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Effects of polygenic risk of schizophrenia on interhemispheric callosal white matter integrity and frontotemporal functional connectivity in first-episode schizophrenia

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Abstract

Background. Schizophrenia is a severely debilitating psychiatric disorder with high heritability and polygenic architecture. A higher polygenic risk score for schizophrenia (SzPRS) has been associated with smaller gray matter volume, lower activation, and decreased functional connectivity (FC). However, the effect of polygenic inheritance on the brain white matter microstructure has only been sparsely reported.

Methods. Eighty-four patients with first-episode schizophrenia (FES) patients and ninety-three healthy controls (HC) with genetics, diffusion tensor imaging (DTI), and resting-state functional magnetic resonance imaging (rs-fMRI) data were included in our study. We investigated impaired white matter integrity as measured by fractional anisotropy (FA) in the FES group, further examined the effect of SzPRS on white matter FA and FC in the regions connected by SzPRS-related white matter tracts.

Results. Decreased FA was observed in FES in many commonly identified regions. Among these regions, we observed that in the FES group, but not the HC group, SzPRS was negatively associated with the mean FA in the genu and body of corpus callosum, right anterior corona radiata, and right superior corona radiata. Higher SzPRS was also associated with lower FCs between the left inferior frontal gyrus (IFG)–left inferior temporal gyrus (ITG), right IFG–left ITG, right IFG–left middle frontal gyrus (MFG), and right IFG–right MFG in the FES group.

Conclusion. Higher polygenic risks are linked with disrupted white matter integrity and FC in patients with schizophrenia. These correlations are strongly driven by the interhemispheric callosal fibers and the connections between frontotemporal regions.

Introduction

Schizophrenia is a severely disabling psychiatric disorder with high estimated heritability (80–85%), which is conferred by a substantial proportion of common variants and their polygenic architecture (Sullivan, 2005). The effects of different genetic variants on schizophrenia are pathophysiologically complex and clinically heterogeneous. To capture the polygenic nature of this complex disorder, polygenic risk score (PRS), a cumulative summary score calculated by summarizing the addictive effects of an ensemble of genetic susceptibility loci, has been widely used to investigate the underlying polygenic architecture of schizophrenia (International Schizophrenia et al., 2009; Schizophrenia Working Group of the Psychiatric Genomics, 2014).

Many studies have highlighted that schizophrenia is characterized by widespread white matter disruptions, predominantly in interhemispheric, frontotemporal, and thalamocortical areas (Ellison-Wright & Bullmore, 2009; Kelly et al., 2018). As proposed by the dysconnectivity hypothesis, disruptive white matter tracts may underlie the anatomical infrastructure for abnormal or inefficient communication in the interconnected brain areas (Ellison-Wright & Bullmore, 2009; Konrad & Winterer, 2008). For example, in previous studies, altered functional connectivity (FC) and activity was observed in the frontotemporal, hippocampus – dorsolateral prefrontal

cortex (DLPFC) in schizophrenia (Benetti et al., 2009). Impaired neural communication between spatially distant cerebral regions may result in failure of proper functional integration within the brain (Friston, 1999), thus giving rise to psychotic symptoms and cognitive impairment in schizophrenia, such as memory impairment and auditory hallucinations (Hubl et al., 2004; Kochunov et al., 2017). White matter integrity is also influenced by genetic factors (Strike et al., 2015). A twin study reported 30–80% heritability of fractional anisotropy (FA) in healthy adolescents and young adults (Chiang et al., 2011), which are exactly the high-risk age of early-onset psychosis, since the critical brain development in this stage could make individuals in this age group particularly vulnerable to the onset of psychopathology (Zhang et al., 2020). While genetic variants associated with the white matter have been reported to overlap with genes related to liability for schizophrenia (Bohlken, Brouwer, Mandl, Kahn, & Hulshoff Pol, 2016a), cortical regions with the highest expression of schizophrenia risk genes were also found to overlap with the areas that showed the greatest reduction in white matter connectivity as well (Romme, de Reus, Ophoff, Kahn, & van den Heuvel, 2017). Furthermore, a study in twins with schizophrenia also pinpointed that the association between lower global FA and increased schizophrenia liability was 83.4% explained by common genes (Bohlken et al., 2016b), indicating that white matter alterations could provide crucial insights into the genetic underpinnings and underlying etiology of schizophrenia.

Emerging studies have investigated the relationship between genetic loading and brain structural and functional measures of schizophrenia. The PRS for schizophrenia (SzPRS) has been linked with frontal hypergyrification (Neilson et al., 2018), DLPFC inefficiency during working memory processing (Walton et al., 2013), decreased hippocampal activity and volume (Chen et al., 2018; Harrisberger et al., 2016; Liu et al., 2020), and reduced hippocampus – medial prefrontal cortex FC (Liu et al., 2020). However, albeit the aforementioned evidence linking white matter and genetic risks of SZ, the association between SzPRS and white matter has been sparsely reported with inconsistent findings thus far. Terwisscha van Scheltinga et al., found a negative association between SzPRS and white matter volume in both patients with schizophrenia and control subjects (Terwisscha van Scheltinga et al., 2013), while Harrisberger et al., reported no association between SzPRS and white matter volume in patients with at-risk mental state and first-episode schizophrenia (FES) (Harrisberger et al., 2018). Furthermore, two studies revealed an association between SzPRS and white matter integrity. A cross-sectional study in a large sample of healthy individuals found no association between FA and SzPRS after correction (Voineskos et al., 2016), while another study in a healthy cohort reported that higher SzPRS was associated with longitudinal increases in mean diffusivity in the splenium, arcuate, and anterior thalamic radiations and cingulum (Alloza et al., 2018). However, this study included males aged approximately 76 years old (Alloza et al., 2018), while the typical age of onset for schizophrenia is in late adolescence and early twenties (Häfner et al., 1994). Moreover, the study of Voineskos et al., was also in a quite wide age span (8–86 years), therefore, the effect of the natural trajectory of neurodevelopment and neurodegeneration cannot be ruled out.

