Brain structural correlates of depressive comorbidity in obsessive–compulsive disorder

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The high comorbidity of obsessive–compulsive disorder (OCD) with major depressive disorder (MDD) suggests common neurobiological substrates. We assessed the contribution of lifetime MDD to brain structural alterations in OCD using magnetic resonance imaging. OCD patients with (n = 33) or without (n = 39) lifetime MDD, and 72 control subjects were assessed. Comparative region of interest (ROI) analyses assessed the contribution of lifetime MDD to gray matter volume alterations in OCD patients. Interregional correlations of gray matter volume were also examined and voxelwise analyses were performed to identify alterations in other brain regions. OCD patients with lifetime MDD showed a larger reduction of medial orbitofrontal cortex (mOFC) gray matter volume. Both OCD groups showed distinct correlations of mOFC gray matter volume with other relevant brain regions. For patients with MDD, this involved the medial frontal gyrus, and right insula and amygdala regions, whereas for those OCD patients without MDD, the rostral anterior cingulate cortex was involved. Our findings support existing evidence suggesting a nonspecific involvement of mOFC alterations in a range of neuropsychiatric disorders. Nevertheless, volume reduction in this region, together with an abnormal pattern of interregional correlations with other emotion-relevant brain areas, may contribute to explain the diathesis for MDD comorbidity in OCD.

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Introduction

The prevalence of depressive symptoms in patients with obsessive–compulsive disorder (OCD) has been estimated in one to two thirds of all cases (Pigott et al., 1994) and, consequently, major depressive disorder (MDD) is often considered to be the major psychiatric comorbidity in OCD (Rasmussen and Eisen, 1992). Although such a high-rate of comorbidity in OCD has been linked to known clinical factors such as greater age, the severity and chronicity of OC symptoms or poor treatment response and outcome (Perugi et al., 1997), very little is currently known as to the underlying pathophysiological mechanisms of depressive episodes suffered by OCD patients.

From a neurobiological perspective, one obvious question regarding the depressive comorbidity of OCD patients is whether it may share similar pathophysiological features to that implicated in MDD alone (Saxena et al., 2001). Although existing data are limited, early work using positron emission tomography (PET) suggested that there might be certain pathophysiological correlates common to unipolar depression, bipolar depression and OCD patients with comorbid MDD (Baxter et al., 1989). Specifically, Baxter and colleagues reported a generalized reduction in the resting-state metabolism of the dorsolateral prefrontal cortex. More recently, this group has reported a pattern of reduced metabolic activity in the left hippocampal region common to MDD patients and patients with concurrent OCD and MDD, but not OCD patients alone (Saxena et al., 2001). Thus, such findings suggest that there may be some common pathophysiological alterations associated with depressive susceptibility in these subgroups, irrespective of patients’ primary clinical diagnoses.

In a recent magnetic resonance imaging (MRI) study carried out by our group, we characterized a pattern of brain structural alterations in a large series of OCD patients involving significant reductions of gray matter volume in the medial frontal gyrus (MdFG), the medial orbitofrontal cortex (mOFC) and the left insulo-opercular region, together with relative volume increases in the ventral striatum and anterior cerebellum (Pujol et al., 2004). In this particular study, no relationship was found between brain alterations in OCD patients and the severity of depressive symptomatology at the time of scanning, assessed by total Hamilton Depression Rating Scale score (HAM-D) (Hamilton, 1960), although we did not
specifically study the association between patients’ history of lifetime depression and brain volumetric measurements.

Current epidemiological and clinical evidence suggests that OCD and MDD appear to co-occur in three major comorbidity patterns: (i) where OCD occurs first; (ii) where there is a concurrent onset of both OC and MDD symptoms; and (iii) where depression precedes the onset of OC symptoms (Demal et al., 1993). Thus, it is possible that our previous assessment of OCD patients’ depressive symptom severity using HAM-D scores may have failed to represent the actual incidence of MDD comorbidity. Therefore, in the current study, we conducted a region-of-interest (ROI) analysis to test the extent to which lifetime history of MDD may contribute to the previously described structural alterations in OCD (Pujol et al., 2004). We also extended our assessment by performing exploratory voxelwise analyses to investigate a possible association of MDD comorbidity with alterations in other brain areas and networks outside these regions.

