White matter microstructure and connectivity in patients with obsessive compulsive disorder and their unaffected siblings

Short/running title: White matter in OCD patients and their siblings

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Acknowledgements:

This work was supported by Research Fund of Izmir Katip Celebi University (Project number: 2016-GAP-TIPF-0024).

Conflict of Interest Statement:

None

Abstract

Objective: We aimed to examine white matter microstructure and connectivity in individuals with obsessive-compulsive disorder (OCD) and their unaffected siblings, relative to healthy controls.
Methods: Diffusion-weighted magnetic resonance imaging (dMRI) scans were acquired in 30 patients with OCD, 21 unaffected siblings and 31 controls. We examined white matter microstructure using measures of fractional anisotropy (FA), radial diffusivity (RD) and axial diffusivity (AD). Structural networks were examined using network-based statistic (NBS).

Results: Compared to controls, OCD patients showed significantly reduced FA and increased RD in clusters traversing the left forceps minor, inferior fronto-occipital fasciculus, anterior thalamic radiation and cingulum. Furthermore, the OCD group displayed significantly weaker connectivity (quantified by the streamline count) compared to controls in the right hemisphere, most notably in edges connecting subcortical structures to temporo-occipital cortical regions. The sibling group showed intermediate streamline counts, FA and RD values between OCD and healthy control groups in connections found to be abnormal in patients with OCD. However, these reductions did not significantly differ compared to controls.

Conclusion: Therefore, siblings of OCD patients display intermediate levels in dMRI measures of microstructure and connectivity, suggesting white matter abnormalities might be related to the familial predisposition for OCD.

Keywords: 1. Endophenotype, 2. Obsessive-compulsive disorder, 3. Neuroimaging
Significant Outcomes

- OCD patients showed reduced fractional anisotropy (FA) and increased radial diffusivity (RD) in cortico-striato-thalamo-cortical (CSTC) circuit than controls.
- OCD patients showed lower streamline counts in visual pathways than controls.
- Sibling group showed intermediate levels between OCD and HC groups with regard to FA, RD and streamline counts.

Limitations

- Cross-sectional nature of the study.
- Most patients were taking psychotropic medication.

Data availability statement:

- The data of the study will be shared on reasonable request.

Introduction

Obsessive-compulsive disorder (OCD) has a lifetime prevalence of around 2.3% in adults (1) and can be severe and chronic. However, neurobiological mechanisms underlying the disorder remain unclear. First-degree relatives of patients with OCD are at greater risk of developing the disorder, and heritability of OCD is estimated at 42–52% (2, 3), suggesting a large familial component to the disorder. Therefore, the
investigation of unaffected first-degree relatives, in addition to OCD patients and healthy controls, may help to distinguish biomarkers of genetic risk without the confounding effects of the burden of illness, medication or clinical state.

Diffusion-weighted magnetic resonance imaging (dMRI) is a widely used neuroimaging technique to investigate white matter (WM) microstructure in psychiatric disorders. The majority of studies investigating WM with this modality have used a measure known as fractional anisotropy (FA), which provides a general index of WM integrity (4). Demyelination or damage to WM results in more isotropic water movement and manifests in lower FA values. To differentiate myelin-related pathology from axonal damage, the component measures from which FA is derived can be studied: an increase in radial diffusivity (RD) may signify increased space between fibers suggesting demyelination or dysmyelination (5), whereas a decrease in axial diffusivity (AD) may suggest axonal injury (6). Although results are mixed, most previous dMRI studies have reported lower FA in patients with OCD as compared to healthy controls, most consistently in the cingulum bundle (7-13) and corpus callosum (8, 10, 11, 14-18). A small number of previous dMRI studies have also investigated RD and AD in OCD patients, which report higher RD values in the forceps major (19), corpus callosum (14, 20) and in widespread WM (21), as well as no between-group difference in AD, suggesting that decreased myelination rather than axonal degeneration may underlie WM pathology in OCD. However, whether these myelin-linked alterations are state or trait dependent remains unclear.

