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Association between gray/white matter contrast and white matter microstructural alterations in medication-naïve obsessive–compulsive disorder

Qihui Niu [a,1], Jianyu Li [b,1], Lei Yang [a,1], Zitong Huang [b], Mingmin Niu [c], Xueqin Song [a], Yuanchao Zhang [b,*], Youhui Li [a,*]

[a] Department of Psychiatry, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, China
[b] School of Life Science and Technology, University of Electronic Science and Technology of China, Chengdu, China
[c] Department of Organization, Zhengzhou Railway Vocational and Technical College, Zhengzhou, China

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ABSTRACT

Intracortical myelin is involved in speeding and synchronizing neural activity of the cerebral cortex and has been found to be disrupted in various psychiatric disorders. However, its role in obsessive–compulsive disorder (OCD) has remained unknown. In this study, we investigated the alterations in intracortical myelin and their association with white matter (WM) microstructural abnormalities in OCD. T1-weighted and diffusion-weighted brain images were obtained for 51 medication-naïve patients with OCD and 26 healthy controls (HCs). The grey/white matter contrast (GWC) was calculated from T1-weighted signal intensities to characterize the intracortical myelin profile in OCD. Diffusion parameters, including fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD) and radial diffusivity (RD), were extracted from diffusion-weighted images to examine the WM microstructure in OCD. Compared with HCs, patients with OCD showed increased GWC in the bilateral orbitofrontal, cuneus, lingual and fusiform gyrus, left anterior cingulate, left superior parietal, right inferior parietal, and right middle frontal cortices, suggesting reduced intracortical myelin. Patients with OCD also showed decreased FA in several WM regions, with a topology corresponding to the GWC alterations. In both groups, the mean GWC of the significant clusters in between-group GWC analysis was correlated negatively with the mean FA of the significant clusters in between-group FA analysis. In patients with OCD, the FA of a cluster in the right cerebellum correlated negatively with the Yale-Brown obsessive–compulsive scale scores. Our results suggest that abnormal intracortical and WM myelination could be the microstructural basis for the brain connectivity alterations and disrupted inhibitory control in OCD.

1. Introduction

Obsessive-compulsive disorder (OCD) is a neuropsychiatric disorder characterized by time-consuming, distressing, or impairing obsessions (repetitive unwanted thoughts, images, or urges) or compulsions (repetitive behaviors or thoughts)(Hirschtritt et al., 2017; Stein et al., 2019). Current pathophysiological theories about OCD highlight the role of dysconnectivity; that is, the complex clinical manifestations of OCD arise from abnormality in inter-regional interactions rather than from abnormality in isolated brain regions(Gursel et al., 2018; Stein et al., 2019). In keeping with this concept, studies have documented abundant evidence of altered connectivity in OCD, involving not only the cortico-striato-thalamo-cortical (CSTC) circuits but also networks outside the CSTC circuits, including the occipital, limbic and motor systems; amygdalo-cortical circuitry; the default mode, central executive and salience networks; and so forth(Anticevic et al., 2014; Chen et al., 2019; Goncalves et al., 2016; Liu et al., 2021; Milad and Rauch, 2012). However, the neurobiological underpinnings of the connectivity alterations remain to be determined.

Myelin, as the coat that wraps around certain nerve axons, is crucial

* Corresponding authors at: School of Life Science and Technology, University of Electronic Science and Technology of China, Chengdu 610054, China (Yuanchao Zhang), Department of Psychiatry, The First Affiliated Hospital of Zhengzhou University, No. 1 East Jianshe Road, Zhengzhou 450052, China (Youhui Li).
E-mail addresses: yuanchao.zhang8@gmail.com (Y. Zhang), qiuliyouhui@126.com (Y. Li).
[1] Qihui Niu, Jianyu Li and Lei Yang contributed equally to this work.

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for efficient neural signaling in the brain(Haroutunian et al., 2014). It increases the speed and reliability of signal transmission, provides structural and trophic support to neurons, and prevents abnormal sprouting of nerve connections(Haroutunian et al., 2014; Jorgensen et al., 2016; Norbom et al., 2019; Sprooten et al., 2019). Therefore, abnormal myelin development or maintenance may contribute to brain connectivity alterations in OCD. Indeed, previous imaging genetic studies have reported myelin-related white matter (WM) abnormalities in OCD(Atmaca et al., 2010; Stewart et al., 2007; Zai et al., 2021). Diffusion tensor imaging (DTI) studies have also found significant WM microstructural changes in OCD, suggesting disrupted WM myelin integrity in this disorder(Dikmeer et al., 2021; Gan et al., 2017; Piras et al., 2021; Saito et al., 2008).

