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Gray Matter Volumes in Obsessive-Compulsive Disorder Before and After Fluoxetine or Cognitive-Behavior Therapy: A Randomized Clinical Trial

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Serotonin reuptake inhibitors and cognitive-behavior therapy (CBT) are considered first-line treatments for obsessive-compulsive disorder (OCD). However, little is known about their modulatory effects on regional brain morphology in OCD patients. We sought to document structural brain abnormalities in treatment-naive OCD patients and to determine the effects of pharmacological and cognitive-behavioral treatments on regional brain volumes. Treatment-naive patients with OCD ($n = 38$) underwent structural magnetic resonance imaging scan before and after a 12-week randomized clinical trial with either fluoxetine or group CBT. Matched-healthy controls ($n = 36$) were also scanned at baseline. Voxel-based morphometry was used to compare regional gray matter (GM) volumes of regions of interest (ROIs) placed in the orbitofrontal, anterior cingulate and temporolimbic cortices, striatum, and thalamus. Treatment-naive OCD patients presented smaller GM volume in the left putamen, bilateral medial orbitofrontal, and left anterior cingulate cortices than did controls ($p < 0.05$, corrected for multiple comparisons). After treatment with either fluoxetine or CBT ($n = 26$), GM volume abnormalities in the left putamen were no longer detectable relative to controls. ROI-based within-group comparisons revealed that GM volume in the left putamen significantly increased ($p < 0.012$) in fluoxetine-treated patients ($n = 13$), whereas no significant GM volume changes were observed in CBT-treated patients ($n = 13$). This study supports the involvement of orbitofronto/cingulo-striatal loops in the pathophysiology of OCD and suggests that fluoxetine and CBT may have distinct neurobiological mechanisms of action.
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INTRODUCTION

Obsessive-compulsive disorder (OCD) is a chronic disorder associated with clinically significant functional impairment (Vikas *et al*, 2009). Available treatments with serotonin reuptake inhibitors (SRIs) and cognitive-behavior therapy (CBT) are effective for most patients, but impairing residual symptoms and treatment non-response are common among this population (Eddy *et al*, 2004). Therefore, understanding brain-modulatory effects of these treatments is essential for further improvement of therapeutic alternatives.

Numerous magnetic resonance imaging (MRI) studies of OCD have demonstrated the presence of brain abnormalities involving cortico-subcortical circuits that interconnect the orbitofrontal cortex (OFC), anterior cingulate cortex (ACC), striatum, and thalamus, as well as temporolimbic regions (Atmaca *et al*, 2008; Busatto *et al*, 2000; Chamberlain *et al*, 2008; Harrison *et al*, 2009; Lacerda *et al*, 2003; Pujol *et al*, 2004; Radua and Mataix-Cols, 2009; Rauch *et al*, 1994; Saxena and Rauch, 2000; Szeszko *et al*, 1999; Valente *et al*, 2005; van den Heuvel *et al*, 2009). However, it is unknown whether such abnormalities may be reversed by specific treatments.

There are indications that SRIs modulate serotonin neurotransmission earlier in certain subcortical regions and later in the cerebral cortex (Blier and Bouchard, 1994;

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el Mansari *et al*, 1995). In the case of CBT, there is increasing evidence implicating the medial prefrontal cortex (medial OFC and rostral/subgenual subregions of the ACC) in the mediation of its therapeutic action (Sotres-Bayon *et al*, 2006; Milad *et al*, 2005). The medial prefrontal cortex is a key regulatory region in the maintenance inhibition of conditioned fear responses believed to underlie obsessive-compulsive symptoms and in the mediation of the extinction process of such fear responses (Milad *et al*, 2005, 2007; Phelps *et al*, 2004; Sotres-Bayon *et al*, 2006). Thus, although successful pharmacological interventions for OCD seem to exert a preferential subcortical-cortical 'bottom-up' regulation in the brain, CBT seems to elicit cortical-subcortical 'top-down' effects (Derryberry and Tucker, 1992; Goldapple *et al*, 2004; Tucker *et al*, 1995).

Although there are a growing number of short-term longitudinal functional neuroimaging studies documenting regional brain activity changes in OCD patients after SRI treatment or CBT (Baxter *et al*, 1992; Benkelfat *et al*, 1990; Perani *et al*, 1995; Saxena *et al*, 2002, 2009; Schwartz *et al*, 1996; Swedo *et al*, 1992), longitudinal MRI studies investigating treatment-related brain morphological changes are still scarce. The few available longitudinal MRI studies in this regard have been limited to the investigation of small groups of children with short illness duration, treated in an open, uncontrolled manner (Benazon *et al*, 2003; Gilbert *et al*, 2000; Lazaro *et al*, 2009; Rosenberg *et al*, 2000; Szeszko *et al*, 2004). Anecdotally, it has been suggested that SRIs are more likely than CBT to modulate brain volumes in OCD patients (Rosenberg *et al*, 2000). However, firmer conclusions are limited because of the lack of longitudinal MRI studies conducted in association with controlled, randomized clinical trials investigating the brain structural effects of these two modalities of intervention.

We attempted to address the above limitations by conducting a longitudinal voxel-based morphometry (VBM) study in treatment-naive adult OCD patients randomized to participate in either a clinical trial with fluoxetine or group CBT. Our aims were threefold: first, to document the profile of brain structural abnormalities associated with OCD without the confounding factor of previous treatment, we compared brain morphometric patterns between treatment-naive OCD patients and healthy controls; second, OCD patients were compared with controls again after treatment (either with fluoxetine or CBT) to examine whether brain volumes would change over the course of treatment; and third, we performed within-group comparisons (separately for fluoxetine- and CBT-treated subgroups) to disentangle possible independent effects of pharmacological and cognitive-behavioral treatment on regional brain morphology.

