


RESEARCH ARTICLE

Structural connectivity associated with familial risk for mental illness: A meta-analysis of diffusion tensor imaging studies in relatives of patients with severe mental disorders

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Abstract

Schizophrenia (SCZ), bipolar disorder (BD), and major depressive disorder (MDD) are heritable conditions with overlapping genetic liability. Transdiagnostic and disorder-specific brain changes associated with familial risk for developing these disorders remain poorly understood. We carried out a meta-analysis of diffusion tensor imaging (DTI) studies to investigate white matter microstructure abnormalities in relatives that might correspond to shared and discrete biomarkers of familial risk for psychotic or mood disorders. A systematic search of PubMed and Embase was performed to identify DTI studies in relatives of SCZ, BD, and MDD patients. Seed-based *d* Mapping software was used to investigate global differences in fractional anisotropy (FA) between overall and disorder-specific relatives and healthy controls (HC). Our search identified 25 studies that met full inclusion criteria. A total of 1,144 relatives and 1,238 HC were included in the meta-analysis. The overall relatives exhibited decreased FA in the genu and splenium of corpus callosum (CC) compared with HC. This finding was found highly replicable in jack-knife analysis and subgroup analyses. In disorder-specific analysis, compared to HC, relatives of SCZ patients exhibited the same changes while those of BD showed reduced FA in the left inferior longitudinal fasciculus (ILF). The present study showed decreased FA in the genu and splenium of CC in relatives of SCZ, BD, and MDD patients, which might represent a shared familial vulnerability marker of severe mental illness. The white matter abnormalities in the left ILF might represent a specific familial risk for bipolar disorder.

KEYWORDS

bipolar disorder, diffusion tensor imaging, familial risk, fractional anisotropy, major depressive disorder, meta-analysis, schizophrenia

Mengyuan Xu and Wenjing Zhang contributed equally to this study and shared first authorship.

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1 | INTRODUCTION

Major psychiatric disorders, such as schizophrenia (SCZ), bipolar disorder (BD), and major depressive disorder (MDD) have a strong familial aggregation, largely due to genetic transmission (Ament et al., 2015; Howard et al., 2019; Ripke et al., 2014). Studies in adults suggested that the increased familial risk for severe mental disorders among relatives of patients with major psychiatric disorders is also increased for disorders other than the one present in the proband (Dean et al., 2010). For instance, offspring of parents with SCZ have an increased risk for developing not only SCZ, but also BD or MDD compared with control offspring (Rasic, Hajek, Alda, & Uher, 2014). These findings suggest that psychiatric disorders share common genetic neurobiological pathways that lead to disease besides those that are disease-specific. From the neuroimaging perspective, one of our previous studies reported decreased gray matter volumes in the right cerebellum across relatives of patients with SCZ, BD, and MDD, suggesting that this brain abnormality was a shared risk structural marker for these conditions, while regional gray matter abnormalities found in neocortex, thalamus, and striatum appeared to be disorder-specific (Zhang et al., 2020). The identification of such transdiagnostic and diagnostic-specific biosignatures underlying psychopathology of different psychiatric disorders may help to improve disease models, diagnostic accuracy, or preventative strategies (Caspi et al., 2014; Goodkind et al., 2015; McGorry & Nelson, 2016).

White matter abnormalities which can be characterized using diffusion tensor imaging (DTI) are also highly heritable (Bertisch, Li, Hopman, & DeLisi, 2010; van der Schot et al., 2009). DTI allows the quantification of the in vivo axonal diffusion of water molecules, reflecting the organization of white matter tracts in the brain (Neil, 2008). Fractional anisotropy (FA) is a measure that reflects the integrity of axonal fibers, and its reduction may reflect a decrease in myelination or in axonal organization (Assaf & Pasternak, 2008). Recent meta-analyses and one mega-analysis of DTI studies in SCZ, BD, and MDD found that decreased FA in the genu and body of the corpus callosum (CC), suggesting decreased prefrontal inter-hemispheric structural connectivity, was a common white matter abnormality across three disorders, especially to SCZ and BD (Dong et al., 2018; Koshiyama et al., 2020; Wise et al., 2016). It has also been proposed that a structural dysconnectivity between frontal areas might be a common neurobiological abnormality to SCZ and BD, whereas that between fronto-temporal or fronto-limbic areas might be specific to SCZ or BD, respectively (O'Donoghue, Holleran, Cannon, & McDonald, 2017). Despite a growing number of DTI studies in individuals at familial risk for SCZ, BD, and MDD in the last decade, little is known about shared versus specific white matter abnormalities as markers of risk for severe mental illness.

Recent efforts have attempted to characterize regional white matter abnormalities in individuals of increased familial risk for severe

mental illness. A systematic review reported that relatives of patients with SCZ exhibited white matter abnormalities in the frontal, temporal, and related bundles, and in the CC when compared with healthy controls (HC), but no consistent white matter alterations were identified among relatives of patients with BD (Arat, Chouinard, Cohen, Lewandowski, & Ongur, 2015). This review study did not compare relatives of either condition directly due to numerous methodological differences between studies, and concluded preliminarily that white matter abnormalities might qualify as endophenotype candidate for SCZ, but not for BD. A recent meta-analysis reported decreased FA in the genu and splenium of the CC in patients with BD and their relatives (Hu, Stavish, Leibenluft, & Linke, 2020).

With these considerations, we performed a meta-analysis of DTI studies in relatives of patients with SCZ, BD, and MDD to investigate the presence of white matter abnormalities as an indicator of familial risk for mental illness. Similar to our previous study of gray matter volume (Zhang et al., 2020), our primary goal was to identify shared and disorder-specific white matter abnormalities across relatives of patients with SCZ, BD, and MDD. We hypothesized that the relatives of patients with these three conditions would exhibit decreased FA in areas of the CC compared with HC as a transdiagnostic biosignature of risk for mental illness.

