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Identifying Schizo-Obsessive Comorbidity by Tract-Based Spatial Statistics and Probabilistic Tractography

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A phenomenon in schizophrenia patients that deserves attention is the high comorbidity rate with obsessive-compulsive disorder (OCD). Little is known about the neurobiological basis of schizo-obsessive comorbidity (SOC). We aimed to investigate whether specific changes in white matter exist in patients with SOC and the relationship between such abnormalities and clinical parameters. Twenty-eight patients with SOC, 28 schizophrenia patients, 30 OCD patients, and 30 demographically matched healthy controls were recruited. Using Tract-based Spatial Statistics and Probabilistic Tractography, we examined the pattern of white matter abnormalities in these participants. We also used ANOVA and Support Vector Classification of various white matter indices and structural connection probability to further examine white matter changes among the 4 groups. We found that patients with SOC had decreased fractional anisotropy (FA) and increased radial diffusivity in the right sagittal stratum and the left crescent of the fornix/stria terminalis compared with healthy controls. We also found changed connection probability in the Default Mode Network, the Subcortical Network, the Attention Network, the Task Control Network, the Visual Network, the Somatosensory Network, and the cerebellum in the SOC group compared with the other 3 groups. The classification results further revealed that FA features could differentiate the SOC group from the other 3 groups with an accuracy of .78. These findings highlight the specific white matter abnormalities found in patients with SOC.

Key words: diffusion tensor imaging/schizo-obsessive comorbidity/schizophrenia/obsessive-compulsive disorder/support vector classification

Introduction

It is unclear whether schizo-obsessive comorbidity (SOC) is a subgroup of schizophrenia,[1] although some researchers have reported that this subgroup may have diagnostic validity.[2,3] Obsessive-compulsive disorder (OCD) occurs in up to 37.5% of schizophrenia patients and these patients typically present with more severe symptoms,[4–6] emotional disturbance,[7] social and neurocognitive deficits,[8] and treatment resistance.[9,10] Moreover, the incidence of SOC is much higher than other comorbid conditions, such as anxiety or depression in schizophrenia patients.[11] This may be due to common neurobiological mechanisms,[12,13] and genetic and environmental pathogenic factors.[14–16] Previous evidence also suggests that positive symptoms of schizophrenia and OCD symptoms could exacerbate one another.[17] Based on these studies, the "double jeopardy" hypothesis has been proposed,[18] which suggests that OCD symptoms could be important exacerbating factors in the pathological development of schizophrenia.[19] The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) also recognizes the existence of OCD in schizophrenia spectrum disorders,[20] highlighting shared and

overlapping clinical manifestations and implying a continuum between obsessions and delusions.[21] There is an increased interest in improving our understanding of SOC and better characterizing patients with SOC clinically and neurobiologically.[22,23]

However, the etiology and neurobiological basis of SOC is not clear. Limited research suggests that the cause of SOC may be related to the many commonalities between schizophrenia and OCD, which include commonalities in pathogenic factors, impaired cognitive function, changed neural circuits,[24] and therapeutic efficacy of serotonin reuptake inhibitors.[25] The "disconnection" hypothesis considers aberrant integration of neuronal networks as a crucial deficit in schizophrenia and OCD patients.[26] White matter changes in these patients could serve as important biomarkers.[27–29] The majority of previous studies have reported that patients with schizophrenia and OCD both exhibit abnormalities in the cortico-striato-thalamo circuitry.[4,30,31] Another study investigated white matter (WM) integrity in patients with schizophrenia only and patients with OCD only and found that both groups showed decreased fractional anisotropy (FA) in the corpus callosum.[32] In our previous resting-state functional connectivity (rsFC) study, we found that patients with SOC showed the strongest rsFC within subregions of the Default Mode Network (DMN) and the weakest rsFC between the DMN and subregions of the Salience Network compared with schizophrenia patients, OCD patients, and healthy controls.[27] However, little is known about whole brain white matter structural network abnormalities in patients with SOC.

In this study, we aimed to investigate tract-based white matter integrity and network-based biomarkers among patients with SOC, schizophrenia, OCD, and healthy controls. We first examined their WM fiber integrity including FA, Mean Diffusivity, Axial Diffusivity, and Radial Diffusivity using traditional Tract-based Spatial Statistics (TBSS). We then examined their Structural Connectivity Probability using Probabilistic Tractography in 264 gray matter regions of interest (ROIs). Traditional TBSS analysis could obtain FA values of white matter subregions within the skeletons of tract based on the Johns Hopkins stereotaxic atlas.[33] Probabilistic Tractography can be used to track structural pathways between specific gray matter regions based on an estimate of the probability density of water diffusion direction,[34] and previous studies have suggested that this approach may improve robustness and sensitivity compared with Deterministic Tractography,[35] especially in tracking white matter with fiber crossings and undulations.[36] Compared with TBSS indices, Probabilistic Tractography has advantages in microstructure and multi-pathway investigations.[37] The combination of TBSS and Probabilistic Tractography could provide a more comprehensive understanding of white matter substrates.

