Altered Development of White Matter in Youth at High Familial Risk for Bipolar Disorder: A Diffusion Tensor Imaging Study

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Objective: To study white matter (WM) development in youth at high familial risk for bipolar disorder (BD). WM alterations are reported in youth and adults with BD. WM undergoes important maturational changes in adolescence. Age-related changes in WM microstructure using diffusion tensor imaging with tract-based spatial statistics in healthy offspring having a parent with BD were compared with those in healthy controls. **Method:** A total of 45 offspring participated, including 20 healthy offspring with a parent diagnosed with BD (HBO) and 25 healthy control offspring of healthy parents (CONT). All were free of medical and psychiatric disorders. Mean fractional anisotropy (FA), radial diffusivity (RD), and longitudinal diffusivity were examined using whole-brain analyses, co-varying for age. **Results:** Group-by-age interactions showed a linear increase in FA and a linear decrease in RD in CONT in the left corpus callosum and right inferior longitudinal fasciculus. In HBO, there was a linear decrease in FA and an increase in RD with age in the left corpus callosum and no relation between FA or RD and age in the right inferior longitudinal fasciculus. Curve fitting confirmed linear and showed nonlinear relations between FA and RD and age in these regions in CONT and HBO. **Conclusions:** This is the first study to examine WM in healthy offspring at high familial risk for BD. Results from this cross-sectional study suggest altered development of WM in HBO compared with CONT in the corpus callosum and temporal associative tracts, which may represent vulnerability markers for future BD and other psychiatric disorders in HBO. J. Am. Acad. Child Adolesc. Psychiatry, J. Am. Acad. Child Adolesc. Psychiatry, 2010; 49(12):1249–1259. **Key words:** bipolar disorder, familial risk, white matter, diffusion tensor imaging, neurodevelopment

Bipolar disorder (BD) is a serious psychiatric illness affecting 1% to 3% of the adult population and remains a leading cause of morbidity, functional impairment, and completed suicide.[1] BD is characterized by difficulties in the regulation of emotions and behavior, as indicated by episodes of mania and depression. BD is highly heritable: the risk of BD is much greater in first-degree relatives of individuals diagnosed with BD.[2,3] Recent evidence has indicated that offspring of parents with BD are at increased risk for BD and other psychiatric disorders, including BD spectrum disorder, anxiety, and depression disorders.[2] Although genetic and environmental factors and their interactions are important in the development of BD, abnormalities of brain structure and function that most likely mediate these effects have yet to be elucidated. Converging evidence from epidemiologic, genetic, and neuroimaging studies has suggested that abnormalities in the development of white matter (WM) may play an important role in the neuropathophysiology of BD.[4] However, the extent to which WM development may be altered in offspring at high familial risk of BD has yet to be determined.


Supplemental material cited in this article is available online.

Diffusion tensor imaging (DTI) is a noninvasive neuroimaging technique that uses the diffusion of water to investigate subtle changes in WM microstructural organization. DTI employs fractional anisotropy (FA), an index of the ratio of diffusional anisotropy in longitudinally aligned versus transverse directions of WM tracts. That is, voxels containing water moving predominantly along the principal diffusion direction, rather than the transverse directions, have a higher FA. Findings from previous DTI studies have suggested that adults with BD have WM abnormalities in prefrontal and subcortical regions implicated in emotional processing and emotion regulation. The majority of these studies, using a region-of-interest approach, have reported WM abnormalities in adults with BD in prefrontal regions,[5-12] including frontotemporal WM abnormalities in the uncinate fasciculus, a major WM tract connecting anterior temporal and orbitomedial prefrontal cortices.[7,10,11] Whole-brain studies in adults with BD have confirmed WM abnormalities, including increases and decreases in FA, in frontotemporal regions. [6,13,14] They also have reported abnormalities in fibers projecting to temporal[13] and occipital cortices.[6,13] Similarly, the few recent studies in pediatric BD also have reported an abnormally lower FA in prefrontal regions.[15-18] Furthermore, lower FA,[15,19] abnormal signal intensity,[20] and abnormal curvature shape[21] of the corpus callosum (CC) have been shown in youth with BD compared with healthy controls. FA decreases in fibers projecting to temporal,[16] frontal,[19] and occipital cortices[15,16] have also been reported in whole-brain studies in youth with BD compared with healthy controls.

One methodologic issue in DTI is the interpretation of changes in FA. A higher FA could reflect greater myelination of WM fibers, a larger number of myelinated fibers, or greater longitudinal versus oblique directional alignment of fibers. To improve the interpretation of changes in FA, including measurements of radial and longitudinal diffusivities (RD and L1, respectively)[22] has been recommended. L1 is an index of the principal—longitudinal—diffusion direction, whereas RD is an average of the transverse directions and an index of the diffusivity in directions that are perpendicular to the principal axis of diffusion. For example, changes in RD in the absence of changes in L1 have been associated with changes in myelin,[23] whereas changes in L1 in the absence of changes in RD have been associated with increases in axon diameter.[24] In a recent study with BD versus healthy adults,[6] we included RD and L1, which contributed to a better interpretation of group differences in FA.

