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White matter microstructure in untreated first episode bipolar disorder with psychosis: comparison with schizophrenia

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Abstract

Objectives—White matter abnormalities have been reported in bipolar disorder. The present study aimed to investigate white matter integrity in untreated first episode patients with psychotic bipolar disorder using diffusion tensor imaging, and to compare observations with those from untreated first episode schizophrenia patients.

Methods—Fractional anisotropy and mean diffusivity were measured in first episode psychotic patients with bipolar disorder ($n = 13$) or schizophrenia ($n = 21$) and healthy individuals ($n = 18$). Group differences were evaluated using voxel based morphometry. Axial and radial diffusivity were examined in regions with altered fractional anisotropy in post-hoc analyses.

Results—Patients with bipolar disorder showed lower fractional anisotropy than healthy controls in several white matter tracts. Compared with schizophrenia patients, bipolar disorder patients showed lower fractional anisotropy in the cingulum, internal capsule, posterior corpus callosum, tapetum, and occipital white matter including posterior thalamic radiation and inferior longitudinal fasciculus/inferior fronto-occipital fasciculus. Lower fractional anisotropy in bipolar disorder was characterized by increased radial diffusion rather than axial diffusion along the orientation of fiber tracts. Across several white matter tracts, both patient groups showed greater mean diffusivity than healthy individuals.

Conclusions—Selectively increased radial diffusivity in bipolar disorder patients suggests structural disorganization in fiber tract coherence of neurodevelopmental origin or alterations in myelin sheaths along fiber tracts. In contrast, increased isotropic diffusion along white matter tracts in schizophrenia patients with alterations in both radial and axial diffusivity suggests increased water content outside of axonal space. Thus, the present results suggest that different pathophysiological mechanisms may underlie white matter microstructural abnormalities in bipolar disorder and schizophrenia.

Keywords

diffusion tensor imaging; first episode psychosis; radial diffusivity; fractional anisotropy; mean diffusivity

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Evidence for white matter abnormalities in bipolar disorder were first observed in deep white matter hyperintensities in conventional magnetic resonance images (1, 2). Abnormal expression of genes involved in regulation of oligodendrocytes in bipolar disorder (3) further increased interest in white matter abnormalities. Diffusion tensor imaging (DTI) is a magnetic resonance technique specifically suited to interrogate the integrity of white matter that capitalizes on structural components restricting the diffusion of water (4). In white matter, axons and myelin form longitudinal axes that restrict water diffusion in directions perpendicular to the orientation of white matter tracts, leading to greater diffusion of water along the orientation of white matter tracts than perpendicular to them. Fractional anisotropy measures the magnitude of this directionally varying diffusion restriction effect as a function of the ratio of diffusivity along the axial axis of fiber tracts relative to radial directions (4). Fractional anisotropy values range from 0 to 1, where 0 indicates isotropic diffusion and 1 indicates diffusion perfectly along the axis of fiber tracts. Because fractional anisotropy represents a ratio, alterations may be due to diffusivity change in either the axial or radial directions, and thus it can be fruitful to examine axial and radial diffusion separately. Mean diffusivity, which complements information provided by fractional anisotropy, represents the mean diffusion coefficient of water molecules in all directions (4).

Prior DTI studies of bipolar disorder have yielded mixed findings. While some groups reported decreased fractional anisotropy in bipolar disorder patients in comparison to healthy controls (5-9), increased fractional anisotropy (10, 11) as well as null results (12, 13) have been reported. In studies that reported altered fractional anisotropy, abnormalities were most commonly found in fronto-limbic circuits, including the anterior corona radiata, orbitofrontal white matter, anterior corpus callosum, and anterior cingulum (5-7, 11, 14). Most of these studies used a region of interest approach with *a priori* hypotheses targeting tracts involved in circuitry supporting emotional regulation. Therefore, other brain regions have been less investigated. Recent studies that used voxel-based morphometry to explore differences across the whole brain have reported additional abnormalities in posterior brain regions, including posterior corona radiata, posterior cingulate, splenium, temporal lobe, and occipital lobes (9, 14). However, some groups did not detect abnormalities in posterior neocortex (6, 10).

