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Microstructural abnormalities of white matter differentiate pediatric and adult onset bipolar disorder

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Abstract

Background—White matter microstructure, known to undergo significant developmental transformation, is abnormal in bipolar disorder (BD). Available evidence suggests that white matter deviation may be more pronounced in pediatric than adult onset BD. This study aimed to examine how white matter microstructure deviates from a typical maturational trajectory in BD.

Methods—Fractional anisotropy (FA) was measured in 35 individuals presenting with first episode BD (type I) and 46 healthy controls (HC) (aged 9–42) using diffusion tensor imaging (DTI). Patients were medication free and close to illness onset at the time of DTI scans. Tract based spatial statistics were used to examine the center of white matter tracts, and FA was extracted from nine tracts of interest. Axial, radial, and mean diffusivity were examined in post-hoc analyses.

Results—The left anterior limb of the internal capsule (ALIC) showed significantly lower FA in pediatric than adult onset BD. The lower FA in BD was due primarily to greater radial rather than a decrease in axial diffusivity.

Conclusions—ALIC connects the frontal lobes with archistriatum, thalamus, and medial temporal regions, and alteration in these pathways may contribute to mood dysregulation in BD. Abnormalities in this pathway appear to be associated with an earlier onset of illness and thus may reflect a greater liability for illness.

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Keywords

diffusion tensor imaging; development; limbic system; anterior limb of internal capsule; affect network

Evidence for white matter abnormalities in bipolar disorder (BD) was first observed in deep white matter hyperintensities in T₂-weighted anatomical magnetic resonance images (1, 2). Abnormal expression of genes involved in regulation of oligodendrocytes provides further evidence supporting the possibility of white matter abnormalities in bipolar disorder (3). Diffusion tensor imaging (DTI) is specifically suited to interrogate the integrity of white matter by capitalizing on structural components restricting the diffusion of water (4, 5). Neuronal membrane and myelin sheaths are cellular structures that restrict the diffusion of water. In white matter where neuronal membrane of axons form tubular shapes, water can diffuse down the longitudinal axis of axons more easily than in radial directions of axonal axis, in which direction diffusion is restricted by neuronal membrane and myelin sheaths. Because DTI measures are derived from Brownian motion of water, this technique takes advantage of axonal membrane shape to tap into integrity of structures within white matter. Fractional anisotropy (FA) reflects the proportion of diffusivity along the axial axis of fiber tracts relative to radial directions (4, 5). Alterations in FA may be due to change in diffusivity in either the axial or radial directions, and thus it can be fruitful to examine diffusion in these directions separately.

Prior DTI studies of BD have had mixed findings. Studies that took a region-of-interest (ROI) approach have focused on prefrontal-limbic circuits theorized to underlie affective dysregulation in BD. In pediatric BD, these studies have found lower FA in the anterior corona radiata (6) and superior frontal white matter (7). In adult BD, findings are more mixed in both direction of findings and location of abnormality, with some reporting lower FA in the anterior cingulum (8) and frontal white matter (9), and others reporting higher FA in the genu of the corpus callosum (10) and frontal white matter (11) or no abnormality in these regions (12). Examinations of specific tracts within the prefrontal-limbic circuit in adults have also yielded mixed findings, with some reporting lower FA in the anterior thalamic radiation (13), which makes up a part of the anterior limb of the internal capsule (14), and others reporting no difference between adult BD and healthy controls in subgenual cingulate or the amygdalo-hippocampal complex (15).

Studies that examined the entire brain using either voxel-based morphometry (VBM) or tract based spatial statistics (TBSS) have found white matter abnormalities in regions beyond the frontal-limbic circuit. In pediatric BD, these included lower FA in superior longitudinal fasciculus (16), posterior corona radiata (17), posterior cingulum (16, 17), corpus callosum (16, 17), fornix (17), and occipital white matter (18). Findings in adults are again more mixed, with some studies reporting lower FA in the corpus callosum (19, 20), posterior thalamic radiation (21), and arcuate fasciculus (21), while others reported higher FA in inferior parietal (22) and occipital white matter (22, 23).