Few previous studies have examined WM abnormalities in unaffected relatives of patients with OCD. The first such study restricted their analysis to brain regions that were found to be abnormal in OCD patients, and reported reduced FA in the right inferior parietal WM and increased FA in the right medial frontal region in unaffected relatives of OCD patients compared to controls (22). The second study used a whole-brain approach and found reduced FA in the arcuate fibers near the superior parietal lobule and anterior limb of internal capsule in siblings compared to controls (23). A subsequent region-of-interest (ROI) analysis revealed lower FA and increased RD in the
left cingulum bundle in siblings compared to controls (12). While these studies provide
the first evidence of WM alterations in relatives of individuals with OCD, the voxel-wise
or brain regional approach can limit the extent to which the findings can be interpreted
in terms of whole-brain networks.

Growing evidence suggests that dysconnectivity of brain networks, rather than
abnormalities in distinct brain regions, might underlie symptom manifestation in
psychiatric disorders (24). The structural connectome is a representation of the whole
brain as a network of cortical and subcortical regions (nodes) and WM connections
between these regions (edges). The network-based statistic (NBS) (25) can be used to
identify connectivity differences in the connectome between groups of individuals. One
previous study has found decreased structural connectivity in patients with OCD
comprising orbitofrontal, striatal, insula and temporo-limbic areas (26). Similarly, a
recent study reported decreased FA-weighted connection strength among frontal-limbic
areas, including the bilateral dorsolateral part and the right medial part of superior
frontal gyrus and the left anterior cingulate and paracingulate gyri in patients with OCD
(27). However, no previous study has examined possible structural network alterations
in relatives of patients with OCD. Given the evidence for WM abnormalities in both
individuals with OCD as well as their unaffected relatives, connectomic analysis using
structural networks might provide further insight into the mechanisms underlying OCD.

Aims of the Study

In this study, we aimed to investigate WM integrity and structural connectivity in patients
with OCD, their unaffected siblings and controls. We hypothesized that patients with
OCD would show lower FA, higher RD and lower structural connectivity compared to
the healthy controls, and that siblings display intermediate alterations across these
measures.
Material and methods

Subjects

A total of 82 participants (30 patients with OCD, 21 siblings of patients with OCD (13 of whom were related to the assessed OCD patients) and 31 healthy controls (HC)) were enrolled in the study. Exclusion criteria for subjects were as follows: (1) any lifetime substance use disorder (except nicotine); (2) current or past history of any serious psychiatric illness, including any psychotic or bipolar disorder, except for OCD in the OCD group; (3) use of psychotropic medication except patients with OCD; (4) current or past history of any significant neurological disorders; (5) history of loss of consciousness for more than 30 minutes; (6) any family history of OCD for HCs; and (7) any severe hepatic, endocrine or renal disease. All subjects were interviewed using the Structured Clinical Interview for DSM-IV Axis I Disorders (28) to exclude participants with past or current comorbid Axis I diagnoses and to confirm the diagnosis of OCD in the clinical group. As depression is a common comorbidity in OCD, patients also performed the Beck Depression Inventory (29) and were only included when their score was 16 or below. In the OCD group, 14 patients with OCD were treated with both antidepressant and antipsychotic medication, 13 patients were treated only with antidepressants and 3 patients were medication free. The groups were matched for age, sex, education level and packs per year of cigarette smoking. Beck Depression Inventory scores were under the cut-off of 16 in the OCD group (mean ± SD; 9.1 ± 3.8). OCD severity was rated with the Dimensional Yale–Brown Obsessive–Compulsive Scale (DY-BOCS) (30). Table 1 shows the demographics and clinical data.

All subjects gave written informed consent to participate in the study. The study was approved by local research and ethics committees.

MRI acquisition
Magnetic resonance imaging was performed using a 1.5 T MR system (GE SignaHDxt, General Electric Medical Systems, Milwaukee, WI, USA). Imaging parameters for T1-weighted structural scan were: TR = 10.7ms, TE = 4.3 ms, matrix = 256 x 256, number of slices = 176, FOV = 256 x 256 mm², NEX = 1, slice thickness = 1 mm. The voxels were therefore isotropic with a size of 1 mm³. All scans were inspected to check for motion artifacts and to rule out gross neuropathology. Diffusion imaging data were acquired in 40 diffusion gradient directions (b-value = 1000 seconds/mm²) and two b = 0 volumes with reversed phase-encoding (right > left and left > right) (repetition time = 6500 ms, echo time = 90 ms, voxel size = 2.1 × 2.1 × 2.1 mm³).

