging study was conducted to test this hypothesis. Depressed individuals and controls were scanned while they attempted to voluntarily down-regulate sad feelings. The degree of difficulty experienced during down-regulation of sadness was higher in depressed individuals. Furthermore, there was greater activation in the right dorsal anterior cingulate cortex, right anterior temporal pole, right amygdala, and right insula in depressed individuals. These results suggest that emotional dysregulation in major depressive disorder is related to a disturbance in the neural circuitry of emotional self-regulation. *NeuroReport* 17:843–846 © 2006 Lippincott Williams & Wilkins.

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Introduction

Recent functional neuroimaging studies have led to the identification of the neural circuitry underlying the voluntary regulation of emotional responses in healthy adults [1–8] and children [9] (for a review, see [10]). The results of these studies have emphasized the pivotal role played by a few areas of the prefrontal cortex (PFC), such as the medial (MOFC) [Brodmann area (BA) 11] and lateral (LOFC) (BA 47) orbitofrontal cortex and the dorsal anterior cingulate cortex (ACC) (BA 24 and 32), in the cognitive regulation of the brain regions associated with emotion.

Growing evidence suggests that a dysregulation of emotion constitutes a core feature of major depressive disorder [11]. Emotional dysregulation may be related to a dysfunction of the neural circuitry underlying emotional self-regulation. Interestingly, in post-mortem neuropathological studies, abnormal reductions of gray matter, glia, and neuronal size have been demonstrated in the MOFC, LOFC, and the dorsal MPFC [12]. In addition, morphometric measures based on magnetic resonance imaging and post-mortem studies of major depressive disorder [13,14] have revealed a left-lateralized, volumetric reduction of the subgenual ACC (part of BA 24).

Several positron emission tomography studies have shown decreased regional cerebral blood flow (rCBF) and metabolism within the dorsal MPFC but increased metabolism and rCBF in the posterior and lateral OFC [15,16] in depressed individuals. Furthermore, abnormally reduced rCBF and metabolism have been noted in the dorsal ACC whereas increased metabolic activity has been found in the subgenual ACC [17,18].

In this study, we used functional magnetic resonance imaging (fMRI) to determine whether there is a dysfunction in the neural circuitry underlying emotional self-regulation in major depressive disorder. Depressed and healthy individuals were scanned while they attempted to voluntarily down-regulate sad feelings externally induced by sad film excerpts. We predicted that there would be greater activation in depressed individuals than in the controls, in brain regions normally implicated in emotional self-regulation. This hypothesis is based on our previous work indicating that a greater degree of difficulty to down-regulate sadness is associated with greater activation of the brain regions involved in the down-regulation of this primary emotion [8].

Materials and methods

Study participants

Twelve unmedicated, unipolar depressed individuals and 12 normal controls took part in the study. Control participants had no history of any axis I disorder or neurological antecedents. Depressed participants received a clinical diagnosis of a major depressive episode (unipolar),

on the basis of the Structured Clinical Interview for the Diagnostic and Statistical Manual for Mental Disorders – Fourth Edition (DSM-IV) and DSM-IV criteria [19]. Exclusion criteria encompassed history or current bipolar disorder, axis I psychiatric diagnoses, current psychotic symptoms, antidepressant treatment within the preceding 6 weeks, current consumption of lithium or major tranquilizers, recent electroconvulsive therapy, history of neurological disease, and head trauma. The 21-item Hamilton Depression Rating Scale (HDRS) [20] was used to assess symptom severity in depressed participants: mean HDRS score was 25 ± 6. Both groups were matched for age (depressed: 43 ± 11 years; control: 45 ± 10 years), sex ratio (depressed: nine women, three men; control: nine women, three men), and years of education (depressed: 12 ± 3 years; control: 12 ± 4 years). Written informed consent was obtained from all participants, and the study was approved by the Research Ethics Committee of Centre Hospitalier de l'Université de Montréal (CHUM), Hôpital Notre-Dame.

