

A Comparative Multimodal Meta-analysis of Anisotropy and Volume Abnormalities in White Matter in People Suffering From Bipolar Disorder or Schizophrenia

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Schizophrenia (SZ) and bipolar disorder (BD) share some similarities in terms of genetic-risk genes and abnormalities of gray-matter structure in the brain, but white matter (WM) abnormalities have not been studied in depth. We undertook a comparative multimodal meta-analysis to identify common and disorder-specific abnormalities in WM structure between SZ and BD. Anisotropic effect size-signed differential mapping software was used to conduct a comparative meta-analysis of 68 diffusion tensor imaging (DTI) and 34 voxel-based morphometry (VBM) studies comparing fractional anisotropy (FA) and white matter volume (WMV), respectively, between patients with SZ (DTI: $N = 1543$; VBM: $N = 1068$) and BD (DTI: $N = 983$; VBM: $N = 518$) and healthy controls (HCs). The bilateral corpus callosum (extending to the anterior and superior corona radiata) showed shared decreased WMV and FA in SZ and BD. Compared with BD patients, SZ patients showed remarkable disorder-specific WM abnormalities: decreased FA and increased WMV in the left cingulum, and increased FA plus decreased WMV in the right anterior limb of the internal capsule. SZ patients showed more extensive alterations in WM than BD cases, which may be the pathophysiological basis for the clinical continuity of both disorders. The disorder-specific regions in the left cingulum and right anterior limb of the internal capsule provided novel insights into both disorders. Our study adds value to further understanding of the pathophysiology, classification, and differential diagnosis of SZ and BD.

Key words: bipolar disorder/diffusion tensor imaging/schizophrenia/voxel-based morphometry/white matter microstructure/fiber crossing

Introduction

Schizophrenia (SZ) and bipolar disorder (BD) are leading causes of disability worldwide.¹ They are classified as two distinct disorders under the current diagnosis framework.² However, the associations between SZ and BD have garnered increasing interest. Studies in families³ and twins⁴ have shown that both disorders aggregate in families, and there is additional evidence showing semblable changes in gene expression in both conditions.⁵ In addition, psychotic symptoms, such as hallucinations or delusions, are not only the typical symptoms of SZ but also occur in extreme manic episodes of bipolar-I disorder.^{6,7} *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) has addressed the differential diagnosis by adding a dimensional assessment of transverse symptom severity.² Nevertheless, the symptomatic overlaps between SZ and BD might indicate that both disorders could share a common pathological mechanism and that the distinct clinical phenotypes of the two diseases should have different pathological bases. Thus, further studies comparing the similarities and differences in neural mechanisms between these two disorders would be valuable for understanding the underlying pathophysiological basis of the clinical spectrum of psychosis. They

would also contribute to a clearer diagnosis and classification, thereby enabling guidance of “precision medicine” to improve the prognosis.

An accumulating amount of evidence on impaired white matter (WM) tracts and abnormal structural and functional connectivity^{8,9} across brain regions have indicated the dysconnectivity between brain regions in SZ and BD.^{10,11} WM alterations have provided remarkable insights into the possible pathophysiology or causes of these disorders. WM abnormalities, in general, include white matter volume (WMV) deficits or disruption of the microstructure of WM pathways.¹² Voxel-based morphometry (VBM) is a whole-brain, automatic method employed to characterize WMV in separate regions quantitatively.^{13,14} Moreover, diffusion tensor imaging (DTI) is used to assess WM microstructure.¹⁵ Importantly, fractional anisotropy (FA) derived from DTI can reflect fiber density, axonal diameter, and myelination in WM, which is thought to be a general measure to observe the microstructure of WM fiber tracts in the brain.¹⁶

The coupling of WMV and FA has been suggested to enhance the understanding of fiber morphometry.^{17,18} Specifically, WMV and FA are positively associated in areas where fiber tracts are organized in parallel. However, in the case of fiber crossing, the association between WMV and FA would become negative. In the two tracts crossing the midline of WM areas, one is thicker (i.e., dominant) and the other(s) thinner (i.e., non-dominant) in healthy controls (HCs). The predominance of the dominant tract forces water to flow mainly in only one direction (i.e., that of the dominant tract), which translates to relatively high FA. Following this hypothesis, Radua et al.¹⁷ demonstrated that an increase in the thickness of a non-dominant tract (e.g., increase of fiber crossing) could lead to increased WMV and decreased FA in patients with obsessive-compulsive disorder. Thus, coordinates-based imaging meta-analysis with novel multimodal methods for a combination of different imaging modalities in the same meta-analysis could offer insights that are not apparent from any given imaging modality alone.¹⁹

Studies have explored the shared and distinct WM abnormalities in BD and SZ.^{20,21} On the one hand, DTI and VBM have shown that both disorders share WM abnormalities in the internal capsule, uncinate fasciculus, and anterior thalamic radiation regions, and there were no differences in WM abnormalities between these two disorders.^{22,23} Conversely, studies have suggested that SZ showed significantly lower FA in the left external capsule, right thalamo-occipital, thalamo-parietal tracts,¹¹ fronto-occipital tracts,²⁴ temporal and occipital WM²⁵ in comparison with BD and HC groups. A VBM study reported that SZ displayed more extensive structural alterations in WMV relative to that in BD.²⁶ Such inconsistent findings have been driven by small sample size, the methods used, sample characteristics, and imaging modalities.

