Subcortical Gray Matter Volume Abnormalities in Healthy Bipolar Offspring: Potential Neuroanatomical Risk Marker for Bipolar Disorder?

CECILE D. LADOUCEUR, Ph.D., JORGE R.C. ALMEIDA, M.D., BORIS BIRMAHER, M.D., DAVID A. AXELSON, M.D., SHARON NAU, M.Sc., CATHERINE KALAS, R.N., KELLY MONK, R.N., DAVID J. KUPFER, M.D., AND MARY L. PHILLIPS, M.D.

ABSTRACT

Objective: A growing number of structural neuroimaging studies have shown that bipolar disorder (BD) is associated with gray matter (GM) volume abnormalities in brain regions known to support affect regulation. The goal of this study was to examine whole-brain regional GM volume in healthy bipolar offspring (HBO) relative to age-matched controls to identify possible structural abnormalities that may be associated with risk for BD. Method: Participants were 20 youths (8-17 years old) with at least one parent diagnosed with BD, and 22 age-matched healthy individuals. All of them were free of Axis I diagnoses. High-resolution magnetic resonance imaging structural images were acquired using a 3-T Siemens scanner. Voxel-based morphometric analyses were conducted using SPM5. Results: Relative to controls, HBO had significantly increased GM volume in left parahippocampal/hippocampal gyrus (p < .05 corrected), following whole-brain analyses. This increase was correlated with puberty but not age in HBO. Region-of-interest analyses on the amygdala and orbitomedial prefrontal cortex did not yield any significant group differences after conducting small volume correction. Conclusions: The pattern of increased GM volume in parahippocampal/hippocampal gyrus in HBO suggests a potential marker for risk for BD. It can also be considered as a potential neuroprotective marker for the disorder because HBO were free of current psychopathology. Prospective studies examining the relationship between changes in GM volume in these regions and subsequent development of BD in HBO will allow us to elucidate further the role of this region in either conferring risk for or protecting against the development of BD. J. Am. Acad. Child Adolesc. Psychiatry, 2008;47(5):532–539. Key Words: risk, bipolar disorder, magnetic resonance imaging, voxel-based morphometry.
excellent research opportunity to study premorbid vulnerability neuroanatomical markers of BD. Furthermore, because this population is entirely free of psychopathology, it is possible to identify potential structural neuroanatomical alterations that may contribute to the protection against subsequent development of BD.

Neuroimaging studies in adult BD have documented a range of morphometric abnormalities in brain regions known to be involved in affect regulation such as prefrontal and anterior cingulate cortices, striatum, thalamus, and amygdala. However, a recent meta-analysis of regional morphometry in adult bipolar disorder suggests significant heterogeneity across studies for several of these brain structures, including the amygdala, left subgenual prefrontal cortex, and thalamus. For example, both increases and decreases in gray matter (GM) volume have been reported in the amygdala, striatum, anterior cingulate gyrus, and regions of the prefrontal cortex. Some studies have indicated amygdalar volume increases in adult individuals with BD type I (BD-I); other studies have found decreased volume and GM density in anterior cingulate and subgenual gyri and ventral prefrontal cortex, whereas others found no significant differences in prefrontal cortical volumes between patients with BD-I versus healthy controls. These inconsistencies may be due to variations in methodology, age at onset, presence of comorbid disorders, exposure to stress, or medication effects.

Few neuroimaging studies have examined volumetric changes in cortical and subcortical structures in pediatric BD. Most of these studies found a decreased GM volume. For instance, some studies reported decreased amygdalar and hippocampal volumes. Others have found decreased GM volume in orbital medial prefrontal cortex (OMPFC), left superior temporal gyrus, and dorsolateral prefrontal cortex in children and adolescents with BD. Some, however, have reported increased GM volume bilaterally in the basal ganglia, thalamus, and left temporal cortices. Findings from these studies suggest that abnormalities in distinct neural regions, most consistently GM volume reductions, within the amygdala, hippocampus, and OMPFC, may be implicated in the pathophysiology of pediatric BD.