One factor that may contribute to inconsistent findings is the clinical heterogeneity of patient samples. Most previous patient participants have had years of illness and heterogeneous medication treatments (8-13). It is difficult to separate direct effects of illness from those that might result from illness progression and acute or chronic drug treatment.

Two studies examined early onset bipolar disorder (5, 14). Kafantaris and colleagues (14) studied adolescents who were recently diagnosed and had taken medication for an average of only 11 weeks. Using voxel-based morphometry, they found that bipolar disorder patients had lower fractional anisotropy than healthy controls in right orbitofrontal, bilateral temporal, and left occipital white matter (14). Adler and colleagues (5) examined a younger group of adolescents who were naïve to medication treatment. Using a region of interest analysis, they found that adolescents with bipolar disorder had lower fractional anisotropy than controls in left superior frontal white matter, but no group differences emerged in posterior or right hemisphere regions. While providing useful information about bipolar disorder patients early in the course of illness, both the Kafantaris and Adler studies examined bipolar disorder patients with childhood or early adolescent onset. To our knowledge, no study has yet examined white matter microstructure in untreated first episode psychotic bipolar disorder patients with a more typical illness onset during late adolescence or young adulthood.

Most DTI studies of schizophrenia have been with chronically ill patients, and these have shown decreased fractional anisotropy of white matter across neocortex (15-17). Morphometric studies of first episode schizophrenia have identified smaller corpus callosum volume and decreased signal intensity in the corpus callosum (18, 19). DTI findings in first episode patients are more equivocal, with many studies reporting no abnormalities and others reporting decreased or increased fractional anisotropy (20-29). Studies by Friedman and colleagues (23) and White and colleagues (28) compared fractional anisotropy in first episode and chronic schizophrenia patients. Both studies showed reduced anisotropy in chronic but not first episode patients, suggesting that fractional anisotropy abnormalities in schizophrenia may increase over the course of illness due to illness-related or medication effects. Within the bipolar literature, the first episode strategy has been employed (14), but not with patients experiencing a first episode of psychosis. This distinction may be important because greater abnormalities and more similarities to schizophrenia have been reported in bipolar disorder patients with a history of psychosis across a broad range of parameters (30, 31). Direct comparisons of white matter structure in chronic bipolar and schizophrenia populations have not found consistent differences in fractional anisotropy, although both groups have been shown to have reduced fractional anisotropy in regions including the uncinate fasciculus, anterior thalamic radiation, and anterior limb of the internal capsule (32, 33).

In the present study, we used DTI to examine white matter microstructure in bipolar disorder (BP) patients with a first episode of psychosis and in first episode schizophrenia (SZ) patients. Patients were free from medications, including antipsychotics, lithium, and other mood stabilizers that might influence DTI measurements (34). We examined fractional anisotropy and mean diffusivity. In regions with altered fractional anisotropy, diffusivity was examined in the both axial and radial directions separately to gain a better understanding of illness-specific white matter characteristics.

Patients and methods

Participants

Patients were recruited from outpatient and inpatient admissions to the University of Illinois at Chicago First Episode Psychosis Program, Chicago, IL, USA. All patients were early in their course of illness, with the onset of their first psychotic symptom occurring six months (median) prior to study entry. The BP group consisted of 13 patients (7 males, 6 females). The SZ spectrum group consisted of 21 patients (17 males, 4 females; 20 schizophrenia, 1 schizophreniform disorder). Patients were unmedicated at the time of scanning. All but one patient was naïve to lithium (one BP patient had 28 weeks of lifetime treatment that ended more than six months before scanning). Lifetime antipsychotic treatment was limited (8 SZ patients had three weeks or less of prior lifetime exposure; 1 BP patient had two weeks of lifetime exposure). No BP patient had a history of anticonvulsant treatment. DSM diagnoses were based on the Structured Clinical Interview for DSM-IV (SCID) (35) and all available clinical data was reviewed together at consensus diagnosis meetings. Symptoms ratings, including the Positive and Negative Syndrome Scale (PANSS) (36), Young Mania Rating Scale (YMRS) (37), and Global Assessment of Functioning (GAF) (38) were obtained to characterize the period immediately before scanning. BP and SZ patients did not differ in severity of positive symptoms of psychosis or general level of functioning (Table 1). A sample of 18 (10 males, 8 females) healthy individuals (CON) with no personal history of Axis I disorders or history among first-degree relatives of psychotic or mood disorders were recruited through advertisements placed in the community. The CON group matched the patient groups on age, sex, and estimated IQ measured by use of the Reading subtest of the Wide Range Achievement Test, 3rd edition (WRAT-3) (39). All subjects had no history of head trauma with loss of consciousness for more than 10 minutes, neurological disorder, or