A meta-analysis is a useful tool to integrate the results from existing studies in an unbiased way.²⁷ Several meta-analyses have been conducted to explore the WM abnormalities in BD and SZ, respectively, which limits understanding of the common pathophysiological basis of the clinical continuum of psychosis.^{28,29} A timely meta-analysis covering studies on the structure of the whole brain using magnetic resonance imaging (MRI) showing WM abnormalities in SZ and BD could reliably identify shared or disorder-specific WM abnormalities between these two illnesses. Such data could provide a reference for future differential diagnoses and treatment development.

In this comparative multimodal meta-analysis of abnormalities of WM structure, we aimed to identify the shared and distinct WM abnormalities in BD and SZ. We hypothesized that both disorders would show significantly decreased WMV and FA in fibers associated with psychotic symptoms, cognition, and emotion relative to that seen in HCs. Moreover, across the spectrum of psychiatric disorders, SZ is regarded as a more serious mental disorder than BD, and the pathological process common to both disorders might be expressed more strongly in SZ.^{20,30} Therefore, we hypothesized that the regions of decreased WMV and FA would be more extensive in SZ compared with that of BD. In addition to common WM abnormalities, we expected a disorder-specific WM abnormality in SZ and BD to be found using multimodal analyses.

Materials and Methods

Literature Searching and Selection of Studies

Our meta-analysis was conducted following the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).³¹ A comprehensive literature search was conducted using Pubmed and Web of Science databases from inception to February 2020 to identify WM studies of VBM and DTI in SZ and BD. The keywords used for the search are detailed in [Supplementary Material](#).

Articles were considered to be eligible if: (i) studies were published in English; (ii) studies were original work (not reviews or meta-analyses); (iii) the overall number of samples in the study was >10; (iv) studies reported the result of voxel-based analysis (VBA) or tract-based spatial statistics (TBSS) or VBM; (v) studies compared patients with SZ or BD and HCs, and reported the alteration of FA or WMV (because the head motion has less of an effect on FA compared with other diffusion metrics, such as mean diffusivity)³²; (vi) studies reported the group difference across the whole brain. Studies were excluded if peak coordinates could not be retrieved after contacting the authors.

Meta-analyses Using Anisotropic Effect Size-Signed Differential Mapping (AES-SDM)

Differences in regional WMV or FA were conducted using AES-SDM software (www.sdmproject.com/),

which has specific templates for WMV and FA.^{33,34} Voxel-based meta-analytic methods have been described.^{35,36} Briefly, ES-SDM uses effect sizes to combine reported peak coordinates that are extracted from databases with statistical parametric maps. This is done to recreate effect-size maps and an effect-size variance map of the differences in WMV or FA between patients and controls. AES-SDM uses an anisotropic non-normalized Gaussian kernel to optimize the recreation of an effect-size map. Meta-analytic WM maps are based on a WM template. Moreover, meta-analytical calculations are based on random-effects models, and account for sample size, inter-study variability, and between-study heterogeneity.³⁶

First, separate analyses within each group (SZ or BD) were conducted to investigate the alteration of WMV and FA with their respective HCs. We adopted the DTI-fractional anisotropy template (non-TBSS) in ES-SDM to combine VBA and TBSS studies. Next, a voxel-wise quantitative comparison was undertaken to assess abnormalities of WMV and FA (relative to HCs) between SZ and BD. Default SDM thresholds were used (voxel $P < .005$, peak height $z > 1$, cluster extent = 10 voxels). Then, to detect regions showing shared abnormalities in both disorders/modalities, following the approach described previously,^{37,38} we used the multimodal analysis section of AES-SDM to conduct conjunction/multimodal analysis.

Meta-regression was conducted within the patient group to examine the effect of potential confounding variables on abnormalities in WMV and FA when the available study data were >10 , and only regions found in the main between-group analysis were included.^{35,36} Furthermore, the main analyses were complemented with additional analyses: (a) analyses of DTI subgroups in the group using identical motion-correction software; (b) analyses of SZ subgroups

in the group which excluded first-episode samples; (c) analyses of age- and sex-matched subgroups; (d) “jackknife” sensitivity analyses to test the replicability of results by repeating analyses iteratively; (e) funnel plots and Egger’s test to assess the publication bias.

Results

Included Studies

We included: 48 DTI experiments comparing SZ patients (1543) with HCs (1612); 32 DTI experiments comparing BD cases (983) with HCs (1163); 24 VBM experiments comparing SZ patients (1068) with HCs (1073); 14 VBM experiments comparing BD patients (518) with HCs (651) ([Supplementary tables S1–S4](#)). Group differences in demographics are presented in [Supplementary materials](#). To ensure that the group differences of the meta-analysis were not due to differences in sex or age, analyses of age- and sex-matched subgroups were done ([table 1](#)).

Regional Abnormalities in FA

DTI in SZ Patients. SZ patients, relative to HCs, showed decreased FA in the corpus callosum (extending to the left anterior corona radiata) and right posterior thalamic radiation ([Supplementary table S5, figure 1a](#)). No regions with increased FA were observed in SZ cases compared with those in HCs.

