Frontotemporal Alterations in Pediatric Bipolar Disorder

Results of a Voxel-Based Morphometry Study

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Context: While numerous magnetic resonance imaging (MRI) studies have evaluated adults with bipolar disorder (BPD), few have examined MRI changes in children with BPD.

Objective: To determine volume alterations in children with BPD using voxel-based morphometry, an automated MRI analysis method with reduced susceptibility to various biases. A priori regions of interest included amygdala, accumbens, hippocampus, dorsolateral prefrontal cortex (DLPFC), and orbitofrontal cortex.

Design: Ongoing study of the pathophysiology of pediatric BPD.

Setting: Intramural National Institute of Mental Health; approved by the institutional review board.

Patients: Pediatric subjects with BPD (n=20) with at least 1 manic or hypomanic episode meeting strict DSM-IV criteria for duration and elevated, expansive mood. Controls (n=20) and their first-degree relatives lacked psychiatric disorders. Groups were matched for age and sex and did not differ in IQ.

Main Outcome Measures: With a 1.5-T MRI machine, we collected 1.2-mm axial sections (124 per subject) with an axial 3-dimensional spoiled gradient recalled echo in the steady state sequence. Image analysis was by optimized voxel-based morphometry.

Results: Subjects with BPD had reduced gray matter volume in the left DLPFC. With a less conservative statistical threshold, additional gray matter reductions were found in the left accumbens and left amygdala. No difference was found in the hippocampus or orbitofrontal cortex.

Conclusions: Our results are consistent with data implicating the prefrontal cortex in emotion regulation, a process that is perturbed in BPD. Reductions in amygdala and accumbens volumes are consistent with neuropsychological data on pediatric BPD. Further study is required to determine the relationship between these findings in children and adults with BPD.

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Pediatric bipolar disorder (BPD) is currently one of the most active and controversial areas of clinical and research interest in child psychiatry. Investigators have systematically described the clinical presentation of pediatric BPD and are now exploring neural mechanisms that might mediate the symptoms of the illness. Specific brain regions whose function might be impaired in children with BPD, and then to follow up on these behavioral results with neuroimaging studies.

Emerging behavioral data in “narrow-phenotype” BPD—ie, children with distinct manic episodes meeting full DSM-IV criteria including abnormally elevated, expansive mood lasting 4 days or more—show that children with BPD may have dysfunction in a circuit involving the amygdala, accumbens area, and prefrontal cortex (PFC). Specifically, behavioral data show that children with narrow-phenotype BPD are impaired in (1) attentional set shifting and reversal learning; (2) recognition of facial emotion; and (3) reward-related processing. These psychological processes are subserved by circuits involving the amygdala, PFC, and ventral striatum (including the accumbens area). However, a dearth of neuroimaging data in pediatric BPD prevents linking these deficits to alterations in specific brain regions, as has been done to some extent in adult BPD research.

Magnetic resonance (MR) imaging studies in adults with BPD have documented a range of morphometric differ-
ences in cortical and subcortical regions involved in emotion regulation, a process whereby initial responses to motivationally salient stimuli are altered in the face of changing goal demands. Specifically, studies in adult BPD have found abnormalities in regions of interest (ROIs) central to both the initial processing of emotional stimuli and response generation. These regions include the amygdala, ventral striatum, temporal lobe, and orbitofrontal cortex. Moreover, studies in adults with BPD have found abnormalities in structures thought to regulate initial emotional responses, including the dorsolateral prefrontal cortex (DLPFC).

Despite an emerging emphasis on the neural circuitry of emotion regulation in adult BPD, there are inconsistencies in the literature. For example, in adults with BPD compared with controls, 3 studies found increased amygdala volume, while 1 study found reduced amygdala volume. Studies of the hippocampus and temporal lobe are also inconsistent, although many studies have found some form of abnormality in BPD. Magnetic resonance imaging studies of adults with BPD have found decreased PFC volume, both of the PFC as a whole and of the subgenual PFC in particular, and a second, more recent study found decreased PFC density. Variability of MR imaging findings in adult BPD extends to investigations of white matter, with some studies, but not others, showing increased white matter hyperintensities in adults with BPD. This inconsistency in results of MR imaging studies in adult BPD may be due in part to methodologic variability of image analysis and patient selection.

