White Matter Changes in OCD Revealed by Diffusion Tensor Imaging

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ABSTRACT

Introduction: The aim of this study was to investigate white matter (WM) abnormalities in obsessive-compulsive disorder (OCD) and its relationship to severity of obsessive-compulsive symptoms.

Methods: Conventional and diffusion tensor imaging were acquired in nine patients with OCD and nine gender- and age-matched healthy volunteers. Changes in fractional anisotropy (FA) and mean diffusivity (MD) were investigated using selected regions of interest (ROIs) analyses and whole brain tract-based spatial statistic analyses. A priori ROIs were placed bilaterally in internal capsule (IC), superior longitudinal fascicule (SLF), cingulate bundle (CB), and corpus calosum (CC).

FOCUS POINTS

- Analyses of white matter (WM) integrity based on regions-of-interest showed that patients with obsessive-compulsive disorder (OCD) exhibited reduced fractional anisotropy values bilaterally in regions of the posterior limb of the internal capsule and in the superior longitudinal fascicle and increased mean diffusivity values bilaterally in the posterior limb of the internal capsule, in the left cingulate bundle and in the splenium of corpus callosum.
- Voxelwise analysis of WM showed that patients with OCD exhibited reduced fractional anisotropy and increased mean diffusivity in regions of the cortical spinal tract (genu and posterior limb of internal capsule and corona radiata) and the superior longitudinal fascicle.
- Severity of obsessive-compulsive symptoms correlated with WM integrity parameters in the left and right anterior limb of the internal capsule, the left and right superior longitudinal fascicle, and the genu of corpus callosum.
Results: ROIs analyses showed that, as compared to healthy volunteers, patients with OCD exhibited reduced FA values bilaterally in regions of the posterior limb of the IC and in the SLF and increased MD values bilaterally in the posterior limb of the IC, in the left CB, and in the splenium of CC. Voxelwise analysis showed that, as compared to controls, patients with OCD exhibited reduced FA and increased MD in regions of the cortical spinal tract (genu and posterior limb of internal capsule and corona radiata) and the SLF. Severity of OCD correlated with WM alterations in different brain regions, ie, the left (rho=0.70 [MD]) and right (rho=0.70 [MD]) anterior limb of the IC, the left (rho=0.97 [MD]) and right SLF (rho=0.81 [MD]), and the genu of CC (rho=0.66 [MD]; rho=0.69 [FA]).

Conclusion: Our findings support the involvement of different WM tracts in OCD and suggest that greater impairment in WM integrity is associated with increased severity of OCD symptoms.


INTRODUCTION

Obsessive-compulsive disorder (OCD) is characterized by recurrent, persistent, and unwanted thoughts, impulses, or images (ie, obsessions) and repetitive behaviors that include, among others, persistent hand washing, checking, and ordering (ie, compulsions). To meet current diagnostic criteria for OCD, a patient must display either obsessions and/or compulsions that result in marked anxiety or distress, are time consuming (take >1 hour a day), or significantly interfere with the person’s normal routine, occupational (or academic) functioning, or usual social activities or relationships.1

Recently, it has been debated whether OCD is really more common than previously thought. For example, while some studies conducted in North-American samples have suggested that the prevalence of OCD may reach up to 3.1% of the general population, surveys in other countries found rates as low as 0.3%.2 Apart from these epidemiological inconsistencies, it is clear that a significant number of individuals in the community suffer from OCD. Therefore, the identification of the etiological factors and the resulting pathophysiological mechanisms involved in this complex disorder is critical for the development of effective treatment programs.

