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Cortical gray matter differences identified by structural magnetic resonance imaging in pediatric bipolar disorder

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Abstract

Objective— Few magnetic resonance imaging (MRI) studies of bipolar disorder (BPD) have investigated the entire cerebral cortex. Cortical gray matter (GM) volume deficits have been reported in some studies of adults with BPD; this study assessed the presence of such deficits in children with BPD.

Methods—Thirty-two youths with DSM-IV BPD (mean age 11.2 ± 2.8 years) and 15 healthy controls (HC) (11.2 ± 3.0 years) had structured and clinical interviews, neurological examinations, neurocognitive testing, and MRI scanning on a 1.5 T GE Scanner. Image parcellation divided the neocortex into 48 gyral-based units per hemisphere, and these units were combined into frontal (FL), temporal (TL), parietal (PL), and occipital (OL) lobe volumes. Volumetric differences were examined using univariate linear regression models with $\alpha = 0.05$.

Results—Relative to controls, the BPD youth had significantly smaller bilateral PL, and left TL. Analysis of PL and TL gyri showed significantly smaller volume in bilateral postcentral gyrus, and in left superior temporal and fusiform gyri, while the parahippocampal gyri were bilaterally increased in the BPD group. Although the FL overall did not differ between groups, an exploratory analysis showed that the right middle frontal gyrus was also significantly smaller in the BPD group.

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Conclusions—Children with BPD showed deficits in PL and TL cortical GM. Further analyses of the PL and TL found differences in areas involved in attentional control, facial recognition, and verbal and declarative memory. These cortical deficits may reflect early age of illness onset.

Keywords

bipolar; brain imaging techniques; child psychiatry; mood disorders

Pediatric bipolar disorder (BPD) is a severe psychiatric illness with significant morbidity whose pathophysiology is largely still unknown. The morbidity associated with this disorder is driven, in part, by the child's inability to modulate affect and cognition; those affected by the disorder have a diminished ability to control the intensity of a response to the environment and the ease of recovery from the response. For example, even in euthymic individuals with BPD, there are enduring impairments in attention, executive functioning, processing speed, and in working and verbal declarative memory that lead to difficulties in daily life (1). In addition, individuals who are genetically at risk for developing BPD have deficits in verbal declarative memory, selective and sustained attention, and in working memory, suggesting that these domains may serve as cognitive endophenotypic markers of the disorder that in turn could implicate areas of pathophysiology in the brain (1). For example, these domains of cognitive functioning are largely under the control of the cerebral cortex and are highly heritable (2–4). Therefore, in order to contribute to a deeper understanding of the neurobiological correlates that underlie the dysfunction associated with the disorder (5), it is critical to study the cerebral cortex, where brain operations occur that govern cognitive abilities (6).

Taken collectively, published neuroimaging (functional, biochemical, and structural) studies indicate that there may be cortical abnormalities in adults and children with BPD (7–12). To understand more fully the differences in the cortex seen in children with BPD, it is critical to assess the lobes of cortical gray matter (GM) and the gyri of each lobe, as different regions of the cortex subserve different cognitive functions. For example, the frontal lobe (FL) is involved in cognition, memory, sensory processing, planning and initiation of voluntary movements, language production, and integration of cognition and affect. The temporal lobe (TL) is integral for auditory processing, language comprehension, semantic memory processing, visual perception, and sensory integration (13). The parietal lobe (PL) is involved in processing tactile and proprioceptive information, language comprehension, speech, writing, and aspects of spatial orientation and perception. The occipital lobe (OL) is involved in visual functions (13). To our knowledge a detailed anatomical assessment of the entire cerebral cortex, using structural magnetic resonance imaging (MRI), has not been carried out in studies in adults with BPD, nor has it been carried out in child studies. Of particular importance is the need to assess the cortex in children with BPD, given that their brains are relatively free from factors known to affect the brain, such as lengthy medication exposure, substance abuse, and electroconvulsive therapies (14).

To our knowledge, this is the first structural neuroimaging study to fully assess the entire cortical GM and subsequently the gyri of the lobes of the cortex in pediatric BPD. Based on prior studies (neuroimaging and neuropsychological), we set out to assess expected alterations in cortical volumes, in pediatric BPD, to determine if these youth might show a specific pattern of cortical GM deficits. Given the data from the prior neuroimaging studies (in both children and adults), we hypothesized that children with BPD would show cortical GM deficits, particularly in sections of the FL, similar to adults with the disorder.

Methods

Subjects

The study was approved by Institutional Review Boards at the Massachusetts General (MGH) and McLean Hospitals. Subjects were recruited through the McLean Hospital Child and Adolescent Outpatient program and professional-patient advocacy groups and healthy controls (HC) were recruited through community newspaper advertisements. Inclusion criteria were: DSM-IV diagnosis of BPD I (mixed or manic-lifetime), age 6–16 years, and right-handedness. Male and female subjects of all ethnicities were recruited. HC, all right-handed, had no DSM-IV Axis I diagnosis based on structured and clinical interviews, and had no family history of affective disorders or psychotic disorders in first-degree relatives. Exclusion criteria for both HC and BPD children were: major sensorimotor handicaps; Full-Scale IQ <70 or learning disabilities; history of claustrophobia, head trauma, loss of consciousness, autism, schizophrenia, anorexia or bulimia nervosa, alcohol or drug dependence/abuse (during 2 months prior to scan, or total past history of ≥ 12 months), active medical or neurologic disease, metal fragments or implants; history of electroconvulsive therapy; and current pregnancy or lactation.

