

## Anterior Cortical Development During Adolescence in Bipolar Disorder

Pablo Najt, Fei Wang, Linda Spencer, Jennifer A.Y. Johnston, Elizabeth T. Cox Lippard, Brian P. Pittman, Cheryl Lacadie, Lawrence H. Staib, Xenophon Papademetris, and Hilary P. Blumberg

### ABSTRACT

**BACKGROUND:** Increasing evidence supports a neurodevelopmental model for bipolar disorder (BD), with adolescence as a critical period in its development. Developmental abnormalities of anterior paralimbic and heteromodal frontal cortices, key structures in emotional regulation processes and central in BD, are implicated. However, few longitudinal studies have been conducted, limiting understanding of trajectory alterations in BD. In this study, we performed longitudinal neuroimaging of adolescents with and without BD and assessed volume changes over time, including changes in tissue overall and within gray and white matter. Larger decreases over time in anterior cortical volumes in the adolescents with BD were hypothesized. Gray matter decreases and white matter increases are typically observed during adolescence in anterior cortices. It was hypothesized that volume decreases over time in BD would reflect alterations in those processes, showing larger gray matter contraction and decreased white matter expansion.

**METHODS:** Two high-resolution magnetic resonance imaging scans were obtained approximately 2 years apart for 35 adolescents with bipolar I disorder (BDI) and 37 healthy adolescents. Differences over time between groups were investigated for volume overall and specifically for gray and white matter.

**RESULTS:** Relative to healthy adolescents, adolescents with BDI showed greater volume contraction over time in a region including insula and orbitofrontal, rostral, and dorsolateral prefrontal cortices ( $p < .05$ , corrected), including greater gray matter contraction and decreased white matter expansion over time, in the BD compared with the healthy group.

**CONCLUSIONS:** The findings support neurodevelopmental abnormalities during adolescence in BDI in anterior cortices, including altered developmental trajectories of anterior gray and white matter.

**Keywords:** Adolescent, Bipolar disorder, Development, Longitudinal studies, Magnetic resonance imaging, Prefrontal cortex

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A unifying neuroanatomical model for the constellation of symptoms of bipolar disorder (BD) has been proposed to include limbic, anterior paralimbic, and heteromodal prefrontal structures, including the amygdala, insula, orbitofrontal cortex (OFC), rostral prefrontal cortex (RPFC), and dorsolateral PFC (DLPFC) (1,2). These highly interconnected structures (3), with their additional connection sites such as the hypothalamus, comprise a system that adaptively regulates processes disrupted in BD, including emotions, impulses, appetitive drives, and circadian rhythms (3). Increasing evidence supports a neurodevelopmental basis for BD (1,4). As acute BD episodes often emerge during adolescence (5), and the system matures during this time (6,7), altered neurodevelopmental trajectories in this system during adolescence are implicated in the development of the disorder (4).

Cross-sectional neuroimaging evidence supports morphologic abnormalities in the amygdala-anterior paralimbic-heteromodal system in adults with BD. Decreased gray matter (GM)

volume in adults with BD has been observed in the amygdala, insula, and frontal cortices, including ventral prefrontal cortex (VPFC), RPFC, and DLPFC (1,8). White matter (WM) abnormalities include decreases in volume and structural integrity in the system connections (9). Postmortem studies are consistent with neuroimaging studies, indicating decreases in amygdala volume and neurons (10) and in frontal neurons, glia, and their markers, including oligodendrocytes and myelination markers (11,12).

Cross-sectional studies of children and adolescents with BD have also shown amygdala volume decreases (13–17). In contrast, cortical volume findings in youths are inconsistent, including decreases or no differences (16,18–23). While there are increasing reports of decreased WM integrity in adolescents with BD, few studies have focused specifically on anterior paralimbic-heteromodal WM integrity and the extent of abnormalities in those regions in adolescents with BD is not clear (24–30).

During adolescence, typical prefrontal developmental changes include synaptic pruning and subtle GM volume decreases and myelination and WM volume increases (6,31). If BD pathophysiology involves abnormalities in these processes, GM and WM trajectories may progressively diverge over adolescence. Some inconsistencies in anterior cortical findings in youths with BD could therefore be related to differences in the developmental times at which adolescents were studied (4,18). However, drawing conclusions about neurodevelopmental processes from cross-sectional studies must be done with caution. Longitudinal studies are needed to elucidate system trajectories in BD.

