



## RESEARCH ARTICLE

# Function–structure coupling: White matter functional magnetic resonance imaging hyper-activation associates with structural integrity reductions in schizophrenia

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## Abstract

White matter (WM) microstructure deficit may be an underlying factor in the brain dysconnectivity hypothesis of schizophrenia using diffusion tensor imaging (DTI). However, WM dysfunction is unclear in schizophrenia. This study aimed to investigate the association between structural deficits and functional disturbances in major WM tracts in schizophrenia. Using functional magnetic resonance imaging (fMRI) and DTI, we developed the skeleton-based WM functional analysis, which could achieve voxel-wise function–structure coupling by projecting the fMRI signals onto a skeleton in WM. We measured the fractional anisotropy (FA) and WM low-frequency oscillation (LFO) and their couplings in 93 schizophrenia patients and 122 healthy controls (HCs). An independent open database (62 schizophrenia patients and 71 HCs) was used to test the reproducibility. Finally, associations between WM LFO and five behaviour assessment categories (cognition, emotion, motor, personality and sensory) were examined. This study revealed a reversed pattern of structure and function in frontotemporal tracts, as follows. (a) WM hyper-LFO was associated with reduced FA in schizophrenia. (b) The function–structure association was positive in HCs but negative in schizophrenia patients. Furthermore, function–structure dissociation was exacerbated by long illness duration and severe negative symptoms. (c) WM activations were significantly related to cognition and emotion. This study indicated function–structure dys-coupling, with higher LFO and reduced structural integration in frontotemporal WM, which may reflect a potential mechanism in WM neuropathologic processing of schizophrenia.

## KEYWORDS

activation, diffusion tensor imaging, fMRI, frontal, schizophrenia, white matter

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**1 | INTRODUCTION**

The mechanism of schizophrenia (SZ) has been postulated through the brain dysconnectivity hypothesis, positing that SZ is the result of ineffective or inefficient communications between brain regions (Dong et al., 2019). As brain grey matter regions interconnect with white matter (WM), which is composed mainly of myelinated axons, WM damage may be an underlying factor in the pathological changes of SZ (Kelly et al., 2018). Neuroimaging studies have also provided broad support for the disturbances of WM in both structural and functional organization in SZ (Dong et al., 2017; Jiang, Luo, et al., 2019). Furthermore, these abnormalities in WM have been linked to cognitive deficits, clinical symptoms and genetic alterations in SZ (Kochunov et al., 2017; Monin et al., 2015). Diffusion tensor imaging (DTI) has revealed widespread WM microstructure abnormalities in SZ patients (Kelly et al., 2018). A recent meta-analysis consisting of 1,963 SZ patients and 2,359 healthy subjects revealed that WM microstructure alterations involve frontal, temporal and occipital lobes, as well as major fibre tracts connecting these regions, with lower fractional anisotropy (FA) in SZ patients (Kelly et al., 2018).

As for WM function, increasing numbers of works have indicated the existence of brain functional activation in WM, as revealed by the blood oxygenation level-dependent (BOLD) signal in functional magnetic resonance imaging (fMRI). For instance, specific regions in WM can be functionally activated in multiple tasks that correspond to different functional demands, including perceptual, language and motor processing demands (Courtemanche, Sparrey, Song, MacKay, & D'Arcy, 2018; Gawryluk, Mazerolle, Beyea, & D'Arcy, 2014). Ji et al. found that the power of low-frequency BOLD fluctuations in the optic radiation was higher in the visual stimulation state than in the resting state, suggesting that BOLD signal in WM could be modulated by physiological states (Ji, Liao, Chen, Zhang, & Wang, 2017). Additionally, BOLD signals within WM exhibited an intrinsic functional organization rather than random noise, even during the resting-state (Peer, Nitzan, Bick, Levin, & Arzyt, 2017). The anatomical bundles in WM can also be identified by DTI tracking with fMRI in the human brain (Ding et al., 2013; Peer et al., 2017). A recent study also reported the similarities between resting-state fMRI, DTI and histological connectivity in non-human primate brains (Wu et al., 2019). This evidence indicates that the fMRI BOLD signal is a novel perspective for investigating WM

dysfunction in brain disorders such as mild cognitive impairment, epilepsy, Alzheimer's and Parkinson's diseases (Ji et al., 2019; Jiang, Song, et al., 2019; Makedonov, et al., 2016). More recently, our study revealed disrupted functional synchronization between WM and grey matter networks in SZ (Jiang, Song, et al., 2019; Jiang, Luo, et al., 2019).

However, it remains unclear whether structural and functional abnormalities detected by DTI and fMRI are localized in common WM tracts or whether there is an association between structural deficits and functional disturbances in WM-specific regions. To address these questions, we developed a DTI-fMRI fusion approach by projecting the WM microstructural features (FA) from DTI and the WM functional signals (BOLD time series) of fMRI onto a common WM skeleton based on the idea of tract-based spatial statistics (TBSS). Using this approach, we examined WM functions estimated by resting-state LFOs in the WM skeleton in 97 patients with SZ and 126 healthy subjects. We investigated common WM tracts with FA and WM function differences and further evaluated their associations.

**2 | MATERIALS AND METHODS****2.1 | Subjects**

The current study recruited 97 SZ patients and 126 healthy subjects (HC) from the Clinical Hospital of Chengdu Brain Science Institute (CHCBSI), China. Psychiatric symptom severity was assessed using the Positive and Negative Syndrome Scale (PANSS). History of major medical or neurological abnormalities, substance abuse, or other contraindications to MRI was considered as the exclusion criteria for all subjects. In addition, to eliminate potential familial effects, we further excluded healthy participants whose first- and second-degree relatives had a history of mental disorders. Two patients were first-episode and 95 were chronic. All of the SZ patients received antipsychotic medications. More information about the subjects is provided in Table 1. Written informed consent was signed by each participant before MRI scanning. The Ethics Committee of CHCBSI approved this study. Some of the patients were part of our previous studies and have been described in prior published studies (Dong et al., 2019) (more details are listed in the Supplementary Materials).

**TABLE 1** Demographic and clinical characteristics of subjects

	Schizophrenia	HCs	p-Value
Number <sup>a</sup>	93	122	—
Gender (female/male)	28/65	41/81	.586 <sup>b</sup>
Age (years)	40.01 ± 11.49	37.95 ± 14.74	.267 <sup>c</sup>
Education (years)	11.47 ± 2.51	11.07 ± 3.07	.299 <sup>c</sup>
White matter volume (mm <sup>3</sup> )	489.96 ± 57.46	495.65 ± 55.09	.463 <sup>c</sup>
Disease duration (years)	15.22 ± 10.27	—	—
Chlorpromazine equivalents (mg/day)	337.96 ± 145.26	—	—
PANSS scores			
Positive score	13.32 ± 5.89	—	—
Negative score	20.7 ± 6.06	—	—
General score	28.19 ± 5.86	—	—
Total score	62.21 ± 13.26	—	—

Abbreviations: DTI, diffusion tensor imaging; fMRI, functional magnetic resonance imaging; HC, healthy control; PANSS, Positive and Negative Syndrome Scale; SZ, schizophrenia.