Indeed, evidence from cognitive and neuroimaging studies (functional and structural magnetic resonance imaging [MRI] and positron emission tomography [PET]) have generally supported existence of functional and structural abnormalities in orbitofrontal cortex, the striatum, and the thalamic grey matter in patients with OCD.3 Based on a frontal-striatal model of OCD, one might predict the existence of abnormalities in the white matter (WM) tracts that connect these structures. Only a handful of voxel-based morphology (VBM) studies have examined WM abnormalities in OCD. Unfortunately, these VBM results have been rather inconsistent. While some VBM studies suggest the presence of WM abnormalities in OCD,4-6 others did not show any significant difference from controls.7,8

More recently, diffusion tensor imaging studies have shown variable fractional anisotropy (FA, a measure of WM integrity) values in different brain regions of patients with OCD, including the anterior cingulate and the internal capsule,9-12 the bilateral semioval center extending to the medial frontal WM; the subinsular WM;13 the corpus callosum12,14; and the parietal WM.3 Some findings suggest that WM abnormalities in OCD may be familial,3 responsive to serotonin reuptake inhibitors (SRIs) treatment,12 and vary according to the severity of different symptom dimensions10,15 and global obsessive-compulsive symptoms.16 Indeed, the gene for oligodendrocyte lineage transcription factor 2, an essential regulator in the development of cells that produce WM (myelin) that is highly expressed in the amygdala, thalamus, and caudate nuclei, has been associated with OCD, particularly in those without Tourette syndrome.17

Despite diffusion tensor imaging (DTI) findings arguing for the occurrence of WM abnormalities in patients with OCD, it is clear that the regions affected by these variations in WM integrity varied to a great extent, limiting our ability to draw conclusions from the existing body of DTI work in OCD. These heterogeneous findings may stem from difficulties in anatomically registering DTI data. Indeed, none of these studies in OCD...
samples have provided non-arbitrary and satisfactory solutions to the question of how to align FA images from multiple subjects in a way that allows for valid conclusions to be drawn from the subsequent voxelwise analysis. Tract-based Spatial Statistics (TBSS) aims to improve the sensitivity, objectivity and interpretability of analysis of multi-subject diffusion imaging studies by carefully tuned nonlinear registration, followed by projection onto an alignment-invariant tract representation (the “mean FA skeleton”).

In this preliminary report, we aimed to investigate the occurrence of WM abnormalities in OCD using two approaches: selected regions of interest (ROIs) analysis and voxelwise whole-brain TBSS analysis. The ROIs were chosen according to traditional fronto-striatal OCD models and recent findings suggesting the involvement of more posterior areas (ie, parietal lobes) in the pathophysiology of OCD, while the voxelwise whole-brain method was adopted to confirm previous findings and capture additional abnormalities that were not addressed by the previous method.

**METHODS**

**Patients’ Clinical Assessment**

Individuals with OCD were consecutively recruited among those seeking treatment in the first author’s private practice or in Anxiety and Depression Research Program of the Federal University of Rio de Janeiro. The inclusion criteria comprised: having OCD as the most significant current psychiatric diagnosis, between 17–65 years of age, and being capable of reading and filling out forms. Exclusion criteria included patients who had cardiac pacemakers, metallic clips, or any other metallic implants or artifacts. Healthy volunteers were matched one-to-one in age, sex, and handedness with the patients with OCD. A local institutional review board approved the research protocol. All participants have provided their signed informed consent before the procedures were fully explained.

**Data Acquisition**

Anatomical images were obtained with a 1.5 Tesla Philips-Intera scanner, using the following pulse sequences: spin-echo T1 weighted (repetition time [TR]/echo time [TE]/Matrix/field of view [FOV]=550 ms/20 ms/256x256/240 mm), turbo spin-echo T2 weighted (TR/TE/Matrix/FOV=3,500 ms/90 ms/256x256/256 mm), inversion recovery T1 weighted (TR/TE/TI/Matrix/FOV=3,000 ms/30 ms/300 ms/256x256/256 mm), and fluid attenuate inversion recovery (FLAIR) (TR/TE/inversion time [TI]/Matrix/FOV=9,000 ms/100 ms/2,300 ms/256x256/256 mm), all with a slice thickness of 5 mm without gap. Diffusion-weighted images (DWIs) were acquired in axial plane with a single-shot, spin-echo echoplanar sequences: Axial: TR/TE=4,000/110 ms, FOV=256 mm, matrix=112x128, slice thickness=5 mm without gap; Sagittal: TR/TE=4,491/121 ms, FOV=256 mm, matrix=112x128, slice thickness=5 mm without gap. Diffusion sensitization gradients were applied in six non-collinear directions (x, y, z, xy, yz, xz), with a b factor of 800 sec/mm².