In sum, studies of pediatric BD have tended to find more consistently lower FA than studies of adult BD. The literature from healthy white matter development is a helpful context in which to consider this pattern of findings. Cross sectional studies of typically developing individuals have found higher FA with age in the corpus callosum, internal capsule, thalamic radiations, corona radiata, arcuate fasciculus, and frontal and temporal white matter (24–26). Lebel and colleagues (26) examined maturation rate across commissural, association, and projection fibers, and reported that callosal fibers and association fibers reach maturity by late childhood and adolescence respectively, while projection fibers continue to mature into

early adulthood. To date, no one has examined how white matter microstructure deviates from a typical maturational trajectory in BD, and whether the inconsistencies in the BD literature may be partially explained by deviations from a normal neurodevelopmental trajectory.

Based on the above, we sought to determine whether early onset BD is associated with greater or more consistent white matter alterations than BD with adult onset. We measured FA in medication free pediatric and adult onset BD during the first episode of illness and investigated FA differences in BD relative to healthy controls. Because each tract follows a different normal developmental trajectory, we first obtained the center of tracts (skeleton) for each participant, then applied tract masks and extracted mean FA within each tract skeleton to evaluate group, age, and interaction effects at the level of the tract. We specifically hypothesized that white matter tracts that connect prefrontal and limbic regions such as the anterior limb of internal capsule (ALIC), anterior corona radiata (ACR), and cingulum would have lower FA in the BD group (6, 27), and that these differences would be more evident in the pediatric onset BD patients.

Methods

Participants

The BD group consisted of 35 patients (age range 11 to 42 years). The healthy control (HC) group consisted of 46 individuals (age range 9 to 37 years). The two groups did not differ in age, gender distribution, handedness, or intelligence quotient (IQ) (see Table 1). IQ was estimated in adults using the Wide Range Achievement Test, 3rd Edition, Reading subtest, and in children using the Wechsler Abbreviated Intelligence Scale, Vocabulary, and Matrix Reasoning subtests. Diagnoses were based on the Schedule for Affective Disorders and Schizophrenia for School Aged Children–Present and Lifetime Version (K-SADS-PL) (28) for the pediatric population, the Structured Clinical Interview for DSM-IV (SCID) (29) for the adult population, and on all available clinical data reviewed at a consensus diagnosis meetings. Patients with BD were all type I, experienced their first episode of mania within the past month, and were unmedicated at the time of scanning. Mania symptoms were assessed with the Young Mania Rating Scale (30). Depression symptoms for pediatric participants were assessed using the Children's Depression Rating Scale–revised (CDRS-R) (28) and for adult participants, the Hamilton Rating Scale for Depression (HAM-D) (31). Comorbid diagnoses and history of prior medication are reported in Table 2. Approximately half of the BD patients have one or more additional comorbid diagnoses and had previously been prescribed psychotropic medication by their primary care physicians before being referred to our psychiatry clinic. All participants and parents of minor subjects provided verbal and written informed consent according to procedures approved by the University of Illinois at Chicago Institutional Review Board (Chicago, IL, USA).

Image acquisition

Participants underwent magnetic resonance imaging (MRI) scans performed on a 3.0 Tesla GE Signa HDx scanner (General Electric Health Care, Waukesha, WI, USA) equipped with a 40 mT/m gradient subsystem using a quadrature head coil. The MRI protocol included a multi-slice axial DTI scan using a customized single-shot echo-planar imaging (EPI) sequence with eddy current correction capabilities (32). The key data acquisition parameters for the DTI scan were repetition time (TR) = 5200 msec, echo time (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 (33), NEX = 2, and total scan time = 4 min 51 sec.

