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Shared abnormality of white matter integrity in schizophrenia and bipolar disorder: A comparative voxel-based meta-analysis

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ABSTRACT

Patients with schizophrenia and bipolar disorder (BD) shared a significant overlap in genetic susceptibility, pharmacological treatment responses, neuropsychological deficits, and epidemiological features. However, it remains unknown whether these clinical overlaps are mediated by shared or disorder-specific abnormalities of white matter integrity. In this voxel-based meta-analytic comparison of whole-brain white matter integrity, we aimed to identify the shared or disorder-specific structural abnormalities between schizophrenia and BD. A comprehensive literature search was conducted up to February 2016 to identify studies that compared between patients and healthy controls (HC) by using whole-brain diffusion approach (schizophrenia: 24 datasets with 754 patients vs. 775 HC; BD: 23 datasets with 705 patients vs. 679 HC). Voxel-wise meta-analyses were conducted and restricted to unified template using seed-based d-Mapping. Abnormal white matter integrity was calculated within each condition and a direct comparison of effect size was performed of alterations between two conditions. Two regions with significant reductions of fractional anisotropy (FA) characterized abnormal water diffusion in both disorders: the genu of the corpus callosum (CC) and posterior cingulum fibers. There was no significant difference found between the two disorders. Our results highlighted shared impairments of FA at genu of the CC and left posterior cingulum fibers, which suggests that, phenotypic overlap between schizophrenia and BD could be related to common brain circuit dysfunction.

1. Introduction

The relationship between schizophrenia and bipolar disorder (BD) has been the focus of a growing number of studies: shared a significant overlap in genetic risk factors (Lichtenstein et al., 2009; Purcell et al., 2009), neuropsychological deficits (Hill et al., 2009; Kumar et al., 2015), pharmacological treatment responses (Maier et al., 2006; Murray et al., 2004) and epidemiological features, hence possibly leading to a common pathogenic mechanisms, and challenging Kraepelinian dichotomy (Craddock and Owen, 2005). The two illnesses continue to rank among the leading causes of disability worldwide, largely because the underlying neurobiological continuum linking the two psychotic disorders remains elusive and hence resulting in limited therapeutic and prognostic value (Frangou, 2014). Therefore, further exploration of the underlying neurobiology of both disorders would be valuable. Diffusion tensor imaging (DTI), a non-invasive MRI technology, is a powerful imaging method for characterizing the integrity of white matter circuitry because it links anatomical and functional neuroimaging together (Assaf and Pasternak, 2008). Although, a few studies have attempted to compare these two conditions, such as Kumar et al. (2015) and Lu et al. (2011), the consistency and replicability of findings in relation to white matter abnormalities in the two psychotic disorders remain uncertain usually due to small sample.

In light of these previous findings, this study therefore aims at conducting a quantitative, voxel-based meta-analytic comparison of all published whole-brain structural MRI studies of white matter abnormalities in patients with schizophrenia and BD to reliably identify shared or disorder-specific white matter abnormalities between two illnesses, which could aid the understanding of pathophysiological basis of the clinical continuum of psychosis. We integrated both widely used whole brain DTI approaches: voxel-based analysis (VBA) and tract-based spatial statistics (TBSS), by using a novel meta-analytic technique which allows us to comparing the effects size between two disorders. In addition, some necessary analyses were conducted to guarantee that our findings were robust and reliable.

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Based on current perspectives of dysconnectivity in psychosis (Nortje et al., 2013; Pettersson-Yeo et al., 2011), we hypothesized both schizophrenia and BD would show decreased white-matter integrity relative to controls and both disorders would show no significant differences in abnormalities of white matter (Cui et al., 2011; Kumar et al., 2015; McIntosh et al., 2008; Sussmann et al., 2009), whereas according to previous independent meta analyses we expected shared white matter abnormalities in frontal white matter to genu of the corpus callosum (CC) (Ellison-Wright and Bullmore, 2009; Wise et al., 2016).

2. Materials and methods

2.1. Study selection

Using PubMed, Web of Knowledge, and Scopus, we conducted a comprehensive literature search of studies published up to February 2016 that used whole-brain approach comparisons between individuals with schizophrenia or BD and healthy controls (HC). The selection of papers for the meta-analysis was conducted according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines (Moher et al., 2009). The search terms were "Schizophrenia" or "schizoaffective" or "Bipolar" and "Diffusion tensor imaging" or "DTI". Next, additional studies were collected by reviewing the reference list of the relevant papers and publications that cited those articles found in the first step, or through the 'related article' function of the PubMed database. Finally, the reference lists of those review articles were inspected for adding more relevant studies. Similar to previous meta study (Wise et al., 2016), exclusion criteria were as follows: (1) age below 18 or above 65, to minimize the effect of neurodevelopment and neurodegeneration as potential confounders on white matter diffusivity (Barnea-Goraly et al., 2005); (2) no HC group; (3) papers that used region of interest method; (4) did not use VBA or TBSS analysis (5) paper that did not report coordinates of effect in original paper and further could not be obtained through contracting the corresponding authors. To avoid sample overlaps, the following selection standard was followed (Wise et al., 2016): (1) the largest sample was included when multiple studies used the same dataset; (2) only the results from the whole group of participants were considered in case of multiple sub-groups analyses; (3) only pretreatment data were included in case of longitudinal studies. Literature Searches indicated forty-four studies (47 datasets) (Ambrosi et al., 2016; Benedetti et al., 2011; Bruno et al., 2008; Buchsbaum et al., 2006; Canales-Rodríguez et al., 2014; Chaddock et al., 2009; Chan et al., 2010; Chen et al., 2012; Cheung et al., 2008; Cui et al., 2011; Ebdrup et al., 2015; Guo et al., 2012; Ha et al., 2011; Hao et al., 2006; Hao et al., 2009; Hubl et al., 2004; Jeong et al., 2009; Jones et al., 2005; Kumar et al., 2015; Lagopoulos et al., 2013; Liu et al., 2010; Liu et al., 2014; Lu et al., 2011; Magioncalda et al., 2016; Mahon et al., 2012; Mahon et al., 2009; Mori et al., 2007; Nakamura et al., 2012; Oertel-Knöchel et al., 2014; Ozcelik-Eroglu et al., 2014; Reid et al., 2016; Schlösser et al., 2007; Seok et al., 2007; Shergill et al., 2007; Sprooten et al., 2013; Sussmann et al., 2009; Szeszko et al., 2005; Szeszko et al., 2008; Versace et al., 2008; Versace et al., 2010; Wang et al., 2011; Wessa et al., 2009; Zanetti et al., 2009; Zeng et al., 2016) meeting criteria for inclusion in the analysis (see Tables 1 and 2 for details). Four studies compared both schizophrenia and BD with control subjects (Cui et al., 2011; Kumar et al., 2015; Lu et al., 2011; Sussmann et al., 2009). A PRISMA flow chart of study selection is shown in Fig. S1 (see Supplementary material). Among the range of measures derived from DTI, fractional anisotropy (FA) was the only one consistently reported in all of studies and was therefore the only one examined in this meta-analysis. Importantly, reduction in FA provides a possible expression of demyelination (Beaulieu, 2002; Song et al., 2002), which existed in both disorders (Davis et al., 2003; Kempton et al., 2008).

