**A multicenter tractography study of deep white matter tracts in bipolar disorder: psychotic features and interhemispheric disconnectivity.**

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**Abstract.**

**Importance.** Tractography studies investigating white matter abnormalities in patients with bipolar disorder have yielded heterogeneous results due to small sample sizes. This limits their generalizability, a critical issue for neuroimaging studies of biomarkers of bipolar disorder.

**Objective.** To study white matter abnormalities using whole-brain tractography in a large international multicenter sample of patients with bipolar disorder type 1 and to compare these alterations between patients with or without psychotic features during mood episodes.

**Design.** A cross-sectional multicenter international q-ball imaging tractography study comparing patients with bipolar disorder 1 to healthy controls, and patients with bipolar disorder with a past history of psychotic features to patients without such a history.

**Setting.** University hospitals.

**Participants.** 118 patients with bipolar disorder and 86 healthy controls.

**Intervention.** Participants were assessed using the Diagnosis Interview for Genetic Study at the French site 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. Q-ball imaging tractography and an automatized segmentation technique were used to reconstruct 22 known deep white matter tracts.

**Main Outcome Measures.** Generalized fractional anisotropy along each reconstructed white matter tract.

**Results.** Compared to controls, patients with bipolar disorder had significant reductions of mean generalized fractional anisotropy 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, gender and acquisition site (corrected for multiple testing). Patients with a past history of psychotic features had a lower mean GFA value than those without, along the body of the corpus callosum (corrected for multiple testing).

**Conclusions.** In this multicenter sample, patients with bipolar disorder 1 had reduced white matter integrity in interhemispheric, limbic and arcuate white matter tracts. Interhemispheric pathways were more disrupted in patients with psychotic symptoms than in patients without psychotic symptoms. Taken all together, these results highlight the existence of an anatomical disconnectivity in bipolar disorder and further underscore a role for interhemispheric connectivity in the pathophysiology of psychosis in BD.

## I- Introduction.

White matter (WM) abnormalities have been widely involved in the pathophysiology of bipolar disorder (BD) [1], mainly using diffusion tensor imaging (DTI) studies [2]. DTI uses the properties of water molecule motion to provide insights into the microscopic structure of brain tissues, i.e. with 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 anatomical information and allows for anatomically driven hypothesis testing on changes of FA. Despite discrepancies [4,5], most studies in BD reported decreased FA values along tracts linking regions involved in emotion processing: 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 bipolar disorder [1].

Tractography studies in BD suffer from relatively small sample sizes (at most 40 patients with BD [9]), thus limiting the generalizability of their conclusions. Multicenter imaging studies including larger samples can help to address these 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 being exploited in a complex clinical condition like BD. On this note, at least 50% of patients with BD experience psychotic features during acute illness phases [13]. Despite substantial overlap in psychotic features and genetic susceptibility between patients with BD and schizophrenia , growing evidence from both 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, whether this subtype relating to different WM alterations when compared to non-psychotic BD remains poorly explored.

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

## II- Methods.

### 2.1 **Participants**

Adult inpatients and outpatients with BD type I (DSM-IV-R) were recruited from university-affiliated participating centers: APHP Henri Mondor hospitals, Créteil and Fernand-Widal hospital, Paris, France; Western Psychiatric Institute and Clinic, UPMC, Pittsburgh, USA and the Central Institute for Mental Health, Mannheim, Germany. Controls, recruited from media announcements and registry offices, had no personal or family history of axis I mood disorder, schizophrenia or schizo-affective disorder. All subjects were clinically assessed by trained raters using the Diagnosis Interview for Genetic Study at the French sites [16] and the Structured Clinical Interview for DSM-IV at the German and US sites [17] and the Montgomery-Asberg 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] at all of the sites.

Symptomatic patients were defined as having a score > 7 on the mood scales. Past history of psychotic features was defined as at least one manic or depressive episode with delusions or hallucinations (DSM-IV-R). Exclusion criteria for all subjects comprised of: the history of neurological disease or head trauma with loss of consciousness and MRI contraindications. Twenty-four patients (20.34%) had participated in a previous single center tractography study [6] with different aims, DTI sequence and processing pipeline. Local ethics committee of each center approved the study and after complete description of the study to the subjects, written informed consent was obtained.