lifetime history of alcohol or drug abuse other than cannabis (2 individuals with BP, 1 with SZ, and 1 CON reported a past history of cannabis abuse). All subjects provided verbal and written informed consent according to procedures approved by the University of Illinois at Chicago Institutional Review Board.

Image acquisition

Participants underwent magnetic resonance imaging (MRI) scans performed on a 3.0 Tesla GE Signa HDx scanner (General Electric Health Care, Waukesha, Wisconsin, USA) with a quadrature head coil. The MRI protocol included a two-dimensional (2-D) axial multislice DTI scan using a customized single-shot echo-planar imaging (EPI) sequence with eddy current correction capabilities (40). The key data acquisition parameters for the DTI scan were TR = 5200 msec, TE = 85.5 msec, field of view (FOV) = 22 cm, slice thickness = 5 mm, slice gap = 1 mm, k-space matrix = 132×132 , imaging matrix = 256×256 , number of diffusion gradient directions = 27, b = 0 and 750 sec/mm², NEX = 2, and total scan time of 4 min 51 sec.

Data processing

Fractional anisotropy, mean diffusivity, axial diffusivity (first or principal eigenvalue), and radial diffusivity (average of the second and third eigenvalues) maps were created by fitting a single tensor model to the raw diffusion data using FSL's Diffusion Toolbox v.2.0 [FDT; Oxford Centre for Functional Magnetic Resonance Imaging of the Brain (FMRIB)'s Software Library, UK; http://www.fmrib.ox.ac.uk/fsl/fdt/fdt_dtifit.html; (41)], and then brain-extracted using the Brain Extraction Tool, (42). A nonlinear transformation matrix was used for registering individual fractional anisotropy maps to standard space created with a high-resolution average of 58 adult fractional anisotropy maps in FSL (http://www.fmrib.ox.ac.uk/fsl/data/FMRIB58_FA.html). This initial transformation matrix was combined with an affine transformation to align the data in fractional anisotropy standard space to $1 \times 1 \times 1$ mm MNI152 standard space, and the resulting transformation was applied in one step to individual data to minimize loss of resolution due to resampling. This resulting transformation matrix was applied to mean diffusivity and axial and radial diffusivity maps to bring all diffusion data into correspondence. Regions where groups differed were checked against white matter atlases provided in FSL.

To evaluate potential effects of head movement on DTI data, the MCFLIRT tool within FSL [Motion Correction using FMRIB's Linear Image Registration Tool, (43)] was used. The 27 different gradient directions were acquired as time series, similar to functional imaging data. We calculated the transformation necessary to register each individual's gradient volume (i.e., gradient direction) to the middle volume in the series to assess effects of head movement. There was no difference between groups in head movement, as measured by either maximum displacement (BP = 0.33 mm; SZ = 0.36 mm, CON = 0.32 mm; $F(2,49) = 0.60$, $p = 0.55$) or mean displacement (BP = 0.2 mm; SZ = 0.21 mm, CON = 0.19 mm; $F(2,49) = 0.74$, $p = 0.48$).

Statistical analysis

Statistical analyses were performed in MNI152 standard space following a voxel-based morphometry approach (44). To exclude gray matter voxels and minimize false positives due to partial voluming, only voxels on the mean fractional anisotropy map that exceeded a conservative fractional anisotropy value of 0.25 were included in analyses.

