# Altered white matter connectivity in patients with schizophrenia: An investigation using public neuroimaging data from SchizConnect

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## Abstract

Several studies have produced extensive evidence on white matter abnormalities in schizophrenia (SZ). However, optimum consistency and reproducibility have not been achieved, and reported low white matter tract integrity in patients with SZ varies between studies. A whole-brain imaging study with a large sample size is needed. This study aimed to investigate white matter integrity in the corpus callosum and connections between regions of interests (ROIs) in the same hemisphere in 122 patients with SZ and 129 healthy controls with public neuroimaging data from SchizConnect. For each diffusion-weighted image (DWI), two-tensor full-brain tractography was performed; DWIs were parcellated by processing and registering T1 images with FreeSurfer and Advanced Normalization Tools. White matter query language was used to extract white matter fiber tracts. We evaluated group differences in means of diffusion measures between the patients and controls, and correlations of diffusion measures with the severity of clinical symptoms and cognitive impairment in the patients using the Positive and Negative Syndrome Scale (PANSS), a letter-number sequencing (LNS) test, vocabulary test, letter fluency test, category fluency test, and trail-making test, part A. To correct for multiple comparisons, a false discovery rate of q < 0.05 was applied. In patients with SZ, we observed significant radial diffusivity (RD) and trace (TR) increases in left thalamo-occipital tracts and the right uncinate fascicle, and a significant RD increase in the right middle longitudinal fascicle (MDLF) and the right superior longitudinal fascicle ii. Correlations were present between TR of left thalamo-occipital tracts, and the letter fluency test and the LNS test, and RD in the right MDLF and PANSS positive subscale score. However, these correlations were not significant after correction for multiple comparisons. These results indicated widespread white matter fiber tract abnormalities in patients with SZ, contributing to SZ pathophysiology.

# Introduction

Schizophrenia (SZ) is a severe and debilitating disorder characterized by disordered thought process and impaired emotional responses. The disconnection hypothesis, according to which compromised functional cerebral integration is implicated in SZ, is a leading SZ pathophysiology hypothesis [1, 2]. Structural white matter fiber tract abnormalities may underlie connectivity abnormalities, resulting in clinical symptoms and cognitive impairments [3]. Structural white matter abnormalities have been reported in patients with SZ. Consistent findings of alterations in myelin pathology, neuronal orientation and density, and oligodendrocyte aberrations in SZ have been reported [4, 5]. Post-mortem histopathological studies could be informative, but samples comprising patients of advanced age and possibly with chronic illness are a significant limitation. These studies are unable to explore white matter alterations at all stages of SZ.

Diffusion-weighted imaging (DWI) has facilitated in-vivo investigation of white matter microstructure alterations as well as the association between white matter changes and clinical symptoms [6, 7]. In 1998, DWI was used for the first time to patients with SZ [8]. Since then, a large body of evidence on white matter abnormalities in SZ has been produced. However, optimum consistency and reproducibility have not been achieved. Several factors contributing to the heterogeneity of the literature have been suggested, including methodological differences between studies, clinical presentation variability of SZ, differences in individual pathogenesis and pathophysiology, and large differences in covariates such as age, sex, chronicity, and medication [9].

To address this heterogeneity, multi-site consortia have been created to coordinate large dataset collections, including the Mind Clinical Imaging Consortium (MCIC) [10], Functional Biomedical Informatics Research Network [11–13], and North American Prodrome Longitudinal Study Consortium [14]. Due to the challenges in combining data from datasets with different protocols and data structures, these efforts have been partially successful. SchizConnect (www.schizconnect.org), a virtual database for SZ and related disorders, was built to address the issue of multiple data repositories [15, 16]. The SchizConnect system provides neuroimaging data in response to user queries, while data remain at the original sources. It mediates data sources from different studies, and provides the imaging and related data as a uniform, semantically-consistent structure by interpreting database specific terminology. Live data, being updated at each data source, can be mediated to allow access to existing datasets.

Several methods are available for diffusion tensor imaging (DTI) quantitative measurements, including voxel-based morphometry (VBM), tract-based spatial statistics (TBSS), and tractography. The VBM and TBSS methods are very popular tools for performing voxel-based DTI analyses. In these methods, all subjects' images are co-registered to a common space, and statistical tests are performed in each co-registered voxel [17]. While these methods have a strength of allowing for automated and relatively fast analysis of entire subjects, methodological issues regarding the quality of image registration and the anatomical specificity have been reported [18, 19]. Tractography can be used to characterize entire white matter tracts and to examine white matter fascicle architecture. Using this method, white matter fiber tracts can be extracted and calculated with a measure of fiber integrity averaged over the extracted tract. Traditional fiber-tracking models cannot provide correct fiber orientations in regions where fiber bundles intersect each other because of orientation heterogeneity [20]. Fiber populations with different spatial orientations in a single voxel can cause an increase in fractional anisotropy (FA), without changes in axonal or myelin integrity [21]. The fiber-crossing problem has been a challenging issue in tractography because the proportion of white matter voxels containing crossing fibers is estimated to be ~90% [22].

Unscented Kalman filter (UKF)-based two-tensor tractography allows for the recovery of branching and crossing fibers because this tractography models the signal as a mixture of two tensors [23]. With this algorithm, Rathi et al. revealed a significant group difference in at least one diffusion measure of 740/1254 fiber bundles between patients with first-episode SZ and healthy controls (HCs) [23].