<sup>a</sup>Represents that four SZ patients and four HCs were excluded from original database (97 SZ and 126 HCs) because they failed to accomplish all of the T1, resting-state fMRI and DTI data acquisitions, or their head motion beyond 2 mm or 2°.

<sup>b</sup>p-Value was obtained by the chi-square test.

<sup>c</sup>p-Value was obtained using the two-sample t test.

## 2.2 | Data acquisition

High-resolution T1-weighted images, resting-state fMRI and diffusion-weighted images were acquired in a 3.0 Tesla GE MRI scanner (DISCOVERY MR 750). Detailed scanning parameters are described in the Supplementary Material.

## 2.3 | Data processing: Skeleton-based WM functional analysis

We developed a DTI-fMRI fusion approach by projecting the WM microstructural image (i.e., the FA image) and the WM functional images onto a common WM skeleton based on the idea of TBSS. This method could achieve the assessment of function-structure coupling at voxel-wise in WM. Figure 1 provided a flowchart of the skeleton-based WM functional analysis.

### 2.3.1 | DTI data processing

The DTI data were preprocessed in FSL (<https://www.fmrib.ox.ac.uk/fsl>). First, eddy current distortions, head motion correction and brain extraction were performed using FSL's "eddy current correction" and the Brain Extraction Tool. Second, the FA image of each subject was estimated using DTIFIT ([https://www.fmrib.ox.ac.uk/fsl/fdt/fdt\\_dtfit.html](https://www.fmrib.ox.ac.uk/fsl/fdt/fdt_dtfit.html)). Next, all subjects' FA images were nonlinearly registered into a common space using the nonlinear registration tool FNIRT. Then, the mean FA images across all subjects were thinned to create a WM FA skeleton. The FA skeleton represented the centres of all WM tracts common to the group. Finally, each subject's FA image was projected

into the FA skeleton to obtain an individual FA skeleton map. In total, this analysis obtained all subjects' FA skeleton maps, which were used for the following statistics.

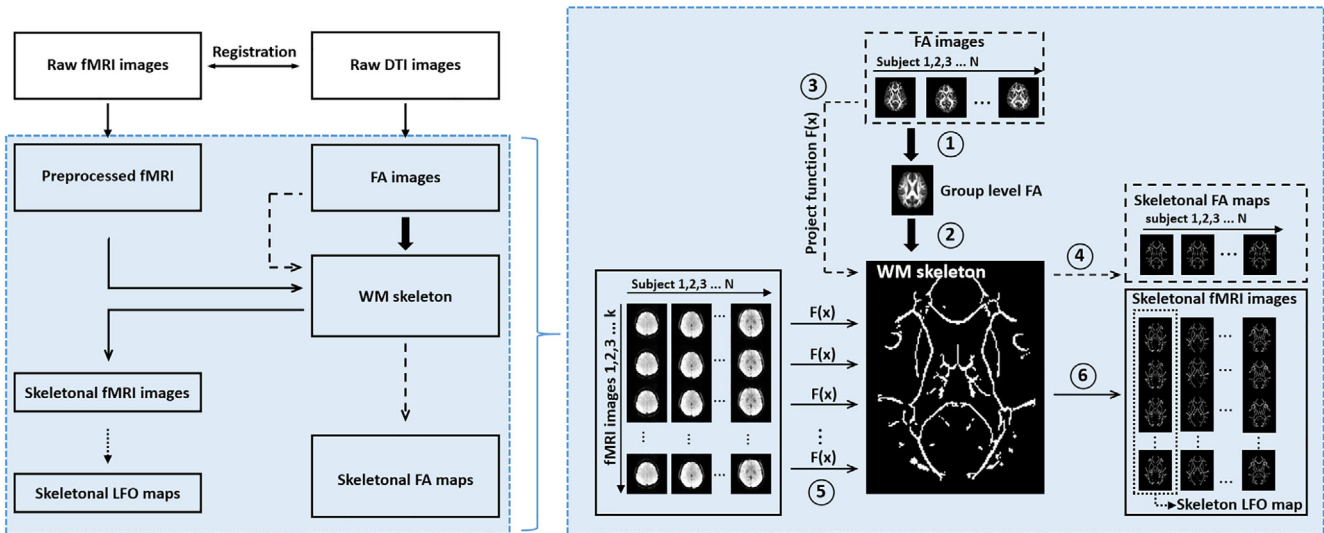
### 2.3.2 | fMRI data processing

First, for each subject's fMRI data, the first five volumes of fMRI time series were removed. Second, pre-processing procedures, including slice-timing correction and head motion correction, were performed. Subjects with maximum head motion >2 mm or 2° were excluded. The mean frame displacement (FD) was also calculated to compare the difference between the two groups. Nuisance signals (24-parameter head motion and cerebrospinal fluid) and linear trend were further regressed out by a multiple linear regression model. Next, for each subject, the pre-processed functional images were registered to corresponding diffusion b0 image and then non-linearly projected onto the FA skeleton using the same transformation function in the DTI analysis. This resulted in a time series of skeletonized functional images. By projecting the functional images to the FA skeleton space, this procedure could theoretically improve sensitivity by reducing heterogeneity between individuals. In addition, this projection can reduce the methodological bias caused by misalignment and misregistration between DTI and fMRI space compared with that in conventional voxel-based analysis (Smith et al., 2006).

