

# A Voxel-Based Diffusion Tensor Imaging Study of White Matter in Bipolar Disorder

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There is evidence from post-mortem and magnetic resonance imaging studies that hyperintensities, oligodendroglial abnormalities, and gross white matter volumetric alterations are involved in the pathophysiology of bipolar disorder. There is also functional imaging evidence for a defect in frontal cortico-subcortical pathways in bipolar disorder, but the white matter comprising these pathways has not been well investigated. Few studies have investigated white matter integrity in patients with bipolar disorder compared to healthy volunteers and the majority of studies have used manual region-of-interest approaches. In this study, we compared fractional anisotropy (FA) values between 30 patients with bipolar disorder and 38 healthy volunteers in the brain white matter using a voxelwise analysis following intersubject registration to Talairach space. Compared to healthy volunteers, patients demonstrated significantly ( $p < 0.001$ ; cluster size  $\geq 50$ ) higher FA within the right and left frontal white matter and lower FA within the left cerebellar white matter. Examination of individual eigenvalues indicated that group differences in both axial diffusivity and radial diffusivity contributed to abnormal FA within these regions. Tractography was performed in template space on averaged diffusion tensor imaging data from all individuals. Extraction of bundles passing through the clusters that differed significantly between groups suggested that white matter abnormalities along the pontine crossing tract, corticospinal/corticopontine tracts, and thalamic radiation fibers may be involved in the pathogenesis of bipolar disorder. Our findings are consistent with models of bipolar disorder that implicate dysregulation of cortico-subcortical and cerebellar regions in the disorder and may have relevance for phenomenology.

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## INTRODUCTION

There is increasing evidence that white matter dysfunction may be an important consideration in the pathophysiology of bipolar disorder. Several studies reported white matter hyperintensities (WMH) in bipolar disorder (eg Aylward *et al*, 1994; Ahn *et al*, 2004), which appear to be one of the most robust and consistent neuroimaging findings in the literature (Norris *et al*, 1997; Stoll *et al*, 2000). More severe WMH have been linked to a greater number of hospitalizations and poorer treatment response (Moore *et al*, 2001). The presence of WMH may be indicative of an interruption in white matter fibers (eg Soares and Mann, 1997; Taylor

*et al*, 2001), and/or an indication of early localized demyelination (Hajek *et al*, 2005).

Post-mortem and magnetic resonance imaging (MRI) studies have provided additional evidence for white matter abnormalities in the pathogenesis of bipolar disorder. In particular, altered expression of oligodendrocyte and myelin genes (Tkachev *et al*, 2003) and a lower density of oligodendroglial (Uranova *et al*, 2004) and glial (Rajkowska *et al*, 2001) cells have been reported in the prefrontal cortex of patients compared to healthy volunteers. MRI studies reported less left hemisphere (Kieseppa *et al*, 2003) and whole-brain (Strakowski *et al*, 1993; Davis *et al*, 2004) white matter volume in patients compared to healthy volunteers. Few studies have investigated regional differences in white matter using MRI, although Bruno *et al* (2004) identified lower white matter density in frontostriatal regions in bipolar patients compared to healthy volunteers using voxel-based morphometry.

A potentially more sensitive technique for the assessment of white matter integrity in bipolar disorder is the use of

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diffusion tensor imaging (DTI), which provides quantitative information regarding tissue water mobility. Fractional anisotropy (FA) is a measure of the coherence of white matter fibers derived from DTI, with higher FA potentially indicative of greater coherence. To date, few DTI studies have investigated the brain white matter in bipolar disorder. Furthermore, the majority of studies included small sample sizes and used a manual region-of-interest approach whose definitions may be potentially unreliable. In addition, findings have been inconsistent with reports of lower (Adler *et al*, 2004, 2006; Frazier *et al*, 2007; Bruno *et al*, 2008), higher (Yurgelun-Todd *et al*, 2007; Haznedar *et al*, 2005), or no differences (Beyer *et al*, 2005) in anisotropy between patients with bipolar disorder and healthy volunteers. A prior study that used tractography reported a significantly increased number of reconstructed fibers between the left subgenual cingulate and left amygdalo-hippocampal (AH) complex in patients with bipolar disorder compared to healthy volunteers without associated group differences in FA in the reconstructed fiber tract (Houenou *et al*, 2007).

Some studies suggest that it may be possible to examine the individual eigenvalues of the diffusion tensor to determine whether FA changes are associated with axial ( $\lambda_1$ ) or radial ( $\lambda_2$  and  $\lambda_3$ ) white matter integrity (Song *et al*, 2002, 2005). Specifically, axial diffusivity ( $\lambda_1$ ) is defined by how much diffusion occurs parallel to a given white matter tract whereas radial diffusivity ( $(\lambda_2 + \lambda_3)/2$ ) represents diffusion of water molecules perpendicular to the white matter tract. Previous work by Song *et al* (2002) demonstrated that white matter radial diffusivity was increased in shiverer mice with a dysmyelinated CNS, suggesting increased water mobility perpendicular to axons due to the lack of myelin sheath. In contrast, axial diffusivity was not affected in these animals suggesting intact axonal integrity. These findings were confirmed using electron microscopy. In addition, the extent of increased radial diffusivity reflected the severity of demyelination and following remyelination there was a concomitant decrease in radial diffusivity (Song *et al*, 2005). The investigation of axial and radial diffusivity could have implications for axonal and myelin-related pathologies, respectively and thus, may have relevance for better understanding FA alterations in the pathogenesis of bipolar disorder.