**dMRI analysis**

As described elsewhere (31), dMRI data were analyzed using the Oxford Centre for Functional MRI of the Brain (FMRIB) Diffusion Toolbox, which is part of FSL (FMRIB Software Library) (32). Data were collected with reversed phase-encode blips, resulting in pairs of images with distortions in opposite directions. The susceptibility-induced off-resonance field was estimated from these image pairs (33) and the two images were combined into a single corrected one. Subsequently, motion and eddy current artefacts were corrected using Eddy (34). A brain mask of the non-diffusion-weighted image was created using the Brain Extraction Tool (35). The diffusion tensor was then calculated with DTIFIT to yield voxel-wise FA, AD and RD maps, which were used in subsequent analyses. The FA images of each subject were then nonlinearily registered to the FMRIB58_FA template using FNIRT. The nonlinear warp was initialized with an affine registration generated with FLIRT (36). The resultant warping transformations were used to resample the FA, AD and RD images into the FMRIB58_FA space. This resampling step was implemented with Applywarp. For voxel-based analyses, the FA, RD and AD maps were smoothed with an isotropic Gaussian kernel with full-width half-maximum of approximately 5mm. The smoothed images of all subjects were merged into 4D volumes, separately for FA, RD and AD.

**Mapping of structural brain networks**
Whole-brain streamline counts were generated using Mrtrix3 (37). Denoising (38), Gibbs ringing removal (39), motion and distortion correction (34) and bias field correction (40) were performed in the preprocessing steps. The single-fibre WM response function was estimated using the tournier algorithm (41). Single tissue constrained spherical deconvolution (CSD) was used to estimate fibre orientation distributions (42). A total of 50 million probabilistic streamlines were generated using anatomically constrained probabilistic fiber tracking (43) for each subject with a length of 10–250 mm, step size of 1 mm and FOD amplitude threshold of 0.1. The SIFT algorithm was also applied to reduce the overall streamline count to 5 million streamlines (44), with consideration given to recent recommendations (45). Network nodes were based on the 90 cortical and subcortical regions comprising the automated anatomical labeling (AAL) atlas (46). Each element of the connectivity matrix was populated with the log-transformed number of streamlines between the corresponding pair of regions (streamline count), which served as a measure of inter-regional connection strength.

Following a previous study in OCD patients (26), any pairs of regions that were interconnected by one or more streamlines in at least 60% for each group were retained while others were set to zero in each group. Then, edges that were present in at least 60% of the all subjects were retained. This resulted in a connection density of approximately 22%. The stability of results was checked using different threshold levels of 30% and 90%.

**Statistical analysis of differences between groups**

We first compared whole-brain FA, AD and RD values between OCD and HC groups using a permutation-based parametric inference method (randomise tool in FSL) (47). Corrections for multiple comparisons were performed with an initial cluster forming threshold of t = 2.3 (10000 permutations). Statistical testing was constrained to voxels comprising a liberal white matter mask. Age, sex and years of education were included as a nuisance covariates in all analyses. Subsequently, for each cluster of voxels
associated with a significant between group difference, cluster-averaged values of dMRI metrics were extracted for each individual, including those from the sibling group. Cluster-averaged dMRI metrics were compared between the sibling and HC groups using independent samples t-tests.

Connection strengths (log-transformed streamline counts) between OCD and HC groups were compared using the network-based statistic (NBS) (25). The NBS localizes differences in connection strengths to specific networks, while controlling the family-wise error (FWE). The primary threshold for the NBS was set to a t-statistic threshold of 3.1 (10000 permutations). Use of the NBS for inference on brain networks mapped with tractography has been described elsewhere (48). Again, age, sex and years of education were included as a nuisance covariates. Akin to the post-hoc dMRI metric analyses, streamline counts were extracted from significant edges for each individual and compared between sibling and HCs using independent samples t-tests.