We focused our investigation within the principal brain regions previously implicated in imaging studies of OCD (OFC, ACC, striatum, thalamus, and temporolimbic structures) (Saxena and Rauch, 2000). *A priori*, we hypothesized that: (1) OCD patients would show significant gray matter (GM) volumetric abnormalities in those brain regions relative to controls; (2) after successful treatment, brain volume abnormalities would be attenuated, resulting in fewer significant differences relative to controls; (3) specifically, given the supposed effect of SRI treatment in modulating the activity of frontal-subcortical and limbic circuits (Bloom and Kupfer, 1995), patients in the fluoxetine group would exhibit more widespread brain effects after treatment; and (4) patients undergoing CBT would present GM volume changes mainly in regions of the medial prefrontal cortex (medial OFC and rostral/subgenual ACC), reflecting the primacy of cortico-subcortical top-down effects associated with extinction processes (Milad *et al*, 2005, 2007; Phelps *et al*, 2004).

MATERIALS AND METHODS

Subjects

This investigation is an arm of a research protocol that involved administering several neurobiological measures to treatment-naive OCD patients who participated in a larger clinical trial intended to investigate the effectiveness of fluoxetine and group CBT in a setting more similar to clinical practice (clinical registration information: http://clinicaltrials.gov—NCT00680602) (Belotto-Silva *et al*, 2011). This project was conducted in our outpatient OCD clinics at the University of São Paulo Medical School, Brazil (protocol, training, and reliability of instruments can be found elsewhere) (Hoexter *et al*, 2009; Miguel *et al*, 2008).

In brief, patients were referred from primary psychiatric services or were recruited through the local media (radio/television/newspapers/internet). Screening procedures included a telephone assessment, conducted by a trained psychologist. Once the subject met the initial requirements, a medical appointment was scheduled in which clinical and psychiatric assessments, structured clinical diagnostic interviews (SCID-I) (First *et al*, 1997), routine blood tests, and an electrocardiogram were obtained. Inclusion criteria comprised: (1) age between 18 and 65 years; (2) primary DSM-IV diagnosis of OCD; and (3) Yale–Brown Obsessive-Compulsive Scale (Y-BOCS) score $\geqslant$16 or at least 10 if only obsessions or compulsions were present (only one patient had total Y-BOCS score $<$16, scoring 2 for obsessions and 13 for compulsions). Patients were excluded if they had: (1) previous exposure to any sort of psychotropic medication (benzodiazepines, antipsychotics, antidepressants, stimulants, mood stabilizers); (2) previous exposure to at least 12 sessions of CBT (only 2 patients had been exposed to CBT before); (3) history of head injury with loss of consciousness; (4) past/current substance abuse or dependence; (5) lifetime history of psychosis; (6) suicide risk; (7) any organic disorders that could affect the central nervous system; (8) contraindications for MRI scanning; and (9) being pregnant.

Controls were selected among college students and hospital and university staff, or were recruited through word of mouth. They were selected according to the same criteria described above (except for the presence of OCD) and had no current history of neurological or psychiatric disorders on the basis of SCID interviews. All participants provided written informed consent, which had been approved by the local Institutional Review Board.

From 623 patients referred to our OCD clinic from 2006 to 2008 (Hoexter *et al*, 2009), 254 were excluded in the telephone screening and 328 were excluded in the psychiatric medical assessment mainly for not being treatment naive (Supplementary Figure S1). In all, 41 OCD patients participated. Similarly, 54 potential healthy controls were

