Original Investigation

A Multicenter Tractography Study of Deep White Matter Tracts in Bipolar I Disorder

Psychotic Features and Interhemispheric Disconnectivity

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IMPORTANCE Tractography studies investigating white matter (WM) abnormalities in patients with bipolar disorder have yielded heterogeneous results owing to small sample sizes. The small size limits their generalizability, a critical issue for neuroimaging studies of biomarkers of bipolar I disorder (BPI).

OBJECTIVES To study WM abnormalities using whole-brain tractography in a large international multicenter sample of BPI patients and to compare these alterations between patients with or without a history of psychotic features during mood episodes.

DESIGN, SETTING, AND PARTICIPANTS A cross-sectional, multicenter, international, Q-ball imaging tractography study comparing 118 BPI patients and 86 healthy control individuals. In addition, among the patient group, we compared those with and without a history of psychotic features. University hospitals in France, Germany, and the United States contributed participants.

INTERVENTIONS Participants underwent assessment using the Diagnostic Interview for Genetic Studies at the French sites or the Structured Clinical Interview for *DSM-IV* at the German and US sites. Diffusion-weighted magnetic resonance images were acquired using the same acquisition parameters and scanning hardware at each site. We reconstructed 22 known deep WM tracts using Q-ball imaging tractography and an automatized segmentation technique.

MAIN OUTCOMES AND MEASURES Generalized fractional anisotropy values along each reconstructed WM tract.

RESULTS Compared with controls, BPI patients had significant reductions in mean generalized fractional anisotropy values along the body and the splenium of the corpus callosum, the left cingulum, and the anterior part of the left arcuate fasciculus when controlling for age, sex, and acquisition site (corrected for multiple testing). Patients with a history of psychotic features had a lower mean generalized fractional anisotropy value than those without along the body of the corpus callosum (corrected for multiple testing).

CONCLUSIONS AND RELEVANCE In this multicenter sample, BPI patients had reduced WM integrity in interhemispheric, limbic, and arcuate WM tracts. Interhemispheric pathways are more disrupted in patients with than in those without psychotic symptoms. Together these results highlight the existence of an anatomic disconnectivity in BPI and further underscore a role for interhemispheric disconnectivity in the pathophysiological features of psychosis in BPI.

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Editorial

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White matter (WM) abnormalities have been widely detected in the pathophysiological features of bipolar disorder (BD),[1] mainly using diffusion tensor imaging (DTI) studies.[2] Diffusion tensor imaging uses the properties of water molecule motion to provide insights into the microscopic structure of brain tissues with fractional anisotropy (FA), a quantitative index that reflects the integrity and coherence of WM.[3]

Few studies have applied tractography methods to BD despite several advantages. Indeed, the virtual reconstruction of entire WM tracts provides comprehensive anatomic information and allows for anatomically driven hypothesis testing for changes in FA. Despite discrepancies,[4,5] most studies in BD reported decreased FA values along tracts linking regions involved in emotion processing, including the uncinate fasciculus,[6-9] the anterior thalamic radiations,[8,9] and the cingulum.[6,10] Such impairments are thought to underpin the emotional dysregulation observed in the patients[11] and are further considered to be a relevant candidate biomarker for BD.[1]

Tractography studies in BD have included relatively small samples (≤40 patients with BD[9]), thus limiting the generalizability of their conclusions. Multicenter imaging studies including larger samples can help to address those issues.[12] Furthermore, a relatively larger sample allows for the disentangling of a heterogeneous sample of patients by focusing on a clinical feature of interest. This possibility is worth exploiting in a complex clinical condition such as BD. At least 50% of patients with BD experience psychotic features during phases of acute illness.[13] Despite substantial overlap in psychotic features and genetic susceptibility between BD and schizophrenia, growing evidence from clinical[14] and genetic[15] studies support the view that BD with psychotic features can be seen as a homogeneous subtype of BD. However, despite the high prevalence of BD with psychotic features, the relation of this subtype to different WM alterations compared with nonpsychotic BD remains poorly explored.

Thus, we designed a large, multicenter, whole-brain tractography study in patients with bipolar I disease (BPI). As our main objective, we probed microstructural properties of 22 major deep WM tracts covering the whole brain in a large sample of BPI patients and controls using Q-ball imaging (QBI) tractography. Our secondary objective was to investigate whether these disruptions were different in subsamples of BPI patients with or without a history of psychotic features.

