Psychoradiologic abnormalities of white matter in patients with bipolar disorder: diffusion tensor imaging studies using tract-based spatial statistics

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Abstract

Background: An increasing number of magnetic resonance imaging studies using tract-based spatial statistics (TBSS) have reported abnormalities of white matter (WM) in patients with bipolar disorder (BD); however, robust conclusions have proved elusive, especially considering some important clinical and demographic factors. The present study performed a quantitative meta-analysis of TBSS studies to elucidate the most consistent WM abnormalities in patients with BD.

Methods: A systematic search was conducted through May 2017 for all TBSS studies comparing the fractional anisotropy (FA) between patients with BD and healthy controls (HC). Anisotropic effect size-signed differential mapping (AES-SDM) meta-analysis was performed.

Results: A total of 22 datasets including 556 patients with BD and 623 HC were identified. Significant FA reductions were identified in the genu and body of the corpus callosum in patients with BD relative to HC. No regions of increased FA were reported. In the subgroup analyses, the FA reduction in the genu of the corpus callosum retained significance in patients with BDI, while the FA reduction in the body of the corpus callosum retained significance in euthymic patients with BD. Meta-regression analysis revealed that the percentage of female patients was negatively correlated with the reduced FA in the body of the corpus callosum.

Limitations: The data acquisition, patient characteristics and clinical variables of the included studies were heterogeneous. The small number of DTI studies using TBSS in patients with BDII, and the lack of other clinical information, hindered the application of subgroup meta-analyses.

Conclusion: Our study consistently identified decreased FA in the genu and body of the corpus callosum, which suggested

that interhemispheric communication may be the connectivity most affected in patients with BD.

Introduction

Bipolar disorder (BD) is a serious chronic disease characterized by the co-occurrence of manic and depressive symptoms, with a worldwide prevalence of approximately 1%[1]. Two main forms are distinguished in the latest Diagnostic and Statistical Manual of Mental Disorders, DSM-5: BD type I (BDI) is the classic manic-depressive disorder, while diagnosis of BD type II (BDII) requires at least one episode of major depression and one hypomanic episode[2]. BD causes severe impairment in work role function and a high lifetime suicide risk; thus there is a pressing need for a better understanding of its neural basis. Magnetic resonance imaging (MRI) has been a useful way to pursue this, and numerous cerebral morphological and functional abnormalities have been reported in patients with BD [3].

In addition to the structural and functional alterations in multiple brain regions, aberrant connectivity between these regions seems to be crucial to the pathogenesis of BD[4, 5] Diffusion tensor imaging (DTI) can probe the white matter (WM) tracts that form the infrastructure of the connectivity. DTI maps the diffusion of water molecules, and the calculated quantity of fractional anisotropy (FA) contains information about the directionality and coherence of neuronal fiber tracts[6, 7].

In studies of patients with BD, however, various regions showing both FA increases and decreases have been reported, for example in the prefrontal WM, temporal WM and cingulum bundle [8-10]. Performing a meta-analysis is a powerful way to integrate the results from many studies in an unbiased way[11]. Therefore, using voxel-based meta-analysis to detect common abnormalities in patients with BD from multiple original studies is of particular importance. To our knowledge there have been three published voxel-wise whole-brain meta-analyses of pertinent DTI studies on BD[12-14]. However, these had some technical limitations. First, all three studies integrated both voxel-based analysis (VBA) and tract-based spatial statistics (TBSS) techniques to compare WM abnormalities between patients with BD and healthy controls (HC). Although VBA and TBSS both explore whole-brain WM alterations, they have inherent methodological differences that make combined meta-analysis problematic. VBA is relatively straightforward and involves spatial normalization of high-resolution images from all