Traditional MR imaging analytic methods—ie, manual tracing of multiple ROIs—may account for some of the inconsistency in the adult BPD neuroimaging literature. Hand tracing is susceptible to both type I and II errors, given its dependence on human raters’ ability to reliably define neuroanatomic regions. A novel, emerging method for MR imaging analysis is voxel-based morphometry (VBM). Voxel-based morphometry provides an objective means of examining the brain voxel by voxel in an automated fashion, determining differences in tissue volume, and avoiding the potential for bias in manual tracing. Moreover, in contrast to traditional manual tracing, VBM facilitates the simultaneous evaluation of multiple regions across the entire brain while generating appropriate voxel-wise statistical values. Such an approach appears particularly valuable for conditions such as BPD, where abnormalities in distributed neural circuitry might be anticipated. Studies have used VBM to evaluate neuropsychiatric disorders, such as Alzheimer disease, obsessive-compulsive disorder, panic disorder, and posttraumatic stress disorder, as well as age-related alterations in gray matter.

Furthermore, a study by Testa et al suggested that VBM detects hippocampal changes in Alzheimer disease with greater sensitivity than traditional morphometry. Thus, VBM may reduce the variability inherent in traditional morphometric MR imaging analyses.

Few MR imaging morphometry studies exist in pediatric BPD. Currently, only 4 published studies have examined volumetric changes in cortical or subcortical structures in adolescents with BPD. Two have found decreased amygdalar volume in adolescents with BPD compared with controls, with one of these also finding a reduction in hippocampal volume. A third study found that adolescents with BPD had decreased left superior temporal gyrus volume. Recently, a fourth study used VBM to evaluate 12 ROIs in 10 adolescents with BPD and found that, compared with controls, the patients had increased gray matter volume bilaterally in the basal ganglia and thalamus, as well as larger left temporal lobes. In addition, investigators have found evidence of increased white matter hyperintensities in children with BPD, but this finding may lack specificity since similar increases have been reported in children with other psychiatric disorders. Clearly, more neuroimaging studies are needed in children with BPD to enhance our understanding of the developmental psychobiology of the illness.

We examined volumetric MR imaging changes in children with narrow-phenotype BPD by means of optimized VBM. We hypothesized that pediatric subjects with BPD would have volume reductions in key areas—including the amygdala, accumbens area, hippocampus, DLPFC, and orbitofrontal cortex—suggested by our behavioral data and by other MR imaging studies.

METHODS

Subjects

Twenty children with BPD, aged 7 to 17 years, were recruited for an ongoing longitudinal neurocognitive and neuroimaging study conducted at the National Institute of Mental Health, Bethesda, Md, and approved by the institutional review board. After the study was explained and before participation, parents and children gave written informed consent and assent, respectively. Subjects were recruited nationwide via material placed on support groups’ Web sites, distributed at professional conferences, and sent to child psychiatrists.

Inclusion criteria for children with BPD were as follows: (1) meeting DSM-IV criteria for BPD, including a history of at least 1 episode meeting full duration criteria for hypomania (≥4 days) during which the child exhibited abnormally elevated or expansive mood and a total of at least 3 other DSM-IV criterion “B” mania symptoms; (2) involvement with ongoing mental health treatment; and (3) presence of a primary caretaker to grant consent and to participate in the research process. Children with irritability only, without elevated or expansive mood, were excluded. Thus, these patients represented the narrow phenotype of pediatric BPD.

Exclusion criteria for pediatric BPD were as follows: IQ less than 70; autistic disorder or severe pervasive developmental disorder; psychosis interfering with the child’s capacity to understand and comply with study procedures; unstable medical illness (eg, severe asthma); medical illness that could cause the symptoms of bipolar illness (eg, multiple sclerosis, thyroid disease); pregnancy; or substance abuse within past 2 months.