2 | METHODS AND MATERIALS

2.1 | Selection procedures

The literature search was carried out independently by two experienced researchers (FGN and MX) using PubMed (<http://www.ncbi.nlm.nih.gov/pubmed>) and Embase, to identify pertinent studies on relatives of patients with SCZ, BD, or MDD published before April 2021. Keywords applied in search were: (a) schizophrenia, bipolar disorder, depression, or depressive disorder or major depressive disorder; (b) relative, sibling, family, families, parent, offspring, twin, or risk; (c) diffusion tensor imaging or DTI. The reference lists of selected original articles were screened for additional relevant studies. Whenever necessary, we contacted the corresponding authors to obtain essential study details for our present analysis.

Studies were included only if they met the following criteria: (a) original papers written in English and published in peer-reviewed journals; (b) conducted whole brain voxel-wise comparisons of FA between relatives of SCZ, BD or MDD patients with HC; (c) reported the significant differences using MNI or Talairach coordinates. Studies were excluded if they: (a) were case reports, reviews, or meta-analyses; (b) performed region of interest (ROI) analyses exclusively without whole brain approach or the peak coordinates could not be retrieved; (c) recruited participants under clinical high risk rather than familial risk, such as participants manifesting prodromal symptoms of

SCZ; (d) different studies from the same group used overlapping data (in such cases, the study with the largest sample among those was included). The flow diagram of literature searching procedures is showed in Figure 1.

By our search strategy, one study enrolled relatives of patients with BD and MDD combined as one group (Macoveanu et al., 2016), thus was considered as one dataset and was included only in the transdiagnostic analysis. Two other studies enrolled relatives of patients with psychotic disorders, but without specifying whether they were relatives of SCZ, BD, MDD or other psychosis (Domen et al., 2013; Koivukangas et al., 2015). Given that our aim of present

main analysis was to characterize the potential shared abnormalities of white matter integrity in high familial risk individuals with major psychiatric disorders, we included these datasets in the primary analysis. Notably, one of these studies provided a sub-analysis for relatives of patients with SCZ, and results from this analysis were included in our disorder-specific analysis for SCZ (Koivukangas et al., 2015).

Some studies included more than one dataset of relative groups and performed separate comparisons of whole brain FA with HC. One enrolled relatives of patients with SCZ and BD as separate groups (Skudlarski et al., 2013), and two datasets were extracted and used for both transdiagnostic and disorder-specific analysis. Lei et al divided

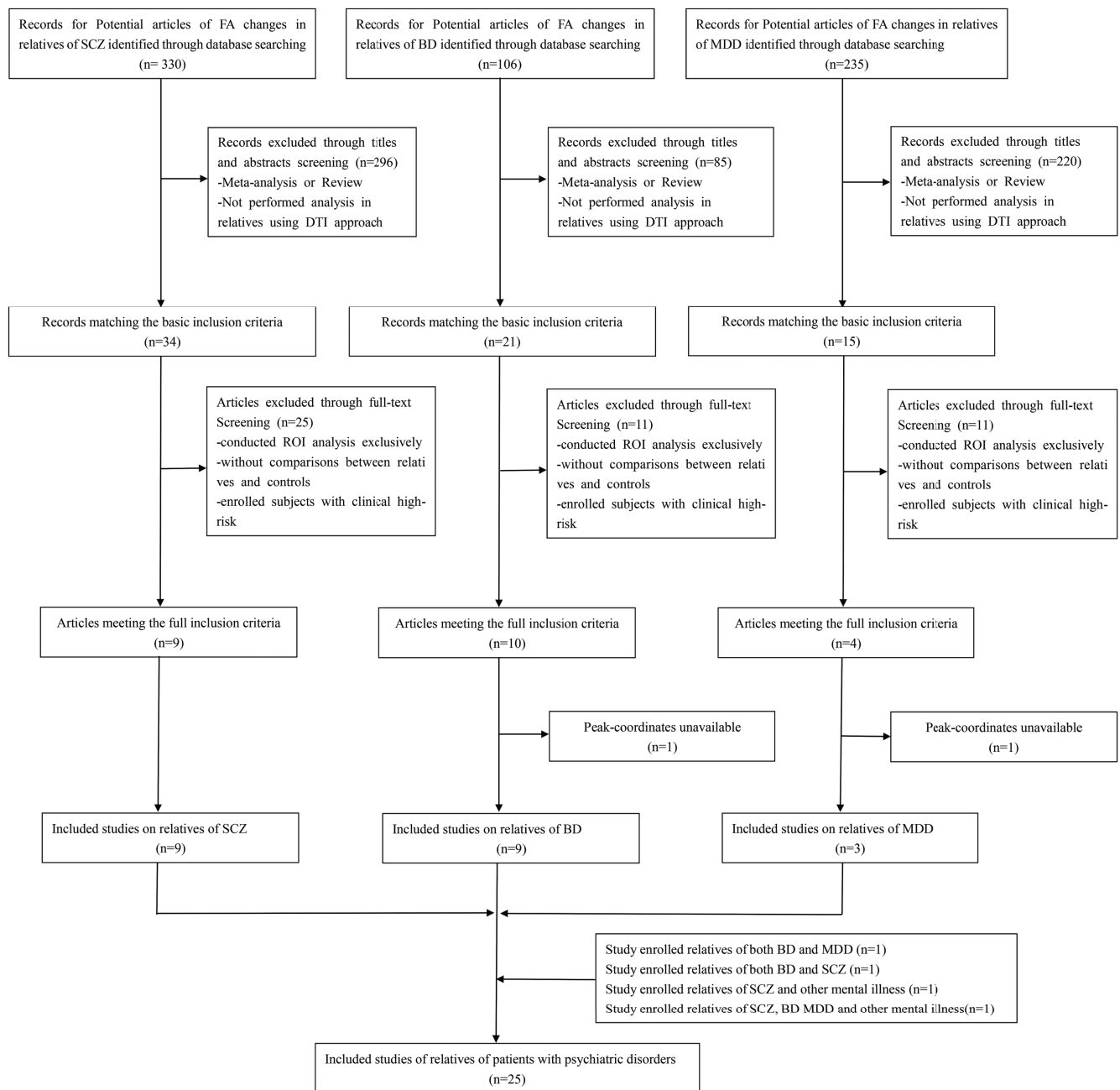


FIGURE 1 The flow diagram of the literature selecting procedures of current meta-analysis. SCZ-schizophrenia, BD-bipolar disorder, MDD-major depressive disorder, ROI-region of interest, DTI-diffusion tensor imaging, FA-fractional anisotropy

the relatives of patients with first-episode SCZ into deficit and non-deficit SCZ relative groups (Lei et al., 2015). Ganzola et al separated the relatives of patients with BD into those who remained well and who developed a MDD diagnosis during the following-up (Ganzola et al., 2018). For those studies, each relative/HC combination was treated as one dataset.