Methods

Subjects

Seventy-two patients with OCD (32 women; mean±SD age of 29.8±10.5 years; range 18–60 years) and 72 control subjects (32 women, 30.1±10.2 years, range 18–57 years), corresponding to the sample previously described (Pujol et al., 2004), were assessed in this study. Patients and control subjects were equivalent in the demographic variables of age, sex, and handedness (11 left-handed subjects per group) assessed by the Edinburgh Handedness Inventory (Oldfield, 1971; see Table 1).

The OCD group consisted of community outpatients consecutively recruited to our research program according to DSM-IV criteria for OCD and the absence of relevant medical, neurological and other major psychiatric diseases. Comorbid anxious and depressive symptoms were not considered as an exclusion criterion, provided that OCD was the principal clinical diagnosis (i.e., the main reason, at time of inclusion, to seek medical assistance). No patient met criteria for Tourette’s syndrome or showed psychoactive drug abuse during a period of 12 months or longer. Patient diagnosis was independently confirmed by two senior psychiatrists using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) Clinician Version (First et al., 1997). Control subjects of similar sociodemographic background also underwent a detailed assessment of their family and medical history and a structured psychiatric interview to exclude psychiatric disorders using the guidelines of Shtasel et al. (1991).

Patient OC symptomatology at the time of scanning was rated using the Yale–Brown Obsessive–Compulsive Scale (YBOCS) and a clinician-rated YBOCS symptom checklist (Goodman et al., 1989). Lifetime depressive symptoms were also determined with the SCID-I Clinical Version (First et al., 1997). Twenty-six patients showed past history of major depressive disorder (MDD), and in nine of them MDD preceded the onset of OCD. In addition, seven OCD patients without a significant past history of MDD fulfilled criteria for a major depressive episode at the time of scanning. A total of 33 OCD patients were considered in the OCD with MDD group and 39 OCD patients without lifetime MDD were included in the OCD without MDD group (OCD alone). After complete description of the study to the subjects, written informed consent was obtained.

MRI acquisition and processing

A 60-slice 3-D spoiled gradient-recalled T1-weighted MRI was acquired for each subject in the sagittal plane using a 1.5-Tesla scanner (Signa, GE Medical Systems, Milwaukee, WI). Acquisition parameters were: TR 40 ms, TE 4 ms, pulse angle 30°, field of view 26 cm, matrix size 256×192 pixels, and section thickness between 2.4 and 2.6 mm. Total acquisition time was 8 min and 13 s. Post-acquisition data were transferred to a Microsoft Windows platform running MATLAB version 6.5 (The MathWorks Inc, Natick, MA) and Statistical Parametric Mapping software (SPM99; The Wellcome Department of Imaging Neuroscience, London, England).

Following visual inspection of the MRI volumes for potential incidental findings or image artifacts, data were prepared for analysis using the optimized preprocessing strategy proposed by Good et al. (2001). Informed by our previous results (Pujol et al., 2004), this procedure was focused on subjects’ gray matter volumes, and involved several automated processes, including (i) the creation of a gray matter study-specific template with the brain images of all the subjects (patients and controls) included in the study; (ii) segmentation of whole-brain native space images into gray matter, white matter and cerebrospinal fluid (CSF); (iii) optimal normalization (with linear and non-linear deformations) of gray matter segments to their tissue specific template to transform images into the Montreal Neurological Institute (MNI) standard stereotactic space (including reslicing images to a final voxel size of 1.5 mm³); (iv) modulation of all voxel values by the Jacobian determinants derived from the normalization step (i.e. to restore volumetric information lost through spatial transformations); and (v) image smoothing with a 12-mm full width at half maximum (FWHM) isotropic Gaussian Kernel. An expanded description of each image preprocessing step is provided in Pujol et al. (2004).