### 2.3.3 | LFOs of the WM skeleton

To characterize the WM activation, we estimate the LFO of the WM skeleton. The amplitude of low frequency fluctuation (ALFF) value

A flowchart of the Skeleton-based White matter Functional Analysis



**FIGURE 1** A flowchart of the skeleton-based white matter functional analysis (SWAF), which was achieved by projecting the microstructural features (FA) of diffusion tensor imaging (DTI) and the white matter (WM) blood oxygenation level-dependent (BOLD) signals of functional magnetic resonance imaging (fMRI) onto a common WM skeleton. (1) The raw DTI images were preprocessed using the FSL (<https://www.fmrib.ox.ac.uk/fsl>) and the individual FA image was further nonlinearly registered into a normalized MNI template. A group-level FA image was obtained by averaging across all subjects' FA images. (2) The group-level FA image was thinned to create a WM FA skeleton. The WM skeleton represented the centres of all WM tracts common to the group. (3–4) Each subject's FA image was projected onto the WM skeleton using the tract-based spatial statistics (TBSS) and yielded the projection function  $F(x)$ . This projection generated a skeletal FA map for each subject. (5–6) The raw fMRI images were registered into DTI b0 space and further preprocessed. Subsequently, the preprocessed fMRI images were projected onto the WM skeleton using the same projection function  $F(x)$  in the FA analysis. Finally, the skeletal fMRI images were temporally filtered (band-pass, 0.01–0.08 Hz), and the amplitude of low frequency fluctuation was calculated to obtain the low-frequency oscillations (LFO) maps

(Zang et al., 2007) was calculated for each voxel and yielded the skeleton-based WM amplitude of low frequency fluctuation (SWALFF) map. Specifically, the time series of a voxel were transformed into the frequency domain using the fast Fourier transform to obtain the power spectrum. The square root was calculated at each frequency and the averaged square root across 0.01–0.1 Hz was taken as the ALFF value. For standardization purposes, the ALFF of each voxel was divided by the skeleton-averaged ALFF value for each subject (Yan, Craddock, Zuo, Zang, & Milham, 2013).

### 2.3.4 | Dynamic LFO of the WM skeleton

To further characterize the temporal dynamics of the LFO in the WM skeleton, we measured time-varying LFO using a sliding window approach (Dong et al., 2019) by quantifying the temporal variability of the SWALFF. Previous studies indicated that window lengths less than  $1/f_{min}$  may increase the risk of spurious fluctuations in the computation of dynamic LFO (Leonardi & van de Ville, 2015). The  $f_{min}$  was the minimum frequency of the time series of resting-state fMRI. A longer sliding window length may hinder the characterization of the temporal variability in the dynamic LFO (Leonardi & van de Ville, 2015). Thus, we used the optimal window length of 50 TRs (100 s) to calculate the dynamics of LFO. Using a window length of

50 TRs and a sliding step of five TRs, the full time series of 250 TRs (500 s) were divided into 40 windows for each subject. In each sliding window, the SWALFF map was calculated with a frequency band of 0.01–0.1 Hz. Subsequently, the coefficient of variation of SWALFF maps across sliding windows was computed to measure the dynamics of the SWALFF (dSWALFF).

### 2.4 | Statistics: Differences in FA, SWALFF and dSWALFF between SZ patients and HCs

For FA skeleton maps, SWALFF maps and dSWALFF maps, two-sample *t* tests were used to compare the differences between SZ patients and HCs. Age, gender and education years were considered as covariates. Multiple comparisons correction was performed using the threshold-free cluster enhancement method ( $p < .05$ , FWE correction) (Smith & Nichols, 2009).

To validate whether these WM differences between SZ patients and HCs from the current sample could also be observed on another independent SZ database, a publicly available SZ database (COBRE) (Cetin et al., 2014), including raw anatomical, diffusion and fMRI data from 62 patients with SZ and 71 HCs, was used to calculate the FA, SWALFF and dSWALFF maps. The detailed subject information from the COBRE database is shown in the Supplementary Material.

## 2.5 | Overlapping of dysfunctional WM tracts with microstructural deficits

To further investigate the associations between WM dysfunction and microstructural deficits, the tracts overlapping with FA-altered voxels and SWALFF-altered or dSWALFF-altered voxels were extracted. The Kolmogorov–Smirnov tests were used to examine the normal distribution of the variables. Subsequently, Pearson's correlation coefficient was calculated between FA values and SWALFF or dSWALFF values in the overlapping tracts.

## 2.6 | Relationships between WM function–structure coupling and clinical variables in SZ patients

We investigated the relationships between WM function–structure coupling and clinical variables in SZ patients. Specifically, the function–structure differences in WM were extracted. To reflect a mismatch between two modality feature alterations, the function–structure ratio (FSR) was calculated as the following formula.

$$FSR = \frac{SWALFF}{FA}$$

Following the normality test by the Kolmogorov–Smirnov test, Pearson's correlation analyses were subsequently conducted to assess the associations between clinical features (PANSS values and duration of illness) and FSR in SZ patients.

## 2.7 | Associations between WM LFO and behaviours

To further examine the relationship between the WM LFO and behaviour variables, an independent sample (HCP database, “100 unrelated subjects” dataset release available at <http://db.humanconnectome.org>) (Van Essen, et al., 2013), including multimodal MRI data and behaviour data from 100 unrelated healthy subjects, was used in this study. Canonical correlation analyses were used to estimate the associations between WM LFO and five behaviour assessment categories (cognition, emotion, motor, personality and sensory). Detailed information about the behaviour analysis is shown in the Supplementary Material.

## 2.8 | Reproducibility analysis on a test–retest database

To investigate the reproducibility and repeatability of SWALFF and dSWALFF in the detection of WM LFO, a publicly available test–retest

database from the Consortium for Reliability and Reproducibility (CoRR, [https://fcon\\_1000.projects.nitrc.org/indi/CoRR/html/data\\_citation.html](https://fcon_1000.projects.nitrc.org/indi/CoRR/html/data_citation.html)) (Zuo et al., 2014) was used to retest SWALFF and dSWALFF maps. The NHU database ([https://doi.org/10.15387/fcp\\_indi.corr.hnu1](https://doi.org/10.15387/fcp_indi.corr.hnu1)) from the CoRR includes 30 healthy adults (mean age: 24.4 years, range: 20–30 years, 15 females). Each participant received 10 scans across 1 month, one scan occur every 3 days. This HNU database was used to test the reproducibility of WM LFO in different scans. The detailed subject information from the HNU database and methods are shown in the Supplementary Material.

## 3 | RESULTS

### 3.1 | Subject information

Four SZ patients and four HCs were excluded from this study because they failed to accomplish all of the T1, resting-state fMRI and DTI data acquisitions, or head motion in these scans was larger than 2 mm or 2°. Two groups showed no significant differences in age, gender, education, FD or WM volume ( $p > .05$ ). Information on the subjects is provided in Table 1.