Data processing

FA measures the standard deviation among diffusivities along the axial and radial axes of fiber tracts and is related to ratio of axial to radial diffusivity (34). Alterations in FA between patients and controls reflect diffusivity change in the axial and/or radial directions. Mean diffusivity represents the average diffusion coefficients of water molecules in three orthogonal directions of the diffusion eigenvectors and complements information provided by FA (34). While primary analyses were done using FA, mean, axial (first or principal eigenvalue), and radial diffusivity (average of the second and third eigenvalues) maps also were created for exploratory analyses by fitting a single tensor model to the raw diffusion data using FSL's Diffusion Toolbox v2.0 [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; (35)], and then brain-extracted using the Brain Extraction Tool (36). We then used the Tract-Based Spatial Statistics (TBSS) (37) tool within FSL to shift the center of white matter tracts across subjects into spatial correspondence so that group differences could be evaluated at the center of tracts. Subjects' FA data were first aligned into a common space using FSL's nonlinear registration tool FNIRT [FMRIB's Nonlinear Registration Tool, (38, 39)], which uses a b-spline representation of the registration warp field (40). Next, the mean FA image was created and thinned to create a mean FA skeleton which represents the center of all tracts common to all subjects. Each subject's aligned FA data was then projected onto this skeleton. This transformation matrix was combined with an affine transformation to align the data to $1 \times 1 \times 1$ mm Montreal Neurological Institute (MNI) 152 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, axial, and radial diffusivity maps to bring all diffusion data into correspondence. To exclude gray matter voxels and minimize false positives due to partial voluming or inter-subject variability at the edge of white matter, only voxels on the mean FA map that exceeded an FA value of 0.30 were included in analyses.

To evaluate potential effects of head movement on DTI data, the MCFLIRT tool within FSL [Motion Correction using FMRIB's Linear Image Registration Tool, (41)] 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 [BD: 0.29 mm, HC: 0.30 mm; $t(79) = 0.46$, n.s.] or mean displacement [BD: 0.17 mm, HC: 0.17 mm; $t(79) = 0.06$, n.s.].

Statistical analysis

Based on prior findings with BD patients (6, 27), we selected nine tracts using ROI masks available in FSL, which were created from a standard-space average of diffusion tensor maps from 81 adults by hand segmentation and included entire tracts rather than spheres within tracts (42). These nine tracts included the corpus callosum (divided into genu, body, and splenium ROIs), internal capsule (divided into anterior limb, posterior limb, and retrolenticular ROIs), external capsule, posterior thalamic radiation, corona radiata (divided into anterior, superior, and posterior ROIs), superior longitudinal fasciculus, cingulum, sagittal stratum, and corticospinal tracts, yielding a total of 27 ROIs (left and right for each except the corpus callosum). These masks were applied to each individual's volume in standard space to extract the mean value of tract skeletons within each mask (FA, mean, axial, and radial diffusivity). These mean values were analyzed using a general linear model with group as a fixed factor and age as a random factor. Bonferroni corrections were applied to analyses with FA to control for type I error rates. The presence of comorbid disorders and

prior exposure to psychotropic medication were entered as covariates in post-hoc analyses to determine if the difference between BD and HC groups remained after these factors were controlled. Mean, axial, and radial diffusivity were analyzed post-hoc in regions where BD and HC groups differed in FA.

Results

FA

Mean FA values within each tract are reported in Table 3. We examined the deviation in the developmental trajectory (i.e., change across age span) of the BD group from the HC group via group $\times$ age interaction. Deviation between BD and healthy controls varied significantly across age [$F(12,42) = 3.88, p = 0.0005$] in the left ALIC after correcting for multiple comparisons. Reduction in FA was greater in the younger BD patients relative to older BD patients (Figs. 1 and 2). This finding remained after the presence of comorbid diagnosis [$F(12,41) = 4.05, p = 0.0003$] and prior medication exposure [$F(12,41) = 4.22, p = 0.0003$] were controlled statistically as covariates. Tracts that showed trend level FA deviation in younger BD patients that were significant without but not with experiment-wise type 1 error protection included the bilateral anterior corona radiata, posterior corona radiata, posterior limb of the internal capsule, retrolenticular part of the internal capsule, left sagittal stratum, left external capsule, and right superior corona radiata (Fig. 1). No tract had a trend level main effect of age, and only one tract had a trend level main effect of group (right sagittal stratum).

