Limbic and Corpus Callosum Aberrations in Adolescents with Bipolar Disorder: A Tract-Based Spatial Statistics Analysis

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Background: Bipolar disorder (BD) is a common and debilitating condition, often beginning in adolescence. Converging evidence from genetic and neuroimaging studies indicates that white matter abnormalities may be involved in BD. In this study, we investigated white matter structure in adolescents with familial bipolar disorder using diffusion tensor imaging (DTI) and a whole brain analysis.

Methods: We analyzed DTI images using tract-based spatial statistics (TBSS), a whole-brain voxel-by-voxel analysis, to investigate white matter structure in 21 adolescents with BD, who also were offspring of at least one parent with BD, and 18 age- and IQ-matched control subjects. Fractional anisotropy (FA; a measure of diffusion anisotropy), trace values (average diffusivity), and apparent diffusion coefficient (ADC; a measure of overall diffusivity) were used as variables in this analysis. In a post hoc analysis, we correlated between FA values, behavioral measures, and medication exposure.

Results: Adolescents with BD had lower FA values than control subjects in the fornix, the left mid-posterior cingulate gyrus, throughout the corpus callosum, in fibers extending from the fornix to the thalamus, and in parietal and occipital corona radiata bilaterally. There were no significant between-group differences in trace or ADC values and no significant correlation between behavioral measures, medication exposure, and FA values.

Conclusions: Significant white matter tract alterations in adolescents with BD were observed in regions involved in emotional, behavioral, and cognitive regulation. These results suggest that alterations in white matter are present early in the course of disease in familial BD.

Key Words: Adolescents, bipolar disorder, diffusion tensor imaging, DTI, fornix, limbic system, MRI, TBSS

Converging evidence from genetic and imaging studies suggests a role for aberrant white matter in the neuropathophysiology of bipolar disorder (BD). However, the extent and location of white matter abnormalities in BD are not fully understood. As in most psychiatric disorders, differences in genetic loading may contribute variance to imaging data, making it more difficult to find significant differences in the relatively small samples typical of imaging studies. Early age of onset and first-degree relatives with a disease are clinical indicators of increased genetic loading; thus, it is hypothesized that children and adolescents with familial BD may have more severe and easier to identify white matter involvement than other individuals with BD.

The hallmarks of bipolar disorder I (BDI) are emotional and behavioral disturbances, as evidenced by episodes of mania and depression (1). In addition, individuals with BDI exhibit cognitive deficits in attention, executive function, response inhibition, and short-term memory (2-5). Multiple investigative modalities have localized brain regions of emotional regulation to the limbic network comprised of the historical Papez circuit (hippocampus, fornix, mammillary bodies, anterior thalamic nuclei, the cingulate gyrus, and the parahippocampal gyrus), as well as the amygdala and thalamus (6–10). Recent data from neuroimaging studies link the emotional, behavioral, cognitive, and vegetative symptoms of BD to dysfunction in several structures and pathways within the limbic network; linked prefrontal regions such as orbitofrontal, dorsal-prefrontal, and subgenual pathways (11–13); and pathways traversing the corpus callosum (14–18). Aberrant connectivity within these circuits may be an important component in the dysfunction observed in BD.

Visual evidence for white matter dysfunction in BD was first observed in qualitative structural brain imaging studies showing an increased rate of white matter hyperintensities (WMH), a highly consistent finding in adults with BD (19–24). However, it is unclear whether children and adolescents with BD have more WMH than control subjects, as there have been both positive (20,22,25) and negative (26) reports. Additional evidence for possible white matter involvement in BD comes from genetic studies that implicate glia- and myelin-related genes as candidate genes in BD (27–29).

Diffusion tensor imaging (DTI), a noninvasive magnetic resonance (MR) based method that uses the diffusion of water to investigate brain structure, is a more sensitive imaging method than qualitative observation for investigating white matter structure. The architecture of white matter, which restricts water movement perpendicular to fiber axis, is especially suitable for DTI analysis, as it allows three-dimensional (3-D) characterization of fiber tracts and comparison of white matter structure between populations.