### 2.2 **Data acquisition**

To minimize between-sites bias, diffusion-weighted (DW) images and T1-weighted images were obtained for all subjects using the same hardware in the 3 MRI acquisition sites (MRI Siemens Magnetom TrioTim 3T Syngo MR B17 (Siemens Medical Solutions), 12-channel head-coil). The MRI protocol included a high-resolution T1-weighted acquisition (echo time = 2.98 ms, repetition time = 2300 ms, 160 slices, 1.0x1.0x1.1 mm) and a shared DW sequence along 41 directions (2.0x2.0x2.0 mm, b=1000 s/mm² plus one b=0 image, echo time 87 or 84 ms, repetition time 14000 ms, 60 or 64 axial slices). Data was assessed for movement, susceptibility and noise artifacts blindly to the diagnosis by two operators (JH and SS) and 12 subjects with significant artifacts or movements were consensually dropped out from the initial sample leading to an analyzed sample of 204 subjects.

### 2.3 **Data processing**

DW MRI data was processed using Connectomist 2.0 and T1 using BrainVISA 4.2 (www.brainvisa.info). The DW slices were corrected for eddy currents, susceptibility induced geometrical distortions and spikes using fieldmap based and Q-space interpolation corrections respectively. Then, an orientation distribution function (ODF) was computed at each voxel

included in this mask using an analytical Q-ball model (spherical harmonic order 6, regularization factor $\lambda$=0.006) [22]. The ODF embeds information about the angular profile of diffusion within each voxel, thus allowing to detect the principal directions of diffusivity similarly to the main eigenvector of the DTI models. However, QBI models render complex fibers configurations such as crossing or bending fibers better by allowing mixture of populations of fibers characterized by different directions within each voxel [23,24]. Equivalently to DTI FA, the generalized fractional anisotropy (GFA) was evaluated from all the computed ODF [24]. A decreased GFA value is thought to indicate loss of integrity or coherence of WM [3].

**2.3.1 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 relies on thresholding the FA map using an arbitrary threshold yielding a mask supposed to mostly contain white matter. But in practice, many regions of interest included in WM are missed especially when partial voluming effects occur due to the limited resolution of FA maps, or due to the inadequacy of the FA threshold in crossings for instance. In order to compute a more robust mask, we used a T1-based propagation tractography mask computed using a published method[25-27]. In this approach, such a mask is driven by the T1 anatomical 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 1A). The mask in T1 space is then registered to the DW data by a linear rigid transformation.Each registration between T1 and DW data and the quality of the propagation mask were visually checked.

We performed whole-brain tractography in each subject native space using a regularized streamline deterministic algorithm (one seed per voxel, forward step 0.5mm, 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 300mm, if the tract streamline propagated outside the mask or if the curvature between two steps exceeded 30°. No between-subject registration was performed.

### 2.3.2 Clustering-based segmentation

To reconstruct WM tracts, whole-brain tractography volumes were then segmented using an automatic segmentation pipeline. This method, based on a clustering technique relying on the definition of a pairwise distance between fibers and described in [25] and [26], allows for an automatized reconstruction and segmentation of anatomical WM tracts in a large sample of subjects. Briefly this method follows five main steps, all performed in the native space of individuals. For a more in depth description of this method, the reader is invited to refer to [25] and [26]. Firstly, the tracts dataset is divided to three subsets depending on their anatomical localization: left/right hemisphere or interhemispheric region (eFigure 1). Secondly, each of these subsets is split into groups of similar length (figure 1C). Thirdly, the WM is fragmented into multiple clusters with dense connectivity using average-link hierarchical clustering and fiber clusters are extracted from this parcellation. Fourthly, an extremity density analysis regroups these clusters according to their extremity into homogeneous fascicles. Fifthly, 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 is registered with a mean centroid atlas in Talairach space using a linear affine transformation and each centroid is matched to its corresponding deep WM bundle of the atlas [26] (figure 1E). This leads to a segmentation of the tractography datasets into 22 known deep WM bundles, allowing a whole brain exploration of WM connectivity.