Behavioral protocol

Blood oxygenation level-dependent (BOLD) signal changes were measured during a sad condition and a down-regulation condition. The behavioral protocol and the stimuli (emotionally neutral and sad film excerpts) were identical to those used in previous fMRI studies conducted by our group [2,8]. To assess the subjective responses of the participants to the stimuli, immediately at the end of each condition they were asked to rate verbally – on a visual analog rating scale ranging from 0 (absence of any emotional reaction) to 10 (strongest emotion ever felt in one's lifetime) – the average intensity of sadness or other primary emotions felt during the viewing of both categories of film excerpts. In addition, following the down-regulation condition, participants were asked to rate verbally – on a visual analog rating scale ranging from 0 (not difficult) to 5 (extremely difficult) – the degree of difficulty experienced while attempting to suppress sadness.

Image acquisition

Echoplanar images were acquired on a 1.5 T system (Magnetom Vision, Siemens Electric, Erlangen, Germany). Twenty-eight slices (5 mm thick) were acquired every 2.65 s in an inclined axial plane, aligned with the anterior commissure–posterior commissure axis. These T2*-weighted functional images were acquired using an echoplanar images pulse sequence (echo-spacing time=0.8 ms, TE=54 ms, flip angle=90°, FOV=215 mm, voxel size=3.36 mm × 3.36 mm × 5 mm, matrix=64 × 64). Following functional scanning, high-resolution data were acquired via a T1-weighted three-dimensional volume acquisition obtained using a gradient echo pulse sequence (TR=9.7 ms, TE=4 ms, flip angle=12°, FOV=250 mm, matrix=256 × 256).

Functional magnetic resonance imaging data analysis

Data were analyzed using Statistical Parametric Mapping software (SPM2, Wellcome Department of Cognitive Neurology, London, UK). Image pre-processing was carried out as previously described [2,8]. To delineate the brain regions associated with voluntary down-regulation of sad feelings, a 'random-effects model' was implemented to compare the brain activity associated with viewing the sad film excerpts in the sad condition and that associated with viewing the sad film excerpts in the down-regulation condition. A 2×2 analysis of variance (group: depressed vs. control; emotional condition: sadness vs. down-regulation) was carried out to compare brain activity in the two groups during down-regulation of sadness. Regression maps were also produced to assess the significance of the relationship between BOLD signal changes (down-regulation minus sad contrast) in the dorsal division of ACC, MOFC, LOFC, and MPFC and the degree of difficulty experienced during the down-regulation condition.

An a priori search strategy was used and a small volume correction was performed in the brain regions (regions of interest) defined a priori. For this a priori search, a corrected probability threshold for multiple comparisons of $P < 0.05$ corrected was used. Only clusters showing a spatial extent of at least 10 contiguous voxels were kept for image analysis. This a priori search strategy encompassed the prefrontal cortical regions normally involved in emotional self-regulation, such as the dorsal division of ACC (BA 24 and 32), MOFC (BA 11), LOFC (BA 47), MPFC (BA 9 and 10), and LPFC (BA 9 and 10). Other regions of interest included the amygdala, insula, and anterior temporal pole (BA 21 and 38). These brain regions have been consistently found to be activated in previous functional neuroimaging studies of sadness [10].

Results

Self-report data

During the sad and down-regulation conditions, the viewing of the sad film excerpts did not produce other significant changes (i.e. >1) in the emotional state than sadness for both groups of participants. The mean level of reported sadness was not statistically different in the two groups of participants during the sad condition (depressed: mean=6.50, SD=2.65; control: mean=4.50, SD=2.39) (Student's t test, $P=0.07$) and the down-regulation condition (depressed: mean=5.17, SD=3.30; control: mean=3.17, SD=2.92) (Student's t test, $P=0.13$). The degree of difficulty experienced while attempting to down-regulate sadness, however, was significantly greater in depressed participants (mean=2.92, SD=1.98) than in controls (mean=1.08, SD=1.08) (Student's t test, $P<0.01$). In addition, for the depressed group, there was a significant positive correlation between the scores on the HDRS and the degree of difficulty reported during the down-regulation of sadness (Pearson's correlation, $r=0.72$, $P<0.05$).

