Cortical Magnetic Resonance Imaging Findings in Familial Pediatric Bipolar Disorder

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Background: *Morphometric magnetic resonance imaging (MRI) studies of pediatric bipolar disorder (BD) have not reported on gray matter volumes but have reported increased lateral ventricular size and presence of white matter hyperintensities (WMH). We studied gray matter volume, ventricular-to-brain ratios (VBR), and number of WMH in patients with familial, pediatric BD compared with control subjects.*

Methods: *Twenty subjects with BD (aged 14.6 ± 2.8 years; 4 female) according to the Washington University in St. Louis Kiddie Schedule for Affective Disorders and Schizophrenia, each with a parent with BD, and 20 age-, gender-, and intelligence quotient–matched healthy control subjects (aged 14.1 ± 2.8 years; 4 female) were scanned at 3 T. Most subjects were taking psychotropic medications. A high-resolution T1-weighted spoiled gradient echo three-dimensional MRI sequence was analyzed by BrainImage for volumetric measurements, and T2-weighted images were read by a neuroradiologist to determine presence of WMH.*

Results: *After covarying for age and total brain volume, there were no significant differences between subjects with BD and control subjects in volume of cerebral (*p = *.09) or prefrontal gray matter (*p = *.34). Subjects with BD did not have elevated numbers of WMH or greater VBR when compared with control subjects.*

Conclusions: *Children and adolescents with familial BD do not seem to have decreased cerebral grey matter or increased numbers of WMH, dissimilar to findings in adults with BD. Gray matter decreases and development of WMH might be later sequelae of BD or unique to adult-onset BD.*

Key Words: MRI, children, adolescents, bipolar disorder, gray matter, neuroimaging

Magnetic resonance imaging (MRI) studies in adults with bipolar disorder (BD) have suggested the presence of assorted global cortical abnormalities, including differences in total brain volume, lobar volume, gray/white matter ratios, ventricular size, and number of white matter hyperintensities (WMH) (reviewed in Strakowski et al 2000). Findings have not always been replicated, however, perhaps owing to small sample sizes, differences in image acquisition, processing and analyses, and heterogeneity of subject samples.

For example, it is unclear whether adults with BD have global abnormalities in gray or white matter volume. Whereas some studies have reported cerebral atrophy (Lewine et al 1995) or decreased gray matter volumes (Lim et al 1999) in patients with BD, other studies have found no differences in these morphometric measures between patients with BD and healthy control subjects (Dewan et al 1988; Pearlson et al 1997; Zipursky et al 1997). Furthermore, when compared with healthy control subjects, patients with first-episode mania were reported to have decreased total white matter and relatively increased gray matter (Strakowski et al 1993a). Differences in patient population (severity of BD, gender), MRI acquisition, and data analysis protocols, and variability in medication exposure might have contributed to these variable findings.

Analyses of cerebral lobe and subregions in BD also have produced varying results, although several reports suggest abnormalities of the prefrontal cortex. These abnormalities include decreased neuronal and glial density in the dorsolateral prefrontal cortex (Rajkowska et al 2001), decreased subgenual prefrontal gray matter (Drevets et al 1997) and glial cells (Ongur et al 1998), and decreased prefrontal gray matter volumes bilaterally (Lopez-Larson et al 2002). Given this convergence of positive histopathologic and morphometric findings, it is likely that prefrontal gray matter is affected in adults with BD.

There are varying data regarding temporal lobe volumes in BD (Norris et al 1997). Studies have reported decreased (Altshuler et al 1991; Hauser et al 1989; Schlaepfer et al 1994), similar (Altshuler et al 1998; Brambilla et al 2003; Johnstone et al 1989; Pearlson et al 1997), and increased temporal lobe volumes in individuals with BD compared with control subjects (Harvey et al 1994). No studies have reported differences in parietal or occipital lobe or cerebellar volumes.