2.2. Recorded variables and contrasts

Once the studies were selected, the following variables were recorded from each article: sample sizes, mean age of participants, sex (male, female), mean illness duration of patient, mean psychiatric symptoms scores on Positive and Negative Syndrome Scale (positive scale, PS and negative scale, NS) for schizophrenia, mean scores on Young Mania Rating Scale (YMRS) and Hamilton Depression Rating Scale 17-Item (HAMD-17) for BD, proportion of medicated patients (antipsychotics for schizophrenia, lithium for BD) in each study, subtype for BD (BD-I,

Table 1
Characteristics of schizophrenia studies included in the meta-analysis.

Study	Analysis	Schizophrenia patients								Healthy controls		
		N	Mean age	Sex (F)	Illness Duration (years)	PS	NS	Antipsychotics (%)	State	N	Mean age	Sex (F)
Buchsbaum et al. (2006)	VBA	63	41.7	19	18.2	15	17.3	95.20%	Chronic	55	42.4	23
Cheung et al. (2008)	VBA	25	28.5	13	0.5	20.4	14.6	0	FE	26	28.2	13
Cui et al. (2011)	VBA	25	25.8	9	3.9	22.5	20.9	100%	Chronic	30	23.9	12
Ebdrup et al. (2016)	TBSS	38	25.9	10	6.25	20.7	22.1	0	FE	38	25.8	12
Eroglu et al. (2014)	TBSS	16	34.3	6	11.62	22.41	21.06	87.50%	Chronic	8	33.88	3
Guo et al. (2012)	TBSS	20	24	11	0.55	22.9	20.9	0	FE	26	23.6	12
Hao et al. (2006)	VBA	21	23.71	9	0.86	NA	NA	100%	FE	21	25.05	11
Hao et al. (2009)	VBA	34	25.44	14	1.69	21.3	22.03	100%	Chronic	34	25.77	14
Hubl et al. (2004)	VBA	26	32.2	10	8.1	20.45	21.95	92.30%	Chronic	13	32	5
Jeong et al. (2009)	TBSS	10	39.6	0	19	NA	NA	100%	Chronic	10	44.1	0
Jones et al. (2005)	VBA	14	34	0	8	NA	NA	100%	Chronic	14	34	0
Kumar et al. (2015)	TBSS	40	33.5	10	9.92	NA	NA	NA	Chronic	41	34.72	7
Liu et al. (2014)	TBSS	17	38.5	10	15.41	21.1	22.9	0	Chronic	17	34.1	11
Mori et al. (2007)	VBA	42	40	16	16.8	NA	NA	100%	Chronic	42	39.2	16
Nakamura et al. (2012)	VBA	58	27.6	20	4.27	NA	NA	100%	Chronic	58	26.4	20
Reid et al. (2016)	TBSS	29	33.8	9	13.4	(BPRS) 10.1	6.3	51.70%	Chronic	20	37.1	6
Schlösser et al. (2007)	VBA	18	29.6	4	NA	NA	NA	100%	Chronic	18	29	6
Seok et al. (2007)	VBA	30	29.6	15	7.5	NA	NA	100%	Chronic	22	30.3	11
Shergill et al. (2007)	VBA	33	32	3	7	NA	NA	93.90%	Chronic	40	34	5
Sussmann et al. (2009)	VBA	28	38	13	16.8	10.5	NA	100%	Chronic	38	37.2	19
Szeszko et al. (2005)	VBA	10	26.9	4	NA	NA	NA	60%	FE	13	28.9	6
Szeszko et al. (2008)	VBA	33	25.1	12	4.25	NA	NA	18.20%	Chronic	30	25.9	12
Wang et al. (2011)	VBA	68	24.13	36	0.75	26.31	19.61	56%	FE	100	25.6	48
Zeng et al. (2016)	TBSS	55	25	33	0.65	46 (BPRS)	NA	0	FE	61	25.33	33

BPRS, brief psychiatric rating scale; F, female; FE, first-episode; M, male; NA, not mentioned in original study; NS, Positive and Negative Syndrome Scale-negative scores; PS, Positive and Negative Syndrome Scale-positive scores; TBSS, tract-based spatial statistics; VBA, voxel-based analysis.

Table 2
Characteristics of bipolar disorder studies included in the meta-analysis.