of the studied subjects to the same stereotactic space [15]. TBSS was specifically developed to analyze diffusion data, and it restricts analysis to the center of major WM tracts by projecting each subject's FA data onto the mean skeleton, thus minimizing the misalignment problems that can arise from regular VBA[16], arguably making TBSS a more accurate technique for detecting WM abnormalities. Second, given the limited number of reported DTI studies, these previous meta-analyses were not able to consider either the potentially different neural alterations in patients with BDI and BDII, or the influence of the mood state (manic, depressed, or euthymic) during MRI scanning. Some of the inconsistencies in reported WM findings may be due to different selection of patient subtypes. For example, Versace *et al*. reported FA increase in the left uncinate fasciculus, left optic radiation and right anterothalamic radiation and FA decrease in the right uncinate fasciculus in patients with BDI compared with HC[17]. Including patients with both BDI and BDII, Haller *et al.* reported FA decrease in the ventral part of the corpus callosum compared with HC[18]. Ambrosi *et al*. reported lower FA in the right inferior longitudinal fasciculus (ILF) in patients with BDII directly compared to those with BDI[19]. These different results may reflect different neural pathophysiologies in BDI and BDII, and so it is important to identify their separate neurobiological markers. Now that increasing numbers of TBSS studies have reported results that take the BD subtypes into consideration, the time is ripe to conduct an updated tract-based spatial meta-analysis to explore how these factors influence WM microstructural abnormalities in patients with BD.

Therefore, the first aim of the present study was to conduct a meta-analysis to identify the most prominent and replicable WM microstructural abnormalities associated with BD. We used Anisotropic Effect Size-Signed Differential Mapping (AES-SDM), a recently-developed meta-analytic technique that has the potential to quantify the reproducibility of neuroimaging findings. AES-SDM enables the results from individual studies to be weighted and controlled for multiple moderators including demographics, clinical information and imaging factors. AES-SDM has the additional advantage over other meta-analytical tools that all the information from contributing studies is used in the same map, including both positive, negative

and null results[20]. AES-SDM has been successfully applied in other neuropsychiatric studies using TBSS, including major depressive disorder and attention-deficit/hyperactivity disorder[21, 22]. The second aim of this study was to perform subgroup meta-analyses based on some important clinical and demographic factors of BD. The third aim was to perform a multiple meta-regression analysis to explore the potential effects of demographic and clinical characteristics on WM microstructural differences, taking advantage of AES-SDM's ability to control for moderators.

Materials and methods

Inclusion of studies

We conducted our meta-analysis according to the "Preferred Reporting Items for Systematic Reviews and Meta-Analysis" (PRISMA) guidelines [23]. PUBMED, Web of Knowledge, MEDLINE, PsycINFO, ERIC, CINAHL, Google Scholar and EMBASE were searched by using the following key words: 1) "DTI" <OR> "diffusion tensor imaging" <OR> "TBSS" <OR> "tract-based spatial statistics" <OR> "fractional anisotropy", and 2) "bipolar disorder" <OR> "bipolar depression" <OR> "mania" to identify relevant articles published up to May 2017. In addition, reference lists of the retrieved articles were manually checked for additional relevant studies.

The inclusion criteria for the study selections were as follows: 1) studies that compared whole-brain FA alteration between patients with BD who were diagnosed according to the DSM-IV criteria and HC; 2) studies that used the TBSS approach for DTI data analysis; 3) studies that reported Montreal Neurological Institute (MNI) or Talairach coordinates of the whole brain contrast of FA; 4) studies were published in English in a peer-reviewed journal; and 5) studies that used significance thresholds for data that were either corrected for multiple comparisons or uncorrected with spatial extent thresholds.

The exclusion criteria were as follows: 1) studies that were case reports or reviews; 2) it proved impossible to obtain the

3-dimensional co-ordinates in stereotactic space (MNI or Talairach), even after contacting the study authors; 3) studies that reported fewer than ten subjects in either the BD or control groups; 4) studies wherein the patients were explicitly recruited to have multiple combined Axis I diagnoses; and 5) the presence of sample overlap with other included studies of larger sample sizes.

Quality assessment and data extraction

Two authors (C.Y and L.L) independently searched the literature, assessed the quality of the retrieved articles and extracted and cross-checked the data. In case of disagreement, another author mediated until a consensus was obtained. Study quality was assessed using a 12-point checklist (see Appendix, Table S1) that was adapted from previous meta-analytic studies[24], and considers not only the demographic and clinical characteristics of the individual study subjects (items 1-4) but also the specific imaging methodology (items 5-10) and the consistency of the conclusions with the results (items 11, 12). Each item was scored as 1, 0.5 or 0 if the criteria were fully met, partially met or unfulfilled, respectively. The quality scores for each study are shown in Table 1.