There have been more consistent findings of increased lateral ventricular size in BD, from both computed tomography (Andreasen et al 1990; Dewan et al 1988; Iacono et al 1988; Nasrallah et al 1982; Norris et al 1997; Pearlson and Veroff 1981; Pearlson et al 1984b; Schlegel and Kretzschmar 1987; Tanaka et al 1982) and MRI studies (Pearlson et al 1984a; Strakowski et al 1993a). Despite other negative findings (Brambilla et al 2001; Harvey et al 1994; Johnstone et al 1989; McDonald et al 1991; Risch et al 1992), a meta-analysis of these studies supported overall lateral ventricular enlargement in adults with BD (Elkis et al 1995). Furthermore, an MRI study found right lateral ventricular volumes to increase with number of prior mood episodes, and that individuals with familial compared with nonfamilial BD had larger lateral ventricles (Brambilla et al 2001). First-episode manic BD patients have also been reported to demonstrate increased third ventricular volumes compared with control subjects (Strakowski et al 1993a), whereas other MRI studies have found no differences in third ventricular volumes (Brambilla et al 2001; Norris et al 1997).

Perhaps the most consistent structural finding in adult BD has been the presence of increased numbers of WMH (Dupont et al

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1987, 1990; Figiel et al 1991; Stoll et al 2000; Swayze et al 1990), areas of abnormally high signal intensity on T2 images compared with surrounding tissue. White matter hyperintensities might represent dilated perivascular spaces, areas of micro-infarcts or hemorrhage, or an as-yet undiscovered neuropathologic entity. Therefore, it is unclear whether WMH are causal to or the result of bipolar illness. For example, patients with BD might have higher rates of alcohol abuse, smoking, and cardiovascular risk factors, such as hypertension, which could contribute to the pathogenesis of WMH (Figiel et al 1991; Strakowski et al 1998); however, increased numbers of WMH have also been reported in adolescents with BD (Botteron et al 1992; Lyoo et al 2002; Pillai et al 2002) who have little in the way of cardiovascular risk factors. By contrast, some studies, including one of first-hospitalization patients, failed to detect increased WMH in BD (Altshuler et al 1995; Brown et al 1992; Krabbendam et al 2000; Sassi et al 2003; Strakowski et al 1993b). Therefore, although there have been varying reports of morphologic brain abnormalities in BD, overall patterns from the literature suggest that adults with BD might have prefrontal, temporal, ventricular, and white matter abnormalities.

Children and adolescents with BD might be better suited for MRI studies than adults because early-onset disorders might be more familial and more severe (Schurhoff et al 2000) and thus carry a higher likelihood of consistent biological abnormalities (Faraone et al 2003). Furthermore, children often have had less exposure to psychotropic medications and less substance abuse, which might confound the interpretation of MRI data in adults. There have been limited brain-imaging studies in pediatric BD to date, however. Botteron et al (1992) reported cerebral structural asymmetry and increased WMH in 10 children with BD compared with 5 control subjects. Friedman et al (1999) studied groups of adolescents with either schizophrenia or BD and found no differences in intracranial or ventricular volumes in either of these groups compared with control subjects. The combined group, however (BD + schizophrenia), had reduced intracranial volume and increased frontal and temporal sulcal size and increased lateral ventricular volume compared with the control group. Additional brain morphometry studies in pediatric BD are necessary to identify possible etiologies for this disorder, provide a basis of comparison to adult studies, and understand the developmental course of BD across different ages.

Therefore, we used MRI to investigate cortical morphometry in a cohort of children and adolescents with familial bipolar I disorder. We previously reported decreased dorsolateral prefrontal N-acetylaspartate (NAA) levels in 13 patients from this cohort compared with healthy control subjects (Chang et al 2003), possibly reflecting decreased neuronal density. Accordingly, we hypothesized that these children with familial BD also would have decreased cerebral gray matter compared with healthy control subjects, specifically in prefrontal cortex. Because of the extant findings from adult studies, we also hypothesized that we would detect increased ventricular-to-brain ratios (VBR) and increased WMH in bipolar subjects compared with control subjects.