In addition to the WM, the cerebral cortex (especially its deep layers) is also myelinated. Myelination of the cerebral cortex is a crucial feature of brain development and occurs in part due to proliferation of myelin from subjacent WM(Norbom et al., 2019). The maturational process of intracortical myelin in humans is protracted and continues throughout adolescence and early adulthood, coinciding with the period of increased risk of developing mental disorders(Haroutunian et al., 2014; Sprooten et al., 2019). As such, abnormal intracortical myelination has been considered to be a candidate mechanism for various mental disorders(Haroutunian et al., 2014). Notably, using longitudinal magnetization transfer imaging (MTI) data, one recent study demonstrated an association between reduced intracortical myelin growth and compulsivity in a large sample of healthy subjects(Ziegler et al., 2019); it is therefore reasonable to speculate that abnormal intracortical myelination may play a crucial role in the pathophysiology of OCD.

Because cholesterol in myelin is a major determinant of the signal intensity in T1-weighted magnetic resonance images(Koenig, 1991; Koenig et al., 1990), T1 signal intensity has been used to infer the myelin structure of the brain. Indeed, strong correlations have been reported between T1 signal intensity and myelin content in both healthy and lesioned WM(Schmierer et al., 2004; Schmierer et al., 2008). The T1 signal intensity of cortical GM has been shown to correspond closely with histologically based myelin profiles(Eickhoff et al., 2005; Norbom et al., 2019). However, absolute tissue intensities in T1 images are notoriously susceptible to spurious field bias effects, which renders them unsuitable for group comparisons. In contrast, the gray/white matter contrast (GWC), defined as a local ratio of the T1-signal intensity, is less prone to be affected by field bias effects as the signal intensities of bias field are smooth and their influence will be largely cancelled out when computing a local intensity ratio. In previous studies, the GWC has been successfully used to characterize the intracortical myelin alterations in various psychiatric disorders such as schizophrenia and bipolar disorder (Jorgensen et al., 2016). However, to our knowledge, no prior study has examined this measure in patients with OCD. Mapping of the intracortical myelin profile in OCD using GWC may provide new insights into the pathophysiology of this disorder.

In this study, we characterized the intracortical myelin profile as well as its relationship with WM microstructural abnormalities in medication-naive patients with OCD (n = 51) as compared with healthy controls (HCs) (n = 26). First, vertex-wise GWC analyses were performed to identify intracortical myelin alterations in OCD. Second, voxel-based analyses of diffusion parameters, including fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD), were performed to identify WM microstructural alterations in OCD. Third, intermodal correlation analyses were performed to explore the relationship between alterations in GWC and diffusion parameters. We hypothesized that patients with OCD would show regionally higher GWC, possibly owing to lower levels of intracortical myelin compared with subjacent WM. We also hypothesized that patient with OCD would show regionally decreased FA and that FA alterations would be coupled with GWC alterations, possibly indicating that the WM microstructural alterations are also myelin-related.

2. Methods

2.1. Participants

Fifty-one medication-naive patients with OCD were recruited from Department of Psychiatry in the First Affiliated Hospital of Zhengzhou University. The diagnosis of OCD was determined by two experienced clinical psychiatrists through a structured clinical interview provided in the Diagnostic and Statistical Manual of Mental Disorders (fifth edition) (DSM-5). The symptom severity of patients with OCD was assessed using the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS)(Goodman et al., 1989). The patients were also evaluated using the 24-item Hamilton Depression Rating Scale (HAMD) and 14-item Hamilton Anxiety Scale (HAMA) to assess their depressive and anxiety symptoms. Exclusion criteria for patients included contraindication to scanning (e.g., metallic implant, pregnancy), inability to tolerate scanning procedures (e.g., due to history of claustrophobia), current or past substance abuse or dependence, history of neurologic disorder, history of bipolar disorder, history of psychosis, current depression (defined as those individuals meeting DSM criteria and/or those with an HAMD score greater than 20), current anxiety (defined as those individuals meeting DSM criteria and/or those with an HAMA score greater than 14), and current mental health disorder (except OCD in the OCD group). For comparison, twenty-six matched HCs were recruited from the local community. The HCs participated in a structured clinical interview for DSM-5 (non-patient version) to exclude current or past history of any psychiatric disorder. Additional exclusion criteria for HCs included contraindication to scanning, inability to tolerate scanning procedures, current or past substance abuse or dependence, and history of neurologic disorders. The detailed demographic and clinical characteristics of all the participants are presented in Table 1. This study was approved by the Ethics Committee of our institution, and written informed consent was obtained from each participant.