**Diffusion Tensor Image Post-processing**

Prior to analysis, patients and healthy volunteers datasets were anonymized and randomized across the subjects and groups (I. E. B.). For each subject and before estimating the specific diffusion maps, all diffusion images were visually inspected for artifacts. Non-diffusion and diffusion images were co-registered to correct for movement artifacts and eddy current distortion effects on echo planar imaging readout. The diffusion tensor for each voxel was calculated based on
the eigenvectors (v1, v2, v3) and eigenvalues (λ1, λ2, λ3) using multivariate fitting and diagonalization. After the fractional anisotropy (FA) and mean diffusivity (MD) maps were calculated from the eigenvalues, color-coded maps were generated from the FA values and three vector elements of v1 to visualize the WM tract orientation (FSL 4.0, FMRIB software).24,25 FA and MD images were brain-extracted (Brain Extraction Tool, FSL) and registered to a common space (Montreal Neurological Institute Template or MNI152) using constrained nonlinear registration (BET, DTIFit toolbox, part of FSL 4.0, FMRIB software).26 The derived FA and MD data were further analyzed using two approaches: a priori ROIs24,27 analyses and the voxelwise whole-brain TBSS.18-28

**ROI Analysis**

ROIs were placed by an experienced neuroimaging investigator (F.T.M.) using a DTI-MRI atlas of human WM for determining fiber tract orientation29 using ROI Editor/DTI Studio software.24 For each subject, fixed-size square ROIs (25 pixels) were outlined on the color-coded FA maps in the axial plane. The ROIs were placed along the genu and splenium of corpus callosum (CC), anterior and posterior limb of internal capsule (IC), superior longitudinal fascicule (SLF) and cingulate bundle (CB) (Figure 1). The ROIs were automatically loaded onto the FA and MD maps and visually checked to confirm their location and ensure that partial volume effects were minimized. Care was taken to standardize the position of ROIs and ensure that each ROI contained homogeneous fiber populations. The mean values and standard deviation of FA and MD measures within each ROI were automatically recorded (Figure 1).

Group comparisons including all ROIs (repeated) on the right and left hemispheres (repeated) for both the FA and MD values were done using Student’s t-tests (P<.05). In patients, correlation analyses were conducted using the parametric Pearson’s coefficient followed by confirmatory non-parametric Spearman’s coefficient to investigate relations between DTI-derived metrics (FA and MD) and clinical metrics (Y-BOCS).