Abnormalities in WM have been observed in individuals at risk for BD.[2,25,26] For example, one study reported decreased left hemispheric WM volume in adult patients with BD and their unaffected twin compared with age-matched healthy individuals.[27] We are aware of only one study to date that, using voxel-based DTI, examined WM tracts in offspring (4 to 12 years old) of parents with BD (n = 7) compared with children with BD (n = 10) and age-matched healthy controls (n = 8).[19] This study reported lower FA in bilateral superior longitudinal fascicule in the offspring of parents with BD and children with BD compared with healthy controls. However, like the children with BD, the majority of the offspring of parents with BD met criteria for another Axis I disorder (e.g., attention-deficit/hyperactivity disorder), which may have had an effect on the DTI findings in this group. Although offspring of parents with BD do exhibit higher levels of psychopathology than community controls,[2] focusing on *healthy* offspring with a parent diagnosed with BD is an important *first step* to improve the ability to identify potential neurodevelopmental vulnerability markers of BD and eliminate the possible confounding effects of psychopathology and/or psychotropic medication in offspring with BD on DTI measurements.

Another important issue is the extent to which WM tracts develop normally in youth at high familial risk of BD. A growing number of studies in healthy youth has suggested important maturational changes in WM during adolescence.[28,29] A recent DTI study reported age-related increases in FA (decreases in RD) in specific WM tracts across adolescence.[28] Given that adolescence is a vulnerable developmental window for the onset of mood disorders such as BD,[30] examining age-related changes in WM tracts in healthy offspring having a parent with BD across adolescence may help elucidate specific neurodevelopmental vulnerability markers of BD.

In this study, we used DTI to examine the development of WM microstructure in healthy offspring having a parent with BD (healthy bipolar offspring [HBO]) versus healthy control offspring of healthy parents (healthy control [CONT]). We conducted whole-brain analysis

using tract-based spatial statistics. Our main focus was on age-related changes in FA across groups. We also explored age-related changes in RD and L1, as complementary measurements to FA, and examined the main effects of group. Given the evidence of abnormal WM microstructure associated with BD, in this cross-sectional study, we tested the hypothesis that HBO would exhibit alterations in the development of WM and as such, unlike CONT, would not show the normative increases in FA (and decreases in RD) in whole-brain WM with age. We further hypothesized that these alterations in WM in HBO would be particularly evident in the CC and frontotemporal regions (i.e., uncinate fasciculus).

METHOD

Participants

The study was approved by the University of Pittsburgh institutional review board. Parents signed consent forms, and youths signed assent forms. A total of 45 healthy offspring participated in the study (Table 1). Of these, 20 were HBO having at least one biological parent diagnosed with BD (13 with BD type I, 6 with BD type II, 1 with BD not otherwise specified) and 25 were age-matched CONT. Parents of the CONT did not have any current Axis I disorder or history of mood disorder or psychotic disorder. Also, first-degree relatives of the CONT did not have any current or history of BD. Participants in the HBO and CONT groups were matched by age (e.g., participants in the CONT group were matched using a maximum of 1 year older or younger than their HBO counterparts). Participants were recruited from an ongoing longitudinal study on the psychiatric symptomatology in offspring of parents with BD (MH #060952-06, Boris Birmaher, M.D., principal investigator).

As part of their participation in this study, diagnostic interviews were conducted with the offspring and their parents using semistructured diagnostic instruments: the Structural Clinical Interview for *DSM-IV* (I and II) was used to ascertain lifetime psychopathology for all parents and the Schedule for Affective Disorders and Schizophrenia for School Aged Children—Present and Lifetime Version (K-SADS-PL) was used to interview parents about their children and children about themselves for the presence of current and lifetime psychiatric disorders. To date, diagnostic reliability of the K-SADS-PL has been high ($\kappa = 0.90$). Final diagnoses were assigned by consensus using best-estimate procedures. The family history-research diagnostic criteria method[31] was used to ascertain the psychiatric history of biological co-parents not seen for direct interview.

Participants in this study who were 8 to 17 years old and who did not endorse any current *DSM-IV* Axis I diagnosis or a history of depression or BD on the K-SADS-PL were invited to participate in the present neuroimaging study. Eligible participants were sent a letter and contacted by telephone for initial screening. Participants and their parents completed the questionnaires noted below *on the day of the neuroimaging scan* to ensure that all participants were *free* of any current *DSM-IV* Axis I psychiatric diagnoses immediately before the neuroimaging evaluation. Parents completed the following questionnaires about their children: the Stony Brook Child or Adolescent Symptom Inventory-4, to assess for *DSM-IV* Axis I diagnoses; the Mood and Feelings Questionnaire, to assess for symptoms of depression; the Child Affect Lability Scale, to assess for

TABLE 1 Demographic and Clinical Characteristics of Healthy Offspring Having a Parent with Bipolar Disorder and Age-Matched Control Offspring of Healthy Parents

	Group			
	HBO (n = 20)	CONT (n = 25)	Statistic	*p* Value
Age at scan (y), mean ± SD	13.2 ± 2.5	13.9 ± 2.6	$t_{43} = -0.94$	.36
Male/female	9/11	7/18	$\chi^2_1 = 0.76$	.35
Socioeconomic status, mean ± SD	41 ± 14.9	47 ± 9.7	$t_{33} = -1.4$	.17
Full-scale IQ, mean ± SD	114.7 ± 13.6	114.6 ± 10.1	$t_{21} = 0.01$	.99
Percentage right-handed	82	82	$\chi^2_1 = 0.001$	.97
MFQ—Parent Version, mean ± SD	3.8 ± 3.7	2.1 ± 4.5	$t_{42} = 1.33$	.19
MFQ—Child Version, mean ± SD	5.5 ± 5.7	5.4 ± 5.4	$t_{41} = 0.07$	.95
SCARED—Parent Version, mean ± SD	6.0 ± 4.7	4.1 ± 5.2	$t_{42} = 1.2$	.23
SCARED—Child Version, mean ± SD	9.2 ± 7.2	8.6 ± 5.5	$t_{42} = 0.31$	.76
CALS, mean ± SD	5.0 ± 4.4	2.8 ± 3.9	$t_{42} = 1.69$	.10