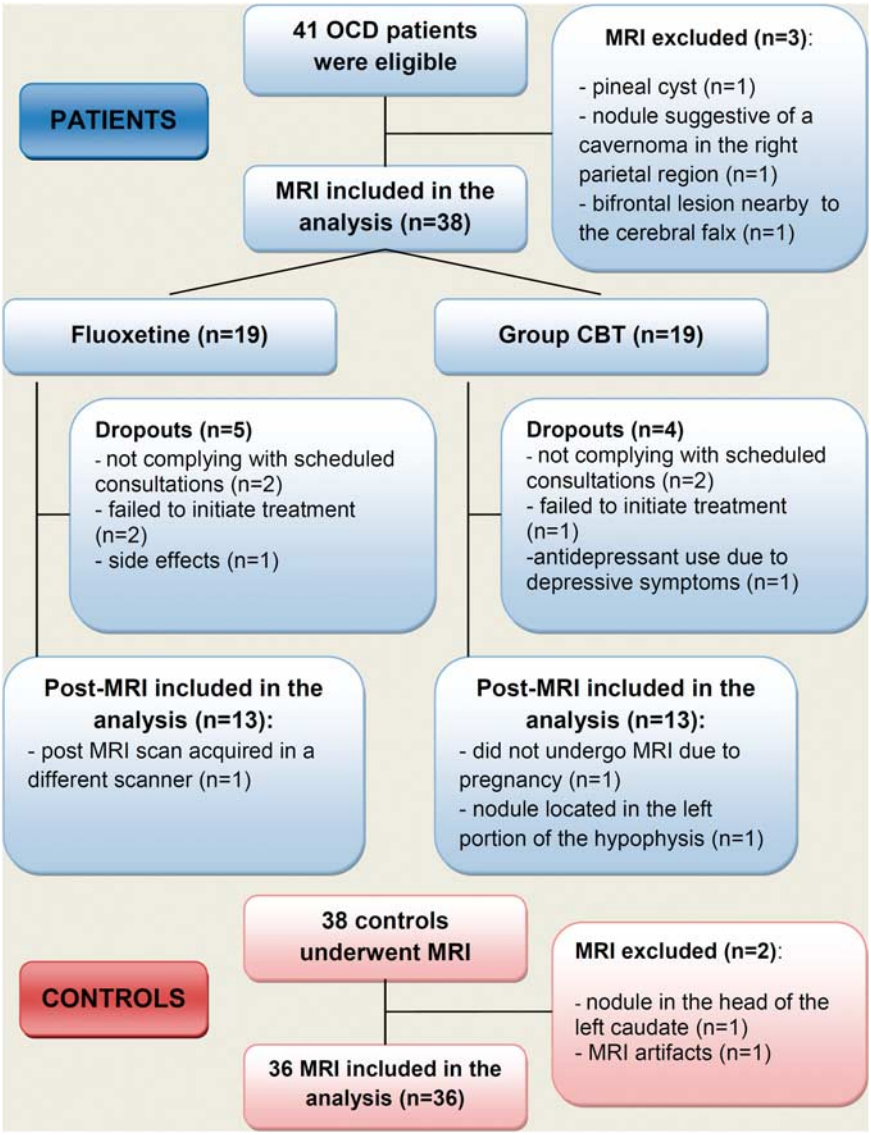

Figure 1 Study flowchart showing the numbers of participants through each stage of the study.

screened, from which 38 who fulfilled all the criteria for study entry were selected. It is noteworthy that three patients and two controls were excluded (Figure 1). Therefore, 38 treatment-naive OCD patients and 36 controls who matched for age, gender, socioeconomic status, level of education, and handedness were studied (Table 1).

Clinical Assessments

The Y-BOCS (Goodman *et al*, 1989), Dimensional Yale–Brown Obsessive-Compulsive Scale (DY-BOCS) (Rosario-Campos *et al*, 2006), Beck Depression Inventory (BDI) (Beck *et al*, 1961), Beck Anxiety Inventory (BAI) (Beck *et al*, 1988), and Clinical Global Impression scale (CGI) (Guy, 1976) were administered before and after 12 weeks of treatment (Hoexter *et al*, 2009) by interviewers who were blind to the type of treatment.

On the basis of the SCID, 13 OCD patients met DSM-IV criteria for current major depression and 10 additional patients had a history of major depression and/or dysthymia. Other SCID-I DSM-IV lifetime diagnoses included agoraphobia ($n=2$), panic disorder with agoraphobia ($n=1$), panic disorder without agoraphobia ($n=3$), specific phobia ($n=13$), social phobia ($n=21$), post-traumatic stress disorder ($n=8$), generalized anxiety disorder ($n=17$), bipolar I ($n=1$), bipolar II disorder ($n=2$), somatization ($n=2$), hypochondriasis ($n=1$), body dysmorphic disorder ($n=5$), anorexia nervosa ($n=3$), bulimia nervosa ($n=2$), binge-eating disorder ($n=2$), skin picking ($n=8$), trichotillomania ($n=2$), intermittent explosive disorder ($n=7$), attention-deficit/hyperactivity disorder ($n=3$), chronic tics ($n=4$), and Tourette's syndrome ($n=2$).

Allocation

A specific mode of randomization was used in this study (Fossaluza *et al*, 2009). In brief, a computer program was developed to sequentially allocate patients to each treatment

Table 1 Clinical and Demographic Characteristics of OCD Patients and Controls

Variable	OCD ($n=38$)	Controls ($n=36$)	Analysis		
	Mean (SD)		*U*	*Z*	*p*-value
Age, years	31.5 (10.2)	27.8 (7.8)	545.5	−1.50	0.13
Age of onset, years[a]	13.1 (7.6)	NA	—	—	—
Illness duration, years[a]	18.2 (10.4)	NA	—	—	—
Y-BOCS scores					
Obsessions	12.2 (3.2)	NA	—	—	—
Compulsions	12.9 (2.5)	NA	—	—	—
Total	25.1 (5.2)	NA	—	—	—
DY-BOCS scores[b]					
Aggression[c]	5.6 (4.6)	0 (0)	216.0	−5.94	<0.001
Sexual/religious[d]	3.4 (4.8)	0 (0)	432.0	−3.99	<0.001
Symmetry[e]	7.6 (3.8)	0.2 (0.5)	85.0	−6.83	<0.001
Contamination[f]	5.5 (5.1)	0 (0)	270.0	−5.46	<0.001
Hoarding[g]	3.2 (3.5)	0.1 (0.4)	323.0	−4.76	<0.001
BDI	17.3 (9.4)	2.6 (2.7)	75	−6.61	<0.001
BAI	17.1 (11.7)	1.9 (1.6)	64.5	−6.72	<0.001
	N (%)		χ^2	df	*p*-value
Gender, female	23 (60.5)	23 (63.9)	0.09	1	0.77
Caucasian	34 (89.5)	28 (77.8)	1.10	1	0.29
Socioeconomic status					
Classes a/b (higher)	23 (60.5)	25 (69.4)	0.64	1	0.42
Classes c/d/e (lower)	15 (39.5)	11 (30.6)			
Level of education[h]					
Higher	14 (36.8)	13 (36)	0.32	2	0.85
Middle	22 (57.9)	22 (61.1)			
Lower	2 (5.3)	1 (2.8)			
Right-handed	37 (97.4)	36 (100)	0.96	1	0.33
Presence of a symptom dimension (DY-BOCS)					
Aggression[c]	29 (76.3)	1 (2.8)	41.473	1	<0.001
Sexual/religious[d]	16 (42.1)	0 (0)	19.339	1	<0.001
Symmetry[e]	34 (89.5)	7 (19.4)	36.693	1	<0.001
Contamination[f]	24 (63.2)	2 (5.6)	26.914	1	<0.001
Hoarding[g]	21 (55.3)	3 (8.3)	18.580	1	<0.001