These WM bundles are comprised of the corpus callosum (CC) (rostrum, genu, body, splenium), and bilaterally of the cingulum with two 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 visually assessed. 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 healthy subjects (4.4% of the total sample). These subjects 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 eFigure2.

For each bundle, we extracted the mean GFA using BrainVisa 4.2 (figure 1F). In this paper the terms “bundles” or “tracts” synonymously refer to reconstructed deep WM tracts.

**INSERT FIGURE 1**

2.3 **Statistical analyses**

We used linear mixed models to compare the mean GFA along each bundle between patients with BD and HC. The model included diagnosis (BD/HC) as a factor of interest, gender 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 of GFA value along a tract between patients with BD and HC, we compared in a post-hoc analysis the mean GFA along this tract between patients with a positive history of psychotic features (BD-PF group) and those with no such a history (BD-noPF group).

To check the robustness of the results, we repeated the primary analysis on homogeneous subsamples of patients. We removed patients taking lithium medication [29]and patients with past history of alcohol dependence or abuse from the dataset. 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 HC matched for age, gender and IQ. A medication load score was computed following a method described in [30]. We explored the relationship between GFA and medication load as well as with illness duration by partial correlation analyses controlling for age and gender. Lastly, we checked that adding IQ to the model did not change the results.

Differences between continuous demographic variables were assessed using Student's t-tests and differences between categorical variables using Pearson's chi-squared tests when suitable assumptions were met. Data was analyzed using PASW 18 (Chicago, IL, USA) and R 2.15.1 with Multtest package (www.r-project.org). Statistical tests were considered significant if corrected p values were $< 0.05$ when applying the False Discovery Rate (FDR)[31] method to correct p values for comparisons of GFA along the tracts (26 comparisons) and of sociodemographic data. Model check was performed using residual QQ plots and outliers detection using leaf plots. If detected, analyses were repeated after removing outliers.

## III- Results.

### 3.1 **Clinical sample.**

118 patients and 86 controls were actually included in the analysis (Table 1). Detailed demographic information for each center is provided in eTable 1. Information about history of psychotic features was missing for one patient (0.85%).Concerning mood state, 38 patients

(32.2%) were symptomatic at the time of scanning: 31 patients had HRS-17 >7 (range: 0-32) or MADRS >7 (range: 0-25), 2 had YMRS>7 (range 0-24) and 5 had both.

**INSERT TABLE 1**

3.2 **Comparison between patients with BD and HC.**

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

**INSERT TABLE 2**

3.3 **Comparison between BD-PF and BD-noPF.**

Among the four bundles included for this comparison, BD-PF patients had a significantly lower mean GFA value than BD-noPF patients along the body of the CC (Table 3, Figure 2). This result remains significant after removing identified outliers.

**INSERT FIGURE 2**

**INSERT TABLE 3**

**3.4 Effect of confounding factors on the BD vs HC comparison.**

Results were unchanged when patients with elevated or mixed symptoms (n=7) (eTable 2), patients currently taking lithium (n=39) (eTable3), or with past alcohol abuse/ dependence (n=25) (eTable 4) were removed from the sample. Similarly, we found significant differences of GFA between the 31 depressed patients and the 31 matched HC except along the splenium (eTable 5). We found no correlation nor between the mean GFA and the medication load (eTable 6) nor between mean GFA and the duration of illness (eTable 7). Adding IQ as a covariate did not change the results (eTable 8). When adding bundle volume as a covariate, all results remained significant.