Statistical analysis

To assess potential differences in the sociodemographic and clinical characteristics of the patient and control groups, we used the one-way ANOVA, Student’s t and χ² tests implemented in the Statistical Package for the Social Sciences (SPSS) version 12.0 (see Table 1). In the same way, global gray matter volumes, obtained from the non-normalized gray matter images, were compared by univariate analysis of variance (ANOVA) with gender, age, and the quadratic and cubic expansions of age (to control for potential non-linear effects of age) as confounding covariates.

Analyses of regional volumetric measurements were carried out using the following three approaches:

1. To examine the contribution of lifetime MDD on the pattern of previously detected brain structural alterations in OCD, we performed a selective region of interest (ROI) volumetric analysis using SPM99 and the additional MarsBaR toolbox (Brett et al., 2002). Specifically, we compared differences in the gray matter volume of six ROIs between the three study groups; OCD with lifetime MDD, OCD alone and healthy subjects, with gender, age, and the quadratic and cubic expansions of age as confounding covariates. ROIs were defined a priori from the six primary clusters that we previously reported as showing significant volumetric alterations in OCD patients versus healthy subjects (Pujol et al., 2004).
As the volume of each ROI was represented by the voxel values within each region, these were summarized by extracting the 1st eigenvariate, a measure that accounted for most of the variance in this defined set of voxels. Three of these ROIs, which were located in the mOFC, MdFG and left posterior insula, corresponded to areas where we observed absolute decreases in gray matter volume, whereas the other three ROIs, corresponding to areas of relative gray matter increases (after controlling for global gray matter volume), were located in the anterior cerebellum, and in the left and right ventral striatal areas. Between-groups comparisons were reported as significant with a threshold of $p < .05$, corrected for the multiple comparisons performed over the six ROIs.

In a post-hoc analysis, we assessed for interregional correlations between the volume of the ROI significantly related to MDD (see Results section below) and the other gray matter regions.

Table 1
Demographical and clinical data of three groups

<table>
<thead>
<tr>
<th>Demographical and clinical variable</th>
<th>Normal control subjects ($n=72$)</th>
<th>OCD alone ($n=39$)</th>
<th>OCD with lifetime MDD ($n=33$)</th>
<th>Statistical value $^a$ ($p$ value)$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean SD</td>
<td>Mean SD</td>
<td>Mean SD</td>
<td>Mean SD</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>30.13 10.23</td>
<td>26.12 8.49</td>
<td>30.13 10.23</td>
<td>3.74 (.026)</td>
</tr>
<tr>
<td>Age of onset of OCD (years)</td>
<td>na na</td>
<td>16.81 5.86</td>
<td>17.21 5.93</td>
<td>.80 (.778)</td>
</tr>
<tr>
<td>Duration of illness (years)</td>
<td>na na</td>
<td>10.26 8.13</td>
<td>16.15 12.04</td>
<td>5.96 (.027)</td>
</tr>
<tr>
<td>HAM-D</td>
<td>10.23 3.87</td>
<td>15.57 5.54</td>
<td>43.5 (&lt;.0001)</td>
<td></td>
</tr>
<tr>
<td>Y-BOCS score (global)</td>
<td>25.56 7.8</td>
<td>28.15 6.2</td>
<td>2.36 (.129)</td>
<td></td>
</tr>
<tr>
<td>Y-BOCS score (obsessions)</td>
<td>13.56 3.31</td>
<td>14.27 3.28</td>
<td>.83 (.366)</td>
<td></td>
</tr>
<tr>
<td>Y-BOCS score (compulsions)</td>
<td>12.00 5.19</td>
<td>13.87 4.21</td>
<td>2.77 (.100)</td>
<td></td>
</tr>
<tr>
<td>Gender distribution (females)</td>
<td>32 44.4</td>
<td>15 38.5</td>
<td>17 51.5</td>
<td>61 (.540)</td>
</tr>
<tr>
<td>Handedness (left-handers)</td>
<td>11 15.3</td>
<td>6 15.4</td>
<td>5 15.2</td>
<td>.011 (.100)</td>
</tr>
</tbody>
</table>