2.2. MRI acquisition and processing

All brain MRI scans were performed on a GE 3 T Discovery MR750 scanner using an 8-channel head coil. T1-weighted images were acquired using a three-dimensional brain volume (BRAVO) imaging

Table 1
Demographic and clinical data for patients with OCD and HCs.

	OCD (n = 51)	HCs (n = 26)	p value
Age (years)	23.02 ± 9.22	26.42 ± 6.04	0.093
Gender (male/female)	28/23	11/15	0.296
BMI (Kg/m^2)	21.13 ± 2.85	20.60 ± 2.11	0.402
Education (years)	13.47 ± 2.70	14.42 ± 1.63	0.103
Duration of illness (months)	41.84 ± 43.94	NA	
Y-BOCS score	22.69 ± 6.64	NA	
Obsessive subscale score	11.88 ± 3.57	NA	
Compulsive subscale score	10.80 ± 3.68	NA	
HAMD score	13.39 ± 3.58	NA	
HAMA score	9.04 ± 3.27	NA	

Note: Data represent mean ± standard deviation. Between-group differences in age, BMI and education were tested using an independent two-sample *t*-test. Between-group difference in gender was tested using a chi-square test. BMI, Body Mass Index; NA, not applicable.
Y-BOCS, Yale-Brown Obsessive-Compulsive Scale. The scores of this scale can be interpreted as follows: 0–7, subclinical OCD; 8–15, mild symptoms; 16–23, moderate symptoms; 24–31, severe symptoms; and 32–40, extreme symptoms.
HAMD, Hamilton Depression Scale. The scores of this scale can be interpreted as follows: 0–7, no depression; 8–20, Symptoms of depression may be present; 20–35, Mild or moderate depressive symptoms; and greater than 35, severe depression.
HAMA, Hamilton Anxiety Scale. The scores of this scale can be interpreted as follows: 0–6 no anxiety; 7–14, symptoms of anxiety may be present; 15–21, there must be anxiety; 22–28, obvious anxiety; and greater than 29, severe anxiety.

sequence (repetition time 8.232 ms, echo time 3.184 ms, inversion time 450 ms, flip angle 12°, matrix 256 × 256, thickness 1.0 mm, no gap, 188 slices, and voxel size 1 × 1 × 1 mm^3). Diffusion-weighted images were acquired using a single-shot echo-planar imaging sequence (repetition time 7100 ms, echo time 61 ms, 64 diffusion directions, b-value 1000 s/mm^2, matrix 128 × 128, field of view 256 × 256 mm^2, thickness 2.0 mm, no gap, and 70 axial slices).

Processing of the T1-weighted MRI data was conducted using FreeSurfer (https://surfer.nmr.mgh.harvard.edu/). Briefly, the T1-weighted images were first corrected for bias-field inhomogeneities and skull-stripped. The resulting volume was segmented to estimate the voxel-based gray/white matter (GM/WM) boundary, which was triangulated to obtain a triangle-based GM/WM boundary surface. The triangle-based GM/WM surface was then topologically-corrected to generate a more refined GM/WM surface (i.e., the white surface). The white surface was deformed outward to yield the triangle-based pial surface. After obtaining these surfaces, the GWC map for each participant was calculated by sampling the signal intensities from the intensity-corrected volume (nu.mgz) using mri_vol2surf command. Specifically, we sampled the WM signal intensity at 1.0 mm into the WM from the white surface and the GM signal intensity at 30 % of the distance from the white surface to the pial surface. The GWC was then computed as 100× (white–gray)/[(white + gray)/2]. Hence, a higher GWC indicates a larger discrepancy between GM and WM intensities, whereas a lower GWC indicates greater similarity between them. Before statistical analysis, the GWC maps of all participants were resampled and smoothed using a heat kernel of 20-mm full width at half maximum (FWHM).

Processing of diffusion-weighted images was conducted using FMRIB software library (FSL https://fsl.fmrib.ox.ac.uk/fsl/). The main preprocessing steps included eddy currents, head motion correction and brain-tissue extraction. A diffusion tensor model was then fitted for each voxel of the preprocessed images to obtain the FA, MD, AD and RD maps. Before statistical analysis, the diffusion parameter maps for all participants were spatially normalized to Montreal Neurological Institute space and smoothed using a Gaussian kernel of 8-mm FWHM.

2.3. Quality control of MRI data processing

For the structural MRI data, the cortical surfaces were visually checked and subject to manual editing, if necessary, according to the software guideline. For the diffusion-weighted MRI data, the individual FA map was visually checked to exclude possible processing and data errors.