Four studies (Hoptman et al., 2008; Koivukangas et al., 2015; Linke et al., 2020; Roybal et al., 2015) reported that a portion of participants was suffering from prodromal syndromes or current psychiatric disorders, and 3 (Koivukangas et al., 2015; Linke et al., 2020; Roybal et al., 2015) among those also reported psychiatric medication use in participants. In addition, one study (Prasad, Upton, Schirda, Nimgaonkar, & Keshavan, 2015) did not clarify the mental status of participants. We included both types of datasets with affected and unaffected relatives in our overall analysis. To minimize the confounding effects of illness burden and medication exposure, we performed subgroup analysis restricted to studies with only unaffected relatives. None of the included studies reported that the participants had any neurological diseases.

Finally, the search strategy identified 671 research papers in the database, of which 25 studies met our inclusion criteria. A total of 28 datasets with 1,144 relatives (mean age: 30.31, female/male = 639/505) of patients with psychiatric disorders and 1,238 matched HC (mean age: 29.17, female/male = 694/544) were ultimately included in the meta-analysis. Among those, 12 datasets recruited 465 relatives of patients with SCZ, 11 datasets recruited 404 relatives of patients with BD, 3 datasets recruited 59 relatives of patients with MDD. Details of demographic and clinical characteristics of study participants and methodological information of the included studies are displayed in Table 1.

2.2 | Data extraction

We followed the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines in conducting our meta-analysis (Stroup et al., 2000). For each selected study, we extracted the following information: sample size, mean age, sex, imaging parameters (i.e., MRI field strength, slice thickness, and number of diffusion gradient directions), correction steps, statistical thresholds, and major findings.

2.3 | Quality assessment

We assessed the quality of completeness of documentation for each selected study with a 12-point checklist which has been adapted frequently in the previous meta-analysis (Gao et al., 2018; Zhang et al., 2020). The checklist was modified to evaluate the documentation of critical variables that were important to our study. Three categories including participants (items 1–4), methods of imaging acquisition and analysis (items 5–10), and the results and conclusions (items 11 and 12) were comprised in the checklist (Figure S1). Each item received a score of 1, 0.5, or 0 based on the criteria that were

fully, partially met, or not met quality criteria, respectively. Of note, this checklist was used just to rate the completeness of published studies, rather than criticize the investigators or the work itself.

2.4 | Meta-analysis of FA abnormalities in overall relatives of psychiatric patients

In order to detect regional differences of FA between relatives and HC, the software Seed-based d Mapping (SDM, formerly Signed Differential Mapping, version 5.15 www.sdmproject.com) was applied as a fundamental toolbox for our coordinate based meta-analysis. This method has been widely applied and validated in several previous meta-analysis studies, especially in neuroimaging studies of psychiatric disorders (Radua et al., 2012; Radua & Mataix-Cols, 2009; Radua & Mataix-Cols, 2012; Radua, Via, Catani, & Mataix-Cols, 2011). It uses effect sizes to combine reported peak coordinates extracted from databases with statistical parametric maps, and re-creates original effect size maps of group differences in FA. The standard ES-SDM thresholds that is, uncorrected $p < .005$ and extent threshold of clusters >10 voxels were used to balance the sensitivity and specificity optimally and to be an approximate equivalent to corrected p -value = .05 in ES-SDM for effect-size (Radua & Mataix-Cols, 2012).

Subsequently, jack-knife sensitivity analysis was used to test the replicability of results, whereas meta-regression methods were used to characterize the impact of clinical and methodological variables on brain changes.

2.5 | Sensitivity and subgroup meta-analysis of relatives

A systematic whole-brain voxel-based jack-knife analysis was conducted to test the replicability of the findings, in which we repeated the main analysis iteratively by discarding different datasets each time. The brain region that remained significant in all or most combinations of studies would be considered highly replicable.

To further investigate the robustness and establish consistency of the statistically significant findings, we performed the following subgroup analyses by excluding studies with potential for clinical or methodological confounding factors: (a) studies with relatives who were unaffected at the time of participation ($n = 23$); (b) studies using 3.0T MR scanner ($n = 21$); (c) studies using the high quality of DTI protocols that is, the field strength of MR scanner was 3.0T, the slice thickness was less than or equal to 3 mm, and the number of diffusion gradient directions was greater than or equal to 30 ($n = 12$); (d) studies with additional correction steps ($n = 25$), including threshold free cluster enhancement (TFCE) correction, AlphaSim correction, false discovery rate (FDR) correction, and Gaussian random field (GRF) correction.