The 264 gray matter ROIs used in Probabilistic Tractography analysis were 5-mm diameter spheres, as identified by Power et al,[38] spanning the cerebral cortex, the cerebellum, and subcortical structures. These ROIs could represent whole brain gray matter structure for enhanced biological interpretability and data validity.[38] Most of these ROIs belong to one of the following brain networks: the Default Mode Network (DMN), the Salience Network, the Dorsal Attention Network (DAN), the Ventral Attention Network (VAN), the Fronto-parietal Task Control Network (FPN), the Cingulo-opercular Task Control Network (CON), the Somatosensory Network, the Memory Retrieval Network (MRN), the Visual Network, the Auditory Network, the Subcortical Network, and the cerebellum. Abnormal connectivity both within and between these networks have been reported in schizophrenia and OCD studies, especially in the DMN,[39,40] which is mainly associated with perceptual disturbances, a key factor in the development of schizophrenia and OCD symptoms.[27]

ANOVA of the TBSS and Probabilistic Tractography analysis were conducted to examine between-group differences. Since it is difficult to correct for multiple groups comparisons with the huge amount of raw data involved (such as 264 × 264 PT network matrix), machine learning may be a viable alternative method to identify biomarkers, predict new samples, and facilitate diagnosis. Therefore, we also adopted machine learning analysis in addition to ANOVA in this study.

We hypothesized that patients with SOC would exhibit extensive white matter changes in cortico-subcortical subregions, including changed FA and connection probability associated with the DMN, the Task-positive Network, and the Subcortical Network, which support the "double jeopardy" and "disconnection" hypotheses.

Materials and Methods

Participants

All participants were recruited from the outpatient clinics of the Department of Psychiatry, Second Xiangya Hospital of the Central South University and the local community in Changsha, China. Inclusion criteria of all participants were as follows: Han ethnicity; age ≥ 16; and IQ ≥ 70 (as estimated with the "common sense," "arithmetic," "similarity" and "digital span" subtests of the Chinese version of the Wechsler Adult Intelligence Scale-Revised).[41] Exclusion criteria for all participants were any diagnosis of physical and neurological disorders/anxiety disorder/depression/autism/known genetic disorders/substance dependence and contraindications for MRI scanning. Healthy controls were excluded if there was a family history of psychiatric disorder. Patients with SOC were excluded if there were obvious drug-induced obsessive-compulsive symptoms. After diffusion tensor imaging (DTI) and T1 quality control procedures, 7 participants were excluded, leaving 116 participants in the final analysis.

The study was approved by the Ethics Committee of the Second Xiangya Hospital of the Central South University. All participants gave written informed consent.

Diagnostic Assessment

To determine schizophrenia and OCD diagnoses, patients were assessed using the Structured Clinical Interview for DSM-IV Axis I Disorder, Patient Edition (SCID-IV) by 2 experienced psychiatrists.[42] For SOC, participants needed to meet the diagnostic criteria of schizophrenia and OCD concurrently, while schizophrenia and OCD patients met the diagnostic criteria of schizophrenia and OCD separately. For healthy controls, the non-patient edition of the SCID was used to confirm the absence of mental disorders.[43] The Positive and Negative Syndrome Scale (PANSS) was used to assess schizophrenia symptoms in the SOC and the schizophrenia groups.[44] The Yale–Brown Obsessive-Compulsive Scale (Y-BOCS) was used to assess obsessive-compulsive symptoms in the SOC and the OCD groups.[45]

MRI Acquisition

MRI data were acquired on a 3.0T Siemens SKYRA MR scanner (Siemens Medical, Erlangen, Germany) at the Second Xiangya Hospital of the Central South University, Changsha, China. 64-direction diffusion weighted images with *b*-value of 1000 s/mm^2 and 10 repetitions of images with a *b*-value of 0 s/mm^2 were acquired with a twice-refocused spin echo pulse sequence: repetition time (TR) = 6400 ms, echo time (TE) = 86 ms, field of view (FOV) = 256 mm, flip angle = 90°, acquisition matrix = 128 × 128, slice thickness = 2.5 mm, slices = 74, and voxel size = 2 × 2 × 2.5 mm^3. T1-weighted anatomical images were acquired with a sagittal-oriented magnetization prepared rapid gradient echo (MPRAGE) sequence. The parameters were as follow: TR = 1900 ms, TE = 2.01 ms, inversion time = 900 ms, FOV = 256 mm, flip angle = 9°, in-plane acquisition matrix = 256 × 256, slice thickness = 1 mm, no. slices = 176, and voxel size = 1 × 1 × 1 mm^3.

Data Analysis

Details on MRI data preprocessing and Support Vector Classification can be found in the supplementary material. In brief, TBSS and Probabilistic Tractography of each participant were preprocessed using the PANDA 1.3.1 (http://www.nitrc.org/projects/panda) pipeline toolbox.[46] After preprocessing and quality control, one-way ANOVA and post-hoc tests of the TBSS and Probabilistic Tractography results among the 4 groups were performed. TBSS results were corrected by Bonferroni correction, while Probabilistic Tractography results were corrected by the False Discovery Rate (FDR). Pearson correlation analysis was performed between FA and connection probability values of clusters with significant group differences and PANSS and Y-BOCS subscale scores within the relevant group with significance level set at $P_{\text{Bonferroni}} < .05$. Moreover, according to previous studies showing the influence of age, gender, and IQ on white matter,[47,48] these 3 factors were entered as covariates in the analysis.