Note: CALS = Child Affect Lability Scale (range, 0-80); CONT = healthy control offspring of healthy parents; HBO = healthy offspring having a parent diagnosed with bipolar disorder; MFQ = Mood and Feelings Questionnaire (range, 0-68); SCARED = Screen for Childhood Anxiety and Related Disorders (range, 0-82).

mood lability; and the Screen for Childhood Anxiety and Related Disorders, to assess for symptoms of anxiety. Offspring completed the child self-report version of the Mood and Feelings Questionnaire and Screen for Childhood Anxiety and Related Disorders. Socioeconomic status was measured with the Hollingshead Four-Factor Index. Handedness was determined using the Edinburgh Handedness Inventory. IQ was determined using the Wechsler Abbreviated Scale of Intelligence. Exclusion criteria included an IQ below 70, a history of head trauma, neurologic disorder, unstable medical illness, presence of metal objects in the body, use of drug and alcohol, and pregnancy.

DTI Acquisition Parameters

Magnetic resonance images were acquired on a 3-T Siemens Magnetom Allegra syngo MR-2004A (Siemens Medical Systems, Iselin, NJ). DTI data were acquired using a coronal diffusion-weighted single-shot spin-echo planar imaging sequence, parallel to the Anterior Commissure-Posterior Commissure (AC-PC) line (repetition time = 4,400 ms, echo time = 76 ms, bandwidth = 1,860 Hz/pixel, flip angle = 90°, field of view = 200 × 200, 34 3-mm-thick slices, no gaps, matrix size = 80 × 128, echo-planar imaging (EPI) factor = 128, acquisition = 6′ 16″). Two b values were used: one b = 0 (no-diffusion weighting) image and six non-coplanar b = 850 s/mm^2 (diffusion-weighting b value) images were acquired with parameters similar to those employed in recent DTI studies.[6,32] Fat saturation was used to remove scalp signal (to control for chemical shift or ghosting artifacts).

DTI Preprocessing

Diffusion-weighted images were processed using the Functional Magnetic Resonance Imaging of the Brain (FMRIB) Software Library (FSL; version 4.1).[33] Images were first inspected for motion artifacts and then registered to the b = 0 image, as a reference, by affine transformations to minimize distortions due to eddy currents and decrease simple head motion using Eddy Current Correction. Images were extracted using the Brain Extraction Tool.[34,35] A DT model was fitted at each voxel, providing a voxel-wise calculation of FA and main diffusion scalar vectors.[36]

DTI Data Analyses

Diffusion-weighted images were analyzed using the FSL. Using a nonlinear registration algorithm, we employed tract-based spatial statistics (version 1.2) in FSL to align FA images. Each subject's FA image was first aligned to a higher-resolution FA standard space (voxel size = 1 mm^3; Montreal Neurological Institute atlas).[37] Then, the derived mean FA image was minimized to generate a template-skeleton embodying the center of all tracts derived from the entire group. An FA with a threshold greater than or equal to 0.20 was set to exclude peripheral tracts that might lead to erroneous interpretations due to anatomic intersubject variability and/or partial volume effects with gray matter. To examine the group-by-age interaction and main effects of group on FA, each subject's aligned FA data were projected onto this template-skeleton mask (volume = 138,148 mm^3) and entered into a whole-brain voxel-wise analysis of FA. We used Randomize (version 2.1; http://www.fmrib.ox.ac.uk/fsl/randomise/index.html), which is a permutation program enabling modeling and inference using standard "general linear model" design, and nonparametric independent t tests (permutation method, n = 5,000, no smoothing factor). Age was modeled as a covariate. To control for multiple statistical testing, we maintained a false-positive detection rate at $p < .05$. The number of contiguous voxels needed to maintain this false-positive detection rate was empirically determined by Monte Carlo simulations implemented in AlphaSim,[38] which was conducted on uncorrected t maps ($p \leq .001$) in FA, employing the WM skeleton mask described above; a dual thresholding of type I error and cluster-size thresholding (CST) were obtained. To help interpret findings in FA, whole-brain voxel-wise analyses of RD and L1[39] were performed in addition to AlphaSim correction ($p < .05$) as described above.

Our main analyses were based on a general linear model. We therefore report *linear* relations between FA (RD, L1) and age. Given that some studies in normative samples have also reported nonlinear relations, we also explored *nonlinear* functions (Table S1, available online). Because these analyses were exploratory, we used $p < .05$ uncorrected. We also explored whether there were any group-by-sex differences.

RESULTS

Demographic and Clinical Characteristics

There were no significant group differences in age, sex, socioeconomic status, IQ, handedness, and mean total scores on the Mood and Feelings Questionnaire, Screen for Childhood Anxiety and Related Disorders, and Child Affect Lability Scale (Table 1).

Whole-brain Analyses of FA and Corresponding RD and L1

Group-by-age interactions for FA were AlphaSim corrected ($p < .05$), with a resulting CST of at least 16 voxels. AlphaSim correction for RD and L1 required a CST of a least 12 voxels. All linear relations between diffusivity measurements and age are reported in Table 2. All nonlinear curve fitting statistics are reported in Table S1 (available online).