2.4. Statistical analyses

Vertex-wise contrasts of the GWC maps between the patients with OCD and the HCs were performed using SurfStat package (https://www.math.mcgill.ca/keith/surfstat/). Specifically, for each vertex on the pial surface, we fitted a generalized linear model (GLM) with diagnosis, age and sex as covariates. A threshold of vertex-wise $p < 0.001$ was applied to define potential clusters of difference. The resulting clusters were corrected at the cluster level for multiple comparisons using random field theory (RFT). The significance level for clusters was set at an RFT-corrected $p < 0.05$.

A vertex-wise correlation analysis for the patient group was performed to examine the relationship between GWC and clinical data, including disease duration and the Y-BOCS, HAMD, and HAMA scores. Specifically, for each vertex on the pial surface, we fitted a GLM with the variable of interest as a covariate. A threshold of vertex-wise $p < 0.001$ was applied to define clusters that are potentially correlated with the variable of interest. The resulting clusters were corrected at the cluster level for multiple comparisons using RFT. The significance level for clusters was set at an RFT-corrected $p < 0.05$.

Voxel-wise contrasts of the FA, MD, AD, RD maps between patients with OCD and HCs were performed using DPABI package (https://rfmri.org/dpabi). Specifically, for each voxel of the FA maps, we fitted a GLM with diagnosis, age and sex as covariates. A threshold of voxel-wise $p < 0.005$ was used to define potential clusters of difference. The resulting clusters were corrected at the cluster level for multiple comparisons using Gaussian random field (GRF) theory. The significance level for clusters was set at a GRF-corrected $p < 0.05$.

A voxel-wise correlation analysis was performed to examine the relationship between the diffusion parameters and the clinical data. Specifically, for each voxel, we calculated a Pearson's correlation coefficient between the diffusion parameter and the variable of interest. A threshold of voxel-wise $p < 0.005$ was applied to defined clusters that are potentially correlated with the variable of interest. The resulting clusters were corrected at the cluster level for multiple comparisons using GRF. The significance level for clusters was set at a GRF-corrected $p < 0.05$.

In addition, for each participant, we extracted the global mean of the GWC/diffusion parameters of all the significant clusters in the between-group analyses. Then, we performed correlation analyses between the mean GWC and the mean diffusion parameter to investigate the relationship between atypical intracortical myelin and WM microstructural abnormalities.

3. Results

3.1. Vertex-based GWC Analysis.

Compared with the HCs, the patients with OCD showed significantly increased GWC in multiple cortical areas, involving the bilateral orbitofrontal cortex (OFC), cuneus, lingual and fusiform gyri, left anterior cingulate cortex (ACC), left superior parietal lobule (SPL), right inferior parietal lobule (IPL), and right middle frontal gyrus (Fig. 1).

3.2. Voxel-based FA analysis

Compared with the HCs, the patients with OCD showed significantly decreased FA in three WM clusters, involving the genu and body of the corpus callosum, bilateral cingulum, left inferior longitudinal fasciculus, inferior fronto-occipital fasciculus, left superior longitudinal fasciculus, left posterior thalamic radiation, right anterior and superior corona radiata, right anterior limb of internal capsule, the WM of the right orbitofrontal cortex, and the temporal pole (Fig. 2 and **Table A1** in **Supplemental Data**). There were no significant differences in other diffusion parameters between the two groups. Nonetheless, subsequent region of interest analyses found decreased AD and RD in one of the significant clusters, and increased RD in the remaining clusters in patients with OCD compared with HCs (**Table A2** in **Supplemental Data**).

3.3. Coupling between GWC and diffusion parameters

In both groups, the mean GWC of the significant clusters in the vertex-based GWC analysis was negatively correlated with the mean FA of the significant clusters in the voxel-based FA analysis ($r = -0.4395$, $p = 0.0279$ for HCs; $r = -0.3102$, $p = 0.0267$ for OCD) (Fig. 3). In both groups, the mean GWC of the significant clusters in the vertex-based GWC analysis was not significantly correlated with the mean MD/AR/RD of the significant clusters in the voxel-based FA analysis.

3.4. Relationships between imaging and clinical data

In the patient group, we identified a significant cluster in which the FA was negatively correlated with the Y-BOCS score. This cluster mainly involved the right cerebellar crus II and cerebellum 8 (Fig. 4). There was no significant correlation between the FA/MD/AR/RD and other clinical data including the disease duration and the HAMD and HAMA scores. The GWC was not significantly correlated with any of the clinical data.