The relationship between white matter alterations and cognitive impairments in patients with SZ has been investigated with inconsistent results. Reportedly, reduced FA in the uncinate and cingulum bundles are correlated with episodic memory and executive function in chronic SZ, respectively [24]. A study in patients with recent-onset psychosis also revealed reduced FA in both uncinate fasciculi correlating with worse verbal learning/memory functioning [25]. Conversely, Samartzis et al. reported that only four of the eight studies examining associations of cognitive variables with DTI measures showed positive findings [26]. Given evidence indicating that cognitive impairments are correlated with poorer functional outcomes [27, 28], whole-brain imaging studies with larger sample size are needed to elucidate the association between white matter integrity and neurocognitive deficits.

Several studies have examined the relationship between white matter integrity alteration and clinical symptoms, reporting high variability of findings. Positive symptoms are positively related to increased FA of the inferior occipitofrontal fasciculus (IOFF), inferior longitudinal fasciculus (ILF), and superior longitudinal fasciculus (SLF) in drug-naïve first episode SZ (FES) and chronic patients [29]. However, no significant correlation was found between positive symptoms and average FA value of any above-mentioned tract in medication-naïve patients with FES [30]. Lener et al. reported that lower FA in the left ILF is associated with greater overall and positive symptoms [31]. Reported white matter tracts associated with negative symptoms vary between studies, including the corpus callosum (CC), uncinate fascicle (UF), ILF, IOFF, and anterior thalamic radiation [29, 30].

We aimed to investigate differences in diffusion indices of white matter fiber tracts between patients with SZ and HCs using UKF tractography. The analysis was focused on intra-hemispheric fiber tracts and the CC. We predicted a significant group difference in diffusion measures of white matter fiber tracts between patients with SZ and HCs. We hypothesized that clinical symptoms and cognitive impairment in patients with SZ is correlated with diffusion indices.

## Materials and methods

### Participants

We obtained three freely available samples [Center of Biomedical Research Excellence (COBRE), MCIC, and Neuromorphometry by Computer Algorithm Chicago (NMorphCH)] from SchizConnect, which comprised 140 HCs and 140 patients on the SZ spectrum encompassing SZ and schizoaffective disorder. In order to protect participant identity, all data were fully anonymized prior to our access. Ten schizoaffective patients were excluded from the 140 patients on the SZ spectrum. We visually inspected T1 and DWIs of all 270 subjects and excluded 19 subjects whose images were not eligible for further analysis. The final data set comprised 129 HC and 122 patients with SZ. Each study sample was obtained in accordance with the Declaration of Helsinki and approved by the local institutional review board committees, with participants' written informed consent. The capacity of patients to provide informed consent was confirmed by completing a questionnaire verifying that they understood the study procedures. Parental consent was not required, as all participants were between the ages of 20 and 66. The current study was approved by the institutional review board of Asan Medical Center (IRB File No. S2017-1996-0001).

## Image acquisition

Information on scanners and acquisition parameters of structural T1 and DWIs, by sample, are summarized in S1 Table.

## Image processing

The average motion estimate of each subject was calculated using the RMSDIFF program distributed with the Functional Magnetic Resonance Imaging of the Brain (FMRIB) Software Library (FSL) (http://www.fmrib.ox.ac.uk/fsl/) [32]. The means of motion estimates in the SZ and HC groups were compared using a Welch's test, and the SZ group had significantly higher motion estimates than that of the HC group (2.340 ± 1.986 vs. 2.010. ± 1.611, respectively; $df$ = 6969.3, $t$ = 7.894, $p$ = < 0.001). DWIs were corrected for motion and eddy current-induced distortions, with the affine registration of all gradient volumes, with the first b = 0 volume (FLIRT: FMRIB Software, Oxford, United Kingdom) [33, 34]. After correction for the motion and eddy current-induced distortions, all images were visually inspected to eliminate images which were not eligible for further analyses. We used UKF tractography implemented in the 3D Slicer (http://www.slicer.org) [35] to perform whole-brain tractography (parameters: seeds per voxels: 10; number of tensors: two; Qm 0.001; Ql 70; Rs 0.015; record length: 1.7; step length: 0.3; and seed FA limit: 0.18) [23].

The Desikan-Killiany atlas of FreeSurfer V. 6.0 [36] was used to parcellate T1-weighted images into discrete anatomical regions. A T1-weighted image was registered into a b = 0 baseline image of DWIs with a non-linear registration method, part of the Advanced Normalization Tools [37, 38]. FreeSurfer parcellated labels were applied to derive anatomical segmentations of DWIs using the same registration transformation. Gray matter (GM)/white matter-transformed parcellated regions of interest (ROIs) on left and right sides were selected; for each structure, GM and white matter ROIs were combined into one ROI. The left (right) tract between ROIs in the same hemisphere was extracted with white matter query language [34] implemented in the 3D Slicer. The CC was also extracted based on previous studies, which reported that patients with SZ had low white matter integrity in the CC compared to controls [39, 40]. White matter query language was developed to automatically dissect white matter tracts from DWI volumes. The operation of white matter query language could be divided into two steps: (1) sets of streamlines per each anatomical region were defined, including all streamlines which had the initial or final point in the region, all streamlines traversing the region, and the streamlines traversing brain areas defined by their relative position to the region, (2) logical operations and compositions with these sets of streamlines per region were assigned to define white matter tracts. The extracted tracts (see S2 Table for information on the anatomical definitions, in white matter query language, used to extract the white matter fiber tracts) included the arcuate fascicle (AF), cingulum bundle (CB), CC, corticospinal tract (CST), external capsule (EC), ILF, internal capsule (IC), IOFF, middle longitudinal fascicle (MDLF), SLF, superior occipitofrontal fascicle, striato-frontal tract, striato-parietal tract, striato-occipital tract, thalamo-frontal tract, thalamo-parietal tract, thalamo-occipital tract, and UF. The diffusion measures [FA, axial diffusivity, radial diffusivity (RD), and trace (TR)] were calculated and averaged over each tract, according to the methods of previous reports [41–43].