To detect disorder-specific FA alterations in relatives, subgroup analyses were also conducted within studies with relatives of patients with SCZ ($n = 12$) and BD ($n = 11$) respectively, but not in relatives of

TABLE 1 Demographic characteristics of participants and methodological information of studies that were included in the meta-analysis

Study	Relatives of which disorder	Sample size (female)		Age, mean (SD)		Methodological aspects				Quality scores
		Relatives	HC	Relatives	HC	MRI scanner (Tesla)	Slice thickness (mm)	Direction	Multiple comparison corrections	
Hoptman et al. (2008)	SCZ	22 (15)	37 (20)	20.05 (4.08)	23.08 (4.04)	1.5	5	8	Yes $p < .05$	12
Hao et al. (2009)	SCZ	34 (14)	32 (13)	25.77 (7.11)	26.59 (5.96)	1.5	4	13	Uncorrected $p < .005$	10.5
Camchong, Lim, Sponheim, and MacDonald (2009)	SCZ	22 (14)	30 (12)	48.5 (8.22)	43.83 (11.39)	3	2.5	30	Yes $p < .05$	12
Knochel et al. (2012)	SCZ	18 (9)	22 (10)	39.35 (10.75)	41.94 (10.51)	3	2	6	Yes, FWE $p < .05$	11
Domen et al. (2013)	SCZ, BD, MDD and other disorders	93 (44)	80 (51)	29.40 (8.8)	30.8 (10.8)	3	1.8	76/81	Yes, TFCE $p < .05$	12
Skudlarski et al. (2013) - sample 1	SCZ	119 (79)	104 (61)	42.5 (1.5)	38.9 (1.3)	3	3	32/30	Yes, TFCE $p < .01$	12
Koivukangas et al. (2015)	SCZ and other disorders	47 (30)	51 (34)	22.3 (0.8)	22.2 (0.7)	1.5	3	40	Yes, TFCE $p < .05$	11.5
Lei et al. (2015) - sample 1	SCZ	37 (21)	37 (19)	42.79 (8.13)	43.13 (9.5)	3	3	15	Uncorrected $p < .001/.01$	10
Lei et al. (2015) - sample 2	SCZ	21 (10)	37 (19)	43.00 (8.23)	43.13 (9.5)	3	3	15	Uncorrected $p < .001/.01$	10
Prasad et al. (2015)	SCZ	21 (19)	29 (20)	22.95 (4.1)	27.14 (6.75)	3	3.2	30	Yes, TFCE $p < .05$	12
Zhou et al. (2017)	SCZ	37 (23)	67 (35)	19.97 (5.36)	21.07 (4.84)	3	2	25	Yes, AlphaSim $p < .05$	12
Ou et al. (2018)	SCZ	22 (6)	22 (6)	23.82 (3.08)	22.22 (3.04)	3	2.5	33	Yes, FDR $p < .05$	12
Wang et al. (2020)	SCZ	99 (40)	130 (70)	21.71 (5.1)	20.95 (4.75)	3	2	25	Yes, GRF $p < .001$	12
Chaddock et al. (2009)	BD	21 (9)	18 (8)	42.5 (13.6)	41.7 (12.2)	1.5	2.5	64	Yes $p < .05$	12
Versace et al. (2010)	BD	20 (11)	25 (18)	13.2 (2.5)	13.9 (2.6)	3	3	NA	Yes, AlphaSim $p < .05$	12
Sprooten et al. (2013)	BD	60 (36)	46 (31)	30.35 (12.5)	30.07 (10.6)	3	3	55	Yes, FWE $p < .05$	12
Mahon et al. (2013)	BD	15 (9)	27 (12)	42.0 (11.7)	40.8 (12.5)	3	2.5	31	Yes, TFCE $p < .05$	11

TABLE 1 (Continued)

Study	Relatives of which disorder	Sample size (female)		Age, mean (SD)		Methodological aspects				Quality scores
		Relatives	HC	Relatives	HC	MRI scanner (Tesla)	Slice thickness (mm)	Direction	Multiple comparison corrections	
Skudlarski et al. (2013) – sample 2	BD	83 (55)	104 (61)	40.6 (2.5)	38.9 (1.3)	3	3	32/30	Yes, TFCE $p < .01$	12
Teixeira et al. (2014)	BD	18 (10)	20 (6)	12.7 (3.1)	12.7 (2.6)	3	2	32	Yes, TFCE $p < .05$	12
Roybal et al. (2015)	BD	25 (13)	16 (10)	15.1 (2.9)	14.5 (2.4)	3	2	60	Yes, TFCE $p < .05$	10
Macoveanu et al. (2016)	BD and MDD	89 (51)	58 (34)	43.4 (12.4)	41.0 (12.8)	3	2	NA	Yes, TFCE $p < .05$	12
Saricicek et al. (2016)	BD	20 (10)	29 (17)	36.3 (10.1)	33.7 (9.2)	1.5	2	32	Yes, FWE $p < .05$	12
Ganzola et al. (2018) – sample 1	BD	78 (37)	61 (34)	21.4 (2.7)	20.8 (2.3)	1.5	2.5	64	Yes, TFCE $p < .05$	12
Ganzola et al. (2018) – sample 2	BD	28 (16)	61 (34)	21.1 (2.9)	20.8 (2.3)	1.5	2.5	64	Yes, TFCE $p < .05$	12
Linke et al. (2013)	BD	36 (17)	36 (20)	14 (3.46)	15 (2.81)	3	2.5	NA	Yes, TFCE $p < .05$	12
Frodli et al. (2012)	MDD	21 (13)	24 (14)	38.1 (14.5)	34.7 (11.0)	3	2.1	61	Yes, TFCE $p < .05$	12
Keedwell et al. (2012)	MDD	18 (18)	15 (15)	22.2 (NA)	22.1 (NA)	3	2.4	30	Yes, TFCE $p < .05$	12
Hung et al. (2017)	MDD	20 (10)	20 (10)	11.1 (1.57)	10.65 (2.12)	3	1.2	NA	Yes, TFCE $p < .05$	11

Abbreviations: BD, bipolar disorder; FDR, False discovery rate; FWE, Family-wise error rate; GRF, Gaussian random field; MDD, major depressive disorder; NA, not available; SCZ, schizophrenia; TFCE, threshold-free cluster enhancement.

patients with MDD due to limited number of studies included ($n = 3$). In exploratory analysis, however, subgroup analysis within studies with relatives of patients with BD and MDD together, two known as mood disorders ($n = 14$), were further conducted.