After a telephone screening interview to ascertain a lifetime history of hypomanic, manic, and depressive episodes, patients thought likely to meet inclusion criteria were invited to the National Institute of Mental Health. The more detailed onsite screening included the Schedule for Affective Disorders and Schizophrenia for School-Age Children—Present and Lifetime Version, a semistructured diagnostic clinical interview instrument, completed with parent and child individually by trained graduate-level clinicians, with established interrater reliability. All diagnoses were based on best-estimate procedures, generated in a consensus conference of research staff led by 1 child
and adolescent psychiatrist and 1 general psychiatrist, both with extensive experience studying children with BPD and related illnesses. We collected the following mood and function ratings on all subjects with BPD: Young Mania Rating Scale,45 Children’s Depression Rating Scale, Children’s Multidimensional Anxiety Scale for Children, and Children’s Global Assessment of Severity.46

Controls (n=20) were matched individually with patients for age and sex. As with subjects with BPD, controls completed a telephone screen, and then graduate-level clinicians completed the Child Schedule for Affective Disorders. Present and Lifetime Version, with the child control and his or her parent separately. Inclusion criteria were negative psychiatric history in the control subject and his or her first-degree relatives; normal results of physical and neurologic examinations; lack of current, regular medication use; and an identified primary care physician. Exclusion criteria for controls were IQ less than 70; ongoing medical illness; neurologic disorder (including seizures); pregnancy; past or present substance abuse; and history of sexual abuse.

MR IMAGING METHODS

MR Imaging Protocol

Images were acquired on a 1.5-T scanner (Signa; GE Healthcare, Milwaukee, Wis). After a sagittal scout sequence, morphometric images were collected by means of an axial 3-dimensional spoiled gradient recalled echo in the steady state with echo time of 3 milliseconds, repetition time of 24 milliseconds, flip angle of 20°, acquisition matrix of 224×224, 1 excitation, and field of view of 22 cm. We also used a 300-millisecond inversion recovery preparation pulse used for T1 weighting with bandwidth of 15.63 Hz. Contiguous 1.2-mm axial section (124 total per subject) were collected with a voxel size of 0.98×0.98×1.2 mm. Head placement was standardized by aligning the nasion.

VBM Overview

As described elsewhere in more detail,28,29,49 optimized VBM analysis involves the following preprocessing of each subject’s brain image (explained in detail in the following sections): (1) brain extraction (removal of nonbrain tissue, such as skull and dura); (2) segmentation (ie, separation of brain tissue into white matter, gray matter, and cerebrospinal fluid); (3) spatial transformation (transformation of tissue maps to common stereotaxic space); and (4) modulation (volume preservation that corrects for unintended changes in total tissue volume produced by spatial transformation). For the extraction step, all MR images were examined by a neuroradiologist and found to be free of clinically significant abnormalities. We removed nonbrain tissue (ie, dura and skull) from the MR images by means of an automated method (Brain Extraction Tool; Oxford Centre for Functional Magnetic Resonance Imaging of the Brain [FMRIB], Oxford, England). Then, using MEDx (version 3.4.2; Medical Numerics Inc, Sterling, Va), we manually removed high-signal areas of the orbits and prechiasmatic optic nerve to increase segmentation accuracy.

For segmentation, each subject’s brain tissue was classified as gray matter, white matter, or cerebrospinal fluid on a voxel-wise basis by means of a highly accurate segmentation algorithm (FMRIB’s Automated Segmentation Tool). Specifically, on the basis of voxel intensity values and spatial continguities derived from hidden Markov random fields, this segmentation algorithm generates a 3-dimensional map for each tissue type, representing the tissue-belonging probabilities for each voxel. On the basis of on these tissue probabilities, the segmentation algorithm generates partial volume estimates that are used in the volumetric analyses.

