Microstructural Differences in the Corpus Callosum in Patients With Bipolar Disorder and Major Depressive Disorder

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ABSTRACT

Objective: It is difficult to distinguish between bipolar disorder and major depressive disorder (MDD) in patients lacking a clear history of mania. There is an urgent need for an objective biomarker for differential diagnosis. Using diffusion tensor imaging, this study investigated the differences in the brain white matter microstructure between patients with bipolar disorder and MDD.

Methods: Participants included 16 patients with bipolar disorder and 23 patients with MDD having depressed or euthymic states based on *DSM-IV-TR* criteria and 23 healthy volunteers. Whole-brain voxel-based morphometric analysis was used to detect any significant differences in fractional anisotropy between patients with bipolar disorder and MDD. The study was conducted between August 2011 and July 2015.

Results: We found a significant decrease in fractional anisotropy values in the anterior part of the corpus callosum in patients with bipolar disorder compared with MDD ($P < .001$), which did not depend on the patients' affective state. This decrease was associated with increased radial diffusivity values ($P < .05$), which was also found in patients with bipolar disorder when compared with healthy volunteers ($P < .05$). We predicted bipolar disorder and MDD in all patients using the fractional anisotropy values, with a correct classification rate of 76.9%.

Conclusions: The present study revealed that patients with bipolar disorder have microstructural abnormalities in the corpus callosum during depressed or euthymic states, which may deteriorate the exchange of emotional information between the cerebral hemispheres, resulting in emotional dysregulation. Our results indicate the possible use of diffusion tensor imaging as a differential diagnostic tool.

J Clin Psychiatry 2017;78(1):99–104
dx.doi.org/10.4088/JCP.15m09851

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Bipolar disorder and major depressive disorder (MDD) are among the top 20 causes of disability[1] and contribute to an increased risk of suicide.[2] Although the presence of manic/hypomanic episodes is crucial in the diagnosis of bipolar disorder, these episodes are reported to occur during less than 10% of the lifetime of individuals with bipolar disorder.[3] It remains difficult for physicians to decide whether to prescribe mood stabilizing or antidepressant medications to a patient with depression lacking a clear history of mania. More accurate diagnosis and appropriate treatment are required; however, the absence of biologically relevant diagnostic markers of bipolar disorder results in its misdiagnosis as MDD in no less than approximately 60% of patients with depression. Inappropriate medication for bipolar disorder misdiagnosed as MDD leads to poor prognosis, increased suicidal and manic tendencies, and greater health care costs.[4,5]

Biomarkers that facilitate early and accurate differentiation of bipolar disorder cases lacking a clear history of mania from MDD cases are a topical issue.[6] Neuroimaging studies of the structural and functional measures of abnormal neural circuitry in individuals with depression is a promising research area with the potential for identifying pathophysiologic processes that may differ between bipolar disorder and MDD. A recent review[3] compared the findings from structural and functional magnetic resonance imaging (MRI) studies examining neural circuitry abnormalities in individuals with MDD and healthy volunteers with results from studies in individuals with bipolar disorder and healthy volunteers. However, few neuroimaging studies have directly compared individuals with bipolar disorder depression and those with MDD.

Diffusion tensor imaging (DTI) is an MRI technique that allows the examination of the density of myelinated fibers in white matter tracts by quantifying the diffusion of water in the brain tissue and the anisotropy of this diffusion movement. In the present study, we hypothesized that there would be an essential structural difference in the neural circuitry between patients with bipolar disorder and those with MDD during depressed or euthymic states. The primary focus of this study was to elucidate the differences in the microstructure of neural circuitry, which may help distinguish bipolar disorder from MDD during depressed or euthymic states. Therefore, we used the DTI method to directly investigate and compare the microstructural changes between the 2 groups of patients with bipolar disorder and MDD, taking the severity of each patient's depressive symptom as a nuisance variable.

