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ORIGINAL ARTICLE

Cortical morphology changes in women with borderline personality disorder: a multimodal approach

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Objective: Borderline personality disorder (BPD) is a devastating condition that causes intense disruption of patients' lives and relationships. Proper understanding of BPD neurobiology could help provide the basis for earlier and effective interventions. As neuroimaging studies of patients with BPD are still scarce, volumetric and geometric features of the cortical structure were assessed to ascertain whether structural cortical alterations are present in BPD patients.
Methods: Twenty-five female outpatients with BPD underwent psychiatric evaluation (SCID-I and II) and a 1.5 T magnetic resonance imaging (MRI) brain scan. The control group comprised 25 healthy age-matched females. Images were processed with the FreeSurfer package, which allows analysis of cortical morphology with more detailed descriptions of volumetric and geometric features of cortical structure.
Results: Compared with controls, BPD patients exhibited significant cortical abnormalities in the fronto-limbic and paralimbic regions of both hemispheres.
Conclusion: Significant morphologic abnormalities were observed in patients with BPD on comparison with a healthy control group through a multimodal approach. This study highlights the involvement of regions associated with mood regulation, impulsivity, and social behavior in BPD patients and presents a new approach for further investigation through a method of structural analysis based on distinct and simultaneous volumetric and geometric parameters.

Keywords: Magnetic resonance imaging; neuroimaging; borderline personality disorder; mental disorders

Introduction

Borderline personality disorder (BPD) is a devastating condition that affects 1 to 2% of the population and causes intense disruption of patients' lives and relationships.[1,2] Emotional and behavioral dyscontrol, as well as affective dysregulation, play a large role in this severe morbidity, and BPD is associated with high rates of suicidality.[1,2] Patients with BPD often exhibit impulsive behaviors (self-mutilation, substance abuse, sexual promiscuity, and binge eating), rapid mood changes, and a propensity toward intense negative emotional states, such as anger, anxiety, and dysphoria.[3,4]

Structural magnetic resonance imaging (MRI) studies have demonstrated volume reduction of cerebral regions associated with affective regulation, such as the hippocampus, amygdala, and anterior cingulate cortex (ACC), which probably constitute part of the neural substrate of BPD symptomatology and would serve as putative endophenotypes for this illness.[4-9] Moreover, a fronto-limbic model of affective dysregulation that also involves prefrontal and frontobasal brain structures has been investigated in this population through functional neuroimaging studies.[2-4,10]

To date, most structural neuroimaging studies performed in BPD have utilized techniques based on voxel-based morphometry (VBM), which combines several geometric parameters including thickness, surface area, and folding. As a consequence, VBM-based findings cannot be attributed to a single biologically meaningful process.[11-13] In addition, the literature has reported that approaches based on cortical thickness seem to be more sensitive than VBM for identification of regional gray matter changes.[14] The routines implemented in FreeSurfer, an automated cortical surface reconstruction method, provide a technique that uses MRI intensity contrasts to obtain accurate volumetric and geometric parameters that have been reliably used to investigate several psychiatric and neurological disorders.[14-17] In addition, accurate methods for measuring cerebral cortical thickness offer a powerful tool for understanding

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the neurobiological basis of a variety of brain disorders.[11,14-17]

Based on the foregoing and on prior neuroimaging studies of BPD, the present study used a multimodal approach based on the FreeSurfer image analysis suite to conduct a more detailed investigation into structural cortical abnormalities in patients with BPD. We aimed to demonstrate that the neuroanatomical alterations in BPD patients comprise multiple cortical features when compared with controls. In addition, we hypothesized that differences in geometric and volumetric parameters would be present in regions associated with BPD, particularly the hippocampus, amygdala, ACC, and prefrontal and frontobasal areas.

Methods

Participants

Patients were recruited from the outpatient clinic of a tertiary referral center (Department of Psychiatry, Universidade Federal de São Paulo, São Paulo, Brazil), and all were receiving psychiatric and psychotherapeutic care at the time of the study. After Ethics Committee approval, the advantages and risks of participation were explained to the patients and informed consent was obtained. The inclusion criteria for the patient group were a current psychiatric diagnosis of BPD and having been treated at the study unit for at least 6 months. Although almost all patients enrolled had a past history of other psychiatric disorders, patients who met current criteria for any axis I or II psychiatric diagnoses besides BPD were excluded.