**Results**

**Participants characteristics**

The groups were matched on age, sex and education level (Table 1).
** Table 1 **

**dMRI metrics**

**OCD vs HC**

Compared to HC group, patients with OCD showed lower FA in a single cluster (MNI-coordinates: x = 102, y = 159, z = 60, cluster size = 3534 voxels, p = 0.033) within the left forceps minor, inferior fronto-occipital fasciculus (IFOF), anterior thalamic radiation (ATR) and cingulum (Fig. 1A, Table 2). The OCD group displayed significantly higher RD values compared to the HC group in one cluster which was in brain regions (MNI-coordinates: x = 106, y = 162, z = 57, cluster size = 3094 voxels, p = 0.049) overlapping with cluster of reduced FA in OCD patients (Fig. 1B, Table 2). AD values did not significantly differ between OCD and HC groups.

**Sibling vs HC**

Mean FA and RD values were extracted from significant voxelwise clusters to examine group differences between the sibling and HC groups. Cluster-averaged FA and RD in the sibling group was positioned in between the values for the HC and OCD groups. However, cluster-averaged FA and RD did not significantly differ between sibling and HC groups (Fig. 1C, Fig. 1D, and Table 2). Furthermore, no significant differences between the sibling and HC groups were found within the white matter mask.

**Figure 1 and Table 2**

**Structural Connectivity**

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OCD vs HC

The NBS identified a single network of significantly lower streamline counts in patients with OCD compared to HCs (p = 0.026). The network contained 9 nodes connected by 8 edges and was right localized. These connections linked the caudate nucleus with the calcarine, middle occipital and superior and middle temporal cortex. Another two edges linked the thalamus with the cuneus and middle occipital cortex. Another two edges linked the calcarine to the inferior occipital cortex and pallidum with the middle occipital cortex (Fig. 2A, Table 3). Together, these results indicate lower structural connectivity in right ventral visual pathways (49, 50) in OCD. No edges showed higher streamline counts in OCD patients compared to HC.

The connectivity results were stable at a streamline threshold of 30%. Specifically, NBS identified a significant cluster of lower streamline counts in patients with OCD compared to controls, which yielded one additional edge (more than the main analysis) that linked the right calcarine to the right pallidum (p = 0.029) (Table S1). Four edges remained significant (p = 0.020) but four edges (right caudate to right calcarine, right thalamus to right cuneus, right pallidum to right middle occipital and right calcarine to right inferior occipital) lost their significance at threshold of 90% (Table S2).

Sibling vs HC

Mean log-transformed streamline counts were extracted from significant edges for posthoc analyses comparing the sibling and HC groups. The sibling group showed intermediate streamline counts between HC and OCD groups across all edges. In two of these edges, siblings displayed significantly lower streamline counts compared to HCs, which linked the caudate nucleus with the calcarine (p = 0.043) and thalamus with the cuneus (p = 0.019) (Fig. 2B, Fig. 2C, Table 3 and Fig. S1). However, these differences did not remain significant after FDR correction for multiple comparisons (across the eight connections).
Exploratory whole-brain analysis revealed no significant differences between sibling and HC groups.

**Figure 2 and Table 3**

**Correlation analysis**

Spearman’s correlation analysis was used to test for relationships between significant dMRI metric values and streamline counts with symptom severity (DY-BOCS total score) within the OCD group. No significant correlations were detected between DY-BOCS total score and significant dMRI metrics values or streamline counts.

**Discussion**

In the current study, we examined patients with OCD, unaffected siblings of OCD patients and healthy controls in order to identify alterations in WM microstructure and connectivity that may be associated with the familial risk for OCD. We found lower WM anisotropy in the left hemisphere involving the limbic pathways (i.e., cingulum and ATR) and cortico-cortical association tracts (i.e., IFOF), as well as in interhemispheric tracts.
(i.e., forceps minor of the corpus callosum) in OCD patients compared to the HC group. Increased RD in the absence of AD changes in the OCD group might indicate a role for reduced myelination in the microstructural changes observed in this group. At the network level, OCD patients showed decreased structural connectivity in edges connecting subcortical structures, specifically caudate nucleus, thalamus and pallidum to temporo-occipital cortical regions within the right ventral visual pathways. Furthermore, although not significant, the sibling group showed intermediate levels between OCD and HC groups with regard to FA, RD and streamline counts in connections found to be abnormal in patients with OCD.