## IV- Discussion.

### 4.1 **Difference of mean GFA between patients and controls.**

This multicenter MRI study compared microstructural properties of 22 WM tracts between BD I patients and HC, using QBI tractography and automatic WM segmentation. Patients with BD had WM alterations along the left cingulum (long fibers), the CC (body and splenium), and the anterior segment of the left arcuate fasciculus. BD-PF patients had lower GFA mean value than BD-noPF patients along the body of CC. To our knowledge this study has the largest recruitment to date of patients with BD in a tractography study. This relatively large sample [32] also allows for the comparison of white matter 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 repeatedly been reported in patients with BD [6,10,34,35], suggesting a relationship between interhemispheric connectivity

abnormalities and BD [36]. In line, we identified a reduced anisotropy along fibers belonging to the body and the splenium of the CC. Interestingly, the patients who experienced psychotic symptoms during mania or depression had lower GFA 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 that bipolar disorder with psychosis could be a biologically relevant subtype of BD. However, the substantial overlaps in white matter abnormalities between BD and schizophrenia prevent us to conclude on the specificity of such difference. Further neuroimaging studies with a dimensional rather than categorical approach of psychosis are needed to understand more-in-depth the role of callosal alterations in the pathogenesis of pychotic 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. Interestingly we found an altered microstructure of the cingulum bundle, formerly reported [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 adds evidence of an anatomical disconnectivity within the cingulum in BD. Former studies reported a decrease of FA along the arcuate fasciculi in patients with BD [6,8] that we specified on the anterior segment of the left arcuate fasciculus. Interestingly, this segment links Broca's area to Geschwind's area and is thought to be involved in memory processing and speech comprehension [43,44]. We found no difference of GFA along this tract between BD-PF and BD-noPF patients in our sample. This does not support the hypothesis of an involvement of the arcuate in hallucinatory or delusional symptoms of patients with BD [8].

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

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

It has been questioned whether mood stabilizers could have an influence in neuroimaging measures. In line with the majority of existing DTI studies [29], we found no relationship between current medication and GFA measures. In order 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 to 31 matched HC, except along the splenium where there was no significant difference. However, interpretation is limited by the possible underpowerment of this comparison.

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 which may have lead to a systematic error. We reduced such potential site effect by sharing hardware, scanning protocol and analysis pipeline across sites.

### 4.2 Strengths and limits of the study.

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

Such advantages are to be balanced against several limitations. We have not explored the inter-rater and inter-sites reliability of the scales used in this study. Despite our effort at harmonization, we have not included a phantom procedure to check the inter-center quality of the acquisitions. We cannot exclude that there was an effect of past medications on our results. Considering the large number of tracts to assess we have not exploited other metrics derived from the ODF. We averaged GFA values along each tract to perform comparisons; very localized decreases of GFA may have been undetected. A common limitation of cross-sectional studies is the inability to determine whether observed alterations precede the onset or develop during the course of the disease. However, our results do not support the hypothesis of a relationship between the duration of the illness and GFA.

## V- Conclusion.

Using whole-brain Q-ball imaging tractography in the first and relatively large international sample of patients with BD and HC, we reported decreased GFA values along interhemispheric tracts, limbic and frontotemporal WM tracts in patients with BD. Patients with psychotic features had lower GFA values than patients without such features along the CC.

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

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Samuel Sarrazin and Josselin Houenou had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

**Conflict of interest disclosures.**

All authors report no competing financial interest to declare.

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Table 1: Demographic and clinical characteristics of patients with bipolar disorder (BD) and healthy controls (HC).

