Schizophrenia Research 204 (2019) 230–237

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Dissociation of fractional anisotropy and resting-state functional connectivity alterations in antipsychotic-naive first-episode schizophrenia

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ARTICLE INFO

Article history:
Received 13 March 2018
Received in revised form 25 July 2018
Accepted 6 August 2018
Available online 16 August 2018

Keywords:
Schizophrenia
Fractional anisotropy
Resting-state functional connectivity
Structural-functional relationship

ABSTRACT

Altered resting-state functional connectivity (rsFC) has been demonstrated between multiple brain regions in schizophrenia. However, whether these alterations are related to fractional anisotropy (FA) alterations in pathways that connect regions with altered rsFC remains unknown. In this study, diffusion tensor imaging and resting-state functional magnetic resonance imaging were performed with 181 antipsychotic-naïve first-episode schizophrenia patients and 173 matched healthy controls. FA was measured using tensor-guided tractography in identifiable pathways between selected pairs of brain regions with altered rsFC as determined by prior meta-analysis. Compared with controls, patients showed significantly decreased FA between right caudate nucleus and right pallidum, right caudate nucleus and right putamen, and right hippocampus and right thalamus. Decreased rsFC was observed between right pallidum and right thalamus, and right insula and right superior temporal gyrus. No significant correlation was observed between FA and rsFC. FA between right caudate nucleus and right putamen was inversely correlated with negative symptoms while rsFC between right pallidum and right thalamus was inversely correlated with positive symptoms. The lack of robust correlations between FA and rsFC and no overlap of these abnormalities indicate that regional rsFC alterations in the early course of schizophrenia are not primarily associated with FA alterations. The observation that positive and negative symptoms are related to different functional and structural disturbances is consistent with this dissociation, and with prior work suggests that different pathophysiological mechanism may underlie positive and negative symptoms in the early course of schizophrenia.

1. Introduction

Resting-state functional connectivity (rsFC) alterations are well established in schizophrenia (Gong et al., 2016; Pettersson-Yeo et al., 2011; Sheffield and Barch, 2016). One key question that remains unanswered is whether these functional alterations associate with fractional anisotropy (FA) alterations between regions whose rsFC are altered. Addressing this question has been challenging, in part because antipsychotic medications affect both brain structure and function (Asami et al., 2012; Lesh et al., 2015; Sarpal et al., 2015; Wang et al., 2013). In fact, opposite changes of rsFC and FA in schizophrenia have been observed after treatment (Lui et al., 2010; Reis Marques et al., 2014). Thus, a large study of never treated patients is a promising approach for investigating the relationship between rsFC and FA alterations (Ren et al., 2013).

Because of the mixed findings from the literature in healthy controls, rsFC and FA were not typically correlated. Previous studies reported that rsFC moderately correlated with FA between brain regions of the default mode (Fjell et al., 2017; Teipel et al., 2010; van den Heuvel et al., 2008) and language networks (Morgan et al., 2009), while others found no significant correlations (Liao et al., 2011; Tsang et al., 2017). Besides, correlations between rsFC and FA were also found in demyelinating diseases such as multiple sclerosis, suggesting the white matter damages might induce rsFC disturbances and increase the relatively low-level correlations often seen in healthy controls (Akbar et al., 2016; Sbardella et al., 2015). However, few studies have directly compared rsFC and FA in the same group of schizophrenia patients, and in those that have done so results have been inconsistent. For example, Camchong et al.

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https://doi.org/10.1016/j.schres.2018.08.005
0920-9964/

(2011) reported decreased rsFC in medial frontal regions related to reduced FA in white matter adjacent to these regions, while Zhang et al. (2012) reported increased rsFC between frontal-parietal cortex and subcortical regions but no significant difference in FA in white matter between these regions. This is the case even in antipsychotic-naive first-episode schizophrenia (Li et al., 2018; Lu et al., 2011). Functional studies have reported decreased (Zhang et al., 2015), increased (Crossley et al., 2009), and no significant differences (Lui et al., 2009) in rsFC between frontal and temporal cortex. Structural studies found reduced FA in fronto-temporal tracts (Cheung et al., 2008; Hao et al., 2006; Szeszko et al., 2005), but this has not been seen in all studies (Lee et al., 2012). The relatively small sample size of most previous studies may be one cause of inconsistency, and thus to the lack of clarity regarding potential relationships between rsFC and FA alterations in schizophrenia.

In this study, we sought to explore the structrual-functional relationship by conducting diffusion tensor imaging (DTI) and resting-state functional magnetic resonance imaging (rs-fMRI) in a large sample of treatment-seeking antipsychotic-naive first-episode schizophrenia patients, avoiding medication confounds and providing the opportunity to better investigate relations between positive symptoms and brain alterations than studies of chronically treated and stable patients, which was one of the important facilities for psychoradiology, an evolving subspecialty of radiology focusing on psychiatric disorders (Kressel, 2017; Lui et al., 2016). Establishing a relationship of functional and structural connectivity is difficult to do in a whole brain context, as defining terminal fields of white matter tracts is challenging and the resolution of DTI does not allow precise tracking of white matter tracts between many brain regions. Therefore, we adopted the approach of selecting pairs of brain regions with altered rsFC as determined by prior meta-analysis (Dong et al., 2018), determining which regions had consistently identifiable white matter tracts between them. We then examined both functional and white matter connections between these pairs of brain regions to identify overlapping and independent alterations in rsFC and FA. Finally, rsFC and FA alterations were correlated with clinical symptoms severity in the patient group.

