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Dynamic mapping of cortical development before and after the onset of pediatric bipolar illness

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Background: There are, to date, no pre-post onset longitudinal imaging studies of bipolar disorder at any age. We report the first prospective study of cortical brain development in pediatric bipolar illness for 9 male children, visualized before and after illness onset. **Method:** We contrast this pattern with that observed in a matched group of healthy children as well as in a matched group of 8 children with 'atypical psychosis' who had similar initial presentation marked by mood dysregulation and transient psychosis (labeled as 'multi-dimensionally impaired' (MDI)) as in the bipolar group, but have not, to date, developed bipolar illness. **Results:** Dynamic maps, reconstructed by applying novel cortical pattern matching algorithms, for the children who became bipolar I showed subtle, regionally specific, bilaterally asymmetrical cortical changes. Cortical GM increased over the left temporal cortex and decreased bilaterally in the anterior (and sub genual) cingulate cortex. This was seen most strikingly after the illness onset, and showed a pattern distinct from that seen in childhood onset schizophrenia. The bipolar neurodevelopmental trajectory was generally shared by the children who remained with MDI diagnosis without converting to bipolar I, suggesting that this pattern of cortical development may reflect affective dysregulation (lability) in general. **Conclusions:** These dynamic trajectories of cortical development may explain age-related disparate findings from cross-sectional studies of bipolar illness, and suggest the importance of mood disordered non-bipolar control group in future studies. **Keywords:** Pediatric, bipolar, MRI, mapping, gray, matter.

Bipolar disorder is a common psychiatric illness that is characterized by severe mood fluctuations and recent studies suggest that the lifetime prevalence of bipolar I disorder in the US is about 3.3% (Grant et al., 2005). Genetic risk for bipolar illness is well established; however, the biological changes associated with illness onset remain unknown (McDonald, Bullmore et al., 2004). Converging structural and functional neuroimaging data suggest that mood fluctuations in bipolar disorder are mediated by abnormalities in limbic–thalamic–cortical and limbic–striatal–pallidal–thalamic circuits which involve the prefrontal and anterior cingulate cortices, the hippocampal–amygdalar complex, the thalamus, and the basal ganglia (Brambilla, Nicoletti et al., 2002; DelBello, Zimmerman, Mills, Getz, & Strakowski, 2004; Drevets, 2000; Frazier, Chiu et al., 2005; Soares & Mann, 1997; Strakowski, DelBello, Adler, Cecil, & Sax, 2000). However, structural neuroimaging studies in adult bipolar disorder have been inconsistent with respect to these abnormalities (Blumberg et al., 2003; Brambilla, Barale, Caverzasi, & Soares, 2002; Brambilla, Nicoletti et al., 2002; Chang, Barnea-Goraly et al., 2005; Drevets, 2000; Drevets et al., 1997; Monkul, Malhi, & Soares, 2005; Soares & Mann, 1997; Strakowski et al., 2000, 1999). A recent meta-analysis of 26 anatomic brain MRI studies of bipolar disorder found the only consistent structural abnormality to be lateral ventricular enlargement, most prominent on the right side (reflecting right sided GM loss) (McDonald, Zanelli et al., 2004). Other trends include white matter hyperintensities, reduced volumes of prefrontal cortex, and altered volumes of sub genual cingulate and other deeper cortical structures such as amygdala, caudate, and thalamus (Bearden, Hoffman, & Cannon, 2001; Beyer & Krishnan, 2002; Beyer et al., 2004; Blumberg et al., 2005; Hajek, Carrey, & Alda, 2005; Strakowski et al., 2000). Such heterogeneity in structural findings, which could be due to methodological differences, sample size or age heterogeneity, or medication status, makes it difficult to delineate these subtle and widely distributed abnormalities (Monkul et al., 2005). A longitudinal study, with a population studied before and after the onset of bipolar illness, would be expected to be more sensitive to the nature and time course of these changes.

Bipolar disorder is more common in children and adolescents than previously thought but the diagnostic criteria for pediatric bipolar illness have been controversial (Lewinsohn, Seeley, Buckley, & Klein, 2002). Many prospective (Birmaher et al., 2006;

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Geller, Tillman, Craney, & Bolhofner, 2004) as well as retrospective (Mick, Biederman, Faraone, Murray, & Wozniak, 2003; Perlis et al., 2004; Schneck et al., 2004) studies indicate that early onset cases resemble the most severe adult cases. Other studies have stressed a more atypical course for pediatric bipolar illness with rapid mood cycling and/or mood irritability as prominent symptoms (Biederman, 2003; Craney & Geller, 2003; Geller et al., 1995). In order to provide basis for research, Leibenluft et al. proposed operational criteria for 'broad', 'intermediate', and 'narrow' bipolar phenotypes where the broad phenotype was characterized by prominent mood irritability and hyper arousal while the narrow phenotype required a frank manic episode, consistent with the DSM-IV bipolar I criteria (Leibenluft, Charney, & Pine, 2003; Leibenluft, Charney, Towbin, Bhangoo, & Pine, 2003).

