Anatomic Evaluation of the Orbitofrontal Cortex in Major Depressive Disorder

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Background: The orbitofrontal cortex (OFC) plays a major role in neuropsychologic functioning including exteroceptive and interoceptive information coding, reward-guided behavior, impulse control, and mood regulation. This study examined the OFC and its subdivisions in patients with MDD and matched healthy control subjects.

Methods: Magnetic resonance imaging (MRI) was performed on 31 unmedicated MDD and 34 control subjects matched for age, gender, and race. Gray matter volumes of the OFC and its lateral and medial subdivisions were measured blindly.

Results: The MDD patients had smaller gray matter volumes in right medial [two-way analysis of covariance \( F(1,60) = 4.285; p = .043 \) and left lateral OFC \( F(1,60) = 4.252; p = .044 \]. Left lateral OFC volume correlated negatively with age in patients but not in control subjects. Male, but not female patients exhibited smaller left and right medial OFC volumes compared with healthy control subjects of the same gender.

Conclusions: These findings suggest that patients with MDD have reduced OFC gray matter volumes. Although this reduction might be important in understanding the pathophysiology of MDD, its functional and psychopathologic consequences are as yet unclear. Future studies examining the relationship between specific symptomatic dimensions of MDD and OFC volumes could be especially informative.

Key Words: Neuroimaging, magnetic resonance imaging, unipolar depression, prefrontal cortex, orbital frontal cortex, OFC

Current hypotheses of the pathophysiology of major depressive disorder (MDD) have emphasized abnormalities in circuits involving several specific regions, including the prefrontal cortex (PFC; Botteron et al 2002; Elliott et al 2002; Fu et al 2001; Mayberg 1997; Soares and Mann 1997a, 1997b); however, the PFC is a large and heterogeneous structure both anatomically and functionally. It includes dorsolateral prefrontal cortex (DLPFC), orbitofrontal cortex (OFC), medial prefrontal cortex, and anterior cingulate and is related to different cognitive processes, including executive functioning, attention, and working memory (Fuster 1999). Hence, it is conceivable that specific subdivisions and structures of the PFC, such as OFC, might be differently involved in the pathophysiology of MDD. Thus, parcellation of the PFC can potentially identify anatomic alterations that may underlie distinct pathophysiologic processes.

The orbitofrontal cortex (OFC) is composed of the ventral-most regions of the prefrontal cortex, extending from the anterior perforated substance posteriorly to the frontal pole anteriorly.

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This region is thought to play a major role in a wide range of functional tasks, including coding of exteroceptive and interoceptive information, emotional processing and memory, recognition of reinforcing stimuli, stimulus-reward association, reward-guided behavior, mood regulation, impulse control, and control of autonomic and motor effector pathways (Price 1999; Zald and Kim 2001). The biological underpinnings of several clinical features of MDD could be related to structural or functional abnormalities of OFC. In animals, OFC lesions result in a lowering of thresholds for aggressive reactions, alterations in appetite, and increases in social withdrawal (Fuster 1989; Raleigh and Steklis 1981). In humans, OFC lesions (secondary to war injuries) are associated with abnormalities in a wide range of affective behaviors including depressed mood, anger, affective instability, irritability, and anxiety symptoms, frequently observed in MDD patients (Grafman et al 1986, 1996).

Recent neurobiological evidence has supported early clinical and neurobehavioral theoretical models regarding the involvement of the OFC in the pathophysiology of depression. In a recent postmortem study, Rakowska et al (1999) found significant decreases in cortical thickness of OFC in MDD patients compared with healthy control subjects. Using magnetic resonance imaging (MRI), Lai et al (2000) and Bremner et al (2002) reported bilateral reductions of OFC volumes in patients with MDD compared with control subjects. MacFall et al (2001) applied statistical parametric mapping analysis and found increased lesion density in elderly MDD patients in the medial orbitofrontal white matter. The potential importance of OFC in the pathophysiology of MDD is also suggested by functional neuroimaging studies; OFC metabolism or regional cerebral blood flow (rCBF) have been shown to be abnormally increased in unmedicated depressive patients (Biver et al 1994; Cohen et al 1992). In addition, significant changes in OFC metabolism or rCBF were observed after treatment with both antidepressants and cognitive–behavioral therapy (Brody et al 1999) and when depression relapse was induced by depletion of tryptophan (Bremner et al 1997). Similar observations were reported in patients with secondary depression associated to Parkinson’s disease (Ring et al 1994) and during experimentally induced sadness in healthy subjects (Baker et al 1997). Finally, in vivo
Magnetic resonance spectroscopy (MRS) studies have also suggested that depression is associated with abnormalities in OFC metabolism (Steingard et al 2000).