2. Materials and methods

2.1. Participants

A total of 203 right-handed antipsychotic-naive first-episode schizophrenia patients (181 with MRI data and 22 without MRI data) and 173 age-, sex-, and handedness- matched healthy controls were recruited at the West China Hospital, Sichuan University from August 2005 to July 2014 (see Tables 1 and S1 for demographics and Fig. 1 for a detailed inclusion and exclusion flowchart of all participants). Diagnoses of schizophrenia were determined using the Structured Interview for the DSM-IV Axis I Disorder, Patient Edition (SCID), symptoms severity was assessed using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1988) and duration of illness was evaluated using the Nottingham Onset Schedule (Singh et al., 2005) with information provided by patients, family members and medical history when available. The full scale PANSS scores were available for 144 patients with MRI data and 20 patients without MRI data (Tables 1 and S1). Healthy controls were recruited from the local community via poster advertisements, and were screened using the non-patient version of the SCID to confirm the lifetime absence of psychotic, mood and anxiety disorders. Healthy controls had no known history of major psychiatric illness in first or second-degree relatives. The following exclusion criteria applied to all participants: life-time drug, tobacco, or alcohol abuse disorder, current pregnancy, and any neurological or systemic illness that might impact brain measures. An experienced neuroradiologist (Lui) reviewed T1 and T2 weighted scans; no gross brain abnormalities were identified in any study participant. The study was approved by the Ethics Committee of West China Hospital. Written informed consent was obtained from all participants, and for minors, parents also provided written informed consent.

Table 1
Demographic and clinical characteristics of antipsychotic-naive first-episode schizophrenia patients and healthy controls.

Characteristics	AN-FES with MRI data (n = 181)	HC (n = 173)	Statistic	*P*
Age, year	24.78 (9.54)	26.38 (9.77)	$t = 1.56$	0.12
Male/female, No.	83/98	88/85	$\chi^2 = 0.89$	0.35
Education, year	11.88 (3.29)	12.81 (3.27)	$t = 2.45$	0.015
Illness duration, year	0.97 (1.72)	NA	NA	NA
PANSS scores				
Total	89.10 (16.71)	NA	NA	NA
Positive symptoms	24.46 (6.24)	NA	NA	NA
Negative symptoms	18.78 (7.82)	NA	NA	NA
General psychopathology symptoms	45.86 (9.32)	NA	NA	NA

Abbreviations: AN-FES, antipsychotic-naive first-episode schizophrenia patients; HC, healthy controls; MRI, magnetic resonance imaging; PANSS, Positive and Negative Syndrome Scale.

2.2. Data acquisition

All MRI scans were conducted on the same GE Signa EXCITE 3T scanner (GE Healthcare, Milwaukee, Wisconsin) with an 8-channel phase array head coil. For the patients, MRI data were collected on the day when clinical diagnosis and symptoms assessment were completed. The daily quality assurance protocol established the stability of the scanner using a water phantom.

High resolution T1 weighted images were obtained using a 3D spoiled gradient (SPGR) sequence (TR = 8.5 ms, TE = 3.4 ms, TI = 400 ms, flip angle = 12°). A field of view of 240 × 240 mm^2 was used, with an acquisition matrix comprising 256 readings of 128 phase-encoding steps, producing 156 contiguous 1-mm coronal slices. The final matrix of T1-weighted images was automatically interpolated in plane to 512 × 512, yielding an in-plane resolution of 0.47 × 0.47 mm^2.

DTI data were acquired using a single-shot echo-planar imaging sequence (TR = 10,000 ms, TE = 70 ms) with a 128 × 128 matrix over a field of view of 240 × 240 mm^2 and 42 axial slices of 3 mm thickness covering the whole brain without gap. Diffusion sensitizing gradients were applied along 15 non-collinear directions (b = 1000 s/mm^2) with a reference image without diffusion weighting (b = 0).

Rs-fMRI data were obtained via a gradient-echo echo-planar imaging sequence (TR = 2000 ms, TE = 30 ms, flip angle = 90°) with a slice thickness of 5 mm (no slice gap), a matrix size of 64 × 64, a field of view of 240 × 240 mm^2, and a voxel size of 3.75 × 3.75 × 5 mm^3. Functional data was comprised of 30 axial slices of 5 dummy volumes and 200 sequential image volumes, acquired in a total imaging time of 410 s. During rs-fMRI scanning, participants were instructed to relax with their eyes closed and without falling asleep or having directed, systematic thought (which was confirmed by a self-report of subjects immediately after scans).