We used permutation-based nonparametric inference within the framework of a general linear model (45). Significance of group differences was determined using a threshold-free cluster enhancement (TFCE) approach (46) that allows both the spatial extent and the

magnitude of all supporting voxels to contribute to evaluating significance in a target voxel. Statistical significance was determined by permuting the pre-enhanced input data 5000 times to define a null distribution against which observed results were compared. This permutation method corrected for multiple comparisons to control experiment-wise type I error rate at $p < 0.05$.

In post-hoc analyses, axial and radial diffusivity were measured in regions where groups differed in fractional anisotropy using masks of such regions to extract measurements from each individual subject's map. *T*-tests were used to evaluate whether axial or radial diffusivity alterations contributed to group differences in fractional anisotropy in these regions. Significance for these exploratory studies was determined at $p < 0.05$ without additional correction for these analyses of regions where fractional anisotropy differences had already survived correction for experiment-wise type I error rate.

Results

Mean diffusivity

Mean diffusivity yields information about the magnitude of water diffusion in all directions. Both the BP and SZ groups showed greater mean diffusivity than the CON group in the cingulum, corpus callosum, corona radiata, internal capsule, tapetum, and occipital white matter including posterior thalamic radiation, inferior longitudinal fasciculus/inferior fronto-occipital fasciculus (Fig. 1). No significant differences between BP and SZ groups in mean diffusivity were found.

Fractional anisotropy

The BP group showed lower fractional anisotropy values than CON in multiple commissural, projection, and association tracts (Fig. 2A). In contrast, the SZ and CON groups showed no significant differences in fractional anisotropy. The BP group had lower fractional anisotropy values than the SZ group primarily in cingulum, internal capsule, and posterior brain regions including the posterior corpus callosum, tapetum, posterior corona radiata, and occipital white matter including posterior thalamic radiation, inferior longitudinal fasciculus/inferior fronto-occipital fasciculus (Fig. 2B).

Axial diffusivity and radial diffusivity within regions where the BP group had reduced fractional anisotropy are presented in Table 2. Within regions where the BP group showed lower fractional anisotropy than CON (Fig. 2A; first two rows of Table 2), the BP group showed greater radial diffusivity than CON but no significant differences in axial diffusivity. A similar pattern was seen in regions where the BP and SZ groups differed (Fig. 2B; last two rows of Table 2), with the BP group showing greater diffusion than the SZ group in radial but not axial directions. Both patient groups showed greater axial diffusivity than the CON group in this analysis. Increased diffusivity in radial directions perpendicular to fiber tracts outweighs the change in axial diffusivity in the BP group, and thus increased radial diffusivity appeared to be a specific factor contributing to lower fractional anisotropy in the BP group.

In regions where the BP and SZ groups differed in fractional anisotropy (Fig. 2B; Table 2), the SZ group showed both increased axial and radial diffusivity compared to CON. This is consistent with observations of increased mean diffusivity in these same regions (Fig. 1). Increases in both axial and radial diffusivity may explain why the SZ group did not differ from CON in fractional anisotropy, as a simultaneous increase in axial and radial diffusivities may not lead to change in fractional anisotropy in this instance.

Discussion

The present study documents that white matter microstructure abnormalities in psychotic patients with bipolar disorder and schizophrenia are evident early in the course of both illnesses, prior to potential confounding effects of illness progression or long-term drug therapy. The study is novel in focusing on the BP subgroup with psychotic features, and in comparing these patients at first psychotic episode with first episode SZ when they were not treated with medications that might impact DTI measurements. Importantly, utilizing measures of specific features of diffusion in white matter tracts, different patterns of alterations were observed in these disorders. The BP group showed decreased fractional anisotropy values, with disproportionate increase in radial diffusivity perpendicular to fiber tracts relative to changes along the axis of fiber tracts. This pattern of findings was observed in cingulum, internal capsule, posterior corpus callosum, tapetum, posterior corona radiata, and occipital white matter including posterior thalamic radiation, inferior longitudinal fasciculus/inferior fronto-occipital fasciculus regions. In patients with first episode SZ, white matter abnormalities involved increased diffusivity that was more isotropic in nature.