METHODS

Participants

Patients with bipolar disorder and MDD were recruited from outpatients treated in the Psychiatry Department of Hospital of National Cerebral and Cardiovascular Center, Nara Medical University, and

Osaka University, Japan. The study was conducted between August 2011 and July 2015. Patients with bipolar disorder (n = 16 [6 women, 10 men], mean ± SD age = 47.1 ± 8.6 years) and patients with MDD (n = 23 [14 women, 9 men]; age, 44.3 ± 9.8 years) participating in this study fulfilled the following inclusion criteria: (1) diagnosis of bipolar disorder or MDD based on the Structured Clinical Interview for *DSM-IV-TR* Axis I Disorders, Research Version, Patient Edition (SCID-I/P)[7]; (2) euthymic or depressive state status, but not manic state (Young Mania Rating Scale [YMRS] < 12),[8] on the day of the MRI scan; and (3) between 20 and 65 years of age. Exclusion criteria were *DSM-IV* diagnoses of substance dependence, history of organic mental disorder, head trauma, loss of consciousness, seizure disorder, or central nervous system disease.

Age- and gender-matched healthy volunteers (n = 23 [10 women, 13 men]; age, 40.5 ± 12.7 years) were recruited locally by poster advertisements. Exclusion criteria were a history or present diagnosis of any *DSM-IV* Axis I diagnosis or any neurologic illness.

Magnetic resonance imaging examinations were conducted once for all patients and healthy volunteers. The patients were subjected to a series of standardized, quantitative measurements of manic symptoms (YMRS), depressive symptoms (Montgomery-Asberg Depression Rating Scale [MADRS][9] score), and cognitive function (Mini-Mental State Examination [MMSE][10]) on the day of the MRI scan.

This study was approved by the institutional review boards of all the participating institutions, and all participants gave written informed consent before enrollment.

Data Acquisition of MRI

All MRI examinations were performed with a 3-Tesla whole-body scanner (Signa Excite HD V12M4; GE Healthcare, Milwaukee, Wisconsin) having an 8-channel phased array brain coil. Diffusion-weighted MRIs were obtained with a locally modified single-shot echo planar imaging sequence by parallel acquisition at a reduction (ASSET [array spatial sensitivity encoding technique]) factor of 2 in the axial plane. Imaging parameters were as follows: repetition time = 17 seconds; echo time = 72 milliseconds; b = 0, 1,000 s/mm^2; acquisition matrix, 128 × 128; field of view (FOV), 256 mm; section thickness, 2.0 mm; no intersection gap; 74 sections. The reconstruction matrix was the same as the acquisition matrix, and 2 × 2 × 2 mm isotropic voxel data were obtained. Motion probing gradient was applied in 55 directions.

To reduce blurring and signal loss arising from field inhomogeneity, an automated high-order shimming method based on spiral acquisitions was used before acquiring the DTI scans. To correct for motion and distortion from eddy current and B0 inhomogeneity, we utilized the FMRIB software, version 5.0.6 (FMRIB Center, Department of Clinical Neurology, University of Oxford, Oxford, England; http://www.fmrib.ox.ac.uk/fsl/). B0 field mapping data were also acquired with the echo time–shift (of 2.237 milliseconds) method based on 2 gradient echo sequences.

Clinical Points

- In patients lacking a clear history of mania, it is difficult to distinguish those with bipolar disorder from those with major depressive disorder (MDD). Misdiagnosis results in inappropriate prescription of medication to the patient with depression. Therefore, identification of an objective biomarker for differential diagnosis is urgently needed.
- In this study, patients with bipolar disorder had microstructural abnormalities in the anterior part of the corpus callosum during the depressed or euthymic state. The fractional anisotropy value from the anterior part of the corpus callosum shown by diffusion tensor imaging may be a prospective stable biological marker for the differential diagnosis between bipolar disorder and MDD.

High-resolution 3-dimensional T1-weighted images were acquired using a spoiled gradient-recalled sequence (repetition time = 12.8 milliseconds; echo time = 2.6 milliseconds; flip angle = 81; FOV, 256 mm; 188 sections in the sagittal plane; acquisition matrix, 256 × 256; acquired resolution, 1 × 1 × 1 mm^3).

Image Processing

Fractional anisotropy (FA) images and 3 eigenvalues (λ1, λ2, and λ3) were generated from each individual by using FMRIB software. First, the brain tissue was extracted using the Brain Extraction Tool in FSL software. Diffusion-weighted images for each of the 55 directions were corrected for eddy current and head motion, and FA values/3 eigenvalues (λ1, λ2, and λ3) were calculated at each voxel using the FSL FMRIB Diffusion Toolbox.