Post-hoc source and age effects

Axial, radial, and mean diffusivity were examined in the left ALIC to elucidate the source of diffusivity that led to deviations in FA development (age effect) between groups (group effect). The age effect in the left ALIC was evaluated using a general linear model with age as a random factor, consistent with our other analyses. The effect of age was significant for mean diffusivity [$F(25,55) = 2.48, p = 0.003$], axial diffusivity [$F(25,55) = 2.12, p = 0.01$], and radial diffusivity [$F(25,55) = 1.70, p = 0.05$]. Whether these age effects varied by group was examined by group $\times$ age interaction, with group as a fixed factor in the general linear model. There was a trend of higher radial diffusivity in younger BD patients [$F(12,42) = 1.92, p = 0.06$]. The pattern of higher mean diffusivity and axial diffusivity with age was similar for the two subject groups [group $\times$ age interaction: mean diffusivity $F(12,42) = 0.70, p = 0.74$; axial diffusivity $F(12,42) = 0.74, p = 0.70$]. This suggests that the difference between BD and healthy controls across age spans in FA may result more from alterations in radial than axial diffusivity.

Discussion

This is the first study to examine white matter deviations in first episode unmedicated BD from mid-childhood through early-adulthood. Results showed greater deviations in white matter microstructure in left ALIC in BD with pediatric onset relative to adult onset. The lower FA in early onset BD was primarily due to higher radial diffusivity. We sought effects that were evident within entire tracts so that interpretation at the level of specific tracts is appropriate. The greater pathology of ALIC in childhood onset cases suggests that the pathophysiology of BD in childhood may be more severe or perhaps differs significantly in fundamental ways for individuals with an earlier onset of illness.

ALIC

Affective dysregulation in BD is believed to be associated with a compromised integration of prefrontal-limbic circuitry. Functional imaging studies of healthy individuals and BD

patients support models of top-down regulation of affect, with prefrontal systems modulating affective arousal in subcortical structures such as the amygdala and ventral striatum (43, 44). In BD, the ability of prefrontal structures to modulate subcortical structures appears compromised. For example, during incidental processing of affective words, BD patients show less activation in ventrolateral and dorsolateral prefrontal regions, accompanied by more activation in the amygdala relative to healthy controls (45, 46). This affective dysregulation model emphasizes the connectivity between different neural systems supported by white matter pathways needed for communication between nodes that comprise the relevant neural systems.

The ALIC contains frontopontine fibers and the anterior thalamic radiation, which contains limbic and thalamo-cortical projections to the frontal lobes (42, 47, 48). Two limbic circuits pass through the ALIC (48, 49). The Papez circuit consists of projections from the hippocampus that connect mammillary bodies, anterior nucleus of the thalamus, and cingulate gyrus. The basolateral limbic circuit consists of projections connecting the orbitofrontal cortex to the dorsomedial nucleus of the thalamus, amygdala and temporal pole. Both of these circuits pass through the ALIC, which is a major conduit between prefrontal cortex and the thalamus. Thus, compromised white matter microstructure in this tract may interfere with the processing of emotional information by the limbic system. The involvement of ALIC in mood regulation has convergent support from clinical studies, where the ALIC is one of the target sites for deep brain stimulation for treatment of intractable depression (50, 51). Abnormality of the ALIC volume or white matter integrity has been documented previously in BD (13).

Of studies that have directly examined white matter integrity of the ALIC in BD, three studies reported lower FA (13, 52, 53) while another did not (6). Those that did find compromised ALIC integrity examined adult, chronic patients, while the study that did not find this abnormality examined pediatric patients. This at first seems contradictory to our findings, which indicated more salient FA compromise in pediatric than adult BD. However, methodological issues may explain this difference. In Pavuluri's study of pediatric BD, a ROI approach was pursued where FA was examined in three ROIs consisting of a small number of pixels (6). Thus the entire ALIC was not sampled as in the present study. Another difference is that our adult BD participants were seen close to the time of illness onset with a limited history of drug treatment, while adult BD patients from the existing literature were typically chronically ill and medicated (13, 52, 53). Medication classes used to treat BD, including lithium and neuroleptics, have been shown to affect gray and white matter (54–57). Further studies are needed to address the potential significance of medication effects on white matter integrity in bipolar disorder and any possible progression of abnormalities over the course of illness to account for differences in some previous studies of chronic patients relative to our adult group, which was seen early in the course of illness.