2.3. Data preprocessing

Preprocessing of DTI data was performed with FMRIB's Diffusion Toolbox (FDT) in FSL (http://www.fmrib.ox.ac.uk/fsl) (Jenkinson et al., 2012). First, the individual DTI was affinely coregistered to its corresponding b_0 image using eddy_correct and FMRIB's Linear Image Registration Tool (FLIRT) to correct for eddy current induced distortion and subtle head motion (Jenkinson et al., 2002). Then the b matrix was rotated according to the transformation matrix (Leemans and Jones, 2009). Second, the diffusion tensor elements (λ1, λ2, and λ3) were

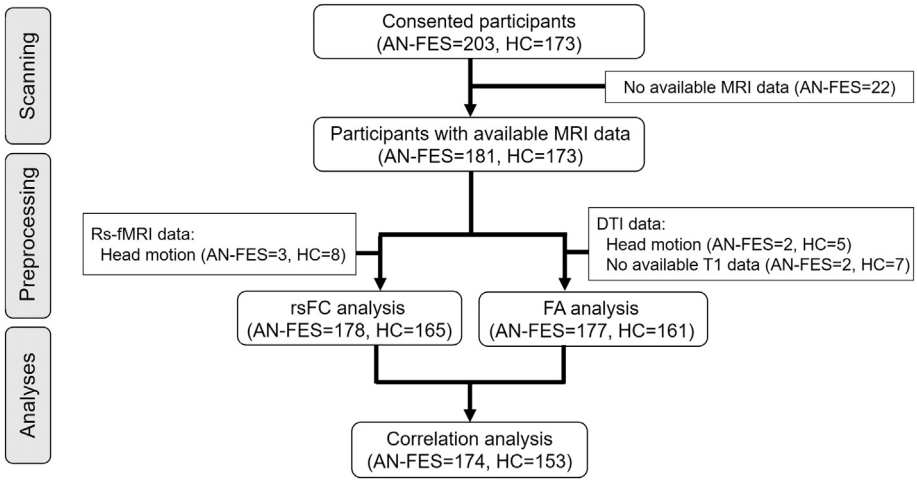

Fig. 1. Detailed inclusion and exclusion flowchart of all participants. Abbreviations: AN-FES, antipsychotic-naive first-episode schizophrenia patients; HC, healthy controls; rs-fMRI, resting-state functional magnetic resonance imaging; DTI, diffusion tensor imaging; rsFC, resting-state functional connectivity; FA, fractional anisotropy.

estimated (Basser et al., 1994) and the corresponding FA value of each voxel was calculated (Basser and Pierpaoli, 1996). Finally, regions of interest (ROIs) were defined in native diffusion space to identify white matter tracts connecting ROIs for each subject as follows: the individual T1-weighted image was also coregistered to the b_0 image in the DTI native space using a linear transformation, the coregistered T1-weighted image was nonlinearly transformed into the ICBM152 T1 template in Montreal Neurological Institute (MNI) space, and then the derived transformation parameters were inverted and used to warp the anatomical automatic labeling (AAL) template from MNI space to DTI native space (see Fig. S1 for examples of registration and parcellation) (Gong et al., 2009).

Preprocessing of rs-fMRI data was performed using SPM8 software (http://www.fil.ion.ucl.ac.uk/spm/software/spm8). For each participant, the first 10 images were discarded to ensure magnetization equilibrium, and the remaining images were corrected for slice time due to the interleaved acquisition, aligned to the middle volume, and realigned using a six-parameter (rigid body) linear transformation. We utilized Friston's 24-parameter model to regress out head motion effects from the realigned data (Friston et al., 1996). White matter signals and cerebrospinal fluid signals were regressed out to restrict analysis to grey matter voxels. Then functional images were spatially normalized to the MNI template, each voxel was resampled to $3 \times 3 \times 3$ mm^3, and a spatial smoothing transformation was performed with an 8-mm full-width half-maximum Gaussian kernel.

Participants with head translation movement > 2 mm or rotation > 2° in DTI or rs-fMRI data would be excluded (Fig. 1). No significant group differences were found in head translation movement or rotation in both DTI and rs-fMRI data.

2.4. Selection of regions of interest

To define brain regions for connectivity analysis, we used the AAL algorithm to parcellate the whole brain into 90 non-cerebellar anatomical regions (Tzourio-Mazoyer et al., 2002). The medial superior frontal gyrus, dorsolateral superior frontal gyrus, anterior cingulate gyrus, middle cingulate gyrus, posterior cingulate gyrus, superior temporal gyrus, insula, caudate nucleus, putamen, and thalamus, were selected as ROIs based on the results of a recent meta-analysis of rsFC alterations in schizophrenia (Dong et al., 2018). As another effect anatomy in the main results of this meta-analysis, cerebellum was dropped because our diffusion tensor imaging sequence did not cover the whole cerebellum (Table S2). Hippocampus (emerged twice in post hoc analyses in Dong et al., 2018) and pallidum (another part of basal ganglion) were also selected (Table S3). These 24 regions (12 regions in each hemisphere) are also frequently reported to have structural and functional abnormalities in antipsychotic-naive first-episode schizophrenia (Gong et al., 2016; Khadka et al., 2013; Li et al., 2018; Li et al., 2017; Pettersson-Yeo et al., 2011; Sarpal et al., 2016; Sheffield and Barch, 2016; Woodward et al., 2012).