| | **BD** | **HC** | | |
|---|---|---|---|---|
| **Categorical variables** | **N (%)** | **N (%)** | **$\chi^2$** | **FDR p** |
| Number of subjects | 118 (100) | 86 (100) | - | - |
| France | 24 (20.34) | 22 (25.58) | - | - |
| Germany | 41 (34.74) | 38 (44.18) | 4.52 (2) | 0.30 |
| USA | 53 (44.91) | 26 (30.23) | - | - |
| Men | 47 (39.83) | 41 (47.67) | 1.25 (2) | 0.49 |
| Right-handed | 111 (96.52) | 84 (97.67) | 0.78 (2) | 0.81 |
| Positive history of episode with psychotic features | 57 (48.30) | - | - | - |
| Lithium | 39 (33.05) | - | - | - |
| Mood stabilizers other than lithium | 64 (54.24) | - | - | - |
| Antipsychotic | 52 (44.07) | - | - | - |
| Antidepressant | 54 (45.76) | - | - | - |
| **Continuous variables** | **Mean (SD)** | **Mean (SD)** | **t** | **FDR p** |
| Mean age at MRI | 36.32 (10.49) | 37.26 (11.22) | 0.61 (202) | 0.67 |
| NART IQ | 108.86 (10.62) | 107.39 (10.06) | 0.99 (201) | 0.52 |
| Mean YMRS (France, Germany, USA) | 2.58 (3.72) | - | - | - |
| Mean MADRS (France, Germany) | 3.49 (5.37) | - | - | - |
| Mean HRS 17 (USA) | 9.86 (7.87) | - | - | - |
| Mean age at onset | 20.75 (7.97) | - | - | - |

Abbreviations: N, number; SD, standard deviation; FDR p, false discovery rate p value.

Table 2: Comparison of mean GFA between patients with bipolar disorder (BD) and healthy controls (HC).

| | BD (n=118) | HC (n=86) | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Mean GFA (SD) | Mean GFA (SD) | Difference of estimated means | 95% CI | F (DF) | Cohen's f for diagnosis effect | FDR p | Cohen's f for covariates (scanner, sex, age) |
| Interhemispheric bundles | | | | | | | | |
| Corpus callosum | | | | | | | | |
| **Body** | **0.101 (0.004)** | **0.102 (0.004)** | **-0.002** | **[-0.003; -0.001]** | **10.145 (1,198)** | **0.23** | **0.03** | **0.21, 0.03, 0.38** |
| Genu | 0.094 (0.004) | 0.094 (0.004) | -0.001 | [-0.002; $3.18\ 10^{-4}$] | 1.803 (1,198) | 0.09 | 0.37 | 0.36, 0.08, 0.66 |
| **Splenium** | **0.113 (0.005)** | **0.115 (0.005)** | **-0.002** | **[-0.003; -0.001]** | **8.391 (1,198)** | **0.21** | **0.03** | **0.31, 0.003, 0.23** |
| Rostrum | 0.096 (0.006) | 0.096 (0.006) | -0.001 | [-0.002; 0.001] | 0.825 (1,198) | 0.06 | 0.53 | 0.68, 0.002, 0.63 |
| Left hemisphere | | | | | | | | |
| Left arcuate | | | | | | | | |
| Direct segment | 0.086 (0.003) | 0.086 (0.003) | $<10^{-3}$ | [-0.001; 0.001] | 0.832 (1,198) | 0.06 | 0.53 | 0.11, 0.04, 0.38 |
| **Anterior segment** | **0.079 (0.004)** | **0.081 (0.003)** | **-0.001** | **[-0.002; -0.001]** | **8.403 (1,198)** | **0.21** | **0.03** | **0.09, 0.08, 0.39** |
| Posterior segment | 0.075 (0.004) | 0.075 (0.004) | $<10^{-3}$ | [-0.001; 0.001] | 0.538 (1,198) | 0.057 | 0.60 | 0.11, 0.16, 0.35 |
| Left uncinate | 0.078 (0.004) | 0.078 (0.004) | $<10^{-3}$ | [-0.001; 0.001] | 0.122 (1,198) | 0.03 | 0.81 | 0.28, 0.03, 0.33 |
| Left cingulum | | | | | | | | |
| **Long fibers** | **0.090 (0.005)** | **0.092 (0.005)** | **-0.002** | **[-0.003; -0.001]** | **7.645 (1,198)** | **0.20** | **0.04** | **0.05, 0.16, 0.14** |
| Short fibers | 0.075 (0.004) | 0.077 (0.005) | -0.002 | [-0.003; $-2.91\ 10^{-4}$] | 5.969 (1,198) | 0.17 | 0.08 | 0.09, 0.11, 0.21 |

Table 2: Comparison of mean GFA between patients with bipolar disorder (BD) and healthy controls (HC) (continued).