There are few neuroimaging studies of pediatric onset bipolar illness (Frazier, Ahn et al., 2005). An early study by Botteron et al. ($n = 10$) showed ventricular enlargement and positive correlations between age and ventricular volumes in 8–16-year-old manic patients (Botteron, Vannier, Geller, Todd, & Lee, 1995). More recent studies report ventricular or sulcal enlargements (Friedman et al., 1999), smaller amygdalar (Chang, Karchemskiy et al., 2005) and anterior cingulate volumes (Caetano et al., 2005; B.K. Chen et al., 2004; Dickstein et al., 2005; Kaur et al., 2005; Wilke, Kowatch, DelBello, Mills, & Holland, 2004), larger putamen (Wilke et al., 2004), larger left temporal lobe volumes (H.H. Chen et al., 2004; Wilke et al., 2004), and smaller left dorsolateral prefrontal cortical volumes (Dickstein et al., 2005). However, inconsistencies remain with reports of smaller left superior temporal gyrus volume, or smaller or unchanged sub genual cingulate volumes (Caetano et al., 2005; H. H. Chen et al., 2004; Kaur et al., 2005; Sanches et al., 2005).

As all the above studies are cross-sectional, sample heterogeneity remains an issue in relation to possible age effects (Monkul et al., 2005). To date, there are no pre–post-onset longitudinal imaging studies of bipolar disorder at any age and thus age effects are not considered in neuroimaging studies of early onset bipolar illness. Similarly, knowing the baseline (pre-onset) state of structure in people with bipolar disorder would help understand the structural differences in bipolar disorder. For the past 15 years longitudinal prospective brain MRI (magnetic resonance imaging) studies have been carried out at the National Institute of Mental Health (NIMH) to explore anatomic brain development in healthy, hyperactive and childhood-onset schizophrenia (COS) participants. As part of our recruitment efforts for the COS cohort, a group of children was identified with similar initial presentation but who did not have schizophrenia, were diagnosed as psychosis not otherwise specified (NOS; DSM IV 298.9), had emotional dysregulation, attention deficit hyperactivity disorder (ADHD) and some developmental disorders. These impairments in multiple domains led to our provisional label of 'multi-dimensionally impaired' (MDI) syndrome (Kumra et al., 1998; McKenna et al., 1994). These children were followed prospectively every two years, with brain MRI rescans, as a clinical contrast group. Over the subsequent 4–8 years, 12 out of 32 MDI subjects (38%) developed a DSM IV defined manic episode and 9 of 12 thus had usable scans before and after the first manic episode (bipolar I diagnosis).

We applied a novel brain mapping technique to the MRI scans of these 9 subjects. Based on prior reports, we hypothesized that brain development in pediatric bipolar illness would show, relative to healthy controls, subtle and progressive regional structural alterations, in prefrontal, orbito-frontal, or temporal cortices laterally and in the anterior cingulate cortex medially. Additionally, to test the specificity of the brain changes, we compared the brain development of MDI children who converted to bipolar I illness to the brain development of an age and gender matched group of 8 'MDI' children who did not convert to bipolar I phenotype.

Methods

Subjects

A group of children (32 to date), initially referred to the NIMH with a diagnosis of COS, received the diagnosis of psychosis NOS (DSM IV 298.9), after drug-free inpatient observation and re-evaluation by two child psychiatrists using structured clinical interview (K-SADS; Kaufman et al., 1997). Their presentation was characterized by transient hallucinations (hallucinations of very short duration, typically precipitated by stress and with frequency of once a week or less), no thought disorder and, most prominently, mood lability, and co-morbid ADHD. These children ($n = 32$ to date) were provisionally labeled as 'multi-dimensionally impaired (MDI)' by the NIMH team (McKenna et al., 1994) and followed longitudinally along with the COS children (Kumra et al., 1998). In parallel with the COS and control groups, prospective brain MRI re-scans on these children were obtained every two years.

At 4–8-year follow up, 12 out of 32 (38%) children had developed DSM IV defined bipolar I disorder diagnosed after a manic episode (Nicolson et al., 2001). Subject records, including structured clinical interviews and videotaped interviews obtained at the time of screening, were re-evaluated blindly by a child psychiatrist to make sure that the bipolar I diagnosis was not missed at initial screening. The age of first manic episode was considered the age of onset of bipolar I illness for this study. Nine out of 12 children with bipolar I disorder had brain MRI scans both before and after the onset of manic episode (total 27 scans) and were selected for the study. All subjects were male. Eight of the remaining 20 atypical psychosis children, who had had three or more scans

