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Longitudinal Diffusion Tensor Imaging Study of Adolescents and Young Adults With Bipolar Disorder

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Abstract

Objective—Longitudinal neuroimaging during adolescence/young adulthood, when bipolar disorder (BD) commonly emerges, can help elucidate the neurodevelopmental pathophysiology of BD. Adults with BD have shown reduced structural integrity in the uncinate fasciculus (UF), a white matter (WM) tract providing major connections between the amygdala and ventral prefrontal cortex (vPFC) important in emotion regulation. In this longitudinal diffusion tensor imaging (DTI) study of adolescents/young adults, we hypothesized differences in age and time-related changes in UF integrity in BD compared to healthy control (HC).

Method—Two DTI scans were obtained in 27 adolescents/young adults with BD and 37 HC adolescents/young adults, on average approximately 2.5 years apart. Interactions between diagnosis with age and with time for UF fractional anisotropy (FA) were assessed. Exploratory analyses were performed including euthymic-only participants with BD, and for potential influences of demographic and clinical factors. Whole-brain analyses were performed to explore for interactions in other regions.

Results—There were significant interactions between diagnosis with age and with time for UF FA ($p < .05$). Healthy control adolescents/young adults showed significant UF FA increases with age and over time ($p < .05$), while no significant changes with age or over time were observed in the

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adolescents/young adults with BD. Significant interactions with age and time were also observed in analyses including euthymic-only participants with BD ($p < .05$).

Conclusion—These findings provide neuroimaging evidence supporting differences in UF WM structural development during adolescence/young adulthood, suggesting differences in the development of an amygdala-vPFC system subserving emotion regulation may be a trait feature of BD neurodevelopment.

Keywords

Bipolar Disorder; Diffusion Tensor Imaging; Adolescent; White Matter

INTRODUCTION

A peak emergence of fully syndromic bipolar disorder (BD) symptoms, including the characteristic emotion dysregulation, occurs during adolescence/young adulthood.^{1–6} Longitudinal neuroimaging investigation during this epoch can improve understanding of the underlying neurodevelopmental pathophysiology.

Cross-sectional neuroimaging research in adults with BD supports differences in an amygdala-ventral prefrontal cortex (vPFC) system that subserves emotional regulation.^{7, 8} A body of magnetic resonance imaging (MRI) studies supports differences between adults with BD and healthy control (HC) adults in gray matter (GM) in the amygdala and the vPFC.^{8–11} More recent diffusion tensor imaging (DTI) studies implicate alterations in the structural integrity of the white matter (WM) of the connections between these brain regions.^{7, 12–33} The uncinate fasciculus (UF), an anterior WM structure critically important in carrying amygdala-vPFC connections,^{34–36} is implicated in emotion regulation,^{35, 37, 38} and has shown decreased structural integrity in adults with BD.^{12, 14, 16–20, 24–28, 32, 33} Decreased WM integrity in broader connections of this system have also been reported in adults with BD, including in cingulum,³⁹ corpus callosum,⁴⁰ and corticospinal tract and superior longitudinal fasciculus¹³.

The amygdala-vPFC system matures during adolescence/young adulthood.^{41, 42} MRI studies in adolescents/young adults with BD support alterations in the neurodevelopment of this system during this epoch.^{5, 7, 43–55} Decreases in amygdala volume has been a consistent finding in adolescents with BD.^{9, 43, 45, 47, 48, 56, 57} Gray matter decreases have also been demonstrated in vPFC in adolescents and young adults with BD, including evidence suggesting altered neurodevelopmental trajectories comprised by greater vPFC GM volume decline with increasing age.^{44, 46, 53}

Adolescence/young adulthood is also an epoch of important WM development.⁵⁸ Preclinical animal and human postmortem studies support this as a time of substantial development of amygdala-vPFC neuronal connections and associated frontotemporal WM.^{41, 59} Consistent with this, DTI studies of typically developing adolescents/young adults have shown age-associated increases in WM fractional anisotropy (FA),^{60–66} a measure of the coordinated directionality of diffusion within WM fiber tracts (i.e., orientation and integrity of the neural fibers).⁶⁷ Cross-sectional DTI studies of adults with BD have demonstrated UF FA

differences,^{12, 14, 16–20, 24–28, 32, 33} and reduced frontal FA has been observed in cross-sectional DTI studies of adolescents/young adults with BD,^{68–73} including in the UF.^{14, 74} In a longitudinal MRI study of regional morphology in adolescents/young adults with BD, decreased volume expansion over time of WM was found in a region carrying amygdala-vPFC connections that includes the UF.⁴⁶