In a recent review of MRI studies conducted in individuals genetically at-risk for BD (i.e., affected and unaffected family members, first-episode patients, and familial bipolar patients), Hajek et al. showed that abnormalities in GM volume represent potential candidate neuroanatomical risk factors for BD. These factors may involve GM volume abnormalities in the subgenual prefrontal cortex, striatum, amygdala, and hippocampus. With regard to research conducted in unaffected relatives of subjects with BD, one study found that genetic liability for BD was associated with GM deficits in the right anterior cingulate gyrus and ventral striatum, whereas another study did not find any differences in GM volume between unaffected relatives of BD patients and healthy controls. These contradictory findings may be attributed to the uncertainty of whether unaffected relatives of bipolar patients in such studies were free of other psychopathology (e.g., depression) at the time of the MRI scan. Moreover, it is difficult to ascertain to what extent differences in GM volume indeed represent neuroanatomical risk factors because neuroimaging studies conducted in individuals at genetic risk (particularly offspring of BD parents) often included those diagnosed with BD. Furthermore, studies that included healthy family members (e.g., discordant twin pairs, first-degree relatives) have been inconsistent in their exclusion criteria (e.g., some participants either met criteria for another Axis I diagnosis or had a history of major depressive disorder). To delineate neuroanatomical risk factors of BD, it is important to control not only for the presence of BD but also for other psychopathology, particularly mood disorders. One way to achieve this goal is to focus examination on offspring of parents with BD yet free of any psychopathology.

Examination of neuroanatomical abnormalities in such healthy bipolar offspring offer several advantages, including the possibility of identifying neuroanatomical abnormalities, potentially predating the onset of BD, that are not confounded by the presence of psychopathology or medication; identifying neuroanatomical abnormalities that may confer risk for, or are protective against, BD to ultimately inform evaluation of risk for subsequent development of BD and subsequent therapeutic intervention; and increasing understanding of the developmental course of BD.

We used voxel-based morphometry (VBM) to examine whole-brain GM volumetric MRI changes in a group of young healthy offspring of parents diagnosed with BD. VBM 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 operator bias that may be present in the more traditional MRI, region of interest–based analytical methods. VBM is particularly useful for the examination of neuroanatomical abnormalities in at-risk populations that may have structural abnormalities in distributed neural systems. Based on the most consistent findings from previous neuroimaging studies conducted in pediatric BD and unaffected relatives of adults with BD, we hypothesized that healthy bipolar offspring would have decreased GM volume in subcortical and prefrontal cortical neural regions involved in affect regulation, including the amygdala, hippocampus, and OMPFC. Because previous findings suggest that some neural regions change in GM volume as a function of age, whereas others change with puberty, we also wished, in exploratory analyses, to examine the relationship between age and pubertal development in neural regions in which GM volume abnormalities were observed in healthy offspring of parents with BD.

METHOD

Participants

Participants were between 8 and 17 years old (Table 1 for participant characteristics). Twenty-two healthy bipolar offspring (HBO) were recruited from an ongoing longitudinal study on the psychopathology and functioning of bipolar offspring conducted at Western Psychiatry Institute and Clinic, University of Pittsburgh (MH 060952-06, Principal Investigator: B.B.). The majority of the 22 healthy low-risk control participants (CONT) were also recruited from the above-described study. A small number were recruited from an ongoing longitudinal study on the neurobiology of pediatric affective disorders (MH 041712, Principal Investigator: N.R.). Participants in HBO and CONT groups were matched within 2 years of age. Data from two participants in the HBO group were not included in the analyses due to excessive noise related to movement. Thus, data from 20 HBO were included in the analyses.

Participants from the above studies were preselected based on specific inclusion criteria. Participants in the HBO group had one parent diagnosed with BD, type I or II. Participants in the CONT group had parents who were free of any Axis I psychiatric disorder. The Structural Clinical Interview for DSM-IV (SCID I and II) was used to ascertain lifetime psychopathology for both parents in each of the groups. The Schedule for Affective Disorders and Schizophrenia for School Age Children-Present and Lifetime Version (K-SADS-PL)26, which is a semi-structured clinical interview, was used to assess the presence of current and lifetime psychiatric disorder in the participants. The K-SADS-PL was conducted within 18 months before the scan by experienced clinical interviewers under the supervision of a child and adolescent psychiatrist; both were blind to the status of the participants. Participants and their parents were interviewed. To date, diagnostic reliability on the K-SADS-PL has been high (κ = .90). Final diagnoses were assigned by consensus using best-estimate procedures. All were free of current DSM-IV Axis I psychiatric diagnosis and history of BO or depression. Two participants in the HBO group had a history of an anxiety disorder; of these, one had a history of encopresis. In addition, all of the participants had an IQ >70, which was determined using WISC-III.27

Eligible participants were contacted and screened for physical or neurological problems and the presence of metal objects in their body. Participants who met these initial inclusion criteria were invited to participate in the study. After providing written informed consent to participate in the study, participants were screened on the day of the scan for current DSM-IV Axis I psychiatric diagnoses reported by parents, using the Stony Brook Symptom Inventory28 to ascertain that they had not developed any new psychiatric disorders since the initial assessment with the K-SADS-PL in their respective studies; presence of metal objects in their body; use of drugs and alcohol; and pregnancy.