Methods

Participants

Adult inpatients and outpatients with BPI (by *DSM-IV-R* criteria) were recruited from the following university-affiliated participating centers: Assistance Publique-Hôpitaux de Paris Hôpital Henri Mondor-Albert Chenevier in Créteil, Hôpital Fernand Widal-Lariboisière in Paris, France; Western Psychiatric Institute and Clinic in Pittsburgh, Pennsylvania; and the Central Institute for Mental Health in Mannheim, Germany, a public foundation associated with the University of Heidelberg. Controls, recruited from media announcements and registry offices, had no personal or family history of Axis I mood disorder, schizophrenia, or schizoaffective disorder. All participants underwent clinical assessment by trained raters (S.S., J.L., M.W., M.P., M.D., A.V., J.A., K.L.D., C.D., N.H., M.-A.D, M.L., and J.H.) using the Diagnostic Interview for Genetic Studies at the French sites[16] and the Structured Clinical Interview for *DSM-IV* at the German and US sites.[17] The Montgomery-Åsberg Depression Rating Scale[18] or the Hamilton Depression Rating Scale 17,[19] the Young Mania Rating Scale,[20] and the National Adult Reading Test[21] were administered at all sites. Symptomatic patients were defined as having a score of greater than 7 on the mood scales. History of psychotic features was defined as at least 1 manic or 1 depressive episode with delusions or hallucinations (*DSM-IV-R*). Exclusion criteria for all participants consisted of a history of neurological disease or head trauma with loss of consciousness and contraindications for magnetic resonance imaging (MRI). Twenty-four of 118 patients (20.3%) had participated in a previous single-center tractography study[6] with different aims, different DTI sequence, and a different processing pipeline. The local ethics committee of each center approved the study, and, after participants received a complete description of the study, written informed consent was obtained.

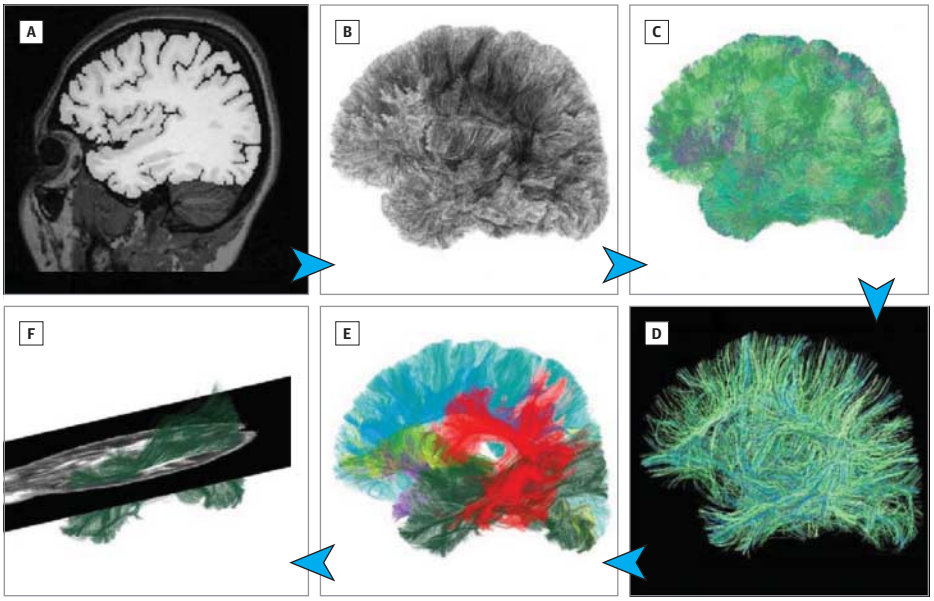
Data Acquisition

To minimize between-site bias, diffusion-weighted (DW) images and T1-weighted images were obtained for all participants using the same hardware in the 3 MRI acquisition sites (3T Magnetom TrioTim syngo MR B17 with 12-channel head coil; Siemens Medical Solutions). The MRI protocol included a high-resolution T1-weighted acquisition (echo time, 2.98 milliseconds; repetition time, 2300 milliseconds; 160 sections; voxel size, 1.0 × 1.0 × 1.1 or 1.0 mm) and a shared DW sequence along 41 directions (voxel size, 2.0 × 2.0 × 2.0 mm; b = 1000 s/mm^2 plus 1 image in which b = 0; echo time, 87 or 84 milliseconds; repetition time, 14 000 milliseconds; 60 or 64 axial sections). Data were assessed for movement, susceptibility, and noise artifacts with both operators (S.S. and J.H.) blinded to the diagnosis. Twelve participants with significant artifacts or movements were consensually dropped from the initial sample, leading to an analyzed sample of 204 participants.