Results

Twenty-eight patients with SOC, 28 schizophrenia patients, 30 OCD patients, and 30 healthy controls participated in this study. The mean age of all participants was 21.87 years (SD = 4.66, range = 16–36 years). Demographic and clinical rating information are shown in table 1.

The 4 groups differed significantly in estimated IQ ($F = 12.70$, df = 3, $P_{\text{Bonferroni}} < .05$). Post-hoc tests showed that the SOC group had lower IQ compared with the OCD group and healthy controls (to OCD: $t = -3.21$, $P_{\text{Bonferroni}} < .05$; to healthy controls: $t = -5.80$, $P_{\text{Bonferroni}} < .05$). The schizophrenia group had lower IQ compared with healthy controls ($t = -4.47$, $P_{\text{Bonferroni}} < .05$).

Table 1. Demographic and Clinical Information of Patients and Healthy Controls

	SOC (n = 28)	SCZ (n = 28)	OCD (n = 30)	HCs (n = 30)	$F/\chi^2/t$	P
Gender (no. M/F)	17/11	16/12	15/15	12/18	2.92	.40
Age (years)	22.32 (5.84)	20.46 (3.78)	22.17 (5.70)	22.47 (2.46)	1.15	.33
IQ	97.29 (17.51)	102.57 (15.55)	110.03 (16.37)	120.30 (10.16)	12.70	.001*
Duration of illness (years)	3.56 (3.68)	1.91 (2.59)	3.85 (4.85)	NA	2.04	.14
PANSS positive score	14.25 (4.78)	16.10 (4.46)	NA	NA	−1.50	.14
PANSS negative score	9.39 (3.20)	9.68 (3.94)	NA	NA	−0.30	.77
PANSS general score	29.43 (6.76)	30.61 (6.37)	NA	NA	−0.67	.51
Y-BOCS obsession score	16.64 (2.90)	NA	15.03 (3.66)	NA	1.85	.07
Y-BOCS compulsion score	12.43 (4.89)	NA	13.07 (3.56)	NA	−0.57	.57

Note: Data are presented as means (SD). HCs, healthy controls; NA, not applicable; OCD, obsessive-compulsive disorder; PANSS, Positive and Negative Syndrome Scale; SCZ, schizophrenia; SOC, schizo-obsessive comorbidity; Y-BOCS, Yale–Brown Obsessive-Compulsive Scale.
*Bonferroni .05 corrected.

In addition, 11 patients with SOC, 7 schizophrenia patients, and 9 OCD patients were prescribed medications (see supplementary table S1). Sixty patients were medication-free. Due to the different types of medications prescribed for different disorders, we could not reliably calculate the equivalent dosage and did not include this as a covariate in the data analysis.

Tract-Based Spatial Statistics

The SOC group had significantly decreased mean FA value of whole brain white matter ($t = -3.66$, $P_{\text{Bonferroni}} < .05$) and increased RD values ($t = 3.17$, $P_{\text{Bonferroni}} < .05$) compared with HCs.

Post-hoc ANOVA in 50 white matter subregions with Bonferroni corrections showed that compared with healthy controls, the SOC group had significantly decreased FA and increased Radial Diffusivity in the right sagittal stratum and the left crescent of the fornix/stria terminalis (table 2 and figure 1). No correlation analysis result survived multiple comparison corrections.

Classification results based on FA values showed an accuracy of .78 between the SOC group and healthy controls; an accuracy of .63 between the SOC group and the schizophrenia group; and an accuracy of .74 between the SOC group and the OCD group. The grand median weight figures are presented in supplementary figure S1.

Probabilistic Tractography

Post-hoc ANOVA with FDR corrections in valid connection probability features showed that compared with healthy controls, the SOC group had increased connection probability between the right precuneus and the left angular gyrus (within the DMN), between the right cerebellum crus1 and the right vermis 6 (the DMN and the cerebellum), between the right medial superior frontal gyrus (medsFG) and the left superior temporal pole (sTP, the DMN and the CON), between the left middle temporal gyrus (mTG) and the left brainstem (the DMN and the Subcortical Network), and between the left insula and the triangular part of right inferior frontal gyrus (itFG, the CON and the Salience Network). There was also significantly decreased connection probability between the left precentral gyrus and the left itFG (the DAN and the FPN).

Compared with the schizophrenia group, the SOC group had increased connection probability between the left precuneus and the left brainstem (the DMN and the Subcortical Network), decreased connection probability between the left middle occipital gyrus (mOG) and the left insula (the Visual Network and the CON), between the left cuneus and the left itFG (the Visual Network and the VAN), within the right inferior temporal gyrus (iTG, the Visual Network and the FPN), and between the left precuneus and the left iTG (the DAN and uncertain network).

Compared with the OCD group, the SOC group had increased connection probability between the left mTG and the left brainstem (the DMN and the Subcortical Network), and decreased connection probability between the precentral gyrus and the right cerebellum crus2 (the Somatosensory Network and the cerebellum)

Compared with healthy controls, the schizophrenia group had increased connection probability between the left middle temporal pole (mTP) and the right thalamus (the DMN and the Subcortical Network), between the left mTP and the right superior temporal gyrus (the DMN and the Auditory Network), between the right postcentral gyrus and the left insula (the Somatosensory Network and the Auditory Network), between the left supplementary motor area (SMA) and the left insula (the VAN and the CON), and within the right middle occipital gyrus (mOG, the Visual Network). There was also significantly reduced connection probability between the left precentral gyrus and the triangular part of left inferior frontal gyrus (itFG, the DAN and the FPN); and within the right middle frontal gyrus (mFG, the Salience Network and the FPN).