Preliminary longitudinal studies of brain morphology in small samples of adolescents/young adults with BD support altered trajectories in VPFC, RPFC, and DLPFC. For example, Kalmar *et al.* (32) found more volume contraction in VPFC and RPFC in adolescents with BD compared to healthy control (HC) adolescents. Studying youths before and after BD onset, Gogtay *et al.* (33) found ventral anterior cingulate GM decreases. These studies did not, however, address possible differences in contributions of GM and WM that could help to reveal mechanisms underlying abnormal trajectories in BD. A study by Farrow *et al.* (34) showed anterior cingulate GM reductions and frontal WM increases in adolescents with BD studied over 2 years; however, follow-up data were not available in the HC group to determine whether findings were disease-related. Thus, longitudinal studies of larger adolescent samples with BD compared with HC adolescents examining different contributions of local GM and WM changes are needed.

The differential patterns of changes in frontotemporal GM and WM changes typical of adolescence have been detected in neuroimaging studies that demonstrate frontotemporal GM decreases and WM increases in healthy adolescents (35–40). Examining maturational trajectories for the two types of tissue is critical to disentangle the GM and WM trajectory alterations that contribute to BD. This is important as it could implicate particular GM and/or WM neurodevelopmental pathophysiologic processes in the disorder. This could aid understanding of the pathophysiology underlying the development of symptoms. For example, detection of disruption of the maturational development within the GM regions and/or the WM of their projections implicated in emotion processing and regulation could help to elucidate the types of neurodevelopmental system abnormalities that contribute to the emergence of complex affective symptoms of BD and how they may change over time during adolescence. Identification of GM and/or WM abnormalities could also, importantly, influence methods for early detection and targeted treatment and prevention strategies.

This investigation tested the hypothesis that anterior paralimbic and heteromodal cortical volume decreases over time are more pronounced in adolescents with BD than HC adolescents by comparing high-resolution structural magnetic resonance imaging (MRI) data in adolescents with and without BD scanned twice over approximately 2 years. To optimize the use of serial data and registration, images obtained at time 2 were registered pairwise to images at time 1 and local volume expansion and contraction were calculated (32). It was further hypothesized that anterior paralimbic and heteromodal trajectory abnormalities in BD would include those of altered GM

decreases and WM increases over time resulting from disruptions in the healthy maturation changes that typically occur in these tissue types during adolescence.

## METHODS AND MATERIALS

### Subjects

Thirty-five subjects with bipolar I disorder (BD I) were scanned at time 1 (T1) (48% female, age range 10–21 years, mean age  $16.8 \pm 2.8$  SD years) and rescanned at time 2 (T2) (age range 13–23 years, mean age  $19.1 \pm 2.9$  years) after a mean interval of  $2.3 \pm .65$  years (range 1.42–3.72 years). Thirty-seven HC subjects without DSM-IV Axis I diagnoses or first-degree relatives with an Axis I diagnosis were scanned at T1 (54% female, age range 11–21 years, mean age  $16.2 \pm 2.7$  years) and rescanned at T2 (age range 13–23 years, mean age  $18.3 \pm 2.9$  years) after a mean interval of  $2.1 \pm .44$  years (range 1.51–3.55 years) (Table 1). The presence or absence of psychiatric disorders and mood state on the scanning day were confirmed by structured clinical interview using the Schedule for Affective Disorders and Schizophrenia for School Aged Children-Present and Lifetime Version (41) for subjects ages  $\leq 18$  years, with subject and parent/guardian interviewed separately, and Structured Clinical Interview for DSM-IV Axis I Disorders (Version 2.0) (42) for subjects  $> 18$  years. Final DSM-IV consensus diagnoses were established by trained and reliable interviewers and a board-certified psychiatrist or mental health clinician with expertise in clinical and research interviews. Family history was assessed by the Family History Screen for Epidemiologic Studies (43). Exclusion criteria included neurological disorders, history of loss of consciousness  $\geq 5$  minutes, or contraindications to MRI scanning. Subjects had no significant medical illness other than treated hypothyroidism in two BD subjects. After explanation of the study, written informed consent was obtained from all subjects  $\geq 18$  years. For subjects  $< 18$  years, the parents or legal guardians provided written informed consent and the subjects provided written assent. The study protocol was performed in accordance with the human investigation committee of the Yale School of Medicine.