Data Processing

We used freely available software to process DW and T1-weighted (Connectomist 2.0 and BrainVISA 4.2; http://www.brainvisa.info) MRI data. The DW images were corrected for eddy currents and noise/spikes with q-space interpolation correction. We then computed an orientation distribution function at each voxel included in this mask using an analytical QBI model (spherical harmonic order, 6; regularization factor λ = 0.006).[22] The orientation distribution function embeds information about the angular profile of diffusion within each voxel, thus allowing detection of the principal directions of diffusivity similar to the main eigenvector of the DTI models. However, QBI models are better at rendering complex fiber configurations, such as crossing or bending fibers, by allowing the mixture of populations of fibers characterized by different di-

Figure 1. Reconstruction of the White Matter Processing Pipeline



A, Tractography mask. B, Whole-brain tractography. C, Segmentation based on fiber lengths. Colors represent different fiber length. Green indicates fibers ranging from 30 to 50 mm; light green, greater than 50 to 80 mm; dark green, greater than 80 to 95 mm; cyan blue, greater than 95 to 110 mm; dark olive green, greater than 110 to 130 mm; purple, greater than 130 to 150 mm; dark blue, greater than 150 to 175 mm; and dark purple, greater than 175 to 300 mm. D, Centroid tracts calculated from each fascicle. E, Final segmented bundles of the left hemisphere and of the interhemispheric region. Blue-green indicates the corpus callosum; light blue, the left cingulum; green, the left frontal thalamic radiations; purple, the left uncinate fasciculus; yellow, the left inferior frontal-occipital fasciculus; dark green, the left inferior longitudinal fasciculus; and red, the left arcuate fasciculus. F, Extraction of the mean generalized fractional anisotropy along the left inferior longitudinal fasciculus.

rections within each voxel.[23,24] In an equivalent process, we evaluated the generalized FA (GFA) from all the computed orientation distribution functions.[24] A decreased GFA value is thought to indicate loss of integrity or loss of coherence of WM.[3]

Whole-Brain Tractography

The definition of the 3-dimensional space within which the fibers are tracked is necessary for tractography algorithms. In most studies, this definition relies on thresholding the FA map using an arbitrary threshold yielding a mask that is supposed to contain mostly WM. However, in practice, many regions of interest included in WM are missed, especially when partial voluming effects occur owing to the limited resolution of FA maps or to the inadequacy of the FA threshold in crossings, for instance. To compute a more robust mask, we used a T1-based propagation tractography mask determined with a published method.[25-27] For this approach, such a mask is driven by the T1-weighted anatomic data. The propagation mask thus includes the entire brain tissue (rather than regions with high FA) and excludes specific areas, such as the sulci skeleton, to prevent the creation of implausible fibers (**Figure 1**A). The mask in T1-weighted space is then registered to the DW data by a linear rigid transformation. Each registration between T1-weighted and DW data and the quality of the propagation mask was checked visually.

We performed whole-brain tractography in native space for each participant using a regularized, streamlined, deterministic algorithm (1 seed per voxel; forward step, 0.5 mm; bilateral propagation)[28] (Figure 1B), which allows for the reconstruction of WM tracts using a step-by-step approach following the multidirectional diffusion orientation.[22] Algorithm propagation was interrupted if the tract length exceeded 300 mm, if the tract streamline propagated outside the mask, or if the curvature between 2 steps exceeded 30°. No between-subject registration was performed.