Image preprocessing and statistical analysis were carried out using SPM8 (Wellcome Department of Imaging Neuroscience, London, England). Each subject's echo planar image was spatially normalized to the Montreal Neurological Institute echo planar image template using parameters determined from the normalization of the image with a b value of 0 s/mm^2 and the echo planar image template in SPM8. Normalized images were spatially smoothed using an isotropic Gaussian filter (8-mm full-width at half-maximum).

Voxel-Based Analysis

Exploratory voxel-based analysis was performed using SPM8 software. The difference in FA values between patients with bipolar disorder and patients with MDD was examined using analysis of covariance (ANCOVA) with age, gender, MADRS scores, and duration of illness as covariates, considering the effects of these factors on the white matter microstructure in patients with bipolar disorder or MDD as reported previously.[11–13] To avoid possible edge effects between different tissue types, we excluded all voxels with FA values < 0.1 (absolute threshold masking). Multiple comparisons were controlled with cluster-extent threshold combined with a height threshold of 0.001, to produce clusters with familywise error of $P < .05$.

Spherical volumes of interest (VOIs) (5-mm radius) were determined from regions in which patients with bipolar

disorder showed significantly higher or lower FA values than patients with MDD. The center of the spherical VOIs was determined from the MNI coordinate with peak *t* value. The regional FA values were calculated by averaging the values for all voxels within the spherical VOIs placed on regions in FA images of patients with bipolar disorder and MDD, and healthy volunteers. The same VOIs were applied to λ1, λ2, and λ3 images. The λ1–λ3 values were extracted, and the mean diffusivity ([λ1 + λ2 + λ3]/3), axial diffusivity (λ1), and radial diffusivity ([λ2 + λ3]/2) were compared.[14]

Statistical Analysis

We used a 2-sample *t* test, Pearson χ^2 test, or analysis of variance (ANOVA) to identify demographic variables in the participants. To examine the difference in the FA, mean, axial, and radial diffusivity values of VOIs in the 3 groups where a significant FA value change was found between patients with bipolar disorder and MDD, we performed ANCOVA using age and gender as covariates. Bonferroni correction was applied to avoid type I errors because of the multiplicity of the statistical analyses. All statistical tests were 2-tailed and reported at $P < .05$. We performed a linear discriminant analysis to find the cutoff point of the age- and gender-adjusted FA values, which could best differentiate patients with bipolar disorder from patients with MDD. Statistical analysis of the data was performed using SPSS for Windows 21.0 (IBM Japan Inc, Tokyo, Japan).

RESULTS

Demographic and Clinical Data

Table 1 summarizes the demographic characteristics of the participants in the study. Among the 3 groups, there were no significant differences in age, gender, or years of education. Patients with bipolar disorder and MDD showed no significant difference in age at onset, duration of illness, or psychiatric scores of MMSE and YMRS. On the basis of the MADRS score, patients with MDD tended to be more depressed than those with bipolar disorder, although the difference was not significant.

All patients with bipolar disorder were on lithium and/or other mood stabilizers during the study, while only 3 subjects with MDD were medicated with these drugs. There was no significant difference in medication with antidepressants, antipsychotics, and benzodiazepine drugs between the bipolar disorder and MDD groups.

Table 1. Summary of the Demographic Characteristics in the Participants of the Study

Characteristic	Bipolar Disorder (n = 16)	MDD (n = 23)	Healthy Volunteer (n = 23)	Statistic	*P* Value
Age, mean ± SD, y	47.1 ± 8.6	44.3 ± 9.8	40.5 ± 12.7	$F_{2,59} = 1.78$	.18
Female, n (%)	6 (37.5)	14 (60.9)	10 (43.5)	$\chi^2 = 2.42$	.30
Education, years	14.6 ± 1.8	14.7 ± 1.9	15.5 ± 1.7	$F_{2,59} = 1.38$	.26
Family history, n (%)	4 (25.0)	6 (26.1)	NA	$\chi^2 = 0.006$	.62
Age at onset, mean ± SD, y	36.6 ± 11.0	38.6 ± 8.1	NA	$t = -0.628$	.53
Duration of illness, mean ± SD, y	10.4 ± 6.3	6.0 ± 7.4	NA	$t = 1.90$	.065
MMSE, mean ± SD	28.8 ± 1.9	29.0 ± 1.5	NA	$t = -0.378$	.71
YMRS, mean ± SD	0.69 ± 2.7	0.0 ± 0.0	NA	$t = 1.00$	.33
MADRS score, mean ± SD	12.0 ± 11.8	18.7 ± 11.0	NA	$t = -1.77$	.085
Medication, n (%)					
Lithium	10 (62.5)	1 (4.3)	NA	$\chi^2 = 15.8$	< .001*
Other mood stabilizer	7 (43.8)	2 (8.7)	NA	$\chi^2 = 6.53$	.015*
Antidepressant	7 (43.8)	15 (65.2)	NA	$\chi^2 = 1.77$	.18
Antipsychotic	6 (37.5)	6 (26.1)	NA	$\chi^2 = 0.577$	.34
Benzodiazepine	13 (81.3)	12 (52.2)	NA	$\chi^2 = 3.47$	.063