## Neurocognitive tests and clinical measures

We selected neurocognitive measures that were commonly included in the three samples, which comprised the letter-number sequencing (LNS) test, vocabulary test, letter fluency test, category fluency test, and trail-making test (TMT), part A. The LNS test was used to measure verbal working memory. The LNS subtest of the Wechsler Adult Intelligence Scale–Third

Edition 16 (WAIS-III) [44] was used in MCIC and NMorphCH samples, whereas the letter-number span test in the Measurement and Treatment Research to Improve Cognition in Schizophrenia consensus cognitive battery [45] was used in the COBRE sample. In COBRE and MCIC samples, general cognitive abilities and achievement were measured using the vocabulary subtest of WAIS-III, whereas the vocabulary subtest of the Wechsler Abbreviated Scale of Intelligence [46] was used in the NMorphCH sample. The letter fluency and category fluency tests assessed executive function [47, 48]. TMT, part A measured the processing speed during the attention and working memory tasks. Additionally, t-scores on the above five neurocognitive measures were obtained from the COBRE sample.

The Positive and Negative Syndrome Scale (PANSS) [49] scores in the COBRE sample and the Scale for the Assessment of Positive Symptoms (SAPS) [50] and the Scale for the Assessment of Negative Symptoms (SANS) [51] scores in the MCIC and NMorphCH samples were used to evaluate the severity of clinical symptoms. We estimated PANSS positive and negative subscale scores from SAPS and SANS scores using a validated conversion equation [52]. Clinical symptom severity was measured by these converted scores in the MCIC and NMorphCH samples and the PANSS scores in the COBRE sample.

## Statistical analysis

For comparison of continuous and categorical variables in the demographic and clinical characteristic data, a Student t-test (continuous variables with equal variance), a Welch's test (continuous variables with unequal variance), and a chi-square test (categorical variables) were adopted. We calculated the means and standard deviations of the diffusion measures in each tract in the HC group separately for the three samples. Raw values of the patients' diffusion measures were normalized into z-scores using the above means and standard deviations in the HC group. Outliers were defined as values below the 1.5 interquartile range (IQR) of the first quartile or above the 1.5 IQR of the third quartile of each diffusion measure in the tracts, and these were excluded from further analysis. Group differences in the z-scores of diffusion measures in tracts were compared using the Approximate Monte Carlo Fisher-Pitman Test [53, 54] with a simulation number of 100,000 because z-scores of diffusion measures were not normally distributed. To correct for multiple comparisons, a false discovery rate of $q < 0.05$ was applied [55]. Spearman's rho correlations were applied to evaluate associations between the diffusion measures, and the neurocognitive measures and clinical symptom severity in patients. All statistical analyses were performed using R packages (version 3.4.3) [56, 57]. A two-tailed $p < 0.05$ was considered significant.

## Results

### Demographic and clinical characteristics

The demographic and clinical characteristics of the participants are presented in Table 1. Mean age did not differ significantly between the HC and SZ groups ($35.8 \pm 11.4$ vs. $35.9 \pm 11.0$, respectively; $df = 248.859$, $t = -0.084$, $p = 0.933$). The SZ group had a larger proportion of males than the HC group (73.8% vs. 66.7%, respectively; $X^2 = 1.19$, $p = 0.275$), but this was not statistically significant. Information on the duration of illness ($15.5 \pm 12.5$ years) was only available from two samples (COBRE and MCIC).

Information on neurocognitive measures was available for 221 of the 251 participants. There were statistically significant differences in all neurocognitive measures between the two groups. The SZ group exhibited significantly lower scores on the letter fluency test, category fluency test, LNS test, and vocabulary test ($df = 219$, $t = 4.707$, $p < 0.001$; $df = 207.751$, $t = 7.923$, $p < 0.001$; $df = 219$, $t = 6.428$, $p < 0.001$; and $df = 168.213$, $t = 6.620$, $p < 0.001$,