Study	Analysis	Bipolar disorder patients									Healthy controls		
		N	Mean age	Sex (F)	Illness duration (years)	HAMA_17	YMRS	Lithium (%)	Subtype	State	N	Mean age	Sex (F)
Ambrosi et al. (2016)	TBSS	25	48.4	12	23.9	14.5	3.5	40%	BD-II	NA	50	48.3	24
Benedetti et al. (2011)	TBSS	40	46.1	30	15	16	NA	35%	BD-I	Depressed	21	39.9	10
Bruno et al. (2008)	VBA	36	39	23	NA	NA	NA	65%	25 BD-I, 11 BD-II	NA	28	NA	15
Canales-Rodríguez et al. (2014)	VBA	40	40.6	15	15.9	NA	1.4	75%	BD-I	Euthymic	40	40.4	15
Chaddock et al. (2009)	VBA	19	43.3	10	15.6	NA	NA	47%	BD-I	Euthymic	18	41.7	8
Chan et al. (2010)	TBSS	16	36.9	4	0.2	NA	3.8	37%	BD-I	Euthymic	16	37.3	4
Chen et al. (2012)	VBA	18	32	0	4.2	3.2	24.8	83%	BD-I	Manic	27	31.3	0
Cui et al. (2011)	VBA	18	27.9	8	4.8	NA	25.9	NA	BD-I	Manic	30	23.9	12
Ha et al. (2011)	VBA	12	37.3	9	13.3	NA	1.4	66%	BD-I	Euthymic	22	34.7	17
Kumar et al. (2015)	TBSS	22	34.7	7	10.7	NA	NA	NA	BD-I	NA	41	33.2	11
Lagopoulos et al. (2013)	TBSS	58	23	41	7.5	13.4	NA	NA	18 BD-I, 27 BD-II, 13BD-NOS	Depressed	40	24.1	24
Liu et al. (2010)	VBA	27	35.4	18	8.3	6.7	0.9	14%	14 BD-I, 13BD-II	Euthymic	21	38.3	13
Lu et al. (2011)	VBA	13	25	6	N	N	24	0	BD-I	Manic	18	24	12
Magioncalda et al. (2016)	TBSS	61	44.6	43	19.6	10.7	9	28%	BD-I	21 Manic,20 Depressed and 20 euthymic	42	44.3	15
Mahon et al. (2009)	VBA	30	33.4	15	NA	NA	NA	NA	25 BD-I,2 BD-II, 3BD-NOS	NA	38	31.9	16
Mahon et al. (2012)	TBSS	29	35	11	12.1	NA	NA	NA	BD-I	Euthymic	15	33.7	7
Oertel-Knöchel et al. (2014)	TBSS	30	39.2	14	10.2	NA	NA	37%	BD-I	Euthymic	32	39.2	16
Sprooten et al. (2013)	TBSS	64	31.7	46	10	NA	1	19%	BD-I	Euthymic	46	30.1	15
Sussmann et al. (2009)	VBA	42	39.6	20	NA	NA	0.6	57%	BD-I	Euthymic	38	37.2	19
Versace et al. (2008)	TBSS	31	35.9	20	12.1	8.6	NA	36%	BD-I	14 Depressed, 17 remitted	25	29.5	14
Versace et al. (2010)	TBSS	15	36.3	14	14.7	14.9	NA	NA	BD-I	Depressed	24	27.7	15
Wessa et al. (2009)	TBSS	22	45.4	11	22	0.1	0.9	45%	14 BD-I, 8 BD-II	Euthymic	21	43	9
Zanetti et al. (2009)	VBA	37	34.1	24	11.6	6.4	NA	32%	BD-I	16 Depressed, 21 euthymic	26	28.8	14

BD-I, bipolar disorder type I; BD-II, bipolar disorder type II; F, female; HAMD-17, Hamilton Depression Rating Scale 17-Item; M, male; NOS, not otherwise specified; TBSS, tract-based spatial statistics; VBA, voxel-based analysis; YMRS, Young Mania Rating Scale.

BD-II), state of patient (schizophrenia: first episode, chronic; BD: Manic, euthymic, depressed, remitted), and image acquisition parameters (magnetic field strength, repetition time, echo time, gradient directions, b-factor) as shown in Tables 1, 2 and Table S1–S4. The coordinates with statistically significant difference were extracted, including the direction of alteration (patient > HC, patient < HC) and the effect size (T value; if the original studies reported the Z or P value, they will be transformed to T value). The study with negative findings was also included in this meta-analysis as this meta-analysis method required.

2.3. Meta-analysis

Voxel-wise meta-analysis was performed on the selected studies using anisotropic effect-size-based algorithms (AES-SDM) software (http://www.sdmproject.com) (Radua et al., 2014) in a standard process. Coordinates and effect sizes (t or z values) were extracted form original reports. Coordinates reported in Talairach space were converted into Montreal Neurological Institute space. AES-SDM uses an anisotropic nonnormalized Gaussian kernel to optimize the recreation of effect-size map (Radua et al., 2012). Then, coordinate-based individual maps were used to calculate a random effect, which takes sample size as well as intra- and between-study variance.

2.3.1. Main analyses

Separated analyses were conducted to investigate the impairments of FA within each disorder group. Next, a voxel-wise quantitative comparison was performed to assess abnormalities of FA (relative to HC) between schizophrenia and BD. As followed by previous study (Wise et al., 2016), to combine VBA and TBSS studies, the TBSS template (FMRIB58 FA skeleton, http://www.fmrib.ox.ac.uk/fsl) in AES-SDM was adopted. This skeleton restricts the analysis to the same white matter tracts. Then, a conjunction analysis between each patient group comparison maps was performed to identify the shared FA abnormalities across both illnesses with the multimodal analysis section of AES-SDM (Radua et al., 2013). Only abnormalities that survived standard thresholding with a voxel-level (height) threshold of $p < 0.005$ with peak $Z > 1$ and a cluster-level (extent) threshold of 10 voxels are reported (Radua et al., 2012). Moreover, systematic whole-brain voxel-based jack-knife sensitivity analysis was performed to test the replicability of the results. Also, the possible existence of publication bias for the brain regions with FA alterations was assessed by Egger's test (Egger et al., 1997) using Stata software (version12.0).