In this study we analyzed FA and axial/radial diffusivity data in a large cohort of patients with bipolar disorder and age- and sex-matched healthy volunteers using a voxelwise analysis. A potentially important advantage of a voxel-based approach is that abnormalities may be identified across the entire brain and with greater reliability compared to region-of-interest approaches. Some evidence suggests that white matter pathways connecting frontal cortical and subcortical structures, which are involved in mood regulation, may be disrupted in patients with bipolar disorder (Strakowski *et al*, 2005b). This disturbance may involve compromised bundle coherence in white matter connections subserving frontal areas, and/or a possible alteration in the myelination of these connective tracts. On the basis of this prior work, we hypothesized that FA would differ between groups in the frontal white matter and in the white matter surrounding subcortical areas. We further analyzed axial and radial diffusivity to ascertain whether FA differences might be

associated with abnormalities in either axonal or myelin-related integrity, respectively.

## MATERIALS AND METHODS

### Subjects

A total of 30 patients with bipolar disorder were recruited from The Zucker Hillside Hospital in Glen Oaks, NY. Diagnoses were based on clinical interview using the SCID for DSM-IV disorders (First *et al*, 1994) and supplemented by medical records and information provided by clinicians and family members, when available. All diagnoses were confirmed through a consensus conference involving psychologists and psychiatrists. The majority of patients had a diagnosis of Bipolar I Disorder ( $n = 25$ ), whereas the remaining patients were diagnosed with either Bipolar II Disorder ( $n = 2$ ), or Bipolar Disorder Not Otherwise Specified (NOS,  $n = 3$ ). All patients were being treated with antipsychotic medications and/or mood stabilizers. Eleven patients had a history of drug use (sedative abuse,  $n = 1$ ; sedative dependence,  $n = 2$ ; alcohol abuse,  $n = 5$ ; alcohol dependence,  $n = 3$ ; cannabis abuse,  $n = 3$ ; cannabis dependence,  $n = 6$ ; cocaine abuse,  $n = 3$ ; cocaine dependence,  $n = 2$ ; amphetamine abuse,  $n = 1$ ; amphetamine dependence,  $n = 2$ ). A total of 38 healthy comparison subjects were recruited from the community through advertisements in local papers and word of mouth. Exclusion criteria for all study participants included any serious medical or neurological condition known to affect the brain. Exclusion criteria for healthy subjects also included any history of Axis I psychiatric illness as assessed by clinical interview (SCID-NP; First *et al*, 2001) or in first-degree relatives. This study was approved by the North Shore—Long Island Jewish Medical Center Institutional Review Board and written informed consent was obtained from all study participants.

### Handedness

Handedness for all participants was assessed using a modified, 20-item version of the Edinburgh Inventory. A laterality quotient was computed for each participant according to the following formula:  $(\text{Total R} - \text{Total L}) / (\text{Total R} + \text{Total L})$ , where Total R and Total L refer to the total number of right- and left-hand items scored, respectively. Laterality quotients derived from this formula ranged from +1.00 (totally dextral) to -1.00 (totally nondextral). A laterality quotient of 0.70 or greater indicated a dextral classification for the subject, whereas subjects with a laterality quotient below 0.70 were classified as nondextral.

### Magnetic Resonance Imaging Procedures

Magnetic resonance imaging examinations were conducted at the Long Island Jewish Medical Center on a GE 1.5 T system. A total of 26 DTI volumes were obtained from each subject that included 25 volumes with diffusion gradients applied along 25 nonparallel directions with  $b = 1000 \text{ s/mm}^2$  and NEX = 2, and one volume without diffusion weighting ( $b = 0$ ; NEX = 2). Each volume consisted of 23 contiguous

5-mm axial slices acquired parallel to the anterior-posterior (AC-PC) commissural line using a ramp sampled, spin-echo, single-shot echo-planar imaging (EPI) method (TR = 10 s, TE = minimum ms, FOV = 22 cm, matrix size = 128 × 128).

To provide a high-resolution anatomical reference, 124 contiguous coronal images (slice thickness = 1.5 mm) were acquired through the whole head using a three-dimensional Fast SPGR sequence with IR Prep (TR = 10.1 ms, TE = 4.3 ms, TI = 600 ms, FOV = 22 cm, matrix size = 256 × 256) producing nominal in-plane resolution of 0.86 × 0.86 mm<sup>2</sup>. In addition, an oblique axial fast spin-echo scan (TR = 4 s, TE = 20/100 ms, FOV = 22 cm, matrix size = 256 × 256) was acquired at the same slice positions as the diffusion tensor images and provided contiguous 5-mm thick proton density (PD) and T2-weighted (T2) images. The fast spin-echo PD and T2 volumes were used for registration, distortion correction of diffusion images, and for image segmentation.

### Image Processing

Image processing was conducted using previously published methods (Szeszko *et al*, 2005a, b, 2008). Briefly, nonbrain regions were removed from the SPGR images using the Brain Extraction Tool (Smith, 2002). Any nonbrain tissue that remained following the automatic brain extraction process was removed manually using MEDx (Sensor Systems Inc., MD, USA). The cropped SPGR images of all subjects were spatially normalized to the Montreal Neurologic Institute's 'Colin27' MRI volume (Holmes *et al*, 1998) using the nonlinear registration module of the Automatic Registration Toolbox (ART; Ardekani *et al*, 2005). For each subject, the SPGR volume was also registered to their fast spin-echo PD/T2 volumes using ART by a rigid-body six-parameter linear transformation (Ardekani *et al*, 1995). To correct for the spatial distortion in the DTI EPI images, the  $b = 0$  DTI volume was registered to the T2 volume using ART. Finally, we registered the FA, axial, and radial images to the stereotactic space of the 'Colin27' template by mathematically combining and applying the operations obtained from the three registration steps: (1) nonlinear within-subject mapping of the  $b = 0$  DTI volume to the T2 volume for distortion correction; (2) six-parameter linear within-subject mapping of the T2 to SPGR volume; and (3) nonlinear between-subject mapping of the SPGR volume to the 'Colin27' reference volume. The accuracy of the registration algorithm used in this study has been demonstrated empirically to be superior to several others in reducing intersubject anatomical variability (Ardekani *et al*, 2005).