*$P < .05$.
Abbreviations: MADRS = Montgomery-Asberg Depression Rating Scale, MDD = major depressive disorder, MMSE = Mini-Mental State Examination, NA = not applicable, YMRS = Young Mania Rating Scale.

Comparisons of FA Values Between Bipolar Disorder and MDD Groups by Voxel-Based Analysis

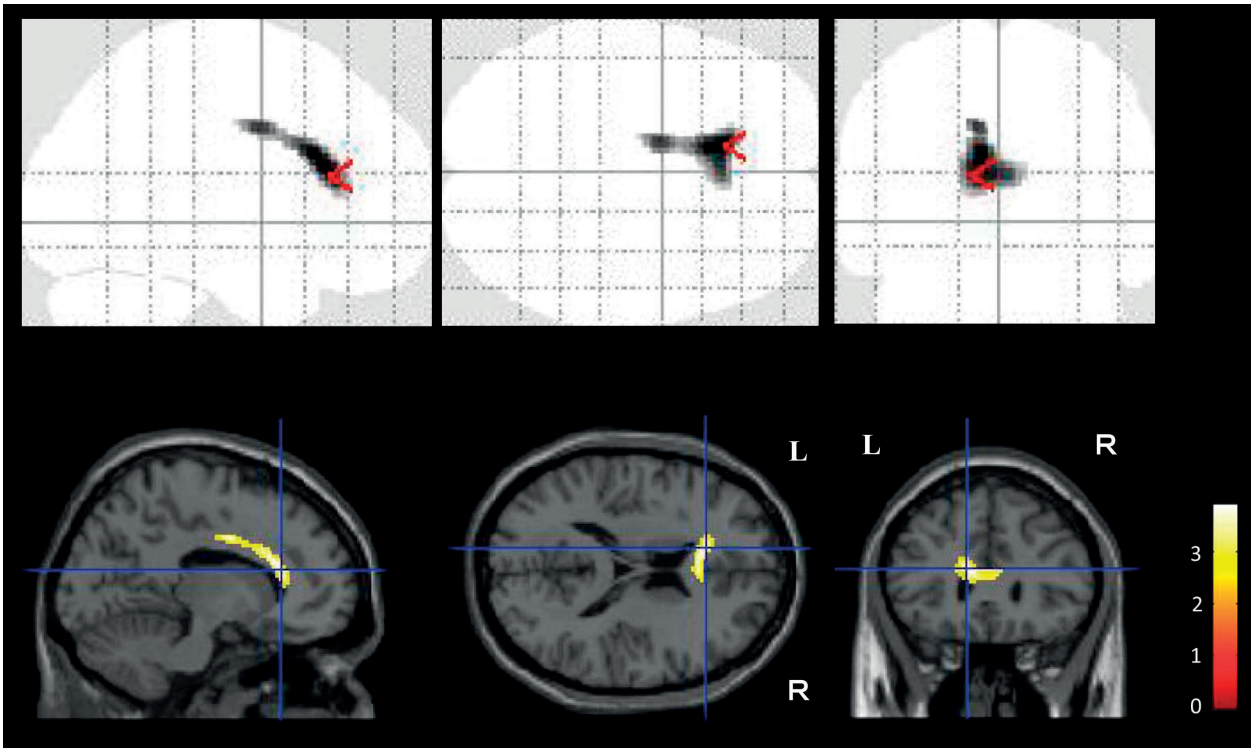
In the voxel-based analysis using age, gender, MADRS scores, and duration of illness as covariates, patients with bipolar disorder compared to those with MDD showed significantly lower FA values in only the anterior part of the corpus callosum (Figure 1). Moreover, none of the corpus callosum regions in patients with MDD had lower FA values than in patients with bipolar disorder. We additionally investigated the differences of FA values between bipolar disorder and MDD groups using affective state (depressive or euthymic state as covariate) in addition to age, gender, and duration of illness. When a MADRS cutoff score of 12 was used, 7 depressive and 9 euthymic patients had bipolar disorder and 17 depressive and 6 euthymic patients had MDD. We found the same results as those found in the analysis before including affective state as covariate in that patients with bipolar disorder showed significantly lower FA values in only the anterior part of the corpus callosum than patients with MDD and that none of the regions in patients with MDD had lower FA values than in patients with bipolar disorder.