Table 2 provides clinical information for the BD subjects at each time point, including information regarding medication, comorbidities, mood states, rapid-cycling, psychosis, and hospitalizations. To improve generalizability, as an estimated

**Table 1. Age, Scanning Interval, and Gender Distribution of the Healthy Control and Bipolar Disorder Groups**

	Healthy Control Subjects	Bipolar Disorder	<i>t</i> Value ( <i>df</i> )	<i>p</i> Value
Age at Time 1 Mean [SD] <sup>a</sup>	16.2 [2.7]	16.8 [2.8]	-.93 (70)	.36
Age at Time 2 Mean [SD] <sup>a</sup>	18.3 [2.9]	19.1 [2.9]	-1.25 (70)	.22
Interval Mean [SD] <sup>a</sup>	2.1 [.4]	2.3 [.7]	-1.86 (70)	.07
Female, <i>n</i> (%) <sup>b</sup>	20 (54)	17 (48)	.22 (1) <sup>c</sup>	.64

<sup>a</sup>Results are from independent sample *t* tests.

<sup>b</sup>Results are from Pearson Chi-square.

<sup>c</sup>Denotes  $\chi^2$ .

**Table 2. Clinical Characteristics of the Group with Bipolar Disorder I (n = 35)**

	First Scan	Second Scan
<b>Medications</b>		
Medication, n (%)	33 (94)	26 (74)
Antipsychotics, n (%)	21 (60)	18 (51)
Anticonvulsants, n (%)	17 (49)	10 (29)
Lithium carbonate, n (%)	8 (23)	6 (17)
Antidepressants, n (%)	6 (17)	5 (14)
Psychostimulants, n (%)	6 (17)	9 (26)
Benzodiazepines, n (%)	4 (11)	4 (11)
Sympatholytic medications, n (%)	1 (3)	1 (3)
Hypnotics, n (%)	1 (3)	–
<b>Lifetime Comorbidities</b>		
Attention-deficit/hyperactivity disorder, n (%) <sup>a</sup>	11 (31)	11 (31)
Conduct disorder, n (%) <sup>a</sup>	4 (11)	4 (11)
Oppositional defiant disorder, n (%) <sup>a</sup>	3 (9)	4 (11)
Separation anxiety disorder, n (%) <sup>a</sup>	1 (3)	1 (3)
Tic disorder, n (%) <sup>a</sup>	1 (3)	1 (3)
Simple phobia, n (%)	3 (9)	3 (9)
Anorexia nervosa, n (%)	1 (3)	1 (3)
Generalized anxiety disorder, n (%)	1 (3)	1 (3)
Obsessive compulsive disorder, n (%)	1 (3)	1 (3)
Panic disorder, n (%)	1 (3)	2 (6)
Binge eating disorder, n (%)	–	1 (3)
Posttraumatic stress disorder, n (%)	–	1 (3)
<b>Substance Use Disorders</b>		
Current substance abuse or dependence: marijuana/alcohol, n (%)	2 (6) / 1 (3)	3 (9) / 1 (3)
History substance abuse or dependence: marijuana/alcohol/cocaine/polysubstance, n (%)	5 (14) / 1 (3) / 2 (6) / 1 (3)	6 (17) / 1 (3) / 2 (6) / 1 (3)
<b>Mood State at Scanning</b>		
Euthymic/elevated (hypomanic + manic + mixed)/depressed, n (%)	22 (63) / 7 (20) / 6 (17)	31 (89) / 3 (9) / 1 (3)
Rapid-Cycling, n (%)	15 (43)	13 (37)
<b>Psychosis</b>		
Current, n (%)	1 (3)	1 (3)
Lifetime, n (%)	16 (46)	17 (49)
<b>Hospitalizations</b>		
n (%)	22 (63)	24 (66)
Mean [SD]	2.0 [2.3]	2.5 [2.6]

<sup>a</sup>These disorders only assessed in subjects ≤18 years of age.

60% of individuals with BD also have a substance use disorder (44), subjects with histories of substance abuse or dependence were included. Subjects were in remission from substance abuse/dependence for >4 months, except four BD subjects with current alcohol and/or marijuana abuse/dependence at either T1 (n = 1) and/or T2 (n = 3). Analyses were also performed excluding subjects with current or lifetime history of substance abuse/dependence.

