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Age-Associated Alterations in Corpus Callosum White Matter Integrity in Bipolar Disorder Assessed Using Probabilistic Tractography

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Abstract

Objectives—Atypical age-associated changes in white matter integrity may play a role in the neurobiology of bipolar disorder, but no studies have examined the major white matter tracts using nonlinear statistical modeling across a wide age range in this disorder. The goal of this study was to identify possible deviations in the typical pattern of age-associated changes in white matter integrity in patients with bipolar disorder across the age range of 9 to 62 years.

Methods—Diffusion tensor imaging was performed in 57 (20M/37F) patients with a diagnosis of bipolar disorder and 57 (20M/37F) age- and sex-matched healthy volunteers. Mean diffusivity and fractional anisotropy were computed for the genu and splenium of the corpus callosum, two projection tracts, and five association tracts using probabilistic tractography.

Results—Overall, patients had lower fractional anisotropy and higher mean diffusivity compared to healthy volunteers across all tracts (while controlling for the effects of age and age^2). In addition, there were greater age-associated increases in mean diffusivity in patients compared to healthy volunteers within the genu and splenium of the corpus callosum beginning in the second and third decades of life.

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Conclusions—Our findings provide evidence for alterations in the typical pattern of white matter development in patients with bipolar disorder compared to healthy volunteers. Changes in white matter development within the corpus callosum may lead to altered inter-hemispheric communication that is considered integral to the neurobiology of the disorder.

Keywords

diffusion tensor imaging; corpus callosum; tractography; neurodevelopment

Introduction

Neurobiological models of bipolar disorder have identified a general framework involving deficient prefrontal modulation of subcortical and limbic structures for conceptualizing mood dysregulation in the disorder (1-4). Such models are consistent with functional magnetic resonance imaging studies reporting deficient control of prefrontal regions in relation to subcortical and temporal structures that have been implicated in mood regulation (5, 6). In particular, the orbital frontal region may serve as a mediator within the anterior limbic network between subcortical limbic regions involved in emotion perception and generation (3). Mood dysfunction in bipolar disorder could relate to abnormalities within circuits subserving automatic in contrast to voluntary emotional processes. The gray matter comprising these networks, including the orbitofrontal cortex, subgenual anterior cingulate gyrus, dorsal anterior cingulate and medial-dorsal prefrontal cortex have been studied extensively in bipolar disorder with the white matter connecting these regions becoming increasingly more widely investigated.

Alterations in white matter connectivity have been implicated in the pathogenesis of bipolar disorder (1) with evidence of white matter hyperintensities (7) and volumetric alterations assessed using structural neuroimaging (8). More recently, however, diffusion tensor imaging has been used as a putative measure of white matter integrity in bipolar disorder (9). Both fractional anisotropy and mean diffusivity are scalar-valued measures that can be computed from the estimated diffusion tensor and reflect the magnitude and anisotropy of the self-diffusion of water molecules in the brain, respectively. Although fractional anisotropy has been widely examined in diffusion tensor imaging studies of bipolar disorder, fewer studies have investigated mean diffusivity, which represents the average of the diffusion tensor or its three eigenvalues, and thus provides complementary information to fractional anisotropy regarding the magnitude of water diffusion within tissues in contrast to the directional preference of diffusion.

Diffusion tensor imaging studies in both pediatric and adult bipolar disorder have provided evidence for abnormal fractional anisotropy in patients compared to healthy volunteers. Adolescents experiencing a first-episode of mania have lower fractional anisotropy in the left superior frontal region (10) and right orbitofrontal region (11). Moreover, lower fractional anisotropy has been observed in both the anterior and posterior corona radiata in pediatric bipolar patients (12). Overall, these findings are broadly consistent with the results of adult studies demonstrating lower fractional anisotropy and a concomitant increase in mean diffusivity (13), especially in projection fibers, such as the left anterior limb of the

internal capsule (14). It should be noted, however, that some adult studies reported higher fractional anisotropy in the bilateral frontal white matter, anterior thalamic radiation and/or cortico-pontine tracts in patients compared to healthy volunteers (15,16). Abnormalities in fractional anisotropy within the uncinate fasciculus have been reported (17) as well as abnormal asymmetry of this white matter tract (18) in patients. Moreover, lower fractional anisotropy has been reported in both pediatric (19) and adult (20) populations within the superior longitudinal fasciculus.

Findings of corpus callosum abnormalities in patients with bipolar disorder assessed using diffusion tensor imaging have been some of the most robust to date in the literature (21-25). James et al. (26) identified lower fractional anisotropy within the anterior corpus callosum among pediatric patients compared to healthy volunteers and that probabilistic tractography from this cluster revealed connections with the prefrontal cortex, including brain regions demonstrating lower density in patients. These findings were subsequently interpreted to suggest that involvement of inter-hemispheric prefrontal tracts may be implicated in the neurobiology of bipolar disorder consistent with neurobiological models of the disorder. Moreover, Linke et al. (27) reported that white matter integrity in the corpus callosum was lower in bipolar patients, but not their unaffected siblings, thus suggesting that inter-hemispheric connectivity could potentially serve as a disease marker for this disorder as in other endophenotype studies in bipolar disorder (28,29).