Functional magnetic resonance imaging data

The 2×2 analysis of variance revealed that, during the down-regulation condition, there was significantly more activation in depressed participants than in controls, in the right dorsal ACC (BA 24, $x=4$, $y=17$, $z=19$, $P<0.01$ corrected, z value=3.60), right anterior temporal pole (BA 21, $x=41$, $y=-9$, $z=-25$, $P<0.05$ corrected, z value=3.46), right amygdala ($x=26$, $y=-6$, $z=-14$, $P<0.01$ corrected, z value=3.30), and right insula (BA 13, $x=34$, $y=8$, $z=3$, $P<0.05$ corrected, z value=3.07) (Fig. 1). Two types of post-hoc analyses were carried out to address the possibility that emotional down-regulation abnormalities and its neuronal correlates might be due to an inherent hyperactivity of the amygdala and insula in depressed participants. One of these analyses showed that during the sad

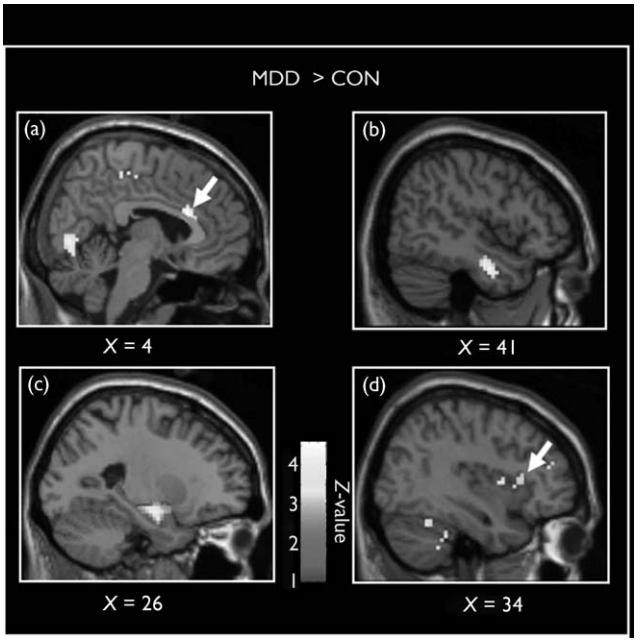

Fig. 1 Statistical activation maps showing significantly more activation in depressed individuals (MDD), relative to controls (CON), in the (a) right anterior cingulate cortex (ACC) [Brodmann area (BA) 24], (b) right anterior temporal pole (BA 21), (c) right amygdala, and (d) right insula (BA 13). Images are sagittal sections for the data averaged across study participants.

condition (sad minus neutral contrast), BOLD activity in the amygdala and insula was not significantly greater in depressed participants than in controls (two-sample t test). In addition, correlational analyses performed to evaluate functional connectivity indicated that there was no significant correlation between the right dorsal ACC (BA 24) and the amygdala and insula.

For the depressed group, the degree of difficulty experienced while attempting to suppress sadness (down-regulation condition) was positively correlated (Pearson's correlation) with significant loci of activation in the right MPFC (BA 10, x=2, y=46, z=21, $P<0.05$ corrected, z value=3.22) (r=0.59, $P<0.05$), right anterior temporal pole (BA 21, x=44, y=3, z=−27, $P<0.05$ corrected, z value=3.90) (r=0.66, $P<0.05$), and left amygdala (x=−22, y=−12, z=−11, $P<0.05$ corrected, z value=3.40) (r=0.79, $P<0.05$). For the control group, positive correlations were noted between the degree of difficulty to suppress sadness and significant loci of activation in the left MPFC (BA 10, x=−6, y=49, z=10, $P<0.01$ corrected, z value=3.81) (r=0.90, $P<0.01$) and left LOFC (BA 47, x=−43, y=17, z=−13, $P<0.01$ corrected, z value=3.79) (r=0.71, $P<0.01$).