### MRI Acquisition and Processing

MRI scans at both time points were obtained using the same 3-Tesla Trio MR scanner (Siemens, Erlangen, Germany). A

three-dimensional magnetization prepared rapid acquisition gradient-echo T1-weighted sequence was used to acquire sagittal images (repetition time = 1500 msec, echo time = 2.83 msec, field of view = 256 × 256 mm<sup>2</sup>, matrix 256 × 256, slice thickness = 1.0 mm without gap, 160 slices, two averages).

Brain volume changes were measured via the Yale Bio-Image Suite software package (Section of Bioimaging Sciences, Department of Diagnostic Radiology, Yale University, New Haven, Connecticut, <http://www.bioimagesuite.org>) running on a Linux workstation (Red Hat Inc., Raleigh, North Carolina). A nonrigid registration algorithm, based on a free-form deformation model and normalized mutual information (45,46), was used to compute the deformations required to establish dense correspondence between T1 and T2 scans for each subject. From these within-subject registered transformations, the degree of local expansion or contraction (percent change) was computed with Jacobian maps, based on the determinant of the Jacobian of the displacement field generated by each transformation, which will be referred to from here on as Jacobian (47). This analysis produced a Jacobian map with a resolution of 1 × 1 × 1 mm<sup>3</sup> where each voxel had a value representing the local volume change required to map an individual subject's T1 scan onto his/her follow-up scan: 1 = no volume change, >1 = T2 scan was larger than T1 scan, and <1 = T1 scan was larger than T2 scan. Jacobian maps were checked to confirm transformations were free of singularities (i.e., |J| ≤ 0). The nonlinear registration algorithm was also applied to transform T1 scans for each subject into standard space by normalizing to the Montreal Neurological Institute template. In a separate step, the individual Jacobian maps were warped to the space of the Montreal Neurological Institute template using the second registration. The Jacobian values were extracted in the region showing group differences in brain volume changes over time for further analyses.

To identify the relative contributions of abnormalities in the trajectories of GM and WM to the region of significant group differences, tissue segmentation into GM and WM was performed for each subject's T1 scan based on the signal intensities corresponding to the two types of matter (FMRIB Software Library [FSL]; FMRIB Analysis Group, University of Oxford, Oxford, United Kingdom; <http://www.fmrib.ox.ac.uk/fsl>). The region showing group difference in common space was then warped back to each subject's segmented T1 scan. Finally, the Jacobian values were extracted separately from the GM or WM segmented subregions for further analyses.

### Data Analysis

The Jacobian values at each voxel throughout the brain were subjected to two-sample *t* tests using BioImage Suite (Yale University) to assess group differences between all HC and all BD subjects. The maps were thresholded at *p* < .05, two-tailed, controlling for the familywise error rate and clusters >50 contiguous voxels (mm<sup>3</sup>) using Statistical Parametric Mapping 8 (SPM8) (Wellcome Trust Centre for Neuroimaging, University College London, London, United Kingdom; <http://www.fil.ion.ucl.ac.uk/spm>). For within-group analysis, the mean Jacobian values within the cluster showing significant group differences in volume change over time, extracted from each participant's

normalized Jacobian maps, were subjected to an independent sample  $t$  test for each group separately using SPSS (SPSS Inc, Chicago, Illinois).

The mean Jacobian values for the GM and for the WM within the cluster showing significant group differences in volume change over time, extracted from each participant's normalized Jacobian maps, were subjected to between-group analyses for each tissue type separately, using two-sample  $t$  tests in SPSS, thresholded at  $p < .05$ , two-tailed. Similar to overall brain parenchyma, within-group analyses were conducted in SPSS using the mean Jacobian values within the cluster of the region of difference for GM and WM, separately, extracted from each participant's normalized Jacobian maps. In addition, the main analyses comparing BD and HC groups were adjusted for age at study entry using analysis of covariance.

Post hoc analyses were performed in SPSS using the mean signal extracted from each participant's normalized Jacobian maps for overall difference and separately for GM and WM. Analyses of variance were used to explore potential main effects of age on Jacobian values across all subjects and within HC or BD groups. Analysis of variance was used to assess for potential effects of gender across all subjects and two-sample  $t$  tests were used to assess for gender effects within groups. Effects of clinical variables were also explored within the BD group at each time point with two-sample  $t$  tests for medication (on/off), medication subclasses present for five or more subjects (on/off) (antipsychotics, anticonvulsants, lithium carbonate, antidepressants, and psychostimulants), the presence or absence of comorbidities present for five or more subjects, including attention-deficit/hyperactivity disorder and substance abuse or dependence, separately for cannabis abuse/dependence, as well as for acute mood episode type (pairwise comparisons of elevated [hypomanic/manic/mixed], depressed, euthymic), rapid-cycling, or lifetime psychosis.