There was a significant group-by-age interac-

TABLE 2 Means, Standard Deviations, and Nonparametric Independent *t* Test Examining Group-by-Age Interaction (Age as Covariate) and Main Effect of Group on Fractional Anisotropy (FA) in Whole-Brain Level Analysis and Radial Diffusivity (RD) and Longitudinal Diffusivity (L1) in White Matter Regions Showing Differences in Fractional Anisotropy between Healthy Offspring Having a Parent Diagnosed with Bipolar Disorder and Healthy Control Offspring of Healthy Parents

	Descriptives		Group × Age Interaction[a,b]			Main Effect of Group		
	Group	Mean ± SD	Voxels (n)	t_{max}	*p* Value	Voxels (n)	t_{max}	*p* Value
Fractional Anisotropy								
Left corpus callosum (body division)	HBO	0.52 ± 0.04	20	3.8	.050	35	4.0	.050
MNI x, y, z: −18, −30, 34	CONT	0.50 ± 0.05						
Right inferior longitudinal fasciculus (temporal cortex)	HBO	0.46 ± 0.07	15	4.3	.050	13	4.1	.050
MNI x, y, z: 49, −23, −22	CONT	0.45 ± 0.10						
Radial Diffusivity								
Left corpus callosum (body division)	HBO	0.54 ± 0.05	12	3.7	.050	12	4.3	.050
MNI x, y, z: −18, 9, 36	CONT	0.53 ± 0.07						
Right inferior longitudinal fasciculus (temporal cortex)	HBO	0.56 ± 0.05	14	4.2	.050	14	3.5	.050
MNI x, y, z: 49, −20, −22	CONT	0.55 ± 0.07						
Longitudinal Diffusivity								
Right inferior longitudinal fasciculus (visual cortex)	HBO	1.19 ± 0.25	28	4.5	.050	26	4.4	.050
MNI x, y, z: 24, −59, −1	CONT	1.19 ± 0.13						

Note: For RD and L1, mean ± SD is reported with a scaling factor of 1,000. Nonparametric independent t test = permutation method (permutations = 5,000, no smoothing factor), including age as a covariate and group-by-age interaction; HBO (n = 20) and CONT (n = 25). CONT = healthy control offspring of healthy parents; HBO = healthy offspring having a parent diagnosed with bipolar disorder; MNI = Montreal Neurological Institute atlas; t_{max} = maximal value of t in reported cluster; WM = white matter.

[a]Monte Carlo simulation with AlphaSim correction was run on uncorrected f statistical maps (p < .001), obtaining a dual thresholding of type I error (AlphaSim p < .05, corrected) and cluster-size thresholding (t-test cluster-size thresholding > 16 voxels for FA and > 12 voxels for RD and L1) to control for multiple voxel-level comparisons.

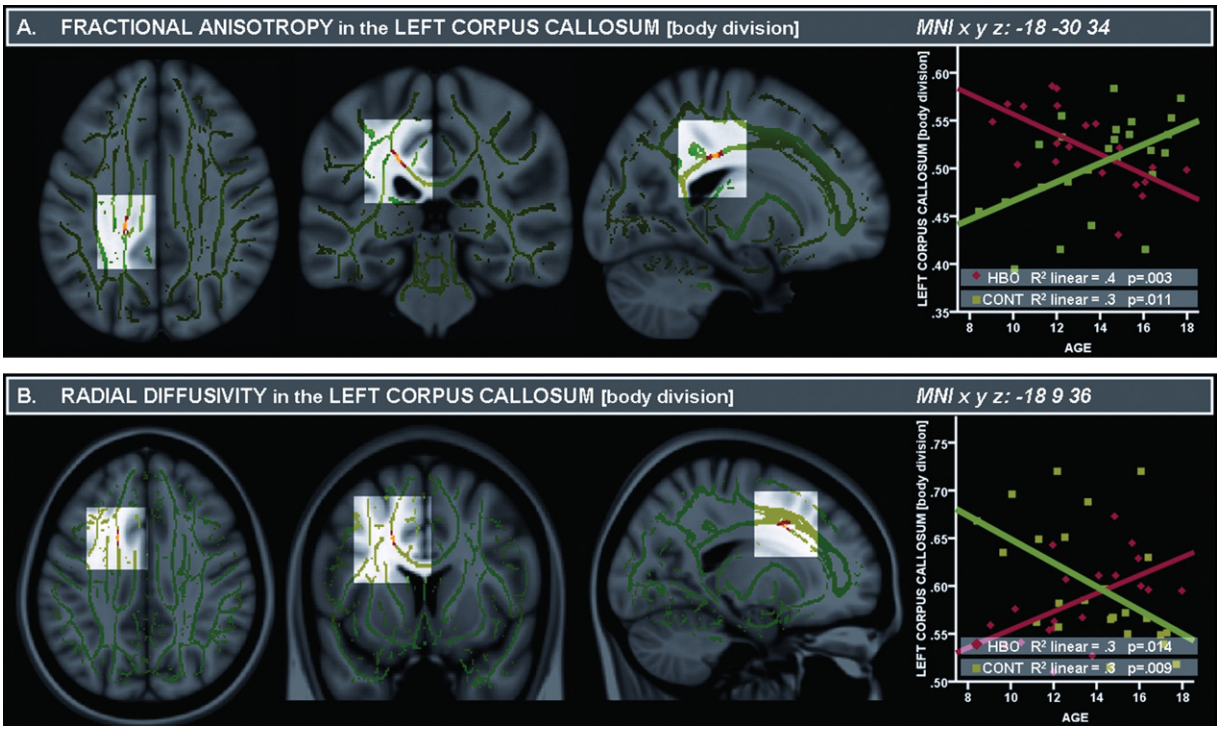
[b]Between FA and age, in the left corpus callosum there was a positive relation in CONT (R^2 linear = 0.3, p = .011) and a negative relation in HBO (R^2 linear = 0.4, p = .003) and in the right inferior longitudinal fasciculus in CONT (R^2 linear = 0.3, p = .004), but no relation in HBO (R^2 linear = 0.0, p = .369). Between RD and age, in the left corpus callosum there was a negative relation in CONT (R^2 linear = 0.3, p = .009) and a positive relation in HBO (R^2 linear = 0.3 p = .014) and in the right inferior longitudinal fasciculus in CONT (R^2 linear = 0.5, p < .001), but no relation in HBO (R^2 linear = 0.1, p = .214). Between L1 and age, in the right inferior longitudinal fasciculus there was a positive relation in CONT (R^2 linear = 0.2, p = .023) and a negative relation in HBO (R^2 linear = 0.4, p = .002).