2.3.2. Additional analyses

To test the moderating effects, heterogeneity analyses, were conducted within each patient group (threshold was $p < 0.005$) and followed up with meta-regression analyses to find sources of variability across studies (Radua et al., 2012). Given the fact the mean age and sex in both disorders are all available and there were 22 studies (91.7%) for schizophrenia, and 19 studies (82.6%) for BD reporting the mean illness duration, 23 studies (95.8%) studies for schizophrenia and 17 studies (73.9%) for BD in which proportion of medicated patients (antipsychotics for former, see Table S3 for the details, only lithium for latter, see Table S4) was most consistently reported in individual studies, these variables were considered in meta-regression analyses. Because the relatively low-frequency reports for PS (54.1%) and NS (45.8%) in schizophrenia and HAMA-17 (43.5%) and YMRS (52.2%), these variables were not considered in meta-regression analyses. Specifically, the potential effect of variables is examined by means of linear regression, weighted by the squared root of the sample size and intra- and between-study variance (Radua and Mataix-Cols, 2009). The main output for each variable is a map of the regression slope, i.e. amount of FA change associated with each variable. Positive SDM-Z value represents positive correlation, and negative value represents negative correlation. In addition, image acquisition parameters (except scanning time) were also included in meta-regression analyses to investigate the possible moderator role. The voxel-level threshold of regression was decreased to $p < 0.0005$ to minimize the detection of spurious relationships (Radua et al., 2012).

Potential differences in clinical and demographic variables between groups were assessed with standard nonparametric tests weighted by sample size. The χ^2 test was used to compare ration of studies using TBSS and VBA methods. When comparing DTI methods, we performed similar analyses to highlight potential confounding variables which were shown to moderate FA differences in meta-regression analyses.

3. Results

3.1. Basis information for each sample

3.1.1. Schizophrenia

Twenty-four studies were included in the mata-analysis (Table 1), including 754 schizophrenia patients and 775 HC. The mean age of patients was 30.8 years; 286 patients (37.9%) were female; and 510 patients (67.6%) were medicated with antipsychotics. 517 patients (69%) were chronic and 237 patients (31%) were first-episode at the time of scanning.

3.1.2. Bipolar disorder

Twenty-three studies were included in this meta-analysis (Table 2), which combined 705 patients and 679 HC. At the time of scanning, 148 patients (21%) were currently depressed, 344 patients (49%) were euthymic, and 82 patients (12%) were manic. For bipolar subtypes, 603 patients (85.5%) were type I and 86 patients (12.2%) were type II. And, 16 patients (2.3%) did not belong to the specified subtype. The mean age of patients was 36.7 years; 401 patients (57%) were female; 296 patients (42.1%) were medicated with lithium.

3.1.3. Comparison between schizophrenia and bipolar disorder

Using Tukey's honest significant difference test, the average age in BD was greater than that in schizophrenia (Mean difference = 5.94, $p = 0.008$), while the sex (Mean difference$_{(female/male)}$ = 1.27, $p = 0.57$) was not observed the difference. The illness duration (Mean difference = 4.22, $p = 0.06$) in BD was different from that in schizophrenia at marginal significant level. We did not compare the proportion of medicated patients (antipsychotics for schizophrenia, lithium for BD) because of the different medicines taken by two disorders. The proportion of studies that used VBA and TBSS methods did not differ between the two conditions ($\chi^2 = 1.29$, $p = 0.20$).

3.2. Meta-analysis of fractional anisotropy abnormalities

3.2.1. FA abnormalities in schizophrenia

Patients with schizophrenia relative to HC illustrated a significantly decreased FA in four clusters (Fig. 1 and Table S5 in Supplement material). The largest cluster exhibited a peak at the frontal white matter via genu of the CC extending to the body of the CC (MNI coordinates: −20, 34, 8; Z = −2.30; $p < 0.001$; 356 voxels). The CC cluster extended laterally, incorporating fibers joining left anterior thalamic radiation, cingulum fibers, inferior fronto-occipital fasciculus and uncinate fasciculus (Fig. 1). Also, patients with schizophrenia showed clusters of decreased FA in the right cingulum fibers (MNI: 10, −38, 20; Z = −2.28; $p < 0.001$; 325 voxels), in the anterior thalamic projections/caudate nucleus (MNI coordinates: −4, −20, 18; Z = −2.69; $p < 0.001$; 92 voxels) and left superior longitudinal fasciculus (MNI coordinates: −34, −52, 30; Z = −2.07; $p < 0.001$; 43 voxels). Neither FA increase nor publication bias (all p-value > 0.05) was found. It should be noted that only results that met the criteria for robustness are reported here, full details were shown in Table S5 in Supplement material. Among the four significant clusters, significant between-study heterogeneity was found in the right cingulum fibers (Z = 2.01; $p < 0.001$). Meta-regression analysis indicated that the reduced FA in the right cingulum fibers was associated with increasing age (slope peak: 22, −50, 18; Z = −2.13; $p < 0.001$) and longer illness duration (slope peak: 24, −52, 20; Z = −2.22; $p < 0.001$). There was no significant moderating effect of image acquisition parameters on main results. Subgroup sensitivity analyses of schizophrenia subtype (chronic and first-episode) further confirmed the robustness of the four clusters described above, which remained significant during the analysis of only chronic or first-episode samples.

3.2.2. FA abnormalities in bipolar disorder

The meta-analysis revealed three clusters of FA reductions: the left cingulum fibers extending to genu of CC (forceps minor)/anterior thalamic radiation/inferior fronto-occipital fasciculus/uncinate fasciculus (MNI: −14, −32, 36; Z = −2.86; $p < 0.001$; 720 voxels), the right anterior superior longitudinal fasciculus (MNI: 30, 26, 16; Z = −1.80; $p < 0.001$; 63 voxels), and the right anterior thalamic projections (MNI: 16, 12, 2; Z = −1.64; $p < 0.001$; 21 voxels), meeting criteria for robustness (Fig. 2 and Table S5 in Supplement material). Neither FA increase nor publication bias (all p-value > 0.05) was found. Among the three significant clusters, left cingulum fibers (Z = 3.06; $p < 0.001$) revealed significant between-study heterogeneity. Meta-regression analysis indicated that the reduced FA in the left cingulum fibers was associated with shorter illness duration (slope peak: −10, −26, 34; Z = 2.85; $p < 0.001$) and younger age (−18, −34, 36; Z = 4.4; $p < 0.001$). No significant moderating effect of image acquisition parameters on main results was observed. Subgroup sensitivity analyses of bipolar subtype further confirmed the robustness of the three clusters identified in the original analysis, which remained significant when limiting the analysis to bipolar type I or only euthymic samples.