Compared with healthy controls, the OCD group had increased connection probability between the left SMA and the left brainstem (the VAN and the Subcortical Network), and between the postcentral gyrus and the left putamen (the Somatosensory Network and the Subcortical Network), and decreased connection probability between the orbital part of the inferior frontal gyrus (ioFG) and the left lingual gyrus (the DMN and uncertain network).

Compared with the OCD group, the schizophrenia group had increased connection probability within the right mOG (the Visual Network), and between the left

Table 2. Significant FA, MD, AD, and RD Differences Between the SOC Groups and HCs

	Regions	SOC	HCs	*t*	*P*	Cohen's *d*
FA	SS.R	4.69E-01 (1.78E-02)	4.88E-01 (2.62E-02)	−4.11	.0001	−0.93
	FX/ST.L	4.43E-01 (2.04E-02)	4.64E-01 (2.04E-02)	−4.09	.0001	−1.03
RD	SS.R	6.16E-04 (2.32E-05)	5.97E-04 (2.36E-05)	3.76	.0002	0.81
	FX/ST.L	6.26E-04 (2.77E-05)	5.95E-04 (2.84E-05)	3.89	.0002	1.11

Note: Bonferroni .05 corrected. AD, Axial Diffusivity; FA, Fractional Anisotropy; FX/ST, crescent of the fornix/stria terminalis; HCs, healthy controls; L, left; MD, Mean Diffusivity; R, right; RD, Radial Diffusivity; SOC, schizo-obsessive comorbidity; SS, sagittal stratum.

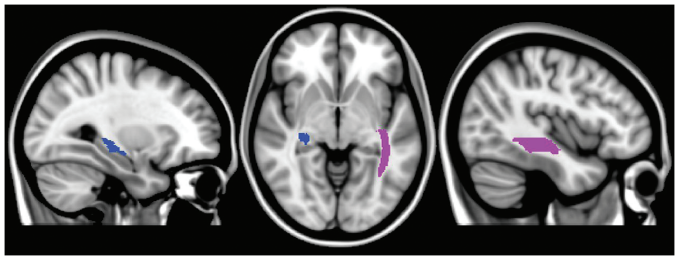

Fig. 1. Significant FA differences between the SOC group and HCs. left regions, left FX/ST; right regions, right SS. FX/ST, the left crescent of the fornix/stria terminalis; HCs, healthy controls; L, left; R, right; SOC, schizo-obsessive comorbidity; SS, sagittal stratum (include inferior longitudinal fasciculus and inferior fronto-occipital fasciculus). For color, please see the figure online.

mOG and the left middle temporal gyrus (mTG, the Visual Network and the DMN) (table 3 and figure 2). No correlation analysis result survived multiple comparison corrections.

Classification results based on connection probability showed an accuracy of .60 between the SOC group and healthy controls; an accuracy of .56 between the SOC group and the schizophrenia group; and an accuracy of .60 between the SOC group and the OCD group. The grand median weight figures are presented see in supplementary figure S2.

In addition, in order to address the potential confounding effect of medication and IQ on the results, we compared the FA and connection probability values between SOC participants on medication (n = 11) and not on medication (n = 17). We found no significant difference. We also compared the FA and connection probability values of SOC patients not on medication (n = 17) and healthy controls. This also did not alter the results. Correlation analysis showed that FA and connection probability values were not correlated with IQ and medication dosage in all patient groups.

Discussion

To the best of our knowledge, the present study is the first study to investigate changes in WM morphology in patients with SOC. We compared 4 indices of white matter integrity and 34 716 connection probability values among the SOC group, the schizophrenia group, the OCD group, and healthy controls, and used FA and connection probability results to classify the SOC group from other groups using machine learning methods. The comparison results revealed that the SOC group had significantly decreased FA and increased Radial Diffusivity in the whole brain, especially in the right sagittal stratum and the left stria terminalis compared with healthy controls; and the SOC group had altered connection probability in the DMN, the Subcortical Network, the Attention Network, the Task Control Network, the Visual Network, the Somatosensory Network, and the cerebellum compared with the other 3 groups. The classification results had an accuracy between .56 and .78 in distinguishing the SOC group from the other 3 groups. These findings may represent underlying neurobiological changes in patients with SOC and may provide insight into the similarities and differences of the structural connectivity patterns among patients with SOC, schizophrenia, and OCD.