Compared to HCs, the OCD group showed lower FA and higher RD values in the anterior cingulum, forceps minor and ATR, which is in line with the classical cortico-striato-thalamo-cortical (CSTC) circuit model of OCD (10, 51-53) and with prior research in this area. Specifically, reduced FA was previously reported in OCD patients within the anterior cingulum bundle (7, 9-11, 13, 51, 54), the forceps minor (8, 10, 11, 14, 16-18, 20) and the ATR (21, 55). However, we also observed alterations outside the CSTC, including within the IFOF, which connects the frontal lobe to parieto-occipito-temporal regions. Thus, our results suggest that microstructural abnormalities in OCD may be more widespread than previously thought.

In addition to microstructural alterations in WM, OCD patients also showed reduced structural connectivity (i.e., streamline counts) compared to healthy controls, between the right caudate nucleus and right temporo-occipital regions and also between the right thalamus and right occipital regions. These findings are in contrast to previous studies using a network-based approach (26, 27). Specifically, Reess et al. (2016) observed decreased structural connectivity in patients with OCD, involving orbitofrontal, striatal, insula and temporo-limbic areas (26); and, Qin et al. (2019) reported reduced FA-weighted structural connectivity between the right superior frontal gyrus and left anterior cingulate gyrus (27). One possible explanation for the mixed findings with regard to the specific connections/subnetworks involved might relate to methodological differences between the studies. For example, we used probabilistic tractography to estimate
structural connectivity, while the two previous studies used a deterministic approach. A previous study reported that probabilistic approaches are superior compared to deterministic tractography in determining visual pathways, which were implicated in the subnetwork identified by our study (56). In addition, Reess et al. (2016) used a different parcellation scheme to construct the connectivity matrix (26) and differences in tractography methods and parcellation schemes have been shown to affect connectome reconstruction (57).

Inconsistencies between our study and previous studies with regard to the spatial location of connectivity deficits in OCD may also be sample-related. Our study included patients with OCD that were mostly treated with psychotropic medications including antipsychotics and different classes of antidepressants, while previous studies included mostly SSRI treated (26) or medication-free patients (27). Indeed, previous studies reported an increase in the FA following antipsychotic (58) or antidepressant treatment (59) including within fronto-striatal structures, which might explain why our structural connectivity findings were constrained to visual pathways. Interestingly, our results were more in line with previous connectivity studies using resting-state functional imaging in patients with OCD. For example, functional connectivity alterations in OCD has been found between the caudate and temporo-occipital regions (60-62) and between the thalamus and occipital cortex (63-65). Speculatively, our findings of reduced structural connectivity between occipital and subcortical structures might be associated with visuospatial deficits, which are observed in patients with OCD (66-70). Given that OCD symptoms are heterogeneous across patients (71), it is possible that our sample contained a greater portion of patients with severe visuospatial deficits, compared to samples from previous structural connectivity studies.

**White matter alterations in siblings**

The sibling group showed intermediate FA and RD values between OCD and HC groups in the cingulum and forceps minor which are spatially in line with previous studies reporting intermediate FA values in the medial frontal regions (22) and
intermediate FA and RD values in cingulum (12) in unaffected siblings of OCD patients. Furthermore, the sibling group also showed intermediate streamline numbers in all edges with significantly lower streamline counts in patients with OCD compared to HCs. It is notable that while streamline counts were lower in sibling compared to HCs (falling between OCD and HC groups), these reductions were not significant. It is possible that intermediate levels might be due to lower expression of high-risk genes in the siblings compared to the OCDs, but future studies investigating larger sample sizes are needed to formally test this hypothesis.