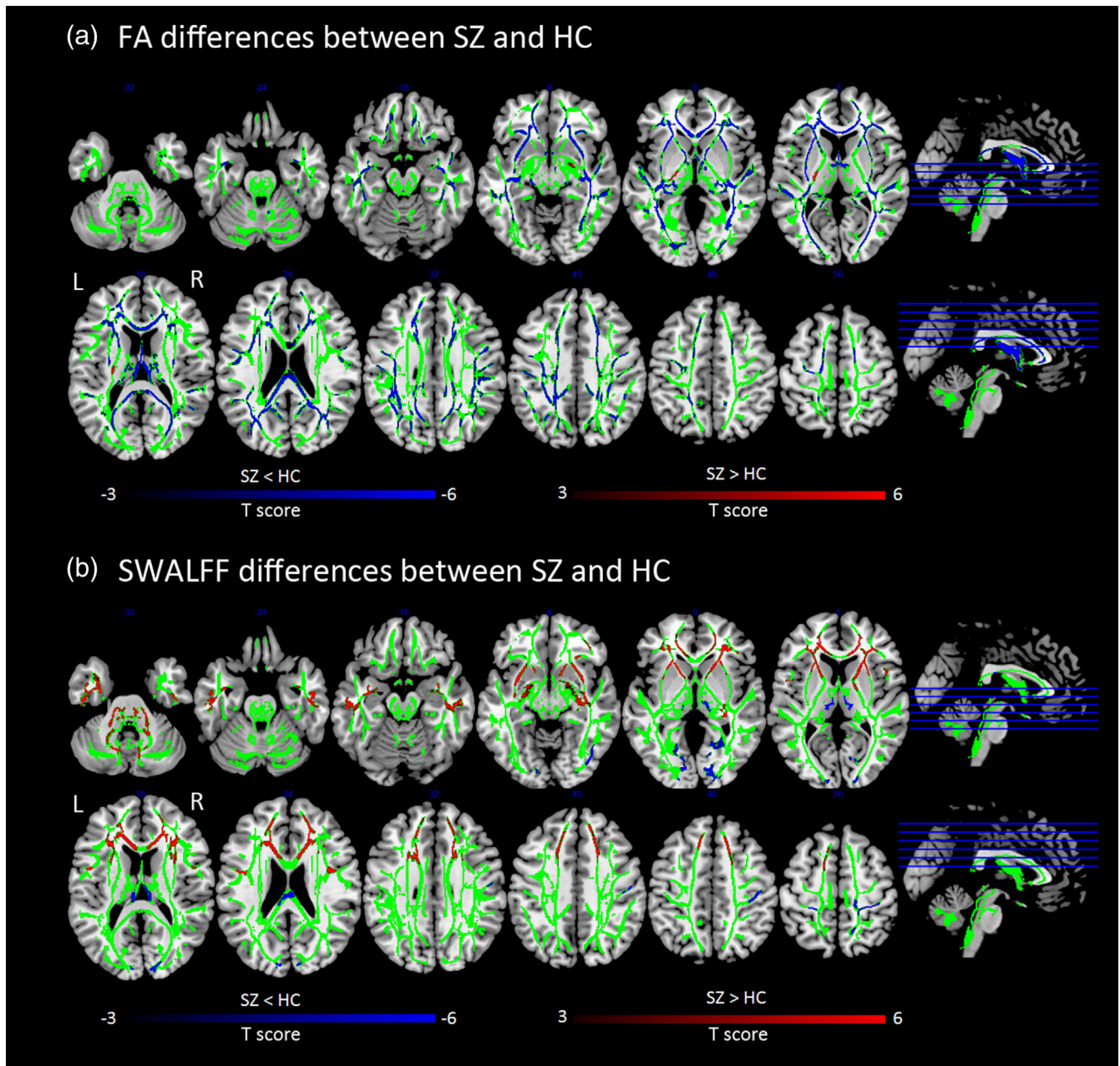
### 3.2 | Differences in FA, SWALFF and dSWALFF between SZ patients and HCs

Two-sample *t* tests ( $p < .05$ , FWE correction) showed widespread FA reductions within a WM skeleton representing all major WM fasciculi in SZ patients and found a significant increase in FA only in the left posterior limb of the internal capsule (PLIC) in the SZ group (Figure 2a). We also applied another WM microstructural measure of the mean diffusivity (MD). The differences in the MD between SZ patients and HCs showed very high spatial overlap with the results of the FA measure (Figure S1), which further validated the widespread WM microstructural deficits in SZ patients.

Compared with HCs, the SZ group exhibited higher SWALFF in WM tracts within the frontal area (anterior corona radiata [ACR] and genu of the corpus callosum [GCC]), temporal regions and anterior limbs of the internal capsule (ALIC) and cerebellum ( $p < .05$ , FWE correction) (Figure 2b). In addition, decreased SWALFF was observed in WM fibres in the occipital area, post-central regions, fornix and splenium of corpus callosum (SCC) of SZ patients compared with that in HCs ( $p < .05$ , FWE correction) (Figure 2b). In addition, increased dSWALFF was observed in the WM tracts of the frontal area (ACR, GCC and orbitofrontal region [OBF]), external capsule and hippocampus in SZ patients compared with that in HCs ( $p < .05$ , FWE correction) (Figure 2c). The effect size (Cohen's *d*) maps of differences in FA, MD, SWALFF and dSWALFF are provided in the Figure S2.

We examined whether different sliding steps could influence the group differences of LFO in WM. In addition to the sliding





**FIGURE 2** (a) Differences of fractional anisotropy (FA) skeleton between schizophrenia (SZ) and healthy controls (HCs). Two-sample *t* tests ( $p < .05$ , FWE correction) showed widespread FA reductions within a white matter (WM) skeleton representing all major WM fasciculi in SZ, and found a significant increased FA only in the left posterior limb of internal capsule (PLIC). (b) Differences of skeleton-based white matter amplitude of low frequency fluctuation (SWALFF) between SZ and HCs. In SZ, enhanced SWALFF in WM tracts within frontal area (anterior corona radiata [ACR] and genu of corpus callosum [GCC]), temporal regions and anterior limb of internal capsule (ALIC) as well as cerebellum ( $p < .05$ , FWE correction). Decreased SWALFF was observed in WM fibres in occipital area, post-central regions, fornix and splenium of corpus callosum (SCC) compared with HCs ( $p < .05$ , FWE correction). (c) Differences of dynamic SWALFF between SZ and HCs. Increased dynamic SWALFF was observed in WM tracts of frontal area (ACR, GCC and orbitofrontal region [OBF]), external capsule and hippocampus in SZ. (d) Overlapped WM tracts of dysfunction (SWALFF-altered and dynamics of the SWALFF (dSWALFF)-altered) with microstructural deficits (FA-altered). The green colour represents the WM skeleton. The blue colour represents the overlapped tracts between FA-altered and SWALFF-altered. The red colour represents the overlapped tracts between FA-altered and dSWALFF-altered. The orange colour represents the overlapped tracts between SWALFF-altered and dSWALFF-altered. The violet colour represents the overlapped tracts among FA-altered, SWALFF-altered and dSWALFF-altered

steps of five TRs in the computation of dSWALFF, multiple sliding steps of three TRs, four TRs, six TRs and seven TRs were also considered to reproduce the main results (Figure S3). Another

COBRE SZ samples showed consistent differences in the FA, SWALFF and dSWALFF, compared with that from HCs (Figure S4).