DTI in BD Cases. Compared with HCs, BD patients showed reduced FA in four clusters: the corpus callosum (extending to the anterior corona radiata), right anterior limb of the internal capsule, left posterior thalamic radiation (extending to posterior corona radiata), and right external capsule ([Supplementary table S5, figure 1b](#)). No regions with increased FA were found in BD compared with those in HCs.

Table 1. Demographic Information of Meta-analysis samples

	SZ		BD	
	Healthy controls	Patients	Healthy controls	Patients
Total study sample				
DTI				
N	1612	1543	1163	983
Female	673	580	576	542
Mean age	30.69	30.36	34.78	36.99
VBM				
N	1073	1068	651	518
Female	416	413	374	277
Mean age	29.50	30.25	35.17	35.99
Age and sex-matched subsample				
DTI				
N	873	763	615	541
Female	369	291	307	311
Mean age	31.87	31.46	32.6	34.73
VBM				
N	683	688	446	402
Female	272	275	258	217
Mean age	30.58	31.25	34.96	36.18

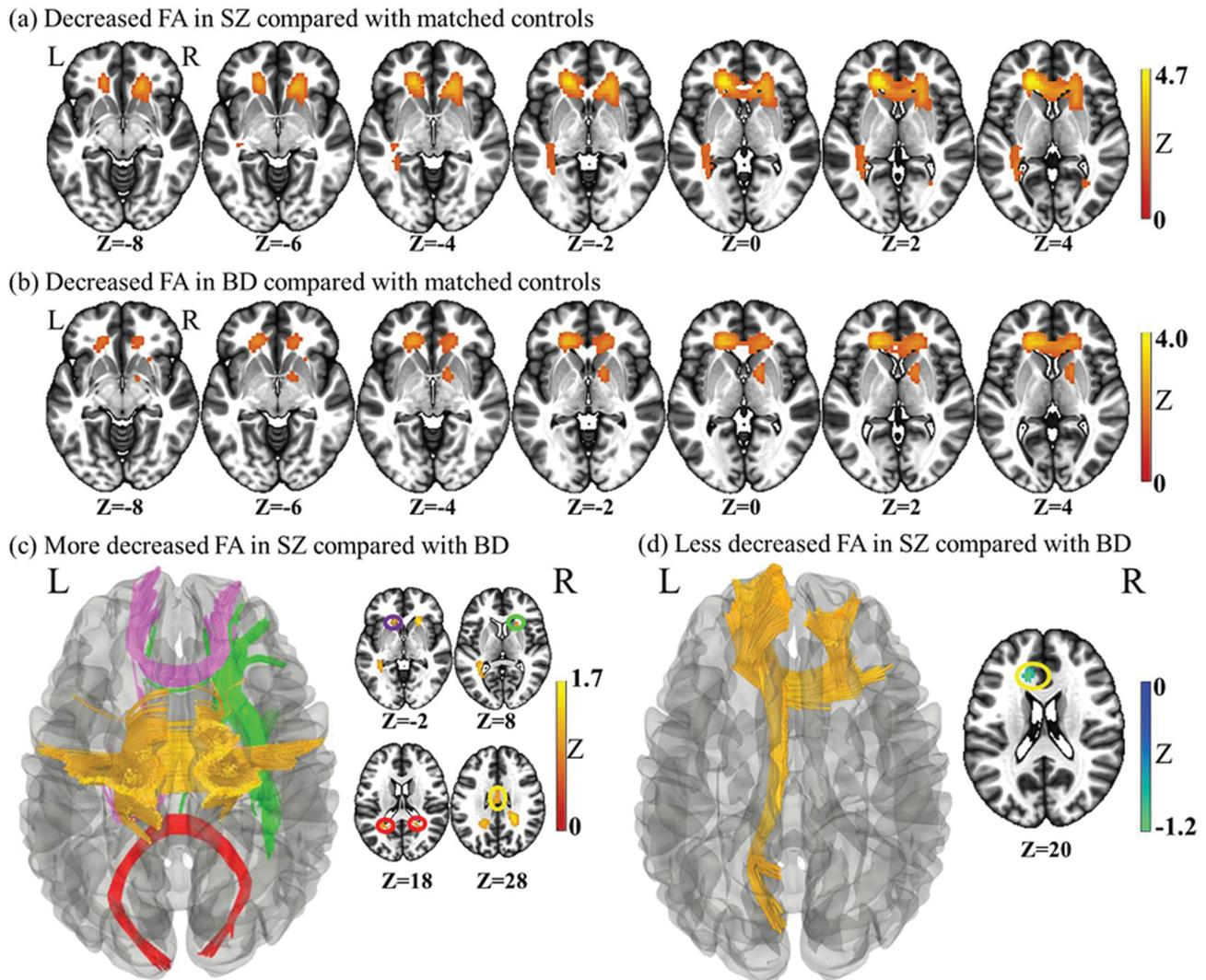


Fig. 1 Whole brain meta-analysis of alterations in schizophrenia and bipolar disorder white matter fractional anisotropy. (a) Two-dimensional (2-D) representation of the significant clusters in the schizophrenia analysis. (b) Two-dimensional (2D) representation of the significant clusters in the bipolar disorder analysis. (c) Three-dimensional (3D) illustration of the more decreased FA in schizophrenia compared with bipolar disorder. The fibers of genu of corpus callosum are in purple, body in orange, and splenium in red. The green parts are the right Anterior limb of internal capsule. (d) Three-dimensional (3D) representation of the less decreased FA in schizophrenia compared with bipolar disorder. The yellow is the left anterior and superior corona radiata. The blue is the left external capsule extending to the posterior limb and Retroleticular part of internal capsule and cerebral peduncle.