Self-Report Measures

Pubertal status was established using the Pubertal Developmental Scale, which is an adolescent self-report scale that produces a continuous score of pubertal change ranging from 1 to 4.29 Socioeconomic status was measured with the Hollinghead Four-Factor Index.30 Handedness was determined using the Edinburgh Handedness Inventory.31

The University of Pittsburgh Institutional Review Board approved the study. After a detailed description of the study and before participation, parents gave written informed consent for their child’s participation in the study. Children gave written informed consent.

MRI Acquisition and Image Processing

Magnetic resonance structural brain images were acquired using a 3.0-T Siemens Allegra MRI scanner at the University of Pittsburgh and Carnegie Mellon’s Brain Imaging Research Center. Three dimensional sagittal high-resolution MPRAGE scans were acquired with the following scan parameters: duration: 6 minutes 7 seconds, TR: 2.48 milliseconds, TE: 1.630 milliseconds, TI: 800 milliseconds, flip angle: 8°, field of view: 200 mm, slice thickness: 0.8 mm, image matrix: 256 × 256, 208 slices. All of the acquisitions covered the entire brain.

### TABLE 1
Demographic Characteristics of Participants

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>HBO</th>
<th>CONT</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>20</td>
<td>22</td>
</tr>
<tr>
<td>Age, y, mean (SD)</td>
<td>13 (2.7)</td>
<td>14 (2.6)</td>
</tr>
<tr>
<td>Sex, male/female, no.</td>
<td>9/11</td>
<td>7/15</td>
</tr>
<tr>
<td>Pubertal scores, mean (SD)</td>
<td>2.7 (0.87)</td>
<td>2.9 (0.81)</td>
</tr>
<tr>
<td>Socioeconomic status, mean (SD)</td>
<td>45 (16.1)</td>
<td>45 (9.1)</td>
</tr>
<tr>
<td>Full Scale IQ, mean (SD)</td>
<td>114.1 (15.4)</td>
<td>114.6 (22.0)</td>
</tr>
<tr>
<td>Handedness, no. right-handed</td>
<td>16</td>
<td>19</td>
</tr>
</tbody>
</table>

*Note: Pubertal scores ranged from 1 to 4. There were no significant group differences for any of these variables. HBO = healthy bipolar offspring; CONT = low-risk control participants.*
Several VBM studies have used the so-called optimized VBM preprocessing.\(^2\) This preprocessing involves a two-step procedure: creation of a study-specific T1 template and tissue priors through segmentation and normalization of the data to the Montreal Neurological Institute (MNI) template using the MNI tissue priors, and resegmentation and nonlinear normalization of scans in native space using the customized GM template, thus optimizing the exclusion of nonbrain voxels after correcting for study-specific imaging protocol properties and anatomic features of the study populations. In the older versions of SPM, this procedure had a circularity problem because the tissue classification required an initial registration with tissue probability maps and the registration required an initial tissue classification. A unified segmentation model, combining both parameters in a single generative model\(^2\) has been introduced in SPM5. As such, with this model, it may not be necessary to perform the so-called optimized preprocessing.

Processing and VBM was performed with the SPM5 package (Wellcome Department of Imaging Neuroscience, London, http://www.fil.ion.ucl.ac.uk/spm), executed in Matlab (Mathworks, Sherborn, MA). The DICOM files were converted to NIFTI-1 (http://nifti.nimh.nih.gov) format. The converted files were then segmented into gray and white matter and normalized using the unified model cited above. Voxel values were modulated by the Jacobian determinants derived from the spatial normalization, thus allowing brain structures that had their volumes decreased after spatial normalization to have their total counts decreased by an amount proportional to the degree of volume discounted. The final voxel resolution after normalization was 2 × 2 × 2 mm. Finally, images were smoothed with a 12-mm gaussian kernel.