With regard to differential patterns of ALIC compromise in early onset vs. adult onset BD, several possible interpretations need to be considered. One is a developmental view in which there may be a maturational delay of white matter integrity in BD, leading to greater deficit in younger patients which ameliorates over time. Longitudinal studies are needed to test this possibility. Alternatively, our data may reflect pathophysiological differences between early- and adult-onset BD, with higher levels of alteration of ALIC pathways in childhood onset patients that may confer an increased risk or vulnerability for illness.

Radial diffusivity may indicate a myelination abnormality in pediatric onset BD

White matter consists of myelin sheaths and axons that they cover. Compromise of white matter microstructure can arise from three broad sources: abnormal myelination, axonal membrane compromise, or decreased coherence of fiber tracts. We found that FA deviation

in the ALIC of BD participants is characterized by a relatively greater alteration in radial diffusivity. In animal models, dysmyelination has been associated with higher radial diffusivity (58, 59). In human developmental studies, projection fibers such as the ALIC mature late, relative to callosal and association fibers, and may not reach maturity until the third decade of life (26). It is not known whether abnormally higher radial diffusivity seen in the ALIC of BD is related to dysmyelination, delayed myelination, or decreased coherence of fiber tracts within the ALIC. Another plausible, though less likely, contributing factor to lower FA in pediatric BD is reduced axonal integrity. It has been shown that the primary determinant of anisotropy is axonal membranes, although myelin is known to modulate the degree of anisotropy (60). Decrease in axial diffusivity is often associated with axonal injury (61). However, the BD and HC groups did not differ in axial diffusivity. This pattern of higher radial diffusivity but no change in axial diffusivity, together with glial abnormalities reported in BD (3, 62–64), point towards pathogenesis related to myelin. However direct links of cellular change with DTI alterations in these disorders remain to be established.

FA in healthy controls

In healthy individuals, most prior studies on FA developmental trajectory have shown increasing FA with age (24, 25, 65–68), although decreasing FA with age (69–72) and no discernable change with age in certain tracts has been reported as well. We did not find increasing FA in our healthy control group for most tracts. The age range studied may explain this difference. In the largest sample of 5- to 29-year-old healthy participants to date, Lebel and colleagues showed that for many white matter tracts in which FA increases with age, the trajectory is curvilinear with most changes occurring before age of 10 (26). The age span for our subjects was 9–42 years-old. Thus we did not have sufficient sample of the age range in which the most dramatic changes are seen. There are two longitudinal studies reporting increasing FA in adolescents in the ALIC (73) and in the anterior thalamic radiation [which passes through the ALIC (68)]. Methodological differences may have contributed to why we did not find increasing FA in the healthy controls. Previous longitudinal studies evaluated voxels within fiber skeletons using TBSS. When significant age effects were found, they were limited to circumscribed regions within tracts. Circumscribed regions of change within white matter tracts are difficult to interpret given limitations in our current knowledge of which specific fibers are located in tract regions. In contrast to these methods, we used TBSS, but we superimposed tract masks over TBSS results and extracted FA values across the entire tract. Thus our results can be interpreted as effects at the level of tracts of interest rather than in small components of them. This method sacrifices fine localization of regional alterations within tracts but gains the ability to make more robust inferences at the tract level. Interestingly, in one of the previous longitudinal studies, Giorgio and colleagues used tractography to identify the corticospinal tract, which passes through the posterior limb of the internal capsule (73). They also found a lack of age-related increase when the entire tract is evaluated, although there were voxels within the posterior limb of the internal capsule that showed increasing FA with age. Together, our data and Giorgio et al. (73) results suggest that caution in interpretation is warranted when age effects are found for localized regions within tracts, as they may not generalize to the entire tract, and our current knowledge of fibers located within specific locations of tracts is very limited.

Furthermore, Lebel and Beaulieu (74) reported longitudinal data on over 100 participants, and they plotted the percent of participants for whom FA either increased, decreased, or did not change over time. Although this study did not evaluate the ALIC, it was interesting even for the tract that showed the most protracted increase in FA, only approximately 50% of the participants demonstrated increasing FA with age. The rest either showed no change or decreasing FA. Together with abovementioned limitations in interpreting age-related

alteration that are localized to circumscribed regions within tracts, developmental FA change in the healthy population is not clear cut and need to be considered with caution.