2.5. Fractional anisotropy

Diffusion tensor models were estimated using a linear least-squares fitting method at each voxel using Diffusion Toolkit (http://trackvis.org/). Fiber tracking was performed in native diffusion space for each subject using the "fiber assignment by continuous tracking (FACT)" algorithm (Mori et al., 1999). Deterministic tractography was terminated if it turned at an angle >45° or reached a voxel with an FA of <0.2. In native diffusion space, tracts connecting ROIs were identified if at least one fiber was between them (Gong et al., 2009; Hagmann et al., 2010). We identified 28 pairs of ROIs from among the 276 ($N = 24 \times 23/2$) pairs examined that were connected by identifiable white matter tracts in all schizophrenia patients and healthy controls (Tables 2 and 3). Secondary analyses were also conducted on the 8 white matter tracts that were identifiable in over 50% participants (Tables S4 and S5). Each pair of ROIs was known to be anatomically connected from prior histology studies or had connecting fibers congruent with the DTI tractography atlas (Catani and Thiebaut de Schotten, 2008; Innocenti et al., 2017; Wakana et al., 2004). The averaged FA of voxels in white matter tracts connecting each pair of ROIs were extracted for each individual (Cui et al., 2013).

2.6. Resting-state functional connectivity

For each subject, representative time series for each ROI was obtained by averaging the preprocessed rs-fMRI data from all voxels in the ROI. We then computed Pearson correlation coefficients between the time series of each pair of ROIs, and their absolute values represented the indexes of inter-regional rsFC strength.

2.7. Statistical analysis

Analysis of covariance was performed to identify group differences of FA and rsFC for each pair of ROIs with identifiable white matter tracts, using age and gender as covariates. Primary analyses were conducted on the 28 pairs of ROIs with identifiable white matter tracts in all participants, and secondary analyses were conducted on the 8 pairs of ROIs with identifiable white matter tracts in over 50% participants. Analyses were corrected for multiple comparisons using the false discovery rate

Table 2
Group differences in fractional anisotropy and resting-state functional connectivity in 28 pairs of regions with identifiable white matter tracts in all participants.

Connections	FA				rsFC			
	AN-FES (n = 177)	HC (n = 161)	*F*	*P*	AN-FES (n = 178)	HC (n = 165)	*F*	*P*
dlSFG.L-mSFG.L	0.40 (0.06)	0.40 (0.06)	0.0021	0.96	0.81 (0.30)	0.87 (0.25)	3.09	0.080
dlSFG.R-mSFG.R	0.36 (0.04)	0.37 (0.05)	1.53	0.22	0.72 (0.30)	0.73 (0.28)	0.020	0.89
dlSFG.L-ACG.L	0.50 (0.06)	0.52 (0.05)	3.63	0.058	0.32 (0.21)	0.35 (0.23)	1.83	0.18
dlSFG.R-ACG.R	0.38 (0.07)	0.39 (0.07)	0.13	0.71	0.41 (0.25)	0.39 (0.22)	0.063	0.80
mSFG.L-ACG.L	0.40 (0.03)	0.41 (0.03)	6.40	0.012	0.51 (0.26)	0.50 (0.24)	0.061	0.80
mSFG.R-ACG.R	0.37 (0.03)	0.38 (0.03)	2.15	0.14	0.59 (0.31)	0.57 (0.24)	0.16	0.69
mSFG.L-MCG.L	0.42 (0.06)	0.43 (0.06)	2.85	0.092	0.22 (0.16)	0.24 (0.17)	1.10	0.30
mSFG.R-MCG.R	0.40 (0.06)	0.40 (0.05)	0.48	0.49	0.22 (0.18)	0.21 (0.15)	0.14	0.71
ACG.L-MCG.L	0.48 (0.04)	0.48 (0.04)	1.41	0.24	0.47 (0.25)	0.51 (0.28)	3.04	0.082
ACG.R-MCG.R	0.44 (0.04)	0.45 (0.04)	1.75	0.19	0.50 (0.25)	0.52 (0.25)	1.44	0.23
MCG.L-PCG.L	0.41 (0.04)	0.42 (0.04)	7.22	0.0076	0.26 (0.19)	0.29 (0.22)	2.11	0.15
MCG.R-PCG.R	0.43 (0.05)	0.44 (0.04)	2.51	0.11	0.34 (0.25)	0.35 (0.24)	0.44	0.51
ACG.L-CAU.L	0.34 (0.05)	0.34 (0.05)	0.22	0.64	0.29 (0.17)	0.26 (0.17)	2.21	0.14
ACG.R-CAU.R	0.35 (0.05)	0.36 (0.05)	1.44	0.23	0.31 (0.19)	0.30 (0.18)	0.54	0.46
CAU.L-PUT.L	0.36 (0.05)	0.38 (0.07)	6.39	0.012	0.55 (0.20)	0.53 (0.21)	0.70	0.40
CAU.R-PUT.R	0.34 (0.05)	0.35 (0.06)	8.18	**0.0045***	0.46 (0.19)	0.47 (0.20)	0.80	0.37
CAU.L-PAL.L	0.42 (0.08)	0.42 (0.07)	0.25	0.62	0.56 (0.19)	0.53 (0.20)	1.80	0.18
CAU.R-PAL.R	0.41 (0.06)	0.44 (0.08)	10.00	**0.0018***	0.50 (0.18)	0.49 (0.20)	0.12	0.73
CAU.L-THA.L	0.39 (0.03)	0.39 (0.03)	0.092	0.76	0.38 (0.21)	0.42 (0.21)	2.54	0.11
CAU.L-THA.R	0.41 (0.02)	0.40 (0.02)	1.61	0.21	0.40 (0.21)	0.40 (0.20)	0.018	0.89
PUT.L-THA.L	0.42 (0.05)	0.41 (0.05)	2.78	0.10	0.40 (0.20)	0.40 (0.19)	0.12	0.73
PUT.R-THA.R	0.43 (0.05)	0.43 (0.05)	0.061	0.80	0.35 (0.21)	0.38 (0.19)	1.30	0.25
PAL.L-THA.L	0.38 (0.04)	0.38 (0.04)	0.00030	0.99	0.40 (0.20)	0.45 (0.20)	3.43	0.065
PAL.R-THA.R	0.38 (0.05)	0.39 (0.05)	0.40	0.53	0.36 (0.21)	0.42 (0.19)	8.51	**0.0038***
HIP.L-THA.L	0.38 (0.06)	0.40 (0.07)	3.02	0.083	0.44 (0.21)	0.41 (0.21)	1.39	0.24
HIP.R-THA.R	0.41 (0.06)	0.43 (0.05)	8.42	**0.0040***	0.36 (0.21)	0.37 (0.21)	0.70	0.40
INS.L-STG.L	0.37 (0.04)	0.38 (0.04)	2.13	0.15	0.60 (0.28)	0.63 (0.22)	1.46	0.22
INS.R-STG.R	0.38 (0.05)	0.39 (0.04)	3.77	0.053	0.51 (0.27)	0.61 (0.26)	9.83	**0.0019***