Indeed, identifying the association between SzPRS and white matter integrity in patients with FES and the matched controls is a high priority. This will allow us to accurately observe the association between polygenic risk, imaging phenotypes, and the onset of psychosis, eliminating the potential confounding effects such as aging, antipsychotic medications, and disease progression, which will facilitate a better understanding of the neurobiology underlying psychosis.

In this study, we aimed to investigate the impaired white matter integrity as measured by FA in FES compared with healthy controls (HC) and further examined the effect of SzPRS on white matter FA. Secondly, we aimed to investigate the impact of SzPRS on FC in the regions connected by SzPRS-related white matter tracts. We hypothesized that increased SzPRS would be associated with decreased white matter FA and decreased FC in the connected regions. Additionally, we also aimed to investigate the associations between SzPRS, SzPRS-related FA/FCs, and psychotic symptoms.

Material and methods

Subjects

Eighty-four drug-naïve patients with FES were recruited from Shanghai Mental Health Center (SMHC). The inclusion criteria for the patients were: (1) consensus diagnosis of schizophrenia or schizophreniform disorder by two psychiatrists based on the Structured Clinical Interview (SCID) for Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV); (2) medication naïve; (3) experiencing first episode onset, and did not meet the criteria of any other Axis I disorder; and (4) aged from 14 to 45. Patients underwent pathophysiological assessments using the Positive and Negative Syndrome Scale (PANSS). Ninety-three HC were recruited from the local community through advertisements. All HC were carefully screened using the Structural Clinical Interview for DSM-IV, Non-Patient Edition (SCID-I/NP) to verify the absence of any history of psychiatric illness or family history. All participants were right-handed. Further exclusion criteria for both the FES and HC groups included suicidal ideation, alcohol or substance use, pregnancy, unstable neurological or physical disease, and absolute contraindications to MRI. Each participant (or the participant's guardian) signed an informed consent form before data acquisition. The study protocol was approved by the ethics committee of SMHC.

Genotype processing and polygenic risk score calculation

We used the LifeFeng Blood DNA Kit to extract genomic DNA from the whole blood of each participant. DNA libraries were prepared using SureSelectXT Human All Exon V6 + UTRs (Agilent). Paired-end sequencing was performed using an Illumina NovaSeq6000 system by following the Illumina protocols for 2×150 paired-end sequencing. The sequences were mapped to the human genome reference build hg19 using BWA version 0.7.15. The workflow of GotCloud version 1.17.5 (Jun, Wing, Abecasis, & Kang, 2015) was carried out to detect single nucleotide variants (SNVs) and small insertions and deletions (InDel). Quality control steps were performed using PLINK version 2.0. Individuals with missingness > 0.05 were excluded, as were single nucleotide polymorphisms (SNP) with missing genotype rates > 0.05, a minor allele frequency < 0.01, and a significant departure from Hardy–Weinberg equilibrium ($p < 0.001$).

SzPRS were estimated using PLINK version 2.0, based on the protocol previously described by Choi et al. (Choi, Mak, & O'Reilly, 2020), with linkage disequilibrium and distance thresholds for clumping of $r^2 = 0.1$ and within a 250 kb window. The SzPRS for each participant was calculated by summing the number of risk alleles (0, 1, or 2) weighted by the strength of

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the association of each SNP with schizophrenia, which was measured by the risk allele effect size (natural log of the odds ratio) from our case–control sample analysis. We used a statistical threshold of 0.1, which has been reported to maximally capture schizophrenia liability in the Chinese population (Wang et al., 2018).

Image acquisition

Imaging data of all subjects were obtained using a 3.0 T Siemens Verio MRI scanner (MRB17, Siemens AG, Erlangen, Germany) with a 32-channel head coil located at SMHC. Foam paddings were placed around the head of the subject to minimize head motion. The 3D structural images were acquired using a T1-weighted MPRAGE sequence with a repetition time (TR) = 2530 ms, echo time (TE) = 3.65 ms, field of view (FOV) = 256 × 256 mm^2, voxel size = 1.0 × 1.0 × 1.0 mm^3, 224 slices, slice thickness = 1 mm, acquisition matrix = 256 × 256, flip angle = 7°, and generalized auto-calibrating partial parallel acquisition (GRAPPA) with acceleration factor 2.

Diffusion-weighted imaging (DWI) data were acquired using a pulsed gradient echo-planar imaging (EPI) sequence with TR = 5000 ms, TE = 90.8 ms, FOV = 220 × 220 mm^2, voxel size = 2.0 × 2.0 × 2.0 mm^3, 74 slices, slice thickness = 2 mm, matrix size = 112 × 112, with 64 gradient directions (b-value = 1000 s/mm^2), and one image with $b = 0$ ($b0$ image).

Resting-stage fMRI images were acquired using an EPI sequence with TR = 2000 ms, TE = 30 ms, FOV = 220 × 220 mm^2, voxel size = 3.0 × 3.0 × 3.0 mm^3, matrix = 74 × 74, slice thickness = 3 mm, 50 slices with a flip angle = 77°, and total data volume = 240. Subjects were asked to close their eyes, relax, and not think of anything specific during the rsfMRI acquisitions.