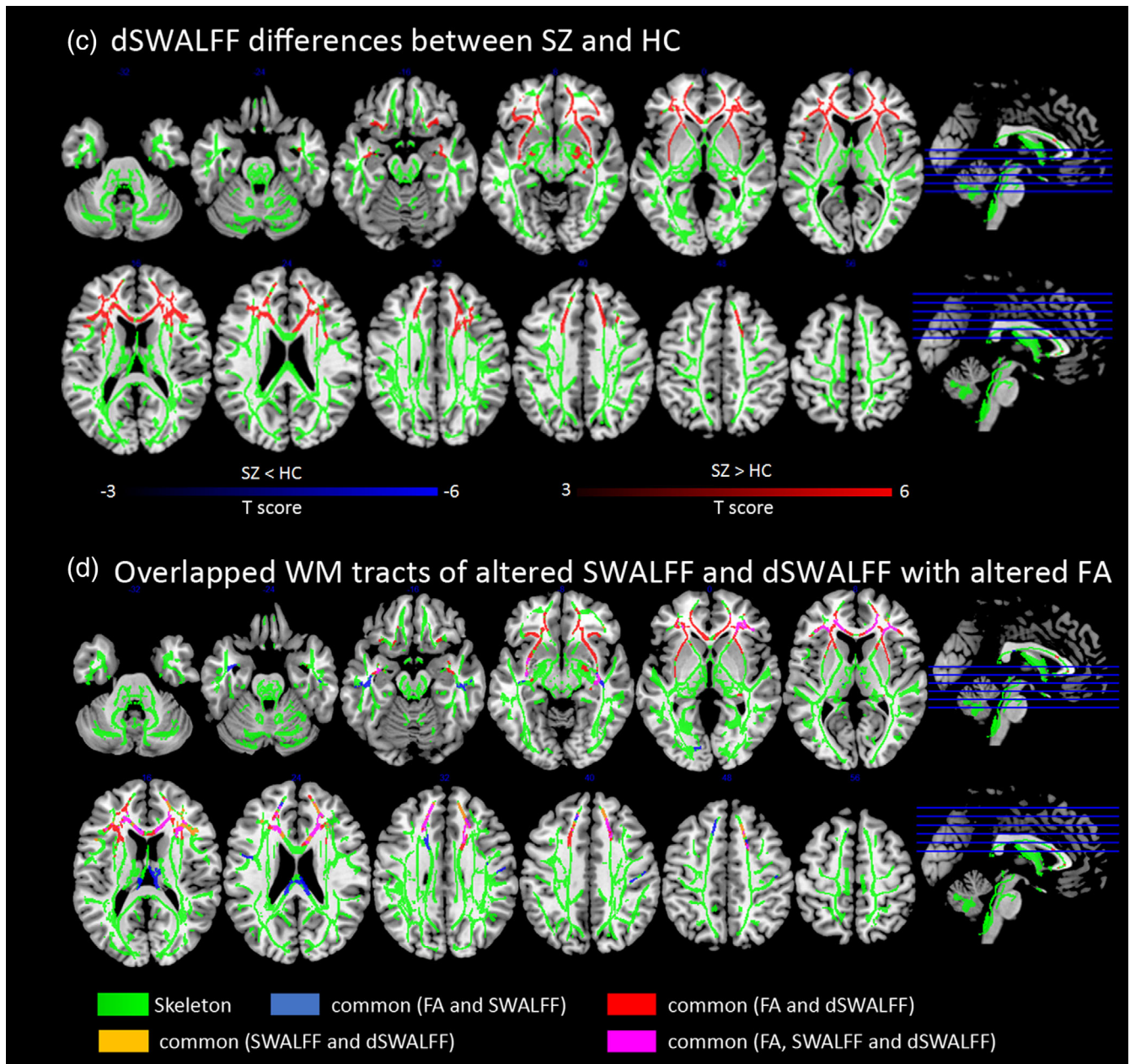


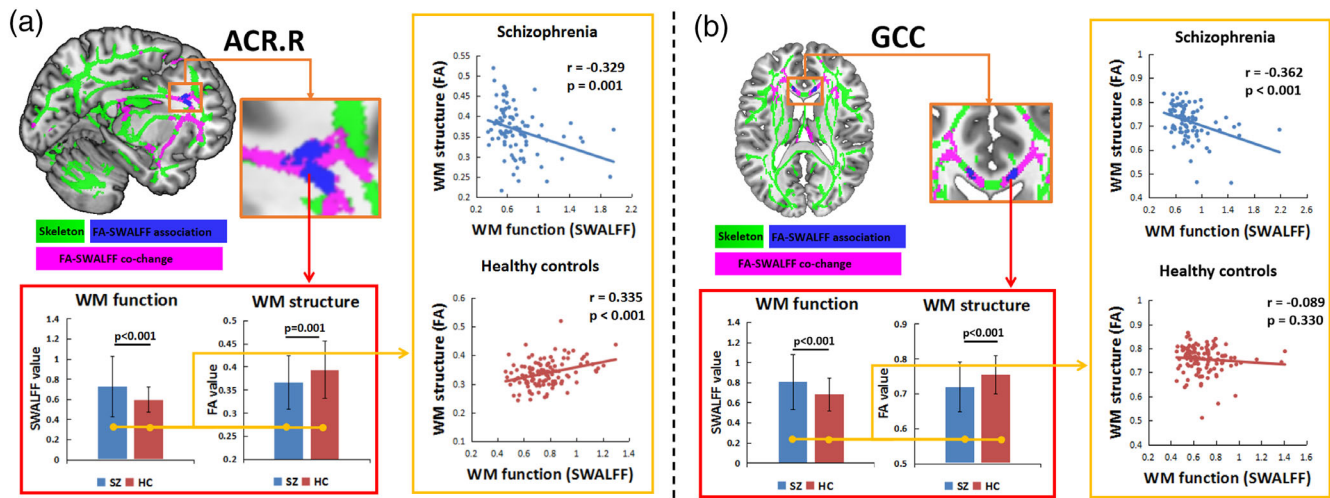
FIGURE 2 (Continued)