Data from previous DTI studies of BD in adults (30–42) and in adolescents (43,44) suggest that patients with BD have white matter aberrations in prefrontal regions, thalamic pathways, the uncinate fasciculus, the corpus callosum, the anterior cingulate, and in fibers between the left subgenual cingulate and left amygdalo-hippocampal complex, as well as in the occipital radiations and the cerebellum. Most of the aforementioned studies used a classic region-of-interest (ROI) based approach that possesses methodological limitations. First, an ROI approach

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provides data only in regard to the brain regions sampled and may miss identifying abnormalities of other brain regions contributing to pathophysiology. Further, even with careful placement of ROIs based on anatomical landmarks on anatomical MR images, different subjects are likely to demonstrate variability in the extent to which different pathways traverse the chosen ROIs. Six whole-brain analyses investigated children (aged 4 years to 12 years) (45), adolescents (44), and adults with BD (36,39,42,46). These studies showed that compared with healthy control subjects, adults with BD had white matter differences in prefrontal, temporal, occipital, and cerebellar regions, as well as in thalamic white matter and the uncinate fasciculus. Children and adolescents with BD had white matter changes in frontal regions, in the superior longitudinal fasciculus I, in cingulate-paracingulate white matter, the corpus callosum in subgenual white matter, and in orbitofrontal white matter.

In this study, we sought to investigate the possibility of white matter alterations in familial pediatric BD and, in particular, to fully interrogate frontolimbic brain pathways. We chose to conduct a whole-brain analysis using tract-based spatial statistics (TBSS 1.0, FMRIB Center, Oxford, United Kingdom), a relatively new software package implemented in FSL (FMRIB Center, http://www.fmrib.ox.ac.uk/fsl/tbss/index.html). Tract-based spatial statistics is a software package specifically designed for the analysis of diffusion-weighted data. It implements carefully tuned nonlinear registration, followed by projection onto an alignment-invariant mean fractional anisotropy skeleton and a stringent statistical analysis. This method addresses many concerns regarding previous methods of whole-brain voxel-by-voxel analyses of diffusion-weighted data, including reliable registration of subjects to a common space, choice of smoothing kernel, and partial volume effects. However, it is important to note that while addressing many issues in voxel-by-voxel DTI analyses, TBSS still has limitations in analyzing small fiber tracts, data with within-scan head motion, and regions of crossing fibers or tract junctions (47). Relevant limitations will be discussed in further detail in the Discussion section. To the best of our knowledge, our study is the first to use TBSS in adolescents with BD.

Based on the above-mentioned literature and the brain circuits implicated in the pathophysiology of BD, we hypothesized that white matter would be disrupted in limbic pathways; prefrontal regions, including dorsolateral, ventral, orbitofrontal, and subgenual pathways; and in the corpus callosum. We further hypothesized that white matter alterations would be correlated with severity of illness, as measured by severity of symptoms of depression and mania, duration of illness, and exposure to medications.

Methods and Materials

The protocol was approved by the Stanford University Administrative Panel of Medical Research in Human Subjects. Twenty-one individuals with BD and 18 healthy volunteers were recruited from an ongoing study of bipolar offspring and from the community. After obtaining oral and written informed consent from parents and oral and written assent from their offspring, semi-structured interviews were conducted. Patients had at least one parent with BDI or bipolar disorder II (BDII) as diagnosed by the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I/P) (48), administered by a trained masters-level clinician and/or board-certified psychiatrist (K.D.C.). All subjects, patients and healthy volunteers, were evaluated by the affective disorders module of the Washington University at St. Louis Kiddie Schedule for Affective Disorders and Schizophrenia (WASH-U-KSADS) (49,50) and the Kiddie Schedule for Affective Disorders and Schizophrenia for School-age Children, Present and Lifetime (K-SADS-PL) (51). Subjects were evaluated either by a board-certified child psychiatrist (K.D.C.) or a trained masters-level research assistant, who were both aware of parental diagnosis. Interrater reliability was established at the outset by rating videotaped interviews, observing trained rater interviews, and performing interviews with observation by a trained rater, as described by Geller *et al.* (52). Diagnostic decisions were ultimately made by a child psychiatrist (K.D.C.) based on personal interview, discussion with the research assistant, and written notes of parental and subject responses to interview questions. Current and lifetime diagnoses were established according to DSM-IV-TR criteria. Parents were euthymic at the time of their own and their child's interviews. Patients in this study all received a diagnosis of BDI. Inclusion criteria for bipolar subjects were age 9 years to 18 years, biological parent with BDI or BDII, and diagnosis of BDI by the WASH-U-KSADS. Exclusion criteria were presence of a pervasive developmental disorder, a neurological condition (such as a seizure disorder), a substance use disorder, IQ less than 80, history of head trauma resulting in loss of consciousness, or presence of metallic implants or braces. Subjects had no medical illnesses, although this was not an exclusion criterion. Age of onset of BD was determined retrospectively as the earliest period to the closest month that patients met criteria for a manic or depressive episode, as defined by the DSM-IV.