In this study, the SOC group showed significantly decreased FA at the right sagittal stratum and the left stria terminalis, suggesting more severe white matter structural changes when schizophrenia and OCD symptoms co-occur, supporting the "double jeopardy" and "disconnection" hypotheses. The sagittal stratum is a cortico-subcortical WM bundle that mainly conveys fibers from the frontal, the parietal, and the occipital cortex to the thalamus and the basal ganglia.[49,50] This finding is consistent with known changes in the cortical-thalamus pathway reported in previous OCD studies,[30] and suggests that altered FA at the sagittal stratum may be associated with obsessive symptoms.[51] In addition, previous behavioral studies have also shown that SOC patients exhibit more severe attentional set-shifting deficit[52] and lower processing speed.[53] Decreased FA at the sagittal stratum may be associated with these kinds of cognitive inflexibility and executive dysfunction.[54–56] The stria terminalis is a pathway connecting the hippocampus, the amygdala, and the hypothalamus.[57] Changes in the striatum terminalis have also been found in schizophrenia and OCD patients in previous studies.[58,59] Decreased FA at the left stria terminalis in patients with SOC in our study may imply excessive anxiety in response to threat monitoring,[60] more severe depression,[61] impaired working memory,[62] and attenuated behavioral inhibition when schizophrenia and OCD symptoms co-occur.[63]

Moreover, the sagittal stratum and the striatum terminalis also showed significantly increased Radial Diffusivity in the SOC group. While FA is usually regarded as an indicator of WM structural integrity,[64] RD is thought to reflect the integrity and thickness of myelin sheets covering the axons and may be a marker of cell atrophy or loss.[65,66] As such, the main underlying mechanism of white matter changes in the SOC group may be due to subtle demyelination rather than axonal alterations.

To further investigate the microstructure of white matter connection, we conducted Probabilistic Tractography analysis and the results also support the "disconnection" hypothesis in SOC patients. We found that patients with SOC had increased connection probability between the precuneus and the angular gyrus compared with healthy controls. The precuneus is the core subregion of the DMN, associated with self-consciousness and self-related mental representations.[67] The angular gyrus is associated with abnormal semantic and episodic memory retrieval.[68] In particular, the left angular gyrus is responsible for

Table 3. Significant Structural Connectivity Probability Differences Between Groups

A. SOC vs HCs

ROI	ROI	SCP in SOC	SCP in HCs	*t*	*P*	Cohen's *d*
PCUN.R(DMN) (15 −63 26)	ANG.L(DMN) (−44 −65 35)	2.67E-03 (3.50E-03)	0 (0)	11.39	.001	0.40
CRUS1.R(DMN) (28 −77 −32)	VER6.R(CB) (1 −62 −18)	2.15E-03 (4.78E-03)	4.69E-04 (8.45E-04)	14.11	.0004	0.48
medsFG.R(DMN) (13 30 59)	sTP.L(CON) (−51 8 −2)	1.50E-03 (4.22E-03)	1.55E-04 (5.94E-04)	12.28	.0009	0.42
mTG.L(DMN) (−58 −30 −4)	BS.L(SCN) (−5 −28 −4)	1.64E-03 (2.20E-03)	7.41E-04 (1.36E-03)	11.53	.001	0.74
poCG.L(DAN) (−32 −1 54)	itFG.L(FPN) (−47 11 23)	8.72E-03 (1.48E-02)	5.49E-02 (8.78E-02)	−12.50	.0008	−0.61
INS.L(CON) (−34 3 4)	itFG.R(SN) (48 22 10)	2.64E-03 (3.50E-03)	6.82E-04 (1.16E-03)	10.90	.001	0.65

B. SOC vs SCZ

ROI	ROI	SCP in SOC	SCP in SCZ	*t*	*P*	Cohen's *d*
PCUN.L(DMN) (−3 −49 13)	BS.L(SCN) (−5 −28 −4)	1.52E-03 (1.69E-03)	3.28E-04 (8.39E-04)	10.83	.001	0.73
mOG.L(VN) (−24 −91 19)	INS.L(CON) (−34 3 4)	1.44E-04 (5.64E-04)	3.07E-03 (5.08E-03)	−11.27	.001	−0.47
CUN.L(VN) (−16 −77 34)	itFG.L(VAN) (−49 25 −1)	7.60E-05 (2.79E-04)	9.33E-04 (1.29E-03)	−12.54	.0008	−0.58
iTG.R(VN) (42 −66 −8)	iTG.R(FPN) (58 −53 −14)	2.18E-02 (2.27E-02)	8.15E-02 (1.46E-01)	−10.72	.001	−0.64
PCUN.L(DAN) (−17 −59 64)	iTG.L(UN) (−50 −7 −39)	0 (0)	4.54E-04 (8.24E-04)	−11.53	.001	−0.44

C. SOC vs OCD

ROI	ROI	SCP in SOC	SCP in OCD	*t*	*P*	Cohen's *d*
mTG.L(DMN) (−58 −30 −4)	BS.L (SCN) (−5 −28 −4)	1.64E-03 (2.20E-03)	8.74E-04 (1.63E-03)	12.84	.0007	0.51
preCG.R(SSN) (20 −29 60)	CRUS2.R(CB) (17 −80 −34)	4.61E-03 (4.09E-03)	9.85E-03 (7.88E-03)	−16.76	.0004	−2.60