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Table 1 Sample demographic

	BP ($N = 9$)	Non-BP MDI ($N = 8$)	Controls ($N = 18$)	BP vs. Non BP MDI		BP vs. NV		Non-BP MDI vs. NV	
				t (df)	p	t (df)	p	t (df)	p
Age at screening	11.9 (3.7)	10.0 (2.3)	–	1.3 (15)	.2	–	–	–	–
Age at diagnosis	16.5 (3.9)	–	–	–	–	–	–	–	–
IQ	90.1 (9.3)	85.3 (11.9)	124.1 (8.8)	.94 (15)	.36	−9.26 (25)	<.001	−9.28 (24)	<.001
Age at first scan	13.3 (3.7)	12.1 (2.5)	13.8 (3.3)	.73 (15)	.47	−.355 (25)	.73	−1.26 (24)	.22
Age at first scan after BP Dx	18.1 (5.2)	–	–	–	–	–	–	–	–
Average scan interval (years)	2.7 (1.4)	2.4 (1.0)	2.7 (1.0)	.58 (33)	.56	−.06 (51)	.95	−.85 (46)	.40
Average age over all scans	16.2 (4.7)	14.4 (2.9)	16.0 (3.7)	1.58 (50)	.12	.16 (78)	.87	−1.84 (72)	.07
Handedness (R/L)	9/0	7/1	17/1						
Medications at screening (numbers taking each)a									
Lithium	3	0	–						
Other MS	2	2	–						
Atypical antipsychotics	4	4	–						
Typical antipsychotics	6	3	–						
Medications at last follow-up*									
Lithium	1	1	–						
Other MS	2	2	–						
Atypicals	3	4	–						
Typicals	0	1	–						

Note: From the entire MDI cohort ($n = 32$), when children who became Bipolar I at follow-up ($n = 12$) were compared to the group who did not become bipolar ($n = 20$), the former had received mood stabilizers more frequently at the time of initial contact (7 (58.3%) vs. 4 (20%); X2 (4.8); df (1); $p = .02$) and had trend level differences (slightly higher scores) on the Bunny Hamburg Mania scale at initial contact (2.75 ± 3.17SD vs. 1.22 ± .73SD; t (−1.9); df (28); $p = .06$) although none met the cut-off for a manic episode. BP – bipolar disorder (narrow phenotype), MDI – multi-dimensionally impaired (psychotic broad phenotype), NV – healthy controls, SD – standard deviation, df – degrees of freedom. MS – mood stabilizers which include valproate and carbamazepine. *At f/u 2 BP patients had discontinued their medications due to being in a manic state.

and were age and sex matched with the bipolar I group, served as a clinical comparison group (see Table 1). These children, who had similar clinical presentation and treatment history at the initial screening (Table 1), have not become bipolar I to date and continue to be classified as MDI (psychosis NOS). All MDI patients also met DSM IV criteria for attention deficit hyperactivity disorder combined type. Additionally, among the bipolar group, 2 patients had co-morbid oppositional defiant disorder (ODD), and 1 had pervasive developmental disorder (PDD). Among the non-bipolar MDI subjects, 3 had ODD, 1 had generalized anxiety disorder (GAD) and 3 subjects had a single episode of major depression and were in full remission.

Control subjects

Eighteen healthy male children and adolescents, matched for age and scan interval with the bipolar as well as non-bipolar 'MDI' groups, were selected from a larger prospective study of normal pediatric brain development (3–4 scans per subject; total 52 scans). Controls were free of lifetime medical or psychiatric disorders as determined by clinical and standardized interviews, and history of major psychiatric illness in first-degree relatives was also exclusionary (Giedd et al., 1996; Gogtay, Giedd et al., 2004).

The research protocol was approved by the NIMH institutional review board. Written informed consent was obtained from parents and controls and patients over 18, and written informed assent was obtained from minors.

Image processing and analysis

MRI images were acquired identically from patients and controls at the NIMH on the same 1.5 Tesla GE scanner and the sequence was consistent throughout the study. T1-weighted images with contiguous 1.5-mm slices in the axial plane and 2.0-mm slices in the coronal plane were obtained using three-dimensional spoiled gradient recalled echo in the steady state (SPGR). Imaging parameters were echo time 5 ms, repetition time 24 ms, flip angle 45°, acquisition matrix 256 × 192, number of excitations = 1, and 24-cm field of view. With each major software/hardware upgrade, the reliability of the data was tested by scanning a set of subjects before and after the upgrade (Giedd et al., 1996). Briefly, for each scan, a radio-frequency bias field correction algorithm was applied (Sled, Zijdenbos, & Evans, 1998). Follow-up scans were first aligned rigidly (using a 6-parameter transformation) to the baseline scan from the same subject and mutually registered scans for each subject were linearly mapped to a standard 3 D stereotaxic space, the ICBM space, using a 9-parameter linear matrix transforming them as previously described (Gogtay, Giedd et al., 2004; Thompson et al., 2003). An extensively validated tissue classifier generated detailed maps of gray matter, white matter, and cerebro-spinal fluid (CSF) using a Gaussian mixture distribution to generate a maximum a posteriori (MAP) segmentation of the data (Shattuck & Leahy, 2001; Zijdenbos & Dawant, 1994), and a surface model of the cortex was then automatically extracted for each subject and time-point, as described previously (Thompson et al., 2003, 2004).