Taken together, the evidence above suggests a neurodevelopmental model for BD in which the developmental trajectory of the amygdala-vPFC system during adolescence is altered, including development of its WM connections. Here, we performed a longitudinal DTI study to compare FA changes with age and over time in the structural integrity of UF WM between adolescents/young adults with BD to HC. We hypothesized that, compared to HC, the adolescents/young adults with BD would have lower magnitude of increases in UF FA with age and over time. To explore for findings consistent with the BD trait and minimize potential confounding effects of acute mood states, UF analyses were also performed including only adolescents/young adults with BD who were euthymic at both time points. Also explored were potential effects of clinical factors, including mood state, medication, and psychiatric comorbidities, on primary findings. Whole-brain voxel-based analyses were performed to explore for diagnosis by age and time interactions outside of our a priori hypothesized region of interest (ROI).

METHOD

Participants

Adolescents/young adults with BD (n=27), and HC adolescents/young adults (without a personal Axis I diagnosis or first-degree relative with BD, n=37), were scanned twice. Participant handedness,⁷⁵ socioeconomic status,⁷⁶ IQ (Wechsler Abbreviated Scale of Intelligence two-subtest [Matrix Reasoning and Vocabulary]),⁷⁷ as well as demographic and clinical characteristics at the time of the first scan (Scan-1) and the time of the second scan (Scan-2), are reported in Tables 1 and 2. Presence or absence of psychiatric disorders, mood state, and comorbidities at each scan were confirmed in participants aged ≥18 years using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID) (Version 2.0),⁷⁸ and in participants <18 years using the Schedule for Affective Disorders and Schizophrenia for School Aged Children-Present and Lifetime Version (K-SADS)⁷⁹ (participant and parent/guardian interviewed separately). Presence of attention-deficit/hyperactivity disorder (ADHD) diagnosis was assessed in participants <18 years using the K-SADS ADHD module, and in participants aged ≥18 years using the SCID and the K-SADS ADHD module worded appropriately for adult symptoms.⁸⁰ Family history was assessed using the Family History Screen for Epidemiological Studies.⁸¹ All participants were without history of neurological disorders, loss of consciousness (>5min), or major medical disorder. The study was performed in accordance with the University Human Investigation Committee. Participants (aged ≥18 years) provided informed consent, and participants (<18 years) provided informed assent and their parents/guardians provided permission. Analyses of cross-sectional DTI data on 41 (64.1%) of the participants have been included in previous reports.^{12, 14, 39, 40, 82}

In the BD group, current comorbidities were included for generalizability given the high comorbidity rate in BD.^{83, 84} All participants included with substance use disorders were in remission: from substance abuse >4 months, from dependence >6 months. Participants with BD were followed in the community between scans, and therefore medications were prescribed as per usual treatment.

MRI Acquisition and Processing

Diffusion-weighted scans at both time points were acquired for each participant using the same 3-Tesla Siemens Trio MR scanner (Siemens, Erlanger, Germany). Diffusion sensitizing gradients were applied along 32 non-collinear directions with b-value=1000 s/mm² and an acquisition without diffusion weighting (b-value=0) (TR=7400ms; TE=115ms; matrix=128×128; FOV=256×256mm² and 40 three-mm slices without gap). Diffusion-weighted data were interpolated to 1.5mm isotropic voxels and then denoised by a 3-dimensional isotropic Gaussian kernel with sigma 2mm full-width-at-half-maximum (FWHM) using BioImage Suite software (<http://www.bioimagesuite.org>). Diffusion eigenvectors and corresponding eigenvalues were acquired after diagonalization of the diffusion-weighted data and used to calculate FA values. The UF ROI was defined based on published methods using probabilistic tract maps.⁸⁵ Mean FA values were extracted separately for right and left UF ROIs for each participant for each scan. For exploratory analyses, whole-brain maps were constructed for each participant and normalized to the standard Montreal Neurological Institute (MNI) template using a tissue probability map of WM as a template, resampled to 2mm³ during normalization and spatially smoothed at 10mm FWHM using Statistical Parametric Mapping 8 (SPM8) software (<http://www.fil.ion.ucl.ac.uk/spm>).