For each subject, we created a white matter mask in stereotactic space as follows. Using the six-parameter linear transformation obtained from the registration process, we resliced the cropped SPGR volume to the same orientation, voxel size, and matrix size as the PD/T2 volumes. First, the resliced cropped SPGR volumes were used as masks to delete the nonbrain regions from the PD and T2 volumes. Second, the resulting image sets (ie the cropped T2, PD, and resliced SPGR volumes) were used as three input channels to the FAST segmentation program (Zhang *et al*, 2001) to segment the brain into white matter, gray matter, and CSF. All individuals' white matter masks were then transformed to standard space using the above registration approach (minus

the distortion correction step), averaged, and conservatively thresholded at 70% to obtain a white matter mask for the entire group. Voxelwise statistical analyses were confined to the voxels comprising this white matter mask.

For each subject an FA map was computed from the 26 DTI volumes following estimation of the diffusion tensor matrix and its eigenvalues for each voxel using methods described previously (Basser, 1995). The diffusion tensor and FA maps were computed in the original native coordinates of the acquired images before any registration operations were applied to the scalar values. The FA map of each subject was transformed into the standard 'Colin27' space as described above. There is evidence that the choice for a smoothing kernel size can influence study findings (Jones *et al*, 2005). It is difficult, however, to select unambiguously the size of the smoothing kernel in the absence of *a priori* information about the spatial dimensions of the effects of interest that may vary from one region to another. In the present study, we prospectively selected the smoothing kernel size to be approximately twice the spacing between voxels and for consistency with a prior study by our group (Szeszko *et al*, 2005a). Thus, both the registered FA and white matter images were smoothed with a three-dimensional isotropic Gaussian kernel of FWHM = 3 mm.

### Statistical Analyses

Group differences in demographic variables were examined using independent groups *t*-tests or  $\chi^2$ -tests. FA values between groups were compared using voxelwise analysis of covariance with white-matter density (obtained from the segmentation process described above) and age as statistical covariates. FA values between patients and controls were considered significantly different at a given voxel if the null hypothesis in a two-tailed *t*-test was rejected at  $p < 0.001$  (Szeszko *et al*, 2005a, 2008). As a measure of false alarm rate, we estimated the false discovery rate (FDR) for the applied *p*-value threshold of 0.001 to be  $q < 0.015$  using the 'FDR' program of the FSL package with the conservative option, which estimates the FDR using the method of Benjamini and Hochberg (1995). As a further protection against multiple comparisons, significantly different FA values (corresponding to a *p*-value of 0.001 or less) were required to be part of a spatially contiguous cluster size of 50 voxels or greater. To confirm selected significant voxelwise findings (ie those that approximated the shape of a circle) circular regions of interest were placed on the raw FA maps in areas that differed significantly between groups and compared in SPSS using independent groups *t*-tests. To investigate the potential effects of substance use and the inclusion of Bipolar II and Bipolar NOS patients on the observed findings we performed several ancillary analyses in SPSS (version 11.5) after importing average FA values that differed significantly between groups from the voxelwise analysis. Specifically, patients without a substance use diagnosis ( $N = 19$ ) and patients with a Bipolar I diagnosis ( $N = 25$ ) were compared to all healthy volunteers, respectively. An additional analysis compared FA data between Caucasian patients ( $N = 18$ ) and Caucasian healthy volunteers ( $N = 15$ ); the only racial subgroup large enough for analysis. In these ancillary analyses FA was compared between groups using independent groups *t*-tests.

**Table 1** Sample Characteristics

|                                    | Bipolar patients (N = 30) | Healthy volunteers (N = 38) | d.f. | Test statistics | p-value |
|------------------------------------|---------------------------|-----------------------------|------|-----------------|---------|
| Age                                | 33.4 (8.7)                | 31.9 (8.6)                  | 66   | $t = 0.74$      | NS      |
| Sex (M/F)                          | 15/15                     | 22/16                       | 1    | $\chi^2 = 0.42$ | NS      |
| Parental social class <sup>a</sup> | 2.8 (1.1)                 | 2.6 (0.86)                  | 1    | $t = 0.88$      | NS      |
| Laterality quotient                | 0.79 (0.39)               | 0.75 (0.59)                 | 63   | $t = 0.34$      | NS      |
| Race <sup>b</sup>                  | 18, 5, 2, 4, 1            | 15, 14, 2, 6, 1             | 2    | $\chi^2 = 3.90$ | NS      |
| Years of education                 | 14.6 (2.2)                | 15.5 (2.0)                  | 64   | $t = -1.62$     | NS      |

Note. Data are presented as mean  $\pm$  SD in parentheses, unless otherwise indicated. There were data missing for the following variables: parental social class (1 patient), laterality quotient (2 patients, 1 healthy volunteer), and years of education (2 patients).

<sup>a</sup>Hollingshead Redlich Scale rated on a scale from 1 (highest) to 5 (lowest).

<sup>b</sup>Race coded as Caucasian, African American, Hispanic, Asian, and other. Because more than 20% of the categories for race had expected frequencies of less than 5 we combined the latter three groups (ie Hispanic, Asian, and other) into a single group for analysis.