The following data were extracted from each selected study: the characteristics of the participants and their illness (sample size, mean age of the subjects, gender, age at onset, illness duration, symptom severity, diagnosis type, drug status, mood states, and comorbidities); MR methodology (magnetic field strength, acquisition voxel size, number of diffusion directions and type of analysis); statistical methodology (statistical threshold and correction methods for multiple comparisons); and the three-dimensional coordinates (for voxel-level quantitative meta-analyses).

AES-SDM method

Voxel-wise meta-analysis

For the voxel-wise meta-analysis of the selected studies to detect FA differences in WM between patients with BD and HC we used AES-SDM (http://www.sdmproject.com)[20]. AES-SDM uses effect sizes to combine reported peak coordinates that are extracted from databases with statistical parametric maps, and recreates original maps of the effect size of FA difference in WM between the patients and controls. The analysis was performed as described in the AES-SDM tutorial and related publications[25]. The MRIcron software was used to visualize AES-SDM maps overlaid on three subgroup analyses onto a high-resolution brain template generated by the International Consortium for Brain Mapping.

The AES-SDM methods are briefly summarized here but have been described in detail elsewhere[26, 27]. First, the peak coordinates of all WM differences at the whole-brain level, and the t-values or z-scores of the regions, were extracted from each dataset. Z-scores for significant clusters were straightforwardly converted to t-statistics using an online converter. Studies reporting no group differences were also included. To avoid any potential bias toward liberally thresholded regions, the peaks that did not appear statistically significant at the whole brain level were excluded [26]. Second, the peak coordinates for each study were recreated with a standard MNI map of the effect size of the group differences in FA by means of an anisotropic Gaussian kernel. We used a relatively wide full-width at half-maximum (FWHM; 20 mm) and DTI-fractional anisotropy (TBSS) templates to control false positive results. Findings from studies reporting no group difference were also recreated with effect size maps, the difference being that all voxels in the effect size group were estimated to have a null effect size. Third, standard meta-analysis was conducted to create a mean map via voxel-wise calculation of the random-effects mean of the study maps, taking into account the sample size, intra-study variance and between-study heterogeneity. The analytical parameters of the AES-SDM were as follows: voxel threshold $p = 0.005$, peak height threshold $Z = 1.00$, and cluster size threshold = 100 voxels.

Jack-knife sensitivity analysis and subgroup analysis

To assess the robustness of the findings, we conducted a systematic whole-brain voxel-based jackknife analysis, in which we iteratively repeated the analysis excluding 1 dataset at a time to establish to what extent the results could be replicated. If a brain region remains significant in all or most of the combinations of studies, the finding is considered highly replicable [26].

When the sample size was sufficient, sensitivity subgroup analyses were conducted to test the robustness of the statistically significant findings of meta-analysis by excluding studies with potential confounds on a one-off basis. We performed subgroup analyses of patients with BDI or BDII, with psychotic or non-psychotic symptoms, during euthymic status or depressed status or mania status, of adult or pediatric patients compared to HC separately if sufficient datasets were available. We also conducted subgroup meta-analysis of studies with corrected results. Jackknife sensitivity analysis was conducted for each subgroup result.

Meta-regression analysis

Meta-regression analyses were performed with age, percentage of female patients, symptom severity (Hamilton Depression Scale, HMAD), age at onset and illness duration in each study as the independent variables. Non-drug therapy status could not be studied due to a lack of reported data. Symptom severity rated by the Young Mania Rating Scale (YMRS) could not be explored by meta-regression because there were only 6 datasets. The results were weighted by the square root of the sample size. To minimize the reporting of spurious relationships, we selected a more conservative threshold of 0.0005 as was done in previous studies[20], requiring abnormalities to be detected both in the slope and in one of the extremes of the regressor, and discarded findings in regions other than those detected in the main analyses. The main output for each variable

was displayed in a map of the regression slope. Finally, regression plots were visually inspected to discard fittings obviously driven by too few studies [26].