tion in the region of the body of the left CC (t_{max} = 3.8; Table 2). This interaction resulted from a positive relation between FA and age in the left CC in CONT (R^2_{linear} = 0.3, p = .011) and a negative relation in HBO (R^2_{linear} = 0.4, p = .003). Furthermore, in a nearby region in the body of the left CC, there was a significant interaction in RD (t_{max} = 3.7; Table 2), which resulted from a negative relation between age and RD in CONT (R^2_{linear} = 0.3, p < .009) and a positive relation in HBO (R^2_{linear} = 0.3 p = .014; Figure 1).

There was also a significant group-by-age interaction for FA in the region of the right inferior longitudinal fasciculus (ILF) in the temporal pole (t_{max} = 4.3; Table 2) that just failed to meet our CST (cluster size = 15). This interaction resulted from a positive relation between age and FA in the right ILF in CONT (R^2_{linear} = 0.3, p = .004) but no relation between age and FA in this region in HBO (R^2_{linear} = 0.0, p = .369). In the same region, there was a significant interaction in RD (t_{max} = 4.2; Table 2) that resulted from a negative relation between age and RD in CONT (R^2_{linear} = 0.5, p < .001) and no relation in HBO (R^2_{linear} = 0.1, p = .214; Figure 2).

There was a significant group-by-age interaction in L1 for a cluster in the region of right ILF in the visual cortex (t_{max} = 4.5; Table 2) that resulted from a positive relation between age and L1 in CONT (R^2_{linear} = 0.2, p = .023) and a

FIGURE 1 (A) Fractional anisotropy (FA) and (B) radial diffusivity (RD) maps depicting (from left to right) coronal, axial, and sagittal views (above) of the left corpus callosum, body division (Montreal Neurological Institute atlas [MNI] x, y, z for FA: −18, −30, 34; MNI x, y, z for RD: −18, 9, 36). Note: RD values are reported on the y axis with a scaling factor of 1,000. The template is the standard MNI-152 1-mm brain template. Colored voxels in red-yellow represent findings significantly different between healthy offspring having a parent with bipolar disorder (HBO) and age-matched control offspring of healthy parents (CONT). Red-yellow indicates higher FA and decreased RD in HBO than CONT ($t \geq 3$; $p \geq 0.05$, corrected: scale ranging from red to yellow). We determined the most probable anatomic localization of each cluster with the atlas tool of the Functional Magnetic Resonance Imaging of the Brain Software Library, version 4.1,[33] using all anatomic templates.



negative relation between age and L1 in HBO ($R^2_{linear} = 0.4$, $p = .002$; Figure 2).

In the region of the CC, there was also a significant main effect of group for FA and RD (FA: $t_{max} = 4.0$ and RD: $t_{max} = 4.2$; Table 2), indicating greater FA (and decreased RD) in HBO compared with CONT. In the region of the right ILF in the temporal pole, there was a significant main effect of group for RD ($t_{max} = 3.5$; Table 2), indicating decreased RD in HBO compared with CONT. FA failed to meet our CST (cluster size = 13, $t_{max} = 4.1$; Table 2). In the region of the right ILF in the visual cortex, there was also a significant main effect of group for L1 ($t_{max} = 4.4$; Table 2), which resulted from significantly greater L1 in HBO compared with CONT.

