White matter microstructure in patients with obsessive–compulsive disorder

Emre Bora, MD; Ben J. Harrison, PhD; Alex Fornito, PhD; Luca Cocchi, PhD; Jesus Pujol, MD; Leonardo F. Fontenelle, MD; Dennis Velakoulis, MD; Christos Pantelis, MD; Murat Yücel, PhD, MAPS

Bora, Harrison, Fornito, Cocchi, Velakoulis, Pantelis, Yücel — Melbourne Neuropsychiatry Centre, Department of Psychiatry, University of Melbourne and Melbourne Health, Victoria, Australia; Fornito — Brain Mapping Unit, Department of Psychiatry, University of Cambridge, UK; Pujol — Institut d’Alta Tecnologia–Parc de Recerca Biomèdica de Barcelona, Centro Radiologico Computerizado Corporación Sanitaria, Barcelona, Spain; Fontenelle — Anxiety and Depression Research Program Institute of Psychiatry (IPUB), Federal University of Rio de Janeiro (UFRJ), Rio de Janeiro-RJ, Brazil; Yücel — Orygen Youth Health Research Centre, Centre for Youth Mental Health, University of Melbourne, Victoria, Australia

Introduction

Most widely accepted models of obsessive–compulsive disorder (OCD) suggest that abnormalities of cortico–striatal circuits involving the orbitofrontal cortex, anterior cingulate cortex, thalamus and striatum play an important role in its pathophysiology. However, recent studies employing whole-brain analyses also indicate more distributed neuroimaging alterations in patients with OCD, implicating parietal, insular and cerebellar regions. One potential explanation of these findings might be abnormality in white matter tracts, which can lead to abnormal connectivity between diverse brain regions.

Diffusion tensor imaging (DTI) is a magnetic resonance imaging (MRI) technique that is suitable for quantitatively investigating whole-brain white matter axonal integrity in vivo. It is based on the measurement of water molecule motion. Axonal structure restricts water diffusion such that it is greater in the axis parallel to the main axis of axons. Fractional anisotropy is a measure of the degree to which water diffusion is constrained in the brain and is widely used as a general index of axonal integrity. Component measures from which fractional anisotropy is derived, the so-called first ($\lambda_1$), second ($\lambda_2$) and third ($\lambda_3$) principal eigenvalues, measure diffusion axial (parallel; $\lambda_1$) and radial (perpendicular; $\lambda = (\lambda_2 + \lambda_3)/2$) to the primary axis of the axon. Previous studies showed that whereas axonal damage leads to marked decrease in $\lambda_1$ (and modest or absent decrease in $\lambda$), demyelination increases $\lambda$ without changing $\lambda_1$. Therefore, axial and radial diffusivity measures provide insights into the specific nature of white matter deficits; the former provides an index of axonal injury, whereas the latter is sensitive to changes in myelination.

To date, 8 studies have examined white matter pathology in patients with OCD using DTI. However, the findings of these studies have been variable (Table 1), and no study has
examined whether axonal injury or abnormal myelination explains the observed findings. In this study, our aim was to extend previous work and to examine alterations in fractional anisotropy as well as measures of axial and radial diffusivity in a sample of patients with OCD and healthy controls using a well-validated Tract-Based Spatial Statistics (TBSS) technique.

**Methods**

**Participants**

We recruited patients with OCD and matched healthy controls. Inclusion criteria for patients with OCD were:
- to be free of medications or to be stable on their medication for at least 1 month,
- to have no other current Axis-I psychiatric diagnosis, and
- to have a current intelligence quotient (IQ) greater than 80.

All patients with a history of neurologic disease, impaired thyroid function and steroid use were excluded. All patients were interviewed with the Structured Clinical Interview for DSM-IV Axis I Disorders, Patient version for diagnosis. The control group underwent the Structured Clinical Interview for DSM-IV Axis I Disorders, Nonpatient edition. General intelligence was assessed using the Wechsler Abbreviated Scale of Intelligence (WASI). The Yale–Brown Obsessive Compulsive Scale (Y–BOCS) was used to assess OCD symptoms within 1 week before scanning. Patients (and controls) were also assessed with Beck Depression Inventory and Beck Anxiety Inventory. All participants gave written informed consent to participate in the study. The study was approved by the Mental Health Research Institute Behavioural and Research Ethics Committee.