**Statistical Analysis**

Between-group statistical comparisons of mean GM volumes were performed with the general linear model based on random field theory. Only voxels with values above an absolute GM threshold of 0.05 entered the analyses, resulting in a search volume of approximately 264,023 voxels. Total whole-brain GM volume, age, and puberty scores were entered as covariates. The latter two were entered because of their known or probable impact on the developing brain. Resulting statistics at each voxel were transformed to Z scores and displayed in a glass brain into standard MNI space at a threshold of Z = 3.32 and an extent threshold of 15 voxels. Statistical significance was set at p < .001, uncorrected for multiple comparisons. Small volume correction was then performed for a priori regions emerging from whole-brain analyses (statistical level, p < .05). Family-wise error (FWE) correction was used to correct for multiple comparisons in non–a priori regions emerging from whole-brain analyses (statistical level, p < .05). For analyses on a priori regions not emerging from whole-brain analyses, region-of-interest analyses were performed on regions defined using automatic anatomic templates derived from the toolbox WFUPickatlas (p < .05, corrected for multiple comparisons using FWE).

To investigate whether observed between-group differences in GM volume were related to age and puberty, we computed Pearson correlation coefficients between these variables and mean proportional GM volume intensity values for significant clusters from all of the between-group analyses in HBO and CONT separately. Statistical thresholds were modified to control for multiple correlations using Bonferroni corrections.

**RESULTS**

**Participant Characteristics**

The two groups did not significantly differ with regard to age (t = −1.25, df = 40; p = .22), pubertal status (t = −0.58, df = 40; p = .57), IQ (t = −0.85, df = 32; p = .93), sex distribution (χ² = 0.77, df = 1,42; p = .38), and socioeconomic status (t = 0.34, df = 34; p = .74).

**VBM**

Both whole-brain contrasts (HBO > CONT and CONT > HBO) yielded significant results at p < .001, uncorrected. HBO had increased GM volume in the left parahippocampal gyrus, extending into the left hippocampus (t = 3.93, Z = 3.57, p < .001: x = −20, y = −18, z = −32, uncorrected). This finding remained significant after small volume correction (t = 3.76, p < .05, Cohen’s d = 1.24; Fig. 1). This finding was also significant without covarying for age and puberty (t = 3.45, p < .001, uncorrected). Furthermore, HBO had decreased GM volume compared to CONT in the right middle frontal gyrus, left middle temporal gyrus, and right caudate nucleus (t = 4.53, p < .001: x = 34, y = 14, z = 40; t = 3.71, p < .001: x = −34, y = −56, z = 30; t = 3.64, p < .001: x = 18, y = 4, z = 30, uncorrected), but these did not survive FWE.

To examine whether there were any differences in GM volume between HBO and CONT in other a priori regions (i.e., amygdala and OMPFC), we conducted separate analyses using WFUPickatlas-defined regions of interest. Results indicated a trend whereby HBO had increased GM volume bilaterally in the amygdala (mean and SD: HBO: right, 0.54 [0.04]; left, 0.56 [0.04]; CONT: right, 0.52 [0.05]; left: 0.53 [0.06]; t = 2.02, p = .025: x = −20, y = −8, z = −16) and the rectal gyrus region of the OMPFC (HBO: right: 0.46 [0.03]; left: 0.45 [0.03]; CONT: right: 0.42 [0.06]; left: 0.42 [0.06]; t = 2.16, p = .018: x = 10, y = 38, z = −22), but these findings did not survive FWE.

**Correlation With Age and Puberty**

Mean GM volume intensity (corrected with small volume correction) in the left parahippocampus/hippocampus significantly positively correlated with pubertal maturation scores in HBO (r = 0.55, p < .05) but not CONT (r = 0.13, p > .05), suggesting that the between-group difference in left parahippocampal/hippocampal
GM volume was more prominent in later stages of puberty. There was no significant correlation between left parahippocampal/hippocampal GM volume with age in either group (HBO: \(r = 0.42, p > .05\); CONT: \(r = 0.06, p > .05\)).

**DISCUSSION**

To our knowledge, this is the first study to report differences in GM volume in young healthy offspring at genetic risk for BD (HBO). The main findings from this study were that compared to age-matched healthy low-risk controls (CONT), HBO had increased, not decreased, GM volume in the left parahippocampus/hippocampus. The increased GM volume in HBO significantly positively correlated with pubertal maturation scores but not age. There were additional increases in GM volume in HBO in other a priori regions, including the amygdala and OMPFC, but these did not survive after controlling for multiple comparisons. Similarly, although HBO showed decreased GM volume relative to CONT in middle frontal and temporal gyrus and caudate nucleus, these too did not survive after controlling for multiple comparisons.