Abbreviations: BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory; df, degree of freedom; DY-BOCS, Dimensional Yale–Brown Obsessive-Compulsive Scale; NA, not applicable; OCD, obsessive-compulsive disorder; U, Mann–Whitney *U*-test; Y-BOCS, Yale–Brown Obsessive-Compulsive Scale.
[a]One data value is missing.
[b]Scores vary from 0 to 15 for each dimension.
[c]Obsessions about harm due to aggression/injury/violence/natural disasters, and related compulsions.
[d]Obsessions concerning sexual/moral/religious obsessions, and related compulsions.
[e]Obsessions about symmetry/'just-right' perceptions, and compulsions to count or order/arrange.
[f]Contamination obsessions and cleaning compulsions.
[g]Obsessions and compulsions related to hoarding.
[h]Higher: complete tertiary education; middle: incomplete tertiary and complete secondary education; incomplete secondary education.

group, in which prognostic factors such as gender, age, and initial Y-BOCS score were inserted in the model. The aim of this method was to minimize differences between groups by balancing possible confounders. Consequently, patients allocated to either group (fluoxetine = 19 and CBT = 19) were less likely to differ significantly in terms of major

clinical and demographical characteristics (Supplementary Table S1).

Fluoxetine Treatment

Patients received fluoxetine (up to 80 mg/day) for 12 weeks, starting at 20 mg/day in the first week, with weekly increases of 20 mg/day (Diniz *et al*, 2010). Medical appointments were scheduled every 4 weeks to monitor side effects and treatment compliance. Of the 14 patients who completed the treatment (74% of the initial sample), all reached the maximal dose of 80 mg/day without reporting major side effects, except for one subject who could not tolerate doses higher than 20 mg/day because of gastrointestinal effects and tremor. In all, 13 post-fluoxetine MRI scans were analyzed. Reasons for not analyzing a second MRI scan and reasons for dropouts are presented in Figure 1. Non-completers were not statistically different from completers in terms of age, age at onset of symptoms, illness duration, Y-BOCS, DY-BOCS, BDI, and BAI scores.

Group CBT Treatment

Patients were divided into subgroups of 6–8 people each and attended a weekly 2-h standardized CBT session for 12 weeks. The groups were coordinated by a psychologist with several years of experience in behavior therapy, who was trained by the author of the group CBT protocol (Cordioli *et al*, 2002; Volpato Cordioli *et al*, 2003). Patients who missed more than two consecutive sessions were considered dropouts. The protocol consisted of (Volpato Cordioli *et al*, 2003): session 1—psychoeducational information; session 2—development of symptoms hierarchies; session 3—introduction to exposure with response prevention—E/RP; sessions 4–7—E/RP exercises and cognitive techniques; session 8—family session, and sessions 9–12—review of E/RP and cognitive techniques. In all, 15 patients (79% of the initial sample) completed the group CBT treatment, and 13 post-CBT MRI scans were analyzed. Reasons for not analyzing a second MRI scan and reasons for dropouts are presented in Figure 1. The non-completers were not statistically different from completers in terms of age, age at onset of symptoms, illness duration, Y-BOCS, DY-BOCS, BDI, and BAI scores.

Image Acquisition and Processing

Patients were scanned at baseline and after 12 weeks of treatment. Healthy controls were scanned just once at baseline, given that there is evidence that such a small period of time does not significantly affect GM measures in healthy subjects as assessed with VBM (Hölzel *et al*, 2011; Lyoo *et al*, 2010; Lazaro *et al*, 2009). Images were acquired using a 1.5-T GE Signa scanner (General Electric, Milwaukee, WI, USA). Contiguous 1.6-mm axial images across the entire brain were obtained (T1-3D SPGR sequence, TE = 4.20 ms, TR = 10.5 ms, flip angle = 15, acquisition matrix = 256×192) and interpolated using ZIP2 to a final voxel size of $0.94 \times 0.94 \times 0.80\,mm^3$ (248 slices). VBM processing was executed using the Statistical Parametric Mapping (SPM5) package (Wellcome Department of Imaging Neuroscience, London, UK), performed in Matlab (Mathworks, Sherborn, MA), using the default parameters implemented in the VBM5 Toolbox (http://dbm.neuro.uni-jena.de/vbm/). This protocol uses the unified segmentation approach (Ashburner and Friston, 2005), which integrates the processes of tissue classification, MRI inhomogeneity bias correction, and spatial normalization to the standard SPM T1-MRI template, based on 152 healthy subjects from the Montreal Neurological Institute (MNI) (Mazziotta *et al*, 1995), using linear (12-parameter affine) and non-linear transformations. The extension of Hidden Markov Random Field approach available in the VBM5 tool box was used, aimed at increasing the quality of image segmentation (Cuadra *et al*, 2005). Subsequently, the final tissue maps of GM, white matter, and brain-spinal fluid were modulated by the Jacobian determinants derived from spatial normalization to the MNI standard space. This enabled brain structures that had their volumes reduced after spatial normalization to have their total counts restored by an amount proportional to the degree of volume shrinkage and thus allowed testing for regional differences in the absolute volume amount of GM (Good *et al*, 2001). Voxel sizes of segmented and spatially normalized images equaled $1 \times 1 \times 1\,mm^3$. Finally, images from OCD patients and controls were smoothed using a 12-mm Gaussian kernel.