During the spatial normalization step, brain images were transformed from their native space to a common stereotaxic space (ie, the Montreal Neurological Institute’s 152-image adult space [MNI]) in which images can be compared across subjects and groups. We attempted to address several concerns that have been raised in the past regarding spatial normalization in VBM.50,51 Some authors have suggested that pediatric MR imaging studies should use pediatric brain templates, rather than adult brain templates such as those in the MNI database, to avoid image registration errors due to age-related changes in brain structures.52 However, another strategy that has been used to address concerns about differences between a study population and the MNI template is to create a study-specific or “local” template.53,54 We created a local template by spatially normalizing each child’s image to MNI space by means of a 12-parameter affine implemented in a registration tool (FMRIB’s Linear Image Registration Tool).54 Spatially filtering the normalized images with a gaussian kernel (full-width half-maximum, 8 mm) and then averaging all of the images, ie, for both children with BPD and control children. Using this template, we then recalculated the spatial transformation for each participant by means of 12-parameter affine and nonlinear normalization (4×4×4-basis function medium regularization) as implemented in Statistical Parametric Mapping 99 (SPM99; Wellcome Department of Imaging Neuroscience, London, England).

A second concern regarding spatial normalization is whether spatial normalization procedures alter the total volume of gray or white matter in a brain image, potentially biasing measures of volume. Optimized VBM protocols include a volume preservation (“modulation”) step that restores prenormalization tissue volume by adjusting voxel-wise intensity (volume) values. During this step, a voxel’s intensity value is increased or decreased according to whether the surrounding region was compressed or expanded during normalization. For example, in the case of a brain region that is stretched during normalization, the intensity values for voxels within that region will be decreased, thereby preserving overall tissue volume. The converse is true for tissue that is compressed during normalization. Specifically, this involves calculating the determinant of the Jacobian matrix for the spatial transformation, thereby providing a compression map for the image—ie, a scaling factor for each voxel—as suggested by Ashburner and Friston.49 Total tissue volume is preserved by multiplying the partial volume estimate map by the corresponding compression map.

STATISTICAL ANALYSIS

Given the lack of neurormorphometry in childhood-onset BPD, we analyzed our results so as to balance both type I and type II error. We selected 5 a priori ROIs based on previous behavioral and neuroimaging research in children with BPD: amygdala, accumbens area, hippocampus, DLPFC, and orbitofrontal cortex.3,34-37 For each a priori ROI, we used individual masks generated by identifying the regions on the single subject template (in MNI space) provided by SPM99. Anatomic criteria for these ROIs are given in previous publications.55-60 For each partial volume estimate, statistical analyses for the comparison of patients with BPD vs healthy controls were carried out by means of the general linear model implemented in SPM99. As noted in the previous paragraph, the determinant of the Jacobian matrix for the spatial transformation was included to model the possible contributions of spatial normalization to group differences. All coordinates presented have been converted from MNI space to that of Talairach and Tournoux.61

We determined voxel-wise volume differences between patients with BPD and controls in the a priori ROIs. Given the
paucity of previous studies, our analyses were conducted at 2 levels. To correct for multiple comparisons, in our primary analysis, we assembled a global mask encompassing all of the ROIs. We report results only for those voxels that remained significant after the application of SPM99’s small-volume correction over this entire global mask.\textsuperscript{24} In a secondary, more liberal set of analyses, we used a small-volume correction for each individual ROI with no additional correction for the examination of multiple ROIs. This analysis, however, does correct for multiple voxel-based comparisons within each prespecified individual ROI. Both primary and secondary analyses covaried for global gray matter differences (analysis of covariance).