Image processing

DTI data

All images were axis-aligned, centered, and visually inspected slice-by-slice by an experienced researcher before preprocessing to exclude severe image artifacts (e.g. multiple dropped signals, gross head motion, or ghosting). Image processing was conducted using FSL v5.0.9 (FMRIB Software Library, http://www.fmrib.ox.ac.uk/fsl) (Smith et al., 2004, 2006). First, DWI images were corrected for eddy currents and minor head motion using the linear image registration tool (FLIRT v6.0). Then, individual binary brain masks were generated through the brain-extraction tool (BET v2.1) based on the b0 image and were manually edited in 3D slicer (http://www.slicer.org). Subsequently, individual voxel-wise FA maps were calculated using DTIFIT embedded in the FMRIB's diffusion toolbox (FDT v3.0). Voxel-wise statistical analysis was performed using tract-based spatial statistics (TBSS) analysis (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/TBSS) (Smith et al., 2004, 2006). The FA images of all subjects were aligned into 1 mm × 1 mm × 1 mm Montreal Neurological Institute (MNI) 152 space using the FMRIB's Nonlinear Image Registration Tool (FNIRT) in FSL. Then, the mean FA image (threshold of 0.2) was created and thinned to generate a mean FA skeleton representing the centers of all tracts common to the group. Each subject's aligned FA image was projected onto the mean FA skeleton, and a 4D file of all skeletonized FA images was generated. The resulting skeletonized FA data were fed into further voxel-wise cross-subject statistical analysis.

rs-fMRI data

Image preprocessing was performed using the default preprocessing pipeline implemented in CONN v.18.b1 (Whitfield-Gabrieli & Nieto-Castanon, 2012), including functional realignment and unwrap, slice-timing correction, outlier identification, direct segmentation and normalization to the Montreal Neurological Institute (MNI) space, and functional smoothing (8-mm FWHM Gaussian filter). Linear regression was performed to remove the confounding effects, including (1) BOLD signals within white matter (10 principle component analysis (PCA) parameters) and cerebrospinal fluid (10 PCA parameters) discarded by CompCor; (2) head motion confound defined by six motion parameters and six temporal derivatives; (3) Artifact Detection Tools (ART)-based (https://www.nitrc.org/projects/artifact_detect) scrubbing parameters containing invalid scans, defined by a framewise displacement (FD) above 1 mm or global BOLD signal changes approximately three standard deviations. Comparison between groups (FES and HC) on mean FD and invalid volume proportions didn't yield a significant difference (online Supplementary Table S1). Participants with more than 20% invalid volumes were excluded from further analysis, resulting in 83 patients and 93 HC for analysis. The resulting time-series were band-pass filtered (0.01–0.08 Hz).

Statistical analysis

The workflow of the statistical analysis in our study is briefly shown in Fig. 1. Demographic and clinical data analyses were conducted using R, version 3.6.1. Chi-squared tests were performed to examine the differences in categorical data, while t tests were used to explore differences in continuous data. Logistic regression was fitted to detect the power of SzPRS to distinguish case–control status using the generalized linear model function in R. The results are shown as mean ± standard deviation, with significant differences considered at $p < 0.05$.

We performed two independent sample t tests to detect differences in FA between patients with schizophrenia and HC using the FSL Randomize program, with 5000 permutations and sex and age controlled as covariates. We assessed whether WM abnormalities in the schizophrenia group were influenced by SzPRS. Regions with significant case–control group differences were defined as the region of interests (ROIs) and fed into further analysis. Then, multiple regressions were then performed separately in the SZ group and HC groups to detect the association between SzPRS and FA values, with 5000 permutations and sex, age controlled as covariates. Threshold-free cluster enhancement (TFCE) was applied to control for family wise-errors (FWE), with a statistical significance (TFCE modified) of $p < 0.05$. Anatomical locations were identified using the Johns Hopkins University DTI-based white-matter atlases in the FSL toolbox (ICBM-DTI-81 Atlas) (Mori, Wakana, Nagae-Poetscher, & van Zijl, 2006). Then, the mean FA values in the SzPRS-related regions were extracted and further analyzed in R to test the association and mediation effects between SzPRS and psychotic symptoms.

For the FC analysis, we focused on the cortical regions connected by the observed SzPRS-related white matter fibers. On top of that, we chose the regions that were commonly identified as disrupted and associated with core symptoms in FES (Brady et al., 2019; Guo et al., 2014; Kuroki et al., 2006; Malla, Bodnar, Joober, & Lepage, 2011; Mwansisya et al., 2017; Orlov et al., 2018; Shah et al., 2017). Finally, N regions were further defined