Comparison of FA Differences Between SZ and BD Patients. Compared with BD patients, SZ patients (relative to respective control groups) revealed greater FA in the genu of the corpus callosum extending to the left anterior corona radiata, and decreased FA in five clusters: (i) left posterior thalamic radiation extending to the left posterior corona radiata and splenium of the corpus callosum and left retrolenticular part of the internal capsule; (ii) the splenium of the corpus callosum extending to the right posterior corona radiata; (iii) the right anterior corona radiata extending to the right anterior limb of the internal capsule and right external capsule; (iv) the body of the corpus callosum; (v) the genu of the corpus callosum (Supplementary table S5, figures 1c and 1d). Decreased FA in the splenium of the corpus callosum

extending to the right posterior corona radiata was found upon meta-analyses of age- and sex-matched subgroups. *Conjunction Analyses.* Conjunction analyses revealed the shared impairments of FA in patient groups relative to HCs to be the corpus callosum extending to the left and right anterior corona radiata, and the left posterior thalamic radiation extending to the left posterior corona radiata (Supplementary table S5). These impairments were retained in meta-analysis of age- and sex-matched subgroups.

Regional Differences in WMV

VBM in SZ Patients. SZ patients, relative to HCs, showed reduced WMV in three clusters: (i) the body of the corpus callosum extending to the left posterior corona radiata:

(ii) the left external capsule extending to the left uncinate fasciculus; (iii) the right external capsule extending to the right uncinate fasciculus (Supplementary table S6, figure 2a). No regions with increased WMV were found. Global WM was decreased significantly compared with that in HCs.

VBM in BD Patients. BD patients, relative to HCs, showed reduced WMV in five clusters; (i) the left anterior and superior corona radiata; (ii) the left external capsule extending to the left retrolenticular part of the internal capsule; (iii) the right posterior limb and retrolenticular part of the internal capsule; (iv) the right anterior corona radiata; (v) the left cingulum (cingulate gyrus) (Supplementary table S6, Figure 2b). No regions with increased WMV were found in the BD group compared with that in HCs. Global WMV was not significantly different between BD cases and HCs.

Comparison of WMV Differences Between SZ and BD Cases. Compared with BD patients, SZ patients (relative to respective control groups) revealed greater WMV in the left external capsule extending to the posterior limb and retrolenticular part of the internal capsule and cerebral peduncle, the left anterior and superior corona radiata (Supplementary figure 2c), and less WMV in the right anterior limb of the internal capsule, the right uncinate fasciculus extending to the external capsule, and the body of the corpus callosum (Supplementary table S6, figure 2d). Greater WMV in the left anterior and superior corona radiata and decreased WMV in the right uncinate fasciculus extending to the external capsule were found in meta-analyses of age- and sex-matched subgroups.

Conjunction Analyses. Conjunction analyses showed that the corpus callosum extending to the corona radiata, the