Differences Between FA and Mean, Axial, and Radial Diffusivity Values of Bipolar Disorder, MDD, and Healthy Volunteer Groups in the Corpus Callosum

Scatterplots of age- and gender-adjusted FA values of patients with bipolar disorder and MDD, and healthy volunteers are shown in Figure 2. The FA values were determined from the VOIs placed on regions in the corpus callosum where significant differences between patients with bipolar disorder and those with MDD were shown by voxel-based analysis (Table 2).

The FA values of patients with bipolar disorder were significantly lower than those of patients with MDD and healthy volunteers. There was no significant difference in FA values between patients with MDD and healthy volunteers. Patients with bipolar disorder showed significantly higher mean, axial, and radial diffusivity values than those of healthy volunteers. There was no significant difference in mean, axial, and radial

Figure 1. Regions With Significant Differences in Fractional Anisotropy (FA) Values Between Patients With Bipolar Disorder and Major Depressive Disorder (MDD)[a]



[a]Sagittal, coronal, and transverse brain views show voxels with significantly lower FA values in patients with bipolar disorder than in patients with MDD. Detected areas shown in this figure were controlled with cluster-extent threshold combined with a height threshold of $P < .001$ to produce clusters with a familywise error of $P < .05$. These statistical parametric mapping projections were then superimposed on representative sagittal (x = −12), coronal (y = 28), and transverse (z = 18) magnetic resonance images. There were no regions with lower FA values in patients with MDD compared with patients with bipolar disorder.

diffusivity values between bipolar disorder and MDD groups or between MDD and healthy volunteer groups (Table 3).

With an FA value of 0.3965 derived from the linear discriminant analysis, we correctly predicted 13 of 16 bipolar disorder and 17 of 23 MDD cases. The correct classification rate was 76.9% ($\chi^2 = 15.9$, $P = .00007$), with a sensitivity of 81.3% and specificity of 73.9% for the discrimination of a patient with bipolar disorder from all patients.

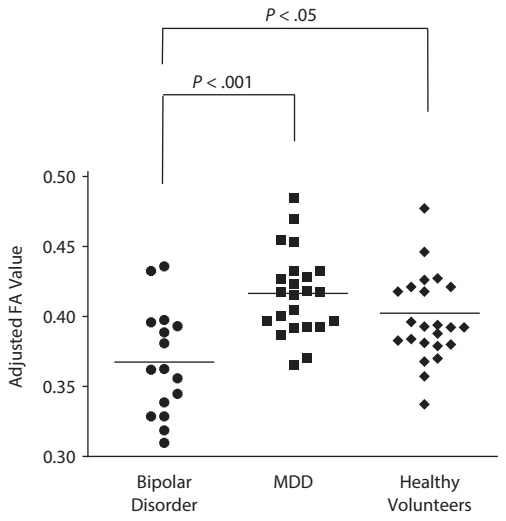
DISCUSSION

The present study shows that bipolar disorder involves a significant decrease in FA values compared to MDD in the anterior part of the corpus callosum. The decrease of anisotropy in the corpus callosum of patients with bipolar disorder has been reported before.[15–17] Our finding, in addition to being in line with the previous studies, is the first to highlight the reduced FA values within the corpus callosum as a sensitive marker for bipolar disorder in the early to middle life stage, compared to MDD, during depressed or euthymic states.