Additional analyses were performed comparing all HC with all BD subjects without current substance use disorders and all HC with all BD without lifetime substance use disorders.

## RESULTS

The BD and HC groups did not differ significantly in gender, age at T1 or T2, or time between scans (Table 1).

Significant differences in overall brain changes over time were observed between groups in one cluster within the right hemisphere, located in the region of the OFC (Brodmann area [BA] 47), and extending into the insula, inferior PFC (BA 44/45),

RPFC (BA 10), and DLPFC (BA 9) (with a local maxima at  $x = 24$  mm,  $y = 24$  mm,  $z = 0$  mm;  $t_{70} = 1.99$ ,  $p < .05$ , familywise error rate-corrected) (Figure 1). Within this region, BD subjects showed tissue reduction over time ( $t_{34} = -2.97$ ,  $p < .01$ ) and HC subjects showed tissue enlargement over time ( $t_{36} = 2.18$ ,  $p < .05$ ). Group differences over time were observed in both GM ( $t_{70} = 3.07$ ,  $p < .005$ ) and WM ( $t_{70} = 3.42$ ,  $p < .001$ ) within this cluster. In GM, the BD group showed significant contraction over time (3.95% tissue reduction,  $t_{34} = -5.29$ ,  $p < .001$ ), whereas the HC group did not demonstrate significant change over time. In WM, the HC group showed significant expansion over time (4.36% tissue enlargement,  $t_{36} = 3.56$ ,  $p < .005$ ), whereas the BD group did not demonstrate significant change over time (Figure 2).

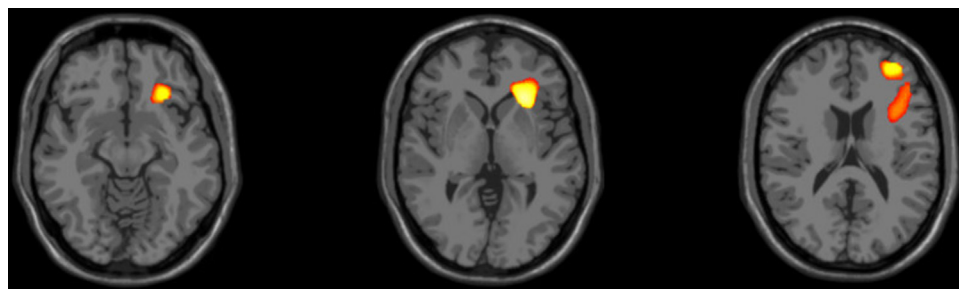
Significant group differences remained after controlling for age in overall tissue [ $Adjusted (Adj)p_{group} = .002$ ,  $p_{age} = .19$ ], GM ( $Adjp_{group} = .005$ ,  $p_{age} = .21$ ), and WM ( $Adjp_{group} = .002$ ,  $p_{age} = .18$ ). Similar results were found when controlling for interscan interval: overall tissue ( $Adjp_{group} = .004$ ,  $p_{interval} = .49$ ), GM ( $Adjp_{group} = .007$ ,  $p_{interval} = .49$ ), and WM ( $Adjp_{group} = .002$ ,  $p_{interval} = .50$ ).

Post hoc analyses of the region showing significant differences for total, as well as for GM or WM, volumes did not reveal any significant effects for demographic and clinical variables at T1 or T2. Findings were similar for overall, as well as for GM and WM, volume reductions in the additional comparisons between the HC group and the BD group without current substance use disorder and the HC group and the BD group without lifetime substance use disorder.