Discussion

The greater degree of difficulty experienced by depressed participants during the down-regulation condition supports the view that a dysregulation of emotion represents a central characteristic of major depressive disorder [11]. Furthermore, the positive correlation found in the control group between the degree of difficulty to down-regulate sadness and a locus of activation in the left MPFC (BA 10) is consistent with an fMRI study recently conducted by our group [8], which demonstrated an involvement of this prefrontal cortical region in voluntary down-regulation of sadness. A region of the MPFC close to that identified in this study has previously been postulated to be implicated in the conscious awareness of one's own emotional state [21]. This cortical region receives sensory information from the body and the external environment via the occipito-frontal cortex (OFC) and is strongly interconnected with cerebral structures such as the amygdala, ventral striatum, hypothalamus, midbrain periaqueductal gray region, and brainstem autonomic nuclei [22]. Such anatomical relationships suggest a role for the MPFC in the integration of the visceromotor aspects of emotional processing with information gathered from the internal (i.e. the subjective and physiological aspects of the sad response) and external (i.e. the sad film excerpts) environments. It thus seems plausible that the significant correlations implicating the MPFC in the controls were related with self-awareness of the emotional state during the down-regulation task. As for the LOFC (BA 47), given the extensive connections sent by BA 47 to limbic structures, such as the amygdala and the hypothalamus [22], the positive correlation noted here between the degree of difficulty to suppress sadness and the voxels activated in the left LOFC suggests that this prefrontal area may be involved in the down-regulation of the visceral and subjective responses externally induced by emotional stimuli.

A wealth of data suggests that the amygdala, the insula, and the anterior temporal pole are implicated in the mediation of the cognitive, physiological, and experiential aspects of emotional responses, respectively [10]. Given this, the positive correlation measured between the degree of difficulty experienced in the down-regulation condition and the loci of activation in the left amygdala and right anterior temporal pole (BA 21) is consistent with the significantly greater degree of difficulty experienced by depressed participants during the down-regulation condition. These results point to a dysfunction in the neural circuitry underlying emotional self-regulation in major depressive disorder. The fact that the down-regulation of sadness was associated with the OFC in controls but not in depressed participants raises the possibility that, in the depressed group, a dysfunction of the OFC resulted in a disinhibition of the limbic/paralimbic regions involved in emotional responses, such as the amygdala and the anterior temporal pole. Furthermore, we have recently shown in children, relative to adults, that a greater degree of difficulty to down-regulate sadness is associated with greater activation of the brain regions underlying the down-regulation of this primary emotion [8]. In view of this, the greater activation seen in the right amygdala, right insula (BA 13), and right anterior temporal pole (BA 21) in depressed participants suggests that the functioning of the neural circuitry of emotional self-regulation was less efficient in the depressed group than in the control group.

One of the key prefrontal components of the neural circuitry that instantiate emotional self-regulation is BA 24 of the dorsal ACC [8]. We hypothesize that emotional dysregulation in major depressive disorder results from a cognitive deficit that is related, at least partially, to a dysfunction of this prefrontal region. This cerebral structure sends anatomic projections to the amygdala and is involved in the modulation of the cognitive and visceral components of emotion [23]. The fact that no negative correlation was

measured in depressed participants between the right dorsal ACC and the amygdala and insula suggests that the ACC was not exerting an inhibitory action on these two brain regions during the down-regulation condition.

Conclusion

In summary, the present findings suggest that emotional dysregulation in major depressive disorder is related to a disturbance in the neural circuitry of emotional self-regulation. This disturbance appears to implicate the dorsal ACC (BA 24), a critical component of this circuitry. We propose that an abnormal functioning of this prefrontal region is related to the degree of difficulty of depressed individuals to self-regulate negative mood and emotional responses.

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