Studies of healthy white matter development have demonstrated an increase in fractional anisotropy from childhood through adolescence and to young adulthood with a concomitant decrease in mean diffusivity over this same time period. These trajectories generally follow a nonlinear path over the lifespan with quadratic models generally providing an excellent fit for the data (30). In one of the largest studies to date Lebel et al. (31) conducted a cross-sectional study of 403 healthy volunteers aged 5-83 to examine 12 white matter tracts using diffusion tensor imaging tractography. These investigators reported that fractional anisotropy peaks between 20 to 42 years of age and mean diffusivity reaches its minima between 18 to 41 years of age. Notably, the fornix and corpus callosum reach their peak fractional anisotropy first and fronto-temporal tracts (cingulum, superior longitudinal fasciculus and uncinate fasciculus) tend to have a more prolonged development. Similarly, in a cohort of 296 healthy subjects aged 8 to 68 years we (30) reported that the anterior thalamic radiation was the first to reach peak fractional anisotropy, followed by the genu and splenium of corpus callosum, corticospinal tract and lastly the association tracts. In general, the projection and commissural fibers mature the earliest, association fibers continue to mature into later ages and fronto-thalamic fibers have a more prolonged development.

An abnormality in the typical trajectory of normal white matter development may contribute to the onset and clinical manifestation of bipolar disorder (32-34). An important gap in the literature are the limited data regarding how white matter changes across the age span in bipolar disorder and more conspicuously whether such effects are evident across both pediatric and adult populations. Prior studies have been either restricted to pediatric or adult cohorts and used linear modeling to assess cross-sectional dependent measures within these age ranges. In one of the few longitudinal studies to date Delaloye et al. (35) did not identify any differences in structural or diffusion tensor imaging measures over a 2-year longitudinal

period in 15 euthymic older bipolar disorder patients and 15 controls. Lu et al. (36) investigated fractional anisotropy using linear modeling in 35 individuals experiencing a first-episode of bipolar disorder and 46 healthy volunteers using diffusion tensor imaging across the age range from 9 to 42. These authors reported that the left anterior limb of the internal capsule demonstrated significantly lower fractional anisotropy in pediatric compared to adult bipolar disorder. The authors suggest that abnormalities in this region may play a role in earlier illness onset and be associated with greater illness susceptibility. Significant strengths of that study include the use of patients who were medication free and close to illness onset at the time of the scan. Blumberg et al. (37) reported a significant diagnosis-by-age group interaction such that compared to controls ventral prefrontal cortical gray and white matter volumes were significantly smaller in patients with bipolar disorder only in young adulthood.

Studies investigating otherwise healthy offspring of patients with bipolar disorder have also shed light on deviations in typical age-associated changes in white matter integrity. Using diffusion tensor imaging Versace et al. (38) investigated group-by-age interactions in 20 healthy offspring with a parent diagnosed with bipolar disorder and 25 healthy control offspring of healthy parents. These authors reported a linear increase in fractional anisotropy and a linear decrease in radial diffusivity among controls in the left corpus callosum and right inferior longitudinal fasciculus. In the healthy bipolar offspring, there was a linear decrease in fractional anisotropy and an increase in radial diffusivity with age in the left corpus callosum and no relation between fractional anisotropy or radial diffusivity and age in the right inferior longitudinal fasciculus. Moreover, the use of curve fitting confirmed linear and showed nonlinear relations between fractional anisotropy and radial diffusivity and age within these regions consistent with the hypothesis that altered development of white matter in the corpus callosum could play a role in future vulnerability to the disorder.

In the current investigation we used probabilistic tractography to map possible deviations in typical age-associated changes in white matter integrity as inferred by diffusion tensor imaging in a large cohort of pediatric and adult patients with bipolar disorder across a wide age range (9 to 62 years). In particular, we used quadratic modeling to assess age-associated changes given that these changes have been demonstrated to follow a nonlinear course (30,39). Based on prior work we hypothesized that there would be group differences in age-associated changes in white matter integrity across the age span examined using quadratic modeling, which would be evident in regions involved in emotion dysregulation (cingulum bundle) and inter-hemispheric processing (corpus callosum).

Methods

Participants

Fifty-seven (20M/37F) patients with a diagnosis of bipolar disorder (mean age = 32.6 SD = 15.2 years) were recruited through inpatient psychiatric units and outpatient clinics at Zucker Hillside Hospital, Glen Oaks, NY. Patient diagnoses were based on the Schedule for Affective Disorders and Schizophrenia for School-Age-Children, Present and Lifetime Version (K-SADS-PL) (40) or the Structured Clinical Interview (SCID) (41) for Axis I

DSM-IV Disorders supplemented by information from clinicians and, when available, family members.