Lowered fractional anisotropy in bipolar disorder is consistent with most prior studies (6-9), including studies of patients early in the course of illness (5, 14). Previous DTI studies in first episode schizophrenia have been equivocal with regard to alterations in fractional anisotropy (21-29, 47). The present study showed similar alterations of radial and axial diffusivity in SZ patients that did not lead to altered fractional anisotropy, which may to a degree account for the conflicting findings across previous studies. Previous studies comparing bipolar disorder and schizophrenia have not found differences in fractional anisotropy (32, 33, 48). These studies examined chronic patients who typically had a mean duration of illness of 10 years or greater. Given findings suggesting that fractional anisotropy is more abnormal in chronic than early course patients with schizophrenia (23, 28), the present results with early course illness patients suggest that white matter abnormalities reflected in a specific increase in radial diffusivity may be intrinsic to bipolar disorder rather than schizophrenia pathophysiology, and thus may confer greater risk for the illness.

Potential biological substrates of DTI findings

One of the primary biological factors contributing to fractional anisotropy is the integrity of axonal membranes (49). Integrity of myelin also influences the degree of anisotropy (50). The effect of myelin on anisotropy measurements is complex, and depends on factors such as axon diameter, degree of myelination, and fiber packing density (49, 50). Decreases in axial diffusivity are often associated with axonal injury, whereas increases in radial diffusivity are more marked after disruption of myelin (51, 52). Thus, alterations in the integrity of myelin represent a possible cause of the increased radial relative to axial diffusivity observed in bipolar disorder. With relevance to neurodevelopmental models of bipolar disorder, increased radial diffusivity may also result from a reduced coherent organization of crossing tracts within fiber bundles. This may be especially pertinent to regions where fiber tracts cross in our findings, such as at the tapetum-posterior corona radiata and thalamic radiation juncture.

Increased mean diffusivity in the SZ group with similar changes in radial and axial directions represents a fundamentally different alteration in white matter structure. In studies that examined mean diffusivity, apparent diffusion coefficient, or trace (which are all scalar measures of diffusivity without being biased by diffusion anisotropy) between schizophrenia and controls, most found no difference between schizophrenia and control groups (16, 21, 53). Only one study reported increased diffusion coefficients in schizophrenia (54), as we found. Methodological differences across studies make direct comparisons difficult. For

example, most studies examined only specific tracts using a region of interest approach, and most patients were on various medications.

Changes in mean diffusivity have been reported in ischemia, where the primary physiological factor contributing to decreased diffusivity is a shift of water from extracellular to intracellular space (49, 55). Change in diffusivity can occur with glial swelling, as glial cells are more isotropic in shape than neurons (55). Thus, the increased mean diffusivity in our SZ group might be associated with increased extra-axonal water fraction, possibility with contributions from alterations to glial cells. Of note, this increased extra-axonal water fraction, including increased glial water content, might contribute to increased diffusivity in the BP group as well, as they also demonstrated increased axial and radial diffusivity compared to CON in some tracts. Thus, this factor may contribute to findings in both psychotic patient groups.

Studies of neuropathological processes in psychotic disorders have tended to focus on pyramidal and glial cells within gray matter (56, 57). Glial cells, including oligodendroglia, are found in both gray and white matter. Oligodendroglia serve as neuronal satellites in gray matter and form myelin sheaths in white matter (58). Glial cell loss and decreased oligodendroglial density in gray matter have been reported in both bipolar disorder (21, 58-61) and schizophrenia (21, 58, 61-65). These histological findings have come from dorsolateral prefrontal cortex and anterior cingulate. It is unclear whether these gray matter findings are related to DTI findings in general, and more specifically, whether they are related to the difference between bipolar disorder and schizophrenia groups in white matter microstructure. This remains an important question for future research.