Different lines of evidence have supported a regional specialization of OFC. Cytoarchitectonic studies have demonstrated that the lateral part of OFC is granular, whereas the medial part is agranular or dysgranular (Carmichael and Price 1994; Morecraft et al 1992). From the embryologic point of view, the medial part derives from an archicortical moiety, whereas the lateral part evolves from a paleocortical moiety (Zaid and Kim 2001). Connectivity studies have found that the medial part is connected with hippocampal formation, ventrolateral parts of the basal nucleus of the amygdala, dorsolateral prefrontal cortex (DLPFC), dorsomedial parts of mediodorsal thalamic nucleus, and anterior cingulate cortex. The lateral part is connected with entoporaithal cortex, ventromedial parts of the basal nucleus of amygdala, DLPFC, ventromedial parts of mediodorsal thalamic nucleus, premotor and parietal cortex, and posterior cingulate cortex (Carmichael and Price 1995a, 1995b). Functional investigations have suggested that the medial part is more involved in “pure” emotional processing, in particular, for negative emotions, whereas the lateral part is involved in formation of associations between emotions, especially positive ones, and cognitions (Baker et al 1997; Drevets et al 1998; Northoff et al 2000).

In this study, we investigated whether patients with MDD had volumetric abnormalities in the OFC and its subdivisions compared with matched healthy control subjects. Based on findings of previous studies, it was hypothesized that MDD patients would have smaller medial and lateral OFC volumes in comparison with healthy control subjects and that the volumes of this structure would inversely correlate with length of illness and number of previous depressive episodes.

**Methods and Materials**

**Subjects**

Subjects were 31 outpatients diagnosed with MDD and 34 healthy subjects. Depression diagnosis was made using the Structural Clinical Interview for DSM-IV (American Psychiatric Association 1994). All patients were drug free for at least 2 weeks preceding the study. Only three patients had previously been exposed to antipsychotic drugs, and none had been exposed to electroconvulsive therapy. Clinical ratings were carried out using the Hamilton Depression Rating Scale (HDRS) (Hamilton 1960). At the time of study participation, 19 patients were acutely depressed, and 12 were euthymic. All subjects were right-handed. Exclusion criteria were any DSM-IV Axis I comorbidity, current medical problems, history of neurologic illness, history of head trauma with loss of consciousness, substance or alcohol abuse in the past 6 months, or history of substance or alcohol dependence at any time.

Healthy control subjects were recruited by advertisement and screened through a diagnostic interview, the Structured Clinical Interview for DSM-IV, nonpatient edition (SCID-NP). Exclusion criteria included any DSM-IV Axis I diagnosis, current medical problems, history of neurologic illness, history of head trauma with loss of consciousness, and positive history of psychiatric disorders among first-degree relatives. Healthy control subjects were matched, as a group, with MDD patients for age, gender, and race. The University of Pittsburgh Institutional Review Board approved the study protocol, and all subjects provided written informed consent after detailed description of the study.

MRI Parameters

The MRI scans were conducted using a 1.5-Tesla General Electric Signa system (GE Medical Systems, Milwaukee, Wisconsin). A sagittal scout series (9 to 11 slices, 5 mm thick with a 1-mm interslice gap) was performed to determine image quality and clarity, as well as subject’s head position. T1-weighted images were acquired by using a three-dimensional spoiled gradient in the steady state pulse sequence that obtained 124 contiguous coronal images, each 1.5 mm thick, with the following imaging parameters: repetition time = 25 msec; echo time = 5 msec; flip angle = 40°; field of view = 24 cm; matrix size of 256 × 192; number of excitations = 1.

The MRI data were identified by scan number alone to retain blindness and analyzed using BRAINS2 software, developed at the University of Iowa Hospitals and Clinics (Andreasen et al 1992). Before tracing, they were spatially realigned, so that the brain anterior–posterior axis was parallel to the anterior comissure-posterior comissure (AC–PC) line, which was horizontal in the sagittal plane, and the interhemispheric fissure was vertical in the axial plane.