**Imaging protocol**

Magnetic resonance imaging was performed using a 3 T GE Signa LX whole-body scanner. Head motion was restricted using a Velcro strap over the forehead. We acquired diffusion imaging data in 28 diffusion gradient directions plus 5 b = 0 reference images using a sequence optimized to collect diffusion-weighted images (repetition time [TR] 6000 ms, echo time [TE] 90 ms, voxel size 1.875 × 1.875 × 2 mm). Data were transferred to a Linux 2.4.27 workstation for image processing and analyses.

**Table 1: Previous diffusion tensor imaging studies in patients with obsessive–compulsive disorder**

<table>
<thead>
<tr>
<th>Study</th>
<th>Groups</th>
<th>Sample characteristics</th>
<th>MRI method</th>
<th>Mean Y–BOCS score</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Szesko et al.11</td>
<td>15 OCD</td>
<td>9 of 15 no comorbid Axis-I diagnoses</td>
<td>VBM</td>
<td>25.9 (mixed OCD symptoms)</td>
<td>FA decrease in bilateral anterior cingulate, parietal, right posterior cingulate, left occipital white matter</td>
</tr>
<tr>
<td></td>
<td>15 HC</td>
<td>Other mood and anxiety disorders</td>
<td>p &lt; 0.001 uncorrected, &gt; 20 voxels</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cannistraro et al.14</td>
<td>8 OCD</td>
<td>No additional Axis-I diagnosis</td>
<td>VBM + ROI, focused on ALIC, cingulum bundle</td>
<td>23.0 (all &gt; 15)</td>
<td>Increased FA in left ALIC and cingulum bundle, decreased FA in right cingulum bundle with very small number of voxels (31–86)</td>
</tr>
<tr>
<td></td>
<td>10 HC</td>
<td>Free of medication for at least 1 mo</td>
<td>Clusters of p &lt; 0.05 and &gt; 20 voxels chosen then subject to cluster level p &lt; 0.005 uncorrected t-test</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yoo et al.22</td>
<td>13 OCD</td>
<td>10 of 13 no Axis-I diagnosis</td>
<td>VBM at baseline, 12 wk after treatment</td>
<td>22.9 (mixed OCD symptoms)</td>
<td>Baseline FA increase in CC, internal capsule and area superolateral to right cingulate</td>
</tr>
<tr>
<td></td>
<td>13 HC</td>
<td>Medication-naive at the beginning</td>
<td>p &lt; 0.001 uncorrected, &gt; 20 voxels</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Menzies et al.13</td>
<td>30 OCD</td>
<td>21 of 30 medicated</td>
<td>VBM + ROI</td>
<td>22.1</td>
<td>Decreased FA in right inferior parietal cortex and increased FA in right medial frontal cortex</td>
</tr>
<tr>
<td></td>
<td>30 HC</td>
<td>No Axis-I diagnosis</td>
<td>p &lt; 0.017 cluster-level corrected</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nakamae et al.19</td>
<td>15 OCD</td>
<td>All medicated</td>
<td>VBM</td>
<td>29.0 (mixed OCD symptoms)</td>
<td>Increased FA in bilateral semioval centre</td>
</tr>
<tr>
<td></td>
<td>15 HC</td>
<td>13 of 15 free of additional Axis-I diagnosis</td>
<td>p &lt; 0.001 uncorrected, 100 voxels</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saito et al.20</td>
<td>16 OCD</td>
<td>13 of 16 medicated</td>
<td>ROI corpus callosum</td>
<td>26.0</td>
<td>FA is decreased in rostrum</td>
</tr>
<tr>
<td></td>
<td>16 HC</td>
<td>No depression or panic disorder</td>
<td>Higher apparent diffusion coefficient in medial frontal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ha et al.19</td>
<td>25 OCD</td>
<td>All men</td>
<td>VBM</td>
<td>20.2</td>
<td>Left anterior cingulate FA reduction (37 voxels)</td>
</tr>
<tr>
<td></td>
<td>25 HC</td>
<td>No clinical depression</td>
<td>p &lt; 0.001 uncorrected, 15 contiguous voxels</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Garibotto et al.17</td>
<td>15 OCD</td>
<td>All men</td>
<td>VBM</td>
<td>28.2</td>
<td>FA reduced in CC (splenium) cingulum bundle, SLF, optic radiation, inferior fronto-occipital fascicule</td>
</tr>
<tr>
<td></td>
<td>16 HC</td>
<td>13 of 15 on medication</td>
<td>p &lt; 0.005 uncorrected, 20 voxels, PDD p &lt; 0.01</td>
<td></td>
<td></td>
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</tbody>
</table>

| ALIC = anterior limb of internal capsule; CC = corpus callosum; FA = fractional anisotropy; HC = healthy controls; MRI = magnetic resonance imaging; OCD = obsessive–compulsive disorder; PDD = principal diffusion direction; ROI = region of interest; SLF = superior longitudinal fascicle; VBM = voxel-based morphometry; Y–BOCS = Yale–Brown Obsessive Compulsive Scale.23 |