3.2.3. FA comparison in schizophrenia and BD

Controlling for age, sex, and illness duration, there were no FA differences between two conditions. Then, the conjunction analysis revealed that the genu of the CC extending to anterior thalamic radiation/cingulum fibers/inferior fronto-occipital fasciculus (MNI: −18, 38, 2; $p < 0.001$) and left posterior cingulum fibers (MNI: −18, −36, 34; $p < 0.001$), were the two regions where both patient groups showed significantly decreased FA (Fig. 3 and Table S5 in Supplement material).

3.2.4. TBSS vs. VBA methods

When compared with studies using VBA, studies using TBSS demonstrated a frequent decrease in right cingulum fibers in schizophrenia (MNI: 10, −38, 20; Z = 1.49; $p < 0.001$) and in the left cingulum fibers (MNI: −16, −30, 34; Z = 2.83; $p < 0.001$) in BD. Mean patient age and illness duration, shown to moderating effect in the right cingulum fibers in schizophrenia, did not differ between TBSS and VBA studies ($p > 0.05$), further suggesting the an unlikely contribution to the measured differences in DTI techniques (Wise et al., 2016).

4. Discussion

To our knowledge, this is the first voxel-based meta-analysis of DTI studies, integrating the VBA and TBSS studies and comparing the shared or disorder-specific alteration of white matter microstructural integrity between schizophrenia and BD. The meta-analytic comparison showed that, compared with HC, both types of patients exhibited significantly reduced FA in the genu of the CC and left posterior cingulum fibers, indicating that the reduced white mater microstructural integrities in two regions were common to both conditions. As predicted, directed effect size comparison showed no difference between schizophrenia and BD.

The largest area observed FA decrease in both disorders was in the genu of the CC connecting bilateral prefrontal and orbitofrontal cortices, suggesting that the impairment of prefrontal interhemispheric white matter connectivity may reflect a common pathophysiological pathway in both psychosis disorders. The prefrontal regions are central to current model of cognitive and emotion dysfunction in both conditions (Couture et al., 2011; Phillips et al., 2008), which was supported by the consistent functional (Baker et al., 2014; Calhoun et al., 2009; Houenou et al., 2011) and morphometric (Arnone et al., 2009;