Abbreviations: AN-FES, antipsychotic-naive first-episode schizophrenia patients; HC, healthy controls; FA, fractional anisotropy; rsFC, resting-state functional connectivity; dlSFG, dorsolateral superior frontal gyrus; mSFG, medial superior frontal gyrus; ACG, anterior cingulate gyrus; MCG, middle cingulate gyrus; PCG, posterior cingulate gyrus; INS, insula; STG, superior temporal gyrus; CAU, caudate nucleus; PUT, putamen; PAL, pallidum; THA, thalamus; HIP, hippocampus; R, right; L, left.
* Differences are significant at $P < 0.05$ corrected with false discovery rate.

(FDR) procedure (Benjamini and Hochberg, 1995; Genovese et al., 2002). Then, we correlated the averaged FA of each of the pairs of ROIs with the corresponding rsFC of the same regions in schizophrenia patients and healthy controls separately. We also correlated the FA of white matter tracts and rsFC in which alterations were detected with total symptoms, positive symptoms, negative symptoms, and general psychopathology symptoms scores of PANSS in patients. The subscales including thought disturbance, activation, paranoid, depression, anergia, and impulsive aggression symptom scores of PANSS were considered in secondary analyses. Statistical tests of differences between Pearson correlation coefficients of structural and functional measures in patients and healthy controls, and of the significance of correlations of brain data and clinical ratings, were performed using the Fisher's *Z*-transform method.

3. Results

3.1. Altered fractional anisotropy

In primary analyses for the 28 pairs of ROIs with identifiable white matter tracts in all participants, FA of white matter tracts was significantly decreased in patients between right caudate nucleus and right pallidum, right caudate nucleus and right putamen, and right hippocampus and right thalamus ($P < 0.05$ corrected with FDR, Table 2 and Fig. 2). In secondary analyses for the 8 pairs of ROIs with identifiable white matter tracts in over 50% participants, significantly decreased FA in patients was found between right dorsolateral superior frontal gyrus and left medial superior frontal gyrus, and bilateral medial superior frontal gyrus ($P < 0.05$ corrected with FDR, Table S4).

3.2. Altered resting-state functional connectivity

In primary analyses, rsFC was significantly decreased in patients between right pallidum and right thalamus, and right insula and right superior temporal gyrus ($P < 0.05$ corrected with FDR, Table 2 and Fig. 2). No significant group difference was found in rsFC in secondary analyses (Table S4).

3.3. Relationship between fractional anisotropy and resting-state functional connectivity

In both primary analyses and secondary analyses, no significant correlation was found between FA and rsFC ($P > 0.05$ corrected with FDR, Tables 3 and S5). In secondary analyses, the FA-rsFC correlation between right dorsolateral superior frontal gyrus and right thalamus of patient ($r = 0.22$) was significantly stronger than that of healthy controls ($r = -0.21$) ($Z = 3.71$, $P = 0.0002$, $P < 0.05$ corrected with FDR). The other correlations did not significantly differ between groups.

3.4. Relationship between alterations and symptoms

We examined relations between structural and functional alterations and current symptoms severity in our acutely ill patient sample. FA within the striatum between right caudate nucleus and right putamen was significantly inversely correlated with negative symptoms ($r = -0.23$, $P = 0.0058$, $P < 0.05$ corrected with FDR) (Fig. 2). RsFC between right pallidum and right thalamus was significantly inversely correlated with positive symptoms ($r = -0.28$, $P = 0.0008$, $P < 0.05$ corrected with FDR) (Fig. 2). In secondary analyses, the relations of FA and rsFC with PANSS subscales are presented in Fig. S2.

