The major symptom dimensions of obsessive-compulsive disorder are mediated by partially distinct neural systems

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Obsessive–compulsive disorder (OCD) is a clinically heterogeneous disorder characterized by multiple, temporally stable symptom dimensions. Preliminary functional neuroimaging studies suggest that these symptom dimensions may have distinct neural substrates. Whole-brain voxel-based morphometry was used to examine the common and distinct neuroanatomical (structural) substrates of the major symptom dimensions of OCD. First, we compared 55 medication-free patients with OCD and 50 age-matched healthy control subjects. Multiple regression analyses were then used to examine the relationship between global and regional grey matter (GM) and white matter (WM) volumes and symptom dimension scores within the patient group. OCD patients showed decreased GM volume in left lateral orbitofrontal (BA47), left inferior frontal (BA44/45), left dorsolateral prefrontal (BA9) and right medial prefrontal (BA10) cortices and decreased bilateral prefrontal WM volume. Scores on the ‘symmetry/ordering’ dimension were negatively correlated with ‘global’ GM and WM volumes. Scores on the ‘contamination/washing’ dimension were negatively correlated with ‘regional’ GM volume in bilateral caudate nucleus and WM volume in right parietal region. Scores on the ‘harm/checking’ dimension were negatively correlated with regional GM and WM volume in bilateral temporal lobes. Scores on the ‘symmetry/ordering’ dimension were negatively correlated with regional GM volume in right motor cortex, left insula and left parietal cortex and positively correlated with bilateral temporal GM and WM volume. The results remained significant after controlling for age, sex, educational level, overall illness severity, global WM and GM volumes and excluding patients with comorbid depression. The reported symptom dimension-specific GM and WM alterations support the hypothesis that OCD is an etiologically heterogeneous disorder, with both overlapping and distinct neural correlates across symptom dimensions. These results have clear implications for the current neuroanatomical model of OCD and call for a substantial revision of such model which takes into account the heterogeneity of the disorder.

Keywords: obsessive-compulsive; neuroimaging; VBM; symptom dimensions
ABBREVIATIONS: BA = Brodmann’s area; GM = grey matter; OCD = Obsessive–compulsive disorder; ROI = regions of interest; VBM = voxel-based morphometry; WM = white matter

Introduction

Current neuroanatomical models of obsessive–compulsive disorder (OCD) propose that specific frontal-striatal and limbic circuits are involved in the mediation of its symptoms (Saxena et al., 1998; Remijnse et al., 2005; Mataix-Cols and van den Heuvel, 2006). Whereas the findings of functional neuroimaging studies have been relatively consistent with this view, structural neuroimaging studies have been far less consistent. For example, the volume of the caudate nucleus, a key structure thought to be involved in OCD, was found to be decreased (Luxenberg et al., 1988; Robinson et al., 1991; Stein et al., 1993, 1997; Aylward et al., 1996; Rosenberg et al., 1997; Bartha et al., 1998), and even increased (Scarone et al., 1992) in OCD patients compared with controls. The same variability applies to other regions of interest (ROIs), including the amygdala (Rosenberg and Keshavan, 1998; Szeszko et al., 1999; Kwon et al., 2003b), thalamus (Gilbert et al., 2000), and the orbitofrontal (Szeszko et al., 1999; Choi et al., 2004; Kang et al., 2004), anterior cingulate (Rosenberg and Keshavan, 1998; Szeszko et al., 2004) and temporal/hippocampal (Kwon et al., 2003) cortices. This obvious lack of replicability among structural neuroimaging studies in OCD can be partially attributed to methodological differences between studies. Small sample sizes have been the norm and some studies have not excluded patients on medication and with comorbid psychopathology. Most morphometric studies in OCD have used manual or semi-automated methods to measure the volumes of brain regions defined a priori as being implicated in OCD, therefore preventing the exploration of other brain regions potentially implicated in the disorder.

The recent use of fully-automated, whole-brain, voxel-based morphometry (VBM) methods (Ashburner and Friston, 2000, 2001; Mechelli et al., 2005), which overcome some of the limitations of the ROI approach, have also produced mixed results. Kim et al. (2001) were the first to report structural abnormalities in OCD using VBM. They compared 25 medication-free OCD patients and 25 healthy controls and reported increased grey matter (GM) volumes in the orbitofrontal, superior and middle temporal, inferior parietal and occipital cortices, thalamus, hypothalamus and insula. They did not investigate differences in white matter (WM) volume. Since the publication of this initial study, three further VBM studies in OCD have appeared (Pujol et al., 2004; Valente et al., 2005; Carmona et al., 2007). In the largest of these studies (n = 72), Pujol et al. (2004) found decreased GM volume in the medial orbitofrontal cortex, dorsomedial prefrontal cortex and the insulo-opercular region, as well as increased GM volume in the ventral putamen and cerebellum. No WM differences were found. Valente et al. (2005) also found decreased medial prefrontal GM volume in their smaller sample of mostly medicated, and comorbid depressive, OCD patients (n = 19). However, they reported increased rather than decreased orbitofrontal and insular GM volumes. Also, the parahippocampal gyri were larger compared with those of healthy subjects. No WM measurements were performed. Finally, in a pediatric OCD sample (n = 18), Carmona et al. (2007) showed decreased GM in dorsal-lateral prefrontal, inferior frontal, medial prefrontal and anterior cingulate cortices, as well as decreased WM in bilateral frontal and right parietal regions.

Based on the current frontal-striatal model of OCD, one might predict abnormalities in the WM tracts that connect the prefrontal cortex with the basal ganglia but only a handful of VBM studies have examined WM abnormalities in OCD. The results of recent diffusion tensor imaging studies, showing decreased fractional anisotropy (a measure of WM connectivity) in the anterior cingulate region and the internal capsule (Szeszko et al., 2005; Cannistraro et al., 2007; Yoo et al., 2007), are consistent with the current model.