Forty-six patients had a diagnosis of bipolar I disorder, 8 had a diagnosis of bipolar disorder II and 3 had a diagnosis of bipolar disorder NOS. Demographics for the pediatric (9 to 17) and adult (18 to 62) participants are provided in **table 1**. Mean age (SD) and sex distribution for the individual bipolar subgroups was: Bipolar I (mean age = 32.8, SD = 15.6 and sex (19M/27F), Bipolar II (mean age = 36.4, SD = 13.2 and sex (0M/8F), and Bipolar NOS (mean age = 18.8; SD = 8.4 and sex (1M/2F). Comorbid diagnoses and concomitant medications for the pediatric and adult cohorts are provided in **table 2**. In addition, we recruited 57 (20M/37F) healthy volunteers who were matched pairwise for age and sex to the patients. All healthy controls were recruited using local advertisements and through word of mouth. All healthy volunteers were assessed using the structured diagnostic interview (Schedule for Affective Disorders and Schizophrenia for School-Age Children - Present and Lifetime Version (K-SADS) (40) or the SCID for DSM-IV disorders Non-Patient Edition (42). None of the matched healthy volunteers had an Axis I diagnosis.

Exclusion criteria for all participants included: (a) MRI contraindications; (b) significant medical illness (c) prior psychosurgery; (d) DSM-IV diagnosis of Tourette's syndrome, schizophrenia, schizoaffective disorder, delusional disorder, brief reactive psychosis, developmental disorder, autism and neurological conditions; (e) DSM-IV mental retardation; (f) stroke and (g) pregnancy. The North Shore-LIJ Institutional Review Board approved all procedures. Written informed consent was obtained from both patients and healthy controls, and from a parent or legal guardian in the case of minors. Written assent was obtained from all minors.

Handedness

All individuals completed a modified version of the Edinburgh Inventory. The total number of right and left hand items was scored and the laterality quotient was computed according to the following formula: (Total R - Total L)/(Total R + Total L) yielding a range from +1.00 (totally dextral) to -1.00 (totally non-dextral). As in our prior published work (30) individuals with a score > 0.70 were considered dextral and the rest were classified as nondextral.

Clinical Ratings

Clinical information was extracted from the mania and depression sections of the KSADS or SCID for patients. A depression score was computed as the sum of the following items: depressed mood, anhedonia, weight change, psychomotor abnormality, worthlessness, recurrent thoughts of death, sleep problems, and fatigue (range = 0 to 3; maximum score = 24). Similarly, we derived a total mania score computed from the following items: elevated mood, grandiosity, racing thoughts, pressured speech, decreased need for sleep, increased goal directed activity and distractibility (range = 0 to 3; maximum score = 21).

DTI Acquisition and Preprocessing

All subjects received a diffusion tensor imaging exam at the North Shore University Medical Center, Manhasset, NY using a GE HD× 3.0 T system (General Electric, Milwaukee, WI). The sequence included volumes with diffusion gradients applied along 31 non-parallel directions (b=1000 s/mm^2) and 5 volumes without diffusion weighting (TR=14 s, TE=min., matrix=128 × 128, FOV=240 mm). Each volume consisted of 51 contiguous 2.5-mm axial slices acquired parallel to the anterior-posterior commissural line using a ramp sampled, double spin-echo, single shot echo-planar imaging method.

All scans were reviewed by a radiologist and all images were visually inspected to ensure that no gross abnormalities were evident. Image processing was conducted using the Functional Magnetic Resonance Imaging of the Brain Software Library (FSL; Oxford, United Kingdom; http://fsl.fmrib.ox.ac.uk/fsl). Eddy-current induced distortions and head-motion displacements were corrected through affine registration of the 31 diffusion volumes to the first b0 volume using FSL's Linear Registration Tool (43). The b-vector table (i.e. gradient directions) for each participant was then adjusted according to the rotation parameters of this linear correction. Non-brain tissue was removed using FSL's Brain Extraction Tool. Fractional anisotropy and mean diffusivity were then calculated at each voxel of the brain by fitting a diffusion tensor model to the raw diffusion data using weighted least squares in FSL's Diffusion Toolbox.

Probabilistic Tractography

The probable trajectories of two inter-hemispheric tracts (splenium and genu of corpus callosum), two projection tracts (cortico-pontine and anterior thalamic radiation), and five bilateral association tracts (inferior fronto-occipital fasciculus, inferior longitudinal fasciculus, superior longitudinal fasciculus, cingulum, and uncinate fasciculus) were traced using previously published methods (30). Within-voxel probability density functions of the principal diffusion direction were estimated using Markov Chain Monte Carlo sampling in FSL's BEDPOSTX tool (44). A spatial probability density function was then estimated across voxels based on these local probability density functions using FSL's PROBTRACKX tool, in which 5000 samples were taken for each input voxel with a 0.2 curvature threshold, 0.5 mm step length, and 2000 steps per sample. For each tract, seed masks, way-points, termination and exclusion masks were defined on the MNI152 T1 1mm template, using the FMRIB58 fractional anisotropy template as a DTI specific reference. Masks were registered to each subjects' diffusion space using FLIRT (43,45), applying the affine parameters obtained by registering the MNI152 1mm T1 brain to the first b0 volume. The resulting tracts were thresholded at a normalized probability value, and visually inspected to confirm successful tracing in each individual. Normal probability values indicate the weighting assigned to each tract to ensure that the most likely tracts were included in the measurement. Successful tracing was defined as the program generating the tract and visual inspection of the results by an operator trained in neuro-anatomy. Mean fractional anisotropy and mean diffusivity of each tract was then extracted for analysis.