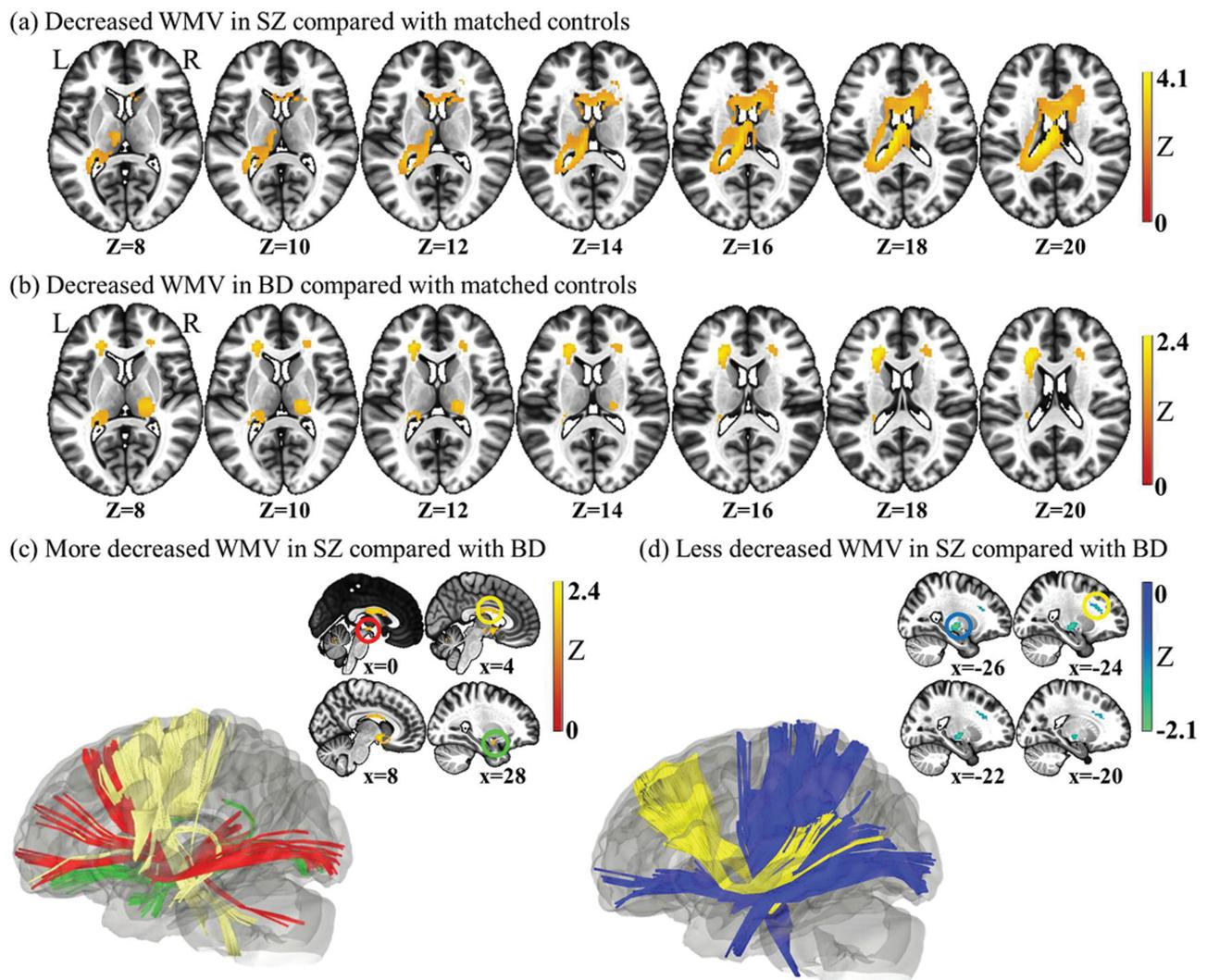


Fig. 2 Whole brain meta-analysis of alterations in schizophrenia and bipolar disorder white matter volume. (a) Two-dimensional (2D) representation of the significant clusters volume reduction in the schizophrenia analysis. (b) Two-dimensional (2D) representation of the significant clusters volume reduction in the bipolar disorder analysis. (c) Three-dimensional (3D) illustration of the more decreased WMV in schizophrenia compared with bipolar disorder. Red indicates right anterior limb of internal capsule. Yellow is the body of corpus callosum. Green parts are right uncinate fasciculus. (d) Three-dimensional (3D) representation of the less decreased WMV in SZ compared with BD. The yellow is the fibers of corpus callosum. The blue is the left pons tracts.

right posterior limb and retrolenticular part of the internal capsule, and the left external capsule extending to the uncinate fasciculus, were the regions where both patient groups showed significantly decreased WMV (Supplementary table S6). Besides the left external capsule extending to the uncinate fasciculus, all other regions survived under meta-analysis of age- and sex-matched subgroups.

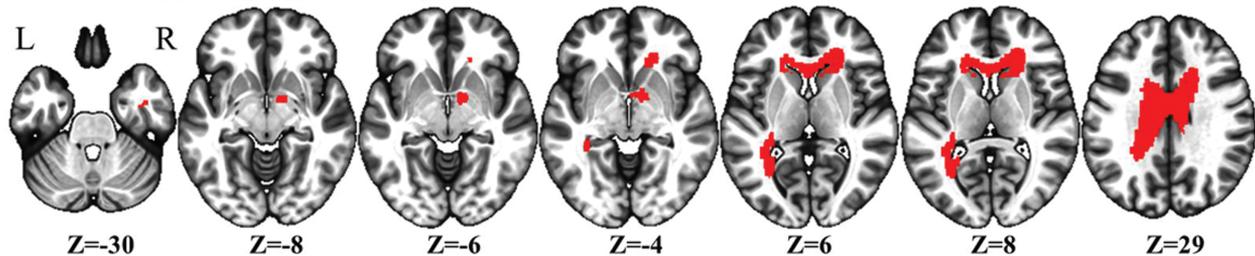
Multimodal Analyses

Multimodal Analyses in SZ. Relative to HCs, multimodal analyses revealed that SZ patients showed decreases in

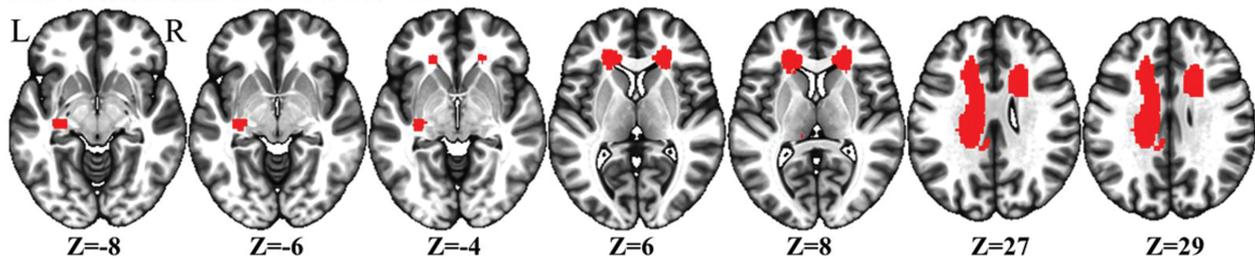
FA and WMV in the body and genu of the corpus callosum extending to the right anterior corona radiata, and the right anterior limb of the internal capsule (Supplementary table S7, figure 3a). The right anterior limb of the internal capsule did not survive meta-analysis of age- and sex-matched subgroups.