D. SCZ vs HCs

ROI	ROI	SCP in SCZ	SCP in HCs	*t*	*P*	Cohen's *d*
mTP.L(DMN) (−44 12 −34)	THA.R(SCN) (6 −24 0)	1.83E-04 (4.61E-04)	0 (0)	11.11	.001	0.36
mTP.L(DMN) (−44 12 −34)	sTG.R(AN) (32 −26 13)	9.66E-04 (1.67E-03)	1.79E-04 (5.97E-04)	10.82	.001	0.52
preCG.L(DAN) (−32 −1 54)	itFG.L(FPN) (−42 25 30)	4.14E-03 (5.72E-03)	1.61E-02 (2.74E-02)	−11.92	.001	−0.55
mFG.R(SN) (31 56 14)	mFG.R(FPN) (38 43 15)	1.75E-02 (3.76E-02)	3.05E-02 (4.87E-02)	−11.75	.001	−0.80
mOG.R(VN) (37 −84 13)	mOG.R(VN) (29 −77 25)	3.84E-01 (4.71E-01)	1.50E-01 (2.16E-01)	13.36	.0006	0.88
poCG.R(SSN) (50 −20 42)	INS.L(AN) (−30 −27 12)	2.15E-04 (6.38E-04)	0 (0)	11.07	.001	0.29
SMA.L(VAN) (−10 11 67)	INS.L(CON) (−34 3 4)	1.00E-01 (7.22E-02)	5.61E-02 (4.36E-02)	10.69	.001	2.25

Table 3. Continued

E. OCD vs HCs

ROI	ROI	SCP in OCD	SCP in HCs	*t*	*P*	Cohen's *d*
ioFG.L(DMN) (−46 31 −13)	LING.L(UN) (−12 −95 −13)	3.99E-03 (4.48E-03)	1.15E-02 (1.12E-02)	−13.10	.0006	−1.14
BS.L(SCN) (−5 −28 −4)	SMA.L(VAN) (−10 11 67)	1.37E-02 (1.09E-02)	7.34E-03 (6.55E-03)	11.13	.001	2.13
PUT.L(SCN) (−15 4 8)	poCG.R(SSN) (29 −39 59)	3.34E-04 (7.00E-04)	0 (0)	10.94	.001	0.35

F. SCZ vs OCD

ROI	ROI	SCP in SCZ	SCP in OCD	*t*	*P*	Cohen's *d*
mTG.L(DMN) (−56 −13 −10)	mOG.L(VN) (−24 −91 19)	3.35E-03 (4.29E-03)	6.96E-04 (1.60E-03)	10.69	.001	0.61
mOG.R(VN) (37 −84 13)	mOG.R(VN) (29 −77 25)	3.84E-01 (4.71E-01)	1.19E-01 (1.16E-01)	11.43	.001	0.83

Note: FDR .05 corrected. Probability values are presented as means (SD). Regions are presented as name (network) (peak MNI coordinates). AN, Auditory Network; ANG, angular gyrus; BS, brainstem; CB, cerebellum; CCrus1, cerebellum crus1 region; CCrus2, cerebellum crus2 region; CON, Cingulo-opercular Task Control Network; CUN, cuneus; DAN, Dorsal Attention Network; DMN, Default Mode Network; FPN, Fronto-parietal Task Control Network; HCs, healthy controls; INS, insula; ioFG, inferior frontal gyrus, orbital part; itFG, inferior frontal gyrus, triangular part; iTG, inferior temporal gyrus; L, left; LING, lingual gyrus; medsFG, medial superior frontal gyrus; mFG, middle frontal gyrus; mOG, middle occipital gyrus; mTG, middle temporal gyrus; mTP, middle temporal pole; OCD, obsessive-compulsive disorder; PCUN, precuneus; poCG, postcentral gyrus; preCG, precentral gyrus; PUT, putamen; R, right; ROI, region of interest; SCN, subcortical network; SCP, structural connection probability; SCZ, schizophrenia; SMA, supplementary motor area; SN, Salience Network; SOC, schizo-obsessive comorbidity; SSN, Sensory/Somatomotor Network; sTG, superior temporal gyrus; sTP, superior temporal pole; THA, thalamus; UN, uncertain; VAN, Ventral Attention Network; VER6, cerebellum vermis 6 subregion; VN, Visual Network.

subjective memory retrieval.[69] It is possible that the increased connection probability between the precuneus and the angular gyrus may strengthen the retrieval of memory related to pathological thinking in patients with SOC.[27]

We also found that SOC patients had increased connection probability between the mTG and the brainstem compared with the OCD group and healthy controls, and had increased connection probability between the precuneus and the brainstem compared with the schizophrenia group. Previous studies have demonstrated that the brainstem is involved in the development of psychotic disorders[70] and may be associated with auditory hallucinations.[71] Our results suggest that the disorganized relationship between interoception and sensory processing may be one possible reason for the more severe symptoms observed in patients with SOC.