Demographic and Clinical Characteristics Analyses

Two-tailed *t* tests were used to compare age at each scan and the interscan interval between BD and HC groups. Chi-squared tests were used to test for differences between the BD and HC groups in sex, and to assess for differences in clinical factors within participants with BD from Scan-1 to Scan-2 when there were >4 participants with and >4 participants without the clinical factor at each time point, including history of psychosis, history of rapid cycling, medication (on/off overall and for antipsychotics, anticonvulsants, antidepressants, and psychostimulants) and comorbid ADHD. Age and sex were explored for differences at Scan-1 and at Scan-2 between euthymic BD versus HC participants, BD with ADHD versus HC participants, and BD without ADHD versus HC participants.

DTI Analyses

UF ROI Analyses—Primary UF ROI analyses were performed using a linear mixed model in SPSS (SPSS Inc., Chicago, Illinois) that included UF FA as the dependent variable, diagnosis (BD, HC) as a between-subjects factor, age, time of scan (Scan-1, Scan-2) and hemisphere as within-subject repeated measures, and sex a covariate. Significant diagnosis with age and/or time interactions were considered supportive of the study hypothesis. For the diagnosis with age interaction, slopes describing the relationship between age and UF FA were estimated and compared between diagnoses post hoc to explain significant effects. For

the diagnosis with time interaction, least square means were estimated and compared between diagnoses post hoc to explain significant effects.

Exploratory UF ROI Analyses for Demographic and Clinical Factors—

Exploratory UF ROI analyses were performed using linear mixed models. To explore for interaction between diagnosis with age and/or time in adolescents/young adults with BD who were euthymic at both time points, similar models to above were used, including participants with BD only if euthymic at both time points ($n=14$). Interactions between age or time with clinical factors present at both Scan-1 and Scan-2 for >4 participants (history of psychosis, antipsychotics, antidepressants, psychostimulants and comorbid ADHD) were explored for between participants with BD with and without these features by adding each factor one at a time to the models, including all participants with BD. Significant interactions are reported.

Exploratory Whole-Brain Analyses—Exploratory whole-brain voxel-based analyses of FA were performed in SPM8. The spatial distribution of diagnosis with age or time findings that overlapped the UF ROI were explored, with whole-brain voxel-based analyses performed within diagnoses to aid interpretation of significant interaction effects, thresholded at $p<.005$ (uncorrected) and spatial extent of 30 contiguous voxels (Figure 1). Whole-brain voxel-based analyses were also performed to assess for potential regions not hypothesized showing interactions of diagnosis with age or time that were considered significant at a family-wise error correction level $p<.05$.³¹

RESULTS

DTI Analyses

UF ROI Analyses—There was a significant interaction between diagnosis with age ($F_{1,221}=7.61$, $p=.007$); HC participants showed increases in UF FA with increasing age ($p=.01$), while participants with BD did not show an association with age ($p=.65$). There was also a significant interaction between diagnosis with time ($F_{1,188}=4.02$, $p=.046$); HC participants showed increases in UF FA from Scan-1 to Scan-2 ($p=.04$), while participants with BD did not show a change over time ($p=.64$).

Exploratory UF ROI Analyses for Demographic and Clinical Factors—When the BD group was comprised only of participants euthymic at both time points, diagnosis interacted significantly with age ($F_{1,179}=6.29$, $p=.013$) and time ($F_{1,149}=4.01$, $p=.047$) in the same directions above. There was a significant interaction between ADHD comorbidity with time ($F_{1,77}=10.58$, $p=.002$), with a significant increase over time in UF FA from Scan-1 to Scan-2 in participants with BD and ADHD (ADHD present at both time points) relative to participants with BD without ADHD ($p=.02$).

Exploratory Whole-Brain Analyses—Diagnosis by age (maxima at MNI coordinates $x=-20$ mm, $y=46$ mm, $z=-6$ mm and spatial extent of 82 voxels) and time (maxima at $x=-14$ mm, $y=54$ mm, $z=-8$ mm and spatial extent of 48 voxels) interaction effects were observed in the left UF ROI region when all participants with BD were included in the analyses. The interaction with age (maxima at MNI coordinates $x=-20$ mm, $y=40$ mm, $z=-$

–6mm and spatial extent of 124 voxels) and time (maxima at $x=-20\text{mm}$, $y=36\text{mm}$, $z=-8\text{mm}$ and spatial extent of 32 voxels) effects were also observed in the left UF ROI region when the BD group was comprised only of participants euthymic at both time points (Figure 1). Post hoc within-group analyses showed the interaction derived from FA increases with age and over time within the HC group that were not observed in the BD group (Figure 1). No additional regions of significant diagnosis by age or diagnosis by time interactions were observed.