Statistical Analysis

Differences in demographic characteristics between groups were assessed using either independent group t-tests or chi-square analyses in the case of categorical data. Given the lack of significant group-by-hemisphere effects we averaged values across hemispheres to limit Type-I error. We used group (patients versus healthy volunteer) and sex as between subjects factors and tract was the within subjects factor (splenium of corpus callosum, genu of corpus callosum, cortico-pontine tract, anterior thalamic radiation, inferior fronto-occipital fasciculus, inferior longitudinal fasciculus, superior longitudinal fasciculus, cingulum, and uncinate fasciculus) in 2 separate analyses investigating fractional anisotropy and mean diffusivity. Both linear and quadratic ($c + a$*Age + b*Age^2) terms were included in each model. Our rationale for using a quadratic model was based on previously published work by our group (30) and others' (39) indicating that quadratic models provide an excellent fit for examining age-associated changes in these tracts across the age span in this study.

We also conducted sensitivity analyses to assess whether age-associated changes in patients who were taking second generation antipsychotics, mood stabilizers, those without comorbidities or with a diagnosis of bipolar I disorder differed from the entire sample of patients. We also considered the effect of age of onset on the results by including it as a covariate in quadratic models. It was not possible to compare subgroups as the number of subjects in each group was too small. We plotted the nonlinear quadratic curves for each of these subgroups to determine whether they were within the confidence regions of the original curve for all the patients.

Results

Sample demographics are provided in **Table 1**. There were no significant group differences in distributions of age, race, sex, handedness or education. In addition, comorbid diagnoses and patient medication histories are provided in **Table 2**. Linear and quadratic model fits for each of the tracts along with R^2 are presented in **Table 3** for descriptive purposes only.

There was a significant main effect of fractional anisotropy such that patients had lower values overall compared to healthy controls across the tracts ($F = 9.18$, $df = 871$, $p = .0025$). In addition, there was a significant main effect of sex ($F = 15.90$, $df = 871$, $p < .001$) such that males had higher fractional anisotropy compared to females. There was a trend for the group × tract interaction to be statistically significant ($F = 1.81$, $df = 863$, $p = .07$). Although the group × age × tract ($F = 4.26$, $df = 854$, $p < .001$) and group × age^2 × tract ($F = 3.81$, $df = 855$, $p < .001$) interactions were statistically significant, post hoc analyses did not reveal any significant group × age or group × age^2 interactions for any of the individual tracts.

Investigation of mean diffusivity revealed a significant main effect of group ($F = 11.45$, $df = 871$, $p < .001$) such that patients had higher mean diffusivity across the tracts overall. In addition, there were significant main effects of age ($F = 4.43$, $df = 871$, $p = .04$) and age^2 ($F = 7.48$, $df = 871$, $p = .006$). A main effect of sex ($F = 7.01$, $df = 871$, $p = .008$) indicated that males had lower mean diffusivity overall compared to females. The group by tract interaction was statistically significant ($F = 3.73$, $df = 863$, $p < .001$) with significant post

hoc effects observed in the genu ($F = 14.87$, $df = 863$, $p < .001$) and splenium ($F = 29.54$, $df = 863$, $p < .001$) of the corpus callosum. Moreover, both the age × group × tract ($F = 5.78$, $df = 854$, $p < .001$) and the age^2 × group × tract ($F = 6.60$, $df = 855$, $p < .001$) interactions were statistically significant. Post hoc analyses revealed a significant group × age^2 interaction for mean diffusivity within the genu of the corpus callosum ($p = .04$; **figure 1**). In addition, for the splenium of the corpus callosum there were significant group × age ($p = .03$) and group × age^2 interactions ($p=.03$; **figure 2**).

Additional analyses for individuals receiving different psychotropic medications (e.g., second generation antipsychotics and mood stabilizers), patients without comorbidities, patients with a diagnosis of bipolar I, and adjustment for age at onset yielded comparable findings as the entire group of patients given that these curves were within the 95% confidence interval for the entire patient sample. Moreover, we note that upon visual inspection the shape of all these curves was comparable to that of the original curve derived for the entire patient sample.

Discussion

To our knowledge this is the largest study incorporating the widest age range in bipolar disorder to examine age-associated changes in putative white matter integrity as inferred by diffusion tensor imaging. Probabilistic tractography was used to examine fractional anisotropy and mean diffusivity within 9 tracts across the age range of 9 to 62 years using both linear and quadratic models. The main finding of our study was a significant group-x-age^2 interaction for mean diffusivity in both the genu and splenium of the corpus callosum. Specifically, although healthy volunteers demonstrated typical age-associated increases in mean diffusivity within these regions across the age span examined, these effects were more pronounced among patients, especially during the second and third decades of life. We also identified significant group main effects such that patients demonstrated lower fractional anisotropy and higher mean diffusivity compared to healthy volunteers overall across the tracts examined. Strengths of the current study include the investigation of multiple tracts, use of probabilistic tractography, wide age range incorporating children, adolescents and adults with bipolar disorder, use of both linear and quadratic statistical modeling and individual age- and sex-matching of patients and healthy volunteers.