Clustering-Based Segmentation

To reconstruct WM tracts, whole-brain tractography volumes were then segmented using an automatic segmentation pipeline based on a clustering technique relying on the definition of a pairwise distance between fibers and described in depth elsewhere.[25,26] This method allows for an automatized reconstruction and segmentation of anatomic WM tracts in a large study sample. In brief, this method follows 6 main steps, all performed in the native space of individuals. First, the data set from the tracts is divided into left or right hemisphere or interhemispheric region subsets, depending on the anatomic localization (Supplement [eFigure 1]). Second, each of these subsets is split into groups of similar length (Figure 1C). Third, the WM is fragmented into multiple clusters with dense connectivity using average-link hierarchical clustering, and fiber clusters are extracted from this parcellation. Fourth, an extremity density analysis regroups these clusters according to their extremity into homogeneous fascicles. Fifth, a centroid tract representing each fascicle is generated, and an average-link hierarchical clustering is performed to merge similar fascicles (Figure 1D). Finally, each volume containing each centroid tract is registered with a mean centroid atlas in Talairach space using a linear affine trans-

formation, and each centroid tract is matched to its corresponding deep WM bundle of the atlas[26] (Figure 1E). This process leads to a segmentation of the tractography data sets into 22 known deep WM bundles, allowing a whole-brain exploration of WM connectivity.

These WM bundles consist of the corpus callosum (CC) (rostrum, genu, body, and splenium) and bilaterally of the cingulum with 2 populations of fibers depending on their length (cingulate part, short and long fibers), the uncinate fasciculi, the arcuate fasciculi (direct, anterior, and posterior segments), the inferior longitudinal fasciculi, the inferior fronto-occipital fasciculi, and the frontal thalamic radiations. Each reconstructed bundle was assessed visually. All bundles were reconstructed for the whole sample except the direct segment of the right arcuate fasciculus, which was missing for 5 patients and 4 controls (4.4% of the total sample). These individuals were not included for the comparison of mean GFA along the direct segment of the right arcuate fasciculus. Examples of WM segmentations are provided in the Supplement (eFigure 2).

For each bundle, we extracted the mean GFA using the BrainVISA software (Figure 1F). In this report, the terms *bundles* or *tracts* synonymously refer to reconstructed deep WM tracts.

Statistical Analysis

We used linear mixed models to compare the mean GFA along each bundle between BPI patients and controls. The model included diagnosis (BPI or control) as a factor of interest, sex as a confounding factor, age as a confounding covariate, and the site of inclusion as a random-effect factor to control for potential site-specific effects.[12] When we identified a significant difference in GFA values along a tract between BPI patients and controls, we compared the mean GFA along this tract between patient groups with and without a history of psychotic features in a post hoc analysis.

To check the robustness of the results, we repeated the primary analysis on homogeneous subsamples of patients. We removed patients taking lithium[29] and patients with a history of alcohol dependence or abuse from the data set. To explore the effect of mood symptoms, we repeated our analyses on a subsample of patients with mixed or elevated mood symptoms. We also compared mean GFA values between the 31 depressed patients of our sample and 31 controls matched for age, sex, and IQ. We computed a medication load score following a method described elsewhere.[30] We explored the relationship between GFA and medication load and that of illness duration by partial correlation analysis, controlling for age and sex. Last, we checked that adding IQ to the model did not change the results.

We assessed differences between continuous demographic variables using 2-sample *t* tests (2 tailed) and differences between categorical variables using Pearson χ^2 tests when suitable assumptions were met. Data were analyzed using commercially available statistical software (PASW, version 18 [SPSS, Inc], and R, version 2.15.1, with the Multtest package [http://www.r-project.org]). Statistical test results were considered significant if corrected *P* values were less than .05 when applying the false discovery rate[31] method to correct *P* values for comparisons of GFA along the tracts (26 comparisons) and for sociodemographic data. Model check was performed using residual QQ plots and detection of outliers using leaf plots. If outliers were detected, the analysis was repeated after removing outliers.

Results

Clinical Sample

We included 118 patients and 86 controls in the analysis (**Table 1**). Detailed demographic information for each center is provided in the Supplement (eTable 1). Information about the history of psychotic features was missing for 1 patient (0.8%). Concerning mood state, 38 patients (32.2%) were symptomatic at the time of scanning; of these, 31 had Hamilton Depression Rating Scale 17 scores of less than 7 (range, 0-32) or Montgomery-Åsberg Depression Rating Scale scores of less than 7 (range, 0-25), 2 had Young Mania Rating Scale scores of less than 7 (range, 0-24), and 5 had both.

Comparison Between BPI Patients and Controls

Compared with controls, patients with BPI had significantly reduced mean GFA along the anterior segment of the left arcuate fasciculus, the body and the splenium of the CC, and the long fibers of the left cingulum (**Table 2**). These results remained significant after removing identified outliers.