Methods and Materials

This protocol was approved by the Stanford University Administrative Panel of Medical Research in Human Subjects. Twenty patients and 20 healthy volunteers were recruited from an ongoing study of bipolar offspring and from the community. After obtaining oral and written informed consent from parents and oral and written assent from their offspring, semi-structured interviews were conducted. Patients had at least one parent with bipolar I or II disorder, as diagnosed by the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID) (First et al 1995), administered by a trained masters-level clinician and/or board-certified psychiatrist (KC). All subjects, patients, and healthy volunteers were evaluated by the affective disorders module of the Washington University in St. Louis Kiddie Schedule for Affective Disorders and Schizophrenia (WASH-U-KSADS) (Geller et al 1996, 2001) and the Schedule for Affective Disorders and Schizophrenia for School-age Children, Present and Lifetime (Kaufman et al 1997). Subjects were evaluated either by a board-certified child psychiatrist (KC) or a trained masters-level research assistant, who were both aware of parental diagnosis. Interrater reliability was established at the outset by rating videotaped interviews, observing trained rater interviews, and performing interviews with observation by a trained rater, as described by Geller et al (1998) (four consecutive patients with 100% agreement on diagnoses). Diagnostic decisions were ultimately made by a child psychiatrist (KC) on the basis of personal interviews, discussion with the research assistant, and written notes of parental and subject responses to interview questions. Current and lifetime diagnoses were established according to DSM-IV criteria. Parents were euthymic at the time of their own and their child's interview. Patients in this study all received a diagnosis of bipolar I disorder. Inclusion criteria for bipolar subjects were age 9–18 years, biological parent with bipolar I or II disorder, and diagnosis of bipolar I disorder by the WASH-U-KSADS. Exclusion criteria were presence of a pervasive development disorder, a neurologic condition (such as a seizure disorder), a substance use disorder, intelligence quotient (IQ) less than 80, or presence of metallic implants or braces. Age of onset of BD was determined retrospectively as the earliest period to the closest month in which patients met criteria for a manic or depressive episode, as defined by the DSM-IV.

Exclusion criteria for control subjects included any DSM-IV diagnosis, parental psychopathology (as assessed by SCID), a first- or second-degree relative with BD (as determined by the Family History Research Diagnostic Criteria; Andreasen et al 1977), neurologic disorders, IQ less than 80, or presence of metallic implants or braces.

Subjects were all outpatients at the time of scanning. Patients with BD were administered the clinician-rated Young Mania Rating Scale (YMRS) (Fristad et al 1995; Young 1978) and completed the Children's Depression Inventory (CDI; Kovacs 1985), with help of a parent if subjects were aged <12 years. Patients with BD had psychostimulants discontinued for 24 hours before the scan, primarily because of a concurrent, separate functional MRI study of attention. They were allowed to continue any other current medications, such as mood stabilizers or antidepressants, owing to the risk of mood destabilization.

MRI Protocol

Magnetic resonance images of each subject's brain were acquired with a Signa 3-T scanner (GE Medical Systems, Milwaukee, Wisconsin). Coronal images were acquired with a three-dimensional volumetric radio frequency spoiled gradient echo with the following scan parameters: repetition time = 35 msec, echo time = 6 msec, flip angle = 45°, number of excitations = 1, image matrix = 256 × 192 pixels, field of view = 24 cm, slice thickness = 1.5 mm, 124 slices, acquired resolution = 1.5 × .9 × 1.2 mm^3. The images were reconstructed as a 124 × 256 × 256 matrix with a 1.5 × .9 × .9 mm^3 spatial resolution.

Imaging Processing and Measurement

Image data were imported into the program BrainImage 5.29 (Stanford Psychiatry Neuroimaging Laboratory; see "Tools" at http://spnl.stanford.edu) for semi-automated image processing and quantification. After image importation, MRI data were corrected for bias field artifact, non-brain tissue was removed with a semi-automated process, and the brains were positionally normalized to a stereotactic space (Talairach and Tournoux 1988). To specify regional differences, each brain was divided into lobes with a semi-automated stereotactic-based parcellation method (Kates et al 1999). The brains were divided into cerebral lobes, cerebellum, and lateral ventricles on the basis of the rater's identification of three anchor points: the anterior commissure, the posterior commissure, and a midsagittal point above the axis created by the first two points. Raters who conducted morphometric analyses were blind to the diagnosis of each subject. Voxels comprising brain tissue were then segmented into gray matter, white matter, and cerebrospinal fluid (CSF) with a semi-automated fuzzy tissue segmentation algorithm (Reiss et al 1998). Ventricle-to-brain ratio was calculated by the following formula: 100 × ventricle CSF/cerebral total tissue volume.