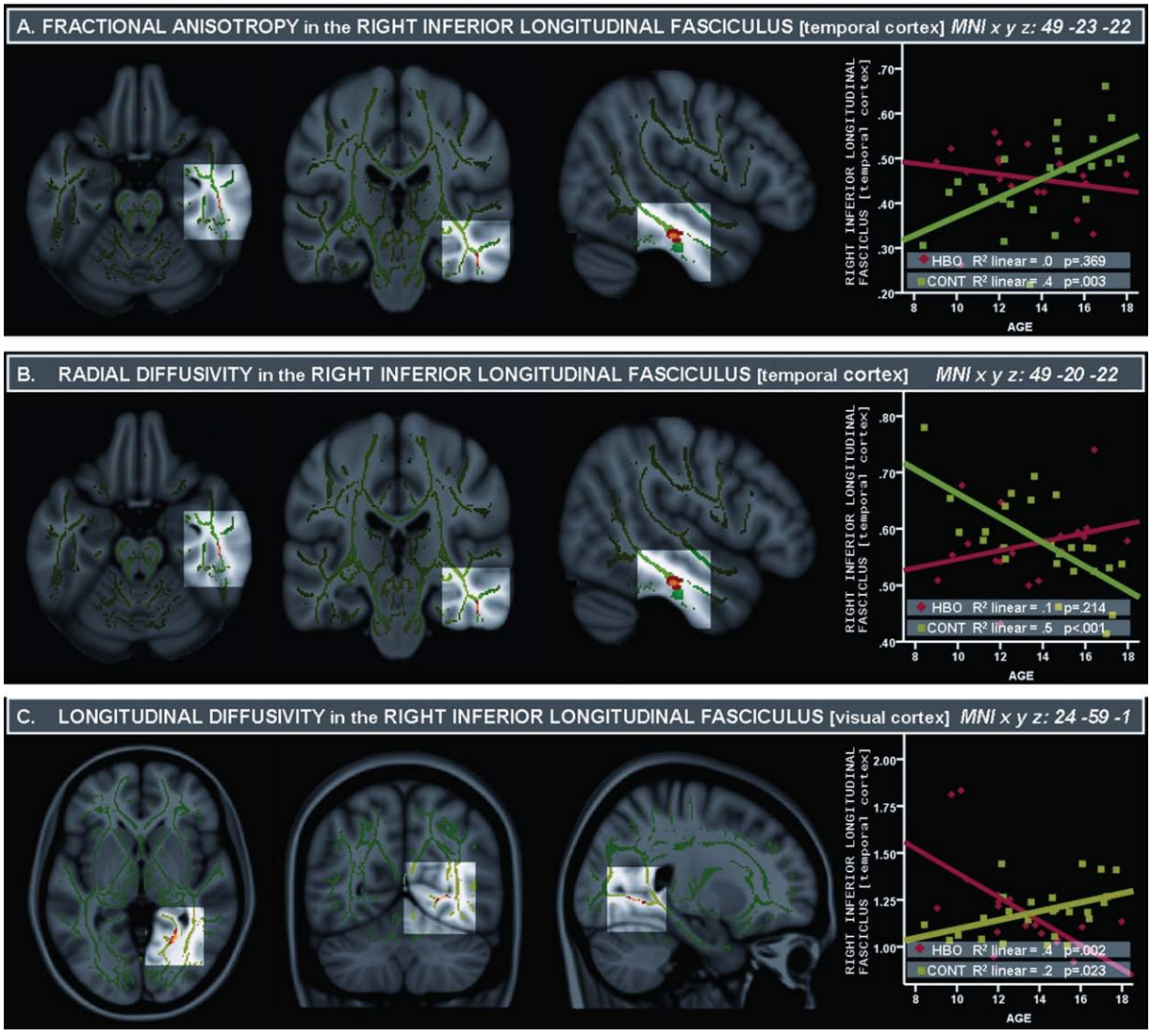
Curve fitting confirmed linear but also showed nonlinear best-curve fits for relations between FA, RD, and L1 and age in the left CC and right ILF in CONT and between FA and L1 and age in the left CC and right ILF (visual cortex) in HBO (Table S1, available online).

Exploratory nonparametric independent-samples Mann-Whitney U tests did not show any significant sex differences in either group in FA and RD in the region of the body of the left CC, in the right ILF (temporal pole), and in L1 in the region of the right ILF in the visual cortex.

DISCUSSION

This is the first study to examine WM microstructure in healthy offspring having a parent diagnosed with BD. The significant group-by-age interactions in this cross-sectional study supported our hypotheses that HBO would not show the same patterns of greater FA (and decreased RD) with increasing age observed in CONT and that these alterations would be particularly evident in the CC and frontotemporal regions. In

FIGURE 2 (A) Fractional anisotropy (FA) and (B) radial diffusivity (RD) maps depicting (from left to right) coronal, axial, and sagittal views (above) of the right inferior longitudinal fasciculus in the temporal cortex (Montreal Neurological Institute atlas [MNI] x, y, z for FA: 49, −23, −22; MNI x, y, z for RD: 49, −20, −22). RD values are reported on the y axis with a scaling factor of 1,000. (C) Longitudinal diffusivity (L1) maps depicting (from left to right) coronal, axial, and sagittal views (above) of the right inferior longitudinal fasciculus in the visual cortex (MNI x, y, z: 24, −59, −1). Note: L1 values are reported on the y axis with a scaling factor of 1,000. The template is the standard MNI-152 1-mm brain template. Colored voxels in red-yellow represent findings significantly different between healthy offspring having a parent with bipolar disorder (HBO) and age-matched control offspring of healthy parents (CONT). Red-yellow indicates higher FA and L1 and decreased RD in HBO than in CONT ($t \geq 3$; $p \geq 0.05$, corrected: scale ranging from red to yellow). We determined the most probable anatomic localization of each cluster with the atlas tool of the Functional Magnetic Resonance Imaging of the Brain Software Library, version 4.1,[39] using all anatomic templates.



particular, our results showed *increases* in FA (decreases in RD) in CONT in the left CC and right ILF, supporting previously documented age-related changes in normative samples. In HBO, however, we observed *decreases* in FA (increases in RD) with age in the left CC and no relation between FA (RD) and age in the right ILF. We next discuss how our findings relate to previous findings in BD and familial risk for BD.