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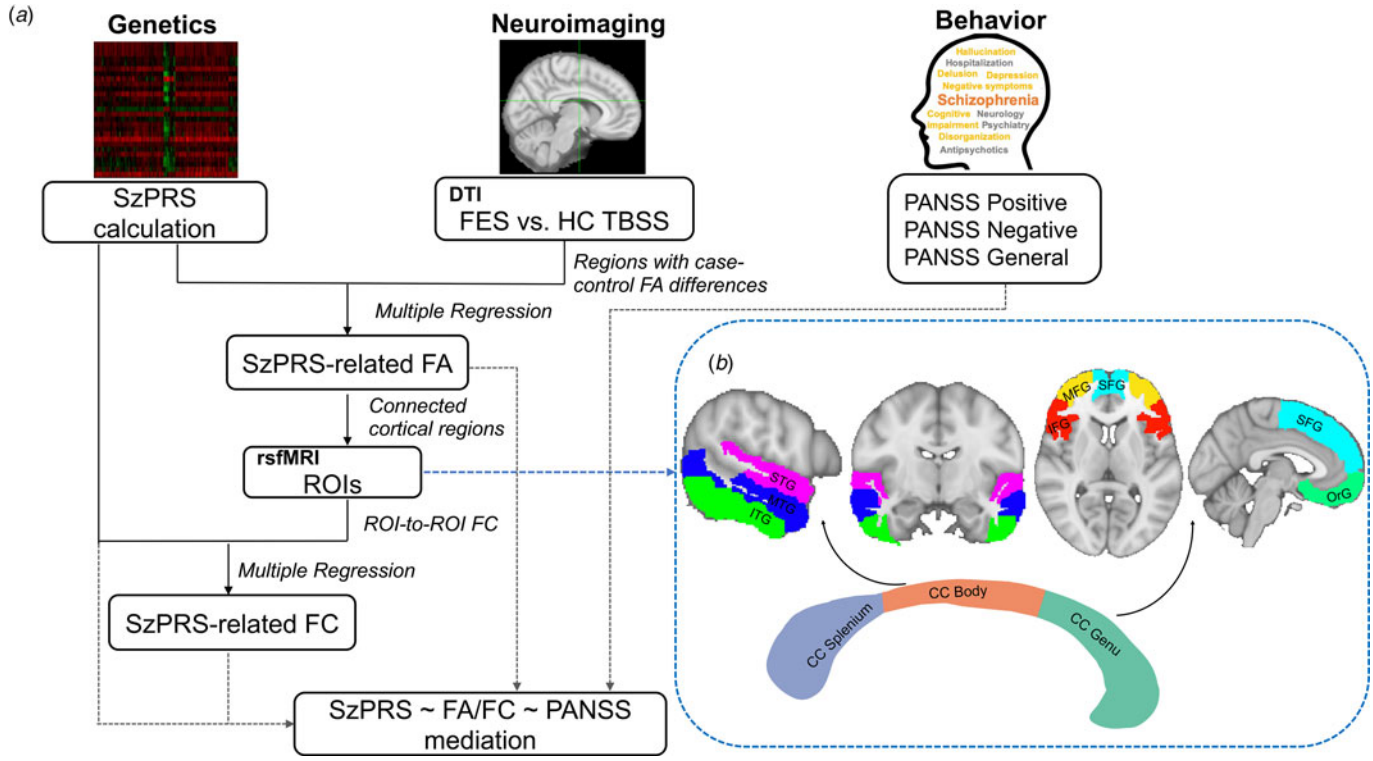

Fig. 1. Workflow of association analysis between PRS for schizophrenia (SzPRS) and fractional anisotropy (FA) / functional connectivity (FC). (*a*) Workflow of statistical analysis in our study. (*b*) Region of interest (ROIs) selected for ROI-to-ROI FC analysis: superior frontal gyrus (SFG), middle frontal gyrus (MFG), inferior frontal gyrus (IFG), superior temporal gyrus (STG), orbital frontal gyrus (OrG), middle temporal gyrus (MTG), and inferior temporal gyrus (ITG).

as ROIs and fed into the FC analysis (Fig. 1*b*). The ROIs are automatically located by masking on the anatomical parcellations of the Human Brainnetome Atlas (Fan et al., 2016). First, ROI-to-ROI connectivity (RRC) metrics were generated at the individual level using CONN toolbox. Thus, an $N \times N$ FC map was created. Then every element in an RRC matrix was defined as the Fisher-transformed bivariate correlation coefficient between a pair of ROIs, resulting in N^2 ROI-to-ROI functional connections (Whitfield-Gabrieli & Nieto-Castanon, 2012). For the second level (group-level) analysis, the correlation estimates were tested for statistical significance. Similarly, multiple regression models were used to detect the relationship between SzPRS and ROI-to-ROI FCs in the two groups, respectively, adjusted for age and sex. Results were reported as significant if $p < 0.05$, with false discovery rate (FDR) analysis level corrected. Then, FC values that showed correlation with SzPRS were extracted and further analyzed in R to test the association and mediation effects between SzPRS and psychotic symptoms.

To further investigate the relationship between psychotic symptoms and FA/FC abnormalities affected by polygenic risks, Pearson's correlation analyses were performed to test the correlations between SzPRS-related FA/FCs and PANSS positive, negative and general scores in patients. The results were considered statistically significant at $p < 0.05$. Mediation analyses were then performed to further examine whether SzPRS is related to psychotic symptoms via abnormalities in FA and FC by the R package 'mediation'. Mediation effects were considered significant if the confidence interval (CI) did not include zero (Preacher & Hayes, 2008).

Results

Demographics, clinical characteristics and SzPRS

The demographic and clinical characteristics of both patients and HC are shown in Table 1. There were no significant differences in age and sex ratio between the FES and HC groups ($p > 0.05$). A significant effect of the SzPRS on distinguishing the FES and HC groups were observed, with a higher score in schizophrenia than in the HC ($B = 13.37$, $p < 0.001$).

Association between SzPRS and FA

We first investigated the differences in the mean FA between the FES and HC groups. Decreased FA in the FES group was distributed over many brain regions, including the genu and body of the corpus callosum, bilateral cerebral peduncle, bilateral corona radiata, bilateral anterior and posterior limb of the internal capsule, bilateral external capsule, bilateral superior longitudinal fasciculus, bilateral superior fronto-occipital fasciculus, and left cingulum (Table 2, Fig. 2). There were no regions with significantly increased FA values in the FES group compared to the HC group. We then analyzed the association between the SzPRS and the FA values in regions that showed case–control differences. Multiple regression analysis revealed a significant negative association between the SzPRS and mean FA in the genu and body of the corpus callosum, right anterior corona radiata, and right superior corona radiata in the SZ group (Fig. 2); however, no associations were found in the HC group. There were no positive associations between the SzPRS and mean FA in any region in either the FES or the HC groups.

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Table 1. Demographic and clinical characteristics

	FES ($n = 84$)	HC ($n = 93$)	t/z	p
Age, mean (s.d.)	23.55 (8.14)	25.39 (6.36)	−1.662[a]	0.098
Gender, male/female	45/39	40/53	1.972[b]	0.160
Duration of untreated psychosis, months	10.74 (19.22)	–	–	–
PANSS Positive Score, mean (s.d.)	18.94 (5.17)	–	–	–
PANSS Negative Score, mean (s.d.)	14.19 (5.50)	–	–	–
PANSS General Score, mean (s.d.)	39.82 (4.90)	–	–	–
PANSS Total Score, mean (s.d.)	72.95 (9.80)	–	–	–

FES, schizophrenia; HC, healthy control; FA, fractional anisotropy; PANSS, Positive and Negative Syndrome Scale.
[a]Independent sample t test.
[b]Chi-squared test.