An overall prefrontal region was initially determined by identification of an anterior border corresponding to the most anterior coronal slice of the positionally normalized brain and a posterior border, defined as the last coronal slice before the most anterior point of the corpus callosum genu was visualized. This prefrontal region was then subdivided into eight subregions (left and right superior, middle superior, middle inferior, and orbitofrontal) based on designated sectors of the Talairach grid (Talairach and Tournoux 1988), as described by Reiss et al (2004).

Magnetic resonance images were read by a pediatric neuroradiologist (PB) to determine the presence or absence of WMH. Lesions were graded according to the severity rating scale of Coffey et al (1990); however, because the WMH observed in our research participants did not always correspond well to the designated categories of this scale, an additional scale was developed to rate overall presence of WMH in each subject. No measures were taken to establish the reliability and validity of this scale; rather, it was intended to more accurately reflect the breadth in location and number of WMH found. This was a qualitative determination, 0–5, based on the number, size, and location of WMH. These ratings were made by a blinded rater using transcribed notes from the pediatric neuroradiologist, according to the following scale: 0 = no indication of any WMH; 1 = 0–4 (few) tiny WMH in basal ganglia (BG) only; 2 = #1 above and presence of 0–4 (few) tiny, supraventricular WMH; 3 = multiple or large WMH in BG and/or supraventricular WMH; 4 = 1 distinct, medium-large WMH in supraventricular WM, or multiple small distinct WMH; 5 = multiple examples of #4 above.

Both the neuroradiologist and the rater were blinded to subject status (bipolar or control). Lesions that were thought to be Virchow-Robin spaces were included because there was no way to be certain they were not a form of WMH.

Statistical Analyses

Data were first examined for normality to conform to the assumptions of the parametric statistics used. Multiple analysis of covariance was used to determine whether the bipolar group and the control group had unique patterns of tissue volume and composition. Analyses of total brain tissue, total gray matter, and total white matter were performed with one-way analyses of variance, with diagnosis as a between-subjects factor. Analysis of covariance (ANCOVA) was used for subregion comparisons, to more accurately quantify group differences after statistically adjusting for the effect of total brain or tissue compartment volumes. A p value of .05 (two-tailed) was chosen as the significance threshold. A ventricle-to-brain-volume ratio was computed to account for individual between-subject differences in total brain volume.

Results

Cohort

Mean age was 14.6 ± 2.8 years for the bipolar group and 14.1 ± 2.8 years for the control group; age range of the entire sample was 9.2–18.6 years. Groups did not differ significantly by age, gender, or IQ (Table 1); however, there was a trend for control subjects to have a higher IQ (p = .06). Mean duration of illness was 1.7 ± 1.8 years.

Mean YMRS score for the bipolar group was 15.4 ± 8.7, and mean CDI score was 15.3 ± 8.7. Three subjects were considered to be currently manic, with YMRS scores greater than 19. One subject was currently depressed, with a CDI of more than 19. Three subjects had substantial mixed symptoms, with YMRS and CDI scores more than 19. The 13 other subjects in the bipolar group had YMRS and CDI scores less than 20 and were considered clinically euthymic.

All subjects in the bipolar group except four were taking psychotropic medications. Of these subjects, 60% had significant past exposure (more than 2 months) to stimulants: 15% to tricyclic antidepressants, 65% to serotonin reuptake inhibitors, 35% to antipsychotics, and 70% to mood stabilizers, including 30% with exposure to lithium, 45% to valproate, and 65% to any mood stabilizer (Table 1). No subjects in the control group had previous exposure to psychotropic medications. Eighty-five percent of subjects in the bipolar group had comorbid psychiatric diagnoses, with attention-deficit/hyperactivity disorder the most common at 85% (Table 1). No subjects in the bipolar group had a present or past substance-use disorder.

Brain Volumes

Total brain and cerebral volumes were not significantly different between groups (Table 2). After covarying for age and total brain volume, there was a trend only for subjects with BD to have decreased total brain gray matter [−4.4%, $F(1) = 2.977$, p = .09] (Table 2). The effect size of this finding was .53. There were no significant differences in total white matter or CSF (Table 2).