In summary, VBM studies in OCD have shown frontal-striatal and limbic abnormalities, although the implicated regions and the direction of the differences between patients and healthy controls have been inconsistent so far. Again, these discrepant findings may be partially attributable to a number of methodological issues, such as insufficient power (with the exception of the Pujol et al. (2004) study), comorbidity, and medication confounds. Another important source of variability is the clinical heterogeneity of OCD. It is becoming increasingly clear that OCD is not a unitary disorder and that it consists of multiple potentially overlapping symptom dimensions (Mataix-Cols et al., 2005; Leckman et al., 2007), which are temporally (Mataix-Cols et al., 2002; Rufer et al., 2005) and transculturally (Matsunaga et al., 2008) stable. Several preliminary functional neuroimaging studies have suggested that these symptom dimensions may be mediated by partially distinct neural systems (Mataix-Cols et al., 2004; Saxena et al., 2004; Lawrence et al., 2007; An et al., 2008). It is therefore plausible that the above inconsistencies in structural neuroimaging studies of OCD can be partially attributable to the clinical heterogeneity of the recruited samples. In support of this idea, Pujol et al. (2004) found that patients with elevated scores on the ‘aggressive/checking’ dimension had significantly reduced GM volumes in the right amygdala. Similarly, Valente et al. (2005) showed a distinct pattern of correlations between various symptom dimension scores and GM volumes, although these analyses were probably underpowered. Clearly, more research is needed in large patient samples to identify the structural neuroanatomical correlates of the major symptom dimensions of OCD employing validated instruments.

The present VBM study aimed to build upon the existing functional neuroimaging literature by examining the common as well as distinct structural (GM and WM) correlates of the major symptom dimensions of OCD (‘contamination/washing’, ‘harm/checking’ and ‘symmetry/ordering’) in a large sample of unmedicated patients (n = 55). If the hypothesis that different symptom dimensions have distinct neuroanatomical substrates is confirmed, the results would have profound implications for the current neuroanatomical model of OCD.
Brain structure of OCD symptom dimensions

Methods

Participants

Fifty-five unmedicated patients meeting DSM-IV criteria for OCD and 50 age-matched healthy controls participated in the study. OCD patients were recruited from the outpatient clinic for anxiety disorders of Stichting Buitenamstel Geestgronden in Amsterdam, the outpatient clinic for anxiety disorders of GGZ Nijmegen, the Netherlands Anxiety, OCD & Phobia Foundation, and by advertisements on the internet. Exclusion criteria were the presence of major somatic disorders, other major psychiatric disorders (except depression) and use of psychotropic medication. Subjects had to be off antidepressive and antipsychotic medication for at least 4 weeks prior to the scan and were asked not to use benzodiazepines during the 2 weeks prior to the scan.

Fifty healthy controls were recruited among hospital and university staff and by advertisements on the Internet. They were interviewed to exclude any psychiatric and somatic disorders. The ethical review board of the VU University Medical Center approved the study and all participants provided written informed consent.

Measures

Diagnoses were established using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I/P) (First et al., 1996). The severity of OCD symptoms was assessed with the 10-item clinician-administered Yale Brown Obsessive-Compulsive Scale (Y-BOCS) (Goodman et al., 1989a, b).

Two complementary methods were employed to ascertain the presence and severity of the most prevalent symptom dimensions in this sample (contamination/washing, harm/checking and symmetry/ordering). First, all patients and controls were asked to complete the Dutch version of the Padua Inventory-revised (Padua-IR) (Sanavio, 1988; van Oppen et al., 1995), a widely used and reliable self-administered measure of obsessive-compulsive symptoms. Here, we were interested in three of its sub-scales: ‘washing’ (10 items; score range 0–40), ‘checking’ (7 items; score range 0–28), and ‘precision’ (6 items; score range 0–24), corresponding to the three major symptom domains under study.

Second, each of the major categories of the Y-BOCS symptom checklist was assigned a score of 0 (absent symptom), 1 (symptom present but not major reason for concern) or 2 (prominent symptom). The major symptom dimension scores were then computed using the algorithm described by Mataix-Cols et al. (1999). Briefly, the ‘contamination/washing’ score was the sum of ‘contamination obsessions’ and ‘washing/cleaning compulsions’ divided by 2; the ‘harm/checking’ score was the sum of ‘aggressive obsessions’ and ‘checking compulsions’ divided by 2; and the ‘symmetry/ordering’ score was the sum of ‘symmetry obsessions’, ‘ordering compulsions’, ‘repeating compulsions’ and ‘counting compulsions’ divided by 4. Dividing by the number of items in each dimension ensured comparable score ranges across dimensions. Because very few patients in our sample endorsed hoarding or sexual/religious symptoms these dimensions were not computed in this study.

Due to administrative problems, Y-BOCS and Padua-IR data were unavailable for eight and five subjects, respectively.

MRI acquisition and processing

All images were acquired using a 1.5T MRI system (Magnetom Sonata, Siemens, Erlangen, Germany) with a standard radiofrequency receiver head coil. The anatomical scans included 160 coronal slices (slice thickness = 1.5 mm) acquired with a 3D gradient-echo T1-weighted sequence (flip angle = 8°; repetition time, TR = 2700 ms; echo time, TE = 4 ms; inversion time, TI = 950 ms; bandwidth, BW = 190 Hz/pixel). In-plane resolution was 256 × 192 pixels (pixel size 1 mm²).

Prior to volumetric analyses, the integrity of the acquired MR images was visually checked using MRtrix (Chris Rorden, http://www.sph.sc.edu/comd/orden/mrtrix.html). Images were processed and analysed using SPM5 (Wellcome Department of Cognitive Neurology, London, UK). The origin of each MR volume was aligned on the anterior commissure.

VBM

First, DICOM images were converted to Analyzeanalyse format, followed by cropping to remove the neck using a registration-based approach employing tools from FSL (FMRIB’s Software Library). Using SPM5 with default priors, images were then segmented to generate, for each subject, modulated GM, WM and CSF probability maps in standard Montreal Neurological Institute (MN1)-152 space and resampled to 2 × 2 × 2 mm³ voxels. These maps were smoothed using a Gaussian kernel of 12 mm full width at half maximum as is customary in VBM, given that the accuracy of cortical registration between subjects is about 1 cm (Ashburner and Friston, 2001), and an absolute minimum threshold of 0.05 was applied. For each tissue type (WM or GM), analyses were restricted to voxels included in a mask obtained by thresholding the corresponding prior probability map at 0.1. In addition to the MN1-152 segments, the GM, WM and CSF probability maps in native space obtained in the same segmentation process were also stored and used to calculate total GM and WM volumes for each individual.