In addition, radial, and axial diffusivity values for clusters that differed significantly between groups from the voxel-wise analysis were imported into SPSS (version 11.5) for further analyses. Independent groups *t*-tests were used to compare patients and healthy volunteers in axial and radial diffusivity values for these clusters. Repeated-measures analysis of variance was used to investigate whether FA differences between groups could be attributed to *specific* abnormalities in axial or radial diffusivity. In these analyses, which were conducted separately for each FA cluster that differed significantly between groups, diffusivity (axial and radial) served as a within-subjects factor and group was the between-subjects factor. We also investigated whether FA along the length of extracted white matter tracts differed between groups using independent groups *t*-tests. In analyses investigating axial and radial diffusivity and FA along white matter tracts  $\alpha$  was set to 0.01 (two tailed) to limit the possibility of a Type-I error.

### Tractography Procedures

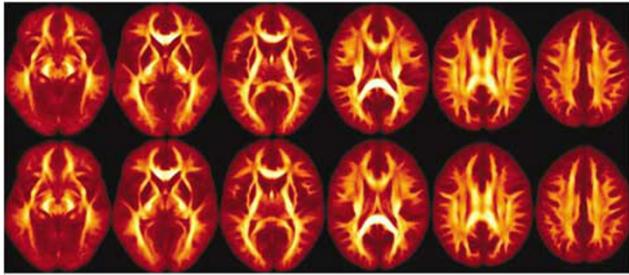
We used DTIStudio to perform tractography as described previously (Ashtari *et al*, 2007), which is based on the fiber assignment by continuous tracking method. A more detailed description regarding this program is provided elsewhere (Jiang *et al*, 2006). We used a threshold of 0.25 for FA values to perform tractography and discontinued tracking if the tract turning angle exceeded 0.70. We imported the clusters identified as significantly different between groups into the DTIStudio software program to extract and identify the white matter fibers that passed through them. Tractography was performed in template space on averaged DTI data from all individuals.

DTIStudio requires both a scalar field representing FA and a vector field representing the principal eigenvector of the diffusion tensor and thus, the average FA and principal eigenvector for all subjects were identified. Using the registration procedure described here and in our earlier work (Szeszko *et al*, 2005a,b, 2008) we obtained a deformation field for each subject that could be used for spatial normalization of the individual's DTI images to Talairach space. This deformation field is a vector-valued function and maps the coordinates of any given grid point in standardized space to its corresponding point in the

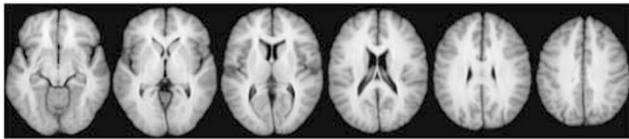
individual's original DTI image space (Ardekani *et al*, 2005). To obtain the group-averaged FA image in Talairach space, we applied the deformation field of each subject to the FA image and computed the average of all spatially normalized FA images to yield the average FA in Talairach space for the group. The principal eigenvector field for the group was obtained by first computing the Jacobian matrix (Kaplan, 2003) of the deformation field at each grid point on the standardized space for all individuals. The eigenvector in each subject's original DTI image space that would be mapped to the particular grid point in the standardized space was then reoriented by premultiplying it with the computed Jacobian (Alexander *et al*, 2001). Reorientation of the principal eigenvector was completed for all individuals at all grid points in standardized space. Thus, at each grid point we obtained as many (reoriented) eigenvectors as there were individuals in the study. Lastly, for each grid point, a principal component analysis (Kent *et al*, 1980) was performed on the reoriented eigenvectors. The principal eigenvector of this analysis was then taken to represent the principal direction of water diffusion for the entire group of subjects at the grid point in question.

### RESULTS

Patients did not differ significantly from healthy volunteers in distributions of age, sex, parental social class, handedness, race, or years of education (Table 1). An illustration of the intersubject registration of the FA maps for patients and healthy volunteers is provided in Figure 1 and the average SPGR images are provided in Figure 2. Voxelwise analysis of the white matter revealed three regions of higher FA in the right and left frontal white matter and one region of lower FA in the left cerebellum in bipolar patients compared to healthy volunteers (Table 2; Figure 3). Circular regions of interest placed on the raw FA maps in the left ( $t = 2.43$ , d.f. = 66,  $p = 0.02$ ) and right ( $t = 1.94$ , d.f. = 66,  $p = 0.06$ ) frontal white matter (corresponding approximately to clusters 2 and 3, respectively) supported the voxelwise results. Independent group *t*-tests revealed significant group differences in radial diffusivity in clusters 1–3 and axial diffusivity in clusters 1 and 4 (Tables 3 and 4). Effect sizes for group differences in axial and radial diffusivity



**Figure 1** Average fractional anisotropy (FA) maps for patients (top row) and healthy controls (bottom row). Images from left to right correspond to  $-5$  mm below the anterior-posterior (AC-PC) plane and 5, 15, 25, 35, and 45 mm above the AC-PC plane.



**Figure 2** Average SPGR images corresponding to  $-5$  mm below the anterior-posterior (AC-PC) plane and 5, 15, 25, 35, and 45 mm above the AC-PC plane.

ranged from 3 to 18%. Repeated-measures analysis of variance for axial and radial diffusivity measures revealed no significant group-by-region interaction for any of the four FA clusters that differed significantly between groups.

Two-dimensional images illustrating fibers passing through clusters 1–4 superimposed onto the color-coded average FA map are provided in Figure 4. Three-dimensional images illustrating fibers passing through these clusters are superimposed onto the average FA map in Figure 5. White matter passing through cluster 1 where FA was lower in patients compared to healthy volunteers appears to correspond to fibers of the pontine crossing tract. The white matter passing through clusters 2 and 3, where FA was higher in patients compared to healthy volunteers, appears to encompass fibers of the corticopontine tract (CPT), corticospinal tract (CST), and superior thalamic radiation fibers. Finally, white matter passing through cluster 4 appears to correspond to fibers of the superior longitudinal fasciculus (SLF). Visual inspection of fiber tracts indicates convergence of white matter from clusters 1–3 in the vicinity of the pontine crossing tract.