Abnormalities of glial cells are consistent with genetic studies showing altered expression of genes involved in myelination in both schizophrenia (3, 57, 66-68) and bipolar disorder (3, 56). Tkachev and colleagues (3) reported downregulation of genes in the oligodendrocyte lineage, growth and differentiation, and mature myelinating oligodendrocytes in both schizophrenia and bipolar disorder, with seemingly more extreme change in bipolar disorder compared to schizophrenia. However, statistical evaluation in that study was conducted only between patient groups and controls and not between patient groups. Evaluation of deep white matter via myelin staining also has shown reduced stain intensity in bipolar disorder and trend level reduction in schizophrenia (59). Thus there is suggestion from postmortem studies of chronic patients of more significant white matter pathophysiology in bipolar disorder than schizophrenia. The present findings of increased radial diffusivity in bipolar disorder (relative to schizophrenia) suggest that white matter pathology is present during the early phase of illness. Thus it is not wholly the results of chronic pharmacotherapy, although animal models suggest that antipsychotic medication does affect oligodendroglia number and gene expression (69, 70). However direct links of cellular change with DTI alterations in these disorders remain to be established.

Potential functional significance of DTI findings

Results of the present study show abnormalities in untreated first episode psychotic BP patients in cingulum, anterior internal capsule, posterior corpus callosum/splenium, tapetum, posterior corona radiata and thalamic radiation, and inferior longitudinal fasciculus/inferior fronto-occipital fasciculus relative to both SZ and CON groups. The posterior corpus callosum contains fibers that connect parietal, occipital, and temporal regions of the two hemispheres, with the temporal projections curving inferiorly via the tapetum into the temporal lobes and parietal projections via posterior corona radiata (71). Thus these fibers connect major perceptual-processing regions of the brain. Posterior cingulate receives input from the temporal, occipital, and parietal regions, and plays functional roles in visual

processing, orientation of the body in space, auditory processing, and monitoring the emotional relevance of sensory stimuli (72).

Functional imaging findings have established alterations of these brain regions in bipolar disorder, including abnormal activation of inferior parietal, temporal, and frontal cortices on visuospatial working memory tasks (73, 74). Abnormal activation of temporal and parietal regions in bipolar disorder have been observed when processing emotional faces (75), and parietal activation during rest has been associated with mania severity (76). White matter abnormalities in pathways that connect bilateral posterior cortical regions with each other and with posterior cingulate cortex may contribute to difficulties integrating complex sensory input and integrating affective contributions to perceptual processes. Integration of these inputs during perceptual processing provides important drive to frontal-limbic systems via cingulum and inferior fronto-occipital fasciculus, and alterations in this circuitry may contribute to emotional dysregulation in bipolar disorder.

Limitations

Certain limitations of the current study need to be noted. First, untreated first episode samples such as ours are small, although our BP sample size is comparable to sample sizes reported in several previous studies. While first episode studies provide important information, the relatively small sample sizes and the restriction to early course effects impose limitations on broader inferences about our findings for bipolar disorder. Statistical power is also limited with a small sample size, although we had sufficient power to detect differences between BP and SZ groups in fractional anisotropy; smaller differences may not have been detected. Second, there was not a longitudinal component to this study, so that potential differential changes in white matter measurements over the course of illness in schizophrenia and bipolar disorder remain to be directly established. Given the apparent presence of such effects in schizophrenia, studies of potential longitudinal studies in bipolar disorder may provide important insights. Third, patients with BP were recruited based on the presence of psychosis. Several studies using a variety of research approaches from genetics to neuropsychology have found greater deficits and greater similarities of this group to schizophrenia than nonpsychotic bipolar disorder patients (30, 31). While this heightens interest in the observed differences between bipolar disorder with psychosis and schizophrenia, the generality of our findings to bipolar disorder patients with no history of psychosis remains to be established. Fourth, from a technical perspective, the spatial resolution in the DTI acquisition used in this study is less than that used in some recent studies, leading to partial volume effects that could bias fractional anisotropy, mean diffusivity, axial and radial diffusivity measurements, particularly in regions with crossing fibers. We avoided analyzing voxels with potentially biased values by restricting our analysis to voxels whose primary constituents are white matter, defined by a conservative fractional anisotropy threshold. Higher resolution data acquisition techniques would help overcome this limitation in future studies. Lastly, no direct link between physiological and psychological features of illness and DTI measures such as radial diffusivity has been established in bipolar disorder or schizophrenia. Thus conjectures from basic neuroscience research remain to be validated by future clinical studies.