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An image analysis technique, known as cortical pattern matching (Ashburner et al., 2003; Thompson et al., 2003; Thompson, Mega, Vidal, Rapoport, & Toga, 2001), was used to better localize cortical differences over time, and increase the power to detect systematic changes (Thompson et al., 2003). This approach matches gyral features of cortical surface anatomy as far as possible across subjects before making cross-subject comparisons, group averages, and statistical maps. This eliminates some confounding anatomical variance, providing increased statistical power for detecting statistical effects on cortical measures, as well as increased ability to localize these effects relative to major sulcal and gyral landmarks. In the cortical matching step, secondary deformations are computed that match gyral patterns across all the time-points, and across all subjects. This allows data to be averaged and compared across corresponding cortical regions. A set of 58 sulcal landmarks per brain constrained the mapping of one cortex onto other matching corresponding cortical regions across subjects. An image analyst, blind to subject identity, gender and age, traced each of 29 sulci and a set of 7 midline landmark curves bordering the longitudinal fissure on the surface rendering of each brain hemisphere, as described in a detailed anatomical protocol available on the internet with established inter- and intra-rater reliability (Thompson et al., 2003).

A time-dependent average 3D cortical model for the group was created by flattening all sulcal/gyral landmarks into a 2D plane along with the cortical model and assigning a color code to retain 3D shape information. Once data were in this flat space, sulcal features were aligned across subjects and time to an average set of sulcal curves. The warped cortical maps were mathematically re-inflated to 3D, producing a crisp average cortical model with gyral features in their mean anatomic locations (Thompson et al., 2000).

To quantify local gray matter, we used a measure termed 'gray matter density' used in many prior studies, which measures the proportion of gray matter in a small region of fixed radius (15 mm) around each cortical point (Sowell et al., 2003; Thompson, Mega, et al., 2001; Thompson et al., 2000, 2003). The GM density measure averages information on gray matter volumes over a small neighborhood (the 15-mm kernel used in this report), providing increased signal to noise, and it averages away some of the noise inherent in resolving the cortical gray matter boundaries in MRI. However, if GM density is used, some localization power is sacrificed, and the approach can average data from opposing sulcal banks. The measure can also index gray matter changes stemming from differences in cortical surface curvature where increased curvature may cause less gray matter to be sampled within the kernel of a fixed radius. Our ongoing work, however, shows that GM density and thickness are very highly correlated across the entire cortex (Narr et al., 2004) and therefore likely index similar maturational processes.

Ratio maps (dynamic sequence)

To compare cortical change between the bipolar or MDI brains with the age- and sex-matched control brains, ratio maps were generated by dividing the GM density regression curves at each of the 65,536 points. These ratios, which estimate the percent difference in GM at each age between patients and controls, were then color coded to visualize a 3-dimensional map and animated into a dynamic sequence (Figure 1).

Statistical analyses

Statistical plots were generated using a mixed model regression analysis (Giedd, Blumenthal et al., 1999; Giedd, Jeffries et al., 1999) for the GM density measures at each of 65,536 points on the entire cortical surface, and also at several specific points of interest over the surface from the areas showing significant differences. Because a nonlinear mixed model was used, inter-subject differences in gray matter density were modeled separately from the intra-individual rates of cortical change, giving additional power to resolve longitudinal changes at each cortical point. Hypothesis tests for model building were based on F statistics with alpha = .05 and also at a more conservative alpha = .01. Specifically, F tests were used to determine if the order of a developmental growth model was cubic, quadratic, or linear with increasing age. If a cubic model was not significant, a quadratic model was tested, and if that was not significant a linear model was tested. Thus a growth model was polynomial/nonlinear if either the cubic or quadratic term significantly contributed to the regression equation.

Significance maps (P maps)

The developmental trajectories (obtained using mixed model regression analyses) between the bipolar and healthy control subjects were also compared statistically at each cortical point using mixed effect models. The regression model was fit at every cortical point regressing gray matter volume against diagnosis, age, age-squared, and age and age-squared by diagnosis. Age was centered at the average age and group differences at the average age were determined using t-tests, and the significance of the group trajectory difference at each point was determined using an F test. The generated p-values for both the difference in GM amount (height of the curve) and the difference in the shape of the trajectories were differentially color coded and re-plotted on the cortical surfaces (Figure 2). Representative mixed model trajectories (graphs) were also generated for individual points of interest over both lateral and medial cortical surfaces (Figure 2).

Supplemental analyses: scan alignment by the onset of bipolar illness

To better reveal how neurodevelopmental changes relate to the age of onset of illness, we also aligned the bipolar subject scans by the age at onset of mania (i.e., age was replaced by the time in years relative to illness onset (first manic episode), e.g, −1 for one year before onset). The control scans were aligned with the bipolar scans and ratio maps were generated similarly against the age-matched mixed model curves of healthy brains and the resulting sequence, the changes (GM ratios) at the beginning were 'before' the onset and those at the end were 'after' the onset (Supplemental Figure 1).