**Tracing Guidelines**

A detailed description of the geometric method used to measure OFC, as well as its validation, are presented elsewhere (Lacerda et al, in press). We traced the OFC manually in the coronal plane. The tip of the genu of corpus callosum was located in the sagittal plane and used as the most posterior slice to be traced in the coronal plane. The last slice traced was the most anterior coronal slice where brain tissue could be identified. The superior limit was divided into two parts to reflect the actual anatomic boundary of the OFC. In the subgenual regions, and specifically from the tip of the genu to the most anterior part of the corpus callosum, the superior boundary was represented by a midpoint at the interhemispheric fissure, five slices (about 5.08 mm below) the intercommissural (AC–PC) line. In the slices ahead of the genu of the corpus callosum, the superior limit was represented by a midpoint placed on the intercomissural line. This “lowering” of the superior limit was done to avoid including subgenual structures that are not part of the OFC (e.g., anterior cingulate).

In all coronal slices, horizontal and vertical crosshairs were placed as tangent lines at the inferior and lateral surfaces of the frontal lobes, respectively. The intersection of these two lines generated two lateral points. These lateral points were then connected to the superior limit point, which was established as described earlier, in each slice. The straight lines connecting the lateral points to the superior limit point composed the lateral boundaries of the tracings. The inferior border was traced following the natural inferior limits of the frontal lobes (Figure 1). The OFC was also subdivided into medial and lateral OFC using the olfactory sulcus as a boundary. This subdivision was not conducted in the most anterior slices where this sulcus disappears. Therefore, the addition of lateral and medial OFC measurements produces smaller volumes in comparison to total OFC volumes.

Total brain volumes (ICVs) were manually traced in the coronal plane, and measured by a well-trained and reliable rater. This measurement included brainstem, cerebellum, temporal lobes, cerebrospinal fluid, dura mater, and sinuses (total cerebral gray and white matter).

**Interrater Reliability**

Two raters (ALT and OY) independently traced the OFC and its subdivisions in each hemisphere of 10 randomly selected...
scans. The intraclass correlation coefficients (ICCs) for gray matter volumes ranged from .976–.997. The rater (MN) had an intraclass correlation coefficient of .975 for the ICV measurements.

Statistical Analysis

We performed all statistical analyses using the SPSS for Windows software, version 11.0 (SPSS, Chicago, Illinois). Alpha was set at $p < .05$. A two-way analysis of covariance (ANCOVA) was conducted with OFC gray matter volumes as dependent measures, diagnosis and gender entered as independent variables, and ICV as a covariate. The same model was used to evaluate the effect of mood state (euthymic vs. acutely depressed patients). Also, we separately examined male and female subgroups by using ANCOVA, with diagnosis as the grouping factor and ICV as a covariate. Spearman correlations were used to identify effects of clinical variables such as age at onset, number of prior depressive episodes, length of illness, and HDRS score (which do not follow a normal distribution) on the OFC volumes. Pearson correlations were performed to examine age effects on the measurements. All statistical tests were two-tailed.

Results

Effect of Diagnosis and Clinical Variables

Table 1 shows demographic and clinical features of the subjects. There were no significant differences between patients and comparison subjects with regard to age, gender, or race. No differences between groups involving ICV were observed [ANCOVA, age as a covariate, $F(1,62) = .129$, $p = .72$]. The number of coronal slices traced for measuring OFC subdivisions did not differ between groups (patients, $37.52 \pm 4.46$ vs. control subjects, $38.62 \pm 3.43$; $t = 1.122$, $df = 63$, $p = .266$). Group comparisons revealed a main effect of diagnosis, with MDD patients showing smaller gray matter volumes in the right medial OFC ($2.90 \pm .65$ vs. $3.17 \pm .79$ cm$^3$; $F(1,60) = 4.285$, $p = .043$), as well as in the left lateral OFC ($2.55 \pm .51$ vs. $2.85 \pm .73$ cm$^3$; $F(1,60) = 4.252$, $p = .044$) compared with control subjects. Also, there were nearly significant trends for decreases in the left medial ($2.51 \pm .52$ vs. $2.72 \pm .69$; $F(1,60) = 3.9$, $p = .053$), and in the right lateral ($2.57 \pm .42$ vs. $2.85 \pm .75$; $F(1,60) = 3.68$, $p = .06$) OFC gray matter volumes. Although patients had reductions in all other OFC volume measurements, the differences did not reach statistical significance (Table 2). Interactions between diagnosis and region (lateral vs. medial), as well as between diagnosis and cerebral hemisphere, were nonsignificant (two-way ANCOVA, $p > .05$). Examining the patient group, we did not find any significant correlation between OFC measurements and HDRS scores, length of illness, or number of previous episodes.