2.6 | Heterogeneity and publication bias

The statistical (between-study) heterogeneity of individual clusters was examined by a random-effects model with Q statistic and tested through a permutation approach. The analytic parameters used were as follows: uncorrected $p < .005$, peak height $z = 1$, and cluster extent = 100 voxels. Moreover, we also created funnel plots of the peaks of major findings and assessed the publication bias for altered regions using the Egger test (Egger, Smith, & Phillips, 1997). A significant publication bias was considered as existent if results of the Egger test showed a p value less than .05.

2.7 | Meta-regression analysis

To find potential effects of demographic and methodological variables on FA abnormalities in relatives, meta-regression analyses were performed using mean age, sex (ratio of female relatives), slice thickness, and number of diffusion gradient directions as independent variables, respectively. A more conservative probability threshold ($p = .0005$) was used to minimize the detection of spurious relationships, requiring abnormalities to be detected both in the slope and in one of the extremes of the regressor, and to discard findings in regions other than those detected in the main analyses.

3 | RESULTS

3.1 | White matter abnormalities in overall relatives

Pooling all 28 datasets into the meta-analysis, the group of overall relatives of patients with SCZ, BD, and MDD together exhibited decreased FA in the genu and splenium of CC compared with HC (Table 2, Figure 2). No areas of increased FA were identified in relatives relative to HC.

3.2 | Jack-knife sensitivity analysis

The whole-brain jack-knife sensitivity analysis revealed that decreased FA in the genu of CC remained significant in all but the combination of datasets without the Zhou et al. (2017). Reduced FA in the splenium of CC was reproducible in all but the combination of datasets without the Wang et al. (2020). The sensitivity analyses suggest that these results are highly reliable. More details are showed in Table S2.

3.3 | Subgroup analyses

3.3.1 | Effects of current psychopathology and methodological effects

Subgroup analysis considering only unaffected relatives of patients with a psychiatric disorder also showed decreased FA in the genu and splenium of CC compared with HC (Table S3). When analyses were limited to methodologically homogeneous groups of studies, those using 3.0T MRI, high quality of DTI protocols and conducting additional correction steps both confirmed decreased FA in the genu and splenium of CC in relatives relative to HC, as found in the primary analysis. In addition, the analyses with studies using high quality of DTI protocols further showed reduced FA in the left cingulum (Table S4, S5, and S6).

3.3.2 | Disorder-specific effects

Subgroup analyses restricted to relatives of patients with SCZ showed decreased FA in the genu and splenium of CC compared with HC (Table 2, Figure 2). Relatives of patients with BD exhibited decreased FA in the left inferior longitudinal fasciculus (ILF) (Table 2, Figure 2). Given the limited number of studies in MDD, we were unable to do a subgroup analysis only with relatives of patients with MDD. When combining the relatives of patients with MDD and BD into a larger subgroup of relatives of patients with mood disorders, we found that relatives showed decreased FA in the genu and splenium of CC, and in the left ILF (Table 2).

3.3.3 | Heterogeneity and publication bias

No significant statistical between-study heterogeneity was identified in the regions with significant inter-group differences in FA ($p > .005$). There was no evidence of publication bias, as suggested by the Egger's test of funnel plot asymmetry in the CC ($p > .05$).

3.3.4 | Meta-regression analysis

In the linear regression analysis, no significant correlations were observed between neither clinical (i.e., mean age or ratio of female relatives), nor methodological variables (i.e., slice thickness or number of diffusion gradient directions), and FA abnormalities (all $p > .0005$).

4 | DISCUSSION

This is the first voxel-based whole brain meta-analysis of DTI studies in relatives of patients with SCZ, BD, and MDD, attempting to characterize the common and disorder-specific FA abnormalities in

TABLE 2 Regional differences in FA between overall and disorder-specific relatives and HC

Region	MNI coordinates			Voxels, n	SDM-Z	p value, uncorrected	Cluster breakdown (voxels,n)
	x	y	z				
Overall relatives < HC							
Corpus callosum	6	28	12	745	-1.314	$p < .005$	Corpus callosum (832) Right median network, cingulum (104) Right anterior thalamic projections (50) Right anterior cingulate/Paracingulate gyri, BA 24 (37) Right anterior thalamic projections (25) Left anterior cingulate/paracingulate gyri (17) Right anterior cingulate/paracingulate gyri (12)
	28	-56	22	469	-1.589	$p < .005$	Corpus callosum (381) Right superior longitudinal fasciculus II (38) Right arcuate network, posterior segment (17)
	-22	-64	28	323	-1.452	$p < .005$	Corpus callosum (210) Left cuneus cortex, BA 23 (18) Left superior occipital gyrus (17) Left superior occipital gyrus, BA 18 (14) Left superior occipital gyrus, BA 23 (13) Left precuneus (10)
Relatives of patients with SCZ < HC							
Corpus callosum	30	-56	28	345	-1.959	$p < .005$	Corpus callosum (289) Right superior longitudinal fasciculus II (23) Right arcuate network, posterior segment (14)
	-16	-64	28	338	-1.756	$p < .005$	Corpus callosum (185) Left cuneus cortex, BA 23 (25) Left superior occipital gyrus (23) Left superior occipital gyrus, BA 18 (17) Left precuneus (15) Left cuneus cortex (15) Left superior occipital gyrus, BA 23 (11)
Right anterior cingulate/ paracingulate gyri	4	32	10	43	-1.060	$p < .005$	Corpus callosum (31)
Relatives of patients with BD < HC							
Left inferior network, inferior longitudinal fasciculus	-34	-66	-2	310	-1.232	$p < .005$	Left inferior network, inferior longitudinal fasciculus (219) Left optic radiations (36) Corpus callosum (33)
Relatives of patients with mood disorders < HC							
Corpus callosum	16	28	14	1,197	-1.088	$p < .005$	Corpus callosum (921) Right anterior thalamic projections (107) Right striatum (45) Right superior longitudinal fasciculus III (33) Right median network, cingulum (32) Right caudate nucleus (30) Right inferior network, inferior fronto-occipital fasciculus (15)

(Continues)

TABLE 2 (Continued)

Region	MNI coordinates			Voxels, n	SDM-Z	<i>p</i> value, uncorrected	Cluster breakdown (voxels,n)
	x	y	z				
Left inferior network, inferior longitudinal fasciculus	-34	-66	-2	263	-1.074	<i>p</i> < .005	Left inferior network, inferior longitudinal fasciculus (203) Left optic radiations (29) Corpus callosum (14)

Note: The regions with cluster size less than 10 voxels are not reported.