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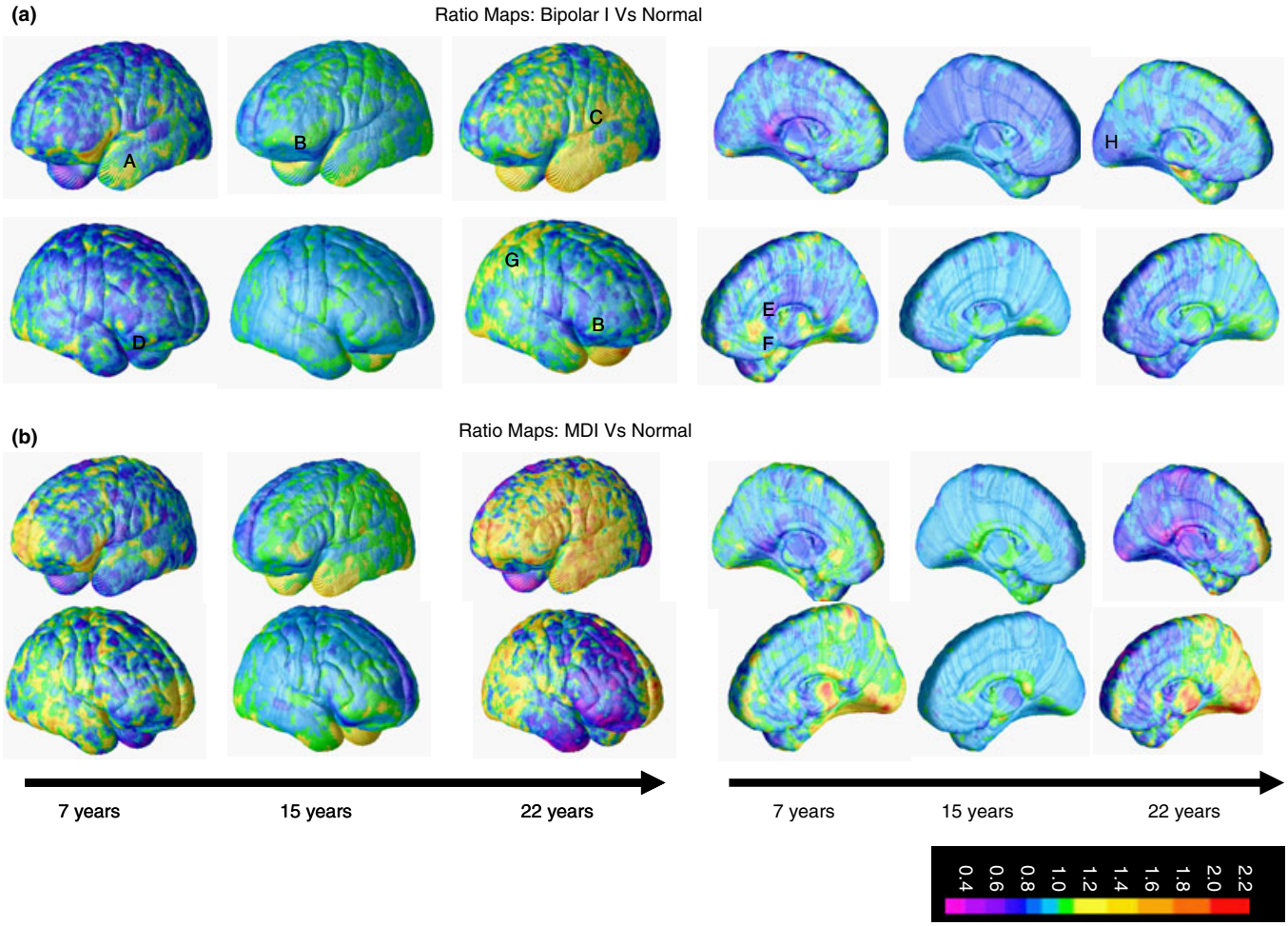

Figure 1 Lateral and medial cortical surfaces showing dynamic sequence of gray matter maturation across the cortex between ages 7 through 22 years. Panel A. 'Multi-dimensionally impaired' (MDI; psychosis NOS) subjects who converted to bipolar I Vs healthy controls. Panel B. MDI (psychosis NOS) subjects who remained MDI vs. healthy controls. Images are *ratio maps* obtained by dividing the average gray matter (GM) volumes in patients by those of healthy controls at each cortical point and plotted longitudinally using quadratic regression models. The side bar shows a color representation of ratios where ratios >1 (yellow–orange–red) indicate that patient brains have larger GM volume at the point while ratios <1 (aqua to blue) indicate smaller GM volume in patients. A – Temporal cortex, B – Ventro-lateral prefrontal cortex (VLPFC) including orbito-frontal region, C – Posterior aspect of superior temporal gyrus and superior temporal sulcus, D – VLPFC on right side, E – Dorsal and Anterior cingulate gyrus, F – Pre and subgenual region of cingulate gyrus, G – Right superior parietal region and H – Posterior cingulate. X-axis – Age in years (range 5–25 years). Y-axis – GM volume at the cortical point (0–.7 units). In both panels the lateral surface views are presented on the left side (3 age snapshots) and medial surface views are presented on the right half of the panel (3 age snapshots)

Results

Sample demographics are shown in Table 1. The three groups were well matched except for IQ, which was higher for controls and was used as a covariate in the analyses. None of the 17 subjects selected for this study met DSM criteria for bipolar I disorder at the initial contact. At 4–8-year follow-up, 9 met the criteria for the bipolar I disorder having had at least one manic episode. Of the 8 non-bipolar MDI comparison subjects, 3 met criteria for major depression at follow-up (in addition to psychosis NOS), while the remaining 5 continued to receive the DSM IV diagnosis of 'Psychosis NOS' only. Two of the 9 bipolar I subjects had discontinued their medications during recent manic episodes as observed at the most recent follow-up.