Psychiatric evaluation

Clinical and socio-demographic data including age, gender, educational attainment, family psychiatric history, and previous psychiatric treatment (including hospitalizations and pharmacotherapy) were collected by means of a questionnaire administered before imaging. The psychiatric evaluation was performed by the same psychiatrist (GMAF) through two structured instruments: the Structured Clinical Interview for DSM-IV Axis I Disorders and its Axis II counterpart (SCID-I and SCID-II respectively).[18,19]

Procedures

MRI scans of 25 female patients that fulfilled diagnostic criteria for BPD at the time of the study were compared to those of controls. The control group consisted of 25 age- and gender-matched healthy volunteers who were also evaluated by the same psychiatrist (GMAF) using the same instruments (SCID-I and SCID-II).[18,19] None of the controls had used antihistamines, alcohol, or other drugs in the 72 hours preceding psychiatric evaluation.

MRI data acquisition

All subjects underwent MRI examination of the brain using a 1.5 T MRI scanner (MAGNETOM Sonata[Maestro Class], Siemens AG, Medical Solutions, Erlangen, Germany) with an eight-channel head coil. Two conventional sequences were performed to rule out structural lesions: a) Axial T2-weighted FLAIR (fluid-attenuated inversion recovery) in a plane parallel to the anterior commissure-posterior commissure (AC-PC) line (TR [repetition time] 8500 ms, TE [echo time] 107 ms, IT [inversion time] 2500 ms, slice thickness 5.0 mm, slice interval 1.5 mm, FOV [field of view] 240 mm, matrix size 256 x 256, NEX [number of excitations]) 1); b) Sagittal T1-weighted gradient-echo volume acquisition for multiplanar reconstruction (TR 2000 ms, TE 3.42 ms, flip angle 15 degrees, FOV 245 mm, 1.0-mm slice thickness with no gaps for a total of 160 slices per slab, matrix size 256 x 256, NEX 1). All patients and controls included in the study had normal images on visual inspection. Scans displaying low image quality or clinical abnormalities were excluded.

Multimodal analysis

The T1-weighted structural MR images were preprocessed using the recon-all pipeline of the FreeSurfer package with standard parameters. This pipeline is documented in detail and freely available at the FreeSurfer website (http://surfer.nmr.mgh.harvard.edu). Further information can be found in the cited literature.[14-17] Five morphometric quantitative measures of the cortex were compared between the study and control groups: average convexity or concavity, mean radial curvature, metric distortion, cortical thickness, and surface area. Further details about these measures can be found in Ecker et al.[12]

Statistics

Clinical and demographic data were presented as mean $\pm$ standard deviation. Age and handedness matching between patients and controls was evaluated using the *t*-test for two independent samples and chi-square test respectively. The statistical significance level was set at 5%. The QDEC graphical interface of FreeSurfer was used to model and test the parameters of a general linear model (GLM) at each vertex across the cortical surface. In this model, we considered the cortical thickness and/or surface area as the response variable, group (BPD or control) as a fixed factor, and age as a nuisance variable. Results were corrected for multiple comparisons using the false discovery rate (pFDR $<$ 0.05). Subcortical structure (i.e., amygdala and hippocampus) volumes were extracted from FreeSurfer output and analyzed using SPSS version 14.0.

Results

Demographic data and global brain measurements

Data from 25 female BPD patients and 25 female controls were included. Groups were matched by gender ($p > 0.99$), age ($p = 0.82$), handedness ($p = 0.79$), and years of schooling ($p = 0.12$). Among BPD patients, the mean duration of the disorder was 16.6$\pm$9.5 years. Regarding

the number and type of psychotropic medications used, all BPD patients were taking at least one medication (antidepressant, mood stabilizer, or antipsychotic) at the time of the study. Twenty-four were taking a mood stabilizer, while 18 were taking antidepressants and 10 were using antipsychotics. At the time of psychiatric evaluation, six patients were on monotherapy, while 13 were taking two psychotropic medications and six patients were taking three psychotropic medications. Demographic data and global brain measurements of patients and controls are shown in Table 1.

FreeSurfer analysis

The segmented left and right hemispheres of both groups were compared through the geometric and morphometric parameters (thickness, volume, area/pial area, depth of sulcus, curvature, and metric distortion) available in the FreeSurfer package. As compared with controls, BPD patients exhibited significant alterations of those parameters in the limbic and paralimbic regions, among others, of both hemispheres. The main findings of multimodal analysis that are significant under a corrected threshold of pFDR = 0.05 are shown in Table 2 and in Figures 1 and 2. No structural differences were observed between groups taking a different number of medications.