Multimodal Analyses in BD. Multimodal analyses in BD patients, relative to that in HCs, revealed shared reductions in FA and WMV in three clusters: (i) the body of the corpus callosum extending to the left corona radiata; (ii) the body, and genu of the corpus callosum extending to the right anterior and superior corona radiata; (iii)

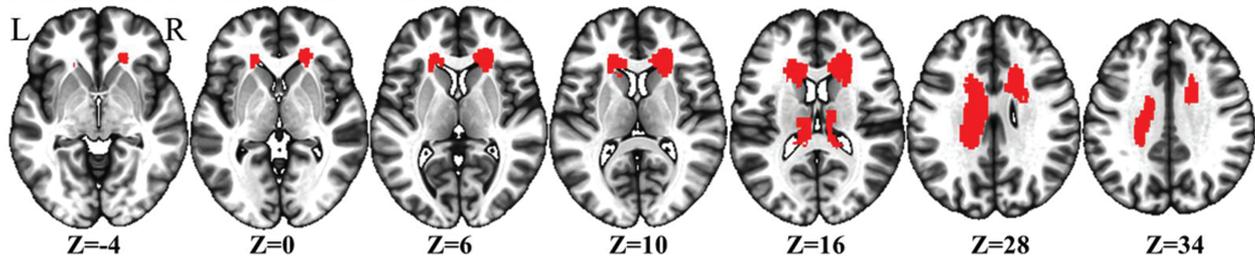
(a) Shared decreased FA and WMV in SZ



(b) Shared decreased FA and WMV in BD



(c) Shared decreased FA and WMV in SZ and BD



(d) Comparison multimodal

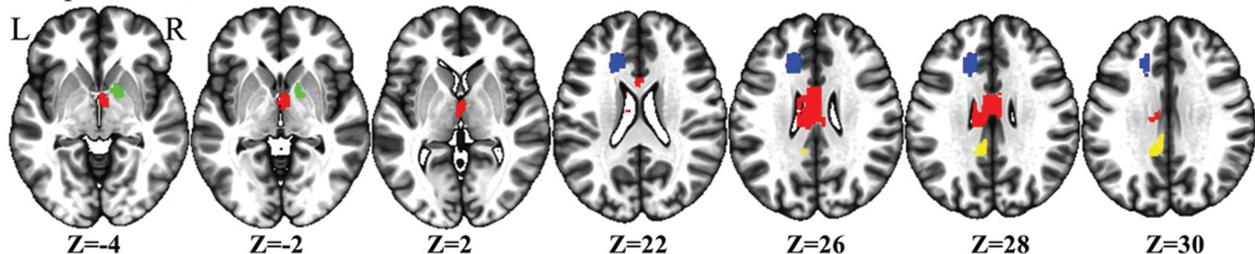


Fig. 3 Multimodal meta-analysis of alterations in schizophrenia and bipolar disorder white matter. (a) The results for shared FA and WMV reduction in the schizophrenia analysis. (b) The results for shared FA and WMV reduction in the bipolar disorder analysis. (c) The common significant clusters between schizophrenia and bipolar disorder. (d) The comparison multimodal results for disorder-specific white matter alterations. Relative to bipolar disorder, blue indicates less reduction in FA and WMV in schizophrenia, green indicates less FA reduction but more WMV reduction, and yellow indicates more FA reduction but less reduction in WMV, and red indicates more reduction in FA and WMV.

the left retrolenticular part of the internal capsule extending to the left sagittal stratum and external capsule (Supplementary table S7, figure 3b). All of these features survived meta-analysis of age- and sex-matched subgroups.

Comparison of Multimodal Analyses Between SZ and BD Cases. Multimodal analyses between BD cases and SZ patients revealed shared reductions in FA and WMV of the WM bundle, including: (i) the left corpus callosum extending to the left anterior and superior corona radiata; (ii) the body and genu of the corpus callosum extending to the right anterior and superior corona radiata; (iii) the splenium of the corpus callosum (Supplementary table S7, figure 3c). The splenium of the corpus callosum was not present in the meta-analysis of age- and sex-matched subgroups.

Multimodal comparison between BD cases and SZ patients (relative to HCs) showed that increased FA and WMV in the genu of the corpus callosum extending to left anterior corona radiata was disorder-specific in SZ patients compared with that in BD patients. Disorder-specific increased FA (but decreased WMV) was seen in the right anterior limb of the internal capsule in SZ cases relative to that in BD patients. Decreased FA (but increased WMV) was disorder-specific in the left cingulum in SZ patients relative to that in BD cases. Compared with BD cases, SZ patients showed greater reductions in FA and WMV in the body of the corpus callosum (figures 3d and 4). The genu of the corpus callosum extending to left anterior corona radiata and the body of the corpus callosum did not survive in the comparison of age- and sex-matched subgroups.