| OCD symptoms $^c$                  |                               |                |                               |                                   |
| Symmetry and ordering             | 12 30.8                       | 10 30.3        | 0.002 (.966)                  |                                   |
| Hoarding                          | 10 25.6                       | 6 18.2         | 0.575 (.448)                  |                                   |
| Contamination and cleaning        | 13 33.3                       | 18 54.5        | 3.280 (.093)                  |                                   |
| Aggressive and Checking           | 26 66.7                       | 23 69.7        | 0.076 (.783)                  |                                   |
| Sexual and religious              | 11 28.2                       | 6 18.2         | 0.996 (.318)                  |                                   |

| Treatment status                  |                               |                |                               |                                   |
| Previous SRIs trials completed    |                               |                |                               |                                   |
| Never treated                     | 3 7.7                         | 2 6.1          | –                             |                                   |
| One previous SRIs trial           | 10 25.6                       | 9 27.3         | –                             |                                   |
| Two previous SRIs trial           | 11 28.2                       | 10 30.3        | –                             |                                   |
| Three or more previous SRIs trial | 15 38.5                       | 12 36.4        | –                             |                                   |
| Previous low dose antipsychotic use | 4 10.3                      | 8 24.2         | 2.517 (.128)                  |                                   |
| Complete behavioral therapy protocol | 22 56.4                     | 19 57.6        | 0.010 (.66)                   |                                   |
| Previous treatment with ECT       | 0 0                           | 1 3.0          | 1.98 (.458)                   |                                   |
| Previous treatment with experimental TMS | 5 12.8                   | 5 15.2         | 0.081 (.1)                    |                                   |
| Stable medication use at time of MRI |                               |                | 0.160 (.997)                  |                                   |
| Medication free (>4 weeks)        | 10 25.6                       | 8 24.2         | –                             |                                   |
| Clomipramine hydrochloride        | 14 35.9                       | 11 33.3        | –                             |                                   |
| Fluvoxetine or fluvoxamine        | 7 17.9                        | 6 18.2         | –                             |                                   |
| Phenytoine sodium                  | 1 2.6                         | 1 3.0          | –                             |                                   |
| Clomipramine with fluoxetine      | 7 17.9                        | 7 21.2         | –                             |                                   |

OCD, obsessive compulsive disorder.
MDD, major depressive disorder.
HAM-D, Hamilton rating scale for depression.
Y-BOCS, Yale–Brown Obsessive–Compulsive Scale.
na, not applicable.
ECT, electroconvulsive therapy.
TMS, transcranial magnetic stimulation.
MRI, magnetic resonance imaging.

$^a$ Two-sample $t$ test for continuous variables, $\chi^2$ test for categorical variables.

$^b$ Two-tailed.

$^c$ Dimensions from Mataix-Cols et al. (1999).

2004). As the volume of each ROI was represented by the voxel values within each region, these were summarized by extracting the 1st eigenvariate, a measure that accounted for most of the variance in this defined set of voxels. Three of these ROIs, which were located in the mOFC, MdFG and left posterior insula, corresponded to areas where we observed absolute decreases in gray matter volume, whereas the other three ROIs, corresponding to areas of relative gray matter increases (after controlling for global gray matter volume), were located in the anterior cerebellum, and in the left and right ventral striatal areas. Between-groups comparisons were reported as significant with a threshold of $p < .05$, corrected for the multiple comparisons performed over the six ROIs.