Discussion

The aim of this study was to conduct an exploratory investigation of structural fronto-limbic abnormalities, particularly in the hippocampus, amygdala, ACC, and prefrontal and frontobasal structures, in a group of 25 female patients with BPD. Toward this end, we used the FreeSurfer image analysis suite, an innovative method that can contribute to this area of research by offering different and simultaneous volumetric and geometric parameters.

Cortical morphology is of great interest in both normal development and in a wide variety of neurodegenerative and neuropsychiatric disorders. However, manual methods for estimating cortical thickness from neuroimaging data are labor-intensive, requiring several days' effort by a trained anatomist. Furthermore, the highly folded nature of the cortex is problematic for manual techniques, frequently resulting in measurement errors in regions in which the cortical surface is not perpendicular to any of the cardinal axes.[11,14-17] On the other hand, the automated alternative methods available based on voxel morphometry (such as VBM) perform only indirect analyses of gray matter concentration and volume, producing an unspecific mixture of geometric parameters including thickness, surface area, and folding.[14-17] As a consequence, VBM-based findings cannot be attributed to a single biologically meaningful process, thus precluding insights regarding important pathophysiological aspects associated with various neuropsychiatric disorders.[11-13] Since evidence suggests that alterations in cortical thickness and surface (pial) area reflect different neurobiological processes and are associated with different genetic mechanisms, approaches based on cortical morphology could contribute to our understanding of the underpinnings of a number of neurodegenerative and psychiatric disorders.[11,14-17] Moreover, studies have noted that such approaches seem to be more sensitive than VBM for identification of regional gray matter changes.[17]

Studies have highlighted that cortical thickness is likely to reflect dendritic arborization or changing myelination at the gray-white matter interface.[20-22] On the other hand, surface area is influenced by the division of progenitor cells in the embryological periventricular area, and is associated with the number of minicolumns.[11-13,20] Finally, geometric differences (depth of sulcus, curvature, and metric distortion) are predominantly linked with the development of neuronal connections and cortical pattern of connectivity, and are thus a marker for cerebral development.[21,22] Therefore, it is likely that the maps produced by approaches based on cortical morphology reflect multiple genetic and/or neurobiological etiologies, which need further investigation.[20-22]

Evidence suggests that the components of the fronto-limbic network, such as the ACC, orbitofrontal cortex (OFC), dorsolateral prefrontal cortex, and amygdala-hippocampus complex, are potentially involved in BPD pathophysiology; these structures have been investigated in previous region-of-interest- and VBM-based studies.[4-6,23] In addition, there is mounting evidence that patients with BPD exhibit deficits in structure and function of the ACC, OFC, and amygdala-hippocampus complex.[4-6,23] Structural neuroimaging studies have already suggested the presence of neuroanatomical

Table 1 Demographic data and global brain measurements* of patients with borderline personality disorder and a control group (data are presented as means ± standard deviation, unless otherwise specified)

Demographic data	BPD	Control group	p-value
Number of subjects, n	25	25	-
Age (years)	32.7±9.1	32.2±7.1	0.82
Female gender, n (%)	25 (100%)	25 (100%)	-
Right-handed subjects, n (%)	21 (84)	20 (80)	0.79
Years of schooling	9.2±6.3	12.8±5.1	0.12
Intracranial volume	1,455.87±107.29	1,463.86±115.00	0.74
Total brain volume	1,300.50±105.15	1,304.61±112.23	0.51
Cortical gray matter volume	463.63±44.09	470.18±39.87	0.68
White matter volume	229.85±27.26	252.38±18.34	0.71

BPD = borderline personality disorder; SD = standard deviation.
* Brain measurements are provided in mm^3.

Table 2 Main findings of a multimodal analysis of patients with borderline personality disorder compared with a healthy control group. Differences between regions in each parameter (*t* statistic) are presented in parentheses.