Abbreviation: BD, bipolar disorder; HC, healthy controls; MDD, major depressive disorder; SCZ, schizophrenia.

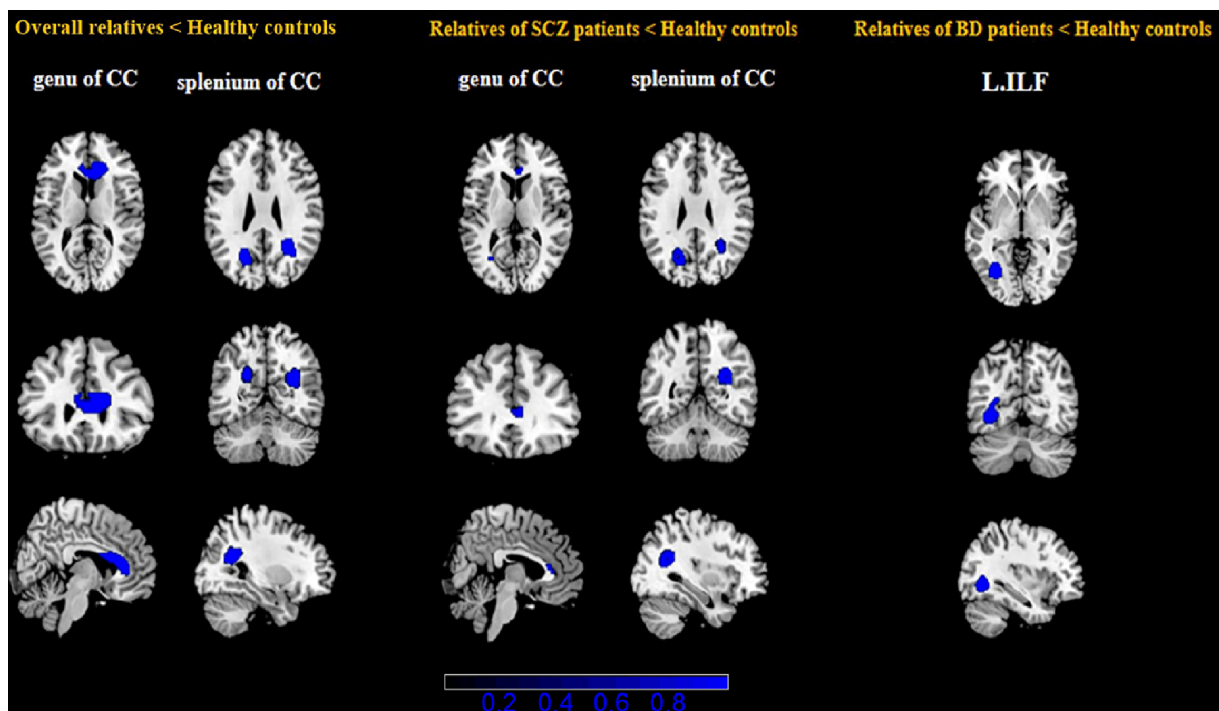


FIGURE 2 Primary and subgroup meta-analyses of FA abnormalities in overall relatives and relatives of patients with SCZ and BD. SCZ-schizophrenia, BD-bipolar disorder, CC-corpora callosa, FA-fractional anisotropy, ILF-inferior longitudinal fasciculus, L-left

individuals at increased familial risk for developing psychiatric disorders. By adopting the ES-SDM meta-analytical approach, our study revealed the presence of decreased FA in the genu and splenium of CC as a shared white matter abnormality in relatives of the three psychiatric disorders compared with HC. Notably, this observation was highly replicable in jack-knife sensitivity analysis, and also maintained across the subgroup analyses in unaffected relatives, and in relatives of patients with SCZ, as well as mood disorders (combining the datasets of BD and MDD). Likewise, this result was reproduced in the subgroup analyses within studies using 3.0T MR scanner, using high quality of DTI protocols and conducting additional correction steps. Moreover, meta-regression analyses did not identify any significant influence on FA in the genu and splenium of CC, from clinical or methodological variables such as sex, mean age, or MRI slice thickness, further suggesting the

stability of the CC abnormality as an imaging marker for genetic vulnerability.

In this meta-analysis we made an effort to investigate the shared and disorder-specific white matter abnormalities in individuals at familial risk across these three major psychiatric disorders. The study of relatives has the potential to identify heritable traits and extend our understanding of the possible etiological processes underlying those disorders, with the advantage of avoiding common confounding factors in imaging studies, such as medication or illness burden. Most of the included studies recruited unaffected and untreated relatives, and subgroup analysis restricted to unaffected relatives confirmed the results as well. This suggests that those abnormalities in relatives may be interpreted as familial risk/vulnerability markers of severe psychiatric disorders rather than of manifestations of established illness. Moreover, we included only studies adopting tract-based spatial

statistics (TBSS) or voxel-based analysis (VBA) methods to demonstrate group differences at a whole skeleton level between relatives and HC, rather than including those using a ROI approach in which comparisons were performed in pre-defined regions. This allowed for a more comprehensive detection of FA abnormalities.