DISCUSSION

This longitudinal DTI study of adolescents/young adults with BD compared to HC adolescents/young adults supports differences with age and over time in WM in the UF, a WM structure critically important in coordinated responses within the amygdala-vPFC circuitry that subserves emotion regulation.^{12, 35, 37, 38} Specifically, over a period of 2.5 years on average, HC adolescents/young adults showed expected increases in UF structural integrity with increasing age and over time,^{60–66} whereas adolescents/young adults with BD did not show those increases. Diagnosis with age and time effects remained significant when including only adolescents/young adults with BD who were euthymic at both time points. Finally, there was a significant interaction between ADHD diagnosis and time in analyses limited to adolescents/young adults with BD, as adolescents/young adults with ADHD comorbidity at both time points showed increases in UF FA over time relative to adolescents/young adults without ADHD at both time points.

The age- and time-related DTI findings provide evidence supporting the neurodevelopmental model of an altered trajectory of amygdala-vPFC development during adolescence in BD. The findings of this study extend previous findings from DTI cross-sectional studies of decreased FA in the region of the UF in adolescents with BD,^{14, 74} and a longitudinal study that revealed decreased WM volume expansion in the region of the UF in adolescents/young adults with BD compared to HC adolescents/young adults,⁴⁶ implicating differences in the development of the structural integrity of the UF during adolescence and young adulthood in BD that may lead to the differences in UF integrity in adults with BD observed previously by our group^{12, 14} and other groups.^{16–20, 24–28, 32, 33}

The UF has a central role in communication between amygdala-vPFC structures and in emotional regulation.^{35, 37, 38} Decreases in UF FA in adults have previously shown an association with amygdala-vPFC functional connectivity.¹² Future longitudinal studies of adolescents/young adults with BD are warranted to investigate relationships between the trajectory of UF WM development with development of functional connectivity and with emotion regulation-related symptoms and behaviors.

The consistent findings observed in analyses limited to adolescents/young adults with BD euthymic at both time points suggest impaired UF development may be a trait feature in adolescents/young adults with BD.³¹ Sample size limited ability to perform meaningful analyses of variation in the age at first scan and in interscan intervals. Future studies in adolescents are needed with larger samples and systematic study of age at first scan and intervals between scans. A prior DTI study in a larger sample ($N=31$) of adults with BD

aged 24–52 years demonstrated negative correlation with age in UF FA,⁸⁶ suggesting older age at time of scan in participants with BD is associated with decreased UF FA. Future study is warranted to help determine whether there are different life stage-related relationships between age and time with UF FA.⁶³

The preliminary findings of different patterns of changes over time in UF WM FA in the BD subgroup without compared to the BD subgroup with comorbid ADHD raise the interesting possibility that these may be separable developmental phenotypes of BD.⁸⁷ It is consistent with a previous cross-sectional neuroimaging report of differences between adolescents with BD with and without comorbid ADHD in WM, including in PFC WM.⁷¹ While more adolescents/young adults with BD and comorbid ADHD were males taking psychostimulants, sex differences were not detected, possibly owing to insufficient power to test for sexually dimorphic effects related to ADHD comorbidity.⁸⁸

The analyses for interactions with age and time provide complementary perspectives, although each with potential limitations. Group differences with age, assessed in cross-sectional samples, could result from inter-individual differences that are not related to development. Observing similar findings in the longitudinal analyses provides further support that the effects are related to changes over time supporting developmental changes. However, it is possible that inter-individual differences, such as differences in medication, could potentially contribute to both types of findings.

The sample in the current report is modest for a longitudinal study. Although mitigated by the within-subjects nature of the data, the multivariate analyses would be optimized by studying a larger sample, especially with respect to potential confounds, particularly within the BD sample where frequency of clinical characteristics were limited. While changes in frequency over time in the sample are of interest, such as the increase in rapid-cycling, sample size did not permit meaningful analyses. Assessment of medication effects were limited further, as it was not varied systematically between timepoints. Greater UF structural integrity abnormalities in acutely depressed than euthymic adults with BD were observed in a cross-section study,⁸⁹ illustrating the need for systematic study of mood states in future longitudinal neuroimaging studies of BD. As we studied adolescents/young adults already diagnosed with BD, it is possible that findings were a consequence of BD episodes.^{70, 89} Future longitudinal studies of youths at risk for BD are warranted.^{90, 91}

In summary, this longitudinal study revealed lower magnitude of UF FA increases with age and over time in adolescents/young adults with BD compared to HC adolescents/young adults, including when adolescents/young adults with BD euthymic at both time points were compared to HC adolescents/young adults, and thus suggests differences in UF WM development during adolescence/young adulthood may be a trait feature of BD.