### 3.3 | Overlapping tracts of FA-altered voxels with SWALFF or dSWALFF alterations

Figure 2d shows the WM tracts overlapping with co-alterations in the microstructure (FA) and LFO (SWALFF and dSWALFF). These overlapping tracts were located in the bilateral OBF, ACR, GCC, ALIC, external capsule, SCC, hippocampus and fornix (Figure 2d). Furthermore, within these overlapping tracts, the right ACR (Figure 3a) shows increased SWALFF ( $T = 4.16$ ,  $p < .001$ , effect size = 0.549, confidence interval [CI] = [0.067, 0.186]) and decreased FA ( $T = -3.25$ ,  $p = .001$ , effect size =  $-0.449$ , CI =  $[-0.044, -0.011]$ ) in SZ compared to HCs. Increased SWALFF ( $T = 4.08$ ,  $p < .001$ , effect

size = 0.540, CI = [0.063, 0.182]) and decreased FA ( $T = -4.13$ ,  $p < .001$ , effect size =  $-0.563$ , CI =  $[-0.053, -0.019]$ ) was found in the GCC in the SZ group (Figure 3b). Significant negative associations between FA and SWALFF were also observed in the right ACR ( $r = -.329$ ,  $p = .001$ ) and bilateral GCC ( $r = -.362$ ,  $p < .001$ ) for SZ patients. Conversely, in the HC group, we only found significant positive correlations between FA and SWALFF in the right ACR ( $r = .335$ ,  $p < .001$ ). In addition, there were negative correlations between FA and dSWALFF in the left external capsule, right OBF and bilateral GCC in SZ (Table S1). These correlations showed significant group differences between SZ and HC by the non-parametric permutation test (Supplementary Materials).





**FIGURE 3** White matter (WM) tract of (a) right anterior corona radiata (ACR) and (b) genu of corpus callosum (GCC) shows increased skeleton-based WM amplitude of low frequency fluctuation (SWALFF) and decreased fractional anisotropy (FA) in schizophrenia (SZ) compared to healthy controls (HCs). The association between FA-altered and SWALFF-altered exhibits the negative correlation in SZ but positive correlation in HCs. SWALFF, skeleton-based white matter amplitude of low frequency fluctuation

### 3.4 | Relationship between clinical variables and WM function–structure coupling in SZ

There was a significant positive correlation between illness duration and FSR in the right OBF, right ACR, right hippocampus and bilateral GCC in the SZ group (Table S2). In addition, the FSR in the right hippocampus was significantly correlated with negative PANSS scores (Table S2). Furthermore, these associations remained significant even after controlling for the effects of education, WM volume and anti-psychotics. Finally, we conducted a correlation analysis between head motion parameter and SWALFF and dSWALFF to preclude the possible effect of head motion in our results. There was no significant correlation between the FD and SWALFF or dSWALFF (all  $p > .05$ ) in the SZ or HC groups, which supported that our results were not dependent upon head motion.

### 3.5 | Association between WM LFO and behaviour scores

Canonical correlation analysis on the HCP database illustrated significant associations between the WM SWALFF and the cognitive features ( $R^2 = .980$ ,  $p < .001$ ) as well as emotional features ( $R^2 = .973$ ,  $p < .001$ ) in healthy subjects (Figure 4a1). Additionally, the dSWALFF was significantly associated with the cognition features ( $R^2 = .909$ ,  $p = .003$ ) (Figure 4a2). In addition, Pearson's correlation analysis showed that the SWALFF in GCC was significantly negatively associated with cognition instruments, including reading decoding, self-regulation/impulsivity and cognition crystallized composite ( $p < .05$ , FDR correction) (Figure 4b1). The dSWALFF in the GCC was negatively correlated with self-regulation/impulsivity ( $p < .05$ , FDR correction)

(Figure 4b2). More details are provided in the Supplementary Materials.

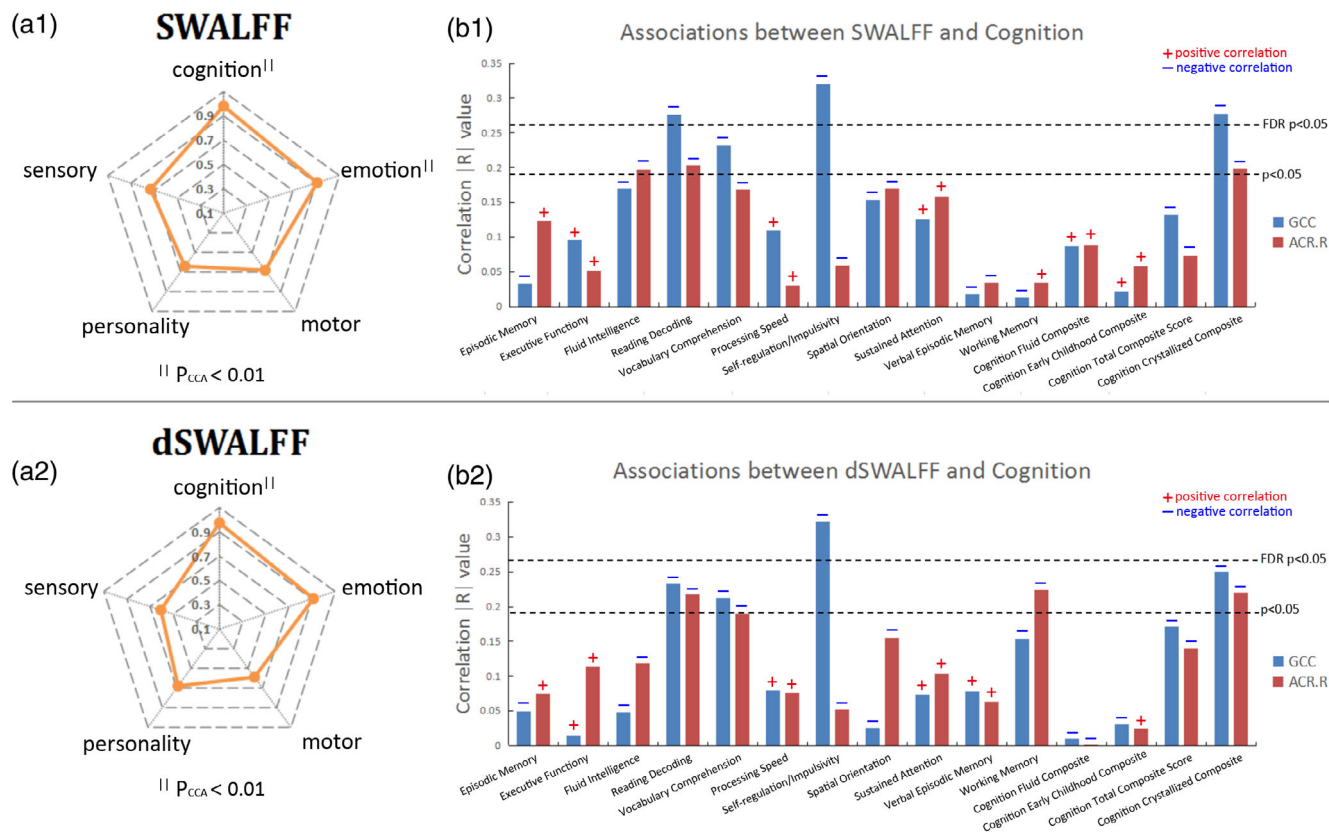
### 3.6 | Reproducibility and repeatability of WM LFO