Statistical analyses

Comparisons between OCD patients and controls were conducted separately for regional GM and WM using (1 × 2) ANOVA as implemented in SPM5. To correct for global GM and WM differences, total GM and WM volumes were added as a regressor (covariate) in the models. The associations between symptom dimension scores within the OCD group and GM/WM volumes were examined using whole-brain multiple regression analyses with the scores of the three major symptom dimensions and total GM/WM volumes as regressors. In addition, to control for potentially confounding variables, we repeated all analyses including age, sex and total YBOCS scores as covariates. Since cluster-based statistics are invalid due to non-stationarity of VBM data (Mechelli et al., 2005), we adopted an a priori voxel-based threshold of P < 0.05 corrected for multiple comparisons, unless indicated otherwise. For our regions of interest (striatum, orbitofrontal cortex, lateral and medial prefrontal cortex, posterior parietal cortex and anterior and medial temporal cortex) we employed an initial threshold of P < 0.001 uncorrected with an extent threshold of 25 voxels, using the small volume correction option implemented in SPM5 to establish whether the observed differences were also significant at a corrected level.

Results

Sample characteristics

There were no statistically significant differences in age, sex and handedness between patients and controls (Table 1). Controls had
Table 1 Sociodemographic and clinical characteristics of the sample

<table>
<thead>
<tr>
<th>Variable</th>
<th>OCD (n = 55)</th>
<th>Controls (n = 50)</th>
<th>Statistics</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men, n (%)</td>
<td>16 (29%)</td>
<td>20 (40%)</td>
<td>$\chi^2 = 1.38$</td>
<td>0.24</td>
</tr>
<tr>
<td>Right-handed, n (%)</td>
<td>49 (89%)</td>
<td>45 (90%)</td>
<td>$\chi^2 = 0.23$</td>
<td>0.88</td>
</tr>
<tr>
<td>Age, mean ± SD (range, years)</td>
<td>33.7 ± 9.19 (IQR – 54)</td>
<td>31.4 ± 7.64 (21–53)</td>
<td>$t$ (df = 103) = 1.37</td>
<td>0.18</td>
</tr>
<tr>
<td>Educational level* mean (± SD)</td>
<td>5.8 (± 1.6)</td>
<td>6.8 (± 1.5)</td>
<td>Mann–Whitney $U = 739.5$, $Z = 3.4$</td>
<td>0.001</td>
</tr>
<tr>
<td>Y-BOCS, total** mean (± SD)</td>
<td>22.83 ± 6.13 (range, years)</td>
<td>10.8 ± 10.18 (0–43)</td>
<td>$t$ (F = 98) = 13.88</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Padua-IR, total; mean ± SD (range)</td>
<td>64.76 ± 26.17 (9–I12)</td>
<td>2.22 ± 4.08 (0–21)</td>
<td>$t$ (F = 98) = 5.36</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Padua-IR, checking; mean ± SD (range)</td>
<td>25.16 ± 799 (0–26)</td>
<td>0.00 ± 0.10 (0–4)</td>
<td>$t$ (F = 98) = 12.01</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Padua-IR, precision; mean ± SD (range)</td>
<td>7.9 ± 5.21 (0–20)</td>
<td>0.80 ± 0.14 (0–4)</td>
<td>$t$ (F = 98) = 9.46</td>
<td>&lt;0.001</td>
</tr>
</tbody>
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*a Using an 8-point scale, one indicates primary school and eight indicates university. **Yale-Brown Obsessive Compulsive Scale (10-item severity score).

Table 2 Frequencies of the major symptom categories of the Yale-Brown Obsessive Compulsive Scale—symptom checklist (n = 47)

<table>
<thead>
<tr>
<th>Symptom categories</th>
<th>Number of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obsessions</td>
<td>34 (72)</td>
</tr>
<tr>
<td>Aggressive</td>
<td>33 (70)</td>
</tr>
<tr>
<td>Contamination</td>
<td>6 (13)</td>
</tr>
<tr>
<td>Sexual</td>
<td>8 (17)</td>
</tr>
<tr>
<td>Hoarding/saving</td>
<td>11 (23)</td>
</tr>
<tr>
<td>Religious</td>
<td>25 (53)</td>
</tr>
<tr>
<td>Symmetry</td>
<td>18 (38)</td>
</tr>
<tr>
<td>Somatic</td>
<td>22 (47)</td>
</tr>
<tr>
<td>Compulsions</td>
<td>37 (79)</td>
</tr>
<tr>
<td>Washing</td>
<td>32 (68)</td>
</tr>
<tr>
<td>Checking</td>
<td>18 (38)</td>
</tr>
<tr>
<td>Repeating</td>
<td>21 (45)</td>
</tr>
<tr>
<td>Counting</td>
<td>7 (15)</td>
</tr>
</tbody>
</table>

a slightly but significantly higher educational level. The mean total Y-BOCS scores were 22.83 (SD = 6.13), corresponding to moderately severe OCD. Ten out of 55 patients with OCD had a comorbid depressive disorder at the time of the scan. As expected, patients had significantly higher scores than controls on all the Padua-IR subscales. All patients endorsed more than one symptom type on the Y-BOCS Symptom Checklist (Table 2). Age of onset negatively correlated with the scores on the symmetry/ordering dimension of the Padua-IR (Spearman’s $\rho = -0.353$, $P < 0.05$) and the Y-BOCS (Spearman’s $\rho = -0.506$, $P < 0.01$), not with the other symptom dimensions.

All patients were unmedicated at the time of the scan. Twenty-four (43.6%) patients were medication naive, and the rest had been medication-free for at least 4 weeks prior to participation in the study. Mean washout period was 26 months (range 1–96 months). Past medication history was as follows: nine (16.4%) paroxetine, five (9.1%) fluoxetine, two (3.6%) fluvoxamine, two (3.6%) venlafaxine and nine (16.4%) used more than one drug in the past, two of whom used antipsychotic medication as an augmentation strategy. Medication history was unavailable from four (7.3%) patients.

