Abstract
The aim of this study is to use a voxel-based morphometry protocol to compare the brains of 18 children with obsessive–compulsive disorder (OCD) with those of a healthy group matched for gender and handedness. Images were acquired with a 1.5-T MRI scanner, spatially normalized, and segmented with an optimized voxel-based morphometry protocol. OCD children presented a 5.93% reduction of gray matter (GM) total volume in comparison with control brains. We identified OCD brain volume reductions in regions that have been extensively related to action monitoring and error signaling processes. Specifically, we found decreased bilateral GM in frontal (significant after Family Wise Error (FEW), multiple comparisons correction) and cingulate regions as well as decreased white matter (WM) in bilateral frontal and right parietal (p < 0.001 uncorrected). Additionally, we found a negative correlation between symptom severity and bilateral hippocampal GM-volume (p < 0.001 uncorrected) as well as a positive correlation between age and GM left caudate volume (p = 0.037 FWE small volume corrected) in the OCD group. As a conclusion, our results point to conflict monitoring structural brain regions as primary deficits in pediatric OCD, and to striatal abnormalities as age-related deficits.

Keywords: Obsessive–compulsive disorder; Child psychiatry; Brain imaging techniques; Conflict monitoring

Current pathophysiological obsessive–compulsive disorder (OCD) models propose a dysregulation of frontal–striatal–thalamic circuits. This system has been involved in monitoring events [1] as well as generating error signals when there is a mismatch between intended and actual performance [15]. Moreover, OCD patients, compared to healthy controls, show larger and longer error signals (as measured by error-related negativity in ERP studies) that correlate with severity symptoms [7]. This exaggerated or false error signaling may be underlying characteristic OCD symptoms, such as the need to perform an action to respond to conflict feelings [18]. Structural neuroimaging studies have partially confirmed fronto-striatal-thalamic models, even if the findings have been heterogeneous. Some studies show basal-ganglia (BG) volume reduction [20], others volume enlargement [19], and still others show no differences [3]. Such discordant results are also found in orbitofrontal cortex (OFC) [12,13]. Discrepancies may stem from the sample nature (adults or children), or the volumetric methods employed (manual or automatic). Regarding the sample, the literature seems to point to specific morphometric abnormalities depending on the OCD-stage. In this sense, children show reduced [21] or normal [22] striatum (caudate/putamen) while adults seem to have increases in the same areas [19]. Concerning the methods as a source of discrepancies, OCD morphometric studies use principally manual region-of-interest (ROI) analysis. There are just three studies [13,19,26] that used voxel-based morphometry (VBM) methods to examine OCD brain abnormalities, all of them with adults. Regardless of the advantages or disadvantages of manual and automatic methods [8], a pediatric VBM study will complement previous studies and help to improve the understanding of OCD pathophysiology. Our aim is to compare the brains of OCD children with those of a control group using an optimized voxel-
This table summarizes clinical and demographical data of our sample.

<table>
<thead>
<tr>
<th></th>
<th>OCD</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>(N)</td>
<td>Boys: 13</td>
<td>Girls: 13</td>
</tr>
<tr>
<td>Age</td>
<td>(\mu), 12.86 (S.D. 2.76) years</td>
<td>(\mu), 13.03 (S.D. 3.04) years</td>
</tr>
<tr>
<td>Laterality</td>
<td>Right-handed: 15</td>
<td>Left-handed: 2</td>
</tr>
<tr>
<td></td>
<td>Cross-dominance: 1</td>
<td></td>
</tr>
<tr>
<td>Drug-treatment</td>
<td>SSRIs: n, 6; (\mu), 13.1 (S.D. 12.8) months</td>
<td>Sertraline: n, 3; (\mu), 6.4 (S.D. 3.0) months</td>
</tr>
<tr>
<td></td>
<td>Citalopram: n, 1; (\mu), 2.3 months</td>
<td>Clomipramine: n, 8</td>
</tr>
<tr>
<td></td>
<td>Drug-na¨ıve</td>
<td></td>
</tr>
<tr>
<td>STAI/T-C</td>
<td>Obsessions: (\mu), 10.28 (S.D. 4.28)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Compulsions: (\mu), 10.94 (S.D. 4.27)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total: (\mu), 21.39 (S.D. 5.88)</td>
<td></td>
</tr>
</tbody>
</table>