Seventy subjects (all outpatients) and their parents (or guardians) signed assent and informed consent forms. Three subjects were found ineligible during interview and one stopped the study because of lack of interest. Sixty-six scans were obtained; three scans were unreadable because of motion artifact (two BPD and one control). Cortical parcellation data have been measured on the first 47 children with readable scans who have participated in this ongoing neuroimaging study; this includes 32 children with DSM-IV BPD and 15 HC. There are no differences by diagnostic group in the breakdown of which acquired scans have or have not been parcellated to date.

Diagnostic procedures

All children underwent diagnostic semi-structured (Kiddie Schedule for Affective and Schizophrenic Disorders: Epidemiologic Version, KSADS-E) (15) and clinical interviews by board-certified child psychiatrists. Additionally, parents were administered an indirect KSADS-E regarding their children by trained raters. These raters, B.A. level, received 4 months of training on the administration of the KSADS-E under the supervision of senior raters and senior investigators (JF, JB). All raters had established a high degree of inter-rater reliability; based on 175 interviews, the mean κ was 0.90 and all disorders achieved κ coefficients >0.82. Final DSM-IV diagnoses were established by the consensus diagnosis of clinical and structured interviews. Both children with elevated, expansive mood and those with irritable mood under the DSM-IV 'A' criteria were included in the BPD group (lifetime). Major depression was also evaluated using the KSADS-E. If there was concurrent mania and depression, a patient was determined to have a mixed state. Current mood state was determined by the child psychiatrist as part of the clinical and structured interviews.

Measures of current psychopathology were obtained by child psychiatrists based on their interviews of both the parent and child, using the Young Mania Rating Scale (a continuous measure of manic psychopathology) (YMRS) (16) and Global Assessment of Functioning (GAF). Each child also received a physical and neurological examination (including Tanner Staging: a I–V scale of pubertal development) (17), and cognitive testing. Children received the Symbol Search, Block Design, Vocabulary, Digit Span, Arithmetic and Coding subtests of the Wechsler Intelligence Scale-Third Edition (WISC-III) (18), permitting the estimation of Verbal (VIQ), Performance (PIQ), and Full-Scale IQ scores, and the Wide Range Achievement Test-Revised (WRAT-R) reading and arithmetic subtests (19,20). The IQ tests were administered by a child neuropsychologist and/or individuals with B.A. degrees trained and

supervised by the neuropsychologist. Handedness was assessed using the Edinburgh Handedness Questionnaire (21). Socioeconomic status was assessed using the Hollingshead method (Hollingshead AA, unpublished data, 1975). The diagnostic procedures for this study are described in greater detail elsewhere (5).

Drug exposure

Antipsychotic doses (converted to chlorpromazine equivalents) (22), as well as number and type (antipsychotic, antidepressant, stimulant, anticonvulsant, lithium) of psychoactive medications at the time of scan were utilized as clinical variables.

Imaging procedures

MRI protocol

Structural imaging was performed at the McLean Hospital Brain Imaging Center on a 1.5 T Scanner (Signa; GE Medical Systems, Milwaukee, WI, USA). Acquisitions included a conventional T₁-weighted sagittal scout series (20 slices), a proton density/T₂-weighted interleaved double-echo axial series [120 slices, slice thickness = 3 mm, field of view (FOV) = 24 cm², TR = 3 s, TE = 30/80 ms, acquisition matrix = 256 × 192, number of excitations = 0.5], and a three-dimensional inversion recovery-prepped spoiled gradient recalled echo coronal series which was used for structural analysis (124 slices, prep = 300 ms, TE = 1 min, flip angle = 25°, FOV = 24 cm², slice thickness = 1.5 mm, acquisition matrix = 256 × 192, number of excitations = 2). All scans were reviewed by a clinical neuroradiologist to rule out gross pathology.

Image analysis

Structural scans were transferred to the NMR Center for Morphometric Analysis (CMA)-Charlestown MGH and coded and cataloged for blind analysis. Imaging analysis was performed in Sun Microsystems, Inc. (Mountainview, CA, USA) workstations with Cardviews software (23).

Gray and white matter segmentation

Brain images were positionally normalized to overcome variations in head position by using a standard three-dimensional coordinate system on each scan that used the midpoints of the decussations of the anterior and posterior commissure lines and the midsagittal plane at the level of the posterior commissure as points of reference for rotation and translation. This 'self-referential' system is based directly on the individual brain, and is not warped to a template atlas. A 'self-referential' system was employed because it is based directly on the topography of the structural features in the individual subject. A mapping strategy based upon the morphological features of the individual provides a system for approaching the problems posed by inter-individual topographic variability, while the template method employs an indirect reference. The advantage of the self-referential method, as opposed to that based on a template, lies in the fact that the self-referential method is not affected by inter-hemispheric and inter-individual variation in the morphology of structures defined by the framing of landmarks (24). The data sets were then segmented into gray, white, and cerebrospinal fluid (CSF) tissue classes using a semi-automated intensity contour algorithm for external border definition and signal intensity histogram distributions for delineation of gray-white borders. This technique, described in detail elsewhere (25–27), yields separate components of neocortex, subcortical gray nuclei, white matter, and ventricular system subdivisions that correspond to the natural tissue boundaries distinguished by signal intensities on T1-weighted images.

Parcellation of the neocortex

The neocortex, as defined by the gray–white matter segmentation procedure, was then divided into 48 parcellation units (PUs) per hemisphere, based on the system originally described by Rademacher et al. (28) and modified by Caviness et al. (23). This is a comprehensive system of neocortical subdivision designed to approximate architectonic and functional subdivisions, and is based on specific anatomical landmarks present in all brains (23,29–31). The collaborators at the CMA (Drs Makris, Kennedy, and Caviness) developed these procedures, trained the technicians, and maintained quality control for the segmentation and parcellation of the data (23).