2. In a post-hoc analysis, we assessed for interregional correlations between the volume of the ROI significantly related to MDD (see Results section below) and the other gray matter regions. The 1st
eigenvariate of the ROI was introduced as the predictor regressor in an SPM anatomical correlation analysis, controlling for global gray matter volume, introduced as a nuisance covariate.

3. Finally, to explore for potential abnormalities of the OCD with a lifetime MDD group in other brain areas beyond the six ROIs described above, we conducted an additional whole-brain voxel-based morphometry (VBM) assessment using SPM99. We used a conjunction analysis to examine brain regions where volumetric differences occurred in OCD patients with lifetime MDD compared to both OCD alone and healthy subjects. The minimum t-statistic of the two comparisons (OCD with lifetime MDD vs. OCD alone, and OCD with lifetime MDD vs. healthy subjects) was used to assess significance (Friston et al., 2005; Nichols et al., 2005). Gender, age, and the quadratic and cubic expansions of age were included as nuisance variables in the analysis.

In voxelwise analyses (analyses 2 and 3 of the above), findings were reported as significant with a threshold of \( p < .05 \) corrected for the multiple comparisons performed over the whole gray matter volume. Nevertheless, results were also explored at a less conservative threshold of \( p < .001 \) uncorrected for multiple comparisons. SPM spatial coordinates of these voxelwise analyses were finally translated into the standard Talairach space using a non-linear transformation of SPM99 space to Talairach space (Brett, 2006). Although new versions of the SPM software have been developed, we used SPM99 to ensure an easier interpretation of the results here presented considering the ones previously reported with the same software version.

Results

Table 1 presents the demographic and clinical characteristics of all three subjects groups. The three groups differed significantly in age, but did not differ in their gender ratio or handedness. OCD patients with lifetime MDD were older than patients with OCD alone. These patients also showed greater depressive symptom at the time of scanning (HAM-D scores) and had a longer illness duration. There were no significant differences between the two patient groups on total YBOCS score, presence of obsessive or compulsive symptoms, or their severity or treatment status.

Global gray matter volume

A univariate ANCOVA, controlling for gender, age, and the quadratic and cubic expansions of age, demonstrated a significant group effect on global gray matter volume \( (F = 3.66; p = .028) \). OCD patients with lifetime MDD showed smaller global gray matter volumes compared to healthy controls \( (mean = 717; SD = 79 \text{ ml}) \) in OCD with MDD patients; \( mean = 763; SD = 78 \text{ ml} \) in control subjects; \( F = 6.66; p = .012 \), but not in comparison with patients with OCD alone \( (mean = 758; SD = 80 \text{ ml}) \). No differences were found between patients with OCD alone and healthy control subjects.

Contribution of lifetime MDD on OCD-related brain structural alterations

Findings from the ROI-driven analysis are reported in Table 2. As anticipated, both OCD groups showed significant alterations of regional gray matter volumes compared to control subjects in the six ROIs. Additionally, we observed a significant and specific reduction of the gray matter volume of the mOFC in OCD patients with lifetime MDD compared to those without. No further differences in the other ROI volumes were seen between these two groups of patients.

Correlations of mOFC volume with other brain regions

To examine for potential structural networks involving the mOFC in the three study groups, we performed SPM anatomical correlation analyses. Such analyses indicated that in patients with OCD alone, the volume of mOFC was positively correlated with the volume of the rostral anterior cingulate cortex (ACC) (peak correlation at Talairach \( x, y, z = -2, 42, 14 \text{ mm} \); \( t = 6.44; \) corrected \( p < .05 \), see Fig. 1). Conversely, for OCD patients with lifetime MDD, mOFC volume was positively correlated with a cluster of voxels located more anterior and dorsal in the MdFG (peak correlation at Talairach \( x, y, z = -2, 48, 25 \text{ mm} \); \( t = 5.93; \) corrected \( p < .05 \), see Fig. 1). Another positive correlation was also observed for this group between the mOFC and the right anterior insula (peak correlation at Talairach \( x, y, z = 47, 16, -11 \text{ mm} \); \( t = 6.33; \) corrected \( p < .05 \); see Fig. 2). Finally, OCD patients with lifetime MDD also showed a negative correlation between mOFC volume and the right amygdala–parahippocampal region (peak correlation at Talairach \( x, y, z = 20, -1, -22 \text{ mm} \); \( t = 5.12; \) corrected \( p < .05 \); see Fig. 3). No significant interregional correlations with the mOFC were observed for the healthy control subjects.