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Fig. 1.

Group differences in mean diffusivity (MD). The bipolar disorder (BP) group (**A**) and the schizophrenia (SZ) group (**B**) both showed increased MD relative to the control (CON) group in widely distributed white matter tracts. There were no regions where the BP and SZ groups differed significantly in MD.

Fig. 2.

Group differences in fractional anisotropy (FA). The bipolar disorder (BP) group showed decreased FA relative to the control (CON) group in commissural, projection, and association fibers (**A**). The BP group also had decreased FA relative to the schizophrenia (SZ) group in the cingulum, internal capsule, posterior corpus callosum/splenium, tapetum, posterior corona radiata, and occipital white matter including posterior thalamic radiation and inferior longitudinal fasciculus/inferior fronto-occipital fasciculus (**B**). There were no regions where the SZ and CON groups differed in FA.

Table 1

Demographic and psychiatric characterization of participant groups

	Bipolar disorder (n = 13)	Schizophrenia (n = 21)	Controls (n = 18)	Statistic
Age	25 (8)	22 (5)	24 (5)	$F(2,49) = 1.30$ $p = 0.28$
Gender (male:female)	7:6	17:4	10:8	$\chi^2(2) = 3.71$ $p = 0.16^c$
Years of education	13 (1)	12 (3)	13 (2)	$F(2,49) = 0.94$, $p = 0.40$
Handedness ^a (R:L:A)	12:1:0	19:2:0	13:4:1	$\chi^2(2) = 3.06$ $p = 0.22^c$
Estimated IQ ^b	93 (14)	92 (14)	99 (9)	$F(2,49) = 1.56$ $p = 0.22$
PANSS Positive	22 (4)	24 (5)	n/a	$t(32) = 1.3$ $p = 0.20$
PANSS Negative	14 (6)	21 (6)	n/a	$t(32) = 3.38$ $p = 0.002$
YMRS	24 (10)	18 (9)	n/a	$t(28) = -1.71$ $p = 0.10$
GAF	43 (6)	39 (7)	n/a	$t(32) = 1.76$ $p = 0.09$
Weeks from first psychotic symptom to study	Median = 14 [IQR: 6–35]	Median = 35 [IQR: 18–78]	n/a	$\chi^2(1) = 4.16$ $p = 0.04$

Means and (SD) are reported unless otherwise noted. PANSS = Positive and Negative Syndrome Scale; YMRS = Young Mania Rating Scale; GAF = Global Assessment of Functioning; IQR = interquartile range.

^aHandedness is by self-report.

^bIQ = an estimate of premorbid intellectual functioning using the Wide Range Achievement Test, 3rd edition, Reading subtest.

^cKruskal-Wallis.

Table 2

Axial and radial diffusivity abnormalities in psychotic bipolar disorder (BP) and schizophrenia (SZ) patients within regions where significant pairwise group differences in fractional anisotropy were found

	Bipolar disorder	Schizophrenia	Controls	Group differences ^a
Analyses within the BP < CON mask^b				
Axial	1.372 (0.120)	1.390 (0.118)	1.293 (0.104)	SZ > CON
Radial	0.760 (0.085)	0.727 (0.079)	0.647 (0.049)	BP, SZ > CON
Analyses within the BP < SZ mask^c				
Axial	1.480 (0.136)	1.478 (0.136)	1.372 (0.125)	BP, SZ > CON
Radial	0.806 (0.093)	0.724 (0.087)	0.675 (0.056)	BP > SZ > CON

Means and (SD) in units of $\text{mm}^2/\text{sec} \times 10^{-3}$ are reported. CON = healthy controls.

^aSignificant post-hoc group differences between BP versus SZ, BP versus CON, and SZ versus CON.

^bSee Figure 2A.

^cSee Figure 2B.