Effect of Demographic Variables

Analyzing the entire sample (patients and control subjects), no significant correlation between age and OFC gray matter volumes emerged (Pearson, $r > .05$). In the patient group, age was significantly and inversely correlated only with gray matter volumes of the left lateral OFC (Pearson, $R = -0.376$, $p = .037$). In the control group, no significant correlation between age and OFC gray matter measurements was observed.

Analyzing the entire sample, there was a main effect of gender with females having smaller left [$F(1,60) = 3.997$, $p = .05$] and right [$F(1,60) = 4.647$, $p = .035$] medial OFC volumes. When analysis involved only women ($n = 46$), there was no diagnosis effect; however, a diagnosis effect was observed when only men ($n = 19$) were included and showed decreased volumes in the left [$F(1,16) = 6.767$, $p = .019$] and right [$F(1,16) = 4.576$, $p = .048$] medial OFC in patients. No significant interaction involving diagnosis and gender was observed.

State Effect

Euthymic patients ($n = 12$) and acutely depressed patients ($n = 19$) had no significant differences in mean OFC volumes (ANCOVA, age, gender, and ICV as covariates; $p > .05$). Differences between euthymic patients and control subjects were nonsignificant; however, acutely depressed patients had smaller right [$F(1,47) = 4.276$, $p = .044$] and left [$F(1,47) = 4.102$, $p = .049$] medial OFC gray matter volumes in comparison with control subjects.

Discussion

The results of this study suggest that patients with MDD exhibit volumetric reductions in medial and lateral OFC gray matter. When men and women were examined separately, differences were observed only in the male subgroup, with male patients exhibiting smaller left and right medial OFC gray matter volumes compared with male control subjects. Additionally, we found decreased medial OFC volumes in acutely depressed but not euthymic MDD patients in comparison to healthy control subjects.

Our findings are concordant with functional neuroimaging studies, as well as postmortem (Ongur et al 1998; Rajkowska et al 1999) and MRI (Bremner et al 2002; Lai et al 2000) morphometric studies examining the OFC in patients with MDD. Mayberg et al (1999) observed significantly reduced activity in orbital-inferior region in depressed patients with Parkinson’s disease compared with both healthy control subjects and patients.
Table 1. Clinical and Demographic Characteristics of the Sample

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients (n = 31) (Mean ± SD)</th>
<th>Controls (n = 34) (Mean ± SD)</th>
<th>F</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>39.26 ± 11.9 (range: 18–59)</td>
<td>37.03 ± 11.88 (range: 18–59)</td>
<td>−.755</td>
<td>.453</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td>1.27</td>
<td>.26</td>
</tr>
<tr>
<td>Male</td>
<td>7</td>
<td>12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>24</td>
<td>22</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td>1.66</td>
<td>.197</td>
</tr>
<tr>
<td>Caucasian</td>
<td>30</td>
<td>30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td>1</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HDRS Score</td>
<td>14.07 ± 1.31 (range: 0–36)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Length of Illness (years)</td>
<td>11.42 ± 10.57 (range: 1–45)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at Onset (years)</td>
<td>27.94 ± 11.64 (range: 12–50)</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

HDRS, Hamilton Depression Rating Scale.

Table 2. Orbitofrontal Cortex (OFC), Gray Matter Volumes in Patients with Major Depressive Disorder (MDD) and Healthy Control Subjects