Exclusion criteria for control subjects included any DSM-IV diagnosis, parental psychopathology (as assessed by SCID-I/P), a first- or second-degree relative with BD (as determined by the family history Research Diagnostic Criteria (53), neurological disorders, IQ less than 80, history of head trauma resulting in loss of consciousness, or presence of metallic implants or braces. Control subjects were not taking psychotropic medications. Subjects were all outpatients at the time of scanning. Patients with BD were administered the clinician-rated Young Mania Rating Scale (YMRS) (54,55) and completed the Childhood Depression Inventory (CDI) (56), the Child Depression Rating Scale (CDRS), and the Conners Rating Scale (57). Questionnaires were completed with the help of a parent if subjects were less than 12 years old. Patients with BD had psychostimulants discontinued for 24 hours before the scan, primarily due to a concurrent, separate functional magnetic resonance imaging (fMRI) study of attention. They were allowed to continue any other current medications such as mood stabilizers or antidepressants due to the risk of mood destabilization.

Subjects were 21 children and adolescents with BD and 18 age-, gender-, and IQ-matched control subjects (Table 1). The diagnosis of BD was based on DSM-IV criteria (1). Standardized cognitive testing using the Wechsler Abbreviated Scale of Intelligence (WASI) (58) was administered to all subjects.

Magnetic resonance images were acquired using a GE-Signa 3-Tesla scanner (General Electric, Milwaukee, Wisconsin). A DTI sequence was based on a single-shot spin-echo echo-planar imaging (EPI) sequence with diffusion-sensitizing gradients applied on either side of the 180° refocusing pulse (59,60). Imaging parameters for the diffusion-weighted sequence were field of view (FOV) = 24 cm, matrix size 128 × 128, echo time (TE)/repetition time (TR) = 106/6000 msec, 19 axial oblique slices, slice thickness 5 mm, skip = 0. The scan was prescribed from the top of the brain and included only the most superior part of the cerebellum. Diffusion gradient duration was $\delta = 32$ msec; diffusion weighting was $b = 900$ sec/mm^2. In addition, a

Table 1. Demographic and Clinical Characteristics of Subjects with BD and Control Subjects

	BD Subjects	Control Subjects
Total Number of Subjects	21	18
Age	16.1 (2.7)	14.5 (2.7)
IQ (WASI) Score	111.4 (8.4)	117.2 (9.2)
Handedness		
Right	20	18
Left	1	0
Gender		
Male	15	14
Female	6	4
Comorbid Diagnosis		
Behavioral disorders[a]	18	None
Anxiety disorders[b]	6	None
Total Number of Comorbid Diagnoses	2.6 (.97)	None
Mood State at Scan		
Euthymic	11	18
Manic	3	None
Depressed	4	None
Mixed	3	None
Family History of Mood Disorders	.51 (.22)	None
Duration of Illness	3.1 (2.3)	None
Medication Exposure		
SSRI	15	
Stimulant	15	
Mood stabilizers	16	
Lithium	6	
Antipsychotics	7	None
Total Number of Categories of Medications Exposed Prior to Scan[c]	3.81 (1.89)	None

ADHD, attention-deficit/hyperactivity disorder; BD, bipolar disorder; CD, conduct disorder; GAD, generalized anxiety disorder; IQ, intelligence quotient; OCD, obsessive-compulsive disorder; ODD, opposition defiance disorder; SAD, social anxiety disorder; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant; WASI, Wechsler Abbreviated Scale of Intelligence.