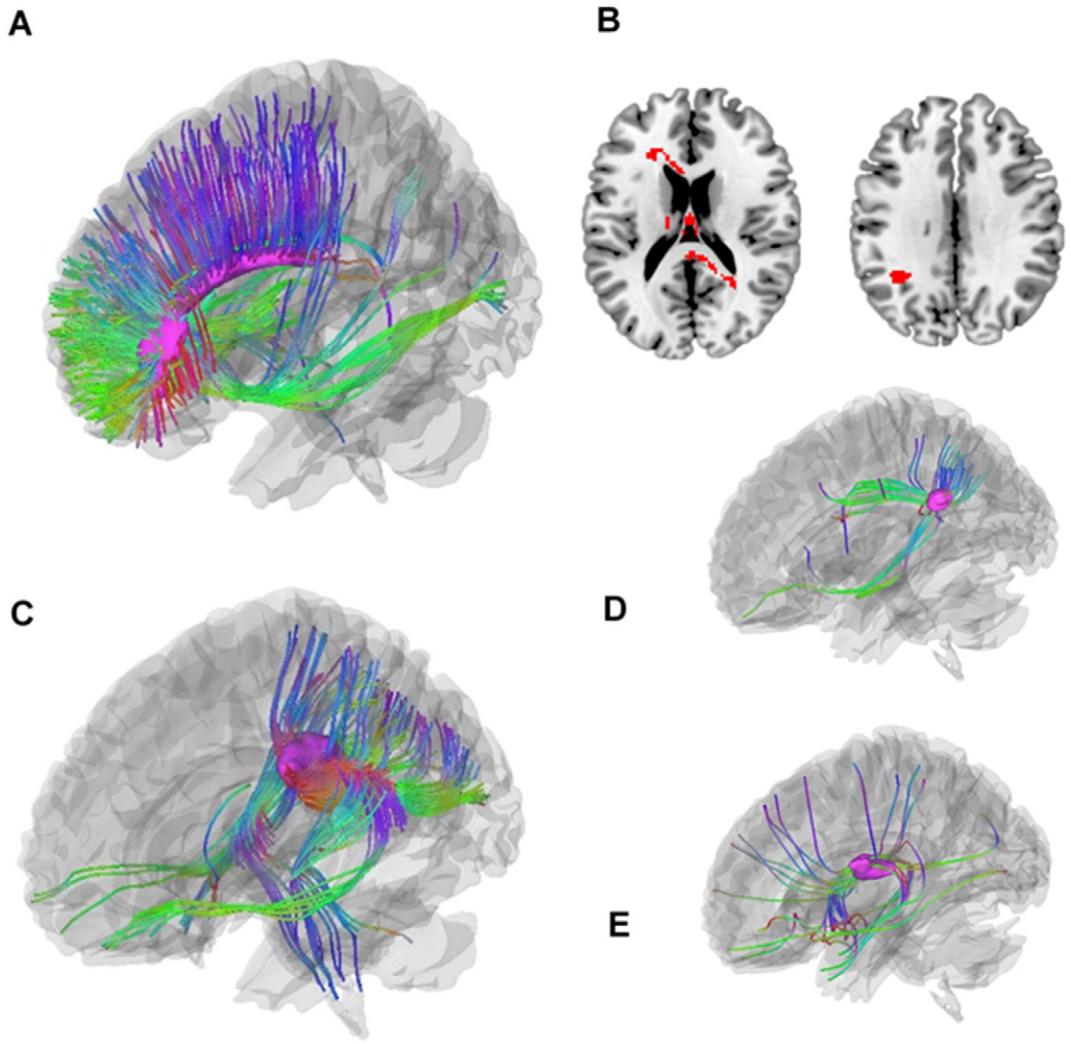

Fig. 1. Decreased FA regions in schizophrenia. (A) Three-dimensional (3-D) illustration of the tracts present in the frontal white matter extending to genu of the CC in schizophrenia. Clusters showing significant effects are in purple (B) Two-dimensional (2-D) representation of the significant clusters in the schizophrenia analysis. (C) 3-D illustration of the tracts present in the cingulum fibers cluster in schizophrenia. (D) 3-D illustration of the cluster encompassing the superior longitudinal fasciculus in schizophrenia. (E) 3-D representation of the anterior thalamic projections/caudate nucleus clusters in the schizophrenia analysis.

Ellison-Wright and Bullmore, 2010) alterations in these areas. Furthermore, the fibers passing through the cluster of the genu of the CC also included uncinate fasciculus (Fig. 3), which connects the orbitofrontal cortex to the temporal pole and the amygdala, forming circuitry essential for social cognition and socioemotional processing, and reduced integrity in this area may underlie the structural basis for the abnormal frontolimbic functional connectivity in both conditions (Anticevic et al., 2012; Phillips et al., 2008). We also observed FA reduction in both patient groups in left posterior cingulum fibers, which plays an important role in neurocognitive functions such as memory, attention, and planning (Delano-Wood et al., 2012; Kantarci et al., 2011), decreased integrity in this tract may underlie the observed impairment of executive functions present in both groups (Barch et al., 2003; Xu et al., 2012). Therefore, the above decreased structural integrity may constitute a common pathway contributing to psychological dysregulation in both conditions.

For BD vs. HC comparison, our present study not only repeated the findings of Wise et al. (2016), that is, BD showed decreased FA in the left cingulum, genu of the CC and right anterior superior longitudinal fasciculus, but also extended the previous findings. Taking advantage of more published papers, we additionally found a reduction of FA in right anterior thalamic radiation projecting to prefrontal cortex, which played a bridge role in integration of thalamo-fronto-striatal loop considered as critical foundation of pathophysiology in BD (McIntosh et al., 2008). For potential moderating effect of clinical variables, consistent with findings in Wise et al. (2016), we found that decreased FA in left cingulum fibers was less associated with increasing age. Moreover, we found the illness duration was associated with the decreased FA. This may provide evidence to confirm their speculative interpretation of illness duration effect (Wise et al., 2016), suggesting that long-term treatment ameliorates deficits of left cingulum fibers in BD.

As predicted, there was no significant FA difference in any areas between schizophrenia and BD. This observation is in agreement with previous four independent studies reporting no differences of FA with DTI (Cui et al., 2011; Kumar et al., 2015; McIntosh et al., 2008; Sussmann et al., 2009) except one (Lu et al., 2011). This meta-analysis also observed FA decreases in the right anterior superior longitudinal fasciculus and anterior thalamic projections in BD and left anterior thalamic projections/caudate nucleus and left superior longitudinal fasciculus in schizophrenia (Table S5), but neither comparison nor conjunction analyses showed alteration in the these regions, thus we cannot confirm whether white matter abnormalities in these areas was different between two disorders or not.