Total cerebral volume and the total gray matter volume did not differ significantly between the bipolar, non-bipolar MDI, and the control groups either at baseline or after adjusting for age (data not shown). Figure 1 (panel I) shows the time lapse sequence of the ratio of GM volumes in bipolar I subjects relative to the healthy subjects, which can also be seen as a 3-D time lapse movie sequence (Supplemental Figure 1). The bipolar subjects showed a different, regionally heterogeneous cortical developmental trajectory compared to the healthy controls.

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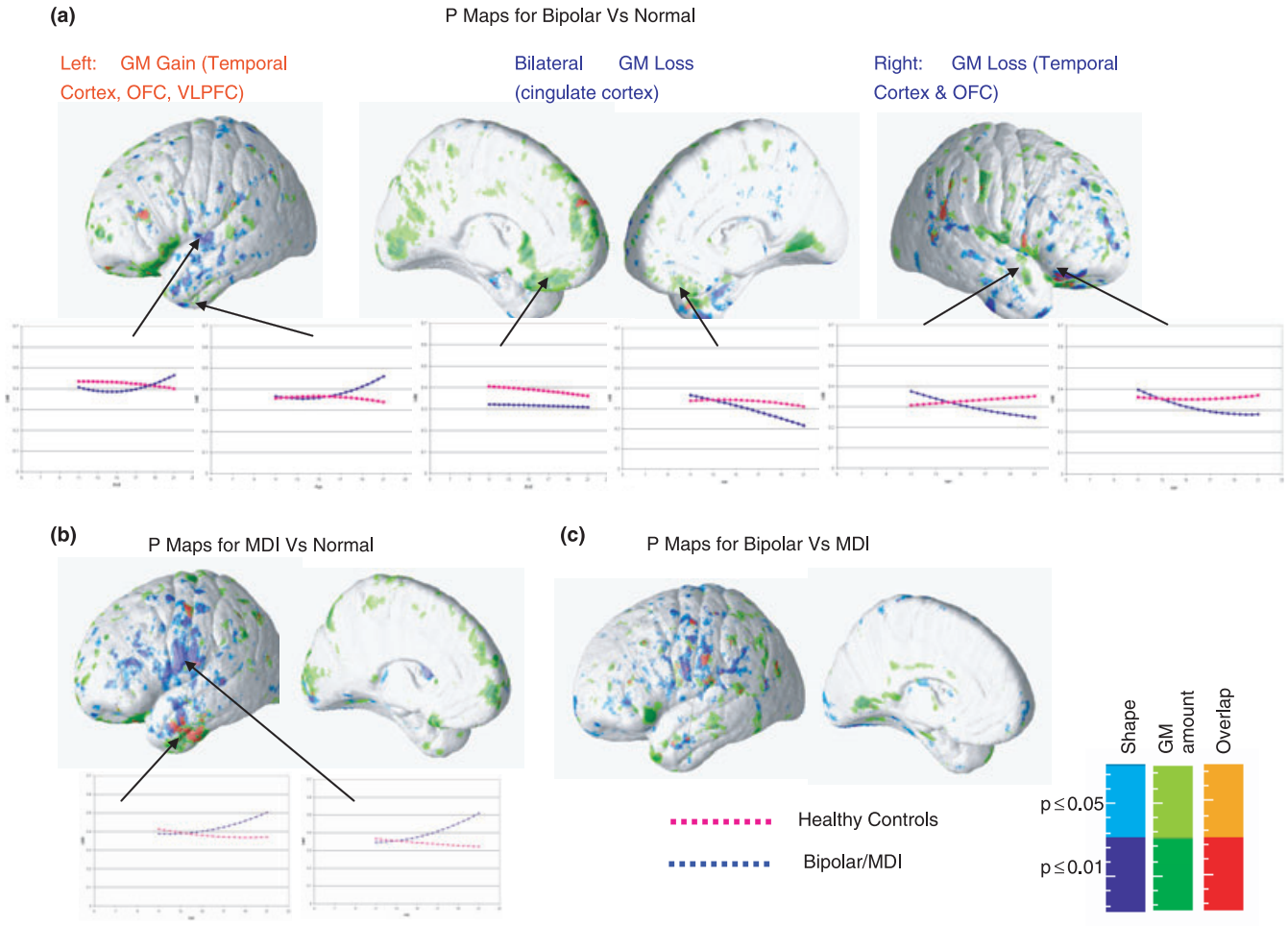