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Clinical Guidance

- This study adds to mounting evidence that bipolar disorder is a serious medical disorder of the brain and particularly that differences in the development of the emotional regulation brain circuitry may underlie the emergence of bipolar disorder in adolescence and young adulthood.
- The identification of differences in the development of the structural integrity of the white matter containing key connections in emotional brain circuitry implicates these connections and mechanisms guiding their development as new potential treatment and prevention targets for bipolar disorder.
- Together, the above provide important information to reduce stigma and great hope as such new findings provide promise that new and more effective treatment and preventive methods are on the horizon.

Figure 1.

White matter regions with differing relationships with age and time in adolescents and young adults with bipolar disorder (BD). Note: The axial-oblique images display the areas in the region of the uncinate fasciculus where fractional anisotropy showed an interaction between diagnosis (BD, healthy comparison) with age (A) and time (B) in analyses including all participants with BD (top row), in analyses including only euthymic participants with BD (middle row), and that showed a positive correlation with age (A) and time (B) within the healthy comparison participants (bottom row) ($p < .005$ uncorrected, >30 voxels). There were no increases observed with age or over time in participants with BD. The top color bar represents the range of F values for the interaction analyses and the bottom color bar represents the range of T values for the within-group analysis. The right side of the image is on the right side of the brain.

Table 1

Demographics

	Healthy control	Bipolar disorder	<i>t</i> (df)	<i>p</i>
Age at time 1 mean [SD]	16.65 [2.08]	17.57 [2.57]	1.57 (62)	0.12
Age at time 2 mean [SD]	19.42 [2.23]	20.07 [2.70]	1.02 (62)	0.31
Interscan interval mean [SD]	2.77 [1.26]	2.49 [0.98]	−0.99 (62)	0.33
Female, n (%)	17 (45.9)	16 (59.3)	0.29 (1)	0.32
Handedness [SD] ^a	79.11 [46.17]	57.30 [68.85]	−1.46 (56)	0.15
Years education [SD]	12.75 [2.14]	12.59 [2.15]	0.28 (61)	0.78
IQ [SD]	108.56 [15.15]	102.37 [15.56]	1.53 (60)	0.13
SES [SD]	38.47 [15.96]	44.38 [13.00]	1.56 (61)	0.12

Note: SES = socioeconomic status

^aHigher values indicate increased right-handedness.

Table 2**Clinical Characteristics**

	<i>Scan-1</i> <i>n (%)</i>	<i>Scan-2</i> <i>n (%)</i>
<i>Current comorbidities</i>		
Attention-deficit/hyperactivity disorder	7 (25.9)	7 (25.9)
History of cannabis dependence	5 (18.5)	4 (14.8)
History of alcohol abuse	3 (11.1)	3 (11.1)
History of polysubstance dependence		1 (3.7)
Simple phobia	2 (7.4)	
Generalized anxiety disorder	1 (3.7)	2 (7.4)
Posttraumatic stress disorder		2 (7.4)
Panic disorder		1 (3.7)
Obsessive-compulsive disorder		1 (3.7)
Binge eating disorder		1 (3.7)
Oppositional defiant disorder ^{a,b}	3 (11.1)	1 (3.7)
Tic disorder ^{a,c}	1 (3.7)	
<i>Mood state, rapid cycling, and psychosis</i>		
Euthymic	15 (55.5)	23 (85.1)
Elevated (hypomania/manic/mixed)	7 (25.9)	2 (7.4)
Depressed	5 (18.5)	2 (7.4)
Rapid cycling	5 (18.5)	10 (37.0)
Lifetime psychosis	12 (44.4)	13 (48.1)
<i>Medications</i>		
Medication	23 (85.1)	20 (74.0)
Antipsychotics	14 (51.8)	11 (40.7)
Anticonvulsants	9 (33.3)	8 (29.6)
Lithium carbonate	5 (18.5)	2 (7.4)
Antidepressants	6 (22.2)	7 (25.9)
Psychostimulants	7 (25.9)	8 (29.6)
Benzodiazepines	6 (22.2)	2 (7.4)
Sedative hypnotics	1 (3.7)	

Note:

^aOnly assessed in participants < 18 years of age; % reported in table is of all participants.^b21.4/7.1%^c7.1/% of participants < 18.