It is extremely difficult to distinguish between patients with bipolar disorder and MDD in clinical practice without a clear history of mania, and quick implementation of an objective biological marker supporting differential diagnosis is necessary. Multichannel near-infrared spectroscopy (NIRS) is applied for the differential diagnosis of patients with depression in some medical institutions. Takizawa et al[18] reported that NIRS could correctly classify 74.6% of patients with MDD and 85.5% with bipolar disorder and schizophrenia. Here, we showed that the age- and gender-adjusted FA values in the corpus callosum could classify 73.9% of patients with MDD and 81.3% of patients with bipolar disorder and that the correct classification rate matched that of NIRS. We believe that the FA value in the corpus callosum is one of the prospective stable biological markers, which is not easily affected by changes in cognition and motivation due to depressive symptoms.

Compared with healthy volunteers, patients with bipolar disorder were found to have a significant decrease in FA values associated with increased radial diffusivity values in the corpus callosum. In studies using the DTI method, decreased anisotropy has often been interpreted as a disruption of myelin associated with increased radial diffusivity values and/or axonal injury associated with the decreased axial diffusivity values.[14] Following this notion, the results of the present study suggest a disruption of myelin. Additionally, compared to healthy volunteers, we found an increase in mean diffusivity values in the corpus callosum of patients with bipolar disorder, which could be due to decreased cellular densities.[14] Reduced glial cell number has previously been reported in patients with bipolar

Figure 2. Scatterplots of the Age- and Gender-Adjusted Fractional Anisotropy (FA) Values in Patients With Bipolar Disorder and Major Depressive Disorder (MDD) and in Healthy Volunteers[a]



[a]The FA values were derived from spherical volumes of interest (5-mm radius) placed on the regions with significantly decreased FA values in patients with bipolar disorder compared to patients with MDD by a voxel-based analysis (height threshold of $P < .001$ with cluster-extent threshold of a familywise error of $P < .05$) (Montreal Neurological Institute coordinates are shown in Table 2). The horizontal lines represent the mean FA values of the 3 groups.

Table 2. Regional Change of Fractional Anisotropy Values Between Bipolar Disorder and MDD Patients

Comparison	Region	MNI Coordinates (x, y, z)	Voxels	*t* Value	*P* Value
Bipolar disorder > MDD	None				
Bipolar disorder < MDD	Corpus callosum	−12, 28, 18	416	5.21	< .001

Abbreviations: MDD = major depressive disorder, MNI = Montreal Neurological Institute.

Table 3. The Values of FA, Mean Diffusivity, Axial Diffusivity, and Radial Diffusivity of the Patients and Controls

	Corpus Callosum (x = −12, y = 28, z = 18)			
Group	FA	Mean Diffusivity ($\times 10^{-4}$)	Axial Diffusivity ($\times 10^{-4}$)	Radial Diffusivity ($\times 10^{-4}$)
Bipolar disorder	0.37 ± 0.05*,†	1.0 ± 0.12*	1.3 ± 0.17*	0.8 ± 0.12*
MDD	0.41 ± 0.03	0.9 ± 0.11	1.3 ± 0.13	0.7 ± 0.13
Healthy volunteers	0.40 ± 0.03	0.9 ± 0.07	1.2 ± 0.10	0.7 ± 0.07

*Significantly different values ($P < .05$) of Bipolar disorder (BD) patients compared with healthy volunteers.
†Significantly different values ($P < .05$) of BD patients compared with MDD patients.
Abbreviations: FA = fractional anisotropy, MDD = major depressive disorder.

disorder at postmortem,[19] and there is evidence of altered oligodendrocyte-associated gene expression in bipolar disorder.[20,21] The decreased mean diffusivity might be due to the reduced number of oligodendrocytes in the corpus callosum of patients with bipolar disorder, which functions to insulate axons with myelin sheaths.[22] Demyelination, manifested as white matter abnormalities, might be related to the altered expression of glia and myelination genes described in patients with bipolar disorder.[15]

The corpus callosum is a white matter midline structure that connects the 2 cerebral hemispheres, allowing interhemispheric communication. Owen et al[23] reported that patients with agenesis of the corpus callosum showed significantly reduced interhemispheric functional connectivity in the resting-state functional MRI. This result suggests that the corpus callosum might connect the cerebral hemispheres functionally. The corpus callosum has been generally studied in order to elucidate the pathophysiology underlying bipolar disorder. There are reviews of imaging studies on the corpus callosum abnormalities in brain volume[24] and white matter microstructure[25] in patients suffering from bipolar disorder. This evidence indicates that the corpus callosum might be important in the development and progression of bipolar disorder. Abnormalities in the corpus callosum may result in altered interhemispheric connections, which could be relevant to the pathophysiology of bipolar disorder.