4. Discussion

Beginning with preselected ROIs with rsFC deficits based on a recent meta-analysis, and then identifying white matter tracts that connected them with DTI data in the present study, we found both rsFC and FA alterations in our large sample of acutely ill, antipsychotic-naive, first-

Table 3
Correlations between fractional anisotropy and resting-state functional connectivity in 28 pairs of regions with identifiable white matter tracts in all participants.

Connections	AN-FES (n = 174)		HC (n = 153)	
	r	*P*	*r*	*P*
dlSFG.L-mSFG.L	−0.022	0.77	−0.030	0.71
dlSFG.R-mSFG.R	0.11	0.15	0.014	0.87
dlSFG.L-ACG.L	0.026	0.73	0.068	0.40
dlSFG.R-ACG.R	0.069	0.36	−0.057	0.49
mSFG.L-ACG.L	−0.12	0.12	−0.13	0.097
mSFG.R-ACG.R	−0.040	0.60	−0.13	0.12
mSFG.L-MCG.L	−0.016	0.83	0.063	0.44
mSFG.R-MCG.R	0.078	0.31	0.058	0.48
ACG.L-MCG.L	0.027	0.73	0.18	0.030
ACG.R-MCG.R	−0.024	0.75	0.042	0.60
MCG.L-PCG.L	−0.029	0.71	−0.12	0.14
MCG.R-PCG.R	−0.027	0.73	−0.061	0.46
ACG.L-CAU.L	0.21	0.0061	0.041	0.62
ACG.R-CAU.R	−0.060	0.43	0.00013	0.99
CAU.L-PUT.L	−0.038	0.62	−0.12	0.16
CAU.R-PUT.R	0.052	0.50	−0.21	0.0084
CAU.L-PAL.L	−0.011	0.89	0.019	0.82
CAU.R-PAL.R	0.043	0.57	−0.064	0.43
CAU.L-THA.L	−0.085	0.27	0.047	0.56
CAU.L-THA.R	−0.099	0.19	0.048	0.56
PUT.L-THA.L	−0.014	0.85	−0.075	0.36
PUT.R-THA.R	0.093	0.22	0.034	0.68
PAL.L-THA.L	−0.081	0.29	0.13	0.099
PAL.R-THA.R	−0.071	0.35	0.059	0.47
HIP.L-THA.L	−0.067	0.38	−0.11	0.17
HIP.R-THA.R	−0.074	0.33	−0.043	0.60
INS.L-STG.L	0.15	0.042	−0.046	0.57
INS.R-STG.R	0.056	0.46	−0.16	0.054

Abbreviations: AN-FES, antipsychotic-naive first-episode schizophrenia patients; HC, healthy controls; dlSFG, dorsolateral superior frontal gyrus; mSFG, medial superior frontal gyrus; ACG, anterior cingulate gyrus; MCG, middle cingulate gyrus; PCG, posterior cingulate gyrus; INS, insula; STG, superior temporal gyrus; CAU, caudate nucleus; PUT, putamen; PAL, pallidum; THA, thalamus; HIP, hippocampus; R, right; L, left.

episode schizophrenia patients. FA alterations in the ROI pairs examined were restricted to intrinsic basal ganglia and thalamo-hippocampal circuitry, while functional alteration was limited to basal ganglia output to thalamus via the pallidum, and between insula and superior temporal gyrus. However, representing the key findings of our study, the lack of robust correlations of these abnormalities were negative findings, even with our relatively rare and large sample in the literature. These findings suggest that these well-established FA and rsFC abnormalities are relatively independent abnormalities, with rsFC alterations observed in the early course of schizophrenia not primarily associating with FA alterations in white matter tracts that connect the regions. Notably, these findings were present in never-treated patients in whom drug effects could not confound data interpretation.

In addition to the findings related to functional and structural alterations and their relationships, we also examined correlations between psychiatric symptoms and brain measurements. We found that FA of intrinsic basal ganglia white matter tracts was correlated with negative symptoms severity, while rsFC of output pathways from basal ganglia to thalamus was correlated with positive symptoms severity. These results provide additional support for the relative independence of functional and structural brain circuitry alterations in schizophrenia and further provide novel evidence that different pathophysiological mechanism might underlie negative and positive symptoms in the early course of schizophrenia. Of particular interest in this regard is the observation that functional alteration of basal ganglia output to thalamus was related to positive symptoms severity. This observation is relatively novel in the rs-fMRI literature, and is consistent with preclinical evidence that basal ganglia-thalamic network dysfunction is relevant to the biology of acute psychosis (Erlij et al., 2012; Gasca-Martinez et al., 2010).

As white matter pathways alterations have been observed in schizophrenia, it is reasonably to hypothesize that this pathology may contribute significantly to widely reported rsFC alterations associated with the disorder (Camchong et al., 2011; Lui et al., 2015; Marenco et al., 2012; Skudlarski et al., 2013). It is widely believed that the major contribution to the direction-dependent diffusion signal which impacts FA values is attributable to axonal membranes hindering the diffusion process of water molecules (van den Heuvel et al., 2008). The decreased FA of specific white matter tracts may be explained by a less dense packing of axonal fibers or microstructural alterations within axons that interfere with water diffusion. With FA alterations widely reported in the schizophrenia literature, our data suggest that reduced FA of white matter tracts is not associated with and is relatively independent from rsFC alterations, and that they may have different clinical correlations.