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Data analysis

We used the FMRIB Diffusion Toolbox, part of the FMRIB software library, to analyze DTI data.\textsuperscript{32} Diffusion-weighted volumes were corrected for Eddy current distortions and head motion. A diffusion tensor model was fit at each voxel, and fractional anisotropy $\lambda_1$, $\lambda_2$, $\lambda_3$ maps were generated.\textsuperscript{26} We used fractional anisotropy axial ($\lambda_1$) and radial (average of $\lambda_2$ and $\lambda_3$) diffusivity maps for further analyses.

Tract-based fractional anisotropy, axial and radial components of patient and control groups were calculated with TBSS.\textsuperscript{34} Fractional anisotropy data were aligned to a standard space (Montreal Neurological Institute 152) fractional anisotropy target by using a nonlinear registration method implemented in the FMRIB software library. A mean fractional anisotropy image was created from all participants, and then the mean image was thinned to create a mean fractional anisotropy skeleton that represented the centres of all tracts common to the participants. This image was thinned to 0.2, then each participant’s aligned fractional anisotropy data were projected onto this skeleton.

Statistical analysis

We used a permutation-based parametric inference method with Randomize V2.1 software to analyze between-group differences.\textsuperscript{33} We performed corrections for multiple comparisons with an initial cluster-forming threshold of $t = 2.0$. We considered results to be significant at $p < 0.05$. For the clusters where we observed significant decreases of fractional anisotropy in patients with OCD, axial and radial diffusivity values were extracted from these clusters for each individual and further analyzed in SPSS 14.0 using Student $t$ tests.

Results

We included 21 patients with OCD and 29 healthy controls in our study. Ten patients were receiving stable doses of medication (selective serotonin reuptake inhibitor $n = 6$, chlorimipramine $n = 3$, venlafaxine $n = 1$). One of the patients had an incidental MRI finding without any clinical sign (possible ischemic lesion in the superior parietal area). The overall Y–BOCS scores of the patient group indicated a mild to moderate degree of symptom severity (mean 19.2, standard deviation [SD] 5.4).

There were no significant between-group differences for age, sex, years of education and IQ (Table 2). There were no significant differences for Y–BOCS between male and female patients with OCD. Patients tended to present with higher levels of subthreshold anxiety ($t_{19} = 2.1, p = 0.05$) and depression symptoms ($t_{19} = 2.1, p = 0.06$).

Tract-Based Spatial Statistics analysis showed a significant between-group difference in only 1 region (Fig. 1). Patients with OCD had lower fractional anisotropy values in the body of the corpus callosum (CC). Excluding the single participant with incidental imaging findings did not change the results. Radial diffusivity in this region was increased in patients with OCD ($t_{19} = 2.9, p = 0.006$), but there were no between-group differences for axial diffusivity ($t_{19} = -0.91, p = 0.36$). Fractional anisotropy reduction in the midbody of the CC was not significantly different between male and female participants ($t_{19} = 0.6, p = 0.55$) and medicated and unmedicated patients ($t_{19} = 0.6, p = 0.54$). In voxel-wise correlation analyses, OCD, depression and anxiety symptoms were not associated with significant changes in white matter connectivity in any of the voxels, including the body of the CC.

Table 2: Demographic and clinical characteristics of patients with obsessive–compulsive disorder (OCD) and healthy controls

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Group; mean (SD)*</th>
<th>$p$ value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, male:female</td>
<td>OCD, $n = 21$</td>
<td>OCD, $n = 21$</td>
</tr>
<tr>
<td>Sex</td>
<td>11:10</td>
<td>14:15</td>
</tr>
<tr>
<td>Age, yr</td>
<td>34.4 (10.6)</td>
<td>31.4 (8.0)</td>
</tr>
<tr>
<td>Education, yr</td>
<td>14.6 (2.2)</td>
<td>15.0 (2.3)</td>
</tr>
<tr>
<td>Full-scale IQ</td>
<td>110.7 (8.1)</td>
<td>113 (10.9)</td>
</tr>
<tr>
<td>Y–BOCS score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>19.2 (5.4)</td>
<td></td>
</tr>
<tr>
<td>Obsessive subscale</td>
<td>9.3 (3.3)</td>
<td></td>
</tr>
<tr>
<td>Compulsive subscale</td>
<td>9.9 (2.6)</td>
<td></td>
</tr>
<tr>
<td>BDI score</td>
<td>10.0 (8.3)</td>
<td>5.9 (5.5)</td>
</tr>
<tr>
<td>BAI score</td>
<td>10.4 (9.0)</td>
<td>5.8 (5.8)</td>
</tr>
</tbody>
</table>