Other brain regions implicated in OCD with MDD

Additional voxelwise analyses were conducted to explore whether other brain regions might distinguish OCD patients with MDD from patients with OCD alone and healthy controls. A conjunction analysis indicated that regional gray matter volumes of OCD patients with lifetime MDD were reduced compared to the other two groups in three primary clusters: one involving the left parahippocampal area (peak correlation at Talairach \( x, y, z = -29, -18, -27 \text{ mm} \); \( t = 4.04; \) see Fig. 4), extending to the fusiform gyrus, and two clusters respectively located in the right (peak correlation at...
Talairach x, y, z: 29, 54, −17 mm; t = 3.50; see Fig. 4) and left (peak correlation at Talairach x, y, z: −41, 51, −12 mm; t = 3.41; see Fig. 4) lateral orbitofrontal cortices. These differences were significant at a less conservative whole-brain uncorrected threshold of \( p < .001 \).

All the above analyses were repeated controlling for potential confounding variables and no relevant changes were observed in the results. Confounding variables included handedness, illness duration and comorbidity pattern (OCD onset before MDD, and OCD onset after MDD). In relation to the depression status (past history of depression vs. first episode at the moment of scanning), although the main results remained unaltered after controlling for this factor, in a post-hoc analysis we detected a significant volume reduction in the left lateral orbitofrontal cortex in OCD with past history of MDD (\( n=26 \)) (\( t=2.7; p= .011 \)) compared to those patients suffering their first MDD episode (\( n=7 \)).

**Discussion**

Our primary finding was that OCD patients with a lifetime history of MDD showed a more pronounced volume reduction in
the mOFC. Interestingly, gray matter volume of the OFC showed an abnormal pattern of correlations with other relevant brain areas, involving the MdFG, insula and parahippocampal–amygdala complex in OCD patients with lifetime MDD, and the rostral anterior cingulate cortex in patients with OCD alone.

Dysfunction of the mOFC has been hypothesized in a range of neurological and psychiatric disorders, which is supported by lesion and neuroimaging studies (Zald and Kim, 2001). To this end, mOFC alterations have been documented in mood and anxiety disorders (Bremner et al., 2002; Drevets, 2000; Rauch et al., 1997), schizophrenia (Crespo-Facorro et al., 2001; Pantelis et al., 2003), personality and neurodevelopmental disorders (Berlin et al., 2005; Girgis et al., 2001), as well as substance abuse disorders (Goldstein and Volkow, 2002; Lubman et al., 2004). Collectively, these data suggest that the mOFC appears to be a region of common pathophysiological vulnerability in disorders characterized by, among other features, significant emotional dysfunction.

In OCD patients specifically, neuroimaging studies have reported reduced volumes of the mOFC (Pujol et al., 2004; Szeszko et al., 1999) as well as altered functional activity (Rauch et al., 1994; Mataix-Cols et al., 2004) and functional connectivity of this region (Harrison et al., 2006). However, in keeping with the above discussion, Rauch et al. (1997) proposed that abnormal functional activation of the mOFC might be relatively non-specific to OCD and generalizable across a variety of anxiety disorders, particularly in response to anxiety-provoking challenges.