Table 2. Tract-based spatial statistics (TBSS) analysis of fractional anisotropy (FA) in FES group and HC group

			MNI coordinates			
Cluster Index	Cluster voxels	1−p value	x	y	z	White matter tracts
FA SZ<HC						
1	17 036	0.996	18	15	33	Anterior, Posterior limb of internal capsule R L Anterior, Superior, Posterior of corona radiata R L Cerebral peduncle R L Cingulum (Cingulate Gyrus) L External capsule R L Genu, Body of corpus callosum Superior longitudinal fasciculus R L Superior fronto-occipital fasciculus R L

SZ, schizophrenia; HC, healthy control; FA, fractional anisotropy; R, right; L, left.

Association between SzPRS and FC

We further investigated whether SzPRS also influenced the FC in the cortical regions connected by the observed SzPRS-related white matter tracts. The genu of the corpus callosum mainly connects the bilateral frontal lobes, while the body of the corpus callosum mainly receives the fibers from the temporal lobes and passes through the corona radiata, which provides an extension to the interhemispheric connection (Demeter, Rosene, & Van Hoesen, 1990; Georgy, Hesselink, & Jernigan, 1993). Based on the neuroanatomical structure, eighty-six frontal and temporal ROIs that commonly show structural and functional disruptions and are associated with core symptoms of FES are selected from the Human Brainnetome Atlas (Brady et al., 2019; Guo et al., 2014; Kuroki et al., 2006; Malla et al., 2011; Mwansisya et al., 2017; Orlov et al., 2018; Shah et al., 2017). 14 ROIs in superior frontal gyrus (SFG), 14 ROIs in middle frontal gyrus (MFG), 12 ROIs in inferior frontal gyrus (IFG), 12 ROIs in superior temporal gyrus (STG), 12 ROIs in orbital frontal gyrus (OrG), 8 ROIs in middle temporal gyrus (MTG), and 14 ROIs in inferior temporal gyrus (ITG) were selected to be fed into the FC analysis (Fig. 1*b*, online Supplementary Table S2). The association in the two groups showed similar patterns as the white matters: FC between the left IFG (inferior frontal sulcus) and left intermediate ventral ITG (A20iv_l, FDR-p = 0.0452), between the right IFG (inferior frontal sulcus) and left intermediate ventral ITG (A20iv_l, FDR-p = 0.0478), between the right IFG (inferior frontal sulcus) and left MFG (inferior frontal junction, FDR-p = 0.0478), and between the right IFG (inferior frontal sulcus) and right MFG (inferior frontal junction, FDR-p = 0.0478) were negatively associated with SzPRS in the SZ group (Fig. 3*a*); meanwhile, there were no associations between FC in any regions and SzPRS observed in the HC group. However, these four SzPRS-related FCs did not show between-group differences ($p > 0.05$, Fig. 3*b*).

SzPRS, SzPRS-related FA/FC, and psychotic symptoms

The associations between the four SzPRS-related FAs, FCs, and PANSS scores were summarized in online Supplementary Table S3. The FC between the right IFG and left intermediate ventral ITG ($R = 0.317$, $p = 0.004$) was found to be significantly associated with PANSS general score; FC between the left IFG and left intermediate ventral ITG also showed a marginal correlation with PANSS general score ($R = 0.205$, $p = 0.062$) (online Supplementary Fig. S1). Regarding the white matter, FA in the right superior corona radiata showed a marginal correlation with PANSS positive score ($R = 0.186$, $p = 0.090$), while FA in the body of corpus callosum showed a marginal correlation with PANSS negative score ($R = -0.185$, $p = 0.091$) (online Supplementary Fig. S1). No significant associations were found between the SzPRS and PANSS scores. The mediation analyses indicated no mediating role of FA or FC in any region between SzPRS and PANSS scores (CI containing zero, $p > 0.05$).

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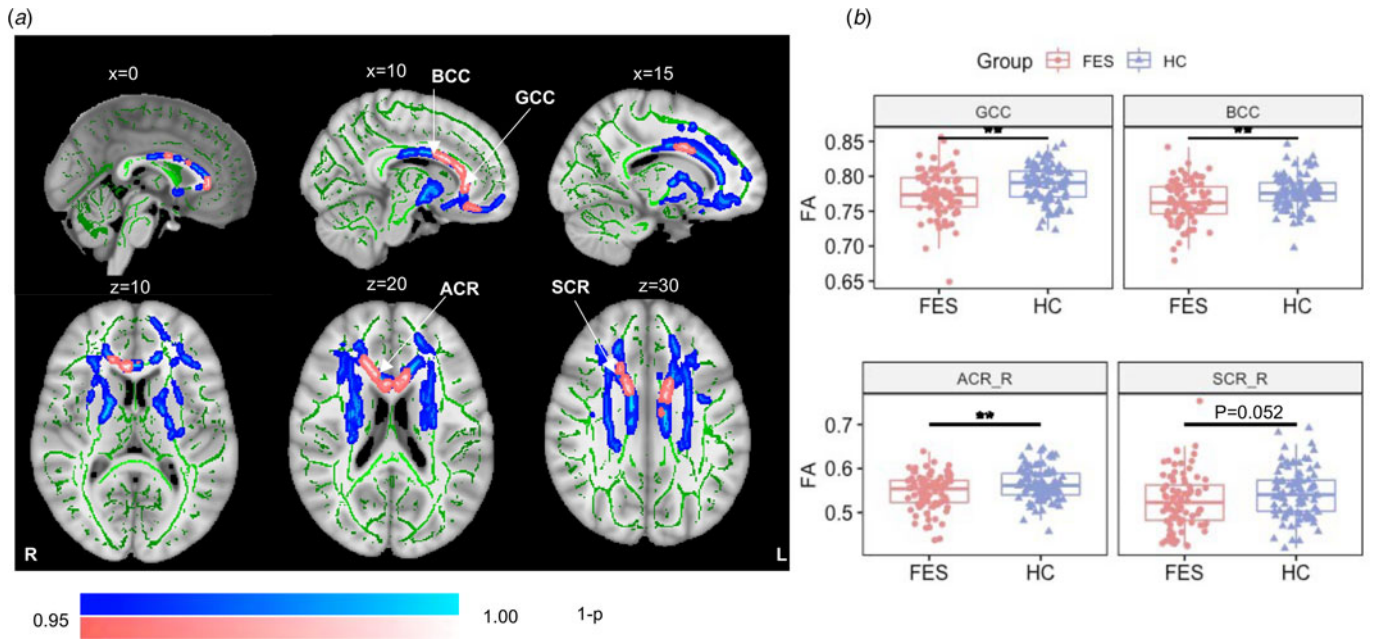