This table summarizes clinical and demographical data of our sample. 
\(\mu\), Mean values; S.D., standard deviation; n, number of patients; STAI/T-C, State Trait Anxiety Inventory for Children.
produced. The Jacobian-modulated GM step allows making inferences about differences in volumes rather than concentrations. (Fifth) Smooth with a Gaussian kernel of 12-mm FWHM. In order to study global volumetric measures, we performed two-tailed t-test means comparisons for independent samples (threshold at $p < 0.05$). Regarding regional morphometric analysis, smoothed GM and WM images were analyzed performing two one-tailed $t$-tests (OCD $>$ controls and controls $>$ OCD) to identify the specific direction of the between-groups differences. Additionally, in the OCD group, we performed two linear correlations between: (a) GM volume and total CY-BOCS and (b) GM volume and STAI/T-C. Results from the regional morphometric analysis and the linear correlations were thresholded at $p < 0.001$ (uncorrected for multiple comparisons); only clusters larger than 40 voxels were analyzed. Provided that our groups were gender, age and handedness matched, we did not apply TBV covariation since we were interested in finding absolute brain differences between the samples; we considered important to minimize type II rather than type I error, this being the first VBM study in OCD children. As shown below, we did not find significant differences between groups concerning GM volume in the BG (thalamus, caudate, putamen and globus pallidus). Due to this fact, secondary hypotheses were tested in order to see whether age or drug treatment could be modulating the volume in these regions. For this purpose, we lowered our threshold to $p < 0.005$ uncorrected and performed post-hoc small volume corrected (SVC) correlations between: (a) BG–GM volume and age and (b) BG–GM volume and pharmacological treatment duration. In order to isolate the effect of drug treatment we also performed a correlation between treatment duration and BG, covarying out the possible effect of age. Results were thresholded at $p < 0.05$ Family Wise Error (FWE)-SVC.

Concerning global differences in GM, WM, CSF and TBV, mean comparisons of global volumetric measures showed that OCD children had a GM total volume reduction of 48.75 ml ($p = 0.01$), representing 5.93% decrement (95% CI: 1.49–10.36% or 12.3–85.2 ml). Regional differences in GM and WM segment volumes are shown in Table 2 and Fig. 1. There were no regions of increased GM or WM in the OCD group in comparison with the control group. OCD brains presented GM reductions in frontal lobe (bilateral middle and inferior triangularis areas, right frontal superior and frontal inferior operculum, and left rolandic operculum) and cingulate cortex (bilateral middle cingulate cortex and bilateral precuneus) as well as WM reductions in frontal (bilateral inferior operculum and left frontal middle gyrus) and parietal regions (right parietal superior). The GM reduction located in the right frontal middle cortex shows a $p$-value of 0.035 corrected for multiple comparisons according to FWE criteria. The FWE-correction prioritizes specificity over sensitivity of the results exerting a strong control over false positive values. Regarding correlation between regional GM volumes and clinical severity, a significant negative correlation was found between symptoms severity (Y-BOCS) and bilateral hippocampal GM volumes (see correlation in Table 2 and Fig. 2). No significant correlations were identified between GM volume and STAI/T-C. Concerning post-hoc BG correlations, we found a significant correlation between age and left caudate volume in the OCD group ($p = 0.037$ FWE-SVC; cluster size 148 voxels), but no age correlation in the control group. In the OCD group, we also identified positive correlations between drug treatment duration and left putamen volumes ($p = 0.005$ FWE-SVC; cluster size 375 voxels), right caudate ($p = 0.014$ FWE-SVC; cluster size 309 voxels) and bilateral thalamus (left, $p = 0.049$ FWE-SVC; cluster size = 1170 voxels; right, $p = 0.003$ FWE-SVC; cluster size = 1386 voxels). None of these correlations survived $p$-value of 0.05 FWE-SVC once we covariate for age’s effect.

Summarizing the main results, our OCD patients showed a 5.93% reduction of total GM. The VBM analysis showed decreased bilateral GM in frontal and cingulate regions as well as decreased WM in bilateral frontal and right parietal.
Table 2
Voxel-based morphometry results