**RESULTS**

As indicated in the Table, the pediatric BPD and control samples were matched for age and sex and did not differ in IQ. In the BPD sample, the mean±SD age was 13.4±2.5 years (range, 8.6-17.5 years). For the control sample, the mean age was 13.3±2.3 years (range, 9.8-17.0 years). Both BPD and control samples were 35% male. There was no significant between-group difference in full-scale IQ (BPD group, 109±13.6; control group, 114±13.3; t\textsubscript{38} = 1.24, P = .22). Onset of BPD symptoms occurred at a mean age of 10.1±3.2 years. At the time of MR imaging, the pediatric BPD sample was on average euthymic (Young Mania Rating Scale—Parent, 7.6±6.3; Children’s Depression Rating Scale—Parent, 26.9±10.2; Multidimensional Anxiety Scale for Children, 34.9±13.2). Children with BPD were moderately functionally impaired (mean Children’s Global Assessment of Severity, 56.0±10.6). All but one were taking psychiatric medications at the time of the scan (mean number of psychotropic medications, 3.4±1.5).

In our primary analysis, the voxel-wise analysis using the general linear model (with analysis of covariance for global gray matter) identified a focus of volume reduction in the left DLPFC (x = −32, y = 42, z = 32; t = 4.32, Z = 4.52; P\textsubscript{corrected} = .04) that survived small-volume correction for all a priori ROIs merged (Figure). No significant between-group differences in volume were found in the voxel-wise analysis using this method in other regions, including the accumbens area, amygdala, hippocampus or orbitofrontal cortex bilaterally.

In our secondary analyses, while covarying for global gray matter, we identified significant volume reductions in 2 individual ROIs: the left amygdala (x = −24, y = 5, z = −15; t = 3.64, Z = 3.35; P\textsubscript{corrected} = .01) (Figure) and left accumbens area (x = −6, y = 9, z = −7; t = 3.96, Z = 3.59; P\textsubscript{corrected} = .004) (Figure). On a whole-brain map thresholded at the P < .05 uncorrected level, these 2 results are part of a larger, contiguous region of volume reduction in the infralimbic cortex. No other significant volume alterations were identified by small-volume correction for each a priori ROI individually.

**COMMENT**

Our current study used VBM, which avoids bias due to manual tracing, to examine neuroanatomic differences between children with narrow-phenotype BPD and controls. Our primary analysis, using correction for multiple comparisons, demonstrated that pediatric patients with BPD had significantly decreased gray matter volume in the left DLPFC. Our secondary analyses, using small-volume correction for each a priori ROI individu-

| Table. Demographic Information in Patients With BPD and Normal Control Sample |
|-------------------------------|----------------|----------------|
| Characteristic               | **BPD** (n = 20) | **Control** (n = 20) |
| Age, mean ± SD, y            | 13.4 ± 2.5      | 13.3 ± 2.3      |
| Age at BPD onset, mean ± SD, y | 10.1 ± 3.2      | NA              |
| Sex, No.                     | Male 13         | Male 13         |
|                              | Female 7        | Female 7        |
| Mood ratings, mean ± SD      | 109 ± 13.6      | 114 ± 13.3*     |
| YMRs-Child                   | 3.9 ± 5.9       | NA              |
| YMRs-Parent                  | 7.6 ± 6.3       | NA              |
| CDRS-Child                   | 22.3 ± 4.6      | NA              |
| CDRS-Parent                  | 26.9 ± 10.2     | NA              |
| MASC                         | 34.9 ± 13.2     | NA              |
| CGAS                         | 56.0 ± 10.6     | NA              |
| BPD type, No.                | I 15            | NA              |
|                              | II 5            | NA              |
| Mood ratings, mean ± SD      | NA†             | NA              |
| YMRS-Child                   | 7.6 ± 6.3       | NA              |
| YMRS-Parent                  | 26.9 ± 10.2     | NA              |
| CDRS-Child                   | 34.9 ± 13.2     | NA              |
| CDRS-Parent                  | 56.0 ± 10.6     | NA              |
| BPD type, No.                | I 15            | NA              |
|                              | II 5            | NA              |
| Mood ratings, mean ± SD      | NA†             | NA              |
| YMRS-Child                   | 3.9 ± 5.9       | NA              |
| YMRS-Parent                  | 7.6 ± 6.3       | NA              |
| CDRS-Child                   | 22.3 ± 4.6      | NA              |
| CDRS-Parent                  | 26.9 ± 10.2     | NA              |
| MASC                         | 34.9 ± 13.2     | NA              |
| CGAS                         | 56.0 ± 10.6     | NA              |
| BPD type, No.                | I 15            | NA              |
|                              | II 5            | NA              |
| Mood ratings, mean ± SD      | NA†             | NA              |