Global GM and WM volumes

Patients with OCD and healthy control subjects did not significantly differ in global GM and WM volumes (GM: 685 ± 74 and 708 ± 72 ml, respectively, $P = 0.11$; WM: 494 ± 59 and 509 ± 64 ml, respectively, $P = 0.21$). However, the ‘symmetry/ordering’ dimension of the Padua-IR was negatively correlated with global GM volume (partial correlation coefficient $–0.42$, $t = –2.84$, $P = 0.007$), with a trend for global WM volume (partial correlation coefficient $–0.35$, $t = –1.96$, $P = 0.057$). This association was independent from age, sex and disease severity (total Y-BOCS scores), which were also included in the models. The correlation between age of onset and global GM or WM volume was not significant and multiple regression analyses showed that the association between symmetry/ordering symptoms and global GM volume remained significant after controlling for the illness onset. Finally, we repeated these analyses excluding the 10 patients with comorbid depression and the results remained unchanged. Scores on the other symptom dimensions did not correlate with global GM or WM volumes.

Regional GM and WM alterations in OCD versus controls

Compared with healthy controls, patients with OCD showed significantly decreased regional volume in the left lateral orbitofrontal cortex (Brodmann’s area (BA) 47), left inferior frontal cortex (BA44/45), left dorsolateral prefrontal cortex (BA9) and bilateral medial prefrontal cortex (BA10). No regions of increased GM volume were found in patients with OCD (Table 3 and Fig. 1). WM volume was decreased in the bilateral prefrontal lobes in patients with OCD (Table 4 and Fig. 2). No regions of increased WM volume were found. These results were independent from age, sex, educational level and global GM/WM volumes, which were included as covariates in the ANOVAs. To control for the effect of comorbid depressive symptoms, we repeated all analyses with comorbid depression (dummy-coded as present/absent) as an extra covariate and yielding nearly identical results. In fact, the exclusion of the 10 depressed OCD patients resulted in even more strongly significant results (increased cluster sizes and $t$-values).
We next conducted a whole-brain regression analysis to examine the relationship between overall OCD symptom severity and regional GM/WM volumes. Total Y-BOCS scores were inversely correlated with GM volume of the left (MNI coordinates $x = 4.95$, $y = 42$, $z = -6$, $t = 5.19$, cluster size $= 753$ voxels) and right ($x = 4.06$, $y = 20$, $z = 16$, $t = 4.45$, cluster size $= 548$ voxels) cerebellar cortex.

Specific neural correlates of OCD symptom dimensions

Multiple regression analyses using the symptom dimension scores of the Padua-IR ($n = 50$) and Y-BOCS symptom checklist ($n = 47$) and controlling for global GM/WM volumes, demonstrated that each of the studied symptom dimensions had a clearly distinct neural substrate. The results using the Padua-IR and YBOCS symptom checklist were remarkably similar (Tables 5 and 6).

Scores on the ‘contamination/washing’ dimension were negatively correlated with GM volume in the bilateral dorsal caudate nucleus (Table 5 and Fig. 3A) and WM volume in the right parietal region (Table 6 and Fig. 4). Scores on the ‘harm/checking’ dimension were negatively correlated with GM and WM volume of the bilateral temporal lobes (Tables 5 and 6, Figs 3B and 4). Scores on the ‘symmetry/ordering’ dimension were negatively correlated with GM volume of the bilateral parietal cortex (Table 5 and Fig. 3C) and positively correlated with bilateral medial temporo-parietal GM and WM volume (Table 6 and Fig. 4). At a slightly lower threshold of $P < 0.001$ uncorrected (extent threshold 25 voxels), we also found that scores on the ‘symmetry/ordering’ dimension negatively correlated with GM volume in the right motor and left insular cortices.

In an additional analysis with age, sex (dummy-coded as man/woman) and total Y-BOCS scores as extra covariates the results appeared to be largely independent from these variables. To control for the effect of comorbid depressive symptoms,
Table 5 Significant whole-brain correlations between regional GM volumes and scores on the three major symptom dimensions of OCD (n = 50 for Padua Inventory, n = 47 for Y-BOCS symptom checklist)