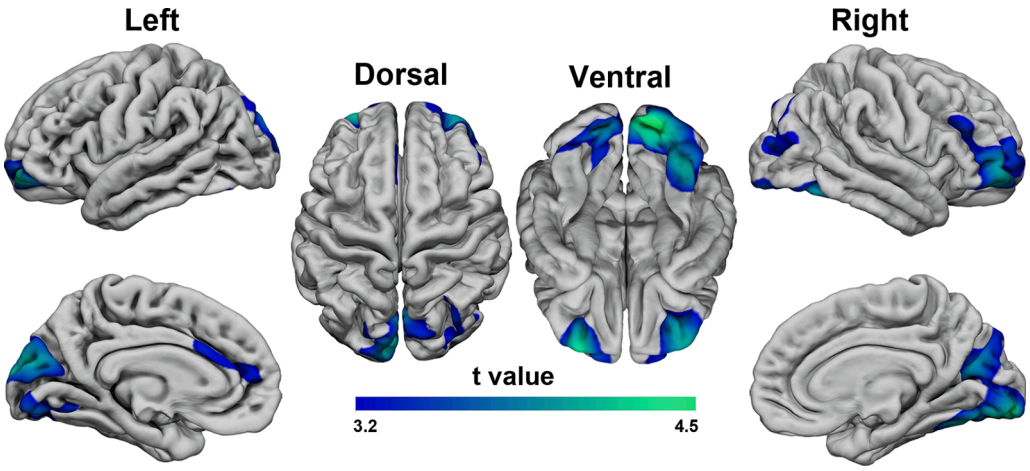

Fig. 1. Brain regions with increased GWC in patients with OCD compared with HCs. The results were RFT-corrected for multiple comparisons. The color bar denotes the *t*-value of the contrast.

4. Discussions

This study examined the intracortical myelin alterations as well as their relationships with WM microstructural abnormalities in medication-naïve patients with OCD. Compared with the HCs, the patients with OCD showed increased GWC in multiple cortical areas, including the orbitofrontal cortex, middle frontal gyrus, and anterior cingulate gyrus, among others. Patients with OCD also showed decreased FA in several WM regions, with a spatial distribution that corresponded with that of the GWC alterations. In addition, intermodal correlation analyses revealed a negative correlation between the mean GWC and the FA of the significant clusters in both groups, suggesting that these two features are tightly coupled. Collectively, these findings suggest that abnormal intracortical and WM myelination could be the microstructural basis for the brain connectivity alterations and the disrupted inhibitory control in OCD.

Myelination of the cerebral cortex is a fundamental feature of human brain integrity and is related to the fine-tuning of neural circuits(Haroutunian et al., 2014; Sprooten et al., 2019). Abnormalities in intracortical myelin have been proposed to account in part for the functional connectivity alterations in several mental disorders(Haroutunian et al., 2014; Huntenburg et al., 2017). Using GWC, this study characterized the intracortical myelin profile in patients with OCD. Compared with HCs, a widespread increase in the GWC was found in patients with OCD. The GWC increase may be a result of lower GM intensity, reflecting reduced intracortical myelin(Jorgensen et al., 2016; Norbom et al., 2019). Our finding is in contrast with previous MTI studies that reported no significant alteration in the magnetization transfer ratio (MTR) after multiple-comparison correction(Glahn et al., 2015; Maleki et al., 2020). The inconsistency may result from differences in the analytical methods and the characteristics of patient samples (such as sex composition, sample size, medicated/unmedicated). In our study, the finding of increased GWC in the orbitofrontal, middle frontal and anterior cingulate cortices is of particular interest because these regions are key nodes of the CSTC circuits and abnormalities in these circuits have been considered a possible mechanism underlying OCD symptoms(Anticevic et al., 2014). Specifically, the OFC is crucially involved in reward-guided learning and decision-making(Beucke et al., 2013; Chamberlain et al., 2008). The middle frontal gyrus, also known as the dorsolateral prefrontal cortex (dlPFC), is associated with executive functions such as working memory, cognitive flexibility, planning, inhibition and task-switching(Goncalves et al., 2016). In particular, the GWC of middle frontral gyrus has been found to be correlated with cognitive set-shifting test scores in healthy adults(Kim et al., 2017). Hence, abnormalities in the OFC and dlPFC may underlie the behavioral and cognitive inflexibility in OCD(Beucke et al., 2013; Chamberlain et al., 2008; Goncalves et al., 2016; Liu et al., 2021). The ACC plays a key role in error detection and conflict-monitoring(Norman et al., 2019). Dysfunction in the ACC could manifest as an overfunctioning of the error detection system and result in the emergence of intrusive and pathological thoughts(Goncalves et al., 2016; Liu et al., 2021; Norman et al., 2019). Within the CSTC circuits, a large number of studies have documented significant functional connectivity alterations (a mixture of both increased and decreased connectivity) in patients with OCD(Goncalves et al., 2016). In addition to the GWC alterations within the CSTC circuits, our study also found significantly increased GWC in several posterior brain regions, involving the IPL and some temporal-occipital cortices, in patients with OCD. These results are partially supported by previous reports of WM abnormalities in temporo-parietal-occipital regions and in long-range fiber bundles connecting these regions(Piras et al., 2013), and point to a critical involvement of posterior brain regions in OCD pathophysiology. The IPL is a key region of the frontoparietal network and has been involved in attention, set shifting and response inhibition (Liu et al., 2021; van den Heuvel et al., 2009). A previous study reported decreased activity in the IPL during inhibition in patients with OCD, and that the activity decrease was correlated with the stop signal reaction time(de Wit et al., 2012). Alterations in the IPL may reflect impaired attention to the stop signal or impaired action reprogramming, resulting in excessive repetitive behaviors(de Wit et al., 2012; Liu et al., 2021). A pattern of both increased activation and decreased functional connectivity in the temporal-occipital cortices has been reported in patients with OCD during a stop signal task(Hampshire et al., 2020). Alterations in these regions are thought to arise from disrupted inhibitory control and be related to hypervigilance in OCD or an expectation of an environment threat(Hampshire et al., 2020). Indeed, recent studies have found that a large portion of intracortical myelin enwraps axons of inhibitory interneurons (parvalbumin-positive cells)(Micheva et al., 2016) and that myelination of parvalbumin interneurons could shape the function of cortical inhibitory circuits(Benamer et al., 2020). It is therefore possible that the reduced intracortical myelination evidenced by increased GWC in the patients with OCD resulted in abnormal inhibitory control through desynchronization of local or long-range neural circuitry(Hampshire et al., 2020), manifesting as altered brain connectivity in this disorder(Huntenburg et al., 2017).