Fig. 2. Voxel-wise tract-based spatial statistics of fractional anisotropy (FA) in first-episode schizophrenia (FES) group and healthy control (HC) group. (a) Significant case–control differences (blue) are drawn on the top of the white matter skeleton (green), with lower FA values found in the FES group compared with the HC group. Significant negative associations between SzPRS and FA value in the FES group are shown in pink within the clusters, including the genu of corpus callosum (GCC), body of corpus callosum (BCC), right anterior corona radiata (ACR), and right superior corona radiata (SCR). Images are shown at a permutation-based threshold of $p < 0.05$ (FEW-corrected). The color bars represent the $1-p$ value (0.95 to 1). (b) Mean FA values in four SzPRS-related regions: GCC, BCC, right ACR, and right SCR. $^{*}p < 0.05$, $^{**}p < 0.01$.

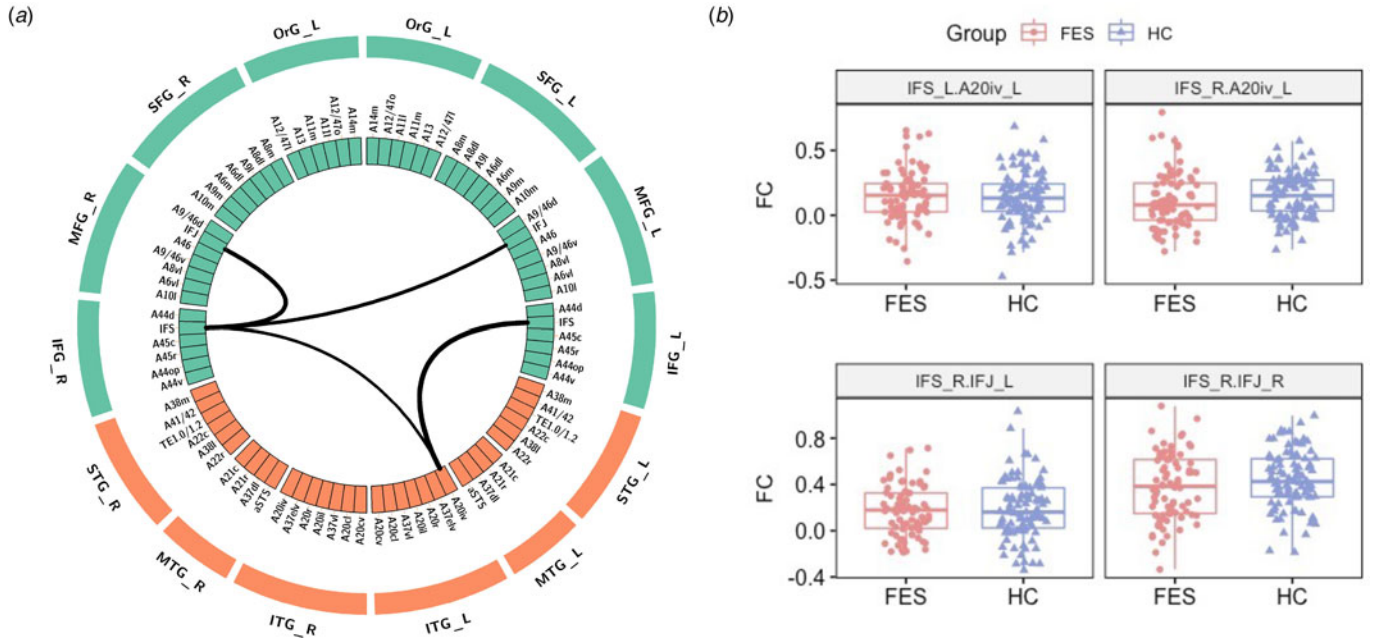

Fig. 3. Functional connectivity (FC) in the first-episode schizophrenia (FES) group and healthy control (HC) group. (*a*) Negative associations between PRS for schizophrenia (SzPRS) and FC are found in the FES group, including left IFG (inferior frontal sulcus, IFS) – left intermediate ventral ITG (A20iv_l), right IFG (inferior frontal sulcus, IFS) – left intermediate ventral ITG (A20iv_l), right IFG (inferior frontal sulcus, IFS) – left MFG (inferior frontal junction, IFJ), and right IFG (inferior frontal sulcus, IFS) – right MFG (inferior frontal junction, IFJ). FCs that showed significant association with SzPRS were drawn in black lines, with thicker lines indicating stronger associations ($p < 0.05$, FDR-corrected). (*b*) Mean values of four SzPRS-related FCs: left IFS – left A20iv, right IFS – left A20iv, right IFS – left IFJ, right IFS – right IFJ.