**Voxelwise Whole-brain Analysis**

To assess the global differences in the WM fiber tracts between the patients and healthy volunteer groups, whole-brain voxelwise statistical analyses of FA and MD data were conducted using TBSS.30 To preserve the original WM structure, keeping the overall tracts intact as much as possible, a voxelwise specific-tuned nonlinear registration method were using to align all subjects FA and MD images into a standard space (using Image Registration Toolkit software).26 All subjects FA images were aligned to the first subject FA image, acting as the reference target FA; this target image is then affine-aligned into MNI152 standard and upsampled to 1x1x1mm (using both the non-segmented and segmented 1x1x1mm MNI152 T1 brain volume); then, both the nonlinear and affine transformations from the target image were applied to each FA subject’s images. All upsampled aligned FA images were averaged to create the mean FA from the whole subjects. The mean FA image was used to generate the mean FA “skeleton” tract, which represents the most “common” tracts along all subjects (the centers of all tracts common to all subjects).18 A suitable threshold was applied (FA>0.2) to restrict the statistical analysis only to WM voxels that were successfully aligned across subjects, maintaining only the subject’s major tract structures. To visually inspect the quality of the alignment between all FA images, after the registration, the mean FA skeleton was displayed on the top of each subject’s aligned FA image to certify that, in general, each subject’s major tracts were well aligned to the corresponding segments of the skeleton. Importantly, our skeleton threshold prevented us from extending beyond the edge of the skeleton, where there is too much cross-subject variability and where the nonlinear registration has not been able to achieve good alignment. Therefore, the peripheral WM tracts (FA<0.2) were, by definition, excluded from further statistical analysis. Finally, each subject’s aligned FA data was “projected” into the mean FA skeleton mask, generating the final projected “skeletonized” FA data.26 Although these parameters were chosen as to be consistent with current approaches using TBSS, it should be emphasized that some limitations may apply. As stated above, this approach is not optimum to assess changes in peripheral regions of the WM tracts and some recent developments may offer improvements.31 To test for significant local FA and MD differences between the healthy and OCD groups, voxelwise cross-subject statistical analysis was made using permutation-based non-parametric inference (5,000 random permutations) on each point of the
resulting “skeletonised” subject’s data, 32 generating the statistical maps \( P<.05 \), fully corrected for multiple comparisons. Although the overlay of the statistical images onto the FA skeleton represents the preformed statistical analysis, the statistical map was “thickened” using spatial smoothing (full width at half maximum=3mm) in order to improve visualization.

**RESULTS**

**Clinical Assessment**

A comparison between the main age, gender, and handedness exhibited by patients with OCD and healthy volunteers is depicted in the Table 1. Data on age at onset of OCD, Y-BOCS, BDI, and CGI scores is described on Table 2.

Besides having OCD as their primary psychiatric disorder, other psychiatric disorders presented by our patients included major depressive disorder \( n=2 \), Tourette syndrome \( n=2 \), panic disorder \( n=1 \), generalized anxiety disorder \( n=1 \), and binge eating disorder \( n=1 \). At the time of the MRI, seven patients were receiving medication for OCD, including fluvoxamine \( n=2 \); sertraline \( n=1 \); clomipramine \( n=1 \); fluoxetine \( n=1 \); paroxetine \( n=1 \); and escitalopram \( n=1 \). In 4 patients, OCD followed a chronic, treatment-resistant course.

**DTI ROIs Analysis**

As shown in Figure 2A, FA values were lower in patients than in healthy volunteers in regions of the posterior limb of the IC \( P=.0017 \) and right hemispheres \( P=.0023 \) and in the SLF \( P=.0054 \) and right hemispheres \( P=.014 \). As shown in Figure 2B, MD values were higher in patients than in healthy volunteers in regions of the posterior limb of the IC \( P=.00012 \) and right hemisphere \( P=.046 \), in the left CB \( P=.0018 \) and splenium of CC \( P=.040 \).

**DTI Voxelwise Whole-brain Analysis**

Voxelwise analysis showed reduced FA and increased MD in regions of the cortical spinal tract (genu and posterior limb of internal capsule and corona radiata) and SLF in OCD patients compared to healthy volunteers (Figure 3).

**Correlation Between DTI Parameters and Clinical Data**

Correlations were found between the severity of OCD measured by Y-BOCS and WM integrity measured by DTI parameters in different brain regions. Of note, all significant correlations according to the parametric Pearson's coefficient remained significant according to confirmatory non-parametric Spearman's coefficient. Changes in FA in the genu of CC were correlated to total Y-BOCS \( r=–.81; P=.016; \rho=–.69; P=.029 \). Overall Y-BOCS was positively correlated to MD values in the genu of CC \( r=.78; P=.023; \rho=.66; P=.035 \), in the anterior limb of the IC \( r=.73; P=.042; \rho=.69; P=.029 \) and left \( r=.79; P=.019; \rho=.69; P=.029 \) hemispheres and in the SLF \( r=.83; P=.010; \rho=.81; P=.007 \) and left \( r=.96; P<.001; \rho=.97; P<.001 \) hemispheres. The relationship between the severity of OCD measured by Y-BOCS and WM integrity measured