At the same time, the SOC group and the schizophrenia group both exhibited decreased connection probability between the left precentral gyrus and the left inferior frontal gyrus compared with healthy controls. Previous studies have shown that these 2 regions may play important roles in social cognition, especially in facial emotion perception.[72,73] The left inferior frontal gyrus is also extremely important for the comprehension of language and eye-expression.[74] The impaired structural connection between the left precentral gyrus and the left inferior frontal gyrus in patients with SOC and schizophrenia may be associated with their poorer psychosocial functioning and performance.[75]

The SOC group exhibited decreased connection probability between the Visual Network including the mOG, the cuneus, and the task-positive network including the insula, the itFG, and the inferior temporal gyrus compared with the schizophrenia group. These results suggest that compared with SCZ patients, patients with SOC may have more severe disorganized sensory processing and integrative abnormalities.[76–79]

The SOC group also exhibited decreased connection probability between the precentral gyrus and the cerebellum compared with the OCD group, while the OCD group exhibited increased connection probability between the postcentral gyrus and the putamen compared with healthy controls. The precentral and postcentral gyrus mainly process sensory input and motor output.[80] Our results suggest that compared with OCD patients, SOC patients may be more inclined to avoid the effort in integrating sensory information in a conflicted environment.[81]

From a network perspective, the DAN and the DMN are normally modulated by the FPN in maintaining dynamic balance between internal perception and the

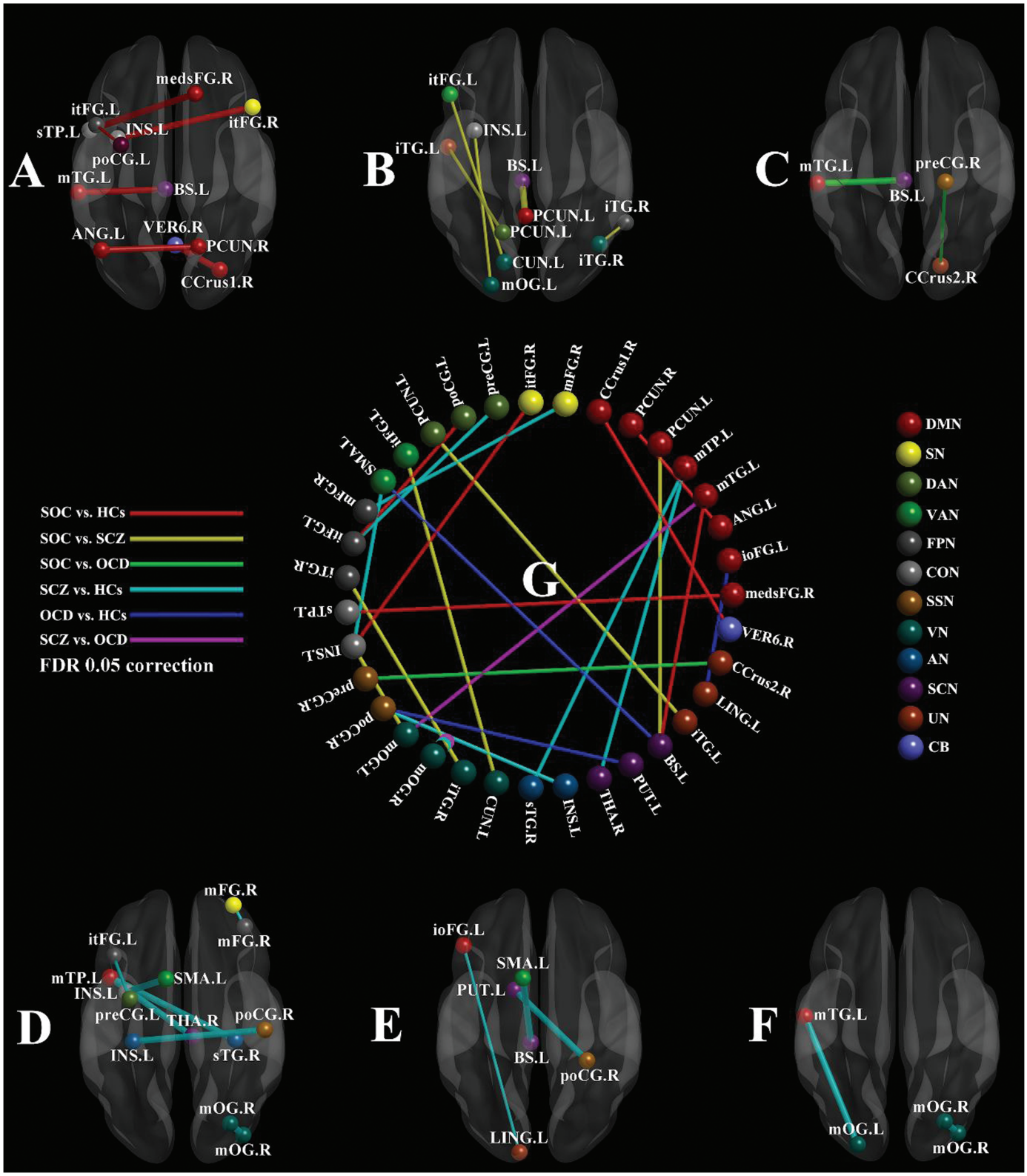

Fig. 2. Significant structural connectivity probability differences between groups. (A) SOC vs HCs; (B) SOC vs SCZ; (C) SOC vs OCD; (D) SCZ vs HCs; (E) OCD vs HCs; (F) SCZ vs OCD; (G) differences between every 2 groups; the thickness of the line segment in A–F represents the sign of the *t* value, bold line is positive *t* value, thin line is negative *t* value. AN, Auditory Network; ANG, angular gyrus; BS, brainstem; CB, cerebellum; CCrus1, cerebellum crus1 region; CCrus2, cerebellum crus2 region; CON, Cingulo-opercular Task Control Network; CUN, cuneus; DAN, Dorsal Attention Network; DMN, Default Mode Network; FPN, Fronto-parietal Task Control Network; HCs, healthy controls; INS, insula; ioFG, inferior frontal gyrus, orbital part; itFG, inferior frontal gyrus, triangular part; iTG,