Comparison Between BPI Patients With and Without Psychotic Features

Among the 4 bundles included for this comparison, BPI patients with a history of psychotic features had a significantly lower mean GFA value along the body of the CC than did those without a history of psychotic features (**Table 3** and **Figure 2**). This result remained significant after removing identified outliers.

Effect of Confounding Factors on the BPI Patients vs Controls

Results were unchanged when patients with elevated or mixed symptoms (n = 7) (Supplement [eTable 2]), patients currently taking lithium (n = 39) (Supplement [eTable 3]), and patients with past alcohol abuse/dependence (n = 25) (Supplement [eTable 4]) were removed from the sample. We also found significant differences in GFA values between the 31 depressed BPI patients and the 31 matched controls except along the splenium (Supplement [eTable 5]). We found no correlation between the mean GFA and the medication load (Supplement [eTable 6]) or between the mean GFA and duration of illness (Supplement [eTable 7]). Adding IQ as a covariate did not change the results (Supplement [eTable 8]). When bundle volume was added as a covariate, all results remained significant.

Discussion

Difference in Mean GFA Between BPI Patients and Controls

This multicenter MRI study compared the microstructural properties of 22 WM tracts between BPI patients and controls

Table 1. Demographic and Clinical Characteristics of Patients With BPI and Healthy Controls

	Patients With BPI (n = 118)	Healthy Controls (n = 86)	Difference Between Variables (*df*)	*P* Value for FDR
Categorical Variables[a]				
Site				
France	24 (20.3)	22 (25.6)	4.52 (2)	.30
Germany	41 (34.7)	38 (44.2)		
United States	53 (44.9)	26 (30.2)		
Male sex	47 (39.8)	41 (47.7)	1.25 (2)	.49
Right-handed	111 (96.5)	84 (97.7)	0.78 (2)	.81
Positive history of PF episode	57 (48.7)	NA		
Use of medication				
Lithium	39 (33.1)	NA		
Mood stabilizer other than lithium	64 (54.2)	NA		
Antipsychotic	52 (44.1)	NA		
Antidepressant	54 (45.8)	NA		
Numerical Variables[b]				
Age at MRI, y	36.32 (10.49)	37.26 (11.22)	0.61 (202)	.67
NART IQ score	108.86 (10.62)	107.39 (10.06)	0.99 (201)	.52
YMRS score (all sites)	2.58 (3.72)	NA		
MADRS score (France and Germany)	3.49 (5.37)	NA		
HRS-17 score (United States)	9.86 (7.87)	NA		
Age at onset, y	20.75 (7.97)	NA		

Abbreviations: BPI, bipolar I disorder; FDR, false discovery rate; HRS-17, Hamilton Depression Rating Scale 17; MADRS, Montgomery-Åsberg Depression Rating Scale; MRI, magnetic resonance imaging; NA, not applicable; NART, National Adult Reading Test; PF, psychotic features; YMRS, Young Mania Rating Scale.

[a] Calculated as number (percentage) of participants. Percentages have been rounded and may not total 100. Differences between variables were assessed using Pearson χ^2 tests.

[b] Calculated as mean (SD). Differences between variables were assessed using 2-sample *t* tests (2 tailed).

using QBI tractography and automatic WM segmentation. Patients with BPI had WM alterations along the left cingulum (long fibers), the CC (body and splenium), and the anterior segment of the left arcuate fasciculus. The BPI patients with a history of psychotic features had lower mean GFA values than those without such a history along the body of the CC. To our knowledge, this study has the largest recruitment to date of BPI patients in a tractography study. This relatively large sample[32] also allows for the comparison of WM connectivity with tractography between patients with and without psychotic features.

To date, interhemispheric disconnectivity has not been incorporated in neural models of BD.[11,33] However, some WM abnormalities of the CC have been reported repeatedly in patients with BD,[6,10,34,35] suggesting a relationship between interhemispheric connectivity abnormalities and BD.[36] In line with previous research, we identified a reduced GFA along fibers belonging to the body and the splenium of the CC. The patients who experienced psychotic symptoms during mania or depression had lower GFA values in the CC. In parallel, similar decreased callosal WM anisotropy was reported in schizophrenia,[37,38] and neuropsychological results suggest that interhemispheric transfer may be impaired in patients with psychosis.[39] Thus, our results support BD with psychosis as being a biologically relevant subtype of BD. However, the substantial overlap in WM abnormalities between BD and schizophrenia prevents us from forming conclusions on the specificity of such differences. Further neuroimaging studies with a dimensional rather than a categorical approach to psychosis are needed to gain a better in-depth understanding of the role of callosal alterations in the pathogenesis of psychotic features.