## DISCUSSION

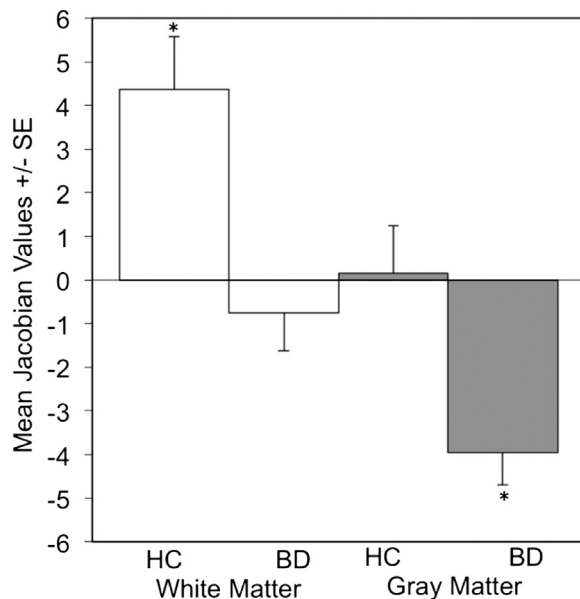
This study demonstrates differences in longitudinal brain changes between adolescents with and without BD. Over approximately 2 years, adolescents with BD exhibited more volume decreases within right anterior paralimbic and heteromodal cortices than HC adolescents. In addition, diverging patterns of GM and WM development in the adolescents with BD, compared with HC adolescents, were observed. Specifically, whereas adolescents with BD showed greater GM contraction over time, they showed less WM expansion compared with healthy adolescents.

The altered trajectory of insular and orbitofrontal cortices early in the course of BD is in line with a recent model of BD implicating a central role for the olfactocentric paralimbic cortices (OPC) during adolescence in development of the disorder (1,20). This is consistent with previous longitudinal studies supporting altered progression in anterior paralimbic



**Figure 1.** Volume change in bipolar disorder, compared with health, during adolescence. The images (Montreal Neurological Institute  $z = -12, 0, 16$  mm) demonstrate the regions of right insula and frontal volume decreases over approximately 2 years in adolescents with bipolar disorder, compared to healthy, adolescents ( $p < .05$  two-tailed, familywise error rate-corrected, cluster  $>50$  voxels).





**Figure 2.** Gray and white matter changes in bipolar disorder, compared with health, during adolescence. The graph shows the percent changes in gray and white matter in the area of group differences over approximately 2 years between the healthy control (HC) and bipolar disorder (BD) groups (\* $p < .005$ ).

regions in BD (32–34). However, other results have also been reported, including increases in parietal and precuneus volumes (48) and no significant differences (49). The discrepancies between these findings with present results may be related to differences in subject characteristics and/or imaging methodologies.

In addition to these GM abnormalities within the OPC, abnormalities in the underlying WM were also observed. Abnormalities included the area of the uncinate fasciculus (UF), a WM tract that courses through the OPC and provides major amygdala–OFC connections (50). Abnormalities in the UF have been demonstrated previously in adults with BD (51–60). The observation of progressive WM abnormalities in BD in this study suggests that the disorder is associated with a disruption in the development of such WM connections to the frontal cortex that typically occurs during adolescence.

The extension of the findings into more rostral, dorsal, and lateral heteromodal frontal regions is consistent with previous cross-sectional and longitudinal studies (1,2,32,34). Similar reductions were not seen in a longitudinal study using a surface area analysis of GM (33). Thus, it is possible that mechanisms that contribute to altered trajectories in GM thickness and WM volume, but not GM surface area, are involved in the development of BD (61).

Group differences over time were not detected in the amygdala, consistent with studies suggesting amygdala abnormalities may already be established by adolescence in BD (4,13–17,62), while abnormalities in anterior cortices and frontotemporal WM connections continued to progress. Progressive differences in amygdala volumes after the first episode of mania in adolescents with BD have been reported (63), suggesting amygdala changes may be some of the first

neural changes associated with BD onset. Adolescents in the current study were not all studied at initial onset. Further study of adolescents before and after the onset of BD is needed.

Longitudinal combined functional and structural neuroimaging studies in adolescents with BD are needed to elucidate the relationships between the abnormalities in morphologic trajectories and functional abnormalities observed in adolescents in anterior paralimbic and heteromodal cortices (64–68). A small cross-sectional functional MRI study, during performance of a prepotent response inhibition task, provided preliminary evidence that HC adolescents exhibit increased rostroventral PFC responses with age, whereas adolescents with BD did not show similar age-related increases (69). This suggested that a pattern of functional abnormalities over time, similar to the structural abnormalities, may be present in BD. There could be differences in clinical presentation in youths and adults. Progressive paralimbic structural abnormalities could be reflected in progressive and/or differing character of impairments in regulating responses to emotional and motivational stimuli. Progressive heteromodal abnormalities could be reflected in progressive and/or differing character of impairments in top-down executive control of behavior. This is suggested by preliminary findings of differences in changes with age in adolescents with BD, compared to healthy adolescents, in heteromodal responses to the need to inhibit maladaptive behavioral responses (69). However, this remains speculative given the paucity of longitudinal data in this area. An alternative interpretation of the results of this study is that the observed changes are reflecting compensatory mechanisms, rather than pathology. Longitudinal studies that investigate both brain structure and function and associated negative and/or positive changes in symptoms and behaviors are needed.