[a]Behavioral disorders = ADHD, ODD, and CD.

[b]Anxiety disorders = GAD, SAD, OCD, phobia, and panic disorder.

[c]Categories of medications = SSRI (selective serotonin reuptake inhibitors), TCA (tricyclic antidepressants), stimulants, antipsychotics, mood stabilizers, and lithium.

T2-weighted image was acquired by removing the diffusion-sensitizing gradients. Diffusion was measured along six noncollinear directions: XY, XZ, YZ, −XY, −XZ, and −YZ. This pattern was repeated four times for each slice with the sign of all diffusion gradients inverted for odd repetitions.

Fractional anisotropy (FA), trace, and apparent diffusion coefficient (ADC) values were the variables of interest. Fractional anisotropy is a measure that reflects the degree of diffusion anisotropy within a voxel (how diffusion varies along different directions). Anisotropy within a given white matter voxel is determined by fiber diameter and density, degree of myelination (61), extracellular diffusion, and interaxonal spacing (62), as well as by intravoxel fiber-tract coherence (63). Trace is a measure of average diffusivity within a voxel, and ADC is a measure of overall diffusivity within a voxel. Changes in these features as a result of disease states can be detected as changes in water diffusion.

Diffusion-weighted images were corrected for eddy current distortions and head motion using linear image registration (automated image registration [AIR] algorithm) (64). Thereafter, DtiStudio (65) (Radiology Department, John Hopkins University, Baltimore, Maryland, https://www.mristudio.org/) was used to generate FA, trace, and ADC maps. First, all individual images were visually inspected to discard slices with artifacts, after which the remaining images were added for each slice. The pixel intensities of the multiple diffusion-weighted images were then fitted to obtain the six elements of the symmetric diffusion tensor. The diffusion tensors at each pixel were diagonalized to obtain pixel eigenvalues and eigenvectors. The FA was calculated in DtiStudio for each voxel according to Basser and Pierpaoli (63) to produce a fractional anisotropy image. The FA images were further processed using TBSS 1.0, an automated, observer-independent, voxel-by-voxel whole-brain between-group analysis. Tract-based spatial statistics (47) was implemented in FSL 3.3 (66) (http://www.fmrib.ox.ac.uk/fsl/). Fractional anisotropy maps from each individual were co-registered using nonlinear registration Image Registration Toolkit (67) (http://www.doc.ic.ac.uk/~dr/software) to the subject closest to the group mean. After image registration, FA maps were averaged to produce a group mean FA image. A skeletonization algorithm was applied to the group mean FA image to define a group template of the lines of maximum FA. This skeleton is thought to correspond to centers of white matter tracts; thus, it ignores voxels at the edges of tracts, which are susceptible to partial volume effects. Fractional anisotropy values for each individual subject were then projected onto the group template skeleton by searching along perpendiculars from the skeleton to find local maxima. The FA skeleton was thresholded to FA $\geq$ .30 to include the major white matter pathways but avoid peripheral tracts that are more vulnerable to intersubject variability and/or partial volume effects with gray matter. Each subject's aligned FA data were then projected onto this skeleton and the resulting data were fed into voxel-wise cross-subject statistics ($t > 1.5$, $p < .05$) using Randomise (v.1.0 in FSL 3.3, FMRIB Center), a permutation program used for inference (thresholding) on statistic maps when the null distribution is not known (68). Analysis was corrected for multiple comparisons and for cluster size.

Behavioral Correlations with White Matter Anisotropy

We used Randomise (68) in whole-brain analyses as well as in analyses restricted to regions of FA group differences to investigate correlations between FA values and depression, mania severity, attention-deficit/hyperactivity disorder (ADHD) severity, and duration of illness. Fourteen subjects with BD participated in this analysis. Mania scores were assessed using the YMRS; depression scores were assessed using the CDI and the CDRS; ADHD severity was assessed using the Conners Rating Scale; and duration of illness was measured in months since onset of mania.