Two types of landmarks specify the boundaries of the PUs: major fissures of the hemisphere and anatomically specified single nodal points along the longitudinal axis of the brain. The fissures and nodal points are easily identifiable. Nodal points are specified by diverse anatomical structures, most of which lie in the cortex itself (e.g. the intersection of two sulci or a sulcus within the hemispheric margin). Four nodal points are specified by subcortical landmarks: the splenium and genu of the corpus callosum, the decussations of the anterior commissure, and the lateral geniculate bodies. The PUs are mainly bounded by the major fissures of the brain (23,28,32). Where the anterior or posterior border of a PU is not completely specified by major fissures, this boundary is closed by a coronal plane through a nodal point (23,28). In this manner, 48 PUs are segmented throughout each cerebral hemisphere. As an example, we describe in detail the anatomic definition of 1 PU: the postcentral gyrus (POG).

On the lateral surface of the hemisphere, the POG is delimited by the central sulcus rostrally and the postcentral sulcus dorsally, whereas its ventral border is the central operculum, which constitutes a portion of the superior lip of the Sylvian fissure. On the dorsolateral surface of the hemisphere, the POG is delimited rostrally by a coronal plane set at the intersection of the central sulcus at the hemispheric margin (plane L) (23,32), and by the callosal marginal sulcus (the posterior most and upward-directed portion of the cingulate sulcus) caudally. Because the POG encompasses the convexity of the cerebral hemisphere, it has a dorsolateral and a dorsomedial section. Anteriorly, the dorsolateral POG borders the central sulcus for most of its extent, as well as the coronal plane set at the intersection of the central sulcus with the Sylvian fissure [nodal point ‘cesyl’; see Ref. (23) for definition of nodal points and coronal planes]. At the dorsomedial surface of the hemisphere, the anterior border of POG is defined by the coronal plane set at the intersection of the central sulcus with the hemispheric margin (coronal plane L). The postcentral sulcus is the posterior border of POG for most of its extent, as well as the coronal plane set at the intersection of the postcentral sulcus with the Sylvian fissure (coronal plane P). Its inferior border is defined as the lateral extent of the superior lip of the Sylvian fissure, such that the parietal opercular region (parietal central operculum) below the POG is excluded from POG. Because POG curves around the hemispheric convexity, its superior/medial/posterior border is the callosal marginal cingulate sulcus. Figure 1 shows the location of POG with respect to other PUs in the cortex.

Following parcellation, volumes are calculated for each PU by multiplying the area measurement of the PU on each slice by the slice thickness, followed by summing across all slices in which the PU appears (27). The PUs are combined into clusters based on lobar and connectivity data into cortical GM volumes of the FL, PL, TL, and OL (see Table 1 and Fig. 2) for the purpose of the initial statistical analysis. When the PUs are considered individually, the mean inter-rater intra-class correlation coefficient (ICC) is 0.75 (range: 0.31–0.96). However, when combined into lobes, the clusters of PUs had an average intra-rater ICC of 0.98 (range: 0.96–0.99). Although the individual PUs provide a high level of detail and anatomical specificity, clusters of PUs (such as the FL, TL, PL, and OL) add flexibility to the analysis by providing higher reliability and by decreasing the number of analyses (33). The hemispheric lobes are defined in Fig. 2.

For lobes in which there was a statistically significant difference between bipolar youth and controls, individual gyri within the lobes were explored for areas of greatest impact. Subunits examined in the PL consisted of: POG, precuneus (PCN), superior parietal lobule (SPL), and inferior parietal lobule (IPL). The TL subunits consisted of: superior temporal gyrus (STG), middle temporal gyrus (MTG), inferior temporal gyrus (ITG), fusiform gyrus (FFG), and parahippocampal gyrus (PHG).

Data analyses

SPSS 11 for Macintosh (SPSS Inc., Chicago, IL, USA) was used for statistical analyses. All statistical tests were two-tailed with α set at 0.05.

Differences in demographic and clinical variables were measured using *t*-tests for continuous variables and chi-square tests for categorical variables. We analyzed our volumetric data on the natural logarithmic scale in order to better control for the variance of these structures (34). We conducted an exploratory MANOVA on the ensemble of log total frontal, parietal, temporal, and occipital cortical volumes controlling for effects of log cerebral volume, age, sex, diagnosis, SES, and Verbal IQ (VIQ). These variables were chosen as covariates because of their known or probable impact on the developing brain. VIQ was chosen rather than FSIQ because the differences between groups were maximized on the VIQ, and thus VIQ might represent the most important confounder in our sample.

We then proceeded to analyze the effects of these covariates on the individual cortical volumes via univariate linear regression models. We fit linear regression models for each log lobe volume (right and left), and we used the same independent variables as in the preliminary MANOVA. We also analyzed the data using the absolute volumes of the structures to determine if the findings were comparable to those transformed to log scale.

Exploratory analyses

To explore whether illness-related variables might be associated with cortical GM volumetric differences in those lobes and gyri found to differ between HC and BPD, we performed exploratory one-way regression models with the BPD group only. These univariate models tested for differences in log volumes using the following variables as covariates: number of psychoactive medications, antipsychotic dose in chlorpromazine equivalents, GAF score, YMRS score, duration of illness, presence or absence of attention deficit hyperactivity disorder (ADHD), presence or absence of psychosis, and current mood state (manic, mixed, depressed, or euthymic).