| | BD (n=118) | HC (n=86) | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Mean GFA (SD) | Mean GFA (SD) | Difference of estimated means | 95% CI | F (DF) | Cohen's f for diagnosis effect | FDR p | Cohen's f for covariates (scanner, sex, age) |
| Left inferior longitudinal | 0.087 (0.004) | 0.087 (0.003) | $<10^{-3}$ | [-0.001; 0.001] | 0.041 (1,198) | 0.01 | 0.87 | 0.19, 0.03, 0.21 |
| Left inferior fronto-occipital | 0.095 (0.004) | 0.096 (0.004) | -0.001 | [-0.002; $2.82\ 10^{-4}$] | 2.107 (1,198) | 0.10 | 0.33 | 0.13, 0.08, 0.24 |
| Left frontal thalamic radiations | 0.074 (0.004) | 0.073 (0.004) | 0.001 | [$-2.53\ 10^{-4}$; 0.002] | 2.207 (1,198) | 0.10 | 0.33 | 0.36, 0.28, 0.22 |
| Right hemisphere | | | | | | | | |
| Right arcuate | | | | | | | | |
| Direct segment | 0.083 (0.004) | 0.084 (0.004) | -0.001 | [-0.002; 0.001] | 0.631 (1,189) | 0.05 | 0.58 | 0.20, 0.03, 0.19 |
| Anterior segment | 0.082 (0.003) | 0.082 (0.004) | $<10^{-3}$ | [-0.001; 0.001] | 0.003 (1,198) | 0.004 | 0.96 | 0.05, 0.21, 0.35 |
| Posterior segment | 0.073 (0.004) | 0.074 (0.004) | -0.001 | [-0.002; $-3.19\ 10^{-5}$] | 4.145 (1,198) | 0.15 | 0.16 | 0.03, 0.04, 0.32 |
| Right uncinate | 0.079 (0.003) | 0.080 (0.004) | -0.001 | [-0.002; $1.67\ 10^{-4}$] | 2.584 (1,198) | 0.11 | 0.30 | 0.20, 0.06, 0.36 |
| Right cingulum | | | | | | | | |
| Long fibers | 0.085 (0.006) | 0.086 (0.005) | -0.001 | [-0.003; $-9.85\ 10^{-5}$] | 3.945 (1,198) | 0.14 | 0.16 | 0.15, 0.11, 0.12 |
| Short fibers | 0.074 (0.004) | 0.076 (0.004) | -0.001 | [-0.002; $-9.92\ 10^{-4}$] | 4.588 (1,198) | 0.15 | 0.15 | 0.08, 0.10, 0.11 |
| Right inferior longitudinal | 0.087 (0.004) | 0.087 (0.003) | $<10^{-3}$ | [-0.001; 0.001] | 0.789 (1,198) | 0.06 | 0.53 | 0.22, 0.06, 0.11 |
| Right inferior fronto-occipital | 0.094 (0.004) | 0.095 (0.004) | -0.001 | [-0.002; $4.72\ 10^{-4}$] | 1.138 (1,198) | 0.08 | 0.49 | 0.11, 0.03, 0.32 |
| Right frontal thalamic radiations | 0.074 (0.004) | 0.074 (0.004) | $<10^{-3}$ | [-0.001; 0.001] | 0.039 (1,198) | 0.01 | 0.87 | 0.24, 0.19, 0.17 |

Abbreviations: GFA, generalized fractional anisotropy; FDR p, false discovery rate p value; SD, standard deviation; 95% CI, 95% confidence interval; DF, degrees of freedom. Bold : significant after FDR correction. Effect sizes for diagnosis effect are reported as Cohen's f.