**Table 1. Demographic and clinical characteristics of participants.**

| Variables | Sample | | | | | | | | Statistical tests[a] | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | COBRE | | MCIC | | NMorphCH | | Total | | | | |
| | HC | SZ | HC | SZ | HC | SZ | HC | SZ | t or $\chi^2$ | df | p |
| Number of participants | 74 | 59 | 19 | 23 | 36 | 40 | 129 | 122 | | | |
| Age, mean (SD), (y) | 38.2 (12.0) | 38.8 (12.9) | 34.8 (11.7) | 34.0 (10.2) | 31.3 (8.4) | 32.6 (6.7) | 35.8 (11.4) | 35.9 (11.0) | −0.084 | 248.859 | 0.933 |
| Male (%) | 77.0 | 76.3 | 47.4 | 73.9 | 55.6 | 70.0 | 66.7 | 73.8 | 1.19 | | 0.275 |
| Age of onset, mean(SD), (y) | | 21.1 (8.3) | | 24.1 (6.7) | | NA | | 22.0 (8.0) | | | |
| Duration of illness, mean(SD), (y) | | 17.7 (13.1) | | 9.9 (9.1) | | NA | | 15.5 (12.5) | | | |
| Medication dose, mean(SD), (mg/day, olanzapine equivalent dose)[b] | | 17.1 (13.2) | | NA | | NA | | | | | |
| Neurocognitive tests[c], mean(SD) | | | | | | | | | | | |
| Trail making test, part A | 23.2 (7.1) | 38.2 (19.3) | 24.7 (7.6) | 31.9 (14.2) | 27.6 (11.2) | 40.8 (15.7) | 24.3 (8.3) | 37.6 (17.4) | −7.159 | 149.488 | <0.001 |
| Letter fluency test | 41.8 (10.7) | 33.0 (11.8) | 41.6 (9.9) | 37.7 (10.5) | 41.5 (11.1) | 35.1 (12.2) | 41.7 (10.6) | 34.6 (11.7) | 4.707 | 219 | <0.001 |
| Category fluency test | 24.3 (4.7) | 18.5 (6.5) | 25.4 (3.5) | 20.0 (5.1) | 21.0 (5.1) | 16.3 (4.3) | 23.8 (4.8) | 18.2 (5.7) | 7.923 | 207.751 | <0.001 |
| Letter-number sequencing test | 15.6 (3.5) | 12.7 (4.4) | 12.5 (1.7) | 10.2 (2.1) | 12.3 (2.9) | 9.8 (2.9) | 14.4 (3.5) | 11.3 (3.8) | 6.428 | 219 | <0.001 |
| Vocabulary test | 61.2 (7.9) | 51.4 (13.6) | 57.2 (3.8) | 45.9 (11.8) | 63.0 (8.6) | 54.7 (12.7) | 60.9 (7.7) | 51.2 (13.2) | 6.620 | 168.213 | <0.001 |
| PANSS[d] | | | | | | | | | | | |
| Total | | 59.8 (16.4) | | NA | | NA | | | | | |
| Positive | | 15.4 (5.4) | | 21.1 (3.7) | | 27.1 (12.0) | | 20.3 (9.5) | | | |
| Negative | | 14.9 (5.5) | | 21.8 (3.1) | | 32.6 (12.1) | | 22.0 (11.4) | | | |
| General | | 29.5 (9.8) | | NA | | NA | | | | | |

Note: COBRE (Center of Biomedical Research Excellence), MCIC (Mind Clinical Imaging Consortium), NMorphCH (Neuromorphometry by Computer Algorithm Chicago), HC (healthy controls), SZ (patients with schizophrenia), SD (standard deviation), PANSS (Positive and Negative Syndrome Scale), NA (not available).

[a] Analyzed using a Student *t*-test (for equal variance), a Welch's test (for unequal variance), and chi-square tests.

[b] Antipsychotic medication dose equivalent to olanzapine at MRI scan.

[c] Information on neurocognitive measures was available from 221 of 251 participants.

[d] PANSS total and three subscale scores were only obtained from COBRE sample. SAPS and SANS scores in the MCIC and NMorphCH samples were converted to PANSS positive and negative subscale scores.

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respectively). The SZ group mean score on TMT, part A was significantly higher than the HC group mean score ($df = 149.488$, $t = −7.159$, $p < 0.001$). Table 1 presents means of the PANSS total scores and three subscale scores in the COBRE sample, converted PANSS positive and negative subscale scores in the MCIC and NMorphCH samples, and olanzapine equivalent dose [58] of the SZ group in the COBRE sample.

## Comparisons of diffusion MRI measures

There were no significant differences in the diffusion measures of the CC between the two groups (AD: $z = −0.946$, $p = 0.611$, FDR corrected; FA: $z = −0.103$, $p = 0.939$, FDR corrected;

**Table 2. Group differences in the diffusion measures of tracts in the left hemisphere[a].**

| Structure | Diffusion measure | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | AD | | FA | | RD | | TR | |
| | z | p[b] | z | p[b] | z | p[b] | z | p[b] |
| left AF | 0.313 | 0.755 | 0.395 | 0.693 | −1.575 | 0.116 | −0.285 | 0.776 |
| left CB | 0.104 | 0.918 | 1.901 | 0.056 | −1.634 | 0.102 | −1.064 | 0.291 |
| left CST | 0.192 | 0.847 | 0.515 | 0.610 | −0.403 | 0.691 | 0.663 | 0.508 |
| left EC | 0.756 | 0.451 | 2.04 | 0.041 | −2.728 | 0.006 | −1.410 | 0.159 |
| left ILF | 0.791 | 0.427 | 2.552 | 0.011 | −2.910 | 0.004 | −1.800 | 0.070 |
| left IC | 0.180 | 0.856 | 1.749 | 0.078 | -2.030 | 0.043 | -1.155 | 0.247 |
| left IOFF | 0.309 | 0.762 | 0.512 | 0.611 | −0.753 | 0.455 | −0.421 | 0.684 |
| left MDLF | 1.261 | 0.207 | 2.594 | 0.009 | −2.869 | 0.004 | −1.086 | 0.281 |
| left SLF i | 1.578 | 0.115 | 1.681 | 0.092 | −1.863 | 0.062 | −1.525 | 0.129 |
| left SLF ii | −0.263 | 0.824 | 2.243 | 0.023 | −2.531 | 0.008 | −1.929 | 0.053 |
| left SLF iii | 1.960 | 0.049 | −0.331 | 0.745 | 0.705 | 0.482 | 0.422 | 0.673 |
| left SOFF | 0.199 | 0.843 | −0.239 | 0.811 | 1.528 | 0.127 | −0.199 | 0.863 |
| left striato-frontal | 0.841 | 0.401 | 1.061 | 0.289 | −1.796 | 0.073 | −0.256 | 0.797 |
| left striato-occipital | −0.973 | 0.334 | 0.270 | 0.788 | −1.588 | 0.113 | −1.430 | 0.153 |
| left striato-parietal | 1.714 | 0.088 | 1.183 | 0.238 | −0.459 | 0.649 | 0.677 | 0.500 |
| left thalamo-frontal | 0.854 | 0.396 | −0.641 | 0.560 | −0.499 | 0.619 | 0.104 | 0.920 |
| left thalamo-occipital | −1.676 | 0.094 | 2.505 | 0.012 | −3.642 | <0.001* | −3.125 | 0.001* |
| left thalamo-parietal | 0.145 | 0.885 | 0.491 | 0.624 | −0.420 | 0.677 | −0.257 | 0.797 |
| left UF | −1.896 | 0.058 | −0.003 | 0.998 | −1.461 | 0.143 | −1.535 | 0.125 |