Emotional dysregulation is a core feature of BD.[11,33] Functional disturbances have been described in the anterior cingulate cortex of patients with BD,[40] a region involved in emotional processing. We found an altered microstructure of the cingulum bundle, as reported previously.[1,8,10,41,42] We were able to specify the localization of these WM alterations along a subsample of cingulum fibers linking the anterior cingulate cortex to posterior parts of the cingulate cortex. This finding adds evidence of an anatomic disconnectivity within the cingulum in BD. Previous studies[6,8] reported a decrease of FA along the arcuate fasciculi in patients with BD that we specified on the anterior segment of the left arcuate fasciculus. This segment links Brodmann area 44/45 and the inferior parietal lobule and is thought to be involved in memory processing and speech comprehension.[43,44] We found no difference in GFA along this tract between BPI patients with and without psychotic features in our sample. This finding does not support the hypothesis of an involvement of the arcuate in the hallucinatory or delusional symptoms of BPI patients.[8]

Of note, left-sided results have been reported in tractography studies,[4,8] challenging those from a meta-analysis of voxelwise DTI studies[2] that found right-sided clusters of reduced anisotropy. Methodological heterogeneity may explain this apparent discrepancy. Indeed, we calculated the mean GFA along each tract, and very focal reductions of GFA may have remained undetected.

Table 2. Comparison of Mean GFA Between Patients With Bipolar Disorder and Healthy Controls[a]

	GFA, Mean (SD)		Estimated GFA Difference, Mean (95% CI)	F Value (*df*)	Diagnosis Effect Size, Cohen *f* Statistic	*P* Value for FDR	Effect Size for Scanner, Sex, and Age, Cohen *f* Statistic
	BPI Patients (n = 118)	Healthy Controls (n = 86)					
Corpus Callosum Interhemispheric Bundles							
Body	**0.101 (0.004)**	**0.102 (0.004)**	**−0.002 (−0.003 to −0.001)**	**10.145 (1, 198)**	**0.23**	**.03**	**0.21, 0.03, and 0.38**
Genu	0.094 (0.004)	0.094 (0.004)	−0.001 (−0.002 to 3.18×10^{-4})	1.803 (1, 198)	0.09	.37	0.36, 0.08, and 0.66
Splenium	**0.113 (0.005)**	**0.115 (0.005)**	**−0.002 (−0.003 to −0.001)**	**8.391 (1, 198)**	**0.21**	**.03**	**0.31, 0.003, and 0.23**
Rostrum	0.096 (0.006)	0.096 (0.006)	−0.001 (−0.002 to 0.001)	0.825 (1, 198)	0.06	.53	0.68, 0.002, and 0.63
Left Hemisphere							
Left arcuate							
Direct segment	0.086 (0.003)	0.086 (0.003)	$<10^{-3}$ (−0.001 to 0.001)	0.832 (1, 198)	0.06	.53	0.11, 0.04, and 0.38
Anterior segment	**0.079 (0.004)**	**0.081 (0.003)**	**−0.001 (−0.002 to −0.001)**	**8.403 (1, 198)**	**0.21**	**.03**	**0.09, 0.08, and 0.39**
Posterior segment	0.075 (0.004)	0.075 (0.004)	$<10^{-3}$ (−0.001 to 0.001)	0.538 (1, 198)	0.057	.60	0.11, 0.16, and 0.35
Left uncinate	0.078 (0.004)	0.078 (0.004)	$<10^{-3}$ (−0.001 to 0.001)	0.122 (1, 198)	0.03	.81	0.28, 0.03, and 0.33
Left cingulum							
Long fibers	**0.090 (0.005)**	**0.092 (0.005)**	**−0.002 (−0.003 to −0.001)**	**7.645 (1, 198)**	**0.20**	**.04**	**0.05, 0.16, and 0.14**
Short fibers	0.075 (0.004)	0.077 (0.005)	−0.002 (−0.003 to -2.91×10^{-4})	5.969 (1, 198)	0.17	.08	0.09, 0.11, and 0.21
Left inferior longitudinal	0.087 (0.004)	0.087 (0.003)	$<10^{-3}$ (−0.001 to 0.001)	0.041 (1, 198)	0.01	.87	0.19, 0.03, and 0.21
Left inferior fronto-occipital	0.095 (0.004)	0.096 (0.004)	−0.001 (−0.002 to 2.82×10^{-4})	2.107 (1, 198)	0.10	.33	0.13, 0.08, and 0.24
Left frontal thalamic radiations	0.074 (0.004)	0.073 (0.004)	0.001 (-2.72×10^{-4} to 0.002)	2.207 (1, 198)	0.10	.33	0.36, 0.28, and 0.22
Right Hemisphere							
Right arcuate							
Direct segment	0.083 (0.004)	0.084 (0.004)	−0.001 (−0.002 to 0.001)	0.631 (1, 189)	0.05	.58	0.20, 0.03, and 0.19
Anterior segment	0.082 (0.003)	0.082 (0.004)	$<10^{-3}$ (−0.001 to 0.001)	0.003 (1, 198)	0.004	.96	0.04, 0.21, and 0.35
Posterior segment	0.073 (0.004)	0.074 (0.004)	−0.001 (−0.002 to -3.19×10^{-5})	4.145 (1, 198)	0.15	.16	0.03, 0.04, and 0.32
Right uncinate	0.079 (0.003)	0.080 (0.004)	−0.001 (−0.002 to 1.67×10^{-4})	2.584 (1, 198)	0.11	.30	0.20, 0.06, and 0.36
Right cingulum							
Long fibers	0.085 (0.006)	0.086 (0.005)	−0.001 (−0.003 to -9.85×10^{-5})	3.945 (1, 198)	0.14	.16	0.15, 0.11, and 0.12
Short fibers	0.074 (0.004)	0.076 (0.004)	−0.001 (−0.002 to -9.92×10^{-4})	4.588 (1, 198)	0.15	.15	0.08, 0.10, and 0.11
Right inferior longitudinal	0.087 (0.004)	0.087 (0.003)	$<10^{-3}$ (−0.001 to 0.001)	0.789 (1, 198)	0.06	.53	0.22, 0.06, and 0.11
Right inferior fronto-occipital	0.094 (0.004)	0.095 (0.004)	−0.001 (−0.002 to 4.72×10^{-4})	1.138 (1, 198)	0.08	.49	0.11, 0.03, and 0.32
Right frontal thalamic radiations	0.074 (0.004)	0.074 (0.004)	$<10^{-3}$ (−0.001 to 0.001)	0.039 (1, 198)	0.01	.87	0.24, 0.19, and 0.17