Table 3: Comparison of mean GFA between patients with bipolar disorder and at least one episode with psychotic features (BD-PF) and patients with bipolar disorder and no history of psychotic features (BD-noPF).

| | BD-PF (n=57) | BD-noPF (n=60) | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Mean GFA (SD) | Mean GFA (SD) | Difference of estimated means | 95% CI | F (DF) | Cohen's f for diagnosis effect | FDR p | Cohen's f for covariates (scanner, sex, age) |
| Interhemispheric bundles | | | | | | | | |
| **Corpus callosum, body** | **0.100 (0.004)** | **0.101 (0.003)** | **-0.002** | **[-0.003;-0.001]** | **8.902 (1,111)** | **0.27** | **0.03** | **0.27, 0.003, 0.46** |
| Corpus callosum, splenium | 0.113 (0.006) | 0.113 (0.004) | -0.001 | [-3.68; 4.825 $10^{-4}$] | 2.485 (1,111) | 0.15 | 0.30 | 0.34, 0.04, 0.27 |
| | | | | | | | | |
| Left side | | | | | | | | |
| Left arcuate, anterior segment | 0.080 (0.003) | 0.079 (0.003) | -0.001 | [-0.002;0.001] | 1.158 (1,111) | 0.12 | 0.49 | 0.14, 0.005, 0.35 |
| Left cingulum, long fibers | 0.089 (0.005) | 0.089 (0.004) | $<10^{-3}$ | [-0.002; 0.002] | 0.046 (1,111) | 0.02 | 0.81 | 0.11, 0.04, 0.17 |

Abbreviations: GFA, generalized fractional anisotropy; FDR p, false discovery rate p value; SD, standard deviation; 95% CI, 95% confidence interval; DF, degrees of freedom; F, F value. Bold: significant after FDR correction. Effect sizes for diagnosis effect are reported as Cohen's f.

Figure 1: Illustration of the processing pipeline.

(A) Tractography mask. (B) Whole brain tractography. (C) Segmentation based on fiber lengths. Colors represent different fiber length. (D) Centroid tracts calculated from each fascicle. (E) Final segmented bundles of the left hemisphere and of the interhemispheric region. (F) Extraction of the mean GFA along the left inferior longitudinal fasciculus.

Figure 2 : Mean GFA along the body of the corpus callosum for patients and controls.

Individual values of generalized fractional anisotropy (GFA) along the body of the corpus callosum for patients with BD (BD), with (BD-PF) or without (BD-noPF) positive history of psychotic features and healthy controls (HC). * $p<0.05$ corrected for multiple testing.