We found opposite patterns of age-related changes between HBO and CONT in the left CC. The CC is a major midline WM tract that is involved in integrating, between hemispheres, sensory-motor functions, attention, language, memory,

and emotional states.[40] Developmental studies have indicated that the CC matures through adolescence into adulthood with a posterior-anterior axonal maturation most likely due to increased myelination.[28] Our findings of normative increases with age in FA in the CC in CONT are consistent with findings from larger cross-sectional studies indicating normative increases in FA (and decreases in RD) with age in adolescence.[28] Thus, our findings of a decrease in FA (and an increase in RD) with age in the CC suggests possible alterations in the development of WM in the CC in HBO. This would support the idea that altered development of the CC may represent a marker for BD.[41]

Previous studies in individuals with BD have reported abnormalities in volume, signal intensity, shape, and microstructure of the CC.[41] Most studies have generally reported lower FA in individuals with BD,[41] with the exception of one study that reported higher FA in the anterior portion of the CC in adult patients with BD versus controls.[42] A recent study in adolescents with familial BD reported lower FA throughout the CC, including the genu and splenium.[15] Few studies have examined the CC of WM in individuals at high familial risk for BD. One study using voxel-based morphometry reported that genetic liability BD was associated with WM deficits in, among other regions, the anterior CC.[26] This study involved adult patients with BD, however, and as such did not evaluate developmental changes in CC as possible vulnerability markers for BD. Longitudinal studies are needed to determine the nature of the developmental changes in the CC of WM during adolescence that may precede the onset of BD or other psychiatric disorders in youth at risk for BD.

Our findings also have indicated differences in the pattern of age-related changes between HBO and CONT in the right ILF. The ILF is a major WM associative tract connecting occipital and temporal cortices that runs laterally and inferiorly to the lateral wall of the temporal horn. This regions is considered part of a "ventral semantic network" with an important role in the visual processing of emotionally salient information, because ILF projections feed information regarding the emotional valence of visual stimuli back to early visual processing cortical regions, thereby enhancing the visual processing of emotionally salient stimuli.[43] Our findings of normative increases with age in FA in the right ILF in CONT are consistent with findings from cross-sectional studies.[28] The absence of such age-related changes in FA (and RD) in the right ILF in HBO suggests alterations in the development of this WM tract in HBO.

Recent findings have shown abnormalities, predominantly lower FA, in the ILF FA in adults with BD compared with healthy controls.[13] However, other studies have not reported abnormalities in the ILF FA in pediatric BD.[15,17] With regard to individuals at high familial risk for BD, previous studies have not reported any differences in the ILF between groups at risk for BD and healthy controls,[19] although one study reported that increasing genetic liability for BD in genetically at-risk adults was significantly associated with lower FA in bilateral portions of the ILF.[44] In light of the potential role of the ILF in emotional information processing, findings of important developmental changes in adolescence in the processing of emotionally salient information,[45] and evidence of abnormalities in emotional information processing in BD,[46,47] it is possible that alterations in the development of this WM tract may also be implicated in vulnerability for BD.[48] For instance, recent evidence of altered emotional information processing in unaffected offspring having a parent with BD[48] has suggested that further research focusing on the ILF and emotional information processing in youth at high familial risk for BD may be warranted.

Unlike the one previous DTI study in children at risk for BD,[19] we did not find any significant alteration in WM in the superior longitudinal fascicule in HBO. The discrepancy between our findings and those from this previous study may be attributed to differences in age range (4-12 versus 8-17 years). Another factor may be that most at-risk youth in the previous study met criteria for an Axis I diagnosis, whereas in our study all were healthy. Given evidence of decreased superior longitudinal fascicule FA in children with attention-deficit/hyperactivity disorder,[49] it is unclear to what extent the presence of psychopathology in the at-risk youth affected findings in the previous study.[19] Further study is required to determine the extent to which age-related changes in FA in this region predispose to BD or other psychiatric disorders in offspring at high familial risk for BD.

A major strength of the present study was that by including age in our statistical model, we were able to document differences in age-related changes in WM microstructure across groups. Another strength was including RD and L1 to help interpret relations between FA and age in HBO compared with CONT. Our findings indi-

cated that there were significant group-by-age interactions in RD. The pattern of RD changes with age in the left CC and right ILF was opposite to those for FA in CONT, which is what has been shown in previous studies with normative samples. However, in HBO, the pattern was the opposite in te CC and there was no relation between FA and RD and age in ILF. There were no significant group-by-age interactions in L1 in these regions, although there was one significant group-by-age interaction in L1 in another region of the right ILF in the visual cortex, resulting from a positive relation between age and L1 in CONT and a negative relation between age and L1 in HBO. Studies in animals[39] and humans[50] have indicated that age-related increases in FA, with decreases in RD, are considered to reflect developmental changes associated with myelination. Thus, one possible interpretation of our main findings in the left CC and right ILF may be that HBO show alterations in the myelination of these WM tracts. Increases in L1 in the absence of changes in RD have been associated with increases in axon diameter/density.[27] One interpretation of age-related changes in LI in the right ILF in the visual cortex may be that HBO show an abnormal pattern of axonal growth in this region with age. Altered development of these WM tracts may then confer increased vulnerability for subsequent development of BD or other psychiatric disorders observed in offspring having a parent with BD.[2]

There were limitations to our study. First, we used a cross-sectional design to examine age-related changes in WM across groups. Although such designs have been used to understand age-related changes in brain development,[28] longitudinal examination with a larger sample will provide a much more in-depth understanding of the developmental trajectories of these WM tracts in HBO, including examination of the role of other developmental factors such as pubertal maturation and sex. Second, we decided to focus initially on healthy offspring having a parent with BD to control for potential confounds related to pathology and/or medication. On the one hand, because certain psychiatric disorders are highly prevalent in this population, this led to a targeted sampling that may have limited the ability to generalize our findings to all offspring of parents having BD. On the other hand, because HBO were healthy, our findings are more closely related to genetic risk for BD and not presence of psychopathology. Nevertheless, the present study represents an initial step toward the identification of altered WM development as a possible vulnerability marker for BD. Future studies will address these issues through longitudinal designs and comparison groups matched on age, sex, and psychiatric disorder (e.g., anxiety disorder, attention-deficit/hyperactivity disorder).