Abbreviations: BPI, bipolar I disoder; *df*, degrees of freedom; FDR, false discovery rate; GFA, generalized fractional anisotropy.

[a] Boldface indicates significant after FDR correction.

Reductions of GFA have been related to microstructural modifications, including decreased axonal diameter or density, reduced myelination, or decreased WM coherence.[3] Involvement of proinflammatory cytokines,[45] a dysfunction of myelination-related genes,[46] and oligodendrocyte dysfunction[47] have been suspected. However, the precise mechanisms underpinning these alterations in BD remain unknown.

An important question has been whether mood stabilizers could influence neuroimaging measures. In line with most of the existing DTI studies,[29] we found no relationship between current medication use and GFA measures. To draw a definitive conclusion, a replication in medication-free patients would be worthwhile. Evidence suggests that mood symptoms may influence FA measures in BD.[48] We did not replicate such findings. Indeed, we found similar significant differences of GFA in a subsample of 31 depressed patients compared with 31 matched controls except along the splenium, where we found no significant difference. However, interpretation is limited by the possible underpowering of this comparison.

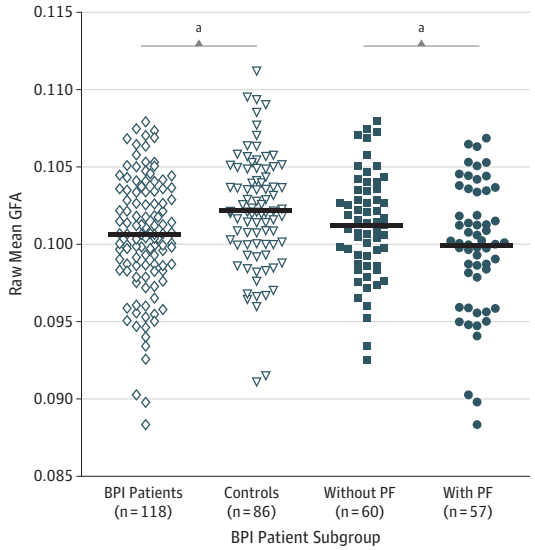
Table 3. Comparison of Mean GFA Between BPI Patients With at Least 1 PF Episode vs No PF History[a]