4.1 | Shared white matter abnormalities in overall relatives

The genu and splenium of CC are respectively known as the main commissure between the anterior and posterior bilateral cerebral hemispheres, which has been showed to be involved in emotion regulation, motor function, and cognitive abilities (Doron & Gazzaniga, 2008; Holleran et al., 2020; Zahr, Rohlfing, Pfefferbaum, & Sullivan, 2009). Aberrant white matter integrity in the genu and splenium of CC have been repeatedly reported in previous meta- or mega-analyses of DTI studies in patients with SCZ (Bora et al., 2011; Kelly et al., 2018; Patel et al., 2011; Zhuo, Liu, Wang, Tian, & Tang, 2016), BD (Favre et al., 2019) and MDD (Chen et al., 2016; Liao et al., 2013), implying an overlapping neuropathology involvement of this brain area in both psychotic and mood disorders. In addition, several studies using other imaging techniques, such as voxel-based morphometry, also reported decreased white matter or gray matter volumes in the genu or splenium of the CC both in individuals at familial risk for BD, MDD, or SCZ, and in patients with recent onset psychosis (Chaim et al., 2010; Francis et al., 2011; Knoche et al., 2012). Epidemiological and genetic studies provide evidence that these three disorders share some common genetic factors (Blackwood et al., 2007; Lichtenstein et al., 2009). There is also evidence that microstructure of white matter of CC is highly heritable (Kochunov et al., 2010). Taken together, these findings support a hypothesis that a genetically-mediated structural vulnerability in the genu and splenium of the CC may be a common pathway in the development of common and severe psychiatric disorders.

Accordingly, our finding of decreased FA in the genu and splenium of CC in the combined group of relatives of patients with SCZ, BD, and MDD may reflect a deficient interhemispheric connectivity between the bilateral brain cortices, providing further evidence for the hypothesis that a disruption of interhemispheric white matter integrity exists before the illness onset, perhaps related to the genetic risk in major psychiatric disorders. This finding could also help to explain the worse motor and cognitive performance, subtle social dysfunction, and increased psychotic or mood symptoms in participants with familial risk for developing major psychiatric disorders (Corfield, Yang, Martin, & Nyholt, 2017; Johansson, Kuja-Halkola, Cannon, Hultman, & Hedman, 2019; Smith, Barch, Thompson, & Csernansky, 2008). Perhaps, such findings might be interpreted as a candidate vulnerability marker for disease risk assessment and preclinical recognition of individuals at increased genetic risk for developing psychiatric disorders. Because the included studies were cross-sectional rather than longitudinal, the predictive value of these

changes in determining later illness onset needs to be examined in future prospective studies.

In addition to the consistent finding of FA reduction in the genu and splenium of the CC, the subgroup analysis of studies using high quality of DTI protocols detected decreased FA in the left cingulum. Using high quality of DTI protocols is good for acquiring better images, with more comprehensive and accurate information about white matter tracts and higher signal-to-noise ratio. The cingulum bundle connects frontal, parietal, and medial temporal areas as one of the prominent white matter tract of brain (Bubb, Metzler-Baddeley, & Aggleton, 2018). It plays important role in many brain functions, especially emotion, motivation, executive functions, and memory (Beckmann, Johansen-Berg, & Rushworth, 2009). SCZ, BD, and MDD are generally associated with widespread white matter abnormalities, manifesting decreased FA in some tracts and pathways, including the cingulum (Bracht, Linden, & Keedwell, 2015; Wang et al., 2008). Beyond that, a few studies of individuals with genetic risk for SCZ and MDD detected reduced cingulum FA as well (Hoptman et al., 2008; Huang, Fan, Williamson, & Rao, 2011; Keedwell et al., 2012). Therefore, the deficits of cingulum bundle may reflect a genetic vulnerability to psychiatric disorders. However, it is of note that studies using high quality of DTI protocols are less than half of all included datasets, this finding required replication in future studies with larger samples.

4.2 | White matter abnormalities in relatives of patients with SCZ

In a subgroup analysis with relatives of patients with SCZ, again it was found that the FA was reduced in the genu and splenium of the CC. Beyond that, the abnormalities of white matter extended to right anterior cingulate. The anterior cingulate is a significant node of the limbic and frontal lobe and critical to emotion integration and executive function performance (Allman, Hakeem, Erwin, Nimchinsky, & Hof, 2001). As such, it is important in cognition, monitoring of reward contingencies (Bush et al., 2002). Anterior cingulate abnormalities have been repeatedly reported in patients with SCZ at different stages of disease (Brugger & Howes, 2017) and considered as a potential core region affected by SCZ (Szeszko et al., 2000). In the current study, white matter impairments were also present in relatives of patients with SCZ, suggesting that the deficits of this region may represent a specific disease vulnerability marker for SCZ. In our previous meta-analysis of shared and specific gray matter volume changes, abnormalities in the anterior cingulate gray matter volumes did not characterize relatives of patients with SCZ (Zhang et al., 2020). A prior meta-analysis reported lower gray matter volumes in the anterior cingulate in individuals with genetic high risk for SCZ and in patients with first-episode and chronic SCZ (Chan, Di, McAlonan, & Gong, 2011). Therefore, in conjunction with previous studies, it could imply that the white matter abnormalities in the anterior cingulate antecedes the disease onset, reflecting familial risk, while gray matter abnormalities reflect the incipient neurodegeneration or already established illness process.

4.3 | White matter abnormalities in relatives of patients with BD and mood disorders

The groups of relatives of patients with BD separately exhibited decreased FA in the left ILF. The ILF contains fibers connecting the occipital and temporal lobes, and also traverses the amygdala, hippocampus, and parahippocampal regions. Current views highlight its role in emotional behavior, visual perception, face recognition and memory (Catani, Jones, Donato, & ffytche, D. H., 2003; Ffytche, 2008; Fox, Iaria, & Barton, 2008). Aberrant ILF integrity has been reported in many studies on patients with BD (Lan et al., 2020; Liao et al., 2013; Ren et al., 2020). Consistent with our finding, FA reduction in the left ILF has been reported in a study using ROI approaches on both affected and unaffected offspring of patients with BD (Versace et al., 2018), and in healthy siblings of patients with BD (Saricicek et al., 2016). Other studies found negative correlations between FA in the ILF with cyclothymic temperament (Sprooten et al., 2011) and genetic liability to BD (Chaddock et al., 2009). However, our finding is not completely in line with all the DTI studies. For instance, Robal et al observed increased bilateral ILF FA in youth individuals under both genetic risk for BD and mood dysregulation (Roybal et al., 2015). Studies on clinical ultra-high-risk individuals such as youth with subthreshold bipolar symptoms also displayed lower FA in bilateral ILF in those participants (Martinot et al., 2014), further implying the existence of structure connectivity impairments before illness onset. Taken together, these findings suggest that the aberrant white matter in the left ILF might be an indicator of familial vulnerability to BD.