In summary, this is the first DTI study using tract-based spatial statistics to document, in healthy offspring having a parent diagnosed with BD compared with age-matched healthy offspring of healthy parents, age-related changes in key WM tracts supporting interhemispheric integration (CC)[40] and semantic and visually salient information processing (ILF),[43] previously reported to be abnormal in BD. We show that, unlike in CONT, HBO exhibit decreases in FA (increases in RD) with increasing age in the CC and no changes with increasing age in the ILF. Our findings suggest altered developmental patterns of WM with age, which may be indicative of potential vulnerability markers for future BD or other psychiatric disorders, in healthy offspring having a parent with BD. &

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TABLE S1 Linear and Non-linear Relationship Between Age and Diffusivity Measures in Healthy Offspring Having a Parent With Bipolar Disorder and Age-matched Control Offspring of Healthy Parents

		Left Corpus Callosum (Body Division)							Right Inferior Longitudinal Fasciculus						
	Equation	R^2	*F*	*df* 1	*df* 2	*p* Value	b1	b2	R^2	*F*	*df* 1	*df* 2	*p* Value	b1	b2
FA		MNI x, y, z: −18, −30, 34							MNI x, y, z: 49, −23, −22 (temporal cortex)						
HBO	Logarithmic	0.4	11.395	1	18	.003	−0.13		0.0	0.713	1	18	.409	−0.07	
	Inverse	0.4	10.264	1	18	.005	1.63		0.0	0.575	1	18	.458	0.83	
	Quadratic	0.4	5.746	2	17	.012	0.00	0.00	0.1	0.624	2	17	.548	0.04	0.00
	Power	0.4	11.117	1	18	.004	−0.26		0.0	0.344	1	18	.565	−0.13	
	Exponential	0.4	11.727	1	18	.003	−0.02		0.0	0.437	1	18	.517	−0.01	
CONT	Logarithmic	0.3	7.886	1	23	.010	0.13		0.3	9.026	1	23	.006	0.26	
	Inverse	0.3	7.860	1	23	.010	−1.60		0.3	8.010	1	23	.009	−3.15	
	Quadratic	0.3	3.783	2	22	.039	0.03	0.00	0.3	5.416	2	22	.012	−0.04	0.00
	Power	0.3	7.659	1	23	.011	0.26		0.2	7.147	1	23	.014	0.59	
	Exponential	0.2	7.422	1	23	.012	0.02		0.3	7.822	1	23	.010	0.05	
RD		MNI x, y, z: −18, 9, 36							MNI x, y, z: 49, −20, −22 (temporal cortex)						
HBO	Logarithmic	0.1	1.233	1	18	.281	0.07		0.2	3.830	1	18	.066	0.11	
	Inverse	0.1	1.290	1	18	.271	−0.84		0.2	3.443	1	18	.080	−1.38	
	Quadratic	0.1	0.997	2	17	.390	0.05	0.00	0.2	2.074	2	17	.156	−0.01	0.00
	Power	0.1	1.160	1	18	.296	0.12		0.2	3.676	1	18	.071	0.21	
	Exponential	0.1	1.018	1	18	.326	0.01		0.2	3.993	1	18	.061	0.02	
CONT	Logarithmic	0.5	19.775	1	23	.000	−0.23		0.5	19.687	1	23	.000	−0.23	
	Inverse	0.5	18.900	1	23	.000	2.80		0.4	18.328	1	23	.000	2.81	
	Quadratic	0.5	9.538	2	22	.001	−0.03	0.00	0.5	9.630	2	22	.001	−0.02	0.00
	Power	0.4	17.851	1	23	.000	−0.43		0.4	16.861	1	23	.000	−0.42	
	Exponential	0.4	17.942	1	23	.000	−0.03		0.4	17.391	1	23	.000	−0.03	
L1									MNI x, y, z: 49, −23, −22 (visual cortex)						
HBO	Logarithmic								0.4	14.380	1	18	.001	−0.87	
	Inverse								0.5	15.575	1	18	.001	11.12	
	Quadratic								0.5	8.822	2	17	.002	−0.40	0.01
	Power								0.5	15.547	1	18	.001	−0.66	
	Exponential								0.4	13.752	1	18	.002	−0.05	
CONT	Logarithmic								0.2	5.434	1	23	.029	0.30	
	Inverse								0.2	4.877	1	23	.037	−3.55	
	Quadratic								0.2	3.238	2	22	.059	−0.06	0.00
	Power								0.2	5.514	1	23	.028	0.25	
	Exponential								0.2	6.006	1	23	.022	0.02	

Note: The independent variable is age. The cubic model could not be fitted due to near-collinearity among model terms. Statistical threshold of $p < .05$ *uncorrected, because these were exploratory analyses. CONT = healthy control offspring of healthy parents; df = degrees of freedom; FA = fractional anisotropy; HBO = healthy offspring having a parent diagnosed with bipolar disorder; L1 = longitudinal diffusivity; MNI = Montreal Neurological Institute atlas; RD = radial diffusivity.*