Assessment of A Publication Bias and Heterogeneity

The Egger's test was non-significant ($P > .05$) but only one that the left external capsule extending to the

retrolenticular part of the internal capsule (peak coordinate: $-32, -14, -6$; $Z = -2.34$; $P < .001$) in the analysis of BD-VBM was significant (Egger's test: bias = 2.26; $t = 2.23$; $P = .046$). Funnel plots revealed that no result was driven by only one study (Supplementary figures S6 and S7).

Complementary Analyses

The results of DTI subgroup analyses in the group of using FSL software motion correction approaches and SZ subgroup analyses in the group of excluding of first episode samples were quite consistent with the findings of the main analyses (Supplementary tables S19 and S20). Jackknife sensitivity analyses showed that our findings were robust and reliable (Supplementary tables S12–15).

Discussion

This is the first comparative multimodal meta-analysis of abnormalities in WM structure in SZ and BD. We integrated VBM studies and DTI studies and compared the shared or disorder-specific alteration of WM microstructure between SZ and BD. Given group differences in age distribution and sex distribution in the included studies, only findings that were retained in meta-analyses of age- and sex-matched subgroups are discussed primarily. The meta-analysis showed that BD and SZ shared reduced WMV and FA in the corpus callosum extending to the left anterior and superior corona radiata, and the body and genu of the corpus callosum extending to the right anterior and superior corona radiata. Moreover, compared with BD patients, SZ cases showed remarkable disorder-specific WM abnormalities: decreased FA (but increased WMV) in the left cingulum and increased FA (but decreased WMV) in the right anterior limb of the internal capsule.

Multimodal analyses showed that SZ cases and BD patients shared reductions in WMV and FA in the corpus callosum extending to the anterior and superior corona radiata. Specifically, studies have demonstrated that abnormalities in the corpus callosum are associated with voice hallucinations in SZ patients.^{39,40} Dong et al.⁴¹ showed that the genu of the corpus callosum connects the bilateral frontal cortices and shared reduced FA between BD cases and SZ cases relative to that in HCs. The bilateral frontal cortices were identified as having a common deficit area in SZ cases and BD patients suffering from delusion.⁴² Moreover, the WM fibers that pass through the splenium of the corpus callosum are diverse. They project bilaterally to three distinct brain regions (occipital, parietal, and temporal lobes^{43–45}), a defect of which could contribute to abnormalities in posterior interhemispheric connectivity in patients. Damage to the temporal, occipital, and parietal lobes has been demonstrated to be related to psychotic symptoms (e.g., hallucinations, delusions).^{42,46} One possibility is that this

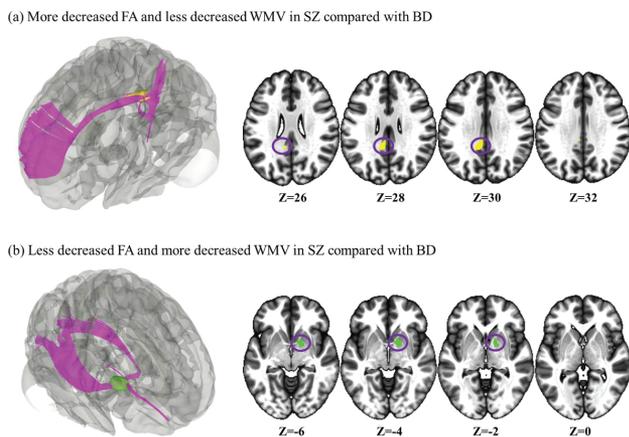


Fig 4. Three-dimensional (3D) illustration of comparison multimodal analysis for disorder-specific white matter abnormalities. (a) Clusters showing significant effects are in yellow. (b) Clusters showing significant effects are in green.

deficit could reflect the psychotic functioning common in SZ and BD.³⁰ However, in our comparative meta-analysis, relative to BD cases, SZ patients showed more severe WM alterations in the splenium of the corpus callosum. The degree of change may have been due to the inclusion of more patients with non-psychotic BD.

In addition, the anterior callosal fibers connect the bilateral frontal cortices, including the cortices associated with several cognitive domains (e.g., working memory, attention, and inhibitory control^{47,48}). Importantly, cognitions such as working memory, attention, and inhibitory control are deficits in SZ and BD.^{47,48} An analysis of callosal thickness showed a positive association in the splenium of the corpus callosum for intellectual scores.⁴⁹ Thus, shared alterations in the corpus callosum might also account for the cognition deficits in SZ and BD. Furthermore, the comparative meta-analysis showed that SZ was associated with more extensive deficits compared with that in BD (figures 1 and 2). SZ patients showed more severe alterations in WMV in the right uncinate fasciculus extending to the external capsule. The uncinate fasciculus is the largest of the three fiber bundles connecting the frontal and temporal lobes,⁵⁰ dysfunctions of which may underlie impairments in memory, language, and social-emotional processing in SZ and BD.⁵¹ A meta-analysis of four psychiatric disorders indicated that a reduction in FA of the uncinate fasciculus was specific to SZ.⁵² However, our results showed that the WMV reduction of SZ was more severe than BD in the uncinate fasciculus. The reduction of FA in the corpus callosum (which is closely related to cognition) showed greater effects in SZ in a large-scale prospective meta-analysis.⁵³ Studies have also indicated that SZ shows more severe cognitive impairment^{30,54} compared with that in BD. Therefore, more extensive and severe degeneration of WM may indicate more severe cognitive deficits.