Analysis of heterogeneity and publication bias

Heterogeneity refers to the between-study variances. A between-study heterogeneity analysis of individual clusters was conducted using a random-effects model with Q statistics, with the threshold of P = 0.005, peak Z =1 and a cluster extent of 10 voxels. Areas showing significant heterogeneity that also overlapped with the main findings were explored using meta-regression analyses to understand the sources of between-study variability. In addition, we assessed publication bias by testing funnel plots using Egger's test via STATA (www.stata.cn), in which any result showing $p < 0.05$ was regarded as having significant publication bias.

Fiber tracking

The DTIquery software (http://graphics.stanford.edu/projects/dti/) and an atlas of human WM anatomy[28] were used to help identify the most probable WM tracts passing through the clusters of voxels that showed significant FA group difference. We used the sample data of a healthy 35-year-old male provided by the DTIquery software. The WM tracts were mapped using streamline tracking techniques and were filtered by tract length and a box-shaped ROI centered on the coordinates of significant clusters.

Results

Included studies and sample characteristics

Systematic search of the databases yielded 883 English research papers. Of these 18 whole-brain TBSS studies with 22 datasets met our inclusion criteria. Figure 1 shows the flow diagram of selection of studies. The included studies compared FA differences in WM between 556 patients with BD (mean age: 38.2 years) and 623 HC (mean age: 39.3 years). Four studies reported subgroup comparisons: in one[29] drug-free patients with BD and patients treated with lithium alone were compared with the same HC group; in another[30] patients with BD with and without a history of suicide attempts were compared to the same HC group; and two[19, 31] included two subgroups of patients with BD, namely, BDI and BDII, which were compared to the same HC group. In these four studies, each subgroup comparison was treated as an independent dataset.

The demographic and clinical characteristics of the samples are reported in Table 1. Of the 556 patients, 57 (10.3%) patients were in a manic state at the time of scanning, 162 (29.1%) were depressive, and 232 (41.7%) were euthymic, while the mood states of 105 (18.9%) patients were not reported. The patients included 411 with the BDI subtype, 87 with the BDII subtype and 58 whose BD subtypes was not mentioned. A total of 165 patients (29.7%) were reported to have comorbidities, which included substance abuse, panic disorder, anxiety disorder, post-traumatic stress disorder, obsessive-compulsive disorder and attention-deficit hyperactivity disorder, among others. Among the 18 DTI studies, two studies[32, 33] involved 36 adolescents with BD.

Pooled meta-analysis of all included studies

The pooled meta-analysis of the 22 datasets with 71 clusters revealed decreased FA in the genu of the corpus callosum and 2 clusters in the body of the corpus callosum in all patients with BD compared with HC (Figure 2 and Table 2). No regions

with increased FA were found. The WM tracts running through these three regions provide interhemispheric connections to the prefrontal, orbitofrontal, inferior temporal and superior parietal cortices (Figure 3). These results showed no significant between-study heterogeneity (P>0.005). Extraction of funnel plots revealed no publication bias. Egger's test showed no significant publication bias in the genu (Egger's P = 0.624) and in the anterior (Egger's P = 0.997) and posterior (Egger's P = 0.228) parts of the body of the corpus callosum.

The whole-brain jackknife sensitivity analysis of the pooled meta-analysis found that all three clusters were highly replicable. The most robust cluster was found in the left genu of the corpus callosum, which was preserved throughout all 22 combinations of the datasets. The other two results in the body of the corpus callosum remained significant in all but 2 and 7 combinations of the datasets, respectively.

Subgroup meta-analysis

The subgroup meta-analysis of the studies of patients with BDI included 13 datasets comparing 346 patients with BDI to 350HC. The FA in patients with BDI was found to be decreased in the genu of the corpus callosum relative to that of HC. Subgroup meta-analysis of the studies of patients with BDII compared with HC or patients with BDI was precluded by the limited number of datasets.