Note: AF (arcuate fascicle), CB (cingulum bundle), CST (corticospinal tract), EC (external capsule), ILF (inferior longitudinal fascicle), IC (internal capsule), IOFF (inferior occipitofrontal fascicle), MDLF (middle longitudinal fascicle), SLF (superior longitudinal fascicle), SOFF (superior occipitofrontal fascicle), UF (uncinate fascicle), AD (axial diffusivity), FA (fractional anisotropy), RD (radial diffusivity), TR (trace).

[a] Approximate Monte Carlo Fisher–Pitman tests were performed to reveal group differences in the z-scores of the diffusion measures of tracts in the left hemisphere.

[b] Uncorrected p-values.

* False discovery rate-adjusted p-value less than 0.05.

RD: $z = -0.980$, $p = 0.598$, FDR corrected; TR: $z = -0.868$, $p = 0.653$, FDR corrected). Group differences in the diffusion measures of the tracts in the left and right hemispheres between the two groups are shown in Table 2 (left hemisphere) and Table 3 (right hemisphere). The SZ group had significantly higher RD and TR of left thalamo-occipital tracts (RD: $z = -3.642$, $p = 0.016$, FDR corrected; TR: $z = -3.125$, $p = 0.043$, FDR corrected) and UF (RD: $z = -4.081$, $p = 0.002$, FDR corrected; TR: $z = -3.393$, $p = 0.035$, FDR corrected) than the HC group. In the SZ group, RD of the right MDLF ($z = -3.093$, $p = 0.046$, FDR corrected) and the right SLF ii ($z = -3.142$, $p = 0.043$, FDR corrected) were significantly higher than the HC group.

We performed the same analyses with age and sex as covariates and identified the same group differences in diffusion measures of white matter fiber tracts (left thalamo-occipital tracts: RD; $z = -3.631$, $p = 0.021$, FDR corrected; TR; $z = -3.121$, $p = 0.040$, FDR corrected; right MDLF: RD; $z = -2.971$, $p = 0.049$, FDR corrected; right SLF ii: RD; $z = -3.132$, $p = 0.040$, FDR corrected; right UF: RD; $z = -4.019$, $p = 0.007$, FDR corrected; and TR; $z = -3.383$, $p = 0.029$, FDR corrected).

## Clinical correlates of diffusion MRI measures

We selected diffusion measures of tracts that showed significant group differences, after correction for multiple comparisons. In the SZ group, correlations between the raw values of the

**Table 3. Group differences in the diffusion measures of tracts in the right hemisphere[a].**

| Structure | Diffusion measure | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | AD | | FA | | RD | | TR | |
| | z | $p$[b] | z | $p$[b] | z | $p$[b] | z | $p$[b] |
| right AF | -0.192 | 0.846 | 0.162 | 0.872 | -1.246 | 0.213 | -0.898 | 0.373 |
| right CB | 1.819 | 0.068 | 0.466 | 0.680 | -1.409 | 0.158 | 0.430 | 0.670 |
| right CST | -0.062 | 0.950 | 0.861 | 0.390 | -1.276 | 0.201 | -0.334 | 0.739 |
| right EC | -0.140 | 0.890 | 0.521 | 0.604 | -1.785 | 0.074 | -1.120 | 0.264 |
| right ILF | 0.528 | 0.598 | 2.177 | 0.029 | -2.259 | 0.024 | -1.697 | 0.090 |
| right IC | 0.782 | 0.436 | 1.407 | 0.159 | -0.952 | 0.343 | -0.280 | 0.781 |
| right IOFF | -0.912 | 0.364 | 0.458 | 0.656 | -2.568 | 0.010 | -1.619 | 0.105 |
| right MDLF | 1.079 | 0.280 | 2.66 | 0.007 | -3.093 | 0.002* | -2.210 | 0.026 |
| right SLF i | 0.526 | 0.603 | 1.255 | 0.211 | -1.540 | 0.124 | -1.405 | 0.164 |
| right SLF ii | 1.292 | 0.197 | 1.894 | 0.056 | -3.142 | 0.001* | -1.583 | 0.114 |
| right SLF iii | 1.226 | 0.220 | 2.585 | 0.010 | -1.814 | 0.070 | -0.862 | 0.392 |
| right SOFF | 0.435 | 0.666 | 1.124 | 0.269 | -1.295 | 0.198 | -1.246 | 0.213 |
| right striato-frontal | 1.756 | 0.078 | 1.421 | 0.156 | -1.106 | 0.270 | 0.292 | 0.770 |
| right striato-occipital | 0.332 | 0.741 | -0.341 | 0.732 | 0.352 | 0.724 | 0.464 | 0.647 |
| right striato-parietal | 1.242 | 0.215 | 2.341 | 0.019 | -1.608 | 0.109 | -1.168 | 0.245 |
| right thalamo-frontal | 0.836 | 0.404 | 0.745 | 0.525 | -2.218 | 0.025 | -1.439 | 0.081 |
| right thalamo-occipital | 0.577 | 0.574 | 1.882 | 0.059 | -2.006 | 0.043 | -1.007 | 0.328 |
| right thalamo-parietal | -0.694 | 0.485 | 0.694 | 0.488 | -1.293 | 0.196 | -0.827 | 0.407 |
| right UF | 0.029 | 0.977 | 2.633 | 0.008 | -4.081 | <0.001* | -3.393 | 0.001* |