While the implications of the lack of parallel FA and rsFC alterations remain to be fully understood, several preliminary explanations and tentative conclusions can be considered. First, alterations in white matter pathway connections do not appear to be a primary factor in causing rsFC alterations in schizophrenia. Our findings also found no significant correlations between rsFC and FA of white matter tracts connecting the selected ROIs in healthy controls, suggesting that even in healthy individuals, at least in the schizophrenia-relevant pathways examined, white matter tracts characteristics are not a primary factor influencing rsFC. Together with differential relations with positive and negative symptoms, these observations suggest that alterations in rsFC may be more synaptically or neurochemically mediated, and thus that these alterations are to a significant degree state-of-illness dependent than persistent traits as has been previously suggested (Lui et al., 2010). This might account for the closer relationship of positive symptoms to rsFC changes, and their robust changes after antipsychotic treatment (Sarpal et al., 2016; Sarpal et al., 2017). Pharmacological studies have found that modulation of the glutamatergic system via blockade of *N*-methyl-D-aspartate receptors can alter rsFC (Hoflich et al., 2015). We have previously shown that initiation of antipsychotic treatment has acute and longer-term impact on resting brain connectivity (Li et al., 2016; Lui et al., 2010) and that antipsychotic treatment response is predicted by glutamate genetics (Stevenson et al., 2016). Thus, alterations in rsFC may be more useful for tracking treatment effects than anatomic measures in terms of remission from acute psychosis. Second, while the relation of white matter changes to psychosis and course of illness remain uncertain, it is possible that persistent alterations in white matter projections of intrinsic basal ganglia and thalamo-hippocampal circuitry might contribute to risk for altered rsFC of basal ganglia-thalamo circuitry and to the emergence of acute psychosis. This possibility remains to be evaluated in clinical and preclinical models (Belujon and Grace, 2008), but FA alterations of white matter tracts might set the stage for rsFC alterations even though they are not closely related after illness onset. Third, FA and rsFC alterations involved different circuitry, and were in turn differentially correlated with negative and positive symptoms severity. These observations are consistent with the view that different pathophysiological mechanism underlay negative and positive symptoms in schizophrenia.

There are limitations to consider in interpreting our findings. First, while this study successfully and directly examined the relations of FA and rsFC alterations, the number of connections we could identify and examine in this way was limited because we pursued a hypothesis-driven ROI approach for data analyses. While findings are clear in circuits we could examine, the nature of effects in other circuits remains to be determined and their abnormalities and patterns may be different. Second, although it is not strictly necessary to have isotropic voxels, DTI tractography typically benefits from smaller isotropic voxels (Mukherjee et al., 2008). According to FDT guidelines, we did not resample the data to make the voxels isotropic (Jenkinson et al., 2012). Continuing evolution of DTI acquisition strategies may in the future expand the range of circuits that can be examined as we did in the present study. For example, as it took several years to collect our large sample of