Statistical Analysis

Comparisons of GM volume were performed between and within groups with VBM using the general linear model (Friston *et al*, 1994). Only voxels with values above an absolute threshold of $p = 0.05$ for differentiating GM from other tissues entered the analyses. A measure of the total amount of GM was entered as confound in an analysis of covariance. In each comparison, two *t*-statistic maps, corresponding to opposite contrasts (volume decrease and increase), were generated and displayed into standard space at a threshold of $p < 0.001$, uncorrected. Each statistical map was then inspected for the presence of clusters of significant differences in regions where volumetric abnormalities had been predicted *a priori* (orbitofrontal, anterior cingulate and temporolimbic cortices, thalamus, and caudate–putamen) using the small volume correction (SVC) method included in SPM toolbox, with the purpose of constraining the total number of voxels included in the analyses. Each region was circumscribed by merging the spatially normalized region-of-interest (ROI) masks that are available within the Anatomical Automatic Labeling SPM toolbox. Anatomical masks were used separately in each hemisphere (left and right, respectively), resulting in search volumes of 7704 and 7976 voxels for the superior lateral OFC; 7104 and 8120 voxels for the middle lateral OFC; 13 520 and 13 631 voxels for the inferior lateral OFC; 5752 and 6848 voxels for the medial OFC; 7696 and 7952 voxels for the caudate nucleus; 8039 and 8438 voxels for the putamen; 8435 and 8174 voxels for the thalamus; 11 200 and 10 504 voxels for the anterior cingulate gyrus; 1760 and 1984 voxels for the amygdala; 7456 and 7568 voxels for the hippocampus; and 7824 and 9056 voxels for the parahippocampal gyrus. Findings of these hypothesis-driven, SVC-based analyses were reported as significant if surviving family-wise error (FWE) correction for multiple comparisons ($p < 0.05$) over the respective

Table 2 Differences in Regional Gray Matter Volumes between Patients with OCD and Controls

Brain region (SVC)[a]	Direction of difference	Coordinates (*x*, *y*, *z*)[b]	BA[c]	Peak *Z*-score[d]	Number of voxels[e]	*p* (FWE)[f]
Overall OCD group (n = 38) vs controls (n = 36)						
Left putamen	Decreased in OCD	−28, 12, 3	—	4.28	819	0.001
OCD subjects without major depression (n = 25) vs controls						
Left putamen	Decreased in OCD	−27, 14, 2	—	4.01	695	0.004
Left medial orbitofrontal cortex	Decreased in OCD	−13, 50, −9	10	3.32	59	0.025
Right medial orbitofrontal cortex	Decreased in OCD	14, 41, −2	10	3.64	49	0.011
Right anterior cingulate cortex	Decreased in OCD	14, 41, 2	32	4.08	418	0.004

[a]Each region was circumscribed using the small volume correction (SVC) approach, with anatomically defined volume-of-interest masks.
[b]Talairach and Tornoux (1988) coordinate of the voxel of maximal statistical significance within each region.
[c]Approximate Brodmann's areas.
[d]*Z*-score for the voxels of peak statistical significance within each volume of interest.
[e]Total number of contiguous voxels in each region that surpassed the initial cutoff of $Z > 3.09$.
[f]Family-wise error (FWE) correction for multiple comparisons at the level of individual voxels within the respective volume of interest.

ROI, with voxel clusters comprising at least 20 voxels. For unpredicted findings in other GM regions, we used the FWE-corrected $p < 0.05$ level over the whole brain. In all analyses, we converted MNI coordinates of voxels of maximal statistical significance to the Talairach and Tournoux (1988) system (Brett *et al*, 2002).

RESULTS

Treatment Outcome

After treatment, OCD patients as a whole exhibited a significant decrease in the severity of obsessive-compulsive symptoms (mean ± SD pre- *vs* post-treatment Y-BOCS: 24.9 ± 5.2 *vs* 16.3 ± 8.1; decrements of 34.5%; $p = 0.001$) and depressive symptoms (pre- *vs* post-treatment BDI: 14.9 ± 8.0 *vs* 9.8 ± 7.6; decrements of 34.2%; $p = 0.007$). Within-group comparisons (fluoxetine-treated = 13 and CBT-treated = 13) revealed significant OCD severity reductions for both treatments subgroups (pre- *vs* post-treatment Y-BOCS: 23.4 ± 5.0 *vs* 14.8 ± 6.3; decrements of 36.7%; $p = 0.005$ for fluoxetine and 26.5 ± 5.1 *vs* 17.7 ± 9.6; decrements of 33%; $p = 0.003$ for CBT), with no statistical difference between treatments. In all, 5 out of 13 fluoxetine-treated patients (38.4%) and 6 out of 13 CBT-treated patients (46.1%) were considered full responders (defined as a minimum reduction of 35% on the Y-BOCS and a 'much-improved' or 'very-much-improved' CGI-improvement scores for OCD).

Subjects also experienced a decrease in depressive symptoms in both treatment subgroups, but this difference was only statistically significant for CBT (pre- *vs* post-treatment BDI: 14.7 ± 9.2 *vs* 9.1 ± 9.0; decrements of 38.1%; $p = 0.018$ for CBT and 15.0 ± 7.1 *vs* 10.5 ± 6.4; decrements of 30%; $p = 0.1$ for fluoxetine).

MRI Comparisons: Treatment-Naive OCD Patients at Baseline *vs* Controls

The total GM volume measured in milliliters in the segmented images was 915.12 ± 61.34 in the OCD group and 932.51 ± 39.26 in healthy control subjects ($t = -1.443$, $df = 72$, $p = 0.153$).

VBM analyses indicated that there was a significantly smaller GM volume in the left putamen (dorsal rostral portions) in OCD patients than in controls (Table 2 and Figure 2a). A similar pattern of between-group differences involving the putamen was seen after exclusion of patients who met criteria for current major depression ($n = 13$) (Table 2). In addition, this subgroup of non-depressed OCD patients also presented clusters of significant smaller GM volume in the left (Table 2, Figure 2b) and right medial OFC (Table 2, Figure 2c) and right ACC (Table 2, Figure 2c).

No clusters of significant greater GM volumes were found within the principal brain areas predicted *a priori* in the OCD sample. There were also no clusters of regional changes of greater or smaller GM volumes in other unpredicted brain regions considering a *p*-value < 0.05, corrected for multiple comparisons over the whole brain. For exploratory purposes, given that other regions appear to be involved in OCD, such as the dorsolateral prefrontal, posterior cingulate, and parietal cortices (Menzies *et al*, 2008; Busatto *et al*, 2000), data of unpredicted GM volumes using a less stringent threshold of $p < 0.001$ for the whole brain (uncorrected for multiple comparisons) are listed in Supplementary Table S2.