**TABLE 1**

**Comparison of Sociodemographic Features Between Groups**

<table>
<thead>
<tr>
<th>Feature</th>
<th>Patients with OCD (SD)</th>
<th>Healthy volunteers (SD)</th>
<th>Mann-Whitney or Fisher Test results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>26.2 (10.4)</td>
<td>28.0 (10.2)</td>
<td>( P=.28 )</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>7/2</td>
<td>7/2</td>
<td>( P=1.0 )</td>
</tr>
<tr>
<td>Handedness (right/left handed)</td>
<td>9/0</td>
<td>9/0</td>
<td>Not applicable</td>
</tr>
</tbody>
</table>

OCD=obsessive-compulsive disorder.


**TABLE 2**

**Description of Some OCD Patients’ Clinical Features**

<table>
<thead>
<tr>
<th>Feature</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at onset of OCS (years)</td>
<td>11.5 (5.0)</td>
</tr>
<tr>
<td>Y-BOCS scores</td>
<td>13.4 (2.8)</td>
</tr>
<tr>
<td>Obsessions</td>
<td>14.9 (2.3)</td>
</tr>
<tr>
<td>Compulsions</td>
<td>28.5 (4.8)</td>
</tr>
<tr>
<td>Total</td>
<td>5.2 (0.4)</td>
</tr>
<tr>
<td>CGI scores</td>
<td>13.4 (7.2)</td>
</tr>
<tr>
<td>BDI scores</td>
<td>3.5 (1.2)</td>
</tr>
</tbody>
</table>

OCD=obsessive-compulsive disorder; OCS=obsessive-compulsive symptoms; Y-BOCS=Yale-Brown Obessive-Compulsive Scale; CGI=Clinical Global Impression; BDI=Beck Depression Inventory.

by DTI parameters in different brain regions is depicted in Figure 4.

**DISCUSSION**

Although some studies have employed DTI to investigate the WM involvement in OCD, the findings of these studies have been inconsistent so far. The impact of specific tracts abnormalities in the severity of symptoms remains unclear. In this preliminary report, we employed DTI to investigate structural WM changes in OCD patients using two approaches: selected ROIs analysis and whole brain voxelwise analysis (TBSS). The main findings were: in both approaches, DTI-derived metrics (FA and MD) were sensitive to detect changes in major WM tracts in patients compared to controls, and changes in DTI-derived metrics in the genu of CC, SLF and anterior limb of IC correlated to patients’ severity of obsessive-compulsive symptoms.

Our finding of a significant relationship between the severity of obsessive-compulsive symptoms and the WM integrity in the anterior portions of the IC is consistent with previous studies. Although not previously reported, our results showing that patients with OCD exhibit reduced FA and increased MD in the posterior limb of IC are consistent with previous investigations showing that these structures enclose parts of the thalamocortical pathways. These thalamic radiations include fibers connecting the ventrolateral, ventral anterior, and ventral posterior nuclei of the thalamus and the prefrontal cortex. Earlier studies have confirmed that capsular genu infarcts lead to a functional deactivation of the ipsilateral frontal cortex, thus leading to a “thalamocortical disconnection syndrome”.

Our findings with regard to the IC dovetail with current models suggesting the occurrence of a hypoactivity of frontal-striatal circuits, particularly the so-called “indirect” pathways, among patients with OCD.

We also found that patients with OCD exhibited reduced FA and increased MD in the SLF, ie, a heterogeneous set of bi-directional fibers that connects the postrolandic regions (ie, parieto-temporal association areas) with distinctive areas of the prefrontal cortex and vice versa.

**FIGURE 1**

**ROIs placement on the FA-weighted color-coded maps**

ROIs were placed in the axial or coronal planes on the FA-weighted color-coded maps and automatically transferred onto the FA and MD maps. ROIs were placed in the genu and splenium of CC and bilateral anterior and posterior limb of IC, bilateral SLF, and bilateral CB.