	GFA in BPI Patients, Mean (SD)		Estimated GFA Difference, Mean (95% CI)	F Value (*df*)	Diagnosis Effect Size, Cohen *f* Statistic	*P* Value for FDR	Effect Size for Scanner, Sex, and Age, Cohen *f* Statistic
	PF History (n = 57)	No PF History (n = 60)					
Corpus Callosum Interhemispheric Bundles							
Body	**0.100 (0.004)**	**0.101 (0.003)**	**−0.002 (−0.003 to −0.001)**	**8.902 (1, 111)**	**0.27**	**.03**	**0.27, 0.003, and 0.46**
Splenium	0.113 (0.006)	0.113 (0.004)	−0.001 (−3.68 to 4.825×10^{-4})	2.485 (1, 111)	0.15	.30	0.34, 0.04, and 0.27
Left Side							
Left arcuate, anterior segment	0.079 (0.003)	0.080 (0.003)	−0.001 (−0.002 to 0.001)	1.158 (1, 111)	0.12	.49	0.14, 0.005, and 0.35
Left cingulum, long fibers	0.090 (0.005)	0.089 (0.004)	$<10^{-3}$ (−0.002 to 0.001)	0.046 (1, 111)	0.02	.81	0.11, 0.04, and 0.17

Abbreviations: BPI, bipolar I disorder; *df*, degrees of freedom; FDR, false discovery rate; GFA, generalized fractional anisotropy; PF, psychotic features.

[a] Boldface indicates significant after FDR correction.

Figure 2. Mean Generalized Fractional Anisotropy (GFA) Along the Body of the Corpus Callosum for Patients and Controls



Individual GFA (an index of all the computed orientation distribution functions) values along the body of the corpus callosum for all patients with bipolar I disorder (BPI), those with psychotic features (PF), those without PF, and healthy controls. History of PF was not available for 1 BPI patient. A decreased GFA value is thought to indicate loss of integrity or loss of coherence of white matter.[3]

[a] $P < .05$ corrected for multiple testing.

Concerning our results, we found medium effect sizes for GFA. Larger samples with adequate statistical power may help to decrease the risk of overestimating "true" effect sizes.[32] On the other hand, we used a multiple scanner design that may have led to a systematic error. We reduced such potential site effect by sharing hardware, scanning protocol, and analysis pipeline across sites.

Strengths and Limitations of the Study

Several strengths of our report should be emphasized. We conducted a multicenter investigation with a relatively large sample of BPI patients in a tractography study, thus reducing the biases associated with recruitment from a single center. We harmonized the MRI acquisition protocol and hardware to reduce site-specific effects. Finally, we performed a multiple testing correction and secondary analyses to check for influences of confounding factors.

Such advantages are to be balanced against several limitations. We did not explore the interrater and intersite reliability of the scales used in this study. Despite our effort at harmonization, we did not include a phantom procedure to check the intercenter quality of the acquisitions. We cannot exclude a possible effect of past medication use on our results. Considering the large number of tracts to assess, we did not exploit other metrics derived from the orientation distribution function. We calculated mean GFA values along each tract to perform comparisons; very localized decreases of GFA may not have been detected. A common limitation of cross-sectional studies is their inability to determine whether observed alterations precede the onset of the disease or develop during its course. However, our results do not support the hypothesis of a relationship between the duration of the illness and GFA.

Conclusions

Using whole-brain QBI tractography in the first, and relatively large, international sample of BPI patients and controls, we found decreased GFA values along interhemispheric tracts and limbic and frontotemporal WM tracts in BPI. Patients with psychotic features had lower GFA values than did patients without such features along the CC.

These results highlight the role of interhemispheric disconnectivity in BPI and further suggest that BPI with psychotic features could be a relevant subtype of BD with specific pathophysiological features. The results also provide additional evidence of the involvement of disturbed connectivity of the cingulum and the arcuate in BPI. Future large multisite studies comparing BPI with other psychotic disorders are warranted to clarify the involvement of these tracts in the pathophysiological features of BD and to study the clinical relevance of such neuroimaging biomarkers.

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