Results

Forty-seven children, 32 with BPD (mean age 11.2 ± 2.8 years), and 15 HC (mean age 11.2 ± 3.0 years) were included in this MRI study. Demographic characteristics of all children are shown in Table 2. The BPD children were taking a number of psychiatric medications: lithium and anticonvulsants (including valproate, carbamazepine, neurontin, and topiramate) ($n = 14$, 43.8%), atypical antipsychotics ($n = 26$, 81.3%), antidepressants ($n = 13$, 40.6%), and stimulants ($n = 8$, 25.0%). The mean number of psychoactive medications for children in this group was 2.4 ± 1.1 . Among those taking antipsychotics, the mean daily dose, converted to chlorpromazine equivalents, was 149.6 ± 87.6 . Half of the BPD group were in a mixed mood state (current) at entry ($n = 16$, 50.0%); others were manic (current) ($n = 6$, 18.8%), depressed (current) ($n = 3$, 9.4%), and euthymic (current) ($n = 7$, 21.9%). Sixty-three percent had comorbid ADHD, 38% had psychotic symptoms, and one had a history of substance abuse. The mean age of onset of BPD was 6.6 ± 4.0 years, and 13 (40.6%) had a history of psychiatric hospitalization.

Observed means and their 95% confidence intervals are shown for each diagnostic group in Table 3. The omnibus test statistic, Pillai's Trace, indicated the presence of a significant group difference among the log lobe volumes ($F = 2.886$, $df = 4,37$; $p = 0.040$). Univariate linear regression models, controlling for the possible effects of age, sex, SES, Verbal IQ, and log cerebral volume, were then examined to determine for which lobes and hemispheres these differences existed. The significant regression models are summarized below. When the volumetric data analysis was repeated using the absolute volumes, rather than the logarithmic volumes, the inferential findings were the same.

Parietal lobe GM volume

The bipolar youth had significantly smaller log right and left PL volumes relative to the HC (right: $B = -0.080$, $t = -2.154$, $p = 0.037$; left: $B = -0.102$; $t = -3.122$, $p = 0.003$), after controlling for the significant effects of age, Verbal IQ, and log cerebral volume (see Table 4 for summary of regression models). Interestingly, both age and Verbal IQ for all children in this study (both BPD and HC combined) showed inverse relationships with PL volume, such that children with higher Verbal IQ scores were more likely to have smaller PL volumes, and older children were more likely to have smaller PL volumes.

When the gyri of the PL were subsequently analyzed to discern if there were sections of that lobe that were clearly more affected than other sections, it was found that the BPD had significant reductions in the right and left POG (right: $B = -0.116$; $t = -2.027$, $p = 0.049$; left: $B = -0.136$; $t = -2.592$, $p = 0.013$).

Temporal lobe GM volume

The bipolar group had significantly smaller log left TL volumes compared with the control group ($B = -0.050$; $t = -2.258$, $p = 0.029$). When we analyzed the functional subsections of the TL, we found that the BPD group had significant reductions in the left volumes of the STG and FFG, but significant increases in bilateral PHG. These findings are summarized in Table 5.

Frontal lobe GM volume

No significant group differences were found in the right or left FL. However, given the consistent findings of abnormal dorsolateral prefrontal cortex (DLPFC) and anterior cingulate gyrus (ACG) in studies of adults with BPD (see Discussion), we elected to assess the middle frontal gyrus (MFG) and the ACG, as well as other sections of FL in an exploratory fashion to discern if there were diagnostic differences in any particular areas of the FL. We did find significant group differences in the right MFG ($B = -0.144$; $t = -2.289$, $p = 0.027$).

Clinical correlations

Regression analyses of clinical variables with the lobes that differed between the two groups (e.g. left TL, right and left PL) and the gyri that differed (e.g. right and left POG, left STG, left FFG and bilateral PHG) were performed. Of the regression analyses performed, the following associations were found to be significant:

1. Within the BPD group, those children with psychotic symptoms had smaller left log TL volumes ($B = -0.092$; $t = -2.066$, $p = 0.048$) than those without psychotic symptoms.
2. The left log PL volumes in the BPD children decreased significantly in association with increasing numbers of psychoactive medications ($B = -0.04$; $t = -2.138$, $p = 0.042$) (when we examined the possible relationship between type of medication and

change in PL volumes, we did not detect any significant or trend relationship between type of medication and PL volume).

3. When we looked at the gyri in the BPD group, we found only that volumes of the left log POG were significantly and positively associated with scores on the GAF ($B = 0.012$; $t = 2.22$, $p = 0.035$).

No associations were found between the lobes or individual PUs and the following clinical variables: antipsychotic dose in chlorpromazine equivalents, YMRS score, duration of illness, presence or absence of ADHD, and current mood state (manic, mixed, depressed, or euthymic).

Discussion

This study provides evidence that there are cortical abnormalities in pediatric BPD, detectable using structural MRI. To our knowledge, this is the first structural MRI study to fully evaluate cortical GM (lobe and gyri) in youth with BPD. We found that bilateral parietal and left temporal lobes showed a reduction in GM in patients with pediatric BPD compared with age equivalent HC, particularly in the following gyri: right and left POG of the PL and the left STG, left FFG. We also found an increase in left and right PHG of the TL in the BPD group. Like in adult studies, we did not find an overall decrease in the FL; however, a set of exploratory analyses indicated that youth with BPD have cortical gray reductions in the right MFG, which comprises about 60% of the DLPFC. This area of the brain has been implicated in the pathophysiology of the BPD (9,12).