In the OCD group, there were no significant linear correlations between GM volumes involving the regions shown to be altered in the between-group comparisons and either of the variables: age at onset of symptoms, illness duration, Y-BOCS, DY-BOCS, BDI, and BAI scores. The threshold for considering a correlation as statistically significant was set at a *p*-value < 0.001, uncorrected for multiple comparisons over the entire brain, after covarying out the effect of the total amount of GM.

We also performed an analysis comparing pre-treatment GM volumes specifically in the OCD subgroup who subsequently completed either the fluoxetine or CBT treatment protocols ($n = 26$) against the control group ($n = 36$). This analysis confirmed the findings of significant smaller GM volume in the left putamen in OCD patients relative to controls (219 voxels; peak coordinates = −27, 13, 2;

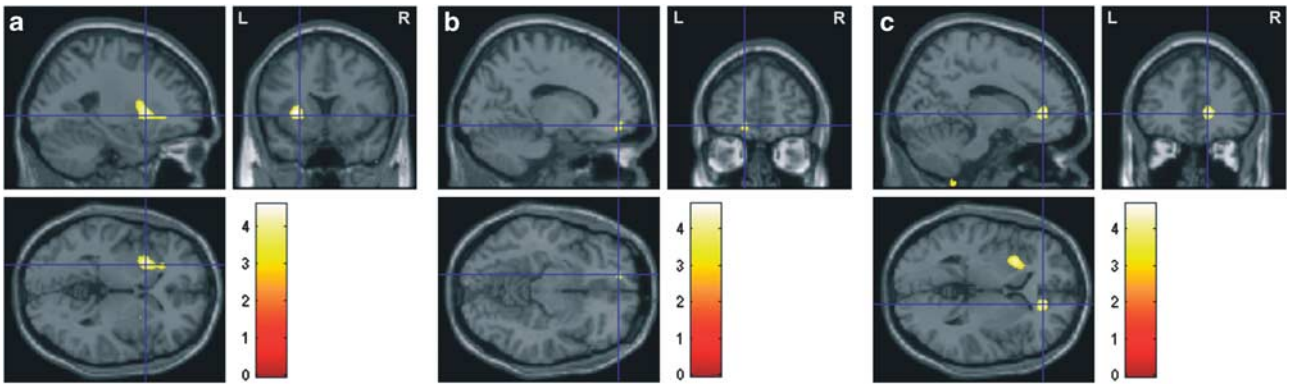

Figure 2 Brain regions where there were foci of significantly gray matter volume differences in obsessive-compulsive disorder (OCD) patients relative to healthy control subjects. (a) Lesser regional gray matter volume in OCD patients ($n = 38$) *vs* healthy controls ($n = 36$) in the left putamen. (b) Lesser regional gray matter volume in OCD patients without major depression ($n = 25$) *vs* healthy controls ($n = 36$) in the left medial orbitofrontal cortex. (c) Lesser regional gray matter volume in OCD patients without major depression ($n = 25$) *vs* healthy controls ($n = 36$) encompassing the right anterior cingulate and medial orbitofrontal cortices.

$Z = 3.59$; peak voxel p-FWE = 0.016) (1350 voxels; peak coordinates = −27, 13, 2; $Z = 3.77$; peak voxel p-FWE = 0.009). No GM alterations involving regions within the medial orbitofrontal and anterior cingulate cortices were observed.

MRI Comparisons: Treated OCD Patients *vs* Controls

The analyses comparing post-treatment GM volumes in OCD patients who completed the treatment protocols ($n = 26$) against the control group indicated that there were no longer significant findings of smaller GM volume in the left putamen in OCD subjects relative to controls, as it had been found in the pre-treatment comparisons between OCD patients and controls. There were no other clusters of significant GM volume differences between treated OCD patients and controls, either in the other areas where volume abnormalities had been hypothesized *a priori* or in unpredicted brain regions.

Pre- *vs* Post-Treatment MRI Comparisons within the OCD Group

To test our hypothesis that fluoxetine and CBT exert different modulations over the volume of brain regions relevant to the pathophysiology of OCD, we conducted voxelwise within-group analysis comparing GM volumes pre *vs* post treatment in the two OCD subgroups (pre *vs* post fluoxetine = 13, pre *vs* post CBT = 13). None of these analyses revealed significant changes in GM volumes after treatment, either with a threshold of $p < 0.001$ or a less stringent threshold of $p < 0.01$, uncorrected for multiple comparisons, nor in other, unpredicted brain regions. Finally, for exploratory purposes, we extracted mean GM volume values from the spatially normalized images of each patient before and after treatment, using bilateral ROI masks placed on the putamen, medial OFC, and ACC. These within-group ROI comparisons showed, in fluoxetine-treated OCD patients ($n = 13$), a significant increase in GM volume in the left putamen ($p = 0.012$) after treatment. Conversely, there were no statistically significant GM volume changes after treatment in any of the ROIs in OCD patients who underwent the CBT program ($n = 13$) (Table 3). It is noteworthy that these results were not influenced by differences in the percentage of changes in comorbid depressive symptoms.

DISCUSSION

This study investigated post-treatment morphometric brain alterations in adult treatment-naive OCD patients participating in a randomized clinical trial comparing pharmacotherapy and psychotherapy. A methodological advantage of enrolling treatment-naive patients in such a study design is the exclusion of potentially confounding effects of previous treatments on GM brain volumes. The VBM analysis revealed, in treatment-naive OCD patients, decreased GM volume in the left putamen compared with controls. In a subgroup of OCD patients without comorbid depression, reduced GM volumes in the bilateral medial orbitofrontal and left anterior cingulate cortices were also observed, reinforcing the involvement of these structures in the pathophysiology of OCD. After successful treatment with either SRIs or CBT, GM volume abnormalities in the left putamen presented in the whole sample of OCD patients were no longer detectable relative to controls. ROI-based within-group comparisons revealed that GM volume in the left putamen significantly increased in fluoxetine-treated patients, whereas no significant GM volume changes were observed in CBT-treated patients.