Morphometric/geometric parameters	Left hemisphere		Right hemisphere	
	BPD < HC (*t* statistic)	BPD > HC (*t* statistic)	BPD < HC (*t* statistic)	BPD > HC (*t* statistic)
Thickness*	Lateral OFC (2.50)† Middle temporal gyrus (2.39) Precuneus (1.79) Insula (1.73) Fusiform gyrus (1.43) Supramarginal gyrus (1.39)	Superior parietal gyrus (2.79)† Superior frontal gyrus (2.78) Inferior parietal gyrus (1.32) Anterior cingulate (1.39) Posterior cingulate (1.31)	Middle frontal gyrus (2.66)† Superior temporal gyrus (2.28) Superior frontal gyrus (2.13) Inferior temporal gyrus (1.85) Precentral gyrus (1.74) Supramarginal gyrus (1.68) Superior parietal gyrus (1.60) Middle temporal gyrus (1.59) Lateral OFC (1.58) Inferior parietal gyrus (1.50) Precuneus (1.49) Medial OFC (1.42)	Postcentral gyrus (2.11)† Parahippocampal gyrus (1.58) Anterior cingulate (1.34)
Area/pial area*	Medial OFC (2.67)† Lingual gyrus (2.51) Insula (2.11) Precuneus (1.98) Posterior cingulate (1.91)	Superior frontal gyrus (2.57)† Superior temporal gyrus (2.44) Inferior temporal gyrus (2.22) Fusiform gyrus (2.07) Paracentral gyrus (1.71)	Insula (3.25)† Lateral OFC (3.19) Supramarginal gyrus (2.98) Lateral occipital gyrus (2.42) Superior temporal gyrus (2.34) Paracentral gyrus (1.74) Medial OFC (1.68) Inferior temporal gyrus (1.66) Superior parietal gyrus (1.46)	Inferior parietal gyrus (3.87)† Middle frontal gyrus (2.78) Postcentral gyrus (2.48) Precuneus (2.03) Fusiform gyrus (1.54)
Depth of sulcus*	Postcentral gyrus (1.97)† Middle temporal gyrus (1.89) Superior temporal gyrus (1.81) Insula (1.80) Anterior cingulate (1.49) Inferior Parietal gyrus (1.44)	Fusiform gyrus (1.53)†	Insula (2.78)† Superior parietal gyrus (2.04) Inferior temporal gyrus (2.00) Middle temporal gyrus (1.60) Postcentral gyrus (1.46)	Middle frontal gyrus (4.25)† Precentral gyrus (1.99) Parahippocampal gyrus (1.73) Precuneus (1.45)
Curvature*	Superior temporal gyrus (4.11)† Lateral OFC (3.58) Precentral gyrus (2.69) Middle temporal gyrus (2.66) Entorhinal cortex (2.39) Lingual gyrus (2.05) Medial OFC (1.39)	Middle frontal gyrus (3.43)† Superior frontal gyrus (2.30) Parahippocampal gyrus (1.80) Posterior cingulate (1.46)	Inferior parietal gyrus (1.97)† Lingual gyrus (1.83) Fusiform gyrus (1.56) Postcentral lobule (1.46) Medial OFC (1.37) Cuneus (1.33)	Precentral gyrus (3.79)† Middle frontal gyrus (3.38) Anterior cingulate (2.82) Middle temporal gyrus (2.60) Parahippocampal gyrus (1.73) Entorhinal cortex (3.10) Postcentral gyrus (1.46) Precuneus (1.45)
Metric distortion (Jacobian)*	Superior temporal gyrus (2.72)† Superior frontal gyrus (2.05) Paracentral lobule (1.92) Postcentral gyrus (1.89)	Middle frontal gyrus (3.02)† Lingual gyrus (2.32) Parahippocampal gyrus (2.04) Precentral gyrus (1.86) Inferior temporal gyrus (1.76) Entorhinal cortex (1.33)	Entorhinal cortex (2.30)† Insula (2.21) Parahippocampal gyrus (2.00) Posterior cingulate (1.99) Precuneus (1.58) Lateral occipital gyrus (1.50) Medial OFC (1.37)	Postcentral gyrus (3.30)† Superior temporal gyrus (3.07) Middle temporal gyrus (1.65) Precentral gyrus (1.50) Paracentral lobule (1.43) Fusiform gyrus (1.32)

BPD = borderline personality disorder; HC = healthy controls; OFC = orbitofrontal cortex.
* Data were corrected through pFDR = 0.05.
† Regions of maximum difference.