Average FA along the four sets of extracted white matter bundles was computed separately for patients and healthy volunteers. White matter FA along fibers of the pontine crossing tract (extracted from cluster 1) had significantly lower mean FA in patients compared to healthy volunteers along its length ( $t = -3.32$ , d.f. = 66,  $p = 0.001$ ). In addition, FA along fibers of the CST and CPT and thalamic radiation fibers extracted from cluster 2 was significantly higher in patients compared to healthy volunteers ( $t = 3.21$ , d.f. = 66,  $p = 0.002$ ), but did not differ significantly between groups for fibers extracted from cluster 3 ( $t = 1.38$ , d.f. = 66,  $p = 0.172$ ). Lastly, white matter FA (extracted from cluster 4) along fibers of the SLF did not differ significantly between groups ( $t = 2.01$ , d.f. = 66,  $p = 0.048$ ) following correction for multiple comparisons.

Ancillary analyses investigated the potential effects of substance use, having a diagnosis other than Bipolar I and race on the observed FA findings. Patients without a substance use diagnosis ( $N = 19$ ) had significantly higher FA in the two right ( $t = 5.06$ , d.f. = 55,  $p < 0.001$  and  $t = 4.17$ , d.f. = 55,  $p < 0.001$ ) and one left ( $t = 3.02$ , d.f. = 55,  $p = 0.004$ ) frontal white matter regions as well as lower FA in the left cerebellum ( $t = -3.30$ , d.f. = 55,  $p = 0.002$ ) compared to healthy volunteers. Patients with a diagnosis of Bipolar I Disorder ( $N = 25$ ) had significantly higher FA in the two right ( $t = 5.27$ , d.f. = 61,  $p < 0.001$  and  $t = 4.42$ , d.f. = 61,  $p < 0.001$ ) and one left ( $t = 4.38$ , d.f. = 61,  $p < 0.001$ ) frontal white matter regions as well as lower FA in the left cerebellum ( $t = -4.04$ , d.f. = 61,  $p < 0.001$ ) compared to healthy volunteers. In addition, restricting analyses to the subgroup of Caucasian subjects ( $N = 33$ ) revealed significantly higher FA in the two right ( $t = 4.00$ , d.f. = 31,  $p < 0.001$  and  $t = 5.79$ , d.f. = 31,  $p < 0.001$ ) and one left ( $t = 3.28$ , d.f. = 31,  $p = 0.003$ ) frontal white matter regions as well as lower FA in the left cerebellum ( $t = -2.51$ , d.f. = 31,  $p = 0.018$ ) in patients compared to healthy volunteers.

## DISCUSSION

These findings suggest that compared to healthy volunteers, adult patients with bipolar disorder have higher FA in the bilateral frontal white matter corresponding approximately to fibers of the CPT/CST and SLF as well as superior thalamic radiation fibers. In addition, FA was lower in the left cerebellar white matter, corresponding approximately to the pontine crossing tract, in patients compared to healthy volunteers. Although we found evidence for higher axial and lower radial diffusivity in regions of FA that differed significantly between groups, we did not find any evidence that group differences were associated with a specific deficit in either measure suggesting that both may contribute to white matter disturbances in bipolar disorder. The use of fiber tractography indicated that FA was significantly different in patients compared to healthy volunteers along the length of extracted white matter bundles comprising CPT and CST, thalamic radiation fibers as well as the pontine crossing tract. Moreover, convergence of fibers from the right and left frontal white matter along with those of the cerebellar region occurred in the pons, suggesting that an integrated network involving the cerebellum, striatum, and frontal cortex may be involved in the pathogenesis of bipolar disorder.

Few studies have assessed white matter integrity in bipolar disorder, especially using a voxelwise approach and thus, our findings are difficult to compare with prior work. Our findings converge with Haznedar *et al* (2005) who reported greater relative anisotropy in 40 patients with bipolar spectrum illnesses compared to 36 sex- and age-matched healthy volunteers in the anterior frontal white matter using a region-of-interest approach. Yurgelun-Todd *et al* (2007) reported that 11 bipolar patients had significantly higher FA in the midline of the genu compared with 10 healthy controls. In contrast, Adler and colleagues reported lower FA in the superior frontal white matter using a region-of-interest approach in 11 medication-naïve adolescent (Adler *et al*,

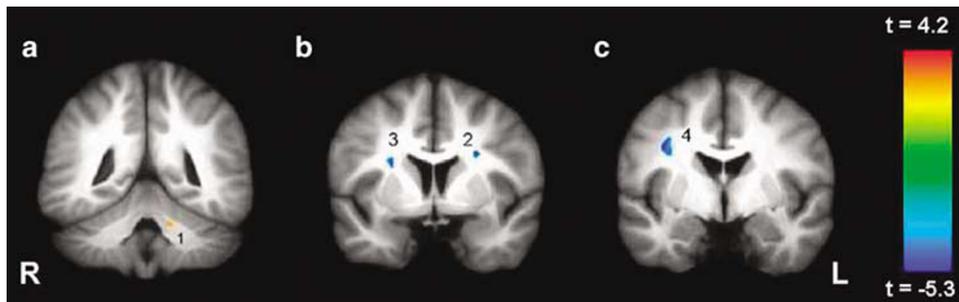
**Table 2** Mean Fractional Anisotropy Values for Patients and Healthy Volunteers

| Brain region            | Bipolar patients<br>(N = 30) | Healthy volunteers<br>(N = 38) | Talairach coordinates <sup>a</sup> (centroid) |     |     | Cluster size <sup>b</sup> |
|-------------------------|------------------------------|--------------------------------|---|-----|-----|---------------------------|
|                         |                              |                                | X   | Y   | Z   |                           |
| <i>Left hemisphere</i>  |                              |                                |   |     |     |                           |
| Cluster 1               | 283.15 (47.85)               | 337.90 (55.95)                 | -14   | -43 | -21 | 50                        |
| Cluster 2               | 338.36 (39.48)               | 300.90 (32.87)                 | -24   | 3   | 24  | 83                        |
| <i>Right hemisphere</i> |                              |                                |   |     |     |                           |
| Cluster 3               | 278.07 (31.80)               | 240.08 (27.09)                 | 24  | 4   | 20  | 126                       |
| Cluster 4               | 267.15 (34.65)               | 227.49 (29.40)                 | 34  | -3  | 29  | 191                       |

Note. Data are presented as mean  $\pm$  SD in parentheses. Fractional anisotropy values are multiplied by a factor of 1000.