Findings reported here were lateralized to the right hemisphere. Lesion studies suggest that right frontal lesions are especially associated with manic symptoms (70,71). Consistent with right-lateralized abnormalities, studies of BD have reported reduced right frontal GM volume (72,73) and right UF WM integrity (53,60). PFC functional abnormalities in mania in BD have also tended to be right-sided (74–77). These findings suggest that the right hemisphere abnormalities observed in this study might be related to increased risk for mania. However, as the number of prior manic episodes could not be reliably calculated in this study, especially for subjects with rapid cycling, it was not possible to discern a relationship between the findings and vulnerability to elevated mood states. Future studies are warranted to clarify this issue.

While this study had a larger sample size compared with previous longitudinal studies in adolescents with BD, the sample size was modest and did not provide ability to definitively assess medication and comorbidity factors. Subjects were taking varying medications and substance and other comorbidity histories also varied. The BD sample only included individuals with BD type I, increasing sample homogeneity, but findings may not generalize to other BD subtypes. Preadult onset BD is associated with worse course and prognosis (78,79). All of the subjects in this study had onset by the teenage years. It is unclear whether findings will generalize to individuals with later onsets.

We previously suggested that progressive abnormalities in BD may advance from more caudal paralimbic regions to more rostral regions (20,32). While age-related changes were not observed in the present study, the sample included a wide age range and small numbers of subjects at each age. Age-related findings might become more evident with more strictly defined age groups and larger samples. Progressive abnormalities reported here, suggested to be related to the development of BD, could also be a result of disease progression, possibly due to neurotoxic effects associated with episodes. The inclusion of small samples at each age and only two longitudinal time points may have limited the ability to model patterns of neurodevelopmental differences that may be differently influenced by different ages; longitudinal studies with larger samples including additional time points are warranted. The majority of subjects were taking psychotropic medications. Previous studies have shown that mood stabilizers such as lithium carbonate are associated with neurotrophic and neuroprotective effects and, in individuals with BD, with increases in GM volume in anterior paralimbic and heteromodal structures (18,80–83). Significant effects of medication were not observed in this study, although power may not have been sufficient to detect differences. Subjects reported varying medication combinations and medications were not studied systematically. Studying medication load would be ideal; however, reliability of reports of specific medications taken and amounts were not clear. These factors can be challenging to overcome when studying individuals with BD, unless, for example, studying never medicated individuals systematically over time in a controlled medication trial. Additionally, 11 BD subjects had either current or past substance abuse or dependence, which could have confounded results. However, comparisons of BD subjects with history of substance use disorders with those without did not show significant differences in the region of the main group differences, and analyses performed between HC subjects and BD subjects excluding those with current substance abuse/dependence demonstrated findings similar to those when including all BD subjects. Comorbidities also varied among the BD subjects. Differing effects were not detected for the presence of attention-deficit/hyperactivity disorder, although power was limited given the small number of subjects with it, and there were not sufficient numbers of subjects to examine potential effects of other comorbidities.

In summary, findings support greater GM reduction and diminished WM expansion in anterior paralimbic and heteromodal cortices in adolescents with BD I, compared with healthy adolescents, implicating anterior gray and white matter developmental abnormalities during adolescence in the disorder. Alterations in anterior GM and WM developmental mechanisms, such as neuronal pruning and/or myelination, may have contributed to differences in neural trajectories observed in adolescents with BD. Findings could aid elucidation of the developmental pathophysiology of BD and help inform strategies to halt progression in the disorder.

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## ARTICLE INFORMATION

From the Departments of Psychiatry (PN, FW, LS, JAYJ, ETCL, BPP, HPB), Diagnostic Radiology (CL, LHS, XP, HPB), Electrical Engineering (LHS), and Biomedical Engineering (XP) and the Child Study Center (HPB), Yale School of Medicine, New Haven, Connecticut.

Address correspondence to Hilary P. Blumberg, M.D., Yale School of Medicine, Department of Psychiatry, 300 George Street Suite 901, New Haven, CT 06511; E-mail: hilary.blumberg@yale.edu.

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