Exploratory ANCOVA of individual cerebral lobe gray matter volumes, with age and total brain volume as covariates, revealed no regions with significantly decreased gray matter (Table 2). Furthermore, subjects with BD did not differ from control subjects in prefrontal gray volume [105.7 ± 14.7 cm^3 vs. 106.0 ± 12.1 cm^3; $F(38) = .006$, p = .94] or any of the eight subregions of prefrontal cortex. There were no differences in VBR between subjects with BD and control subjects (Table 2).

Chi-squared analyses (and Fisher's exact test when cells were expected to have fewer than 5 individuals) revealed that there were no significant differences between subjects in the bipolar and control groups in terms of number having grade 1 WMH [$\chi^2(1) = .10$, p = .75] or those having grade 2 or 3 [$\chi^2(1) = 3.2$, p = .07], as according to the Coffey et al (1990) scale (Table 3). According to our own rating scale, there were no differences between the bipolar and control groups in terms of number having a "4" or "5" rating (4 vs. 1: $\chi^2 = 1.9$, p = .17).

Because many of our subjects had lithium exposure, reported to possibly increase gray matter volume (Moore et al 2000b), we

Table 1. Demographic Characteristics of Subjects

	Bipolar	Controls	*p*
n	20	20	
Age (y), mean (SD)	14.6 (2.8)	14.1 (2.8)	.59
Gender, % male	80	80	
SES, mean (SD)	4.2 (.8)	4.5 (.7)	
Race, *n* (%)			
African American	1 (5)	0 (0)	
Hispanic	1 (5)	2 (10)	
Asian	0 (0)	3 (15)	
Caucasian	18 (90)	15 (75)	
IQ, mean (SD)	109.5 (11.4)	116.0 (9.5)	.06
Handedness, % right	95	95	
Comorbid Diagnoses, *n* (%)			
ADHD	17 (85)	0 (0)	
Anxiety Disorder	7 (35)	0 (0)	
Oppositional Defiant Disorder	12 (60)	0 (0)	
YMRS Score	15.4 (8.7)		
CDI Score	15.3 (8.7)		
GAF Score	54.3 (8.0)		
Duration of Illness (y), mean (SD)	1.7 (1.8)		
Past Psychotropic Medication Exposure, %			
Stimulants	60	0	
TCAs	15	0	
SSRIs	65	0	
Atypical ADs	50	0	
Lithium	35	0	
Valproate	45	0	
Antipsychotics	35	0	
Any mood stabilizer	65	0	

SES, socioeconomic status; IQ, intelligence quotient; ADHD, attention-deficit/hyperactivity disorder; YMRS, Young Mania Rating Scale; CDI, Children's Depression Inventory; GAF, Global Assessment of Functioning; TCAs, tricyclic antidepressants; SSRIs, selective serotonin reuptake inhibitors; ADs, antidepressants.

performed further analyses based on the presence of past lithium exposure. Subjects with BD were divided into those who had and had not been treated with lithium for at least 3 months (n = 7 vs. 13). An ANCOVA covarying for age and total brain volume was performed, with lithium exposure as a factor and cerebral gray matter volume as the dependent variable. There were no significant differences in cerebral gray matter volumes between those with and without lithium exposure [638.9 ± 38.4 cm^3 vs. 692.8 ± 64.5 cm^3; $F(1) = .077$, $p = .78$]. When only subjects with BD and no lithium exposure were compared with control subjects, there were still no differences between the groups in terms of cerebral gray matter volume [$F(1) = 1.50$, $p = .23$]. The correlation between duration of illness and total cerebral gray matter volume was not significant (Spearman's = −.11, $p = .63$).

Table 2. Mean (SD) Brain Regional Volumes (in Cubic Centimeters) in Bipolar Subjects and Control Subjects

Brain Region	Bipolar	Control	*p*
Total Brain Volume	1484.3 (128.6)	1522.5 (110.1)	.35
Total Cranial Volume	1291.4 (118.0)	1327.5 (100.0)	.34
Cerebrum–Gray	676.6 (62.3)	707.1 (52.3)	.09
Cerebrum–White Matter	458.1 (45.4)	471.1 (53.7)	.91
Cerebrum–CSF	142.8 (33.7)	136.6 (18.5)	.18
Frontal Lobe–Gray	241.4 (24.0)	250.1 (18.2)	.51
Prefrontal Cortex–Gray	105.7 (14.7)	106.0 (12.1)	.34
Parietal Lobe–Gray	157.4 (16.7)	166.6 (14.6)	.13
Temporal Lobe–Gray	152.9 (15.2)	162.2 (14.9)	.10
Occipital Lobe–Gray	75.7 (12.1)	79.4 (10.6)	.74
VBR	1.21 (.53)	1.07 (.45)	.22

CSF, cerebrospinal fluid; Gray, gray matter; VBR, ventricle-to-brain ratio.