<sup>a</sup>Talairach coordinates represent the centroid of the region.

<sup>b</sup>Cluster size is reported as number of voxels.



**Figure 3** White matter regions where fractional anisotropy (FA) was significantly ( $p < 0.001$ ; 50 voxels) different in patients compared to healthy volunteers. A description of these regions can be found in the text and in Table 2.

Note: images are in radiologic convention.

**Table 3** Mean Radial Diffusivity Values<sup>a</sup> for FA Clusters that Differed Between Patients and Healthy Volunteers

| Brain region            | Bipolar patients<br>(N = 30) | Healthy volunteers<br>(N = 38) | Test statistics | d.f. | p-value | Effect size <sup>b</sup> |
|-------------------------|------------------------------|--------------------------------|-----------------|------|---------|--------------------------|
| <i>Left hemisphere</i>  |                              |                                |                 |      |         |                          |
| Cluster 1               | 2716.81 (169.20)             | 2570.39 (203.43)               | $t = 3.17$      | 66   | 0.002   | 0.132                    |
| Cluster 2               | 2771.41 (129.54)             | 2898.41 (184.02)               | $t = -3.20$     | 66   | 0.002   | 0.135                    |
| <i>Right hemisphere</i> |                              |                                |                 |      |         |                          |
| Cluster 3               | 2818.31 (124.22)             | 2943.17 (147.42)               | $t = -3.71$     | 66   | <0.001  | 0.173                    |
| Cluster 4               | 2861.63 (109.96)             | 2938.80 (135.12)               | $t = -2.53$     | 66   | 0.014   | 0.089                    |

Note. Data are presented as mean  $\pm$  SD in parentheses.

<sup>a</sup>Values are in units of  $\mu\text{m}^2/\text{s}$ .

<sup>b</sup>Effect size = partial  $\eta^2$ .

2006) and 9 previously treated adult (Adler *et al*, 2004) patients with bipolar disorder compared to healthy volunteers. Beyer *et al* (2005) did not find any group differences in FA between 14 patients with bipolar disorder compared to 21 healthy individuals in the superior frontal, middle frontal, and inferior frontal white matter using a region-of-interest approach. In a voxelwise analysis of DTI data, Bruno *et al*

(2008) found a region of lower FA near the junction of the middle temporal and inferior gyri. Frazier *et al* (2007) reported that children with and at-risk for bipolar disorder have lower FA along the SLF compared to healthy controls, and that children with the disorder showed reduced FA in the cingulate-paracingulate white matter compared to both the at-risk and healthy control groups. Different findings among

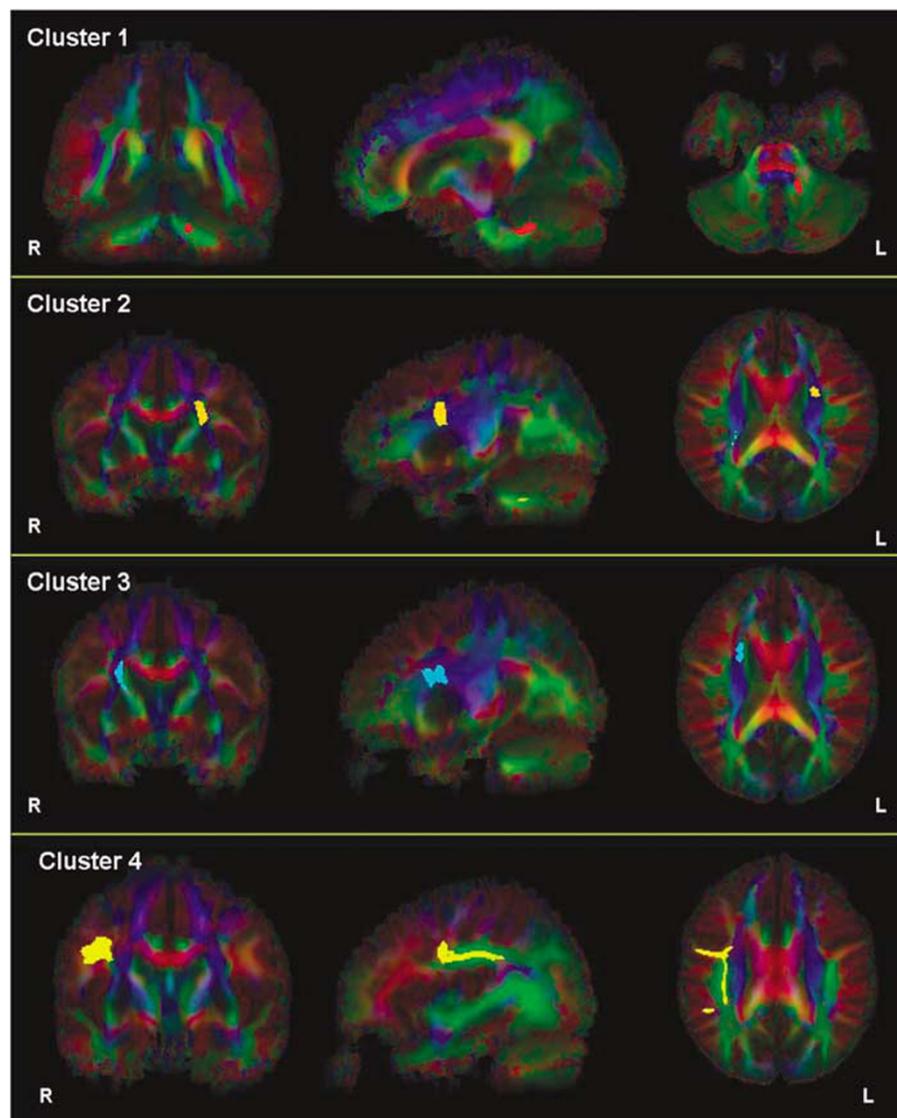
**Table 4** Mean Axial Diffusivity Values<sup>a</sup> for FA Clusters that Differed Between Patients and Healthy Volunteers