**FIGURE 2.**

**ROI differences in FA and MD maps**

A. Fractional Anisotropy

B. Mean Diffusivity

Data displayed are mean and standard deviation.

(A) FA values are dimensionless.

(B) MD values are given in mm²/s x 10-3. Significant differences between patients and controls measurements are marked in the figure. Cing R (right CB); Cing L (left CB); Ant IC R (right anterior limb of IC); Ant IC L (left anterior limb of IC); Post IC R (right posterior limb of IC); Post IC L (left posterior limb of IC); SLF R (right longitudinal SLF); SLF L (left SLF); Genu CC (genu of the CC); Splen CC (splenium of CC).

* P<.05
† P<.005

ROIs=regions of interest; FA=fractional anisotropy; MD=mean diffusivity; CC=corpus calosum; IC=internal capsule; SLF=superior longitudinal fascicule; CB=cingulate bundle.

A significant correlation between MD and the severity of OCD symptoms was also found in these fibers. These results are consistent with the increasingly recognized role played by posterior brain regions, particularly the angular and supramarginal gyrus, in OCD. Parietal systems are related to several cognitive abilities that may underlie the clinical expression of obsessions and compulsions (including executive functioning, response inhibition, and visuospatial processing). While some patients have developed OCD after parietal vascular lesions, a variety of functional and structural neuroimaging data support the role of parietal dysfunction in primary OCD, including findings from studies with single photon emission tomography (SPECT), PET; functional MRI (fMRI); magnetic resonance spectroscopy; and voxel based morphometry (VBM). Recent studies suggest that this parietal dysfunction in OCD may be familial, positively correlated with the “symmetry/ordering” dimension scores and amenable to treatment with serotonin reuptake inhibitors.

In our study, patients with OCD displayed higher MD values in the left CB than those exhibited by healthy controls. Indeed, it has been demonstrated that neurons from the anterior CB act as salience detectors when faced with conflict and difficult or emotional stimuli. The CB has been reported to be either structurally and functionally abnormal in previous studies employing DTI, VBM, SPECT, fMRI, and PET in OCD. Nevertheless, the exact type of such abnormality is presently not entirely clear. For example, some DTI studies concur with ours in that patients with OCD exhibited reduced anisotropy in the CB, either bilaterally or in the left CB, especially among individuals with the predominance of aggressive obsessions and checking compulsions. In contrast, Cannistraro and colleagues reported higher FA in the left CB of patients with OCD, whereas Duran and colleagues were unable to find any specific WM volume deficits in both CBs in their VBM study. Possible explana-
Our study has several limitations. We could not clarify whether the WM abnormalities observed in the aforementioned regions reflect the primary phenomenon on the pathophysiology of OCD or a just a consequence of severe OCD symptoms. We enrolled a small number of clinically heterogeneous subjects under different doses of distinct types of serotonin reuptake inhibitors. The TBSS method may be less sensitive where the WM is less compact (ie, outside the “WM skeleton”) for. The effects observed in ROIs that were not detected by the TBSS analysis should be considered of preliminary nature, and must therefore be replicated in future studies. Finally, we were unable to evaluate the impact of several interesting and potential confounding factors (such as the predominance of different dimensions of obsessive-compulsive symptoms) on our DTI findings. As reported above, emerging evidence suggest that different symptoms dimensions of OCD may be associated with distinctive types of WM deficiency.

CONCLUSION

By using TBSS and ROI analysis, our findings provide support to the contention that OCD may be associated with different patterns of WM abnormalities in the IC, the SLF, the CB, and the CC. Importantly, changes in IC, SLF and genu of CC were correlated to severity of obsessive-compulsive symptoms. Taken together, these results add to the evidence that OCD is associated with large-scale disruption in brain systems or networks that extends beyond the more traditional fronto-striatal models. Additional DTI studies are warranted to extend these preliminary findings to patients with different obsessive-compulsive symptom dimensions.

REFERENCES