The findings of this study are in sharp contrast to the majority of structural MRI studies carried out in adults with BPD that found no difference in cortical GM volumes relative to controls (35–41). There is only one study that found diffuse cortical GM deficits in BPD adults; however, that study had a relatively small sample size and was performed on adults who were chronically ill and who had had lengthy histories of hospitalization, two factors that could contribute to cortical GM deficit (8). In addition, that study assessed overall GM rather than analyzing the cerebral lobes or gyri within cortical GM. In another anatomic MRI study, Lopez-Larson et al. (9) did not find an overall volumetric decrease in the FL, but when they applied a subregion-specific analysis, they found that adults with BPD had smaller left prefrontal gray (middle and superior) and smaller right prefrontal gray (inferior and middle). However, this study did not examine the entire cerebrum.

Other imaging modalities in adults with BPD have indicated biochemical differences and GM density abnormalities in the FL. For example, using voxel-based morphometry, two groups have assessed cortical GM in adults with BPD. McIntosh et al. found that BPD patients had subcortical gray (smaller thalamus) but not cortical GM deficits (42). In contrast, Lyoo et al. found that BPD adults had decreased GM density in the left anterior cingulate and in the right inferior frontal gyrus, but not in other cortical GM regions (10). Using spectroscopy, Cecil et al. found that BPD adults had decreased N-acetyl aspartate in the FL GM (11), implying neuronal dysfunction in that area.

Therefore, the results of the MRI studies in adults with BPD are not consistent in their findings regarding cortical GM differences. Possible reasons for the differences include differences in MRI acquisition protocols, image analysis, region or range of brain structures selected for analysis (many of the studies focus on the FL only), and patient populations. For example, many publications do not report on the proportion of BPD subjects in their sample who have psychotic features, even though this clinical information is probably routinely assessed and could help support or refute a possible association between illness severity and degree of anatomic difference. The majority of structural MRI studies in adults have not found differences in GM volume in those with BPD. Differences between the adult studies and our

findings may be accounted for by a number of the above factors, as well as the difference in age of onset of the disorder and age at time of imaging. The findings of our study may be unique to pediatric BPD. The hypothetical uniqueness of these structural findings to early-onset illness would be further elucidated through long-term longitudinal imaging projects that include both children and adults with BPD.

Given the FL findings in some adult studies, one might expect the emerging neuroimaging literature in pediatric BPD to also implicate the FL. However, none of the published structural MRI studies in pediatric BPD have examined the cerebral cortex (5,43–48). A recent, voxel-based morphometry study in adolescents with BPD reported GM deficits in the medial TL, orbito-frontal cortex, and the ACC (7), suggestive of more diffuse GM deficits in children affected by the illness. In addition, Chang et al. found some areas of cortical dysfunction when studying youth with BPD (with familial BPD) performing a variety of cognitive tasks while undergoing a functional MRI study (12). These authors found that 12 males (ages 9–18 years) with familial BPD relative to matched HC, had greater activation in several areas including four cortical regions: the bilateral ACC, left DLPFC, and right IFG on a visuospatial working memory task. In viewing negatively valenced pictures, BPD subjects had greater activation in bilateral DLPFC, IFG, and right insula, while on positively valenced pictures, BPD subjects had greater activation in several cortical areas including the left middle/superior frontal gyrus and left ACC. These prior child studies, in addition to our study, indicate there might be more diffuse cortical deficits in these early-onset cases relative to the majority of studies that have been performed in adults with the disorder, highlighting the importance of the impact of age at onset of illness and perhaps age at time of scan on brain anatomy and function in those that suffer from the disorder. The findings of decreased temporal and parietal GM affecting specific gyri of these lobes (and the FL) may be unique to pediatric onset BPD relative to the adult onset form of the disorder.

The differences found between our study and previously reported studies in children and adults with BPD may be in part accounted for by the unique parcellation method employed here. In fact, in the BP literature, this is the first report of cortical volumetry using parcellation methods, which analyze anatomic subunits of the cerebral cortex. Parcellation involves a careful delineation of the gyri and nuclei which comprise each lobe, followed by a summation of these subunits; most other methods for studying the cortex have subtracted CSF and white matter from the segmented cerebrum to estimate the cortical volume. Differences in field strength or image quality, for example, may therefore lead to over- or underestimates of cortical volumes across sites. Other reasons that may account for the inconsistent findings across studies include differences in acquisition parameters, type of scanner, region of interest, anatomical definitions, use of semi-automated versus automated methods of measurement, and statistical analyses, as these factors are not consistent across.

In order to determine the uniqueness of these findings to early-onset BPD, a review of the adult and child brain MRI studies in psychotic disorders is warranted, given the clinical, genetic and imaging literature that have suggested that there may be an overlap between schizophrenia and BPD (49–56). A number of MRI studies performed in adults and children with schizophrenia (COS) have reported diffuse cortical GM deficits (8,32,57,58). For example, in a study that used similar methods to ours, adults with schizophrenia were found to have relatively diffuse cortical GM deficits, with the greatest reductions in the middle frontal gyrus and paralimbic brain regions (frontomedial and fronto-orbital cortices, anterior cingulate and paracingulate gyri and the insula) (32). Additionally, these authors found that the supramarginal gyrus, an area with dense connections to the prefrontal and cingulate cortices, was reduced. They also found subtle increases in other cortical areas with strong reciprocal connections to the paralimbic areas that were volumetrically reduced (32).