| Brain region            | Patients<br>(N = 30) | Healthy volunteers<br>(N = 38) | Test statistics | d.f. | p-value | Effect size <sup>b</sup> |
|-------------------------|----------------------|--------------------------------|-----------------|------|---------|--------------------------|
| <i>Left hemisphere</i>  |                      |                                |                 |      |         |                          |
| Cluster 1               | 4279.51 (262.12)     | 4470.48 (290.18)               | $t = -2.81$     | 66   | 0.007   | 0.107                    |
| Cluster 2               | 4746.60 (230.53)     | 4630.00 (249.46)               | $t = 1.98$      | 66   | 0.052   | 0.056                    |
| <i>Right hemisphere</i> |                      |                                |                 |      |         |                          |
| Cluster 3               | 4324.71 (176.95)     | 4244.93 (241.16)               | $t = 1.52$      | 66   | 0.134   | 0.034                    |
| Cluster 4               | 4229.08 (149.54)     | 4056.30 (207.18)               | $t = 3.84$      | 66   | <0.001  | 0.183                    |

Note. Data are presented as mean  $\pm$  SD in parentheses.

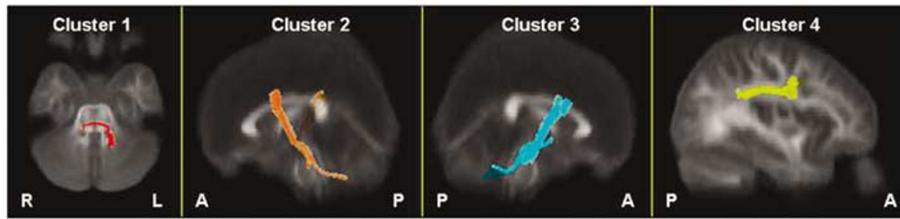
<sup>a</sup>Values are in units of  $\mu\text{m}^2/\text{s}$ .

<sup>b</sup>Effect size = partial  $\eta^2$ .



**Figure 4** 2D images illustrating fibers passing through clusters 1–4, respectively, superimposed onto the color-coded average fractional anisotropy (FA) map of all subjects.

Note: images are in radiologic convention. Fibers passing through clusters 1–4 are illustrated in red, orange, blue, and yellow, respectively.



**Figure 5** 3D images illustrating fibers passing through clusters 1–4, respectively, superimposed onto the average fractional anisotropy (FA) map of all subjects.

Note: fibers passing through clusters 1–4 are illustrated in red, orange, blue, and yellow, respectively.

studies may be related to sample size, differences in image acquisition and post-processing as well as the use of region-of-interest *vs* voxel-based analysis approaches and diagnostic heterogeneity.

Although findings of higher FA in the frontal white matter among patients compared to healthy volunteers in our study most likely reflect an alteration in white matter connectivity, it is difficult to interpret the physiological significance of these findings, particularly in bipolar disorder because the pathophysiology is not well understood. One possible interpretation of the finding of higher FA in the frontal white matter is that it reflects greater coherence and/or directionality of white matter bundles in patients compared to healthy volunteers. In this regard we investigated whether group differences could be attributed to axonal or myelin-related properties of the white matter. Although significant group differences in axial and radial diffusivity were evident for some clusters of FA that differed between groups, we did not find support for preferential involvement of either diffusivity measure as a contributing factor to these white matter abnormalities. Inspection of the range of FA values observed in this study suggests that they may be in the vicinity of crossing fibers and thus, the finding of higher FA in patients could lead to the opposite interpretation, ie a loss of crossing fibers in patients. Similarly, Hoenou *et al* (2007) reported a greater number of reconstructed fibers between the left AH and left subgenual cingulate in bipolar patients compared to healthy volunteers. As these authors point out, this may be related to an increase in strength and/or volume of the pathway between regions or, alternatively, a loss of orthogonal or crossing fibers in patients compared to healthy subjects, which may have permitted their fiber-tracking algorithm to work easier in patients to yield a concomitant greater number of fibers between regions of interest.