Limitations

Certain limitations of the current study need to be noted. First, we utilized a cross-sectional design to evaluate deviations in white matter integrity across the age span in BD. We do not know if the age effects shown are developmental in nature and reflect delayed maturation that ameliorates with age, or if they reflect an altered maturation of white matter pathways in those most likely to have an early onset of illness during childhood. Second, from a technical perspective, the spatial resolution in the DTI acquisition used in this study was limited, which could lead to partial volume effects that could bias FA, mean, axial, and radial diffusivity measurements. We minimized this problem by not analyzing voxels with potentially biased values by restricting our analysis to voxels whose primary constituents are white matter, and then further constrained statistical analyses to centers of tracts to minimize potential partial volume effects. Higher resolution data acquisition techniques would help overcome this limitation in future studies. Third, while white matter abnormalities were statistically significant after correction for multiple comparisons only in the left ALIC, alterations in multiple other tracts were significant before correction for multiple comparisons. Thus, it is possible that white matter alterations in ALIC are more consistently pronounced than alteration in other white matter pathways in BD, rather than being a highly specific site of neuropathology. Future studies are needed to evaluate the full extent of age-related white matter alterations throughout the brain in BD.

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Fig. 1.

Skeleton of the center of tracts derived from tract based spatial statistics (in green). The left anterior limb of the internal capsule (in red) has a different trajectory of fractional anisotropy between bipolar disorder and healthy controls across the age span. In brown are tracts that showed a trend for a different trajectory between groups across age (shown are bilateral anterior and posterior corona radiata, right superior corona radiata, bilateral posterior limbs of the internal capsule, bilateral left retrolenticular part of the internal capsule, and left external capsule; left sagittal stratum is not shown).

Fig. 2.

Fractional anisotropy (FA), axial diffusivity, radial diffusivity, and mean diffusivity for anterior limb of the internal capsule (ALIC) are plotted on the y-axis, with age on the x-axis. The group $\times$ age interaction for FA is due to radial diffusivity, which also showed a trend effect of group $\times$ age interaction, with greater discrepancy between bipolar disorder (BD) and healthy controls (HC) in childhood than in adulthood. There was a significant age effect for axial, radial, and mean diffusivity, with all participants showing increasing diffusivity in the left ALIC.

Table 1

Demographic and psychiatric characterization of participant groups

	Bipolar disorder (n = 35)	Healthy controls (n = 46)	Group difference
Age, years	19 (8)	20 (6)	$t(79) = 0.73$, n.s.
Age distribution (under 18/18+ years), n	19/16	21/25	Mann–Whitney U -test $Z = 0.76$, n.s.
Male/female, n	17/18	22/24	Mann–Whitney U -test $Z = 0.07$, n.s.
Handedness ^a (right/left), n	34/1	44/2	Mann–Whitney U -test $Z = 0.35$, n.s.
IQ ^b	100 (14)	104 (12)	$t(79) = 1.32$, n.s.
YMRS ^c	26 (10)	n/a	n/a
CDRS-R ^d	42 (12)	n/a	n/a
HAM-D ^e	30 (8)	n/a	n/a

Values are presented as mean [standard deviation (SD)] unless noted otherwise. YMRS = Young Mania Rating Scale; CDRS-R = Children's Depression Rating–Scale revised; HAM-D = Hamilton Rating Scale for Depression; n.s. = not significant; n/a = not available.

^aHandedness is from the Annett Behavioral Handedness Index.

^bIQ = an estimate of premorbid intellectual functioning in adults using the Wide Range Achievement Test, 3rd edition, Reading subtest. In children, the Wechsler Abbreviated Intelligence Scale, Vocabulary, and Matrix Reasoning subtests was used.

^c_n = 33.

^d_n = 21.

^e_n = 14.