<table>
<thead>
<tr>
<th>Structure (Brodmann area)</th>
<th>MNI^a (x, y, z)</th>
<th>Peak^b Z-score</th>
<th>p-value (FWE)-corrected^c</th>
<th>Cluster size (voxels)^d</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GM</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frontal lobe</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R frontal mid. (45)</td>
<td>40, 39, 21</td>
<td>4.39</td>
<td>0.035</td>
<td>2104</td>
</tr>
<tr>
<td>R frontal inf. tri. (45)</td>
<td>53, 27, 21</td>
<td>3.42</td>
<td>0.594</td>
<td></td>
</tr>
<tr>
<td>R frontal mid. (6)</td>
<td>41, 5, 42</td>
<td>3.48</td>
<td>0.610</td>
<td>318</td>
</tr>
<tr>
<td>R frontal inf. oper. (44)</td>
<td>44, 13, 35</td>
<td>3.41</td>
<td>0.846</td>
<td></td>
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<tr>
<td>R frontal mid. (9)</td>
<td>25, 29, 42</td>
<td>3.41</td>
<td>0.601</td>
<td>236</td>
</tr>
<tr>
<td>R frontal inf. oper. (44)</td>
<td>46, 7, 22</td>
<td>3.41</td>
<td>0.601</td>
<td>292</td>
</tr>
<tr>
<td>L frontal mid. (45)</td>
<td>−41, 31, 34</td>
<td>3.62</td>
<td>0.391</td>
<td>1961</td>
</tr>
<tr>
<td>L frontal inf. tri. (45)</td>
<td>−48, 28, 20</td>
<td>3.33</td>
<td>0.680</td>
<td></td>
</tr>
<tr>
<td>L frontal inf. oper. (8)</td>
<td>26, 59, 22</td>
<td>3.40</td>
<td>0.611</td>
<td>130</td>
</tr>
<tr>
<td>L frontal mid. (48)</td>
<td>−45, 23, 30</td>
<td>3.14</td>
<td>0.845</td>
<td></td>
</tr>
<tr>
<td>L rolандic oper. (48)</td>
<td>−52, 3, 16</td>
<td>3.23</td>
<td>0.771</td>
<td>70</td>
</tr>
<tr>
<td>Cingulate cortex</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>R cing. (23)</td>
<td>1, −26, 50</td>
<td>4.04</td>
<td>0.119</td>
<td>9399</td>
</tr>
<tr>
<td>R precuneus</td>
<td>16, −43, 42</td>
<td>3.55</td>
<td>0.464</td>
<td></td>
</tr>
<tr>
<td>L cing. (23–24)</td>
<td>−2, −10, 47</td>
<td>3.75</td>
<td>0.285</td>
<td></td>
</tr>
<tr>
<td>L precuneus</td>
<td>−14, −42, 45</td>
<td>3.46</td>
<td>0.552</td>
<td></td>
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<tr>
<td><strong>WM</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Frontal lobe</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R frontal inf. oper.</td>
<td>48, 21, 12</td>
<td>3.42</td>
<td>0.359</td>
<td>164</td>
</tr>
<tr>
<td>L frontal mid.</td>
<td>−27, 54, 3</td>
<td>3.39</td>
<td>0.387</td>
<td>76</td>
</tr>
<tr>
<td>L frontal inf. oper.</td>
<td>−41, 18, 12</td>
<td>3.23</td>
<td>0.531</td>
<td>113</td>
</tr>
<tr>
<td>Parietal areas</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R parietal sup.</td>
<td>22, −50, 59</td>
<td>3.24</td>
<td>0.523</td>
<td>92</td>
</tr>
<tr>
<td><strong>Correlation (GM/CY-BOCS)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Limbic regions</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R hippocampus</td>
<td>23, −31, −5</td>
<td>3.53</td>
<td>0.624</td>
<td>237</td>
</tr>
<tr>
<td>L hippocampus</td>
<td>−19, −25, −8</td>
<td>3.77</td>
<td>0.397</td>
<td>626</td>
</tr>
</tbody>
</table>

Regions of decreased GM and WM in OCD children in comparison with healthy matched controls. The lower part of the table shows GM regions correlating with CY-BOCS scores. L, left; R, right; mid., middle; inf., inferior; sup., superior; cing., cingulate; tri, triangularis; oper., operculum.

^a Montreal Neurological Institute (MNI) coordinates of the voxel of maximal statistical significance within each region.

^b Peak Z-score for the voxel of maximal statistical significance within each region.

^c Statistical significance after multiple comparison family-wise error (FWE), which rejects false positives.

^d Total number of contiguous voxels in each region that outlive p < 0.001. Given the voxel size (0.94 × 0.94 × 2) each voxel represents 1.77 mm³.