White matter bundles extracted from the clusters that differed significantly between groups corresponded approximately to the CPT, CST, pontine crossing tract and superior thalamic radiation fibers, and thus, are broadly supportive of models of altered cerebellar–striatal–prefrontal connectivity in bipolar disorder (Green *et al*, 2007; Strakowski *et al*, 2005b). For example, mood dysregulation in bipolar disorder may result from deficits in frontal cortical modulation of cortical and subcortical structures involved in emotion generation (Green *et al*, 2007; Strakowski *et al*, 2005b). Recent evidence indicating that bipolar mania is characterized by reduced frontal inhibition of amygdala activity supports this hypothesis

(Foland *et al*, 2008). Other evidence from fMRI studies reported overactivation in frontosubcortical regions in patients with bipolar disorder (Blumberg *et al*, 2003; Chang *et al*, 2004; Strakowski *et al*, 2005a; Chen *et al*, 2006; Marchand *et al*, 2007; Wessa *et al*, 2007). Alterations in the white matter comprising cortical–subcortical pathways could thus conceivably be one mechanism of deficient modulation, although the relationship between FA and the BOLD response remains to be elucidated. Nevertheless, our data support the hypothesis for dysregulation in white matter comprising cortical and subcortical pathways, which may have relevance for the phenomenology of the disorder. For example, higher FA in the vicinity of the right SLF in patients with bipolar disorder may involve a large association pathway interconnecting right hemispheric brain regions (Makris *et al*, 2005) and the cognitive functions that they subservise, which may have relevance for the neuropsychology of bipolar disorder.

Higher FA in CST and CPT as well as superior thalamic radiation fibers in bipolar patients could have implications for serotonin synthesis, transport, and regulation throughout the brain (Alenina *et al*, 2006). Haddjeri *et al* (2000) describe a serotonergic feedback loop wherein stimulation of frontal cortical 5-HT<sub>1A</sub> receptors inhibits the firing of serotonergic neurons in the pontine raphe nuclei. Abnormalities in the raphe nuclei have been documented in bipolar disorder (Baumann *et al*, 2002), as have abnormalities in the serotonin-transporter (5-HTT) system (eg Sun *et al*, 2001; Cannon *et al*, 2006) in both medicated and unmedicated patients. In addition to possible serotonergic implications, abnormalities along the fiber tracts extracted in our analysis may also have implications for abnormalities in noradrenergic transport. Some investigators reported abnormalities involving the locus coeruleus in bipolar patients (eg Baumann *et al*, 1999), a region of the pons that serves as a main source of noradrenergic transmission throughout the brain. Abnormalities in fiber pathways relevant to serotonergic and noradrenergic transmission, which may include the regions of higher FA observed in the present study, could have implications for the pathophysiology and pharmacotherapy of bipolar disorder.

The finding of abnormal FA in the left cerebellar white matter, which appears to be part of the pontine crossing tract, is consistent with the hypothesis that the cerebellum is important in psychiatric illness and mood regulation (Schmahmann, 2000; Strakowski *et al*, 2000; Konarski *et al*, 2005). In particular, a disruption in cerebellar and corticocerebellar connectivity has been proposed as a major neurobiological mechanism of emotional dysregulation

(Schmahmann, 2000). Our findings converge with prior work implicating cerebellar abnormalities in first-episode bipolar patients compared to healthy volunteers (Adler *et al*, 2007). In addition, lower volume in the cerebellar vermis has been reported in bipolar patients who have undergone multiple affective episodes compared to first-episode patients and healthy volunteers (Mills *et al*, 2005), suggesting that the cerebellum undergoes structural changes concomitant with illness progression. Consistent with this finding, Monkul *et al* (2008) reported that young male bipolar patients demonstrate a significant negative correlation between cerebellar vermal volume and number of previous affective episodes. Moorhead *et al* (2007) conducted a longitudinal tensor-based morphometry study and reported progressive cerebellar tissue loss over a 4-year period in bipolar patients relative to controls. This tissue loss correlated inversely with the number of affective episodes that occurred during the 4-year study period. Interestingly, the region of significant loss in that study was a large cluster of gray and white matter in close proximity to the region of lower FA identified among patients in the present study.

There were several limitations to this study that should be acknowledged. The range of FA values reported here may suggest that clusters identified as abnormal may lie in regions of crossing fibers, and there is evidence that the single tensor model may not perform optimally in estimating FA in regions of fiber crossing and/or bending (Basser *et al*, 2000; Behrens *et al*, 2007; Kabasawa *et al*, 2008). In addition, it should be acknowledged that the anisotropic shape of the voxels and slice thickness may have biased FA and subsequent tractography analyses (eg Oouchi *et al*, 2007), especially for the cerebellar region. As with any voxelwise analysis there is the increased risk for a Type-I error, although we limited this possibility by restricting the analysis to the white matter and by using a conservative mask. Our patient sample was somewhat heterogeneous in terms of diagnosis, and included participants with a history of substance abuse, although ancillary analyses suggested neither of these was mediating factors. All patients were receiving psychotropic medications, however, and the potential effect of these medications on the brain white matter is largely unknown. In addition, we could not assess other possible factors that could influence white matter, including hydration and nutrition, and the potential clinical and cognitive correlates of these white matter abnormalities were largely unexplored. Although misregistration of images may be an issue with all VBM-style analyses, including the present study, we provided empirical data that our algorithm, in particular, minimizes this issue. Moreover, group effects were observed using manual region-of-interest placements, which were comparable to voxelwise analyses, suggesting that any misregistration of images did not appreciably affect study findings. It is also conceivable that the use of multiple NEX in our DTI sequence may have led to underestimation of motion artifacts (Smith *et al*, 2007) and the lack of cardiac gating may have led to additional artifacts (Skare and Andersson, 2001). Lastly, future studies could incorporate newly developed approaches to examining white matter tracts including the use of tract-based spatial statistics (Smith *et al*, 2006).

In sum, we report evidence for white matter abnormalities as assessed using DTI in a large cohort of patients with bipolar disorder compared to healthy volunteers. The use of tractography indicates that thalamic radiation fibers, and fibers of the corticospinal, corticopontine, and pontine crossing tracts may be involved in the pathogenesis of the disorder. Future studies could examine the relationship between white matter abnormalities in bipolar disorder and functional brain activity, as well as the cognitive and clinical correlates of these abnormalities.

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## DISCLOSURE/CONFLICT OF INTEREST

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