The abnormalities of FA in relatives of patients with BD also extended to the splenium of CC, but not to the genu. Interestingly, when grouping the relatives of BD and MDD, we did find reduced FA in genu of CC, which is consistent with several studies in patients with BD and MDD (Cui et al., 2020; Cyprien et al., 2016; Ren et al., 2020). A prior meta-analysis in individuals at familial risk for BD reported decreased FA in genu of the CC (Hu et al., 2020). The included studies of the prior and our current meta-analysis were not quite identical. Specifically, we included the Saricicek et al. (2016) and excluded the Linke et al. (2013) studies, while they did the opposite for both studies. Thus, the sample size of all BD relatives of our study ($n = 404$) was a little bit larger than the prior study's ($n = 378$). In addition, we used different versions of analysis software. Those differences would be the possible reasons that led to the discrepancies with a previous meta-analysis. Another possible explanation for this phenomenon is that we may lack statistical power to detect this abnormality due to the sample size of group of relatives of BD patients. Given that a separate analysis with relatives of MDD only was not doable due to a limited number of studies, we could not determine whether the absence of FA reduction in the genu of CC in relatives of BD is the consequence of limited statistical power and/or is driven by the studies of relatives of patients with MDD. Future studies with larger sample size are needed to clarify this issue.

4.4 | Limitations and conclusions

Some limitations are noteworthy with regard to interpretation of our findings. First, we only included studies that used whole brain approaches. Furthermore, due to the limited number of primary studies using other DTI measures such as mean diffusivity, axial diffusivity, and radial diffusivity, the analyses were restricted to FA abnormalities. Investigations using ROI approaches and other MR modalities or measures in individuals at familial risk for mental illness are required to help further understand the genetic risk contributions to brain structure. Second, we used the older version of SDM software for the reason of it has been extensively applied in previous studies of meta-analysis and well accepted in the field of neuroimaging. Furthermore, given the difficulty to obtain the T-maps of whole original analyses from the studies we included, we only used the peak coordinates to do the analyses. Third, only a small portion of included studies contained additional clinical information of participants such as the sub-clinical symptoms, intelligence quotient and education levels, thus the regression analysis could not be conducted to detect the effects of those clinical variables on white matter abnormalities and their associations. Fourth, it should be noted that few of the studies included individuals over 40 years of age, past the average age of illness onset for SCZ, BD, or MDD. This, along with the cross-sectional nature of the studies, limits our ability to understand to what extent our findings represent vulnerability or protective markers for developing mental illness. Prospective studies are required to answer these questions. Fifth, our main focus was to identify common and disorder-specific white matter abnormalities in familial risk individuals of several major psychiatric disorders, thus we only carried out analysis on relatives but not probands. In addition, as the reported information in the original studies were limited to relative vs control comparisons, thus the direct comparisons of FA between the relatives of patients with SCZ, BD, and MDD could not be conducted. Sixth, the inclusion criteria for the subgroup analysis of high-quality studies is somewhat arbitrary as no consensus has been reached for this notion. Finally, due to the limited number of studies, the separate analysis on relatives of MDD patients was not performed. Future studies with relatives of individuals at familial risk for MDD could examine whether white matter deficits in the CC and left ILF also represent genetic vulnerability for developing MDD.

In summary, our current voxel-based whole brain meta-analysis of DTI studies indicates that relatives of patients with severe mental illness exhibit common white matter impairments in the genu and splenium of CC, suggesting the interhemispheric dysconnectivity might be a shared genetic contribution across different major psychiatric disorders. Subgroup meta-analysis identified abnormalities in the left ILF which might represent specific correlates to genetic risk for BD. Future work with larger sample of participants collected from multi-center studies and with a broader spectrum of psychiatric disorders is greatly encouraged to characterize the common brain changes that might represent general genetic vulnerability for severe mental illness, and specific changes that could help differentiate them.

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CONFLICT OF INTEREST

Dr. Wenjing Zhang consults to VeraSci. Dr. Nery's spouse is an employee of Eli Lilly & Co. Dr. DeBello has received research support from Amarex, Johnson & Johnson, Pfizer, Otsuka, Shire, Sunovion, Supernus and Lundbeck. She is a consultant to Akili, CMEology, Johnson & Johnson, Lundbeck, Neuronetics, Pfizer, Sunovion, Supernus, and Takeda. The other authors declare no competing interests.

AUTHOR CONTRIBUTIONS

Dr. Fabiano G. Nery, Wenjing Zhang, and Su Lui, and Mengyuan Xu contributed to the design of the study. Mengyuan Xu, Dr. Paul Hochwalt and Fabiano G. Nery contributed to the paper searching and selection. Mengyuan Xu, Chengmin Yang, Naici Liu, Jiao Qu and Hui Sun, and Dr. Wenjing Zhang contributed to the data extraction and statistical analysis. Dr. Wenjing Zhang, Melissa P. DeBello, Su Lui and Fabiano G. Nery, and Mengyuan Xu contributed to the interpretation of the results. Mengyuan Xu and Dr. Wenjing Zhang, Su Lui, and Fabiano G. Nery contributed to the drafting of the manuscript, while all authors revised the manuscript critically for important intellectual content and gave approval of the version to be published. Dr. Wenjing Zhang and Su Lui obtained funding to support this work.

DATA AVAILABILITY STATEMENT

All relevant data are presented within the paper and the supplementary materials.

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