<table>
<thead>
<tr>
<th>Region</th>
<th>Patients (n = 31) (Mean ± SD)</th>
<th>Controls (n = 34) (Mean ± SD)</th>
<th>F_{1,60}</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total OFC</td>
<td>12.41 ± 2.22</td>
<td>13.4 ± 3.6</td>
<td>2.473</td>
<td>.121</td>
</tr>
<tr>
<td>Right</td>
<td>6.52 ± 1.21</td>
<td>6.98 ± 1.87</td>
<td>1.873</td>
<td>.176</td>
</tr>
<tr>
<td>Left</td>
<td>5.89 ± 1.09</td>
<td>6.42 ± 1.82</td>
<td>2.885</td>
<td>.095</td>
</tr>
<tr>
<td>Medial OFC</td>
<td>5.41 ± 1.12</td>
<td>5.89 ± 1.46</td>
<td>4.407</td>
<td>.04</td>
</tr>
<tr>
<td>Right</td>
<td>2.9 ± 0.63</td>
<td>3.17 ± 0.79</td>
<td>4.285</td>
<td>.043</td>
</tr>
<tr>
<td>Left</td>
<td>2.51 ± 0.52</td>
<td>2.72 ± 0.69</td>
<td>3.9</td>
<td>.053</td>
</tr>
<tr>
<td>Lateral OFC</td>
<td>5.1 ± 0.87</td>
<td>5.68 ± 1.41</td>
<td>4.609</td>
<td>.036</td>
</tr>
<tr>
<td>Right</td>
<td>2.57 ± 0.42</td>
<td>2.84 ± 0.75</td>
<td>3.68</td>
<td>.06</td>
</tr>
<tr>
<td>Left</td>
<td>2.53 ± 0.5</td>
<td>2.84 ± 0.73</td>
<td>4.252</td>
<td>.044</td>
</tr>
</tbody>
</table>

with Parkinson’s disease who did not suffer from depression. There was also an inverse correlation between metabolic rates in this area and depression scores. Liotti et al (2002) described significant decreases in regional cerebral blood flow in medial OFC in acutely depressed and remitted MDD patients after provocation of sadness with autobiographic memory scripts in a positron emission tomography study. Lai et al (2000), examining geriatric MDD patients, reported a bilateral volumetric reduction of OFC compared with healthy control subjects. In a recent study, Bremner et al (2002) found a significantly smaller gyrus rectus, structure that composes the medial OFC, in adult patients with MDD in remission. Additionally, MacFall et al (2001) found increases in density of small neurons were observed. These findings suggest that neuronal atrophy or developmental abnormalities may underlie neuronal size reduction in the rostral part of OFC. Interestingly, primate studies have demonstrated that nonpyramidal neurons of these cortical layers are the preferential targets for serotonergic afferents (Rajkowska et al 1999; Schwartz and Goldman-Rakic 1984; Solomon and Goldman-Rakic 1988), a neurotransmitter system that has been incriminated in the pathophysiology of depressive disorders (Middlemiss et al 2002).

A significant inverse correlation between age and left lateral OFC gray matter volume was found among patients but not control subjects. This is in accordance with findings from neuroimaging studies suggesting that aging and MDD exert distinct and independent effects on brain. These changes appear to be more pronounced in older depressive patients, particularly in prefrontal cortex regions (Nobler et al 1999). Decreases in OFC gray matter with advancing age, although not found in our study, have also been reported in healthy subjects (Tisserand et al 2002). This discrepancy relates to the age range involved in these studies, with ours involving primarily young adults. Some authors (e.g., Bremner et al 2002; Rajkowska 1999) have proposed that the neurotrophic effect of glucocorticoids, which are increasingly secreted during stress, may be implicated in volume reductions of brain structures observed in MDD. The functional consequences of the reduced size of OFC subdivisions in patients with MDD remain unclear; however, OFC abnormalities, through dense interconnections with brain structures that have putative involvement in MDD pathophysiology, such as basal ganglia, thalamus, amygdala, and hippocampus, may mediate distinct depressive symptoms, for example, blunting of emotional affect and impaired social functioning (Bremner et al 2002; Zald and Kim 2001). Consistent with this, OFC lesions in humans as well as in primates have been associated with social and emotional behavior impairments (Fuster 1989; Grafman et al 1986, 1996; Raleigh and Steklis, 1981). Furthermore, several functional neuroimaging studies (Bechara et al 1994; Blair et al 1999; Elliott and Dolan 1998; Elliott et al 1999, 2000; Maguire et al 1999; Meunier et al 1997; Nobre et al 1999) have demonstrated the activation of this region during different neuropsychological tasks in which MDD patients have been found to perform poorly (Barton and Morley 1999; Beats et al 1996; Hughes et al 1985; Persad and Polivy 1993; Sackeim and Wegner 1986; Thomas et al 1999; Williams et al 2000).