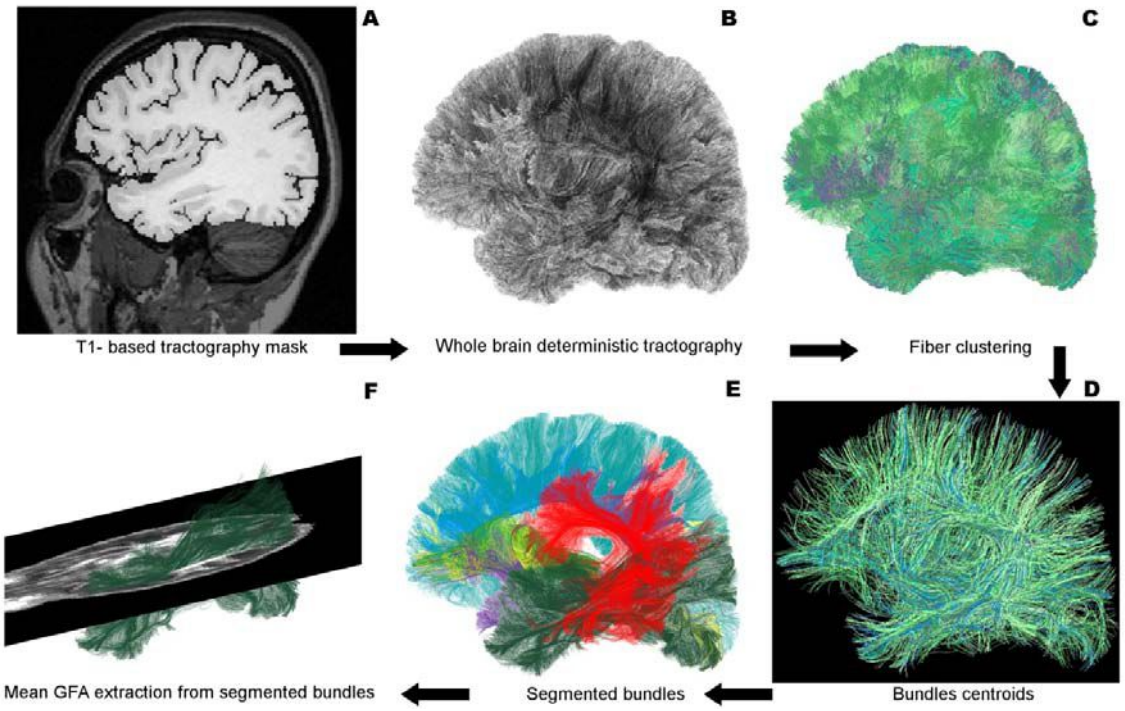


Figure 1: Illustration of the processing pipeline.

(A) Tractography mask. (B) Whole brain tractography. (C) Segmentation based on fibers lengths. Colors represent different fibers length. (D) Centroids tracts calculated from each fascicle. (E) Final segmented bundles of the left hemisphere and of the interhemispheric region. (F) Extraction of the mean GFA along the left inferior longitudinal fasciculus.

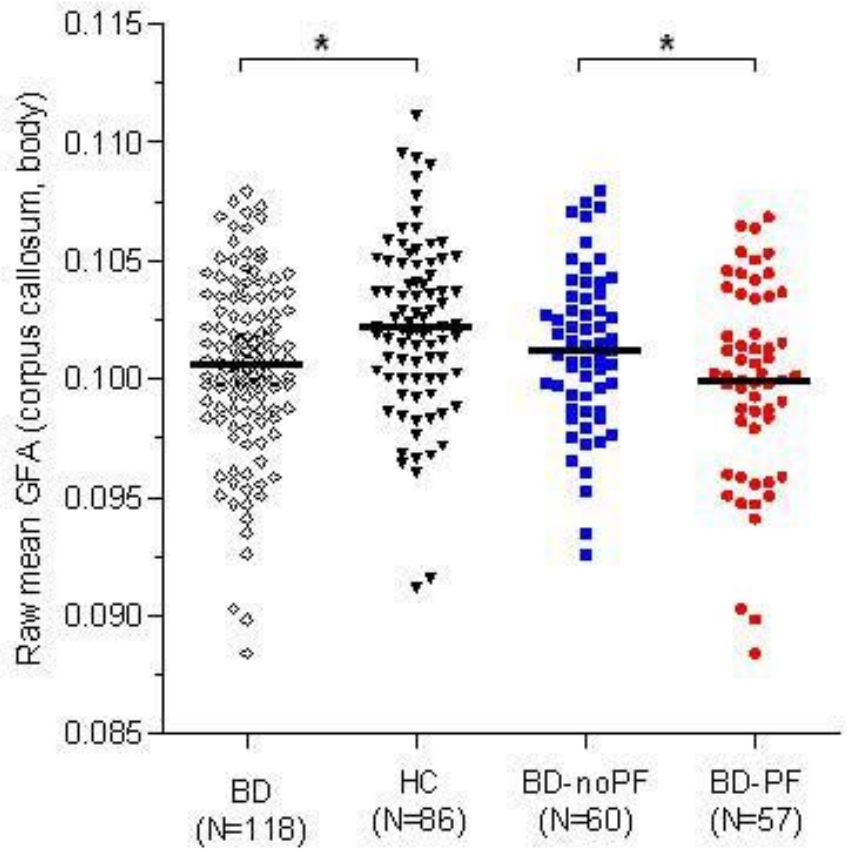


Figure 2 : Mean GFA along the body of the corpus callosum for patients and controls.

Individual values of generalized fractional anisotropy (GFA) along the body of the corpus callosum for patients with BD (BD), with (BD-PF) or without (BD-noPF) positive history of psychotic features and healthy controls (HC). * $p<0.05$ corrected for multiple testing.