The findings from our study are consistent with the hypothesis that alterations in typical age-associated changes in white matter integrity may play a role in the neurobiology of bipolar disorder. Few studies have investigated age-associated changes in white matter integrity using diffusion tensor imaging in patients with bipolar disorder compared to healthy volunteers and thus it is difficult to compare these findings with prior work. Moreover, prior work has been either restricted to pediatric or adult cohorts and used linear modeling to assess cross-sectional dependent measures. In one study Lu et al. (36) investigated fractional anisotropy using linear modeling in 35 first-episode medication-free patients close to illness onset at the time of the scan and 46 healthy volunteers within the age range of 9 to 42. These authors reported that the anterior limb of the internal capsule showed significantly lower fractional anisotropy in pediatric compared to adult bipolar disorder. Differences between our study and Lu et al (36) may relate to methodological differences (i.e., their use of tract

based spatial statistics compared to our use of probabilistic tractography) and the age range investigated.

The findings from the current study in healthy volunteers converge with prior work from our group (30) demonstrating quadratic age-associated changes in fractional anisotropy in 296 healthy volunteers from age 8 to 68 years in the splenium and genu of the corpus callosum. Moreover, consistent with other studies (31,46) our findings indicate that healthy volunteers demonstrated gradual age-associated increases in mean diffusivity that were comparable in both the genu and splenium of the corpus callosum. The significant group × age^2 interactions (**Figures 1 and 2**), however, indicate that age-associated changes were more pronounced among patients with bipolar disorder compared to healthy volunteers across the age range examined. Our data further suggest that there are regional differences in age-associated changes involving the corpus callosum in patients with bipolar disorder. Specifically, while patients demonstrated more pronounced age-associated changes beginning around 10 years of age compared to healthy volunteers in the splenium this effect was evident among patients beginning around 30 years of age in the genu. Moreover, compared to healthy volunteers, patients with bipolar disorder demonstrated greater mean diffusivity prior to the age of 30 in the genu (in contrast to the splenium) indicating that age-associated changes in these two corpus callosum regions may differ from each another in bipolar disorder. In this regard it is noteworthy that prior work in healthy volunteers (47) reported differential age-associated maturational changes in caudal versus rostral aspects of the corpus callosum. Our findings are therefore consistent with the hypothesis that a disruption in a network of corpus callosum subregions may contribute to aberrant neurodevelopment in bipolar disorder.

Of the major white matter tracts investigated in this study significant age-associated changes were restricted to the genu and splenium of the corpus callosum, which is the largest white matter tract in the brain and is responsible for the majority of communication between homologous cortical regions in the right and left cerebral hemispheres (48). The finding of abnormal age-associated changes within the corpus callosum in patients compared to controls may thus have implications for inter-hemispheric prefrontal functioning. In a prior study Leow et al (49) identified abnormalities in inter-hemispheric integration among patients with bipolar disorder identified using network analysis of diffusion-weighted magnetic resonance imaging data. Moreover, James et al (26) reported lower fractional anisotropy in the anterior corpus callosum of pediatric patients compared to matched healthy volunteers. Furthermore, the use of probabilistic tractography from this abnormal cluster demonstrated that this region was connected to the prefrontal cortex, including those regions whose density was lower in bipolar disorder associated with psychosis. Taken together the results of the current investigation in combination with prior work are consistent with neurobiological models of bipolar disorder that implicate dysregulation in ventral prefrontal regions, which may contribute to deficient modulation of subcortical and limbic structures.

In the current study we also identified lower fractional anisotropy and higher mean diffusivity in patients with bipolar disorder compared to healthy volunteers overall. Thus, we did not find any evidence for white matter abnormalities, assessed using fractional anisotropy and mean diffusivity, specific to any tract, thus implicating global white matter

abnormalities in the neurobiology of bipolar disorder. The majority of prior work investigating white matter as inferred from diffusion tensor imaging in bipolar disorder has focused mainly on the investigation of fractional anisotropy. In a recent review and meta-analysis of 10 voxel-based studies (including 252 patients and 256 controls) and 5 tract based spatial statistics studies in bipolar disorder that used effect-size signed differential mapping Nortje et al (50) reported that 61 clusters of fractional anisotropy in the brain differed significantly between patients and healthy volunteers and that all major white matter tracts were implicated. Less research has investigated mean diffusivity, especially in the corpus callosum, although several studies reported greater mean diffusivity in patients compared to healthy volunteers (51-53,9). Greater mean diffusivity within the corpus callosum has been observed in both first-episode patients with schizophrenia and bipolar disorder (54) suggesting that it may represent a common pathologic process to these disorders. Moreover, Oertel-Knöchel et al (51) reported that greater mean diffusivity was identified in the splenium and the truncus of the corpus callosum in patients with bipolar disorder compared to healthy volunteers, which predicted executive dysfunction among patients.