Table 2

Comorbid diagnoses and prior medication taken by bipolar disorder patients (n = 35)

No. of patients with comorbid diagnosis	19 (54)
ADHD	10 (29)
Learning disorder	1 (3)
Conduct disorder	1 (3)
ODD	1 (3)
GAD	2 (6)
Social phobia	1 (3)
PTSD	1 (3)
Cannabis use history	3 (9)
Cocaine use history	1 (3)
Hallucinogen use history	1 (3)
No. of patients with history of exposure to prior medication class	17 (49)
Second-generation antipsychotics ^a	12 (34)
Mood stabilizers ^b	11 (31)
Antidepressants ^c	10 (29)
Psychostimulants ^d	8 (23)
Non-stimulant for ADHD ^e	1 (3)

Values are presented as n (%). ADHD = attention-deficit hyperactivity disorder; ODD = oppositional defiant disorder; GAD = generalized anxiety disorder; PTSD = posttraumatic stress disorder.

^aRisperidone, aripiprazole, quetiapine, and ziprasidone.

^bLithium, divalproex, oxcarbazepine, lamotrigine, carbamazepine, and gabapentin.

^cSertraline, bupropion, fluoxetine, escitalopram, and venlafaxine.

^dMethylphenidate immediate- and long-acting forms, mixed amphetamine salts, and dexamethylphenidate.

^eAtomoxetine.

Table 3Mean fractional anisotropy and (standard deviation) within each white matter tract of interest^a

	Bipolar disorder (n=35)	Healthy controls (n=46)	Group × age interaction (p-value)
ALIC-L	0.51 (0.03)	0.53 (0.02)	0.0005
ALIC-R	0.52 (0.03)	0.53 (0.03)	n.s.
PLIC-L	0.67 (0.03)	0.69 (0.02)	0.027
PLIC-R	0.67 (0.03)	0.68 (0.02)	0.012
RLIC-L	0.56 (0.03)	0.58 (0.02)	0.014
RLIC-R	0.56 (0.03)	0.57 (0.02)	0.007
PTR-L	0.59 (0.03)	0.61 (0.04)	n.s.
PTR-R	0.60 (0.04)	0.62 (0.04)	n.s.
EC-L	0.43 (0.02)	0.44 (0.02)	0.030
EC-R	0.43 (0.03)	0.44 (0.02)	n.s.
ACR-L	0.46 (0.04)	0.48 (0.03)	0.006
ACR-R	0.47 (0.04)	0.48 (0.03)	0.030
SCR-L	0.48 (0.03)	0.49 (0.03)	n.s.
SCR-R	0.47 (0.03)	0.48 (0.02)	0.009
PCR-L	0.44 (0.03)	0.46 (0.03)	0.009
PCR-R	0.45 (0.03)	0.47 (0.02)	0.028
Cingulum-L	0.45 (0.04)	0.47 (0.03)	n.s.
Cingulum-R	0.43 (0.04)	0.45 (0.03)	n.s.
CC-genu	0.63 (0.03)	0.65 (0.03)	n.s.
CC-body	0.49 (0.05)	0.51 (0.04)	n.s.
CC-splenium	0.72 (0.03)	0.74 (0.03)	n.s.
SLF-L	0.46 (0.03)	0.47 (0.03)	n.s.
SLF-R	0.45 (0.03)	0.46 (0.03)	n.s.
SS-L	0.49 (0.04)	0.50 (0.03)	0.018
SS-R	0.50 (0.04)	0.52 (0.03)	n.s.
CST-L	0.48 (0.03)	0.49 (0.03)	n.s.
CST-R	0.48 (0.03)	0.49 (0.03)	n.s.

L = left; R = right; ALIC = anterior limb of internal capsule; PLIC = posterior limb of internal capsule; RLIC = retrolenticular part of internal capsule; PTR = posterior thalamic radiation; EC = external capsule; ACR = anterior corona radiate; SCR = superior corona radiate; PCR = posterior corona radiate; CC = corpus callosum; SLF = superior longitudinal fasciculus; SS = sagittal stratum; CST = corticospinal tract.

^aThe group × age interaction term's associated p-values are reported before correction for multiple comparisons. No tract had a trend level age effect, and only one tract had a trend level group effect (SS-R, $p = 0.04$ before correction for multiple comparisons). Uncorrected p-values above 0.10 are indicated with n.s. (not significant). Bonferroni corrected p-value required for statistical significance was $p < 0.0018$.