Compared with HCs, this study showed decreased FA in several WM tracts involving the corpus callosum, cingulum, and inferior fronto-occipital fasciculus, among others, in patients with OCD. Our results are consistent with previous reports(Dikmeer et al., 2021; Gan et al., 2017; Piras et al., 2021) and provide evidence for the notion that the pathophysiology of OCD is not limited to the CSTC circuits but also

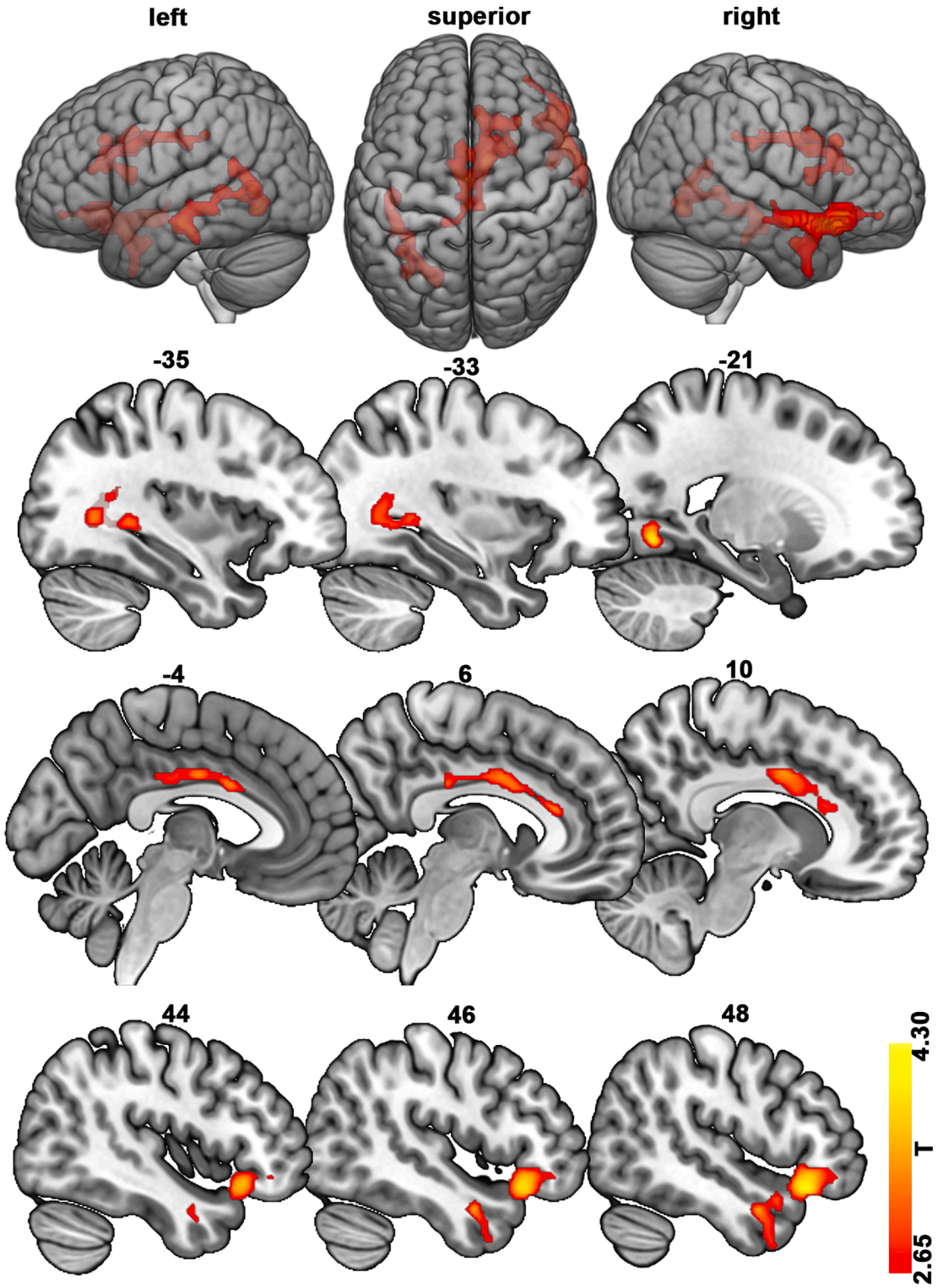

Fig. 2. Brain regions with decreased FA in patients with OCD compared with HCs. The results were GRF-corrected for multiple comparisons. The color bar denotes the t value of the contrast.

involves abnormalities in more extended brain regions(Anticevic et al., 2014). The decreases in WM FA could be the microstructural basis for the disrupted structural and functional connectivity in distributed brain networks in OCD. More interestingly, the WM tracts showing decreased FA in this study are clinically relevant and