<table>
<thead>
<tr>
<th>Cluster size</th>
<th>t</th>
<th>Spearman’s $\rho$</th>
<th>Peak coordinates (MNI)</th>
<th>Anatomical region</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>x  y  z</td>
<td></td>
</tr>
<tr>
<td>Negative correlations with the contamination/washing dimension of Padua Inventory</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>116</td>
<td>3.99</td>
<td>-0.34*</td>
<td>-12  4  18</td>
<td>Left caudate nucleus</td>
</tr>
<tr>
<td>63</td>
<td>3.96</td>
<td>-0.39**</td>
<td>14  2  18</td>
<td>Right caudate nucleus</td>
</tr>
<tr>
<td>Negative correlations with the contamination/washing dimension of Y-BOCS symptom checklist</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No significant results</td>
</tr>
<tr>
<td>Negative correlations with the harm/checking dimension of Padua Inventory</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3303</td>
<td>5.44</td>
<td>-0.49**</td>
<td>40  14  -30</td>
<td>Right temporal lobe</td>
</tr>
<tr>
<td></td>
<td>5.18</td>
<td>-0.41**</td>
<td>52  4  -36</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5.17</td>
<td>-0.43**</td>
<td>48  -30  -24</td>
<td></td>
</tr>
<tr>
<td>2237</td>
<td>5.03</td>
<td>-0.39**</td>
<td>-48  -34  -26</td>
<td>Left temporal lobe</td>
</tr>
<tr>
<td></td>
<td>4.60</td>
<td>-0.40**</td>
<td>-56  2  -8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4.58</td>
<td>-0.46**</td>
<td>-58  -14  -14</td>
<td></td>
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<tr>
<td>Negative correlations with the harm/checking dimension of Y-BOCS symptom checklist</td>
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<tr>
<td>49</td>
<td>3.92</td>
<td>-0.40**</td>
<td>54  -58  -16</td>
<td>Right temporal lobe</td>
</tr>
<tr>
<td>32</td>
<td>3.77</td>
<td>-0.38**</td>
<td>50  -32  -24</td>
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<tr>
<td>Negative correlations with the symmetry/ordering dimension of Padua Inventory</td>
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</tr>
<tr>
<td>510</td>
<td>4.63*</td>
<td>-0.52**</td>
<td>30  -24  62</td>
<td>Right motor cortex</td>
</tr>
<tr>
<td></td>
<td>4.30</td>
<td>-0.38**</td>
<td>30  -60  62</td>
<td>Right parietal cortex</td>
</tr>
<tr>
<td></td>
<td>3.87</td>
<td>-0.35*</td>
<td>14  -36  70</td>
<td></td>
</tr>
<tr>
<td>47</td>
<td>4.12*</td>
<td>-0.44**</td>
<td>-38  -16  10</td>
<td>Left insular cortex</td>
</tr>
<tr>
<td>44</td>
<td>3.82</td>
<td>-0.32*</td>
<td>-16  -56  66</td>
<td>Left parietal cortex</td>
</tr>
<tr>
<td>Negative correlations with the symmetry/ordering dimension of Y-BOCS symptom checklist</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>142</td>
<td>4.26</td>
<td>-0.59**</td>
<td>-54  -38  40</td>
<td>Left parietal cortex</td>
</tr>
<tr>
<td>Positive correlations with the contamination/washing dimension of Padua Inventory</td>
<td></td>
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<td></td>
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<td>No significant results</td>
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<td>Positive correlations with the harm/checking dimension of Padua Inventory</td>
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<td>No significant results</td>
</tr>
<tr>
<td>Positive correlations with the harm/checking dimension of Y-BOCS symptom checklist</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>No significant results</td>
</tr>
<tr>
<td>Positive correlations with the symmetry/ordering dimension of Padua Inventory</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>87</td>
<td>4.54*</td>
<td>0.50**</td>
<td>-8  -50  50</td>
<td>Left precuneus</td>
</tr>
<tr>
<td>Positive correlations with the symmetry/ordering dimension of Y-BOCS symptom checklist</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>105</td>
<td>4.33</td>
<td>0.41**</td>
<td>-56  -14  -12</td>
<td>Left temporal lobe</td>
</tr>
<tr>
<td>48</td>
<td>3.59</td>
<td>0.43**</td>
<td>28  6  -32</td>
<td>Right temporal lobe</td>
</tr>
</tbody>
</table>

*There were significant negative correlations in the caudate nucleus bilaterally (left: x, y, z = –16, 10, 18, t = 3.40, cluster size = 7, Spearman’s $\rho = -0.40**$; right: x, y, z = 16, –4, t = 3.43, cluster size = 4, Spearman’s $\rho = -0.44*$), which did not survive our a priori extent threshold of >25 voxels.

**P<0.001 uncorrected and minimal cluster size of 25 voxels. *Spearman’s correlation significant at P<0.05, **Spearman’s correlation significant at P<0.01.

Figure 2 Decreased regional WM volume in OCD patients (n = 55) compared with healthy controls (n = 50) in bilateral prefrontal regions. Results shown at $P<0.001$ uncorrected and minimum cluster size of 25 voxels.
we repeated all analyses excluding the 10 OCD patients with comorbid depression and similar results were found.

Discussion

To our knowledge this is the first study to explore the structural GM and WM correlates of the major symptom dimensions of OCD in a large unmedicated patient sample. Previous efforts were limited by the inclusion of small sample sizes (Valente et al., 2005) or a substantial proportion of patients on medication (Pujol et al., 2004; Valente et al., 2005). Furthermore, we addressed this question using two different measures of each symptom dimension to ensure that the results were robust and replicable. In our analyses, care was taken to control for global illness severity (YBOCS severity scores) and a range of potentially confounding variables, which allowed us to separate the common as well as distinct neural substrates of the major symptom dimensions of OCD.

Common neuroanatomical substrates in OCD compared with healthy controls

Overall, patients with OCD showed significantly decreased GM volume in the left lateral orbitofrontal (BA47), left inferior frontal (BA44/45), left dorsolateral prefrontal (BA9) and bilateral medial prefrontal (BA10) cortices compared with healthy control subjects.

Table 6 Significant whole-brain correlations between regional WM volumes and scores on the three major symptom dimensions of OCD (n = 50 for Padua Inventory, n = 47 for Y-BOCS symptom checklist)

<table>
<thead>
<tr>
<th>Cluster size</th>
<th>t</th>
<th>Spearman’s ρ</th>
<th>Peak coordinates (MNI)</th>
<th>Anatomical region</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>x   y    z</td>
<td></td>
</tr>
<tr>
<td>Negative correlations with the contamination/washing dimension of Padua Inventory</td>
<td>135 4.08</td>
<td>−0.43**</td>
<td>28   −56   38</td>
<td>Right parietal</td>
</tr>
<tr>
<td>Negative correlations with the contamination/washing dimension of Y-BOCS symptom checklist</td>
<td>97   4.11</td>
<td>−0.46**</td>
<td>36   −68   34</td>
<td>Right parietal</td>
</tr>
<tr>
<td>Negative correlations with the harm/checking dimension of Padua Inventory</td>
<td>564 4.91</td>
<td>−0.40**</td>
<td>36   0     −22</td>
<td>Right temporal</td>
</tr>
<tr>
<td>Negative correlations with the harm/checking dimension of Y-BOCS symptom checklist</td>
<td>200 4.61</td>
<td>−0.39**</td>
<td>−38  −14   −20</td>
<td>Left temporal</td>
</tr>
<tr>
<td>Negative correlations with the harm/checking dimension of Padua Inventory</td>
<td>44   4.14</td>
<td>−0.46**</td>
<td>−16  −14   −18</td>
<td></td>
</tr>
<tr>
<td>Negative correlations with the harm/checking dimension of Y-BOCS symptom checklist</td>
<td>207 4.21</td>
<td>−0.43**</td>
<td>34   −2     −24</td>
<td>Right temporal</td>
</tr>
<tr>
<td>Negative correlations with the symmetry/ordering dimension of Padua Inventory</td>
<td>94   4.02</td>
<td>−0.44**</td>
<td>34   −38   −12</td>
<td></td>
</tr>
<tr>
<td>Negative correlations with the symmetry/ordering dimension of Y-BOCS symptom checklist</td>
<td>204 4.51</td>
<td>−0.48**</td>
<td>−32  −8    −24</td>
<td>Left temporal</td>
</tr>
<tr>
<td>Negative correlations with the harm/checking dimension of Padua Inventory</td>
<td>37   3.93</td>
<td>−0.45**</td>
<td>−18  −14   −16</td>
<td></td>
</tr>
<tr>
<td>Negative correlations with the harm/checking dimension of Y-BOCS symptom checklist</td>
<td>48   3.85</td>
<td>−0.42**</td>
<td>46   26    20</td>
<td>Right prefrontal</td>
</tr>
<tr>
<td>Negative correlations with the symmetry/ordering dimension of Padua Inventory</td>
<td>47   3.77</td>
<td>−0.41**</td>
<td>−44  24    24</td>
<td>Left prefrontal</td>
</tr>
<tr>
<td>Negative correlations with the symmetry/ordering dimension of Y-BOCS symptom checklist</td>
<td>100 3.71</td>
<td>0.35*</td>
<td>36   28    −20</td>
<td>Right temporal</td>
</tr>
<tr>
<td>Positive correlations with the symmetry/ordering dimension of Padua Inventory</td>
<td>71   3.72</td>
<td>0.45**</td>
<td>−30  −16   −20</td>
<td>Left temporal</td>
</tr>
</tbody>
</table>