In addition to the corpus callosum, we identified the shared WM abnormalities in the anterior and superior corona radiata, and the WMV reduction of the left anterior corona radiata was more serious in BD than that in SZ. The corona radiata includes descending and ascending fibers with the thalamus and cerebral cortex. Morphological and functional studies have indicated that the corona radiata is closely related to the medial prefrontal cortex and anterior cingulate, which are involved in the top-down regulation systems that organize emotion processing.^{55,56} The corona radiata is also the pathway interconnecting the anterior insula,⁵⁷ which has consistent gray-matter loss across mental illnesses, and which is related to emotional and executive dysfunction in disorders.^{55,58} Impairment of emotional processing and executive function has also been observed in BD and SZ.^{59,60} Damage to the corona radiata may indicate impairment of emotional processing and executive function. In particular, BD showed a more severe and stable reduction in WMV in the left anterior corona radiata,

relative to that in SZ. The anterior corona radiata contains reciprocal connections between the anterior thalamus and prefrontal cortex, and plays a part in the neural circuitry of emotion regulation.⁵⁵ Thus, more severe damage to the anterior corona radiata may indicate more serious emotional impairment, which is consistent with BD-prominent emotional symptoms.

Disorder-specific increased FA but decreased WMV was seen in the right anterior limb of the internal capsule in SZ cases compared with that in BD patients. The alteration of the anterior limb of the internal capsule in BD has been demonstrated.⁶¹ The anterior limb of the internal capsule contains the anterior thalamic peduncle, which connects the medial and anterior thalamic nuclei with the prefrontal cortex and the cingulate gyrus.⁶² Dysconnectivity in the thalamo-cortical loop (the intercept point of which is represented by the internal capsule) might be involved specifically in the pathophysiological development of cognitive dysfunctions observed in SZ.⁶³

Decreased FA (but increased WMV) was found in the left cingulum (including the WM of the cingulate gyrus) in SZ cases relative to BD patients. The left cingulum is part of the limbic system. The latter is a group of interconnected cortical and subcortical structures linking visceral states and emotion to cognition and behavior.⁶⁴ WM dysconnectivity within the limbic system may lead to a range of cognitive and emotional problems that are found frequently in SZ and BD.^{54,65} The current study extended a previous large-scale DTI meta-analysis that indicated SZ and BD feature comparable changes in the limbic system, such as the fornix and cingulum.⁵² Furthermore, the disorder-specific left cingulum, decreased FA but increased WMV in the SZ cases relative to BD patients, might indicate the SZ showed more fiber crossings than BD in the left cingulum, according to the fiber crossing hypothesis.¹⁷ This disorder-specific WM alteration may also be due to changes in membrane permeability or the presence of non-axonal components (e.g., cells, vessels, interstitial fluid). Importantly, FA can reflect myelination in WM, and lithium and antipsychotic agents influence the structure of cell membranes and myelin sheaths,^{66,67} which may also affect increases and decreases in fiber crossing. Furthermore, meta-regression analysis showed that the reduction in FA was associated with the frequency of medication use, which may affect WM microstructure. The impact of medication on WM remains an area of research for the future. In summary, disorder-specific regions provided novel insights into distinguishing BD from SZ.

Our study had five main limitations. First, our study was based primarily on peak coordinates rather than “raw” statistical brain maps, which may have caused a bias in the results.¹⁷ Second, the results of meta-regression analyses should be viewed cautiously because they were driven by a small number of studies or did not overlap with the between-group differences found in the main analyses.¹⁷ Third, although motion correction or

minimizing of head-motion approaches were reported in all DTI studies but one¹⁵ (Supplementary tables S1 and S2), different motion-correction software (e.g., FSL, DTIPrep, SPM) can affect neuroimaging findings substantially.⁶⁸ We encourage researchers in this field to make great efforts to minimize head motion (e.g., by using foam pads, dental rests, or bite bars)^{69–71} and use standardized motion-correction software. Four, the influence of medication was complicated: we employed the frequency of medication use for meta-regression and not the type of drug. Five, our meta-analysis focused on WM alterations. To minimize the impact of head motion, we used only FA as the DTI metric.³² Non-use of other DTI indices (e.g., mean, radial, or axial diffusivity) or advanced diffusion-MRI measures (e.g., from diffusion kurtosis imaging, free-water imaging, neurite orientation dispersion, and density imaging) was a limitation of our meta-analysis. It would be valuable to include more indices and focus on gray matter in future investigations.

Conclusions

This meta-analysis showed that BD and SZ share widespread abnormalities in WM. There may be a pathophysiological basis for these seemingly similar behavioral phenotypes and the clinical continuity of both disorders. SZ and BD differ with regard to the left cingulum and right anterior limb of the internal capsule. The current study would be beneficial for understanding the pathophysiology, classification, and differential diagnoses of SZ and BD.

Supplementary Material

Supplementary material is available at *Schizophrenia Bulletin*.

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Conflict of Interest

The authors have declared that there are no conflicts of interest in relation to the subject of this study.

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