Discussion

Although there were trends approaching significance in our gray matter analyses, we found no statistically significant differences in overall gray matter volume, VBR, or number of subjects with significant WMH in our child and adolescent subjects with familial BD. These findings are largely dissimilar from most MRI findings reported to date in studies of adults and children with BD. There are several possible reasons for these findings, as we will discuss here.

Although not significant at our designated threshold α of .05, we did detect a trend for overall decreased gray matter in patients with BD compared with control subjects ($p = .09$). This decrease in cortical gray matter (4.3%) was not as robust as the 9.4%–16.8% reported in adult samples with BD (Lim et al 1999; Lopez-Larson et al 2002). Decreased gray matter in the context of normal total brain volume indicates an abnormal developmental trajectory in pediatric BD. Specifically, this finding suggests that there might be abnormal neurodevelopmental (e.g., synaptic pruning) mechanisms associated with early-onset BD, resulting in aberrant reduction of neuropil in particular brain areas. Decreased gray matter volume also could be due to glial loss, as has been reported in subgenual prefrontal cortex in adults with familial BD (Ongur et al 1998).

Decreased gray matter might also result from neuronal loss caused by atrophy or neurotoxic processes. This concept is supported by spectroscopic studies that have found larger dorsolateral prefrontal decreases in NAA in adult BD (left = 8.9%, right = 6.3%) (Winsberg et al 2000) than in pediatric BD (left = 1.2%, right = 4.2%) (Chang et al 2003). Perhaps if our subjects were reassessed in adulthood, gray matter volumes would become more discrepant compared with control subjects. We did not, however, find a significant inverse correlation of duration of illness with gray matter volume in our subjects with BD, possibly owing to the small range of duration of illness in our subjects. Studies performed on subjects before BD development would be necessary to further clarify whether developmental abnormalities or neurodegeneration is responsible for these findings.

Exploratory analyses revealed no significant differences in lobar gray volumes, including prefrontal gray volume, contrary to our hypothesis. Therefore, in conjunction with our significance level indicating a trend only, it is also possible that patients with early-onset, familial BD simply do not have less cerebral gray matter than healthy control subjects. Other studies failed to find gray matter differences in adults with BD (Harvey et al 1994; Hoge et al 1999; Zipursky et al 1997). Additionally, one study of first-episode patients found increased gray-to-white-matter ratios

Table 3. Presence of White Matter Hyperintensities

	Bipolar *n* (%)	Control *n* (%)	χ^2	*p*
Deep White: Grade 1	9 (47)	10 (50)	.10	.75
Deep White: Grade 2 or 3	3 (16)	0 (0)	3.2	.07
Periventricular White	4	5	.14	.71
Deep White	12	10	.40	.53
Subcortical Gray	17	13	1.3	.26

compared with control subjects (Strakowski et al 1993a) but did not comment on total gray volumes. Our findings could not be accounted for by lithium exposure, which might increase gray matter volume in adults (see the discussion of limitations below).

We found no differences in VBR in children with BD compared with healthy control subjects. Increased VBR might reflect on overall loss of brain tissue. Previous reports have suggested that atrophy of specific structures in the temporal lobe, such as hypothalamus and thalamus, could account for increased third ventricle volume (Strakowski et al 1993a). Similarly, decreased amygdalar and hippocampal size could lead to increased lateral ventricular volume at the temporal horns. Abnormalities in these structures have been implicated in BD, and there have been previous reports of decreased volume of amygdala and hippocampus in adolescents with BD (Blumberg et al 2003; DelBello et al 2004); however, we did not examine ventricular volume changes in these specific areas. Overall, lack of differences in VBR is consistent with our findings of similar total brain volume and gray/white matter volumes. Because adults with BD have been found to have ventricular size correlated with number of mood episodes (Brambilla et al 2001; Strakowski et al 2002), it is possible that our subjects were again too early in their illness to have these changes in ventricular volume.