There is some evidence for dissociation of function within the OFC. Lateral OFC has been shown to be involved in integration between emotions and cognitions, and processing of positive emotions (Baker et al 1997; Drevets et al 1998; Northoff et al 2000). Also, it is part of frontostratial circuits, which involve dorsolateral prefrontal cortex, lateral OFC, striatum, and anterior cingulate, where “executive control” is largely processed (Bradshaw and Sheppard 2000). Medial OFC has been described as the OFC subdivision associated with “pure” emotional processing, especially for negative emotions (Northoff et al 2000). It is of interest that a bias toward processing of mood-congruent information has been consistently reported in MDD, with patients showing a tendency to perform better when responding to stimuli with a negative emotional valence (Elliott et al 2002). The hypothesis regarding the functional dissociation between medial and lateral OFC, however, has limitations. Few studies with injured war veterans have examined its occurrence in humans. Besides the limited number of subjects examined, the boundary between lateral and medial OFC has not been precisely described in those studies, so that lesions classified as medial often also affect lateral OFC and vice versa. In addition, as described earlier, even in animal studies, the evidence for functional dissociation within the OFC is limited, and different parcellation schemas have been proposed (e.g., medial × lateral OFC, inferior convexity × caudal OFC; Northoff et al 2000; Rolls 1996).
In our study, volumetric alterations of the medial OFC were observed in the acutely depressed, but not in the euthymic patients. This finding is in line with functional and neurochemical brain imaging studies that have found state-dependent abnormalities in patients with mood disorders (Kato et al 1991, 1992; Kennedy et al 2001); however, this observation must be considered preliminary in view of the small sample sizes and the nonrigorous matching of these subgroups.

Gender differences were observed in this study, with male patients exhibiting more volumetric alterations than female patients. This is consistent with other studies showing more pronounced neuroanatomic abnormalities in men compared with women with MDD, as well as other neuropsychiatric disorders. For instance, male patients with a first episode of MDD appear to have more pronounced structural abnormalities of the hippocampal formation (Frodl et al 2002). Similarly, Briellmann et al (2000) found more pronounced brain atrophy in men with temporal lobe epilepsy, whereas schizophrenia appears to affect men more severely than women (Roy et al 2001). These findings could be explained in part by a potential neuroprotective effect of estrogens, suggested by both studies with animals and humans (Alkayed et al 1998; Miller et al 1998; Singer et al 1998). Additionally, estrogens could limit the adverse sequelae of hypercortisolaemia because of dysfunction of the hypothalamic-pituitary-adrenal axis reported in depression (Piccinni and Wilkinson 2000). On the other hand, testosterone has been suggested to increase vulnerability to neurotoxic processes, at least in animals (Nishino et al 1998). Furthermore, several studies have reported gender differences in symptom presentation in depression, with women more frequently having increased appetite, hypersomnia, fatigue, and psychomotor retardation (Frank et al 1988; Young et al 1990), whereas depressive men may have more insomnia and agitation (Khan et al 2002). Neuropsychiatric abnormalities such as the ones observed here might explain these clinical differences. Alternatively, men may present a higher neurobiological threshold to develop MDD, necessitating more pronounced brain structural alterations to develop depressive symptoms.

The results of our study should be interpreted with caution, in light of several methodologic limitations. To our knowledge, this is the first study to separately evaluate both medial and lateral OFC volumes in MDD. For the lateral OFC findings, this is the first time that reduction in MDD patients is reported, and independent replication of these results is needed. Additionally, the olfactory sulcus was considered as the boundary between medial and lateral parts of the OFC, which may not reflect the actual borders of these structures; however, although these subdivisions have been demonstrated to be both functionally and cytoarchitectonically relevant, there is no widely accepted anatomic landmark used as a reference for subdividing the OFC (Lacerda et al, in press). Finally, the lack of relationship between OFC volumes, length of illness, and number of episodes may be due to difficulties in accurately retrieving these clinical data retrospectively, on the basis of patient report.

In conclusion, our findings suggest that patients with MDD have reduced lateral and medial OFC gray matter volumes. Although this reduction may be important in understanding the pathophysiology of MDD, its functional and psychopathologic consequences are still unclear. Our findings also have potential implications for functional neuroimaging studies in this field because differing volumes between patients and control subjects for specific brain regions are relevant when one interprets functional differences between groups. Future studies examining the relationship between relevant symptom dimensions of MDD and OFC volumes could be especially informative.

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