Results

Between-Group Differences

There were no significant differences between groups in age [$t = 1.5$ (36), $p < .14$] or IQ [$t = 1.5$ (36), $p < .14$] (Table 1).

Subjects with BD had lower FA values than control subjects in the left mid to posterior cingulate gyrus; the fornix; in white matter extending from the fornix to the thalamus; in the genu, body, and splenium of the corpus callosum; and in parietal corona radiata bilaterally (Figures 1 and 2). There were no regions with significantly higher FA in the BD group. There were no significant differences between groups in trace and ADC

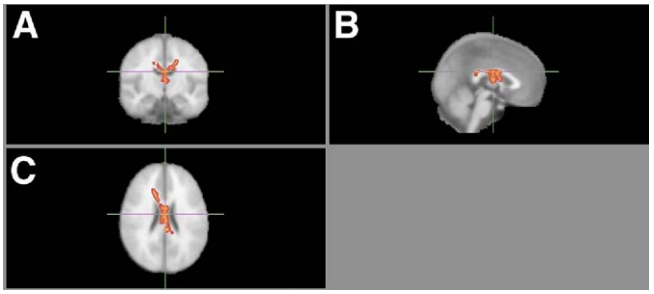

Figure 1. Coronal **(A)**, sagittal **(B)**, and axial **(C)** views of regions of significant fractional anisotropy (FA) differences between adolescents with bipolar disorder and control subjects. Group differences are mapped onto an average T1 Montreal Neurological Institute (MNI) template (95) (group differences were "thickened" for visualization purposes). FA, fractional anisotropy; MNI, Montreal Neurological Institute.

values. To further validate our results, we used our cluster of group differences to generate a region of interest at the point of maximal differences between groups, which was at the corpus callosum/fornix junction. We used those ROIs to extract FA values, which were further analyzed using an independent sample *t* test in SPSS (SPSS Inc., Chicago, Illinois) (Figure 2). It is important to note that 3 T EPI images are prone to image distortions in ventral brain regions. Therefore, the lack of orbitofrontal differences in our sample should be interpreted with caution, as this negative finding may have been a result of such distortions.

Behavioral Correlations

There were no significant correlations between FA values and depression severity, mania severity, ADHD severity, duration of illness, or medication exposure.

Discussion

In this whole-brain DTI study of children and adolescents with familial BD, white matter FA values were decreased in the BD group compared with the control group within the limbic system (the fornix and the cingulate gyrus) and in white matter extending from the fornix to the thalamus. In addition, significant FA differences were seen throughout the corpus callosum, as well as in parietal white matter. Some regions in which we observed structural white matter differences were previously reported in ROI studies of adults with BD, including the corpus callosum and thalamic fibers (32,69).

Dysfunction within the anterior limbic system and associated prefrontal regions has been hypothesized to contribute to the combination of affective, cognitive, and vegetative symptomatology in BD (11,13,69). In our study, we found evidence for white matter disruption in limbic structures including the fornix and the mid-posterior cingulate. The fornix is located at the center of the limbic system and contains pathways that extend into the thalamus, hippocampus, and the nucleus accumbens, brain regions important for emotional regulation and reward processing that have been implicated in BD (8,9,70–73). The only previous report of fornix involvement in BD is a case report by Xu *et al.* (74) describing a BDII patient who had an intraventricular tumor impinging the fornix, which, the authors hypothesized, caused irritability and hypomanic symptoms. Lack of previous imaging reports of structural differences in the fornix in BD compared with control subjects may be explained by the anatomic characteristics of the fornix, a thin structure devoid of gray matter and surrounded by cerebrospinal fluid (CSF), which makes the fornix difficult to investigate with most neuroimaging modalities that require normalization and smoothing. Tract-based spatial statistics analysis does not use smoothing; it uses a sample specific white matter skeleton, which increases the chances of observing the fornix. However, since the fornix is a very thin structure, we cannot rule out partial volume effects accounting for at least some of the fornix findings. Another interpretation of our results would be that the fornix differences between groups are in fact differences of fornix thickness. Given these caveats, the fornix findings in our study should be interpreted with caution and serve as a data point to encourage future studies to investigate this structure more thoroughly in BD.