Studies of COS indicate deficits in cortical GM (57,59), including abnormalities in gyral folding (60) and altered metabolism of proton-containing compounds such as creatine and choline (61). Interestingly, the cortical abnormalities seen in COS may shift and progress over time, as suggested by a large longitudinal study of COS which indicated that the cortical gray volume deficits begin in the PL and progress anteriorly during adolescence to include the later maturing TL and FL (62). Adult studies comparing BPD to schizophrenia and HC tend to find no GM deficits in BPD patients and diffuse deficits in the schizophrenic patients, or they find GM volumes in BPD subjects that are between those of the HC and schizophrenia groups (8, 39). Although the results are mixed as to whether or not adults with schizophrenia and BPD have similar neuroimaging findings in the cerebral cortex, it appears that children with BPD have a much more similar pattern of cortical GM findings to individuals affected by schizophrenia.

Conversely, pathological studies of the FL in BPD adults versus adults with schizophrenia indicate that individuals with BPD actually have a cellular pattern that is unique to BPD and very different from those who suffer from schizophrenia. Several studies report a reduction in glial cells of the subgenual prefrontal cortex and reductions in the neuronal and glial cell densities in the DLPFC, as well as reductions in the non-pyramidal neurons in layer II of the anterior cingulate cortex (63–65). In fact, Rajkowska et al. report that there is a ‘morphologic signature’ of BPD consisting of decreased neuronal and glial cell density in association with glial hypertrophy which is distinct from the pattern seen in schizophrenia where there are elevations in neuronal density (64). Interestingly, even though some studies indicate that schizophrenia and BPD may be on a continuum clinically and neurobiologically, there may be different cellular mechanisms that lead to final phenotypic commonalities seen between these two conditions.

Our structural MRI findings of abnormalities in FL, TL, and PL GM in children with BPD is more consistent with findings from the schizophrenia imaging literature (both child and adult) than with the findings from studies of adults with BPD. It could well be that those with early-onset and late-onset BPD illness have different neurobiological correlates and underlying pathophysiology, or alternatively the findings herein may just be a byproduct of early age of onset or age at time of imaging. Nonetheless, pediatric BPD is highly heritable just as is childhood-onset schizophrenia. Our cortical GM findings may in fact be less of an endophenotypic pattern for a specific diagnosis, but rather may represent a pattern that is a hallmark of highly heritable disorders that manifest at an early age with dysfunction in the following domains: attention, affective regulation, working memory, and declarative memory. These areas of cognitive deficit are shared between schizophrenia and BPD.

Finally, relatively little is known about the profile of brain change in children and adolescents and its modulation during neuropsychiatric illnesses such as BPD. GM deficits have been implicated in some studies of adults with BPD (8). In addition, we also know that GM loss occurs normally during childhood and adolescents. Therefore, assessing the cerebral cortex during this critical time of change in the GM and comparing matched HC to BPD, has the extraordinary potential to inform the field about the dynamics of the disease state on brain developmental processes.

Typically, in the healthy child brain overall GM volume increases in early childhood and then declines after puberty and white matter progressively increases (66). The healthy child brain has the most robust GM loss early on in the PL, which matures earlier than the FL and TL (66,67). As the GM is decreasing, there is a parallel process of increased myelination occurring (67). The peak loss of GM occurs around age 12 for both the PL and FL, with the most robust changes occurring in the PL pre- and postpuberty. Peak GM loss occurs around age 16 for TL, while the OL has mild GM increases until age 20 (66); GM loss in the OL is less pronounced

and more linear. Up until adulthood (age 40 years), much of the cortical GM declines, while myelination increases with simultaneous improvements in cognition and behavior (67).

In our sample, both age and Verbal IQ for all children (both BPD and HC combined) showed inverse relationships with PL GM volume, such that children with higher Verbal IQ scores were more likely to have smaller PL volumes, and older children were also more likely to have smaller PL volumes, which may reflect normative brain dynamics occurring across this age range. Interestingly, FL and PL GM volumes peak approximately 1 year earlier in females than in males, corresponding to their younger onset of puberty and suggesting a possible association between sex hormones and GM maturation. In our sample, it is notable that OL volume is relatively preserved, whereas the PL and TL volumes are decreased in BPD children. The pattern of lobe differences in GM volume may be related to the age of onset of BPD illness in these youths. For example, the mean age of illness onset in our sample occurred during late latency (6.6 years), a time of robust hormonal shifts that predate physical puberty, concurring with GM loss and white matter growth in the brain.

Children with BPD appear to have a decrease in cortical GM as seen here and in the study by Wilke et al. (7), while most studies indicate that adults with the disorder have relative preservation of cortical GM. The decrease in GM is also somewhat regionally specific, with the most pronounced decrease found in the PL, an area of the brain that may be particularly vulnerable to derangement during latency age and early adolescence because of the pronounced changes that typically occur in its GM during those years. It is of note that in our BPD sample, the reduced volume of the POG (in the PL) was significantly associated with the greater number of psychoactive medications, which provides a crude reflection of severity of illness and/or perhaps of greater degree of comorbidities. Additionally, POG volume correlated with overall functioning as reflected in the GAF. The finding in the PL is not entirely expected based on studies of adults; however, from a clinical perspective most children with BPD have sensory reactivity to their environment, which would dovetail with the PL and the TL findings. For example, the POG in the PL, in particular, is the primary somatosensory cortex, involved in perception, and is the major recipient of projections from the lateral, medial and superior sectors of the ventro-posterior lateral thalamus (the principal relay for the ascending somatosensory pathways). The finding in the FFG is also somewhat unexpected. The FFG is a heteromodal cortex and is the transmodal gateway for the recognition of faces and objects. Individuals with BPD have abnormal activation when processing emotional faces which might implicate aberrant function rooted in the loops involving the fusiform gyri (68).