Abnormality of the corpus callosum was found in the anterior part including the genu, which interconnects the bilateral prefrontal areas.[26] Thus, interhemispheric communication between the prefrontal association areas may be altered in the brains of patients with bipolar disorder. Prefrontal areas are known to have a regulatory function over emotional processes.[27] Shobe[28] presented a remarkable model concerning emotional regulation. The model describes that the right hemisphere mediates the identification and comprehension of emotional stimuli, and the left hemisphere processes emotional information that has been shared within the hemispheres via the corpus callosum. Further, any microstructural abnormalities in the corpus callosum would degrade the exchange of emotional information between the hemispheres. The resulting emotional dysregulation could trigger the affective instability and mood swings present in patients with bipolar disorder.

There are several limitations to the present study. First, the sample size of our study was not large enough to elucidate the moderate size differences between groups. Second, patients with bipolar disorder compared to those with MDD tended to have a longer duration of illness. Although our analysis included duration of illness as a covariate, this tendency should be taken into consideration. Third, the patients had exposure to mood stabilizers, antidepressants, antipsychotics, and benzodiazepine drugs. Previous studies have not yet shown any evidence of the effect of these drugs on the white matter microstructures. Even if they exert some effect on the white matter, in our study, there were no significant differences in these medications with these drugs between the bipolar disorder and MDD groups (Table 1), and our result on the differences in the FA values between the groups would have remained unchanged even if we had considered the effect of these drugs. On the other hand, more patients with bipolar disorder than patients with MDD

were medicated with lithium and other mood stabilizers (Table 1). Lithium is suggested to have a protective effect on the white matter tracts,[29] and valproate is reported to have a protective effect on the white matter changes in patients with bipolar disorder.[30] The mood stabilizers will normalize the alterations in the white matter structures, and the differences in FA values between bipolar disorder and MDD might have been larger if we had considered the effect of the mood stabilizers. Fourth, the present study could not show significant microstructural difference between MDD and healthy volunteer groups, in contrast with the previous DTI studies,[31–33] which showed lower FA value in patients with MDD when compared to healthy volunteers. This may be attributed to the small sample size and the effect of medications on brain structures. Further studies with increased numbers of the drug-free patients are necessary to overcome these limitations.

In conclusion, the present study revealed that patients with bipolar disorder had microstructural abnormalities in the anterior part of the corpus callosum during depressed or euthymic state. Further, patients with bipolar disorder might have the essential pathological characteristics of demyelination manifested as white matter abnormalities. Abnormalities in the corpus callosum deteriorate the exchange of emotional information between the cerebral hemispheres, especially in the prefrontal areas, resulting in emotional dysregulation. We suggest the possibility that the FA value in the frontal corpus callosum may be one of the prospective stable biological markers for differential diagnosis between bipolar disorder and MDD. Further investigation with a larger number of patients with bipolar disorder is needed to clarify if and how myelin damage of the corpus callosum affects the clinical presentation and treatment response in patients with bipolar disorder.

Submitted: February 3, 2015; accepted October 7, 2015.

Online first: August 30, 2016.

Drug names: lithium (Lithobid and others).

Potential conflicts of interest: None reported.

Funding/support: This research was supported by Grants-in-Aid for Scientific Research, (C) 24591740, from the Japan Society for the Promotion of Science, and by Grant for Research on Psychiatric and Neurological Diseases and Mental Health (H25-51) from the Japan Ministry of Health, Labour, and Welfare.

Role of the sponsor: These sponsors had no role in the design and conduct of the study.

Acknowledgments: The authors thank the staff of the MRI facility at the Department of Investigative Radiology, National Cerebral and Cardiovascular Center in Japan for subject care and data acquisition during the MRI procedure.

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