correspond well with the cortical regions showing significant GWC increase in patients with OCD. Specifically, the corpus callosum, the largest WM tract interconnecting homotopic cortical areas of the two cerebral hemispheres (with the anterior half connecting frontal cortices, the isthmus connecting primary motor, somatosensory and auditory cortices, and the splenium connecting parietal, temporo-occipital and visual cortices)(Fabri et al., 2014), plays a key role in interhemispheric communication and cognitive processes, and decreased FA in this tract has been linked to OCD symptom severity(Saito et al., 2008). The cingulum bundle originates

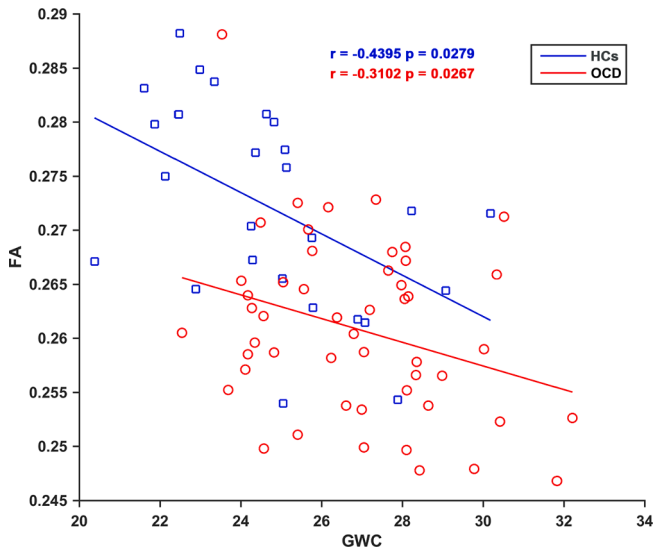

Fig. 3. Negative correlations between GWC and FA in patients with OCD and HCs.

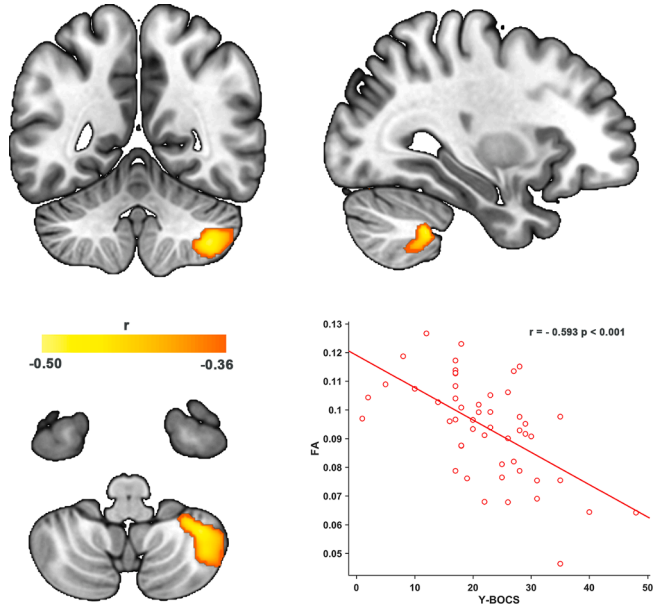

Fig. 4. Brain regions showing a negative correlation between FA and Y-BOCS in patients with OCD. The color bar denotes the Pearson's correlation coefficient.