**Increased radial diffusivity in patients with OCD**

Consistent with previous studies (12, 14, 19, 20), FA differences were mainly due to increases in RD values in both OCD and sibling groups suggesting myelin-related WM alterations. In line with this hypothesis, a recent longitudinal study in healthy adolescents and young adults reported increased compulsivity is tied to slower myelination in frontostriatal regions (72). Although the mechanisms underlying myelin-related abnormalities in OCD are still unknown, previous studies have implicated myelin-related genes in OCD, such as oligodendrocyte lineage transcription factor 2 (OLIG2) (73-75) and myelin oligodendrocyte glycoprotein (MOG) (76). OCD is further linked to genetic variants related to glutamatergic, dopaminergic, and neurodevelopmental pathways that influence neural circuit establishment (77). Thus, genetic factors may contribute to myelin-related WM abnormalities in OCD and could further underlie the increase we observed in RD values.

The current study has several potential limitations. The most obvious is the cross-sectional nature of the study. Thus, potential differential changes in WM abnormalities over the course of illness in OCD remain to be directly established. Second, our sample was relatively small, which limits power for detecting between-group comparisons. Third, the field strength of 1.5 Tesla should be noted. Fourth, although similar to previous studies within clinical populations, our acquisition protocol (40 diffusion gradient directions at a b-value of 1000 s/mm²) was not ideally suited to CSD (78).
However, it has been shown that CSD outperforms classical diffusion tensor model for datasets acquired with comparable protocols (79). Fifth, recent work indicates that the SIFT method can potentially lead to erroneous inference when applied to pathological connectomes (45). Future methodological work should focus on investigating the impact of streamline filters on structural connectomes mapped in psychiatric cohorts. Sixth, dMRI is an intrinsically noise-sensitive and low-resolution technique which has limited capacity to resolve crossing, converging or diverging fibers and the neurobiological meaning of dMRI metrics remains unclear (80). In addition, symptom severity was assessed within the patient group only using the DY-BOCS, and thus we may have underestimated subclinical symptoms within the sibling and HC groups. Finally, most patients were taking psychotropic medication, however detailed medication information was not available for this study. Structural and functional alterations have been reported following psychotropic medication in patients with OCD (81, 82). Therefore, we could not reliably disentangle effects of medication on dMRI metrics and structural connectivity within the OCD group.

In conclusion, this is the first study to examine WM structural networks in unaffected siblings of patients with OCD. While OCD patients displayed WM connectivity deficits in a widespread network of brain regions connecting temporo-occipital cortical regions and subcortical structures, their unaffected siblings displayed intermediate decline as compared to controls, suggesting that WM abnormalities in both microstructure and connectivity relate to familial predisposition for OCD.
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Fig. 1 Regions of A) reduced fractional anisotropy, B) increased radial diffusivity in the OCD group relative to the HC group. Boxplot of C) fractional anisotropy and D) radial diffusivity values in significant clusters showed significant differences between OCD and HC groups. Group means are demarcated by the “+”. Radial diffusivity: ×10^{-3} \text{mm}^2/\text{s}.
Fig. 2  A) Lower structural connectivity in patients with OCD compared to HC  B) and C) Bar graphs showing mean streamline counts from edges showed significant differences (uncorrected level) between SIB and HC groups (Red color edges in A). Error bars represent the standard error of the mean.


<table>
<thead>
<tr>
<th></th>
<th>OCD (n=30)</th>
<th>SIB (n=21)</th>
<th>HC (n=31)</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>32.4 ± 10.0</td>
<td>30.4 ± 10.2</td>
<td>32.3 ± 8.5</td>
<td>F= 0.323, p= 0.725</td>
</tr>
<tr>
<td>Education (years)</td>
<td>12.1 ± 3.9</td>
<td>12.6 ± 3.8</td>
<td>13.0 ± 4.6</td>
<td>F= 0.789, p= 0.558</td>
</tr>
<tr>
<td>Sex (Male/Female)</td>
<td>13/17</td>
<td>8/13</td>
<td>13/18</td>
<td>x²= 0.262, p= 0.877</td>
</tr>
<tr>
<td>Pack years of smoking</td>
<td>3.5 ± 5.9</td>
<td>4.6 ± 8.1</td>
<td>5.7 ± 8.2</td>
<td>x²= 1.295, p= 0.523</td>
</tr>
<tr>
<td>OCD age of onset</td>
<td>25.0 ± 9.7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DYBOCS severity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Aggressiveness</td>
<td>6.7 ± 4.6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Sex/Religion</td>
<td>3.9 ± 4.6</td>
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<td></td>
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</tr>
<tr>
<td>- Symmetry/Ordering</td>
<td>4.7 ± 4.5</td>
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<tr>
<td>- Contamination/Cleaning</td>
<td>6.0 ± 4.8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Hoarding</td>
<td>1.5 ± 3.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Miscellaneous</td>
<td>3.3 ± 4.4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Total</td>
<td>17.7 ± 5.1</td>
<td></td>
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</tr>
</tbody>
</table>