Note: AF (arcuate fascicle), CB (cingulum bundle), CST (corticospinal tract), EC (external capsule), ILF (inferior longitudinal fascicle), IC (internal capsule), IOFF (inferior occipitofrontal fascicle), MDLF (middle longitudinal fascicle), SLF (superior longitudinal fascicle), SOFF (superior occipitofrontal fascicle), UF (uncinate fascicle), AD (axial diffusivity), FA (fractional anisotropy), RD (radial diffusivity), TR (trace).

[a] Approximate Monte Carlo Fisher–Pitman tests were performed to reveal group differences in the z-scores of the diffusion measures of tracts in the right hemisphere.

[b] Uncorrected p-values.

* False discovery rate-adjusted p-value less than 0.05.

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above diffusion measures and the neurocognitive measures were evaluated (Table 4). There were Spearman's rho correlations between TR in the left thalamo-occipital tracts, and the letter fluency test ($r = -0.236$, uncorrected $p = 0.018$) and the LNS test ($r = -0.198$, uncorrected $p = 0.048$). However, these two correlations did not survive after correction for multiple

**Table 4. Correlations between the diffusion measures and neurocognitive characteristics of the participants[a].**

| Structure | Diffusion measure | Trail making test, part A | | Letter fluency test | | Category fluency test | | Letter number sequencing test | | Vocabulary test | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | r | $p$* | r | $p$* | r | $p$* | r | $p$* | r | $p$* |
| left thalamo-occipital | RD | -0.013 | 0.894 | -0.162 | 0.107 | -0.027 | 0.788 | -0.194 | 0.053 | -0.135 | 0.18 |
| left thalamo-occipital | TR | 0.037 | 0.711 | -0.236 | 0.018 | -0.066 | 0.516 | -0.198 | 0.048 | -0.137 | 0.176 |
| right MDLF | RD | -0.103 | 0.307 | -0.149 | 0.138 | -0.144 | 0.152 | -0.146 | 0.146 | -0.174 | 0.082 |
| right SLF ii | RD | -0.076 | 0.447 | -0.154 | 0.123 | -0.023 | 0.818 | -0.101 | 0.311 | -0.103 | 0.301 |
| right UF | RD | 0.01 | 0.921 | -0.156 | 0.12 | -0.077 | 0.444 | -0.005 | 0.964 | -0.171 | 0.088 |
| right UF | TR | -0.056 | 0.578 | -0.128 | 0.201 | -0.019 | 0.848 | -0.025 | 0.805 | -0.17 | 0.09 |

Note: MDLF (middle longitudinal fascicle), SLF (superior longitudinal fascicle), UF (uncinate fascicle), RD (radial diffusivity), TR (trace).

[a] Spearman's rho correlations were conducted to evaluate associations between the raw values of the diffusion measures and neurocognitive characteristics.

* Uncorrected p-values.

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comparisons. Using the COBRE sample, we evaluated t-score associations of the neurocognitive measures with the diffusion measures. We observed correlation between RD in the right UF and TMT, part A scores ($r = -0.326$, uncorrected $p = 0.019$), which did not remain significant after correction for multiple comparisons. There was an association between RD in the right MDLF and PANSS positive subscale score ($r = 0.212$, uncorrected $p = 0.023$), which did not reach statistical significance after correction for multiple comparisons. With information about medication dose at the MRI scan in COBRE sample, we examined associations of olanzapine equivalent dose with diffusion measures. Associations of olanzapine equivalent dose, and RD in the right MDLF and SLF ii ($r = 0.285$, uncorrected $p = 0.030$; $r = 0.294$, uncorrected $p = 0.026$, respectively) did not remain significant after correction for multiple comparisons.

## Discussion

We examined the integrity of CC and white matter fiber tracts connecting ROIs within the same hemisphere in patients with SZ. We used UKF tractography to extract white matter fiber tracts with public neuroimaging data from SchizConnect. To the best of our knowledge, this is the first study to investigate white matter fiber tracts in patients with SZ using public neuroimaging data from multiple data repositories. We found significant RD and TR increases in left thalamo-occipital tracts and the right UF, and a significant RD increase in the right MDLF and right SLF ii in patients with SZ. There were correlations between TR of left thalamo-occipital tracts, and the letter fluency test and the LNS test, and RD in the right MDLF and PANSS positive subscale score. However, these correlations were not statistically significant after correction for multiple comparisons.