Although age-associated differences in mean diffusivity were observed across the age span between groups, these effects were not evident in the investigation of fractional anisotropy. While both fractional anisotropy and mean diffusivity can be computed from the estimated diffusion tensor, they are quantitatively different in that the latter reflects the magnitude and former the anisotropy of the self-diffusion of water molecules. Few studies have examined both fractional anisotropy and mean diffusivity in bipolar disorder within the same regions and thus comparisons to prior work are difficult to make. Our findings suggest, however, that the underlying putative white matter integrity of these regions may be affected by the average of the diffusion tensor or the total diffusion within a voxel in contrast to the directional preference of water diffusion. Although the underlying neurobiological mechanisms contributing to such differences are not well known, fractional anisotropy may not be particularly sensitive to underlying pathology if water diffusion changes proportionally along the direction of all three eigenvectors (i.e., higher axial and higher radial diffusivity). Thus, the investigation of fractional anisotropy coupled together with mean diffusivity could potentially capture abnormalities more accurately. For example, Acosta-Cabronero et al. (55) reported that greater absolute mean diffusivity was more sensitive to abnormal networks implicated in Alzheimer's disease compared to typical measures of fractional anisotropy.

There were several limitations to this study that should be acknowledged. Patients with bipolar disorder were at different stages of treatment and it is conceivable that a selection bias could occur with older patients (33). Given that our study is cross-sectional longitudinal studies are critical to inform the field regarding potential neurodevelopmental changes in bipolar disorder. We acknowledge that the pediatric sample was small in the context of the age range examined and could have the potential to skew results over the more heavily weighted adult sample. Also, factors such as the inclusion of diagnoses other than Bipolar I disorder, which could potentially influence age-associated changes (56), comorbidities, age at onset and different medication classes/types could conceivably influence the observed findings, although ancillary analyses that considered these variables were consistent with

findings from the larger sample. The investigation of complementary measures could also be informative given some studies reported that both white matter volume and fractional anisotropy was lower within the corpus callosum in patients compared to controls (9). We also acknowledge several methodological issues that may have influenced the observed findings. The use of affine versus non-affine registration could contribute to different results and given brain size differences between children and adults the use of a population atlas could be informative. In our study, however, all brains were normalized to the standard MNI template and it has been demonstrated empirically (57,58) that standard magnetic resonance imaging templates are appropriate for subjects in this age range. We did not determine the cardiovascular status of subjects and it is acknowledged that such indices could be associated with the dependent measures investigated in this study (59). We also could not determine whether abnormal age-associated changes in the genu and splenium in patients with bipolar disorder reflect the same or independent pathological processes (47) or possibly reflect state versus trait-related manifestations of the disorder (60).

In sum, we report abnormalities in age-associated changes in putative white matter integrity (i.e., mean diffusivity) within the genu and splenium of the corpus callosum across a wide age range of 9 to 62 years in a large cohort patients with bipolar disorder compared to healthy volunteers.