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Discussion

In this study, we found decreased FA in schizophrenia in many cerebral regions, including the genu and body of corpus callosum, bilateral cerebral peduncle, bilateral corona radiata, bilateral limb of the internal capsule, bilateral external capsule, bilateral superior longitudinal fasciculus, bilateral superior fronto-occipital fasciculus, and left cingulum. Among these commonly identified regions, our study pinpointed that, in patients with schizophrenia, but not healthy participants, SzPRS was negatively associated with the mean FA in the genu and body of corpus callosum, right anterior corona radiata, and right superior corona radiata. Similar patterns were observed in FC analysis, with a higher SzPRS associated with lower FCs in the left IFG – left ITG, right IFG – left ITG, right IFG – left MFG, and right IFG – right MFG observed in patients with schizophrenia instead of the HC. Thus, our results suggest that higher polygenic loading is associated with a more severe disrupted white matter integrity and FC, which is strongly driven by the interhemispheric callosal fibers and the connected frontotemporal regions.

In line with previous large-sample studies (International Schizophrenia et al., 2009; Li et al., 2017; Schizophrenia Working Group of the Psychiatric Genomics, 2014), we observed significant higher SzPRS in the FES group compared with the HC group. We also found decreased white matter FA in schizophrenia located in many commonly identified regions, including the genu and body of corpus callosum, bilateral cerebral peduncle, bilateral corona radiata, bilateral limb of the internal capsule, bilateral external capsule, bilateral superior longitudinal fasciculus, bilateral superior fronto-occipital fasciculus, and left cingulum. These results are consistent with the findings of the ENIGMA Schizophrenia DTI Working Group, which reported that the most prominent differences between schizophrenia and HC were conferred by white matter tracts of the frontotemporal, interhemispheric and corticothalamic regions (Kelly et al., 2018). Our results also showed both higher genetic vulnerability and more severe brain deficits in patients with schizophrenia, which may underlie the pathophysiological basis of schizophrenia as suggested by previous studies.

Among the regions with loss of integrity that significantly differed between schizophrenia and healthy participants, we found that within the FES group, but not HC, only four tracts showed a significant negative correlation between mean FA and SzPRS, that is, genu of the corpus callosum, a body of corpus callosum, right anterior corona radiata, and right superior corona radiata. As the largest white fiber bundle in the brain, the corpus callosum connects homologous regions of two cerebral hemispheres. The genu joins the left and right frontal lobes, while the body connects the bilateral temporal lobes and contains thickly myelinated commissural fibers for motor, somatosensory and auditory cortices (Kochunov et al., 2012; Mulert et al., 2012). Thus, the corpus callosum plays a crucial role in interhemispheric communication, information transfer and integration, and underlies many psychotic symptoms and cognitive impairments such as auditory hallucinations and working memory deficits (Kochunov et al., 2012; Mulert et al., 2012). As the fibers that repeatedly display the strongest case–control effects (Cetin-Karayumak et al., 2020; Kelly et al., 2018), disrupted interhemispheric callosal fibers in schizophrenia have been commonly interpreted as a consequence of abnormal neurodevelopment (Cetin-Karayumak et al., 2020; Kelly et al., 2018; Kochunov et al., 2012).

It has been postulated by the neurodevelopment hypothesis that schizophrenia is caused by environmental and genetic insults that occur during the perinatal period, early childhood, or adolescence, leading to perturbed axonal pruning and myelination; which in turn causes altered integrity and deviation from the normal developmental trajectory of the cerebral white matter, thus setting the stage for schizophrenia (Cetin-Karayumak et al., 2020; Kochunov et al., 2012; Murray, Bhavsar, Tripoli, & Howes, 2017; Rapoport, Giedd, & Gogtay, 2012). This model has been supported by numerous imaging studies in individuals at clinical high risk for psychosis (CHR), which reported a disrupted white matter prior to the onset of psychosis (Karlsgodt, Jacobson, Seal, & Fusar-Poli, 2012; Tang et al., 2019). Specifically, a multi-site, large-sample DTI study in patients with schizophrenia and HC identified moderate to large effect sizes for case–control differences in interhemispheric callosal fibers, which emerged even at 14 years of age, providing evidence for neurodevelopmental abnormalities of the interhemispheric connections (Cetin-Karayumak et al., 2020). Furthermore, myelination of the corpus callosum is initiated at 4 months of age and matures in adolescence to young adulthood (Kochunov et al., 2012; Tanaka-Arakawa et al., 2015), coinciding with the age of peak risk for developing schizophrenia (Cetin-Karayumak et al., 2020; Karlsgodt et al., 2012), which makes individuals in these age groups more vulnerable to genetic risks and other environmental factors that occur in the early stages of the lifespan. As an extension to the interhemispheric connection, the corona radiata serves as a link between the corpus callosum and cerebral cortex, and jointly connects the bilateral frontal cortex with CC; thus, it has been associated with hallucinations and many cognitive impairments in schizophrenia (Curcic-Blake et al., 2015; Wakana, Jiang, Nagae-Poetscher, van Zijl, & Mori, 2004). The corona radiata consists of a mixture of various projections, associations, and callosal fibers (Wakana et al., 2004). In particular, it contains fiber tracts that are associated with primary motor and sensory functions, such as the corticospinal tract and corticothalamic fascicle (Wakana et al., 2004), making the corona radiata one of the most prominent early maturing tracts and, thus, more prone to be affected by genetic architecture (Kochunov et al., 2012). Our findings are further supported by the DTI studies in twins and pedigrees, which pinpointed a 79% heritability of corpus callosum FA and 57% heritability of corona radiata FA (Glahn et al., 2013; Vuoksimaa et al., 2017), indicating that the white matter FA of these fibers is highly dominated by the genetic substrate. Therefore, the observed association between higher genetic loading and lower white matter FA in patients with schizophrenia in our study might reveal a neurodevelopmental abnormality in interhemispheric callosal fibers, suggesting that genetic deficits could underlie the disruption of normal neurodevelopment trajectory, which in turn leads to the 'disconnection syndrome' in schizophrenia (Ellison-Wright & Bullmore, 2009). Moreover, the lack of association between FA and SzPRS in healthy individuals is reasonable since the SzPRS of HC is significantly lower than the patients, which is far less likely to raise structural alterations than the patients. However, Simões et al., reported no significant correlation between the SzPRS and FA or MD, with a trend-level negative effect of SzPRS on FA in the bilateral cingulum, bilateral superior longitudinal fasciculus, and bilateral right corpus callosum, etc. This discrepancy could be due to the cross-diagnostic sample of Simões et al., that involved schizophrenia, bipolar disorder (BD), SZ/BD relatives, and HC, while our study was performed in drug-naïve