Fluoxetine and Group CBT Treatment Outcomes

Weekly group CBT has been shown to be as effective as fluoxetine treatment in reducing obsessive-compulsive symptoms. This study adds to evidence from earlier papers that weekly group CBT is as effective as selective SRIs in treating OCD (Sousa *et al*, 2006). It is important to highlight that the group approach lowers costs considerably, hence making CBT accessible to a larger numbers of patients.

Table 3 Region-of-Interest Analysis of Gray Matter Volume Differences in OCD Patients Before and After Treatment

Group	Brain region	Pretreatment, mean (SD), cm^3	Post-treatment, mean (SD), cm^3	Difference (%)	*Z*-score	*p*-value[a]
Fluoxetine	Left putamen	3.63	3.82	5	−2.50	0.012
	Right putamen	4.05	4.18	3.1	−1.62	0.1
	Left mOFC	3.43	3.41	−0.6	1	0.32
	Right mOFC	4.26	4.27	0.2	−0.27	0.78
	Left ACC	7.01	6.97	−0.6	−0.62	0.53
	Right ACC	5.86	6.06	3.3	−1.15	0.25
CBT	Left putamen	3.91	3.9	−0.2	−0.56	0.57
	Right putamen	4.38	4.32	−1.4	−0.85	0.39
	Left mOFC	3.41	3.4	−0.3	−0.27	0.78
	Right mOFC	4.26	4.26	0	0.000	1
	Left ACC	7.08	7.12	0.6	−0.51	0.61
	Right ACC	5.87	6.04	2.8	−1.26	0.21

Abbreviations: ACC, anterior cingulate cortex; mOFC, medial orbitofrontal cortex; OCD, obsessive-compulsive disorder.
[a]Wilcoxon's test for paired comparisons.

Baseline Brain Volume Abnormalities in Treatment-Naive OCD Patients *vs* Controls

Neuroimaging studies have implicated a dysfunction of frontostriatal regions in the pathophysiology of OCD (Insel, 1992; Rauch, 2000; Saxena *et al*, 2000). Although the direction of regional GM volumetric abnormalities reported in the literature has not always been consistent across morphometric MRI studies, our results converge with the findings from two recent VBM meta-analysis that demonstrated GM alterations in OCD patients encompassing territories within the striatum, orbitofrontal, and anterior cingulate cortices (Radua *et al*, 2009; Rotge *et al*, 2010). It is noteworthy that although our results showed putaminal decrements in OCD, Radua and Mataix-Cols (2009) and Rotge *et al* (2010) demonstrated increased GM within this region. Another recent VBM meta-analysis demonstrated that OCD was associated with greater putaminal volume, whereas the opposite was observed in other anxiety disorders (such as posttraumatic stress disorder and panic disorder) (Radua *et al*, 2010). Inconsistencies in the direction of these abnormalities may be partially interpreted as a consequence of methodological differences across separate MRI studies, such as small and heterogeneous samples of OCD participants, matching criteria, voxelwise statistical testing, and image processing details (Ferreira and Busatto, 2010; Menzies *et al*, 2008). In this study, aiming to investigate a real-world OCD population, we did not exclude many comorbidities including several anxiety disorders, which may have added variability to our findings. Moreover, an alternative explanation for such a disparity is the fact that we investigated treatment-naive adult OCD patients. This may be an important difference, given that the majority of studies included in these meta-analyses investigated OCD patients who were currently taking or had already taken medication. The few studies that investigated treatment-naive patients were performed in children with a short illness duration. Therefore, our results may suggest that previous exposure to medication, regardless of whether OCD patients were medicated or non-medicated at the time of MRI scanning, may also have an important role in the variability of results. It is equally important to highlight, given that OCD and major depressive disorder are mediated by distinct but partially overlapping neural systems (Cardoner *et al*, 2007; Saxena *et al*, 2001), that our baseline findings of altered GM volumes were present in the OCD sample independently of the presence of current major depression.

In particular, the dorsal subregion of the rostral putamen implicated in this study receives projections from the dorsolateral prefrontal cortex (critical to higher cognitive processes), as well as premotor and motor areas (involved in motor planning and execution) (Haber, 2003). Thus, alterations in this striatal subregion could be related to cognitive and motor impairments that are highly frequently reported in OCD patients (Chamberlain *et al*, 2005; Menzies *et al*, 2008), such as mental inflexibility and impaired motor inhibition.

Our finding of smaller GM volume in the medial OFC and ACC is consistent with previous results reported in imaging studies of OCD (Pujol *et al*, 2004; Rauch *et al*, 1994; Valente *et al*, 2005, Radua *et al*, 2009; Rotge *et al*, 2010). Given their connections with the ventral striatum, amygdala and insula, the medial OFC, and ACC are important regulatory nodes monitoring motivation and emotional responses (Cardinal *et al*, 2002; Phillips *et al*, 2003). Recently, functional imaging studies have provided evidence that cortical connectivity of different subregions within the striatum, involving both cognitive and emotional processing, is disrupted in OCD (Harrison *et al*, 2009). Therefore, our findings of GM abnormalities in specific subregions of the striatum (putamen), OFC, and ACC provide structural substrate for functional connectivity alterations observed in OCD. The exact neurobiological mechanisms underlying how morphometric changes of specific brain regions may influence actual physiological activity of the putative cortico-striatal loops are not fully understood. It may be speculated that alterations in GM volumes could be due to changes in the number of neurons, glial cells, or synaptic arborization that could ultimately inhibit or facilitate

cortico-striatal communication. It is remarkable that surgical treatments for treatment-refractory OCD, such as stereotactic ablation and deep brain stimulation that intent to modulate specific cortico-striatal circuits (Greenberg *et al*, 2010), target regions closely located to our putaminal finding.