The subgroup meta-analysis of euthymic patients with BD included 7 datasets comparing 187 euthymic patients with BD to 199 HC. Relative to the HC, patients in the euthymic state exhibited decreased FA in the body of the corpus callosum. Subgroup meta-analyses of the manic patients or the depressed patients compared to HC was precluded by the limited number of datasets.

The subgroup meta-analysis of adult patients with BD (age>18 years) included 20 datasets comparing 520 adult patients

with BD to 585 HC. The adult patients were found to have decreased FA in the genu and the body of the corpus callosum, sharing two clusters with the results of the pooled meta-analysis. Subgroup meta-analysis of adolescent patients was precluded by the lack of datasets.

The subgroup meta-analysis of the studies with corrected results included 19 datasets comprising 513 patients with BD and 565 healthy controls. The results were consistent with the pooled meta-analysis (Table S2), showing few effects of the uncorrected results on the overall conclusions.

Only five included studies[34, 35] that reported WM alterations in psychotic patients with BD. One study included only BD patients with psychosis, and the other 4 studies only reported the percentage of patients with psychosis and did no subgroup analysis. The limited number of studies precludes the detection of WM abnormalities comparing psychotic with non-psychotic patients with BD.

The subgroup jackknife sensitivity analyses of the bipolar subtypes, mood states and adult subjects as well as the corrected studies found the meta-analysis results to be highly replicable when focusing only on the BDI, euthymic, adult and corrected subgroups.

Meta-regression analysis

The results of the meta-regression analysis showed that the percentage of female patients with BD that was driven by 21 datasets was negatively associated with FA reduction in the body of the corpus callosum ($p<0.0005$, Figure 4). However, the results should be interpreted with some caution, seemingly driven by two outlier studies with very high site effects[36, 37]. No effects of the HAMD scores, mean age, age at onset or illness duration on WM alterations were detected.

Discussion

The current study pooled the largest number of TBSS studies to date in patients with BD to conduct a quantitative meta-analysis. To the best of our knowledge, no similar work has been reported, especially regarding the clinical and demographic effects of BD subtypes, psychotic features, mood states, age and gender. Voxel-wise meta-analysis using AES-SDM revealed that patients with BD have decreased FA in the genu of the corpus callosum and in two clusters in the body of the corpus callosum; these results were robust under jack-knife analysis. A significant negative association was found between the percentage of female patients and the FA in the body of the corpus callosum. Subgroup analyses of the BDI studies, euthymic studies, and adult studies reproduced the significant findings of decreased FA in the genu and the body of the corpus callosum. These results may suggest that abnormalities in WM tracts may be involved in the pathological mechanism of BD.

The corpus callosum is the largest WM bundle that connects the bilateral cerebral hemispheres, integrating emotional, cognitive, motor and sensory functions[38-40]. We found decreased FA in the genu and body of the corpus callosum in patients with BD compared to HC, a finding that was consistent with the findings of two other DTI studies using a region-of-interest method focusing on the corpus callosum[41, 42]. This brain region has been increasingly implicated in patients with BD: for example, a multicenter structural MRI study reported decreased mid-sagittal area of the body of the corpus callosum in patients with BD compared to HC[43]. It is tempting to speculate that impaired interhemispheric communication is important in the pathophysiology of BD[42]. The recent meta-analysis by Wise *et al.* that reported patients with BD showed decreased FA in the left cingulum, the left genu of the corpus callosum and the right anterior superior longitudinal fasciculus compared to HC[14]. Our findings are not completely consistent with those of previous meta-analyses, for we found no significant abnormalities in any other tracts than corpus callosum. There are several possible reasons for this. First, the previous meta-analyses included both TBSS and VBA studies; as mentioned in the Introduction we only included TBSS studies, as there is reason to believe that these can more accurately identify WM abnormalities[16]. Second, we were able to include many more TBSS studies than

the previous meta-analyses, thus increasing the precision of effect size estimates. Third, the clinical samples in our included studies differed in detail from those in the previous meta-analyses.