Data are presented as mean ± standard deviation. HC, healthy controls; OCD, patients with obsessive-compulsive disorder; SIB, unaffected siblings; DYBOCS, dimensional scale for the assessment of the presence and severity of obsessive-compulsive symptoms.
Table 2. FA and RD values from the significant clusters in which decreased FA and increased RD were observed in OCD patients compared to HC.

<table>
<thead>
<tr>
<th></th>
<th>OCD (n= 30)</th>
<th>SIB (n= 21)</th>
<th>HC (n=31)</th>
<th>OCD vs HC</th>
<th>SIB vs HC</th>
</tr>
</thead>
<tbody>
<tr>
<td>FA</td>
<td>0.434 ± 0.028</td>
<td>0.456 ± 0.025</td>
<td>0.463 ± 0.024</td>
<td>p = 0.033</td>
<td>p = 0.341</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>t = 4.307</td>
<td>t = 0.963</td>
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<tr>
<td>RD</td>
<td>0.655 ± 0.038</td>
<td>0.625 ± 0.035</td>
<td>0.618 ± 0.029</td>
<td>p = 0.049</td>
<td>p = 0.466</td>
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<tr>
<td></td>
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<td></td>
<td></td>
<td>t = -4.238</td>
<td>t = -0.737</td>
</tr>
</tbody>
</table>

Data are given as mean (standard deviation). HC, healthy controls; OCD, obsessive-compulsive disorder; SIB, unaffected siblings; FA, fractional anisotropy; RD, radial diffusivity; RD: ×10⁻³ mm²/s.
Table 3 Decreased streamline counts in OCD patients compared to HC
<table>
<thead>
<tr>
<th>Network edges</th>
<th>OCD vs HC</th>
<th>SIB vs HC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NBS t-statistics</td>
<td>(uncorrected level)</td>
</tr>
<tr>
<td>1 R Caudate to R Temporal Middle</td>
<td>3.76</td>
<td>p = 0.365</td>
</tr>
<tr>
<td>2 R Caudate to R Temporal Superior</td>
<td>3.31</td>
<td>p = 0.302</td>
</tr>
<tr>
<td>3 R Caudate to R Calcarine</td>
<td>3.87</td>
<td>p = 0.043</td>
</tr>
<tr>
<td>4 R Caudate to R Occipital Middle</td>
<td>4.20</td>
<td>p = 0.406</td>
</tr>
<tr>
<td>5 R Thalamus to R Cuneus</td>
<td>3.64</td>
<td>p = 0.019</td>
</tr>
<tr>
<td>6 R Thalamus to R Occipital Middle</td>
<td>4.03</td>
<td>p = 0.118</td>
</tr>
<tr>
<td>7 R Pallidum to R Occipital Middle</td>
<td>3.32</td>
<td>p = 0.307</td>
</tr>
<tr>
<td>8 R Calcarine to Occipital Inferior</td>
<td>3.71</td>
<td>p = 0.731</td>
</tr>
</tbody>
</table>
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Dikmeer, N; Besiroglu, L; Di Biase, MA; Zalesky, A; Kasal, MI; Bilge, A; Durmaz, E; Polat, S;  
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Title:  
White matter microstructure and connectivity in patients with obsessive-compulsive disorder  
and their unaffected siblings

Date:  
2020-10-22

Citation:  
Dikmeer, N., Besiroglu, L., Di Biase, M. A., Zalesky, A., Kasal, M. I., Bilge, A., Durmaz, E.,  
with obsessive-compulsive disorder and their unaffected siblings. ACTA PSYCHIATRICA  

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