*Spearman’s correlation significant at P < 0.05, **Spearman’s correlation significant at P < 0.01.
was more laterally localized. Recently, Shin et al. (2007) investigated cortical thickness in OCD and reported cortical thinning of the medial orbitofrontal cortex and scores on the ‘harm/checking’ dimension (Padua-IR) in the OCD group (n = 50). This left-right asymmetry is consistent with our results.

Decreased GM volume of the medial prefrontal cortex (BA 9/10) has consistently been found by others (Pujol et al., 2004; Valente et al., 2005). Volume reduction of the dorsolateral prefrontal cortex has been described both in adults (Shin et al., 2007) and in children (Carmona et al., 2007) with OCD. Dorsolateral prefrontal involvement in OCD corresponds with results from recent functional neuroimaging studies, showing decreased recruitment of the dorsolateral prefrontal cortex during neuro-cognitive testing (van den Heuvel et al., 2005; Remijnse et al., 2006). Medial and dorsolateral prefrontal regions are also involved in emotion regulation and cognitive control processes. Theoretical models of emotion perception suggest a reciprocal interaction between ventral and dorsal circuits in the brain underlying emotional processing (Phillips et al., 2003a). Although this model needs to be tested experimentally in more detail, it is a useful model for psychiatric disorders (Phillips et al., 2003b) and OCD in particular (Mataix-Cols and van den Heuvel, 2006). Decreased volume of these dorsal regions may underlie the impaired cognitive control during emotional processing and cognitive functioning found in OCD (Remijnse et al., 2005).

Reduction of prefrontal GM volume was accompanied with bilateral prefrontal WM volume reduction. At a lower statistical threshold, these regions of decreased WM volume were found to extend into the internal capsule. Although most previous VBM studies did not investigate WM volumes (Kim et al., 2001; Valente et al., 2005) or did not observe WM volume alterations (Pujol et al., 2004), Carmona et al. (2007) also found prefrontal WM volume reduction in their pediatric OCD patients. Decreased WM volume may underlie altered cortico-cortical and cortico-subcortical connectivity in OCD but direct evidence from the few published diffusion tensor imaging studies to date is limited (Szeshko et al., 2005; Cannistraro et al., 2007; Yoo et al., 2007).

**Figure 3** (A) Negative correlations between regional GM volume in the bilateral caudate nucleus and scores on the ‘contamination/washing’ dimension (Padua-IR) in the OCD group (n = 50). **(B)** Negative correlations between regional GM volume in the bilateral temporal cortex and scores on the ‘harm/checking’ dimension (Padua-IR) in the OCD group (n = 50). **(C)** Negative correlations between regional GM volume in the right motor and parietal cortex and scores on the ‘symmetry/ordering’ dimension (Padua-IR) in the OCD group (n = 50). Results shown at P < 0.001 uncorrected and minimum cluster size of 25 voxels.
There was an inverse correlation between disease severity and bilateral cerebellar GM volume. Although the cerebellum is traditionally considered to be essential for the coordination of movement and motor learning, recent studies have indicated that the cerebellum is also involved in cognitive and emotional processes (Middleton and Sherman, 1998; Schmahmann and Caplan, 2006). In OCD cerebellar involvement has been reported often, but the direction of the effect is inconclusive so far since both decreased (Nabeyama et al., 2008) and increased (Tolin et al., 2008) activation and decreased (Kim et al., 2001) and increased (Pujol et al., 2004) volume has been described. The cerebellar correlation with disease severity found in the present study parallels the recent finding that decreased cerebellar activation normalized with symptom improvement after 12 weeks of cognitive behaviour treatment (Nakao et al., 2005; Nabeyama et al., 2008).

Taken together, these results are consistent with the view that there are some global neural abnormalities present in OCD that may reflect the loss of normal inhibitory processes (Chamberlain et al., 2005; Menzies et al., 2007). These abnormalities would be common to most patients with OCD and, according to recent work, even their unaffected first-degree relatives (Chamberlain et al., 2007; Menzies et al., 2007). However, the diagnostic specificity of these findings still remains to be established as difficulties in inhibitory processes and alterations in the corresponding brain regions may not be exclusive to OCD. Most notably, attention deficit and hyperactivity disorder is also characterized by such abnormalities (Rubia et al., 2005; Smith et al., 2006). It is therefore plausible that these are general vulnerability factors for a number of neuropsychiatric problems including OCD. This is supported by the fact that overall symptom severity of OCD did not correlate with any of the above regions but with the cerebellum bilaterally instead.