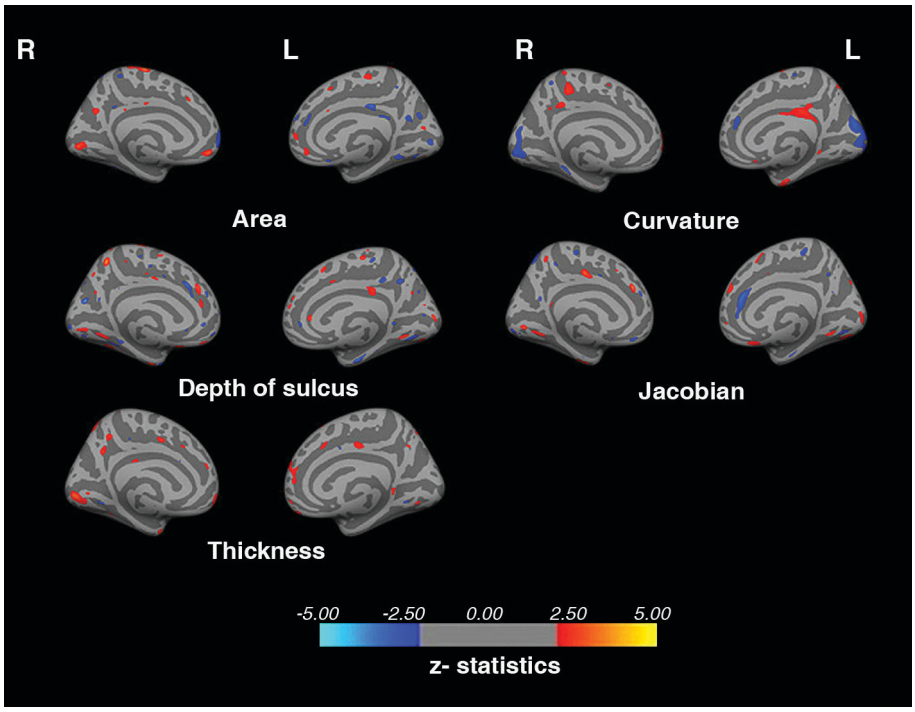

Figure 1 Multimodal cortical features (area, deformation/Jacobian, curvature, depth of sulcus, and thickness) comparisons between BPD and controls represented in an inflated brain surface (medial vision). Red/yellow colors represent reduced regions in BPD and blue/purple colors represent increased regions in BPD. Values were corrected through FDR = 0.05 for display. BPD = borderline personality disorder; FDR = false discovery rate.

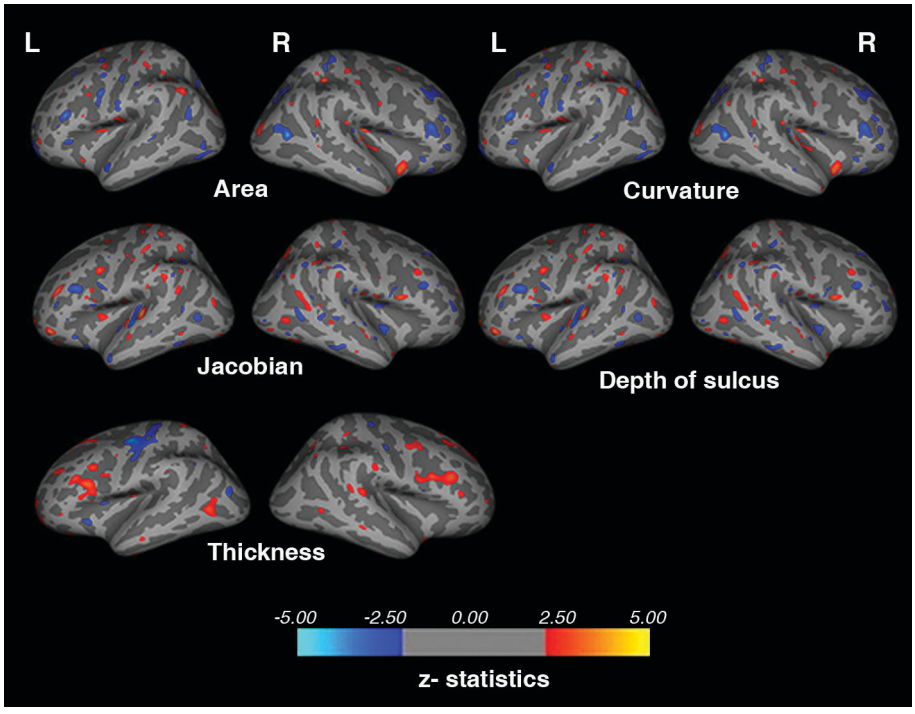

Figure 2 Multimodal cortical features (area, deformation/Jacobian, curvature, depth of sulcus, and thickness) comparisons between BPD and controls represented in an inflated brain surface (lateral vision). Red/yellow colors represent reduced regions in BPD and blue/purple colors represent increased regions in BPD. Values were corrected through FDR = 0.05 for display. BPD = borderline personality disorder; FDR = false discovery rate.