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FES, regardless of the effect of antipsychotics. Moreover, the methodological difference could also be the reason leading to such discrepancy, considering that Simões et al., tested the association between SzPRS and FA on the whole-skeleton basis, while our study focused on the regions that showed WM disruptions in the FES group (compared with HC), which narrowed down the areas tested in the analysis. Further studies using other methodology/measures such as tractography or WM connectome are also needed to examine the effect of SzPRS on white matter, providing more detailed evidence for this hypothesis.

We further investigated whether SzPRS also influences the FC in the regions mainly connected by CC and CR. We observed negative associations between SzPRS and FCs in the left IFG – left ITG, right IFG – left ITG, right IFG – left MFG, and right IFG – right MFG. A similar pattern was reported by Liu et al., who found that lower hippocampus –mPFC FC in schizophrenia was correlated with a higher SzPRS (Liu et al., 2020). Such association between higher genetic loading and decreased FC was only observed in the group of patients rather than in healthy participants, which is consistent with our findings in white matter FA. Disruption of frontotemporal integration has been reported in several functional neuroimaging studies in schizophrenia (Lawrie et al., 2002; Mwansisya et al., 2017; Pettersson-Yeo, Allen, Benetti, McGuire, & Mechelli, 2011). The fronto-temporal regions harbor many regions that play a critical role in the core pathophysiology of schizophrenia, including the language comprehension and production centers that underlie the auditory verbal hallucinations, thus has been a commonly identified target for treatments such as transcranial direct current stimulation (tDCS) (Bose et al., 2018; Lawrie et al., 2002). As posited by the dysconnectivity hypothesis, abnormal communication in spatially disparate cerebral regions might stem from the disrupted white matter tracts that connected these regions (Ellison-Wright & Bullmore, 2009; Konrad & Winterer, 2008), and may result in a failure of proper functional integration within the brain, thus giving rise to psychotic symptoms and cognitive impairments in schizophrenia (Hubl et al., 2004; Kochunov et al., 2017). Hence, the negative association between polygenic risks and FCs in frontotemporal regions in schizophrenia observed in our study could be interpreted as a penetrance of genetic effects based on the anatomical connectivity of the white matter fibers. Nevertheless, such interpretation should be rendered with caution, since we failed to find a diagnostic group difference in these four FCs. It is likely that the common genetic variants of schizophrenia and the functional integration may not share a direct mechanism. That being said, genetic loading may affect these four FCs via other adjacent impaired frontotemporal regions. Further studies using other measures such as effective connectivity (EC) are needed to investigate this hypothesis and test if casual dynamic connectivity was associated with polygenic risks within the frontotemporal regions.

As an additional analysis, we investigated the associations between SzPRS, SzPRS-related FA/FCs, and psychotic symptoms. We first tested the association between SzPRS-related FA/FCs and PANNS scores. We found a significant positive correlation between PANSS general scores and the FC between the right IFG and left intermediate ventral ITG. Regarding the white matter, FA in the right superior corona radiata was marginally positively correlated with PANSS positive scores, while FA in the body of corpus callosum showed a marginal negative correlation with PANSS negative scores. However, in line with the previous findings of Liu et al. (Liu et al. 2020), no associations were found between PANSS scores and SzPRS. These results serve as evidence that the effect of genes may show higher penetrance at the biological level than at the behavioral level, and could be detected by biologically proximate approaches such as neuroimaging phenotypes (Wang et al., 2018). We further tested the mediation effect of SzPRS-related FAs and FCs and found no mediating role of FA or FC in any region between SzPRS and PANSS scores.

The generalizability of our results is subject to certain limitations. First, our sample size was relatively small, raising the possibility of Type II errors. Future studies are needed to replicate our results using a larger dataset. Second, our study is a cross-sectional case–control study; thus, we could not establish a causal relationship between polygenic risks and imaging phenotypes. Future studies are needed to validate our findings within a birth cohort or CHR cohort to examine the relationship between polygenic risk, white matter dysconnectivity, and the onset of psychosis. It would also be of interest for future studies to examine whether polygenic risks influence the effect of antipsychotics on brain structure and function in schizophrenia. Third, we did not consider the impact of rare variants, gene-gene interactions, or environmental effects. Although we identified the association between polygenic risks, white matter integrity, and FC, we lack a complete understanding of the underlying functional pathways of the genes that contribute to the relationship with imaging traits. We plan to address these questions in our future studies.

In conclusion, our study found a replicable, widespread disruption of white matter integrity in patients with FES. We observed an association between higher polygenic risks and more severely disrupted white matter integrity and FC, which is strongly driven by interhemispheric callosal fibers and the connected frontotemporal regions. Such associations were observed only in the schizophrenia group rather than the healthy control group. Our findings identified the effect of polygenic risks on brain structure and function, providing new insights into the etiology and pathogenesis of this disorder, and provided potential neuroimaging phenotypes for the improved identification and intervention in schizophrenia.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0033291721004840.

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Ethical standards. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

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