These regions have been previously involved in action and conflict monitoring [28]. Provided that there are no previous VBM studies on children, our results cannot be compared with other pediatric studies. However, our cingulate results coincide with the three VBM-OCD studies [13,19,26] and the right frontal middle GM reduction (p = 0.035 FWE-corrected) was also reported in two of them [13,19]. Our frontal and cingulate findings may nevertheless have an important bearing on OCD.
pathophysiology. Neuropsychological studies have reported that OCD patients show deficits related to frontal cognitive abilities, such as executive functioning and cognitive-behavioral flexibility [6]. In fMRI studies [28] frontal (BA 9, 44, 45, and 46) and cingulate cortices (BA 23 and precentral) have been found to be active during conflict monitoring tasks. Moreover, specific OCD fMRI studies [15] have shown a different pattern of activation of these regions in comparison to controls during action monitoring tasks. These results support an initial deficit in the action monitoring system in OCD children. In this sense, the typical OCD feeling of “not just right” could be interpreted as an exaggerated or false error detection [18], and thus partially explained by our findings. Indeed, cingulate cortices have been associated with overactive error monitoring, as measured by the error-related negativity in ERP studies [7,27] as well as in fMRI studies [5,25]. Apart from these frontal and cingulate findings, our study is the first to detect a significant negative correlation between CY-BOCS scores and bilateral GM volumes in the parahippocampal region. The negative correlation with CY-BOCS scores points to an association between clinical severity and hippocampal damage at the onset of the illness. Two hypotheses can be advanced to explain this finding. On the one hand, the hippocampal abnormalities could be related to memory OCD deficits. There is strong evidence that OCD is associated with low memory confidence as well as memory biases towards threatening information [17,23,24], specifically when it concerns the ability to recall if a behavior was actually performed or merely imagined [16]. On the other hand, bilateral smaller hippocampi have also been found in other psychiatric conditions, and hence it suggests that hippocampal reduction is more a case of neurodevelopmental damage than an illness-specific abnormality [14]. The main discrepancy of our results with previous OCD structural studies is the lack of BG deficits in our sample. The BG, especially caudate nucleus and putamen, have been extensively associated to routine performance and reinforcement [4,11,29]. This fact has made these regions (together with its OFC connections) suitable candidates to explain OCD pathophysiology.

Two possible hypotheses could explain our lack of BG results: (a) the dynamic pattern of the illness and (b) the duration of pharmacological treatment. In relation to the developmental nature of the illness, behavioral OCD pathological habits, such as the repetition of routines, could specifically affect the normal development of the BG. In fact, the largest structural OCD study to date [19] found a positive correlation between age and striatal abnormalities, which was interpreted as the anatomical expression of enduring striatal dysfunction. Therefore, the absence of striatal alterations [22] – or even the finding of a reduction, rather than an increase of striatal volumes [21] – could be expected in pediatric populations. Regarding the time of pharmacological exposure, Valente’s VBM study [26] found a negative correlation between duration of treatment and bilateral GM volumes of the head of caudate nuclei. To see whether our study supports any of these two hypotheses, we performed age and drug-treatment BG correlations. We found that subjects’ age positively correlated with left caudate volume in the OCD group but not in the control group. Concerning pharmacological treatment duration, we observed positive correlations between drug exposure duration and left putamen, right caudate and bilateral thalamus that do not pass multiple-comparison correction once we covariate for age effect. Thus, we did not find the negative correlation previously reported by Valente [26]. One should take into account that the mean treatment duration in Valente’s study is clearly smaller (mean = 47.6 days, S.D. = 41.9; and range 3–120) than our subjects’ mean treatment duration (10.04 months; S.D. = 10.05; and range 0.2–33.8). This difference in drug-treatment duration, in addition to the young age of our sample, could be partially responsible for the discrepancies concerning the effect of pharmacological time exposure on caudate volumes. However, our drug treatment positive correlation do not support 0.05 FWE-SVC once we covariate for age affect, which seems to indicate that the duration of pharmacological exposure is, by itself enable to explain BG results. Future studies could clarify this point. As a conclusion, our study pointed to GM and WM early OCD abnormalities associated with conflict monitoring circuits. We also found a significant negative correlation between CY-BOCS scores and bilateral GM volumes in the parahippocampal region. Other deficits previously found in adults (striatum and OFC) are absent in our study. However, according to our results, it seems that the dynamic nature of the illness could be modulating the normal striatum development in OCD children. Finally, given

Fig. 2. CY-BOCS correlation. Negative correlation (thresholded at p < 0.001) between CY-BOCS scores and GM volume in bilateral hippocampi. Sided scatter plots show the correlation between the GM volume (y-axis) of left (LH) and right (RH) hippocampus and CY-BOCS scores (x-axis). Gray dots represent real values and black dots adjusted values.
that this is the first VBM study in OCD children our analyses
gave priority to sensitivity over specificity, and thus they should
be taken with caution waiting for future replications.

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