Our findings of increased parahippocampal/hippocampal GM volume in HBO are in sharp contrast to findings from MRI studies in adult and pediatric BD. Although some studies have found hippocampal differences between adult BD patients relative to healthy controls,\(^3^4\) most studies typically have not found any significant differences in parahippocampal or hippocampal GM volume.\(^3^5\) Decreases in hippocampal GM volume have been reported in adolescent BD,\(^1^2,1^3\) suggesting the involvement of the hippocampus in the pathophysiology of adolescent BD that may represent a particular characteristic of early-onset BD. Our findings are congruent, however, with previous data from studies in adults at risk for BD; a study that compared adult monozygotic twins discordant for BD found a smaller right hippocampus in the twin with BD relative to the twin without BD.\(^3^6\)

The finding of increased GM volume in the parahippocampus/hippocampus in HBO is particularly interesting because of the potential role of these regions in the regulation of stress and emotional responses. The hippocampus has been implicated in inhibition of the stress response via inhibitory connections with many of the subcortical structures involved in this response.\(^3^7\) As part of the limbic system, the parahippocampal gyrus has multiple direct connections with the hippocampus and amygdala,\(^3^8\) and it has been suggested that a dynamic relationship between the amygdala and parahippocampal gyrus may confer a protective effect against potentially harmful experiences.\(^3^9\) Previous findings indeed indicate that individuals with parahippocampal gyral, but not amygdalar, resections show abnormal

---

**Fig. 1** Anatomical localization of increased gray matter (GM) volume following whole-brain voxel-based morphometry analyses in healthy bipolar offspring (HBO) \((n = 20)\) compared to control participants \((n = 22)\). Color scale represents \(T\) scores, increasing from red to white. MNI coordinates. A, Left parahippocampal/hippocampal gyrus. Cluster size: 124 voxels, \(t = 3.93, Z = 3.57, p_{\text{uncorrected}} < .001 (x = -20, y = -18, z = -32)\); small volume correction: \(p < .05\). B, Box plot of GM volume intensity (with SD) in the region of increased GM volume for the HBO and control groups.
Our findings in HBO allow a recent study reported on examining behavioral or neural systems. Thus, examining behavior or neural systems in the normal appraisal of emotional information, which may become dysfunctional in adult BD.

Although it is possible that the pattern of increased GM volume in the left parahippocampus/hippocampus in HBO represents a potential neuroanatomical risk marker for BD, this interpretation is problematic given that decreased rather than increased GM volume in the hippocampus has been reported in youths with BD. Moreover, it is unlikely that sudden morphological changes occur specifically with BD onset. Elucidating the role of this region in the subsequent development of BD in genetically at-risk pediatric populations can be addressed only by longitudinal studies examining subcortical development before and after the onset of the disorder.

Another interpretation of the observed GM increase in HBO is that it may have a potential role in protecting against or delaying subsequent development of BD, given that HBO in our study were completely free of any Axis I disorder. Pediatric or adult BD onset is often preceded and/or accompanied by other psychiatric disorders such as disruptive behavior disorders or anxiety disorders. It is therefore possible that the HBO in our sample represent a potentially emotionally resilient group despite being at risk for BD. The pattern of increased rather than decreased GM volume observed in our HBO group may be interpreted as being associated with successful affect regulation that acts as a compensatory mechanism against the development of mood or anxiety disorders or because of being exposed repeatedly to situations (e.g., family conflict) that require these bipolar offspring to regulate their affect. The latter interpretation would be consistent with recent evidence demonstrating that cognitive activity itself can alter brain morphology in certain relevant brain structures. Thus, examining behavior or neural systems associated with affect regulation in these bipolar offspring would allow us to begin addressing this question.

The significant positive correlation between left parahippocampal/hippocampal GM volume and pubertal maturation in HBO, but not CONT, may be further support of the protective role of this GM volume increase in HBO. Although there is no evidence directly linking BD with puberty onset, large-scale studies examining BD age at onset (e.g., STEP-BD) report a high frequency of first episodes occurring between 13 and 18 years (i.e., during puberty). If structural neural abnormalities reported in youths with BD are potential mediators for the development of BD, then it is plausible that the increased parahippocampal/hippocampal GM volume associated with pubertal maturation in HBO could play a neuroprotective role by providing additional neural resources in affect regulation. Furthermore, this increase in parahippocampal/hippocampal GM volume could not be attributed to an effect of age because there was no significant correlation between parahippocampal/hippocampal GM volume and age in either HBO or CONT.