from the temporal pole and terminates in the OFC and plays important roles in executive function, decision-making and emotional processing (Wu et al., 2016b). The inferior fronto-occipital fasciculus connects the frontal lobe (involving the OFC, frontal pole, and the inferior, middle, and superior frontal gyri) to the posterior parietal (involving IPL and SPL) and occipital cortices (involving the cuneus, lingual and fusiform gyrus, and so on)(Wu et al., 2016a) and has been implicated in OCD phenomenology such as excessive attention to irrelevant details. In addition to the aforementioned correspondence between the GWC and FA alterations, our study also revealed a negative correlation between the mean FA and mean GWC of the significant clusters in both groups, suggesting that these two features are tightly coupled. In this context, one is tempted to speculate that the FA decreases in OCD could be driven predominantly by disrupted WM myelin integrity. This speculation is supported by our finding of altered RD in the three WM clusters and also by previous imaging-genetic studies reporting an association of myelin oligodendrocyte glycoprotein gene variants with WM volume in OCD (Stewart et al., 2007; Zai et al., 2021). However, we cannot rule out the involvement of other pathologic factors such as axonal damage in causing the decreased FA in OCD.

In addition, we found that the FA of a cluster in the right cerebellum was negatively correlated with the Y-BOCS score in patients with OCD. This finding is consistent with previous studies reporting significant correlations of cerebellar GM volume and functional connectivity with Y-BOCS scores in patients with OCD(Anticevic et al., 2014; van den Heuvel et al., 2009; Xu et al., 2019) and suggests a critical involvement of the cerebellum in OCD-symptomology. The neural mechanism underlying the relationship between cerebellar FA and Y-BOCS scores remains unknown and may relate to the cerebellum's role in inhibitory control(Clark et al., 2020; Hampshire et al., 2020). Indeed, the cerebellum has been found to be reciprocally connected with regions of the CSTC circuits(Xu et al., 2019)and play a pivotal role in executive functions such inhibitory control(Clark et al., 2020; Norman et al., 2019). It has been proposed that the cerebellum could modulate the CSTC circuits (especially the prefrontal cortices) restraining ongoing actions when environmental conditions change in response to new external and internal stimuli, thereby facilitating flexible behavioral control(Miquel et al., 2019). Since we did not find significant FA alteration in the cerebellum, the negative correlation between cerebellar FA and Y-BOCS may imply that the FA of this region could be an indicator of effective inhibitory control in patients with OCD.

Some limitations should be addressed. First, although the GWC has been suggested as a proxy for intracortical myelin, the exact microstructural underpinnings of this measure are likely highly complex. Studies using other surrogate measures such as the T1-T2 ratio are needed to validate the current findings. Second, the relatively small sample size of the HCs was not quite balanced with those of patients with OCD, which may, to some extent, affect the results of the between-group contrasts. Third, this study was conducted cross-sectionally, which does not allow us to delineate the dynamic profiles of the alterations in intracortical myelin and WM microstructure in these patients. Future studies utilizing a longitudinal design are required to further pursue this issue. Last, although the GWC was computed from images corrected for intensity inhomogeneity (or bias field), its effect on the results of the between-group contrasts cannot be ruled out completely.

This study examined intracortical myelin and WM microstructural abnormalities in medication-naïve patients with OCD compared with HCs. We found increased GWC and decreased FA in multiple brain regions in the patients with OCD. We additionally found a tight coupling between the GWC and FA in both groups, possibly indicating that the FA decreases could be driven predominantly by disrupted WM myelin integrity. Collectively, these findings suggest that abnormal intracortical and WM myelination could be the microstructural basis for the brain connectivity alterations and the disrupted inhibitory control in OCD.

CRediT authorship contribution statement

Qihui Niu: Data curation, Writing – original draft. **Jianyu Li:** Software, Writing – original draft. **Lei Yang:** Data curation, Writing – original draft. **Zitong Huang:** Software, Writing – original draft. **Mingmin Niu:** Data curation, Writing – original draft. **Xueqin Song:** Data curation, Writing – original draft. **Yuanchao Zhang:** Conceptualization, Methodology, Supervision, Writing – original draft. **Youhui Li:** Conceptualization, Data curation, Supervision, Writing – original draft.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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