FA is an index derived from DTI for evaluating anisotropy in white matter. FA abnormalities in patients with demyelinating disease were reported in early DTI studies [59]. Therefore, FA was considered a proxy for myelin integrity. Although myelination contributes to FA, other factors, including the axon itself and tract geometry, can influence FA [21, 60]. Relatively pure deficits in myelin can cause a modest increase in RD, with anisotropy preservation [21]. RD may be a more useful diffusion index than FA to reflect subtle impairment of myelin integrity and for examining white matter fiber integrity in early-course SZ. TR, as an index of the magnitude of water diffusion, has been used to quantify white matter abnormalities in previous DTI studies [42]. While RD change is reported to be associated with myelin neuropathology [61], TR increase has been attributed to general microstructural white matter pathologies. Our results showed RD and/or TR increases in patients with SZ, with no significant FA decreases. A previous study suggested RD as a demyelination surrogate [62]. However, a study with simulated data demonstrated that a simplistic biological RD interpretation should be avoided because of inter-individual variation in underlying tissue and interactions between anatomical and scanning parameters [63]. Neurobiological correlates of RD abnormality with SZ need to be studied further.

We showed that RD and TR of the left thalamo-occipital tract in the SZ group were significantly increased compared with the HC group. Contrary to our findings, several studies on the connectivity of thalamo-cortical networks in patients with SZ have reported that patients with SZ show no significant differences in functional or structural connectivity of the occipital cortex with the thalamus compared with HCs [64–66]. Conversely, patients with SZ display significantly decreased FA in optic radiations compared with HCs [67, 68]. Optic radiation structure and correlations of structure measures with visual masking performance in patients with SZ were investigated [69]. Although there are no significant differences in diffusion indices or tract volume between the patients and HCs, a correlation between the tract volume of optic radiations and visual masking performance is found in patients with SZ. Visual

perception dysfunction in patients with SZ has been well-characterized in several studies [70–72]. Our findings suggest that impairment of the integrity of optic radiations and structural thalamo-occipital connectivity contributes visual perception dysfunction neural bases in patients with SZ.

MDLF was initially defined as a long association fiber tract connecting the superior temporal gyrus and temporal pole with the angular gyrus [73]. Patients with chronic SZ have a significant mean FA decrease in MDLF of both hemispheres compared with HCs [74]. Consistent with these results, we showed that the SZ group had significantly higher RD of the right MDLF than the HC group. Although the function of MDLF remains unclear, MDLF may be associated with attention, language [75], and functions connected with high-level auditory [76] and visual processing [77]. Six major fiber connections of MDLF, including temporo-parietal and temporo-occipital connections, were reported, expanding the human MDLF classification [77]. Given the extensive connectivity of the human MDLF to various cortical structures, it is possible that MDLF is implicated in SZ pathophysiology.

Impaired white matter integrity within the prefrontal, temporal, and parietal lobes in patients with SZ has been reported, along with abnormalities within fiber bundles such as UF and SLF that are connecting these regions [6, 9]. UF and SLF abnormalities have been reported in patients with FES, chronic SZ, and drug-naïve SZ [9, 26, 78, 79]. Our study adds to this literature by showing impaired white matter integrity of the right UF and SLF in patients with SZ.

Verbal fluency is consistently impaired over time and is related to these patients' clinical and functional outcomes [80]. Verbal fluency tests are used to measure executive function; the performance of a patient with SZ on these tests can be predicted by their working memory or processing speed, depending on cognitive impairment severity [81]. Working memory deficit, as a core neurocognitive impairment, has been extensively reported and studied in patients with SZ [82–84]. The LNS test is used to measure executive function working memory, and it requires transient working memory as well as additional mental manipulation of the information [85]. Here the association between verbal fluency, the LNS test, and the diffusion measures did not reach statistical significance. It may be possible that various functions required for verbal fluency and the LNS test are related to the integrity of several white matter fiber tracts, rather than a specific white matter fiber tract. Further studies concerning the entire brain connectivity may be needed to address associations of structural measures with neurocognitive variables.

The relationship of white matter alterations and clinical symptoms in SZ has been examined with inconsistent evidence. Viher et al. reported that negative symptoms are related to white matter microstructure of the prefrontal and right temporal lobes, but no association of white matter microstructure and positive symptoms was found [86]. Conversely, Lener et al. showed that lower FA in the genu is associated with greater positive symptom and none of the correlations with negative symptoms are significant [31]. We found the correlation of RD in the right MDLF and PANSS positive subscale score; however, the correlation did not survive after correction for multiple comparisons. The reason for this negative finding may be heterogeneity in illness duration of the SZ group, medication effects on symptom severity, and different scales for measuring symptom severity in the three samples.