Our current findings suggest a common alteration of mOFC gray matter volume in OCD patients with and without MDD, but where the presence of comorbid depression had an additive effect of augmenting this pattern of volumetric reduction. This finding appears to be consistent with neuroimaging studies of primary depression, where prominent alterations of the mOFC have been reported, including reduced structural volume (Bremner et al., 2002; Lacerda et al., 2004), reduced basal metabolic activity and perfusion in severe patients (Drevets, 2000; Mayberg et al., 1994), and blunted functional responsiveness of this region following psychological and pharmacological challenges (Bremner et al., 2003; Liotti et al., 2002). Similarly, this appears to be in line with other neuroimaging studies of MDD and MDD comorbidity in OCD, where common alterations linked to depressive symptomatology have been reported (Baxter et al., 1989; Saxena et al., 2001).

Anatomical alteration in the OFC region, therefore, may be considered a marker of psychiatric illness that is particularly prominent when OCD and MDD co-occur in the same patients. Nevertheless, our correlation analysis may well suggest a different role for OFC changes in the pathophysiology of OCD and comorbid depression. Taken together, the observed interregional correlations appear to support the notion that psychiatric disorders, in general, evolve from dysfunction of distributed brain systems rather than distinct alterations (Aouizerate et al., 2004; Crespo-Facorro et al., 2001; Drevets, 2000; Goldstein and Volkow, 2002).

OCD patients without MDD showed a positive structural correlation of mOFC volume and the rostral division of the ACC. Both regions have been consistently implicated in functional imaging studies of OCD over the past decade (Rauch et al., 1994) and have become central to most pathophysiological models of this illness (Aouizerate et al., 2004). Evidence from cognitive neuroscience also implicates a role for both regions in higher-order behavioral processes such as complex decision making, emotional self-awareness and action monitoring (Paus, 2001; Gusnard et al., 2001). Action monitoring, in particular, appears to have certain phenomenological relevance in explaining aspects of OC symptomatology and, in recent studies of OCD patients, has been linked to functional alterations of the rostral ACC and OFC regions (Maltby et al., 2005; Ursu et al., 2003). Thus, extending our previous study (Pujol et al., 2004), this observation of a structural interrelationship between the mOFC and rostral ACC provides additional support for a relevant medial–frontal contribution to OCD (Yücel et al., 2007).

In OCD patients with lifetime MDD, mOFC volume showed a differential pattern of regional correlations involving the medial prefrontal cortex, insula and parahippocampal–amygdala complex. Specifically, we observed a positive correlation of mOFC volume with the medial prefrontal cortex, a brain region that has become increasingly implicated in functional imaging studies of emotion processing, including a role in the voluntary regulation of mood, as well as the emotional appraisal of self and others (Teasdale et al., 1999; Gusnard et al., 2001; Phan et al., 2005). In patients with
MDD, reduced activation of the medial prefrontal cortex has been linked to impaired capacity for emotional self-awareness and emotional stability (Liotti et al., 2002), while preserved activity in this region has been proffered as a functional marker of good treatment response (Saxena et al., 2003) and endophenotype for resilience to mood disorders (Kruger et al., 2006).

We observed a positive correlation between the mOFC and the right insular cortex, which is also supported by their well-known anatomical connectivity profile (Ongur and Price, 2000). Functional imaging studies of healthy subjects have linked activation of the right insula to aspects of negative emotional processing, such as the perception of sadness and disgust as well as anxiety (Phillips et al., 2003). Several functional and structural neuroimaging studies have reported selective changes of the insular region in patients with OCD (Mataix-Cols et al., 2004; Phillips et al., 2000; Pujol et al., 2004) and MDD (Beauregard et al., 2006; Cardoner et al., 2003; Davidson et al., 2003). Those insula alterations specifically related to OFC alterations may perhaps be more relevant in the context of OCD with comorbid MDD.