Figure S5 showed the mean correlation coefficient between the SWALFF maps obtained from repeated scans and paired subjects in one scan. The mean coefficients (intra-subject) between the SWALFF maps generated from repeated scans were very high ( $>0.85$ ). The mean coefficients (inter-subject) between subjects also showed good consistency ( $>0.65$ ). There were no significant differences between correlations of different paired scans. In total, there was a high degree ( $>0.8$ ) of consistency within subjects and good consistency ( $>0.6$ ) between subjects for the SWALFF map. In addition, Figure S7 showed high consistency in SWALFF for WM tracts.

## 4 | DISCUSSION

In this study, DTI revealed widespread FA reductions within major WM fasciculi in SZ patients. Meanwhile, using resting-state fMRI, the investigation of WM function showed hyper-LFO in WM tracts of the frontotemporal–thalamic–cerebellar pathway and the hypo-LFO of primary perception–motor and interhemispheric tracts in SZ patients. We integrated these findings into the global WM abnormalities from both microstructure deficits and dysfunctions, which extended the assumption of the dysconnectivity hypothesis of SZ. The predominant finding of this study indicated a reversed pattern of microstructural deficits and dysfunction in localized WM regions (frontotemporal tracts including ACR, OBF, hippocampus, ALIC and





**FIGURE 4** Associations between white matter (WM) activations and behaviour scores. (a) The canonical correlation coefficient between WM activations (skeleton-based WM amplitude of low frequency fluctuation [SWALFF] (a1) and dynamics of the SWALFF (dSWALFF) (a2) and five behaviour assessment category (cognition, emotion, motor, personality and sensory). <sup>||</sup> represents a significant positive correlation by the canonical correlation analysis ( $p_{CCA} < .01$ ). (b) The Pearson's correlation coefficient between WM activations (SWALFF (b1) and dSWALFF (b1)) in GCC and ACR.R and each cognition instrument

GCC) in SZ patients. Concretely speaking, the key results show that (a) WM LFO was significantly increased in SZ patients, while the microstructure FA of WM was reduced; (b) the association between function and structure was significantly positively correlated in HCs but was negatively correlated in SZ patients; and (c) by using the FSR to measure the coupling of function–structure, we observed that the FSR was positively related to illness duration and clinical symptoms in SZ patients. Taken together, function–structure association may be one of the potential mechanisms of the dysconnectivity hypothesis of SZ.

#### 4.1 | WM global abnormalities: Widespread FA decreases

Highly consistent with a prior meta-analysis evaluating DTI data from 1,963 SZ patients and 2,359 HCs (Kelly et al., 2018), we found widespread FA reductions within major WM fasciculi in SZ patients. These major fibres included the WM tracts of frontotemporal, occipital, interhemispheric (corpus callosum and fornix) and corticothalamic (corona radiata and ALIC) regions, suggesting widespread WM microstructure deficits in SZ (Kelly et al., 2018). Reduced FA in these

regions has been reported in first-episode and chronic SZ patients and in high-risk individuals (Aydin, Uçok, & Guler, 2008; Bora et al., 2011) and has been associated with illness duration and the severity of positive, negative and cognitive symptoms (Rosenberger et al., 2012; Whitford et al., 2010). In addition, this study also observed increased FA in the PLIC in SZ patients, probably because of aberrant axonal pruning and/or fibre organization (Klauser et al., 2017; Kubicki et al., 2005). In total, the widespread distribution of FA reductions may support the concept of SZ as a disorder of global structural dysconnectivity.

#### 4.2 | WM global abnormalities: hyper-LFO and hypo-LFO

In addition to the conventional measure (i.e., FA) in WM microstructure, we adopted a novel measure for investigating WM dysfunction in SZ by fMRI. WM dysfunction has been examined in brain disorders such as mild cognitive impairment, epilepsy, Alzheimer's and Parkinson's diseases using resting-state fMRI (Chen et al., 2017; Ji et al., 2019; Makedonov, et al., 2016). For instance, Jiang et al. reported increased functional connectivity within the WM regions

located under the Rolandic and pre-central/post-central areas in unmedicated patients with benign epilepsy with centrotemporal spikes (Jiang, Song, et al., 2019). In the current study, by mapping the resting-state LFO on the WM skeleton, we found widespread LFO abnormalities across WM major tracts, with hyper-LFO in frontotemporal regions, ALIC and cerebellum and hypo-LFO in occipital and post-central regions compared with LFO in HCs. As the ALIC connects the thalamus and frontal cortex, the WM tracts showing hyper-LFO may be integrated into the frontotemporal-thalamic-cerebellar pathway. In addition, the occipital and post-central regions are important hubs of visual and sensorimotor processing; thus, the WM pathway showing hypo-LFO may be integrated into primary perception-motor tracts. The hyper-LFO (hypo-LFO) of the frontotemporal-thalamic-cerebellar (primary perception-motor) pathway was consistent with results from previous grey matter LFO studies in SZ (Xu, Zhuo, Qin, Zhu, & Yu, 2015), indicating multiple impairments, including sensory integration, motor regulation and cognitive and emotional dysfunction in SZ (Xu et al., 2015). Furthermore, a negative correlation was demonstrated between the cognitive impulsivity (Barch, et al., 2013) and SWALFF as well as dSWALFF in the GCC. Impulsiveness is a prominent clinical symptom in SZ (Reddy et al., 2014). Previous studies found that DTI measured WM integrity reduction in frontal regions was associated with increased impulsivity in SZ (Hoptman et al., 2002). Additionally, this study also found hypo-LFO in interhemispheric WM tracts (fornix and SCC), extending the abnormalities of interhemispheric functional communication in SZ (Agcaoglu et al., 2018; Wang et al., 2019). In general, these abnormalities in WM LFO in the resting state may extend the understanding of the pathophysiology of SZ from the perspective of WM dysfunction.