The WM fibers passing through the genu of the corpus callosum connect the bilateral prefrontal cortices, which are known to play a role in decision-making, attention, reward processing, and emotion regulation [44, 45]. Previous structural studies found decreased volume in both the ventral and dorsal prefrontal cortex in patients with BD [46, 47], and several functional studies have observed decreased dorsal and ventral prefrontal activity in patients with BD during language tasks and executive-related tasks[48, 49]. Additionally, several studies have reported that the ventral prefrontal cortex is implicated in the "top-down" regulation of emotional processing in patients with BD[50, 51]. The FA reduction in the genu of the corpus callosum in the present study suggests impaired prefrontal interhemispheric connectivity, perhaps leading to neurocognitive deficits in e.g. processing speed and working memory[52], and to emotional dysregulation in patients with BD. Our subgroup analysis of patients with BDI reproduced the finding of decreased FA in the genu of corpus callosum compared with HC, which was consistent with the findings of some previous DTI studies[64, 65]. There are clinical differences between BDI and BDII. In the DSM-V, BDI is the classic manic-depressive disorder, while BDII features depressive and hypomanic episodes; furthermore, the clinical manifestations and treatments are different between BDI and BDII[66, 67]. FA reduction in the genu of the corpus callosum reflected a disconnection of the paralimbic system which plays a central role in emotional regulation[3, 68], and might lead to manic-type behaviors such as inappropriate euphoria, excessive psychomotor behavior, hypersexuality and paranoia, which are consistent with the clinical characteristics of patients with BDI [68].

The pathobiological interpretation of FA reduction is complex because it can be influenced by many factors, such as regional myelination levels, intra- and extracellular volume, the degree of intra-voxel fiber crossing, axonal density and average axonal diameter[53]. Previous studies have suggested that abnormalities in the corpus callosum that are detected early in pediatric patients with BD may be due to altered myelination during neurodevelopment[54]. Meanwhile, several studies have

reported a reduction of myelin-producing oligodendrocytes in the prefrontal cortex , in patients with BD[55-57]. The genu of the corpus callosum and the prefrontal cortex are both late-myelinating areas and are therefore more vulnerable to damage than the early-myelinating splenium[58, 59,60]. Thus we speculate that the FA reduction in the genu of the corpus callosum may be related to a reduction of myelination, and may result in a pathobiological process that directly slows the transfer of interhemispheric information in patients with BD[39]. To help confirm this hypothesis, further studies with more DTI indices, such as axial diffusivity (AD) and radial diffusivity (RD), would be useful, as there is evidence from animal studies that AD is primarily an axonal marker and RD is primarily a myelin marker[61-63].

Our finding of decreased FA in the body of the corpus callosum in patients with BD compared with HC was consistent with several previous studies[69-71]. The body of the corpus callosum connects several areas, including the lateral primary motor cortex, supplementary motor areas (SMA), primary sensory cortex and parietal cortex[72]. Previous functional studies showed that the rostral part of the SMA, the pre-SMA, is involved in memory storage, learning, transition, and motor and speech control, and the pre-SMA connects to the cingulated gyrus, which is part of the limbic system related to cognitive and emotional regulation[73], while the caudal part of the SMA, the SMA-proper, and the primary motor area are responsible for motor function. Together, the SMA may be a transitional region of the limbic and motor system, which plays an important role in the translation of emotion into motor actions[73]. Though emotional dysfunction is one of the main symptom of BD, previous studies have shown that patients with BD also have motor impairments such as psychomotor retardation[74], agitation[75], attentional deficits and impairments in fine motor skills [76-79]. We therefore suggest that the FA decrease in the body of the corpus callosum might be related to motor and emotional dysfunction in patients with BD. Interestingly, our subgroup analyses of euthymic patients with BD and adult patients with BD replicated the FA decrease in the body of the corpus callosum. This finding was consistent with one previous study which found that euthymic patients with BD had decreased FA in the body of the corpus callosum compared to unaffected siblings[60]. Several studies have reported that brain structural and functional

abnormalities are related to current mood states in patients with BD[80, 81]. Our results may indicate a persistent callosal dysconnectivity in euthymic patients with BD, which is consistent with the observation that cognitive impairment and executive dysfunction still exist in euthymic patients with BD[82, 83].