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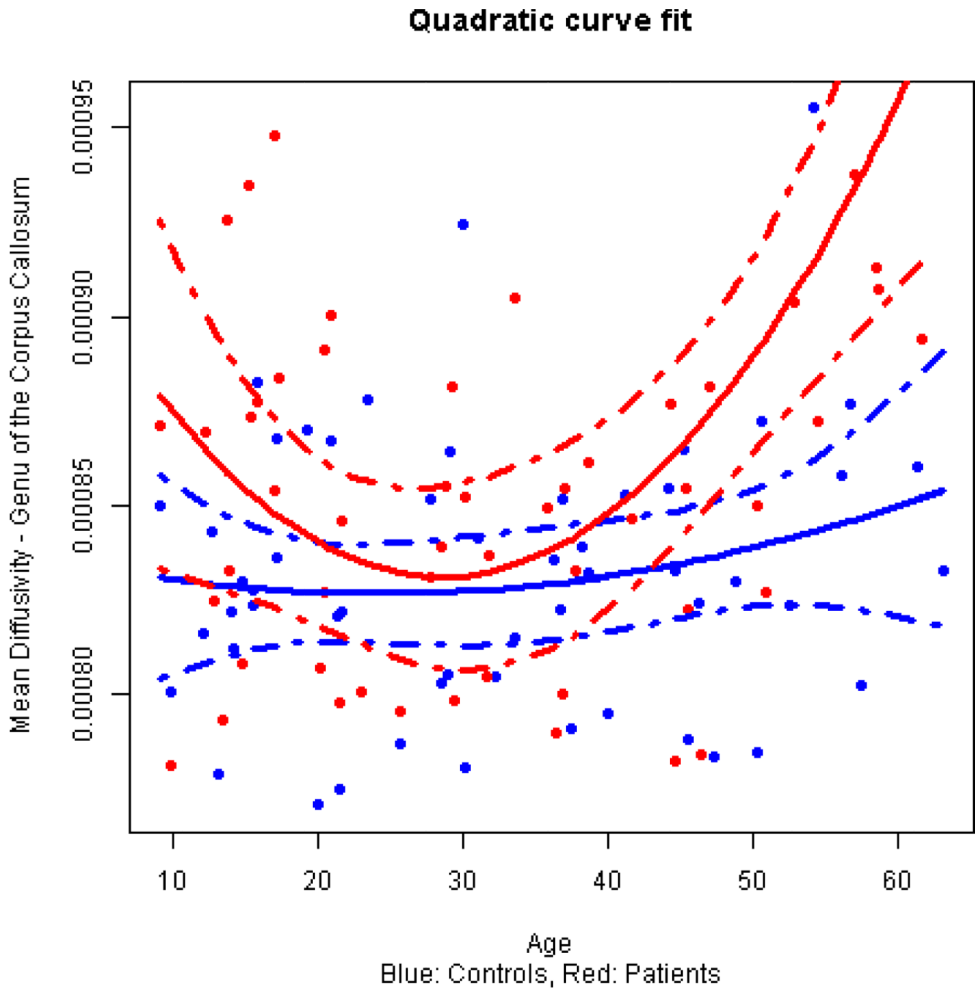
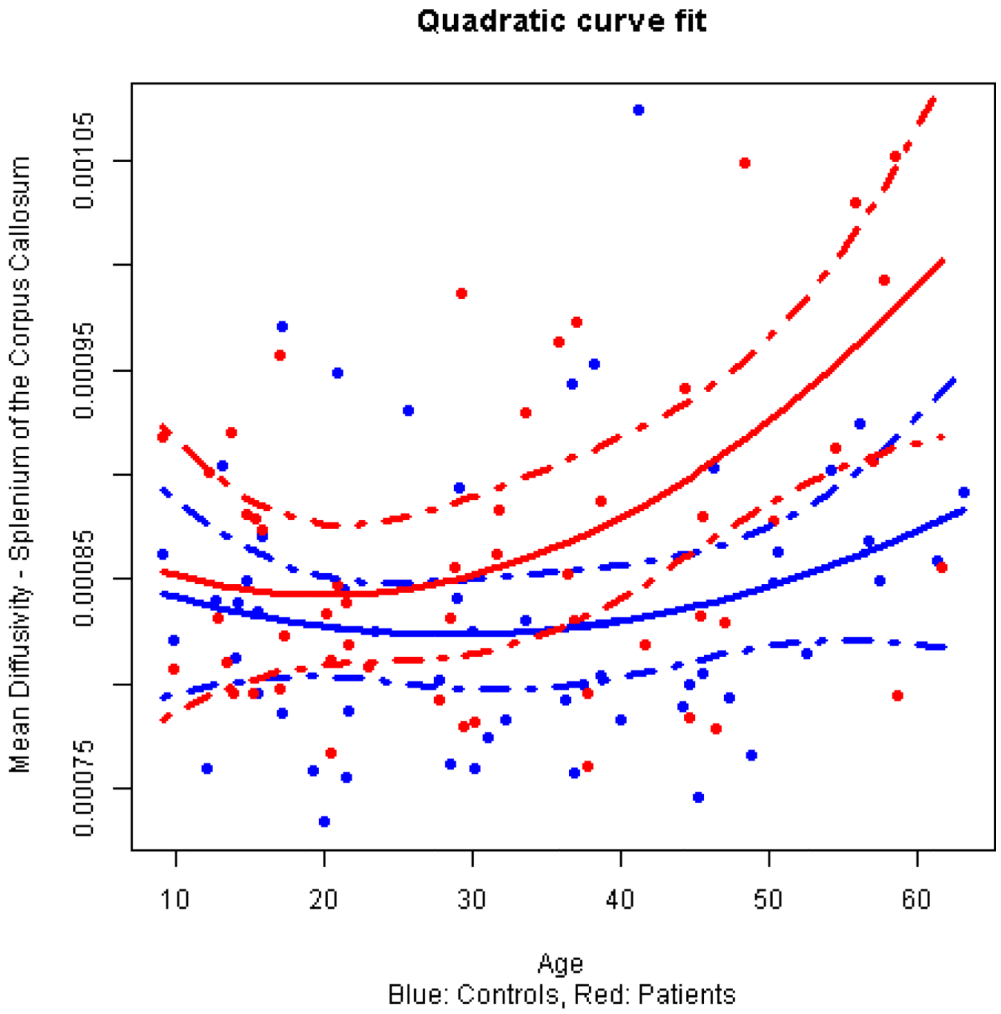


Figure 1.

Age-associated Changes in Mean Diffusivity in the Genu of the Corpus Callosum in Patients with Bipolar Disorder and Healthy Volunteers.



Note: units are 10^{-3} mm^2/s

Figure 2.

Age-associated Changes in Mean Diffusivity in the Splenium of the Corpus Callosum in Patients with Bipolar Disorder and Healthy Volunteers.

Table 1

Sample characteristics

Pediatric Sample Characteristics					
	Bipolar Disorder (N=14)	**Healthy Volunteers (N=14)**	**Statistic**	**df**	**P value**
Mean Age (SD)	14.2 (2.5); range = 9 to 17	14.2 (2.5); range = 9 to 17	t = 0.02	26	NS
Sex (M/F)	2/12	2/12	$\chi^2 = 0$	1	NS
Education (years)	7.5 (2.7)	7.8 (2.7)	t = 0.24	25	NS
Edinburgh Score	0.62 (0.53)	0.78 (0.41)	t = 0.78	25	NS
Age at Onset	11.2 (2.4)	--	--	--	--
Mania Score	16.9 (4); range = 7 to 21	--	--	--	--
Depression Score	14.6 (7); range = 3 to 23	--	--	--	--