#### 4.3 | Relationship between the function and structure in WM of SZ

The predominant finding of this study indicated a reversed pattern of microstructural deficits and dysfunction in localized WM regions of the ACR, OBF, hippocampus, ALIC and GCC, which can be concluded to be frontotemporal tracts. Concretely speaking, the FA of the frontotemporal tracts was significantly reduced in SZ patients, indicating an impaired structural basis for information transmission (Kelly et al., 2018). In contrast, the LFO of frontotemporal tracts was increased in SZ patients may relate to high functional loading induced by aberrant self-referential processing in SZ (Kuhn & Gallinat, 2013). These results are consistent with previous studies reporting that reduced structural integrity was paralleled by higher functional connectivity in SZ, which may suggest that the impact of structural deficits can be compensated by an increase functional integration (Cocchi et al., 2014). Wu et al. have reported that resting-state functional connectivity between white and grey matter shared notable similarities with diffusion- and histology-derived anatomic connectivities in non-human primate, suggesting a positive association between WM function and structure (Wu et al., 2019). The current study also observed that higher SWALFF correlated with higher FA in healthy human

brain, indicating a positive function-structure coupling. However, the positive relationship between SWALFF and FA was not found in SZ patients, suggesting the dys-coupling between function and structure in WM.

#### 4.4 | WM function-structure dys-coupling: Relationship with clinical variables

In further work, we used the FSR to measure the coupling of the WM function structure in SZ patients. A higher FSR reflects more severe dys-coupling. The current study found that the duration of illness was positively correlated with the dys-coupling of function and structure in the ACR, OBF, hippocampus and GCC. Our results were consistent with previous findings showing that the duration of illness was negatively associated with FA (Kelly et al., 2018) because of the calculation of dys-coupling using the reciprocal value of FA. These associations remained significant even when controlling for education, WM volume and drug effects. This finding is also consistent with many DTI studies reporting no detectable relationship between medication and FA (Kelly et al., 2018; Samartzis, Dima, Fusar-Poli, & Kyriakopoulos, 2014). As age was highly correlated with illness duration, it was understandable that these associations were no longer significant after controlling for age. In the future, a longitudinal design will be necessary to distinguish the effects of age and illness duration. In addition, the dys-coupling of function-structure in the HIP was positively correlated with negative symptoms in SZ patients, consistent with previous findings of the negative relationships between negative symptoms and FA in WM (Kelly et al., 2018). Recently, non-invasive neuromodulation method, such as transcranial magnetic stimulation (TMS), has shown potential to treat SZ (Chen et al., 2019). WM function may be helpful for understanding how TMS affects the distant cerebral cortex via WM tracts. Taken together, these findings confirmed a positive relationship between the function-structure dys-coupling and the severity of illness in SZ patients.

#### 4.5 | Skeleton-based WM functional analysis

Regarding the methodological aspect, fMRI processing in WM should be very careful because WM signals have weaker signal noise ratio than GM and easily mixed by neighbouring GM signals due to partial volume effects (Gawryluk, Mazerolle, & D'Arcy, 2014). Previous studies usually segmented the functional images into GM and WM mask before spatial normalization and smooth (Ji et al., 2019; Peer et al., 2017). However, it is very difficult to precisely delineate the optimal WM mask, especially in functional images. Even we determine the optimal WM mask in each subject's image (i.e., original space), the mask would be non-linearly transformed during spatial normalization. In addition, how to estimate whether the voxel belongs to WM or GM, it should be probabilistic rather than absolute (0 or 1); thus, it may be arbitrary to choose the absolute threshold to make WM mask. Alternatively, we used the DTI (i.e., FA images) to estimate

the weighted parameters to those voxels who are closer to the centre of the WM tract. Finally, measurement in reliability is required for both research and clinical use (Zuo, Biswal, & Poldrack, 2019). There was a high degree (>0.8) of consistency within subjects and good consistency (>0.6) between subjects for the SWALFF maps from multiple scans in a short time-frame (10 scans across 1 month), which suggested the reliability of the WM LFO. In addition, the WM LFO changes were consistent in two independent SZ sample, indicating the sensibility in detection of the disease-related alterations.

#### 4.6 | Limitations

The current study has certain limitations. First, most of the SZ participants were chronic and were taking antipsychotic medications. Although no correlation was observed between medication and WM differences, it is difficult to rule out the effect of medication on WM alterations. Second, the present study is a cross-sectional design. As SZ is a progressive psychiatric disorder, a longitudinal design is needed to investigate the dynamic changes in WM dysfunction and microstructural properties in SZ. Third, accounting for cognitive, environmental and genetic factors linked to SZ (Devor et al., 2017; van Rheenen et al., 2018), neuropsychological assessment and genetic research are required for a deeper understanding of WM dysfunctions observed in this study. Fourth, previous studies have suggested that the hemodynamic alterations in the BOLD signal in WM may be associated with the energy demands for spiking activity, the maintenance of resting potential and housekeeping processes (Gawryluk, Mazerolle, & D'Arcy, 2014). However, unlike grey matter, the physiological basis of functional activation in WM remains undetermined. In addition, future work should further address some methodological issues, such as the effects of head motion, respiration and other artefacts on WM function. Finally, this study only used the ALFF to assess the LFO of WM. It is unable to deny that the functional connectivity has the potential to uncover the potential connectivity among WM regions. Future work is needed to investigate the functional connectivity within WM and the relationship between functional connectivity and ALFF in WM to provide more evidence for the brain dysconnectivity hypothesis of SZ. Although this study found the correlation between the resting-state LFO of WM and assessments in cognition and emotion based on a data-driven strategy, hypothesis-driven studies and task-state fMRI experiments are needed to further confirm the relationship between WM fMRI and cognition/emotion and underlying neural mechanisms in future work.

#### 4.7 | Conclusion

This study indicated global WM abnormalities and a reversed pattern of microstructural deficits and dysfunction in localized WM tracts in frontotemporal regions in SZ patients, which suggested function-structure dys-coupling with increased functional activations and

reduced structural integration in SZ patients. Furthermore, function-structure dys-coupling was positively related to illness duration and clinical symptoms in patients with SZ. In conclusion, function-structure dys-coupling may be one of the potential mechanisms of the dysconnectivity hypothesis of SZ.

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#### CONFLICT OF INTEREST

The authors declare no conflict of interest.

#### AUTHOR CONTRIBUTIONS

**Cheng Luo** and **Dezhong Yao**: Designed the study and supervised the project. **Shicai Li**, **Xufeng Song** and **Mingjun Duan**: Managed the experiments and data collection. **Yuchao Jiang**, **Xiangkui Li**, **Huan Huang** and **Xuan Li**: Undertook the data analysis. **Yuchao Jiang** and **Cheng Luo**: Wrote and revised the manuscript. All authors reviewed the manuscript and approved the final manuscript.

#### DATA AVAILABILITY STATEMENT

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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