The significant differences found in the analysis of FL and TL PUs, although exploratory in nature, are not surprising. The middle frontal gyrus is partly involved in working memory, executive function, and complex attention, all domains of impairment in BPD. The PHG was significantly increased and it is a structure that subserves olfactory, emotional, and visceral functions, with its major behavioral role in the area of memory and learning. It is also the major route of reciprocal connection between the prefrontal cortex and the hippocampus. The relative increase in both the left and right parahippocampal volumes is found in conjunction with a relative decrease in volume of the right MFG, which comprises about 60% of the DLPFC, and with a relative decrease in hippocampal volume in BPD youth (5). The left STG is involved in auditory language processing and has a role in reading and comprehension. These differences in GM volume may be the result of abnormal pruning, early myelination (or abnormal myelination), and/or cell loss in the GM (67,69).

The generalizability of our study's findings depends on the reliability and validity with which the BPD diagnosis is made in this population. Diagnostic stability and illness progression cannot be adequately assessed in a cross-sectional study such as this. Several authors have documented that approximately 30% of adult patients with BPD requiring hospitalization are

given a different diagnosis upon follow-up (70,71). Therefore our child and adolescent sample may in fact be heterogeneous, and only longitudinal follow-ups will clarify the stability of diagnosis. We have recently begun a longitudinal study that will allow us to re-scan the children in our sample, and evaluate changes in both brain structure and diagnosis.

Another limitation of this study relates to the assessment of depressive symptoms. Documentation of these symptoms was obtained from the semi-structured and clinical interviews, but no rating scales for depressive symptoms were included in the study. A further limitation of this study is that not all the BPD subjects were in the same mood state at the time of scanning, which could potentially obscure the findings. Additionally, most of the youths were on medications during the time of the study, and medication effects on brain structures in children have been reported previously (72). Of note, children with BPD have a number of comorbid conditions, which might also have influenced the findings. Comorbid ADHD and psychosis were assessed in relation to the volumetric findings in this study and the only association found was between being psychotic and having a smaller left TL. There was no association of these findings with ADHD. However, given the comorbidities in this sample, it is difficult to say that the volumetric differences seen were solely the result of having BPD. It may well be that having a certain comorbid presentation such as BPD and ADHD could have an additive or subtractive affect on certain brain structures.

Finally, the number of independent analyses was minimized by combining the PUs into lobes for the initial analysis, thus decreasing the likelihood of false-positive results. Of course, the possibility of type I errors still exists and may be a factor in this study. We did not carry out corrections for multiple comparisons given that we only looked at individual PUs if a significant group difference in lobe volumes was observed.

Despite its limitations, this report describes one of the largest MRI studies to date in pediatric BPD. We found cortical GM abnormalities in the PL and TL as well as in the following specific gyri: increased bilateral PHG, and decreased bilateral POG, left STG, left FFG, and right middle frontal gyrus. These findings, if confirmed in longitudinal studies, could be key regions underlying the pathophysiology of the multimodal dysregulation often found in BPD. In addition, these GM findings need to be evaluated along with patterns of white matter development and change. White matter parcellation in this cohort is ongoing and a larger sample size is currently being accrued in order to further assess these findings. Finally, our findings warrant further investigation in children at risk for BPD to learn if these GM changes are state- or trait-dependent.

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Fig 1.

Parcellation of the neocortex. AG = angular gyrus; CGa = cingulate gyrus, anterior; CGp = cingulate gyrus, posterior; CN = cuneal cortex; F1 = superior frontal gyrus; F2 = middle frontal gyrus; F3o = inferior frontal gyrus, pars opercularis; F3t = inferior frontal gyrus, pars triangularis; FMC = frontal medial cortex; FOC = frontal orbital cortex; FP = frontal pole; JPL = juxtaparacentral lobule LG, lingual gyrus; OP = occipital pole; OF = occipital fusiform gyrus; OLi = lateral occipital cortex, inferior; OLs = lateral occipital cortex, superior; PAC = paracingulate cortex; PCN = precuneus; PHa = parahippocampal gyrus, anterior; PHp = parahippocampal gyrus, posterior; POG = postcentral gyrus; PP = planum polare; PRG = precentral gyrus; SC = subcallosal cortex; SCLC = supracalcarine cortex; SGa = supramarginal gyrus, anterior; SGp = supramarginal gyrus, posterior; SPL = superior parietal lobule; T1a = superior temporal gyrus, anterior; T1p = superior temporal gyrus, posterior; T2a = middle

temporal gyrus, anterior; T2p = middle temporal gyrus, posterior; T3a = inferior temporal gyrus, anterior; T3p = inferior temporal gyrus, posterior; TFa = temporal fusiform, anterior; TFp = temporal fusiform, posterior; TO2 = middle temporal gyrus, temporooccipital; TO3 = inferior temporal gyrus, temporooccipital; TOF = temporooccipital fusiform gyrus; TP = temporal pole.

Fig 2.
Three-dimensional surface reconstruction of the neocortex. Red = frontal lobe; yellow = parietal lobe; green = occipital lobe; blue = temporal lobe.