Figure 2 Significance maps for differences in longitudinal gray matter (GM) development in patients compared to healthy controls using mixed model regression analyses at each cortical point. *P*-values were generated at each cortical point for both difference in height (GM amount at average age) and difference in shape of the trajectories (using mixed model regressions) between bipolar and controls at each cortical point. For difference in GM amount (height) *p*-values at <.05 are represented by 'aqua', and $p < .01$ are shown with 'blue' color. For shape differences between the trajectories, *p*-values at <.05 are shown with 'light green' and $p < .01$ are shown with 'dark green' color. Points where both the 'GM amount' and 'trajectory' are significantly different are shown as either 'orange' ($p < .05$) or 'red' ($p < .01$). Individual trajectories are plotted at representative points for both groups. Panel A. Significance maps for MDI subjects who converted to bipolar I (narrow) vs. healthy controls. Panel B. Significance maps for MDI subjects who remained psychosis NOS vs. healthy controls. Panel C. Significance maps for direct comparison between the bipolar and MDI

Specifically, on the left lateral cortical surface, the bipolar subjects showed a gradual increase in GM volume relative to controls over time (ratio >1; yellow to orange color), most prominently post first manic episode, on the anterior and middle portions of the middle and inferior temporal gyri, and middle portion of the superior temporal gyrus (Figure 1A, C). Prominent differences in the GM volume (bipolar larger than controls) were also seen in the left ventrolateral prefrontal cortex (VLPFC), including parts of the left orbitofrontal cortex (OFC) (Figure 1B). In contrast, on the right, the bipolar subjects showed overall loss relative to controls in GM volume which was most significant in the right OFC relative to controls (Figures 1B and 2). Small areas of right superior parietal cortex also showed gain in GM volume (Figure 1G).

On the medial cortical surface, bipolar subjects showed bilateral GM loss relative to controls in anterior and sub genual cingulate cortices, most prominently in the sub genual regions (Figure 1E, F respectively). The GM loss in these regions for bipolar subjects was significant bilaterally, but on the left side, the GM trajectories of GM (loss) did not differ from controls throughout the age range (Figure 2A). Additionally, bipolar subjects also showed significant GM loss in posterior cingulate region on the left side (Figure 1H).

Psychosis NOS (MDI) subjects who had similar initial clinical presentation, but did not convert to the narrow phenotype bipolar I at follow-up, showed a similar but more widespread pattern of cortical GM changes compared to controls (Figure 1; panel B), which was also apparent on the p-maps (Figure 2;

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panel B). The significant GM gain on left side involved most of the temporal, inferior parietal and prefrontal cortices and the significant GM loss on right side was also more pronounced involving prefrontal and temporal cortices (Figure 1, panel B; Figure 2, panel B). These subjects also showed significant bilateral GM loss in anterior and sub genual cingulate regions compared to controls (Figure 1, panel B; Figure 2, panel B) and also in the posterior cingulate regions. The GM maps did not look different when the 3 subjects who had diagnosis of major depressive episode were removed from the group.

However, when GM amounts were directly compared for bipolar and MDI subjects, the differences in GM amount were not significant (Figure 2, panel C green), although the sub genual GM loss appeared 'qualitatively' more prominent for the bipolar group (Figure 2, panels A&B).

The GM differences (p-maps) between the patient groups and controls did not change significantly (data not shown) when re-plotted after adding total IQ as a covariate to the model. When developmental trajectories were visualized by aligning the scans by age at first manic episode, the results remained consistent with and even sharpened the unaligned time sequences, suggesting that the changes were more consistently related to the time of first manic episode.

Discussion

This is the first time that the dynamic progression of cortical brain development has been mapped and visualized in pediatric bipolar illness and tracked both before and after onset of first manic episode (conversion to bipolar I diagnosis). Brain changes in pediatric bipolar illness were subtle and followed a distinct neurodevelopmental trajectory when compared to childhood-onset schizophrenia. The changes were bilaterally asymmetrical with more prominent gain on the left, prominent loss on the right and bilateral loss in the cingulate cortices medially. Thus the GM development proceeded in a sub-regionally variable manner as apparent from the individual trajectories. However, the bipolar and non-bipolar MDI patient groups did not differ with respect to their pattern of GM development.

There remains a controversy regarding whether schizophrenia and bipolar illness are indeed separate entities since they share several clinical features and genetic susceptibility markers (McDonald, Bullmore et al., 2004; Walker, Curtis, & Murray, 2002). A recent linkage analysis suggested that this genetic overlap may be particularly prominent between psychotic bipolar phenotype (as in this study) and schizophrenia (Park et al., 2004). Our results for the first time show that in spite of such overlap, these two conditions follow distinct neurodevelopment trajectories. In schizophrenia, the brain shows loss of GM volume which appears to be an exaggeration of the normal GM development (Gogtay, Giedd et al., 2004; Thompson, Vidal et al., 2001), while the brain changes in bipolar illness are heterogeneous, lateralized, and marked by enlarged GM volumes over time in some regions, thus strongly suggesting that these two illnesses are distinct neurobiological entities.