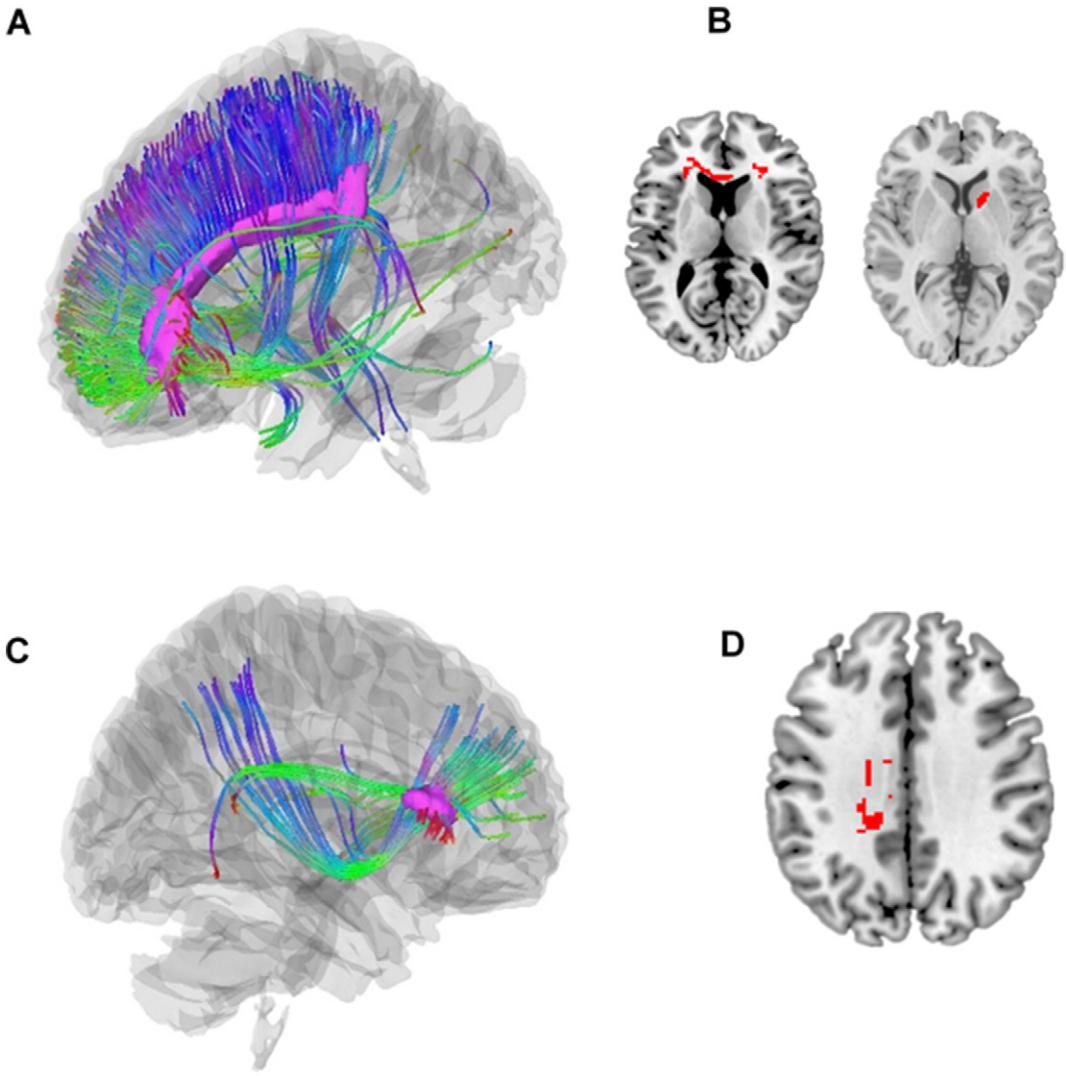

Fig. 2. Decreased FA regions in bipolar disorder (BD). (A) 3-D illustration of the tracts present in the genu of the CC cluster, cingulum fibers and anterior thalamic projections cluster in BD (B) 2-D representation of the CC and superior longitudinal fasciculus clusters in the BD analysis. (C) 3-D illustration of the cluster encompassing the superior longitudinal fasciculus in BD. (D) 2-D representation of the cingulum fibers clusters in the BD.

In previous meta-analysis (Wise et al., 2016), major depression and BD are both characterized by abnormalities in white matter tracts of the genu of the CC, and BD was associated with more reduced white matter integrity in the left posterior cingulum when comparing to major depression. Combining with our findings, it seems to be inferred genu of the CC may represent the common alterations of FA in psychotic and affective disorders, in spite of lack of direct comparison between schizophrenia and major depression. This speculation is parallel to current high genetic correlation among three disorders (Lee et al., 2013). It also might implicate that BD and schizophrenia showed the more decreased FA in left posterior cingulum relative to major depression. The presumption was consistent with the more cognitive impairment described in BD and schizophrenia (Barch et al., 2003; Xu et al., 2012). Comparison of FA among three disorders, considering simultaneously other measures of diffusivity such as mean, radial or axial diffusivity, would illuminate the more nature of WM changes underpinning psychotic and affective disorders.

Compared with studies using VBA, studies based on TBSS demonstrated more decreases in posterior cingulum fibers in schizophrenia and BD. As discussed by Wise et al. (2016), TBSS makes an improvement particularly when making comparison samples of brain disorder with enlarged lateral ventricles (Smith et al., 2006). Because there has been an appreciable evidence of ventricular enlargement in both conditions (Sayo et al., 2012; Strakowski et al., 2005) and the posterior cingulum fibers is close proximity to the lateral ventricles, these evidence might illuminate the observed difference between VBA and TBSS. In light of these, TBSS may be a more sensitive technique to detect white matter abnormalities nearby the ventricular system, such as in posterior cingulum fibers observed here.

Our meta-regression analyses showed the reduction of FA in the right cingulum fibers was more pronounced with increasing age and illness duration in schizophrenia, which may reflect a neurodegenerative process (Bora et al., 2011; Schnack et al., 2016). In BD, studies with increased age of patient or with longer illness duration of patient had less reductions of FA in the left cingulum fibers. This might reflect that long-term treatment ameliorates deficits in this area (Wise et al., 2016). But, notwithstanding the fact that meta-regressions are exploratory and should be interpreted cautiously as they do not directly calculate the corresponding relationships within each patient group (Wise et al., 2016).

In summary, this meta-analysis provides strong evidence for the shared alterations of white matter microstructure in genu of the CC and posterior cingulum fibers, indexed by decreases of FA. Although the accurate cause of variations of anisotropy is still not full known, one possible explanation is that FA decrease might reflect demyelination (Song et al., 2002). Therefore, results here suggest possible defects