*Abbreviations: BPD, bipolar disorder; CDRS, Children’s Depression Rating Scale; CGAS, Children’s Global Assessment of Severity; MASC, Multidimensional Anxiety Scale for Children; NA, not applicable; SSRI, selective serotonin reuptake inhibitor; YMRS, Young Mania Rating Scale.‡ Controls had neither medical nor psychiatric illness. They were not taking medication regularly for medical or psychiatric reasons. Thus, mood ratings were not collected.† Medications at the time of magnetic resonance imaging include categories that are not mutually exclusive, ie, subjects may have been taking more than 1 psychiatric medication concurrently.
ally, disclosed volume reduction of the left amygdala and left accumbens area. Thus, our work provides evidence of prefrontal abnormalities in pediatric BPD, while suggesting that amygdala and accumbens abnormalities may also be present.

Volume reduction in Brodmann area 9, surviving correction for all the gray matter in the combined ROIs, is our primary finding. Previous research demonstrated that the DLPFC regulates emotion by directing attention away from the emotional context of stimuli. Moreover, Davidson suggested that circuitry encompassing the DLPFC and amygdala is involved in emotion regulation. Specifically, data suggest that the DLPFC exerts an inhibitory influence on regions, such as the amygdala, that are involved in the generation of negative emotional states.

Regarding the DLPFC’s role in the pathophysiology of BPD, other structural MR imaging studies document decreases in PFC gray matter volume in adults with BPD, and functional MR imaging studies in adults with BPD show reduced DLPFC activation, compared with controls, while attending to emotional faces.
tages in this regard. Of note, postmortem studies by Bau-
region in humans. Voxel-based morphometry, with its re-
reliably, and to some debate concern the boundaries of the
may be due to the difficulty of tracing such a small region
prefrontal abnormalities.3 This apparent inconsistency
highlights both the limited ability of behavioral tasks to
localize brain abnormalities and our improoundstanding of structure-function relationships in develop-
mentally psychopathologies. Obviously, further research
is needed to delineate the precise manner in which pre-
frontal dysfunction contributes to the pathophysiology
of BPD in both children and adults.

The accumbens area, a region integral to reward behav-
ior, showed some evidence of volume reduction in sub-
jects with BPD in our secondary analyses. This finding may
be relevant to behavioral data suggesting that children with
BPD and controls respond differently on a decision-
making task involving reward and punishment.5 Previous
animal research has shown that midbrain dopamine pro-
jections into areas including the accumbens are key to the
appetitive and desire aspects of reward behavior.70-73 Few
neuroimaging studies have evaluated functional or mor-
phometric changes in the accumbens area in subjects with
mood disorders, despite the fact that altered reward and
pleasure seeking are central to both mania and major de-
pressive disorder. The lack of such morphometric studies
may be due to the difficulty of tracing such a small region
reliably, and to some debate concern the boundaries of the
region in humans. Voxel-based morphometry, with its re-
liance on standard-space coordinates, may provide advan-
tages in this regard. Of note, postmortem studies by Bau-
mann et al4 demonstrate volume reduction of the left
accumbens area in adults with BPD. Given the centrality
of dysregulated reward behavior in BPD, additional re-
search regarding accumbens structure and function in pa-
tients with the illness is warranted.

Many neuroimaging studies using a variety of tech-
niques, including morphometric and functional MR im-
ageing as well as positron emission tomography, have
evaluated amygdala changes in BPD. However, the di-
rection of these changes (ie, increased or decreased size
or activation) is inconsistent in adults with BPD.14-17,19,34-73
Moreover, a recent study found no alteration in amyg-
dala volume in medicated adults with BPD.79 In older ad-
olescents with BPD, 2 studies using traditional hand-
traced morphometry have shown decreased amygdala
volume in comparison with control subjects.34,35 Now,
using optimized VBM in children and adolescents with
BPD, we have obtained evidence suggesting volume re-
duction of the left amygdala. Taken as a whole, these stud-
ies provide evidence of volume reduction in pediatric BPD.
Additional work is necessary to determine whether these
morphometric changes are associated with functional
amygdala abnormalities in pediatric BPD.