BAI = Beck Anxiety Inventory; BDI = Beck Depression Inventory; IQ = intelligence quotient; Y–BOCS = Yale-Brown Obsessive Compulsive Scale; SD = standard deviation.

*Unless otherwise indicated.
†Student $t$ test or $\chi^2$ test (for sex).
Discussion

Several DTI studies have previously reported CC abnormalities in patients with OCD. However, to our knowledge, no studies to date have investigated the axonal versus myelin contributions to the identified abnormalities in white matter integrity. By examining axial and radial diffusivity in patients with OCD, we have demonstrated that impaired white matter integrity in the body of the CC in this patient group is driven by a myelin abnormality. This finding is consistent with preliminary genetic data suggesting that polymorphism of a gene that is an important regulator for the development of cells producing myelin is associated with OCD. Myelination in some brain regions such as the CC continues into adolescence and early adulthood, a period during which the onset of OCD is typically observed. As such, neurodevelopmental irregularities leading to abnormal myelination might have a role in the pathophysiology of OCD. However, this hypothesis needs support with longitudinal and postmortem studies.

The CC body includes interhemispheric fibres connecting associative areas in parietal lobes in both sides of the brain. Despite not being part of traditional OCD networks, there is increasing evidence for parietal lobe abnormalities in patients with OCD, and OCD has been reported in patients with right parietal multiple sclerosis. The parietal lobe was also found to be the only region in which white matter connectivity was decreased in relatives of patients with OCD. Neurocognitive studies also suggest parietal dysfunction in patients with OCD. In this study, we did not find any white matter deficit of the parietal lobe itself, but this might reflect the fact that TBS S only assesses the most common fibre pathways across individuals, typically excluding fibres penetrating the cortical mantle; thus, our methodology may have limited sensitivity in regions near the grey/white matter boundary. It is also possible that we were unable to detect white matter abnormalities in broader regions inside and outside of the CC owing to the inclusion of patients with less severe obsessive-compulsive symptoms in the current study. Previous studies that have detected such abnormalities have typically included patients with more severe obsessive-compulsive symptoms.

Previous DTI studies of patients with OCD have reported variable findings. Some have found abnormalities in different regions (white matter tracts within the anterior cingulate, medial frontal and occipital cortices). Furthermore, the direction of the changes has been conflicting. For example, fractional anisotropy was reported to be both decreased and increased for the anterior cingulum bundle. Methodological differences can explain some of these findings; only 1 of these studies corrected their findings, and the sample sizes of most studies have been small (n < 15). Potential misalignment of the white matter tracts, medication effects and differences in the content and severity of obsessive-compulsive symptoms might be other issues that can explain inconsistent findings.

Limitations

One of the limitations of our study is its cross-sectional nature. Also, the potential effect of antidepressant treatment is another issue. In our study, we found no differences between medicated and unmedicated patients, suggesting our results are not attributable to such effects. However, our method for examining the effect of medication was not optimal since currently unmedicated patients were not medication-naive. Another potential issue relates to the influence of history of comorbid depression, as indicated by recent structural neuroimaging work in patients with OCD. In this study, only current comorbid depression was considered as an exclusion criterion. Therefore, follow-up studies investigating the effects of illness-related factors and treatment are necessary to better understand the nature of white matter abnormalities in patients with OCD.

Conclusion

Studies with larger sample sizes to examine potential differences with respect to OCD patient subtypes or major symptom dimensions will be a valuable extension of the current work. Other DTI methods like tractography could provide information about the integrity of individual white matter tracts.

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Contributors: Drs. Bora and Yücel designed the study. Dr. Yücel acquired the data. All authors analyzed the data and approved publication of the article. Drs. Bora and Forino wrote the article, which Drs. Bora, Harrison, Forino, Cocchi, Pujol, Fontenelle, Velakoulis, Pantelis and Yücel critically reviewed.

References