The interpretation that this parahippocampal/hippocampal GM volume increase in HBO plays a neuroprotective role remains speculative until longitudinal follow-up studies are conducted to determine who will go on to develop BD. Moreover, future studies examining regional neural activity during emotional information processing or affect regulation tasks in HBO without Axis I disorder will allow us to examine the extent to which abnormal patterns of parahippocampal/hippocampal activity during these tasks may accompany the increase in GM volume in these regions in HBO.

Our findings of increased GM volume in the parahippocampus/hippocampus are in contrast with some MRI studies conducted in individuals who are at high risk for BD. However, it is important to note that most of these studies included healthy control participants who, although not meeting criteria for BD, either had a history of mood disorder or met criteria for other psychiatric disorders. Our findings in HBO allow us to address questions not only regarding the nature of neuroanatomical abnormalities that may confer risk for BD but also how such abnormalities may protect against the development of BD. They also provide a neuroanatomical focus for future study of the neurodevelopmental trajectory of BD in youths at genetic risk for BD.

The left-sided localization of the parahippocampal/hippocampal GM volume increase in HBO is additionally interesting. The left more than the right hemisphere has been linked with positive emotion processing. However, the interpretation that this pattern of increased parahippocampal/hippocampal GM volume in HBO is associated with affect regulation in these bipolar offspring would allow us to begin addressing this question.
increased left amygdalar activity to positive emotional stimuli. However, our findings are inconsistent with the reported decreased GM volume in bilateral hippocampus in adolescent BD. Nevertheless, these findings suggest that it is possible that increased left-sided parahippocampal/hippocampal GM volume in HBO may, in particular, protect against abnormal positive emotion processing that may be associated with the development of BD.

One important point that merits discussion is with regard to the potential limitation of the VBM technique. First, given that the computation of VBM statistical parametric map requires several thousands of independent statistical comparisons, the likelihood of type I error is increased. As such, it is important to include appropriate corrections to protect against type I error to ensure that results reflect statistically significant differences. The recommended approach to control for type I error in VBM is to include voxel-wise corrections such as the FWE correction, which we used in this study. However, these corrections are rather conservative, thereby potentially increasing type II error. The latter point is particularly relevant given our sample size. One way to circumvent this potential limitation could have been to conduct analyses on hand-traced data. However, such an approach encompasses its own set of limitations. For instance, hand tracing is subjective to tracer position of anatomical landmarks and is restricted to predefined regions of interest, at the expense of detecting differences observed in whole-brain analyses. In this regard, hand tracing encompasses its own source of error, particularly given the level of accuracy, reliability, and training of the research staff. A methodological strength of VBM in this regard is that VBM enables researchers to conduct whole-brain analyses and is sensitive to systematic differences in GM volume. Furthermore, by using automated anatomical templates, it is possible to replicate findings in a different sample or to investigate the same regions in different populations or research centers.

In addition, the findings from the present study are limited by certain factors, including the relatively small sample size, although such sample sizes do provide adequate power to detect medium to large effect sizes. The stringent criteria we used in recruiting our sample, namely, the absence of any Axis I disorder, necessarily limited the number of participants in the present study and the ability to match on sex or exclude the few offspring with a parent with BD-II. Another limitation is related to the cross-sectional design, which prevented examination of neurodevelopmental trajectories underlying BD. The next stage, therefore, is to follow HBO participants in the present study to allow examination of the extent to which increased GM volume in the parahippocampus/hippocampus may be associated with the subsequent development of BD or another mood disorder.

In summary, findings from this study using VBM analyses are the first to show increased GM volume in the parahippocampus/hippocampus in healthy offspring at genetic risk for BD. Prospective studies examining the relationship between alterations in these regions and subsequent development of BD in these healthy offspring will allow us to increase our understanding of the role of this and other regions in either conferring risk for or protecting against the development of BD.

Disclosure: Dr. Birmaher has participated in forums sponsored by Solvay Pharmaceuticals and Abcomm, Inc., and has received royalties from Random House. Dr. Kupfer has served on the advisory boards of Eli Lilly, Forest, Pfizer, and Solvay-Wyeth, and has been a consultant to Servier Amerique. The other authors report no conflicts of interest.

REFERENCES


30. Hollingshead AB. *Four Factor Index of Social Status*. New Haven, CT: Yale University Department of Sociology; 1975.