Table 1
Parcellation unit definitions of the frontal, parietal, temporal, and occipital lobes

Frontal lobe	Parietal lobe	Temporal lobe	Occipital lobe
Basal forebrain	Angular gyrus	Anterior & posterior parahippocampal gyrus	Intracalcarine cortex
Anterior cingulate gyrus	Posterior cingulate gyrus	Insula	Lingual gyrus
Central operculum	Precuneus	Heschl's gyrus *	Cuneus
Superior frontal gyrus	Parietal operculum	Planum polare *	Occipital fusiform gyrus
Middle frontal gyrus	Postcentral gyrus	Planum temporale *	Occipital pole
Inferior frontal gyrus, pars opercularis and pars triangularis	Anterior and posterior supramarginal gyrus	Anterior and posterior superior temporal gyrus *	Inferior and superior occipital lateral gyrus
Frontomedial cortex	Superior parietal lobule	Anterior, posterior, and temporo-occipital middle temporal gyrus	Supracalcarine cortex
Frontal operculum		Anterior, posterior, and temporo-occipital inferior temporal gyrus	
Fronto-orbital cortex		Anterior, posterior, and temporo-occipital fusiform gyrus	
Frontal pole		Temporal pole	
Paracingulate gyrus			
Precentral gyrus			
Subcallosal cortex			
Juxtaparacentral lobule			

* These parcellation units form the superior temporal gyrus.

Table 2

Demographic characteristics of pediatric bipolar patients (n = 32) and healthy controls (n = 15)

Characteristic	Controls (n = 15)	Bipolar disorder (n = 32)
Age	11.2 ± 3.0	11.2 ± 2.8
Handedness score (right minus left)	17.2 ± 4.8	14.9 ± 10
No. of males (%)	10	21
No. of females (%)	5	11
Proportion Caucasian	14 (93.3)	31 (96.9)
Height (cm)	145.8 ± 15.0	145.3 ± 14.2
Weight (kg)	44.5 ± 16.4	49.5 ± 14.9
Head circumference (cm)	54.7 ± 2.0	54.5 ± 1.3
Tanner Stage I (%)	8 (53.3)	17 (53.1)
Hollingshead Socioeconomic Scale I (%), Mean ± SD	10 (66.7), 56.7 ± 9.6	8 (25), 51.1 ± 9.6
Current Global Assessment of Functioning	68.7 ± 2.2	49.8 ± 6.4
Young Mania Rating Scale	0.9 ± 1.2	25.3 ± 8.3
Verbal IQ	114.9 ± 11.4	99.2 ± 14.5
Comorbidities		
ADHD (%)	N/A	20 (62.5)
Psychotic features (%)	N/A	12 (37.5)
Anxiety disorder (%)	N/A	20 (62.5)

Values in parenthesis are in percentage. N/A = not applicable.

Table 3Observed mean (cm³) and standard deviations of lobe volumes (95% confidence intervals)

Structure	Control (n = 15)	BPD (n = 32)
Total cerebral volume	1183.1 ± 57.9 (1151.0–1215.2)	1132.6 ± 99.8 (1096.7–1168.6)
Total frontal	302.1 ± 22.8 (289.5–314.8)	285.5 ± 29.6 (274.8–296.1)
Total parietal	134.1 ± 15.6 (125.5–142.7)	123.5 ± 14.0 (118.4–128.6)
Total temporal	160.8 ± 9.8 (155.4–166.3)	148.5 ± 17.9 (142.02–154.9)
Total occipital	139.9 ± 14.5 (131.9–147.9)	134.1 ± 18.4 (127.4–140.7)

Table 4

Regression estimates for lobe volumes

Covariate	Estimated effect	Standard error	t-statistic	p-value
Right frontal				
Log total cerebral volume	1.029	0.104	9.895	<0.001
Left frontal				
Log total cerebral volume	1.020	0.099	10.339	<0.001
Right parietal				
Log total cerebral volume	0.605	0.189	3.196	0.003
Diagnosis	-0.080	0.037	-2.154	0.037
Age	-0.020	0.005	-3.660	0.001
Verbal IQ	-0.002	0.001	-1.944	0.059
Left parietal				
Log total cerebral volume	0.579	0.166	3.488	0.001
Diagnosis	-0.102	0.033	-3.122	0.003
Age	-0.017	0.005	-3.505	0.001
Vocab IQ	-0.002	0.001	-2.498	0.016
Right temporal				
Log total cerebral volume	1.159	0.122	9.506	<0.001
Left temporal				
Log total cerebral volume	1.108	0.127	8.722	<0.001
Diagnosis	-0.050	0.022	-2.258	0.029
Right occipital				
Log total cerebral volume	1.172	0.204	5.757	<0.001
Left occipital				
Log total cerebral volume	0.979	0.203	4.823	<0.001

Table 5

Regression estimates for significant lobe subunits

Covariate	Estimated effect	Standard error	t-statistic	p-value
Right postcentral gyrus				
Diagnosis	−0.116	0.057	−2.027	0.049
Left postcentral gyrus				
Diagnosis	−0.136	0.053	−2.592	0.013
Left superior temporal gyrus				
Diagnosis	−0.127	0.041	−3.064	0.004
Log total cerebral volume	0.949	0.239	3.963	<0.001
Age	0.016	0.007	2.318	0.025
Left fusiform gyrus				
Diagnosis	−0.103	0.050	−2.069	0.045
Log total cerebral volume	0.986	0.277	3.561	0.001
SES raw score	−0.006	0.002	−2.535	0.015
Left parahippocampal gyrus				
Diagnosis	0.138	0.062	2.234	0.031
Log total cerebral volume	0.881	0.359	2.454	0.018
Right parahippocampal gyrus				
Diagnosis	0.146	0.065	2.247	0.030
Log total cerebral volume	0.833	0.376	2.213	0.032
Right middle frontal cortex				
Diagnosis	−0.144	0.063	−2.289	0.027
Log total cerebral volume	1.324	0.321	4.126	<0.001
Verbal IQ	−0.005	0.002	−2.890	0.006