external environment.[82] The decreased connection probability found in our study between the DAN and the FPN, together with the increased connection probability found within the DMN, between the DMN and the CON and the cerebellum, and between the CON and the Salience Network in patients with SOC may indicate dysfunctional self-regulation and disrupted homeostasis associated with pathological thinking and behavior.[83] Patients with SOC may be more focused on internal states and lose control over the external environment.[27,77] These results are consistent with previous rsFC research in SOC patients,[9] further corroborating the homogeneity of DMN-related functional and structural connectivity changes in patients with SOC. However, we did not observe any abnormality in the striatum in the SOC group and the schizophrenia group. This may be due to the fact that the patients in the present study were in remission and the striatum is sensitive to antipsychotics.[84,85]

Lastly, the relatively high accuracy rate (.78 by FA features) in distinguishing SOC patients from healthy controls in our study supports the possibility of using machine learning in classifying schizophrenia spectrum disorders. The accuracy of classification using connection probability features was consistently lower than using FA features in the present study, indicating changes in FA features may be better regulated than changes in connection probability. Moreover, the fornix exhibited the largest weight in classification between the SOC group and the OCD group and healthy controls. This result suggests that the fornix may also play an important role in the neurobiological development of schizophrenia spectrum disorders.[66]

Important limitations of this study include the relatively small sample size and lack of investigation of cognitive function in our patient groups. The functional implications of the observed WM changes are speculative and require verification in future studies. We also cannot rule out the confounding effect of medications due to the inclusion of some medicated patients, although our results showed no correlation between antipsychotic dosage and Y-BOCS scores in the SOC group. We also compared the diffusion values between SOC patients not on medication and the other groups and found no significant changes in the results. Secondly, IQ is another important confounding factor in our study. A previous study has reported that IQ may be positively correlated with myelin water fraction in frontal white matter in healthy people.[47] Although we took IQ as a covariate in our analysis and did not find any significant correlations between various white matter indices and IQ in all of our participants, the potential confounding effect of IQ on our results could not be completely excluded. Thirdly, although the TBSS results in the SOC group support the "double jeopardy" hypothesis, our connection probability results did not convincingly corroborate this hypothesis. The neurochemical basis of connection probability changes in patients with SOC needs further investigation. Fourthly, the weight of the classification results is not exactly the same as the ANOVA results. The practical physiological meaning behind this needs further investigation. More reliable and accurate classification should be carried out in the future with a much larger and a more homogeneous sample such as unmedicated first-episode patients characterized by a specific set of clinical symptoms. Fifthly, the Y-BOCS was not administered in the schizophrenia group and the PANSS was not administered in the OCD group, which might have limited the validity of our results. As all our participants were in clinical remission, it is also difficult to ascertain whether patients with SOC really had more severe symptoms. Sixthly, we did not examine the incidence of drug-induced OCD symptoms. A previous study which investigated 430 medicated schizophrenia patients reported that the incidence of drug-induced OCD is 1.4%, most of which were caused by clozapine.[86] Drug-induced OC symptoms is a key confounding factor in all studies investigating SOC and should be addressed in future studies. Finally, recent studies suggest that free-water signal correction or elimination procedures should be included in DTI data preprocessing due to the complicated shape of the fornix and the partial volume effects of ventricular water.[87,88] Neurite orientation dispersion and density imaging analysis is another advanced method for estimating the microstructural complexity of dendrites and axons. However, our imaging protocol and scanning parameters did not fit the requirement of these procedures.[89] Future studies should consider incorporating these novel approaches.

In conclusion, despite these limitations, our main results are stable regardless of medication dosage and IQ differences. We found extensive cortico-subcortical and perceptual processing-related WM changes in patients with SOC. These changes may indicate specific superimposed effects and neural adaptation of combined schizophrenia and OCD symptoms associated with more far-ranging and longitudinally stable deficits in perception, cognition,[90] emotion, and behavioral control in SOC

inferior temporal gyrus; L, left; LING, lingual gyrus; medsFG, medial superior frontal gyrus; mFG, middle frontal gyrus; mOG, middle occipital gyrus; mTG, middle temporal gyrus; mTP, middle temporal pole; OCD, obsessive-compulsive disorder; PCUN, precuneus; poCG, postcentral gyrus; preCG, precentral gyrus; PUT, putamen; R, right; SCN, subcortical network; SCP, structural connection probability; SCZ, schizophrenia; SMA, supplementary motor area; SN, Salience Network; SOC, schizo-obsessive comorbidity; SSN, Sensory/Somatomotor Network; sTG, superior temporal gyrus; sTP, superior temporal pole; THA, thalamus; UN, uncertain; VAN, Ventral Attention Network;VER6, cerebellum vermis 6 subregion; VN, Visual Network. For color, please see the figure online.

patients compared with patients with only schizophrenia or only OCD,[6] supporting the "disconnection" hypothesis of schizophrenia spectrum disorders and partially supporting the "double jeopardy" hypothesis of SOC.

Supplementary Material

Supplementary data are available at *Schizophrenia Bulletin* online.

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