The mid to posterior cingulate also is important for modulation of response to emotional stimuli (75). Lack of inhibitory control within a network comprised of the dorsal anterior cingulate, posterior cingulate, and dorsolateral and dorsomedial prefrontal regions is thought to play a role in emotional dysregulation in affective

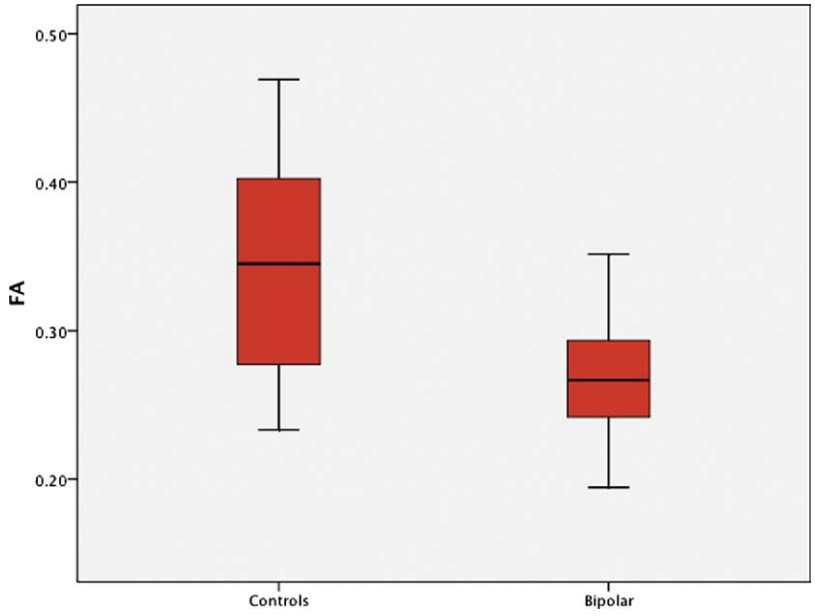

Figure 2. FA values between groups at the junction of the fornix and corpus callosum (region of peak FA difference) ($t = 3.83$, $p < .0001$). FA, fractional anisotropy.

disorders (76). Specifically in BD, several imaging modalities demonstrated involvement of the posterior cingulate, including reduced volume in adult patients with first-episode mania (77), reduced functional connectivity with the amygdala in children with BD (78), increased activity in subjects with BD during an emotional versus neutral go/no-go task (76), decreased activity in pediatric BD subjects watching negatively valenced visual stimuli (13), and increased metabolism in depressed subjects with BD when compared with control subjects (9).

Neuroimaging studies conducted in children and adolescents with BD suggest that abnormalities in frontolimbic brain regions occur early in the course of illness, especially in the amygdala and basal ganglia (12). Further, it has been suggested that BD is a neurodevelopmental condition in which disease manifestations should be evident along the course of central nervous system maturation (79). Subcortical areas, such as the amygdala, might represent sites of initial abnormalities and subsequently these could extend to prefrontal cortical regions that continue to develop into adulthood. Our analysis suggests that some involvement exists in white matter pathways underlying limbic and neocortical areas quite early in the disease course. It is likely that prefrontal involvement is not fully expressed in functional or anatomical abnormalities until later in adulthood (80,81).