**Distinct neural substrates across symptom dimensions**

The most important contribution of the present study is that different symptom dimensions appear to have distinct neural substrates. High scores on the ‘contamination/washing’ dimension were negatively correlated with the volume of the dorsal parts of the bilateral dorsal caudate nucleus. Many previous morphometric and functional neuroimaging studies have implicated the caudate nucleus in OCD, although the direction of the findings has been inconsistent (Remijnse et al., 2005). Because the contamination/washing symptom dimension is one of the most prevalent in OCD
(Rasmussen and Eisen, 1992; Mataix-Cols et al., 1999) it may be assumed that previous studies consistently included a large proportion of these patients. Furthermore, contamination-related anxiety is particularly amenable to symptom provocation procedures and this probably played a role in the selective recruitment of these patients in such studies.

At this stage, the functional implications of decreased volume of the dorsal caudate nucleus in patients with prominent washing symptoms remain speculative. However, a possible hypothesis is that the lack of control on compulsive behaviour due to dorsal striatal dysfunction results in conditionally reinforced washing rituals accompanied by relatively increased ventral striatal involvement. The dorsal striatum has been implicated in habit learning and action initiation (Yin et al., 2004). Considering the phenomenological overlap between OCD and addiction (Hollander et al., 2007), these addiction studies may be relevant to understand the striatal role in cleaning behaviour in contamination-related OCD.

The progression from initial drug use to habitual drug use and ultimately to compulsive drug seeking behavior corresponds with a transition at the neural level from prefrontal cortical to striatal control and from ventral to dorsal striatal involvement (Everitt and Robbins, 2005; Volkow et al., 2006; Everitt et al., 2008). In Huntington’s disease, a neurological frontal-striatal disease with often co-morbid obsessive-compulsive behaviour, the striatal atrophy also shows a dorsal-ventral gradient (Douaud et al., 2006). Initially, the atrophy mainly affects the dorsal caudate nucleus relatively sparing the ventral striatum.

Turning to the ‘harm/checking’ symptom dimension, we found that the scores on this dimension were strongly negatively correlated with both GM and WM volume in the bilateral anterior temporal poles. The anterior parts of temporal lobes including the amygdala and parahippocampal cortices have close connections with the hippocampal formation, the medial and orbitofrontal prefrontal areas and the ventral striatum (Kondo et al., 2005; Munoz and Insausti, 2005). This finding is consistent with that of Pujol et al. (2004) who found a significant inverse correlation between scores in this dimension and right amygdala volume.

Checking rituals are most often associated with obsessions about harm and aggression (Mataix-Cols et al., 2005; Leckman et al., 2007). In OCD, patients with high scores on this symptom are at elevated risk from having comorbid anxiety and mood disorders, including panic disorder (Hasler et al., 2005; Rosario-Campos et al., 2006). Consistently, volume reduction in similar regions has been described in panic disorder (Massana et al., 2003a, b) which, like OCD patients with harm/checking symptoms, is characterized by the overestimation of threat.
Interestingly, temporal lobe atrophy in patients with frontotemporal dementia appears to mediate complex compulsive behaviour such as checking rituals (Rosso et al., 2001). Rosso et al. (2001) found that atrophy in frontal and subcortical regions was not associated with the development of such compulsive behaviours. Temporal lobe epilepsy is another condition associated with OCD symptoms, with compulsions being more frequently observed than obsessions (Isaacs et al., 2004). The involvement of the anterior temporal lobes in OCD has often been overlooked so far and our results suggest that this might be partially due to the heterogeneity of the disorder. Remarkably, in the current study, GM and WM volumes were inversely correlated with scores on the ‘harm/checking’ dimension and positively correlated with scores on the ‘symmetry/ordering’ dimension. This indicates that recruiting different proportions of patients with these predominant symptom presentations may result in different results or even non-significant results, as these may cancel each other out.

The temporal lobe volume reductions may also be viewed with respect to the neuropsychological hypothesis of altered memory function in OCD patients with predominantly checking rituals.

**Figure 4** Significant correlations between regional WM volumes and scores on the major symptom dimensions of OCD ($n=50$). (Top panel) ‘contamination/washing’ dimension; (middle panel) ‘harm/checking’ dimension; (bottom panel) ‘symmetry/ordering’ dimension. Results shown at $P<0.001$ uncorrected and minimum cluster size of 25 voxels.
One of the proposed aetiologies for checking behaviour is the inability to accurately recall whether an activity is completed correctly (Rachman, 2002). Paradoxically, repeating checking results in even more distrust in one’s own memory (van den Hout and Kindt, 2003, 2004). Although the confidence in memory seems to be more impaired than memory per se, there is some evidence for this so-called memory-deficit theory, with checkers showing more non-verbal memory deficits than non-checkers (Cha et al., 2008).

Finally, scores on the ‘symmetry/ordering’ dimension were inversely correlated with global GM volume. There was also a trend in the same direction for global WM volume. No other symptom dimensions were associated with global GM/WM volumes. Patients with high scores in this dimension are known to have an earlier age of onset of their OCD (Leckman et al., 2003; Mataix-Cols et al., 2005) and also an increased risk of having an affected family member (Alsobrook et al., 1999; Hanna et al., 2005a, b). Therefore, OCD patients with high scores on this symptom dimension may have a more neurodevelopmental and familial form of the disorder. Consistently, the only paediatric VBM study in OCD to date found reduced global GM volumes in patients compared with controls (Carmona et al., 2007). Even though Carmona et al. (2007) did not describe their sample in detail, younger samples tend to include a substantial proportion of patients endorsing symmetry/ordering symptoms (Stewart et al., 2007).

After controlling for global GM and WM volumes, scores on the ‘symmetry/ordering’ dimension were inversely correlated with regional GM volume in motor, parietal and insular cortices and positively correlated with regional GM and WM volume in the bilateral anterior temporal poles. However, the correlations with motor and insular cortices need to be interpreted with caution given that these were only significant at a lower statistical threshold. Correlations with motor and somatosensory regional abnormalities are consistent with the known association between the symmetry/ordering dimension of OCD and comorbid tics or Tourette's Syndrome (Leckman et al., 1997; Mataix-Cols et al., 1999). The positive correlations with grey and white volume in the anterior temporal pole in OCD patients with predominantly symmetry/ordering symptoms, is interesting in this respect: Peterson et al. (2007) recently reported increased volume in anterior temporal structures such as the amygdala and hippocampus in a large sample of patients with Tourette’s Syndrome. The negative correlation between GM volume of the motor cortex and the symmetry/ordering dimension as found in the present study is inconsistent with the results of Gilbert et al. (2008), who found motor cortex volume negatively correlating with the contamination/washing dimension. However, in the Gilbert et al. (2008) study, correlation analyses were only conducted for regions that showed significant volumetric differences between patients and controls. In the present study we performed whole-brain correlations between symptom dimension scores and regional GM volume, which limits comparability between the two studies.