Meta-regression analysis found that FA in the body of the corpus callosum (decreased overall in patients with BD compared with HC) was negatively associated with the percentage of female patients. This result may indicate that female patients have lower FA values in the body of the corpus callosum than male patients. Sex differences are observed in clinical characteristics of BD. Female patients with BD may be more likely to have comorbidities and depressive symptoms which may result in high suicide risk and impaired occupational function[2]. The sex differences of FA in the body of the corpus callosum may be related to differences in the clinical aspects of BD. A series of morphological studies reported smaller corpus callosum in female patients than in male patients with BD[84-86]. However, one study reported no significant difference in the integrity of the body of the corpus callosum when comparing male with female patients with BD[58]. These inconsistencies may have resulted from the different demographic characteristics, data acquisition methods and other confounding factors in studies of patients with BD.

Medication exposure is an important potential confounder, and understanding the effect of medications on WM abnormalities in patients with BD is critical for the interpretation of results. Because only one primary study enrolled unmedicated patients with BD, we could not exclude the confounding influences of medication. Several imaging studies have evaluated the effect of psychotropic medications on WM changes in patients with BD. One structural MRI study reported larger bilateral temporal lobe WM volumes in patients with BD taking antipsychotic medications than in patients not taking antipsychotics[87]. Among patients with BD, longer duration of lithium treatment is associated with increased FA, suggesting that this medication might enhance white matter integrity[88]. In another study, decreased FA was found in subjects treated with lithium, but not in those who were unmedicated; however, there were no significant difference on direct comparison of lithium-

using with non-lithium-using patients[89]. It has been reported that lithium and other mood stabilizers can improve WM integrity and promote the myelination by acting on neuroglial signaling pathways and by increasing neurotrophic factors[90, 91]. Further studies designed to detect the effect of medication exposure on WM changes in patients with BD are needed.

Limitations

First, the subjects varied in sociodemographic and clinical characteristics. Although we performed subgroup analyses of patients with BDI, euthymic patients with BD, and adult patients with BD, the limited datasets precluded comprehensive subgroup analyses (in particular of the important contrast, BDI vs BDII) and meta-regression analyses. Further research is needed investigating the contribution of other clinical characteristics, such as age of onset, comorbidities and disorder severity. Second, the heterogeneity of MRI image acquisition including voxel size, field intensity of the MR system, diffusion direction, and slice thickness, may influence the accuracy of the results of our meta-analysis. Third, the main meta-analysis included primary studies all except one of which enrolled medicated patients, so the confounding influences of medication could not be excluded. Fourth, the meta-regression finding that the percentage of female patients with BD was negatively related to the FA in the genu of the corpus callosum was driven by two outlying studies. Fifth, it has been reported that more than 50% of patients with BD will experience psychotic symptoms in their lifetime, and it is hard to accurately distinguish BD from other psychiatric disorders in patients with psychotic symptoms [92]. However, data limitations precluded a subgroup analysis of psychotic vs. non-psychotic patients with BD. As 5 of our primary studies included psychotic patients with BD, we could not exclude the effects of psychosis features on our results. Future studies comparing psychotic versus non-psychotic patients with BD are needed to elucidate this.

Conclusion

We qualitatively and quantitatively reviewed what has become a large number of published TBSS studies on patients with BD. Meta-analysis of FA findings found that the most robust and replicable WM differences were in the genu and body of the corpus callosum. These WM tracts connect the bilateral frontal, temporal and parietal cortices, indicating the importance of disrupted interhemispheric communication in the pathophysiology of BD. Subgroup analyses found WM structural differences in patients with BDI, adult and euthymic patients. Furthermore, the results of the meta-regression analysis shed light on the structural underpinnings of the sex differences in the clinical manifestations of patients with BD. Attention should be given in future studies to the differences in clinical type, mood states, and demographic characteristics, in order to better define the neural mechanisms in patients with BD. Differentiating mood- and type-related WM abnormalities is important for elucidating the core pathophysiology of BD and will give better insight into the nature of the disease. The present study also adds to the development of psychoradiology (https://radiopaedia.org/articles/psychoradiology), the branch of radiology that applies clinical imaging to psychiatry and psychology[94, 95].

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