Finally, we found that mOFC volume was negatively correlated with gray matter volume of the right amygdala–parahippocampal region in OCD patients with MDD. Studies of non-human primates have characterized strong bidirectional projections and functional modulation between the amygdala and ventromedial prefrontal regions (Paus, 2001), which has, in part, been confirmed by human neuroimaging studies and linked to negative emotion perception and affect (Phillips et al., 2003). Our observation of a negative volumetric association between these regions may fit with recent evidence for an altered functional coupling of the amygdala–ventromedial prefrontal regions in individuals with a higher genetic susceptibility to depression (Pezawas et al., 2005; Heinz et al., 2005), as well as findings of an inverse correlation between OFC and amygdala activity in patients with depression in PET studies (Drevets, 2000). Our finding may suggest some role for an altered OFC–right amygdala relationship in the development of lifetime depression in patients with OCD. Nevertheless, the specific mechanisms mediating this process will need to be elucidated, given that in some ROI-focused studies (Szeshko et al., 1999), OCD patients showed volumetric reduction in both the amygdala and OFC, as did the subgroup of patients with prominent aggressive obsessions and checking compulsions in our previous voxelwise study (Pujol et al., 2004).

The data derived from our study suggest that additional structures could contribute to MDD comorbidity in OCD. We detected a tendency to gray matter volume reduction in the right and left lateral OFC and left parahippocampal region. Such findings are in concordance with several studies suggesting a relevant role of these regions in emotion regulation and MDD pathophysiology (Zald and Kim, 2001; Bremner et al., 2002; Drevets, 2000; Lacerda et al., 2004). Indeed, reduced metabolic activity in the left hippocampal area has specifically been related to MDD–OCD comorbidity (Saxena et al., 2001).

There are some methodological limitations to this study that should be considered. Firstly, we have not used the latest version of the SPM software, which introduces some modifications in the segmentation algorithm (Ashburner and Friston, 2005). Although we cannot rule out the possibility that this may have affected the accuracy of our results, we preferred to avoid any confounding effects due to a change in the software version and ensure a straightforward interpretation of the results in relation with our

![Fig. 4. Statistical parametric map showing regions with reduced gray matter volumes in OCD patients with MDD, involving (A) right and left lateral orbitofrontal cortices and (B) left parahippocampal area. Voxels below p < .001 (uncorrected) are displayed. L, left.](image-url)
previously reported data (Pujol et al., 2004). Secondly, the relatively high slice thickness used in the present study may have limited the spatial resolution of our findings. Furthermore, the study groups reported here were not strictly matched in terms of the number of subjects in each group, age distribution, and illness duration. We have attempted to minimize this limitation by accounting for subjects’ age and gender in all statistical comparisons, although this is obviously not as ideal as having strictly matched groups. We also included patients with a different MDD clinical status (i.e., past history, current or first episode) in the OCD and MDD groups. A differential effect of MDD status over brain structure cannot be totally excluded, as suggested by prior studies (Lacerda et al., 2004). Indeed, we found a more pronounced volume reduction in left lateral OFC in OCD patients with a past history of MDD compared to those with a first current MDD episode. Although we found no differences in treatment status between both patient groups, including the number of previous trials of antidepressants, the use of antipsychotics or physic treatments, an influence of treatment history on our volumetric findings cannot be definitively excluded (Gilbert et al., 2000; Lieberman et al., 2005). Finally, our study is limited to a sample of patients with OCD as their primary diagnosis and, thus, our findings could be extended or complemented by future studies including MDD patients without OCD comorbidity.

In summary, our findings support existing evidence suggesting a non-specific involvement of the mOFC in the pathophysiology of a range of neuropsychiatric disorders, including OCD. Comorbid depression in OCD appears, primarily, to have an additive effect on gray matter volume alterations in OCD patients, including a more pronounced volumetric reduction in the mOFC and a more diffuse pattern of abnormal structural covariances with other limbic and paralimbic regions. These brain structural alterations could impair emotional regulation and increase the risk or diathesis for major depression.

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