Although frontal-striatal and limbic brain regions have long been implicated in OCD, less attention has been paid to the possible involvement of the parietal cortex in the pathophysiology of the disorder (Menzies et al., 2008). Previous structural (Szeszko et al., 2005; Valente et al., 2005; Kitamura et al., 2006; Carmona et al., 2007), resting state (Kwon et al., 2003a), and activation (van den Heuvel et al., 2005) neuroimaging found abnormalities in this brain region. Because the parietal cortex is known to be involved in attention and visuospatial processes (Posner and Petersen, 1990; Cabeza and Nyberg, 2000) as well as various executive functions, such as task switching (Sohn et al., 2000), planning (van den Heuvel et al., 2003) and working memory (Veltman et al., 2003), parietal dysfunction may contribute to the cognitive impairments found in some OCD patients (Menzies et al., 2008). The present study showed a negative correlation between parietal WM volume and the washing dimension, and parietal GM volume and the symmetry dimension. Although we consider it premature to interpret the functional implications of these findings, they indicate that the parietal cortex is particularly involved in these symptom dimensions. One recent study found that set-switching abilities may be particularly impaired in OCD patients with predominant symmetry/order symptoms (Lawrence et al., 2006), but replication is needed.

**Strengths and limitations**

The use of two different measures of OCD symptoms is a particular strength of the present study because clinician and self-administered measures of OCD symptoms are not perfectly correlated (Mataix-Cols et al., 2004). The fact that we obtained similar results using both types of scales adds to the robustness of the findings. All patients were medication naïve or medication-free for at least 4 weeks prior to inclusion. Although a washout period of 4 weeks may not be sufficient to mitigate all the effects of long-term medication use, this is a methodological advance compared to most previous VBM studies in OCD (Pujol et al., 2004; Valente et al., 2005; Carmona et al., 2007). The effects of psychotropic medication on brain morphometry have been shown mainly for antipsychotic medication, with for example olanzapine treatment resulting in increased volume of the caudate nucleus (Okugawa et al., 2007). However, the use of selective serotonin reuptake inhibitors may also present a confounder in morphometric studies in patients, given that these drugs stimulate neurogenesis. Both in humans (Becker and Wojtowicz, 2007) and non-human species (Lau et al., 2007; Sairanen et al., 2007) antidepressive treatment results in enhanced cell proliferation in the hippocampus, the subventricular zone and the medial prefrontal cortex.

Another methodological advantage of the present study is the parallel investigation of both GM and WM morphometry. The only previous VBM results showing WM abnormalities in OCD were based on a small paediatric sample (Carmona et al., 2007). The investigation of GM and WM in the same subjects provides a more complete insight into the neural systems involved in the disorder.

The present study is not without limitations, however. A weakness is the lack of quantitative measures of comorbid depressive symptoms. Recent re-analyses of the Pujol et al. (2004) sample showed that OCD patients with comorbid major depressive disorder had larger volume reductions in the medial orbitofrontal cortex than OCD patients without comorbid depression.
In the present study, no volume reduction was found in the medial orbitofrontal cortex, which may reflect that only 10 of our 55 OCD patients had a comorbid depression. Whereas we found that the exclusion of these 10 depressed patients did not modify the overall results, we could not completely rule out that subclinical depressive symptoms (measured dimensionally) had an effect on our findings. Our control group was significantly higher educated than the patient group but the inclusion of education level as a covariate in the analyses did not modify the results. We did not assess general intellectual function and did not use a structured instrument to assess handedness. With regard to our statistical method, it should be recognized that although the use of uncorrected thresholds carries an obvious risk of Type I error, adopting whole-brain correction for multiple comparisons may be overly conservative; however, the use of small volume correction may present problems due to non-stationary smoothness of VBM data. Because of the small number of patients endorsing hoarding and sexual/religious obsessions, we had to restrict our analyses to the major, i.e. more prevalent, symptom dimensions of OCD. Preliminary neuropsychological (Lawrence et al., 2006) and functional neuroimaging (Mataix-Cols et al., 2004; An et al., 2008; Tolin et al., 2008) studies suggest that compulsive hoarding may constitute yet another neurobiologically distinct dimension of OCD.

Conclusion and future directions

The current study demonstrates common as well as distinct neuroanatomical substrates for the major symptom dimensions of OCD. Between-group analyses revealed that there are some global neural abnormalities present in OCD that may reflect the loss of normal inhibitory processes (Chamberlain et al., 2007). However, the diagnostic specificity of these findings still remains to be established and it is plausible that decreased prefrontal GM and WM volume is a general vulnerability factor for a number of neuropsychiatric problems including OCD. Multiple regression analyses within the patient group revealed that distinct neural systems may be underlying the major symptom dimensions of OCD, although causal relationships cannot be inferred. Our results further confirm the hypothesis that OCD is not a homogeneous disorder and that adopting a quantitative multidimensional approach has great promise in further understanding the set of problems we collectively call OCD (Mataix-Cols et al., 2005; Mataix-Cols, 2006; Mataix-Cols and van den Heuvel, 2006). These results have clear implications for the current psychobiological model of OCD (Saxena et al., 1998; Remijnse et al., 2005; Mataix-Cols and van den Heuvel, 2006) and call for a substantial revision of the model that takes into account the heterogeneity of the disorder. The results of the current study add to a growing neuroimaging literature (Mataix-Cols et al., 2004; Saxena et al., 2004; Lawrence et al., 2007; An et al., 2008; Gilbert et al., 2008) and will hopefully lead to more hypothesis-driven research into the common and specific neural substrates of these symptom dimensions. multimodal imaging protocols will be necessary to understand the complex relationship between biochemistry, structure and function in relation to each of the major symptom dimensions of OCD.

References


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