The corpus callosum, the major interhemispheric commissure, connects most of the neocortical areas and is comprised of extensive networks subserving motor and sensory abilities as well as memory, attention, language, intelligence, and emotional states (82–86). The corpus callosum develops throughout childhood and adolescence as evidenced by increased size (87), decreased signal intensity (88), and an increase in fractional anisotropy values (89). In adults with BD, the corpus callosum is smaller (16,90) and the corpus callosum signal intensity (CCSI) is lower (15) compared with healthy control subjects. In children and adolescents with BD, the corpus callosum has reduced CCSI and altered shape but no change in size compared with healthy control subjects (17,18). Our finding of reduced FA throughout the corpus callosum in children and adolescents with BD is in contrast to the previous finding of increased FA in the genu of the corpus callosum in adults with BD (35). This discrepancy may indicate an abnormal maturation process in the corpus callosum occurring in individuals with BD, with lower FA in adolescence representing reduced coherence or aberrant myelination with increasing FA with age. The underlying structural changes resulting in increased FA in adulthood are not yet understood and this observation should be further validated and investigated. A possible cause for an increase of FA with age is a change in the extracellular compartment. For example, abnormal perivascular structures that develop with age may present a barrier to anteroposterior flow of extracellular fluid and thus increase callosal anisotropy (91). The discrepancy in corpus callosum FA findings between adults and adolescents also may be due to the different methods used in the two studies. Yurgelun-Todd *et al.* (92) used an ROI analysis and suggested that increased FA values in the genu of the corpus callosum in adults with BD may represent reduced FA in one fiber tract in regions of crossing fibers, resulting in a net increase in FA. We used TBSS, which investigates only the skeleton of white matter tracts. It is likely that within the core of the genu, fibers are more compactly packed with less crossing fibers. Thus, with TBSS we are more likely to observe the true reduction in FA if present.

In this study, we identified reduced FA values in BD with no significant changes in trace values between adolescents with BD and control subjects. This observation is emerging as a consistent finding among studies in BD (30,35). Typically with loss of myelin or axonal integrity, reduced FA is observed with concurrent increase in trace values or average diffusivity. However, trace is not expected to change with reduced fiber tract coherence (30). Combining these two measures of water diffusion in white matter thus offers clues to the nature of white matter pathology in BD and suggests reduced fiber tract coherence is present early in the course of the disease. In our study, there also were no significant changes between groups in ADC values. This finding is not as consistent among studies. While a previous DTI study in adolescents with BD did not find any ADC differences between adolescents with BD and control subjects (41), another study reported increased ADC values in adolescents with BD; however, their analysis was not as stringent as ours (uncorrected), which may account for this difference (39).

The following limitations should be noted in the current study. Most subjects were taking medication at the time of scanning and/or had psychotropic medication exposure history, the effects of which on DTI scans are largely unknown. However, in our sample, there were no significant correlations between white matter structure and medication exposure. In addition, our subjects had significant ADHD symptoms. As ADHD comorbidity is quite common in this population, it likely represents a phenotypic manifestation of early-onset BD (93). Thus, it is difficult to delineate with certainty whether some or all of our DTI findings are associated with ADHD type symptoms (e.g., inattention, hyperactivity) versus mood-related symptoms. However, our analysis revealed no significant correlations between ADHD severity and FA values both in a whole-brain analysis and when restricting analysis to regions of between-group differences. In addition, a previous DTI study in children with ADHD showed a different pattern of white matter involvement than that observed in our sample (94). Future studies investigating children and adolescents with BD with and without comorbid ADHD may be able to differentiate patterns of white matter involvement in this population.

Another limitation is in our post hoc behavioral analysis, which should be regarded as exploratory as it included only a subset of our sample and may have been negative due to lack of power.

In summary, we observed significant white matter tract alterations in adolescents with BD within pathways involved in emotional, behavioral, and cognitive regulation. These same pathways have previously been implicated in the pathophysiology of BD. Our results suggest that widespread alterations in white matter are present early in the course of the disorder. An intriguing and important follow-up study will be to investigate whether early treatment of BD normalizes the development of these pathways and if improvement of particular symptoms is associated with structural changes in regional white matter anatomy. Thus, longitudinal and intervention studies of children with and at high risk for developing pediatric-onset BD will be critical for elucidating the role of white matter abnormalities in this disorder.

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Otsuka America Pharmaceutical, Inc., and GlaxoSmithKline; serves on the Speakers Bureau for Abbott Laboratories, AstraZeneca Pharmaceuticals, Bristol-Myers Squibb, and Eli Lilly and Company; and serves on the Advisory Board for Abbott Laboratories and Eli Lilly and Company.

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