Adult Sample Characteristics					
	Bipolar Disorder (N=43)	**Healthy Volunteers (N=43)**	**Statistic**	**df**	**P value**
Mean Age (SD)	38.6 (12.5); range = 20 to 62	38.7 (12.6); range =19 to 61	t = .035	84	NS
Sex (M/F)	18/25	18/25	$\chi^2 = 0$	1	NS
Education (years)	14.2 (1.8)	15.7 (2.0)	t = 3.43	83	NS
Edinburgh Score	0.77 (0.53)	0.79 (0.44)	t = 0.19	84	NS
Age at Onset	24.7 (8.7)	--	--	--	--
Mania Score	8.2 (6.8); range = 0 to 21	--	--	--	--
Depression Sore	6.5 (5.4); range = 0 to 20	--	--	--	--

Notes. Data were missing for education (2 patients), clinical scores (6 patients), age at onset (6 patients) and handedness (1 patient) Standard Deviations are in parentheses.

Table 2

Comorbid Diagnoses and Patient Medication History

	Pediatric N=14	Adults N=43
Patients with a Comorbid Diagnosis	8 (57.1%)	37 (86.1%)
ADHD	6 (42.3%)	0 (0%)
Anxiety disorders [a]	5 (35.7%)	21 (48.8%)
ODD	3 (21.4%)	0 (0%)
Substance use disorders [b]	2 (14.3%)	28 (65.1%)
Nocturnal enuresis	1 (7.1%)	0 (0%)
Eating disorders [c]	0 (0%)	3(7.0%)
Patients with Medication Exposure at the Time of the Scan	9 (64.3%)	37 (86.1%)
Mood stabilizers [d]	1 (7.1%)	36 (83.7%)
Second generation antipsychotics [e]	6 (42.9%)	32 (74.4%)
Sedative hypnotics [f]	1 (7.1%)	15 (34.9%)
Antidepressants [g]	1 (7.1%)	12 (27.9%)
Anti-Parkinson medications [h]	0 (0%)	7 (16.3%)
First generation antipsychotics [i]	0 (0%)	2 (4.7%)
Psychostimulants [j]	1 (7.1%)	0 (0%)

ADHD: attention deficit hyperactivity disorder, ODD oppositional defiant disorder;

[a] Social phobia, panic disorder with agoraphobia, panic disorder without agoraphobia, obsessive compulsive disorder, post traumatic stress disorder, specific phobia, anxiety disorder NOS, generalized anxiety disorder;

[b] Alcohol abuse, alcohol dependence, cannabis abuse, cannabis dependence, cocaine abuse, cocaine dependence, hallucinogen dependence, opioid dependence, sedative hypnotic abuse, sedative hypnotic dependence;

[c] Bulimia nervosa, eating disorder NOS;

[d] Lithium, divalproex, carbamazepine, lamotrigine, topamax;

[e] Risperidone, Abilify, Geodon, Zyprexa, Risperdal, Saphris, Seroquel;

[f] Ativan, Xanax, Klonopin;

[g] Celexa, Lexapro, Moclobemide, Pamelor, Prozac, Zoloft;

[h] Cogentin, amantadine;

[i] Haldol, Haldol deconoate;

[j] Concerta.

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Table 3

Linear and Quadratic Model Fits

	Linear (group-x-age)			Quadratic (group-x- age^2)		
Tracts	**R^2**	**F value**	**p-value**	**R^2**	**F value**	**p-value**
Fractional anisotropy						
Corpus collosum-genu	0.26	0.01	0.91	0.27	0.10	0.74
Corpus collosum-splenium	0.18	1.11	0.29	0.19	1.76	0.18
Superior longitudinal fasciculus	0.10	2.27	0.13	0.10	2.06	0.15
Cingulum	0.23	1.72	0.19	0.23	1.71	0.19
Inferior fronto-occipital fasciculus	0.31	0.19	0.66	0.31	0.11	0.74
Inferior longitudinal fasciculus	0.18	0.31	0.57	0.18	0.35	0.55
Cortico-pontine tract	0.04	0.37	0.54	0.04	0.20	0.65
Anterior thalamic radiations	0.15	0.36	0.54	0.15	0.03	0.86
Uncinate Fasciculus	0.14	0.00	0.99	0.14	0.04	0.84
Mean diffusivity						
Corpus collosum-Genu	0.23	2.96	0.08	0.24	4.56	0.03
Corpus collosum-splenium	0.27	4.72	0.03	0.27	5.02	0.02
Superior longitudinal fasciculus	0.07	0.12	0.72	0.07	0.05	0.82
Cingulum	0.15	1.19	0.27	0.14	0.43	0.51
Inferior fronto-occipital fasciculus	0.22	0.35	0.55	0.22	1.04	0.31
Inferior longitudinal fasciculus	0.12	0.04	0.84	0.12	0.04	0.83
Cortico-pontine tract	0.07	1.33	0.25	0.07	1.57	0.21
Anterior thalamic radiation	0.10	0.04	0.84	0.11	0.42	0.51
Uncinate Fasciculus	0.10	0.10	0.75	0.11	0.41	0.52

Note: Data presented for descriptive purposes only.