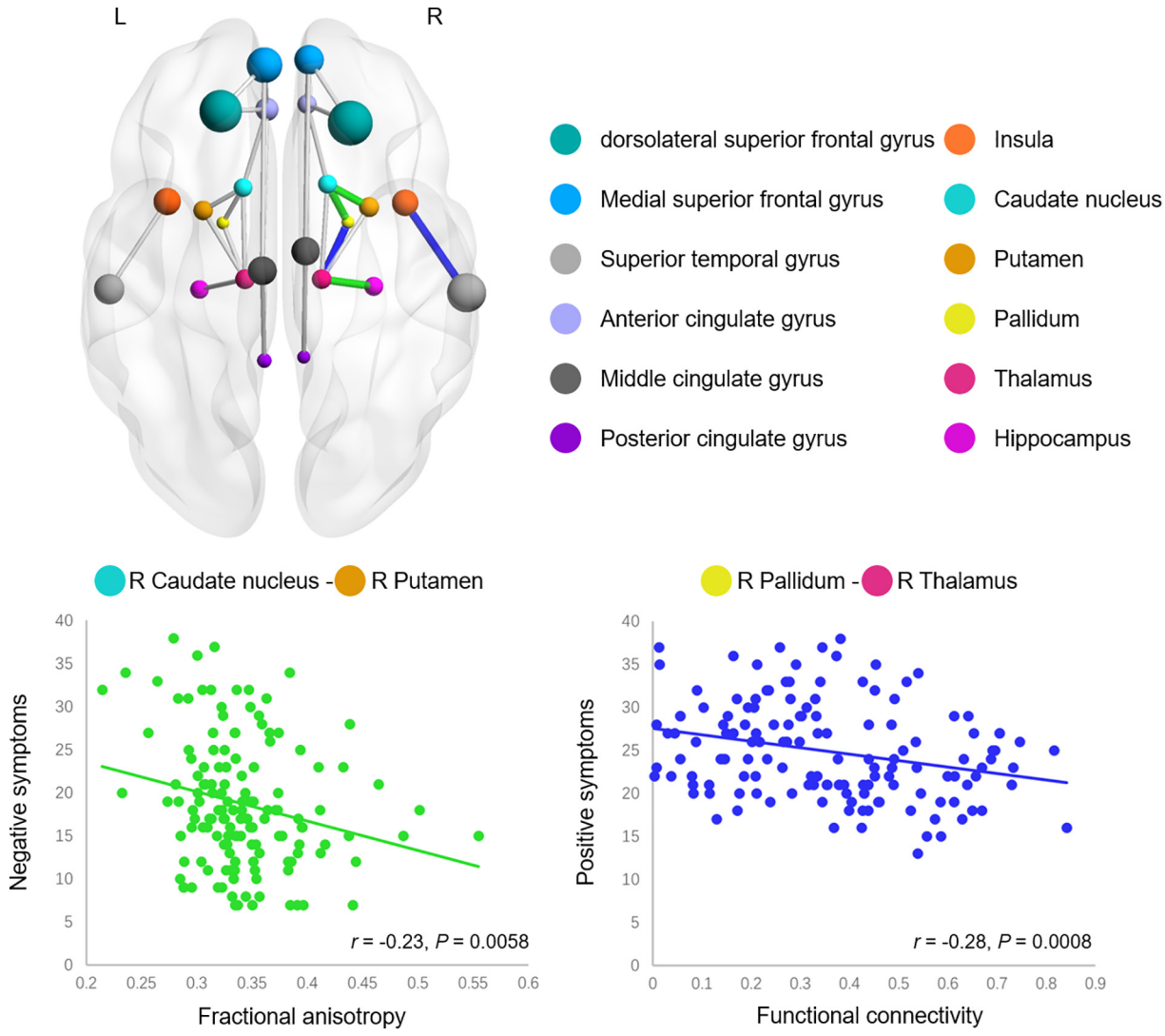

Fig. 2. Circuits with decreased fractional anisotropy are noted in green and those with decreased resting-state functional connectivity are noted in blue. Their correlations with the scores of Positive and Negative Syndrome Scale are presented in the scatterplots on the bottom. R, right; L, left.

never treated patients, we acquired only one b_0 image and 15 diffusion directions due to the technique and scan time limitations at the beginning of the project. The signal-to-noise ratio (SNR) was also not optimized and reproducibility experiment of the techniques was absent in our study. Isotropic voxels, multiple b_0 images, more diffusion directions, and newer diffusion-weighted schemes (e.g., Q-ball and diffusion spectrum imaging) will be applied in future research, providing greater SNR and less bias in fiber tractography (Mukherjee et al., 2008). Third, our rs-fMRI data were too short to conduct censoring of volumes with motion artifacts, which can influence the rs-fMRI data and cause spurious results (Power et al., 2015). Fourth, our analyses of parallels of FA and rsFC were restricted to circuits where rsFC abnormalities had been previously reported and with identifiable white matter tract in majority of participants (Tables 2, S4, and S6). Alterations in other regions and pathways may be relevant to the illness. Also, it is noteworthy that though previous meta-analysis reported alterations in specific pathways, in most cases we did not detect such functional alterations in our study except for connection between insula and superior temporal gyrus (Tables 2 and S6). As our sample was relatively rare and large, the reasons for our findings in this regard are uncertain. The absence of drug therapies and the early course of illness of our patient cohort may be relevant factors.

The lack of robust correlations between FA and rsFC and no overlap of these abnormalities indicate that rsFC alterations observed in the early course of schizophrenia are not primarily associated with the loss of FA in white matter tracts that connect the regions. The observation that positive and negative symptoms are related to different functional and structural disturbances is consistent with this dissociation, and with prior work suggests that different pathophysiological mechanism may underlie positive and negative symptoms in the early course of schizophrenia.

Conflict of interest

Prof. Sweeney has consulted to Takeda. The other authors report no conflict of interest.

Contributors

Su Lui conceived the study and designed the protocol. Jieke Liu, Li Yao, Wenjing Zhang, and Yuan Xiao acquired the MRI data. Wei Deng collected the sample and did the psychological ratings. Jieke Liu, Li Yao, and Fei Li analyzed the MRI data and conducted the statistical analyses. Jieke Liu, Li Yao, John A. Sweeney, Qiyong Gong, and Su Lui interpreted the study findings and developed the manuscript. Jieke Liu and Li Yao wrote the first draft of the manuscript that was revised and approved by all authors.

Role of the funding source

This study was supported by National Natural Science Foundation of China (grant numbers 81371527, 81671664, 81621003), Program for Changjiang Scholars and Innovative Research Team in University of China (PCSIRT, grant number IRT16R52), Fundamental Research Funds for the Central Universities (2018SCUH0011), and Science and Technology Project of the Health Planning Committee of Sichuan (18ZD035). Prof. Gong would like to acknowledge the support from Changjiang Scholar Professorship Awards of China (award number T2014190). Prof. Lui would like to acknowledge the support from Chang Jiang Scholars of China (award number Q2015154) and the National Program for Support of Top-notch Young Professionals (award number W02070140). The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Acknowledgement

We want to thank all participants in this study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2018.08.005.

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