The variable age of onset raised the question of whether the estimated mixed model trajectories represent the time course of changes for the entire sample at each point. We carried out a second analysis on bipolar children using scans aligned by age at first manic episode (a strategy that has been used before to understand cognitive changes in longitudinally mapped Alzheimer's disease brains where the scans were aligned by mini mental status exam scores) (Janke et al., 2001). These 'aligned' developmental trajectories agree with and even sharpen the initial observations, suggesting that for the bipolar group these changes are related more to the onset of mania than to chronological age.

Our anatomic findings of cortical GM changes of gain and loss are reported by other adolescent and adult onset bipolar studies (Brugge, Volkov, Garell, Reale, & Howard, 2003; Harvey, Persaud, Ron, Baker, & Murray, 1994; Lochhead, Parsey, Oquendo, & Mann, 2004; McDonald, Zanelli et al., 2004; Pearlson et al., 1997; Wilke et al., 2004), but the observation most consistent with studies of mood disorder patients generally (Botteron, Raichle, Drevets, Heath, & Todd, 2002; Drevets et al., 1997; Hirayasu et al., 1999; McDonald, Zanelli et al., 2004; Nugent et al., in press) is the bilateral GM loss in the sub genual cingulate cortex. These results could explain some of the inconsistencies in the literature. For example, as seen in the trajectories for the left superior temporal cortex (Figure 2, panel A), bipolar subjects had smaller GM volume before illness onset, which became larger after the illness onset, and such varying patterns are seen in different regions (Figure 2, panel A). Cross-sectional studies performed at various points along these trajectories may yield differing results (e.g., larger or smaller GM volumes compared to controls).

However, whether and how bipolar illness is uniquely different from other mood disturbances remains unclear as our results show significant overlap between the GM trajectories of MDI subjects with and without conversion to bipolar I. This lack of specificity precludes further speculations regarding our observations, but highlights the importance of longitudinal studies on larger samples and of affective disorder contrast groups in the study of bipolar disorder.

Three of 9 bipolar subjects were taking lithium, and 3 others were taking other mood stabilizers at initial scan (Table 1). Mood stabilizers, particularly lithium, may increase GM volumes (Manji, Moore, & Chen, 2000; Sassi et al., 2002) in bipolar illness. However, in a separate longitudinal analysis of total

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and lobar brain volumes on our larger MDI cohort, the mean rates of change with age (i.e., 'slopes') for our atypical psychosis (MDI) patients on mood stabilizers ($n = 10$) did not differ significantly from those for the MDI patients not maintained on these medications ($n = 8$; $t = .75$, $df = 16$, $p = .46$) (Gogtay, Sporn et al., 2004). Similarly, in our larger sample of longitudinally studied COS patients ($n = 39$), mood stabilizers had no detectable effect on GM slopes (Sporn et al., 2003). Thus it is unlikely that the increased GM volumes seen in this study are solely due to a medication effect.

This study has important limitations. The analysis was done using 9 bipolar I subjects, 8 matched atypical psychosis subjects and 18 controls, with total of 81 scans. Although the generated anatomical models had adequate statistical power, it is still a small sample to detect subtle differences, e.g., in the degree of sub genual cingulate loss between bipolar and unipolar patients. However, the rarity of patients scanned before and after the onset of bipolar illness makes these data unique. Second, all the children at initial screening had some psychotic features and thus this group is not representative of more typical bipolar I phenotype. Third, the remaining psychosis NOS subjects are still within the age of risk for bipolar conversion and we continue to follow these subjects longitudinally. While the high co-morbidity of ADHD for this sample should be taken into account while interpreting the results, our larger cortical thickness analyses in longitudinally studied ADHD subjects showed no overlap with the patterns seen here in bipolar I or psychosis NOS children (Shaw et al., 2006). Finally, the control samples could not be matched for IQ; however, covarying for the total IQ did not significantly alter the findings.

Despite the limitations and heterogeneity of the sample, our findings reveal important information on cortical development in affective disorders in general and stress the importance of studying longitudinal data on matched sub groups of mood disorder patients.

Supplementary material

The following supplementary material is available for this article:

Supplemental Figure 1 Aligned by illness onset: top, left lateral and left and right medial views of gray matter trajectory in bipolar subjects compared to the normal controls, after the scans were aligned by illness onset. The images are *ratio maps.* First bipolar scans are aligned by the illness onset and then matched control scans are also aligned to the bipolar scans. Ratio maps are then generated and color coded as described in Figure 1 above. Areas A–H: Same as in Figure 1.

Supplemental files 3D animated time-lapse sequence of gray matter maturation across the cortex in bipolar illness between ages 7 through 22 years. The movies are ratio maps described in Figure 1. A – bipolar/normal left lateral view; B – bipolar/normal right lateral view; C – bipolar/normal left medial view; D – bipolar/normal right medial view; and E – psychosis NOS/normal left lateral view. Color representation on scale bar same as in Figure 1.

Supplemental files

This material is available as part of the online article from: http://www.blackwell-synergy.com/doi/abs/10.1111/j.1469-7610.2007.01747.x

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