abnormalities of limbic structures in both the right and left hemispheres in BPD patients.[7,8,24-27] As these areas are associated with affective regulation, such reductions might be biological substrates of BPD symptomatology.[5,6,25-27] The present study revealed significant morphological abnormalities of cortical thickness, volume, mean curvature, metric distortion, surface area, and depth of sulcus in such areas among BPD patients. These findings are in agreement with previous structural neuroimaging studies involving BPD patients, and highlight the involvement of these areas in the regulation of mood reactivity, impulsivity, and social behavior, which are considered dysfunctional in these patients.[2-6]

Furthermore, studies have also observed structural alterations of the superior (precuneus and postcentral gyrus) and inferior parietal cortices in BPD patients, suggesting a possible role of parietal structures in dissociative symptoms and identity disturbance in women with BPD.[28-30] In addition, other studies have found dysfunctions of structural connectivity involving parietal and temporal areas in female BPD patients.[5,30] Given the role of the parietal cortex in the integration of many emotional and cognitive functions, such as sensory information and visuospatial processing, this raises the possibility that dysfunction of such processes in BPD may be at least partly caused by parietal impairment.[28-30]

Although significant reductions in limbic and paralimbic areas have been reported even in adolescents with first-presentation BPD, such findings have not been observed as specific for BPD.[31,32] Moreover, the development of volume alterations during the course of BPD has also been suggested in the literature, but this hypothesis has yet to be clarified through longitudinal studies.[31,32] However, despite the wide variability of neurobiological processes associated with each morphometric and geometric parameters, almost all of the morphological alterations observed in BPD patients in the present study occurred in limbic and paralimbic regions, which reinforces the involvement of these areas in the pathophysiology of BPD.

Since the present study included a large number of patients taking psychiatric medication, the potential effect of psychotropic drugs on brain structures and their possible effect on neuroimaging should be considered. Recent biological theories on the pathophysiology of psychiatric disorders have stated that symptoms could be a consequence of aberrant intrasynaptic neurotransmitter concentrations, probably associated with impairment of structural plasticity and resulting in gray matter volume reductions. In accordance with this hypothesis, psychotropic drugs may act by correcting the neurotransmitter dysfunctions and, consequently, the volume reductions.[33-35] Longitudinal studies utilizing structural neuroimaging techniques comparing drug-naïve patients before and after psychotropic treatment have observed positive effects[33,34,36] or no brain structure modification[35] after psychotropic treatment, while functional neuroimaging studies have observed enhancements in neuroplasticity and in brain connectivity.[37-40]

The findings reported herein should be interpreted in the context of a number of limitations. The relatively small number of patients enrolled may preclude wider conclusions. In addition, these findings cannot be applied to all BPD patients, especially to male subjects. Since we aimed to examine a homogeneous group of BPD patients and because both gender and handedness are known to be potential confounders for structural brain analyses, the study was restricted to women. Some relevant clinical aspects of BPD, such as impulsivity, suicidality, and suicide attempts, were not assessed through specific instruments in the present study, and also constitute an important limitation. Moreover, since we chose to enroll only BPD patients with no current psychiatric comorbidity so as to refine our analysis, the generalizability of the present findings to the typical BPD patient, who presents with various psychiatric comorbidities, should be interpreted with caution. Finally, although FreeSurfer analysis of cortical morphology could present a series of limitations regarding segmentation errors, intensity normalization, pial surface misplacements, skull strip errors, and topological defects,[11,14-17] no BPD patients or controls had to be excluded from this study for such reasons.

In conclusion, the present study observed significant cortical morphologic alterations in BPD patients as compared with healthy age- and gender-matched controls and provides new possibilities for neuroimaging studies in BPD through a novel method of structural analysis that can contribute to this line of research by offering more detailed descriptions of volumetric and geometric cortical surface features.[11-13] The present results can also contribute to further investigations of more specific neurobiological processes involved in the pathophysiology of BPD. Although these data support the hypothesis of limbic, paralimbic, and parietal involvement in the pathophysiology of BPD symptoms, additional neuroimaging studies of BPD patients are highly encouraged to improve our understanding of the biological underpinnings of this disorder.

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Disclosure

The authors report no conflicts of interest.

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