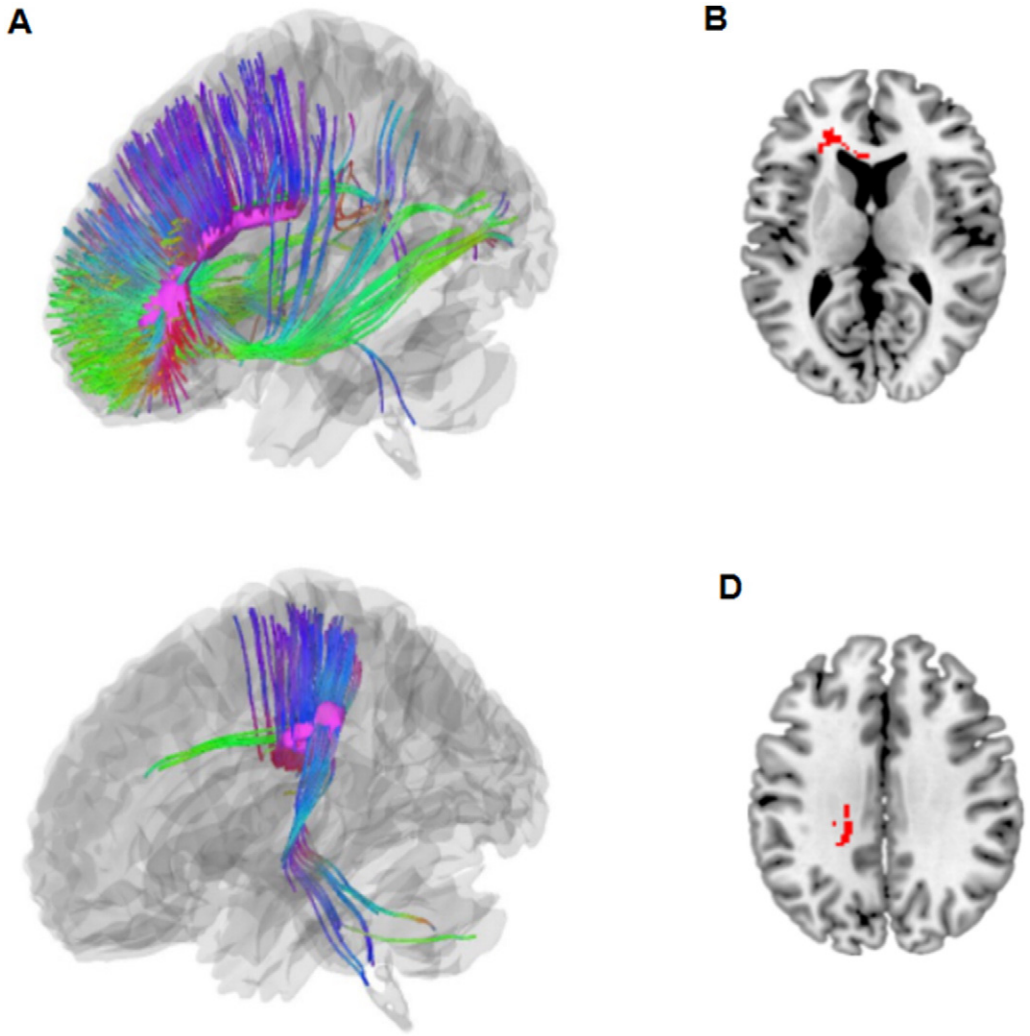

Fig. 3. FA comparisons of schizophrenia and BD. (A) Three-dimensional illustration of the tracts present in the cluster centered on the genu of the CC in the schizophrenia and BD conjunction analysis. (B) Two dimensional representation of genu of the CC in schizophrenia and BD conjunction analysis.(C) Three-dimensional illustration of the tracts present in the cluster centered on the left posterior cingulum fibers in the schizophrenia and BD conjunction analysis. (D) Two dimensional representation of posterior cingulum fibers in schizophrenia and BD conjunction analysis. Red areas indicate areas that showed decreased FA in both conditions.

in myelination along with a degree of 'disorganization' underlies abnormalities of fiber structure in schizophrenia and BD. While conventional diagnostic descriptions have failed to capture Kraepelin's concept in a convincing fashion, augmenting this clinical information with neurobiological observations such as the one reported here brings new prospects for making progress in understanding psychosis (Kumar et al., 2015).

4.1. Strengthens and limitations

This work extends previous DTI meta-analyses (Ellison-Wright and Bullmore, 2009; Wise et al., 2016), especially in schizophrenia in several ways. First of all, as to our knowledge, we integrated the first meta-analyses evidence of shared white matter integrity linking the two psychotic illnesses – schizophrenia and BD, which is a necessary step to aid the understanding of pathophysiological basis of the clinical continuum of psychosis. Second, we included a much larger body of publications than previous meta-analyses, including TBSS studies. This may reduce the chance of type I/II errors and improve the precision of locations. Third, we went further than previous meta-analyses to guarantee that our findings were robust and reliable by excluding any findings that jackknife sensitivity analyses and visual inspection of the results suggested.

Although significant, this study has several limitations, many of which are generally applicable to meta-analyses. First, peak-based meta-analyses are based on summarized (i.e., coordinates from published studies) rather than raw statistical brain maps, and this approach may result in less accurate results (Radua et al., 2014). Second, this meta-analysis was also limited as we did not consider other measures of diffusivity such as mean, radial or axial diffusivity. These measures may illuminate the nature of underlying WM changes contributing to alterations in FA (Beaulieu, 2002). It was not possible, however, to include these measures in this meta-analysis, as few studies reported these values together in original studies (only 13 datasets among the forty datasets). Third, comparing clinical symptom between two disorders, including the psychotic and depressive symptoms would provide more comprehensive view to understand psychosis, however, such comparison cannot be calculated due to few report and different tools of clinical assessment used in original dataset. Fourth, although there were a few marginally significant clinical variables, such as age and illness duration in two patient groups, we taken them as covariates to minimize the confounding effect on the main findings. Future researchers should collected the multi-cites, large numbers of

homogeneous samples, which would shed more light on our standing of the etiology of the two conditions. In addition, in the present study we only did the meta-regression for proportion of taking lithium because of the complicated drug condition in BD. This may limit the full understanding of potential moderating effects of drug on the main result, although the moderating effect of lithium was not observed in BD. Finally, this meta-analysis focused on the comparison of the white matter abnormalities, future multimodal meta-analytic comparison between two disorders would be appreciated to comprehensively understand the pathophysiological basis of the clinical continuum in psychosis.

4.2. Conclusion

In line with current perspectives of disconnections, our meta-analysis showed shared white-matter dysconnectivity in genu of the CC and left posterior cingulum fibers links the two psychotic illnesses and might be related to the similar risk factors for the two disorders. TBSS may be a more sensitive technique to detect white matter abnormalities in these regions compared with VBA. Future studies should focus on the exact underlying cause of these white matter microstructural abnormality and using DTI combined with neuropsychological, genetic and environmental variables would shed more light on our understanding of the etiology of schizophrenia and BD.

Role of funding source

The funding source had no role in study design, interpretation of results, in the writing of the report or in the decision to submit the article for publication.

Author contributions

Debo Dong had full access to all the data in the study and takes full responsibility for the integrity of the data and accuracy of the data analysis.

Study concept and design: Debo Dong.
Acquisition, analysis or interpretation of data: All authors.
Drafting of the manuscript: Debo Dong, Cheng Luo.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Debo Dong, Xuebin Chang, Yulin Wang, Yuchao Jiang.
Administrative, technical, or material support: Cheng Luo, Dezhong Yao.
Study supervision: Cheng Luo, Dezhong Yao.

Conflict of interest

The authors report no biomedical financial interests or potential conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.schres.2017.01.005.

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