Of note, the left amygdala and accumbens peaks of vol-
ume reduction are contiguous within the infralimbic cor-
tex if whole-brain results are examined at the P < .05 level.

This contiguity highlights some of the strengths and limi-
tations of VBM, compared with hand-traced morphom-
etry. Hand-traced morphometry may be more definitive
than VBM in ascertaining between-group differences in
the volume of specific, well-defined structures, such as
the hippocampus or amygdala. Conversely, VBM may en-
able detection of more localized structural abnormali-
ties within these regions, and may demonstrate volume
alterations in areas that are difficult to hand trace, such
as the accumbens.80 Comparative studies of hand trac-
ing and VBM are needed, including the effect of sample
size on results from both methods, as only one such pub-
lished study exists.33

Interestingly, all of the significant abnormalities that we
observed in children with BPD were left sided. Consider-
able data examine the relationship between lateralized brain
dysfunction and psychopathology. This includes neuro-
psychological, electrophysiologic, and neuroimaging stud-
ies of patients with brain lesions or psychiatric illness.
Studies of brain-injured patients, for example, suggest that
left-sided damage may predispose to depression.81,85 How-
ever, other findings implicate right-hemisphere dysfunc-
tion in mania.82,86 In any case, virtually all of this research
examined adults. Since lateralization occurs relatively late
in development, these results obtained in studies of adults
may not be generalizable to children.87 Additional re-
search is needed to examine directly the role of lateralized
brain dysfunction in pediatric BPD.

Our study differs from previous MR imaging investi-
gations in pediatric BPD in a number of respects. First,
our study is unique with respect to BPD diagnosis and
subjects’ mood state. Specifically, all of our subjects met
diagnostic criteria more stringent than those of DSM-IV-
TR, in that they all met the “A” criterion of mania re-
quiring elevated, expansive mood, rather than irritable
mood. This is important given the nonspecificity of ir-
rritability in child psychiatric disorders.88 In contrast, 3
of the 4 other studies in pediatric BPD included patients
with a history of only irritable mania, and 1 of the 4 stud-
ies included subjects with BPD “not otherwise speci-
fied.”30 Moreover, our subjects were scanned while eu-
thyemic on average; patients in the other studies were in
manic-mixed,35,37 euthymic,36 or heterogeneous mood
states. Second, since all 4 previous morphometry stud-
ies evaluated older adolescents (up to age 21 years) and
1 study specifically excluded prepubertal subjects, our
study is the first, to our knowledge, to examine prepu-
bertal and young adolescent subjects with BPD.34-37 Third,
the only previous study of VBM in adolescents with BPD
included only 10 subjects.56 Our current findings high-
light the need for developmentally oriented imaging work
to evaluate both state- and trait-related morphometric dif-
fences in prepubertal children with BPD.

Our study was limited, in part, by the fact that 19 of
20 children with BPD were taking psychotropic medi-
cations at the time of MR imaging. This is not uncom-
mon given the ethical issues inherent in discontinuing
medication in children with severe psychiatric illnesses.
Further work is necessary to dissociate neuronal alter-
ations secondary to BPD and those resulting from phar-
macologic treatment.
In summary, our study is novel in its use of VBM to systematically examine MR images for structural brain alterations in children with narrow-phenotype BPD. In patients, we found volume reduction in the left DLPFC (Brodmann area 9), and evidence suggesting reductions in the amygdala and accumbens area. Further work might elucidate the association between these findings and the unique developmental aspects of pediatric BPD, such as high comorbidity with attention-deficit/hyperactivity disorder and frequent cycling. Additional study is also required to determine state-trait plasticity of these neural structures.

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