The present study has several methodological limitations. First, we did not separate the patients into FES and chronic SZ groups. There are different patterns of white matter impairment among individuals at high clinical risk of psychosis, those with FES, and those with chronic SZ [9]. Particularly, there is disruption in the integrity of the white matter fiber tracts in the right hemisphere of patients with FES, but not chronic SZ [87, 88]. Although this separation may have revealed different patterns of disruption in white matter fiber tracts between patients with FES and chronic SZ, a smaller sample size derived by dividing the

patients into FES and chronic groups may have reduced the statistical power of this study. Second, antipsychotics use was not considered because information about medication use was not available in all three samples. Findings on the effects of antipsychotics on diffusion measures in patients with SZ remain inconclusive. Specifically, while a few studies have shown no association between antipsychotics use and changes in diffusion measures [89, 90], other studies have revealed such effects [91–93]. Further studies are needed to investigate this association. Third, changes within the white matter of patients with SZ may be confounded by age and sex. Accelerated FA decline with age in patients with SZ has been reported [94]; this effect is more prominent in specific tracts that mature later in life [95]. A relationship between neurodevelopmental changes in white matter and age has been suggested [96]. Although, in the present study, all the group differences in diffusion measures remained significant after adjustment for age and sex, the effect of age and sex on diffusion measures could not be entirely disregarded. Fourth, three different samples were included. Although the raw values of the patients' diffusion measures were normalized, it was not possible to entirely disregard the effect of different protocol parameters on the calculated diffusion measures. A certain sample may have influenced the positive findings of this study. We conducted the same analyses separately for the three samples, and there were no significant group differences in any diffusion measure of tracts after correction for multiple comparisons (see S3 Table for details on the group differences in the diffusion measures, by sample). We also performed analyses to compare the means of the diffusion measures among the three samples in the SZ and HC groups. The diffusion measures of some fiber tracts had significant sample-differences among three samples in the SZ group; however, the diffusion measures which showed significant group-differences between the SZ and HC groups did not have significant sample-differences in the SZ group. A larger sample size, achieved by combining the three samples, provided greater statistical power that contributed to this study's positive findings. Fifth, the angular resolution of DWI acquired in the MCIC sample was relatively low. DWI data having low angular resolution may lead to inaccurate fitting during extraction of white matter fiber tracts with a two-tensor model [97]. To account for this problem, the MCIC sample was excluded, and the same analyses were performed again. The results showed that the SZ group had significantly higher RD of left thalamo-occipital tracts (RD: $z = -3.280$, $p = 0.034$, FDR corrected) and RD and TR of right UF (RD: $z = -3.740$, $p = 0.018$, FDR corrected; TR: $z = -3.513$, $p = 0.029$, FDR corrected) than the HC group. Three of the six significant diffusion measures remained significant. Future research that considers the effect of low angular resolution in the two-tensor model is needed to verify the significance of findings in this study. Sixth, we did not account for the effect of motion artifacts on the diffusion measures. A previous study [98] reported that artifacts from even small head motion can induce spurious group differences in the diffusion measures. We conducted the same analyses with covariates of age, sex, and motion estimate. The results showed no significant group differences in the diffusion measures after correcting for multiple comparisons (left thalamo-occipital tracts: RD; $z = 1.932$, uncorrected $p = 0.052$, TR; $z = 1.934$, uncorrected $p = 0.054$, right MDLF: RD; $z = 1.783$, uncorrected $p = 0.074$, right SLF ii: RD; $z = -2.115$, uncorrected $p = 0.034$, right UF: RD; $z = -2.183$, uncorrected $p = 0.029$, TR; $z = 2.099$, uncorrected $p = 0.036$). This linear regression approach is somewhat arbitrary because the diffusion measures are not linear with respect to motion parameters [98]. The motion estimates used in our study were skewed, therefore a statistic, instead of mean and standard deviation, was required to reflect central tendency and dispersion of the motion estimates. Other motion measures which can capture within-volume motion were also needed to comprehensively reflect motion artifacts, however, we were not able to obtain such motion measures in this study. Future research that comprehensively evaluates the influence of motion artifacts on the diffusion measures is needed to validate our significant findings.

Disruption of the white matter integrity in patients with SZ is seen in the left thalamo-occipital tracts, right MDLF, right SLF ii, and right UF. These results indicate widespread white matter fiber tract abnormalities in patients with SZ, which is consistent with the disconnection hypothesis of SZ. Further studies are needed to elucidate the association between diffusion measures and clinical symptoms of SZ.

## Supporting information

**S1 Table. Scanners and imaging parameters by sample.** COBRE (Center of Biomedical Research Excellence), MCIC (Mind Clinical Imaging Consortium), NmorphCH (Neuromorphometry by Computer Algorithm Chicago), DWI (diffusion weighted imaging).
(DOCX)

**S2 Table. Anatomical definitions of white matter query language.** AF (arcuate fascicle), CB (cingulum bundle), CC (corpus callosum), CST (corticospinal tract), EC (external capsule), ILF (inferior longitudinal fascicle), IC (internal capsule), IOFF (inferior occipitofrontal fascicle), MDLF (middle longitudinal fascicle), SLF (superior longitudinal fascicle), SOFF (superior occipitofrontal fascicle), UF (uncinate fascicle).
(DOCX)

**S3 Table. Group differences in the diffusion measures of tracts in the Center of Biomedical Research Excellence (S3.1), Mind Clinical Imaging Consortium (S3.2), Neuromorphometry by Computer Algorithm Chicago (S3.3) samples.** AF (arcuate fascicle), CB (cingulum bundle), CST (corticospinal tract), EC (external capsule), ILF (inferior longitudinal fascicle), IC (internal capsule), IOFF (inferior occipitofrontal fascicle), MDLF (middle longitudinal fascicle), SLF (superior longitudinal fascicle), SOFF (superior occipitofrontal fascicle), UF (uncinate fascicle), AD (axial diffusivity), FA (fractional anisotropy), RD (radial diffusivity), TR (trace).
(DOCX)

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## Author Contributions

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