Also contrary to our hypotheses, we did not find any increased incidence of WMH in our subjects. Our finding of an absence of increased WMH in patients with BD contradicts many such positive findings in both adults (Altshuler et al 1995; Dupont et al 1987, 1990; Figiel et al 1991; Hauser et al 2000; McDonald et al 1999; Swayze et al 1990; Woods et al 1995) and children and adolescents (Botteron et al 1992; Pillai et al 2002) with BD; however, many of these studies had inconsistent and nonstandardized protocols for determining presence and size of WMH. For example, the researchers in the Pillai study used their own scale to grade WMH, inconsistent with most other WMH studies of adults with BD, which have used the scale used here (Coffey et al 1990, based on Fazekas et al 1987). Therefore, we used the Coffey scale as well as our own qualitative rating scale, but we still did not detect differences between groups. Our subjects with BD might have been too early in their illness to have yet demonstrated such white matter abnormalities. One hypothesis for increased WMH in BD is that patients with BD might have higher cardiovascular risk factors, such as higher rates of smoking, poor diet, or weight gain from medications (Stoll et al 2000). These factors might contribute to a higher incidence of ischemic events in white matter. Our subjects are likely too young to have had such ischemic events. Furthermore, our subjects differ from those in previous studies, in that each had at least one parent with BD and overall a high rate of familial BD. Therefore, familial pediatric BD might not be linked to WMH; conversely, it is possible that children and adolescents with less familial BD might develop the disorder primarily through environmental mechanisms, such as prenatal or perinatal trauma, perhaps leading to hypoxia and ischemic events in deep white matter.

Finally, none of our subjects had known histories of significant substance abuse. As mentioned previously, this advantage of studying children rather than adults might also explain findings that are discrepant between the two age groups. That is, it is possible that some findings reported in studies of adults with BD might be accounted for by chronic use of alcohol and other drugs.

Our sample size might have prevented a significant finding. We calculated the difference in cerebral gray matter volume between groups to have an effect size of .53. Thus, for a two-tailed test our power to detect a statistically significant difference was only .375. Increasing our sample size from 20 to 50 for each group would result in a more suitable power of .75. Previous studies of cortical volumes in pediatric BD have included only 15–31 subjects (Botteron et al 1992; Friedman et al 1999), and none have specifically examined gray matter, so despite being underpowered this study represents a significant advance in this area.

Nonetheless, our relatively small sample size precluded further statistical analyses regarding age of onset, gender, or medication exposure. These analyses could point to differences in developmental trajectories depending on pubertal or gender status. Although none of our subjects with BD had a history of substance abuse, almost all had a history of psychotropic medication exposure, and 35% had taken lithium at some point. Lithium might increase both NAA (Moore et al 2000a) and gray matter volume (Moore et al 2000b) in humans, possibly accounting for our negative findings; however, we did not find a correlation of lithium exposure and gray matter volume in our subjects with BD. When subjects with lithium exposure were removed from the analysis, the findings did not change. The influence of other mood stabilizers, antidepressants, stimulants, and antipsychotics on brain volumes is unknown. Furthermore, this was a relatively homogenous cohort of bipolar offspring with pediatric-onset bipolar I disorder. Thus, these results might not be generalizable to all subjects with BD.

Overall, our findings suggest that there might be developmental differences that account for differences in MRI findings between children and adults with BD. That is, decreased gray matter might be a phenomenon that begins to occur early in the course of BD and continues throughout adulthood. Similarly, white matter deficits and enlarged ventricles might not be observed until later in the course of the illness. It is also possible however that familial pediatric BD is neurobiologically distinct from adult-onset BD. If this is the case, then it is not clear how to interpret our data in light of the adult data. Most MRI studies of adult BD did not report age of onset, so their cohorts might consist of mixed ages of onset. This heterogeneity might also account for some of the inconsistencies of findings among these MRI studies. Longitudinal studies beginning at an early age in affected (BD) and unaffected children at high risk for developing BD would be necessary to determine whether and when these children begin to differ in neurodevelopment, and whether they continue to exhibit increasingly decreased gray matter into adulthood. This type of investigation would also help clarify the time, if any, of onset of WMH and ventricular enlargement in the course of BD.

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