MRI Findings in OCD Patients after Treatment with Fluoxetine or CBT

The results of our post-treatment comparison between OCD patients and healthy controls suggest that GM volume abnormalities in the left putamen were attenuated after treatment. These findings may indicate that OCD treatment, regardless of the modality used modulates GM volumes in OCD patients. If it is the case, this interpretation is consistent with several functional imaging studies that have reported metabolic normalization after either pharmacotherapy or behavior therapy for OCD (Baxter *et al*, 1992; Perani *et al*, 1995; Saxena *et al*, 2002; Swedo *et al*, 1992).

However, the above interpretation has to be made cautiously, as there are other plausible explanations for these results. Loss of significant GM differences between post-treated patients and controls does not necessarily prove major changes in regional GM volume in OCD subjects, but may reflect minor effects or even increased experimental noise at follow-up.

One second alternative interpretation is that modulation of brain volume abnormalities would be the result of only one of the two specific treatments, either SRI or CBT, rather than reflecting overall effects of clinical improvement *per se*. Indeed, although the voxelwise within-group comparisons of pre- *vs* post-treatment MRI data did not show significant volumetric brain changes after treatment in OCD patients, our exploratory ROI analysis demonstrated a significant left putaminal volume increase after fluoxetine treatment, whereas no volume changes after CBT were observed in any of the brain regions investigated. Interestingly, a longitudinal VBM study reported volume increments in the striatum of OCD children after exposure to selective SRIs (Lazaro *et al*, 2009). It is noteworthy that this finding was obtained only when a less stringent threshold was used. It is possible that GM modifications after treatment were not detectable by VBM because of a limitation of this approach in investigating subtle changes spread throughout large portions of specific GM nuclei (Szeszko *et al*, 2008). In this sense, ROI approaches may be more suitable for detecting subtle GM changes that take place over an entire anatomical brain structure, in contrast to VBM, which requires a more robust GM volume change localized in particular discrete areas. It has been suggested in previous longitudinal morphometric neuroimaging investigations that neurobiological changes after treatment may be specific to SRIs rather than to CBT (Benazon *et al*, 2003; Gilbert *et al*, 2000; Lazaro *et al*, 2009; Rosenberg *et al*, 2000; Szeszko *et al*, 2004). In this regard, given that the majority of longitudinal volumetric studies were performed in children with short illness duration, our findings complement previous data by demonstrating similar results in chronic adult patients. We speculate that different neural pathways and neurotransmitters are associated with each type of intervention. It has been demonstrated that modulations in serotonergic neurotransmission by SRIs mediate neuroplasticity (neurogenesis and gliogenesis) in various cortical and subcortical structures involved in OCD (Czeh *et al*, 2007; Kodama *et al*, 2004; Soumier *et al*, 2009). On the other hand, given the role of the medial prefrontal cortex in the modulation of extinction memory of conditioned fear response (Milad *et al*, 2005, 2007; Phelps *et al*, 2004), it is postulated that the brain sites of action of CBT primarily encompass regions within the medial OFC and rostral/subgenual ACC. In recent years, there has been increasing interest in the glutamatergic system in OCD (MacMaster *et al*, 2008) and its role in extinction learning (Davis and Myers, 2002). Previous studies have shown that glutamatergic manipulation within the medial prefrontal cortex enhances synaptic plasticity and facilitates consolidation of extinction (Burgos-Robles *et al*, 2007).

Finally, although we did document medial OFC and ACC volume abnormalities in OCD patients, there were no GM volume changes after treatment in any regions of the frontal cortex in either the fluoxetine or CBT OCD subgroups. Speculatively, given that SRIs are considered to modulate serotonin transmission earlier in subcortical regions and later in cortical ones (Blier and Bouchard, 1994; el Mansari *et al*, 1995) and that treatment effects with SRIs and CBT can be delayed beyond 12 weeks (Greist *et al*, 1995), volumetric changes in frontal cortical territories may require longer periods to take place. Moreover, given the impossibility of patients to choose the type of treatment, the lack of a within-group CBT effect on MRI volumes could have been due to variability in the engagement to perform that intervention.

Methodological Considerations and Conclusions

The results reported herein must be interpreted with caution because of several limitations. First, the small sample size, mainly in the follow-up arm of the study, may have limited our power to detect differences in other brain regions. Second, the CBT approach was applied in a group setting, which may be different than providing one-to-one treatment. Third, given that we adopted broad inclusion criteria to build a setting closer to clinical practice, our OCD patients presented many comorbidities which may have added variability to our findings. Fourth, our randomized clinical trial did not include a placebo-treated group. Fifth, we did not perform a second MRI scan in controls. Sixth, GM volume within-group differences were only observed in the ROI analyses, whereas no within-group differences were detected in the VBM approach. This limits the robustness of the *post hoc* tests. Therefore, our findings that fluoxetine and CBT may have different treatment effects on the brain should be interpreted as exploratory and deserve replication before generalization.

In conclusion, our results of smaller GM volume in the putamen, medial OFC, and ACC of treatment-naive OCD patients highlight the involvement of orbitofrontal/cingulo-striatal loops in the pathophysiology of OCD. ROI exploratory analyses suggest that fluoxetine and CBT may have distinct neurobiological mechanisms of action. Further MRI studies are warranted using placebo-controlled designs in larger samples of OCD patients, with longer follow-up

periods to allow investigation as to whether GM changes reported herein may be replicated and extended to other brain regions after different treatment interventions.

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DISCLOSURE

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Supplementary Information accompanies the paper on the Neuropsychopharmacology website (http://www.nature.com/npp)