



Morphometric hemispheric asymmetry of orbitofrontal cortex in women with borderline personality disorder: A multi-parameter approach



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ARTICLE INFO

Article history:

Received 31 August 2013

Received in revised form

23 April 2014

Accepted 1 May 2014

Available online 9 May 2014

Keywords:

Magnetic resonance imaging

Cortical thickness

Multimodal analysis

ABSTRACT

Functional imaging studies have implicated the orbitofrontal cortex (OFC) in the pathophysiology of borderline personality disorder (BPD). To date, however, volume-based magnetic resonance imaging (MRI) studies have yielded mixed results. We used a surface-based processing approach that allowed us to measure five morphometric cortical features of the OFC, including volumetric (cortical thickness and surface area) and geometric (mean curvature, depth of sulcus, and metric distortion – three indicators of cortical folding) parameters. Participants comprised 25 female BPD patients with no other current psychiatric comorbidity and 25 age- and gender-matched healthy controls who received structural MRI scans. Images were processed using the Freesurfer package. All BPD patients had a history of comorbid psychiatric disorder(s) and were currently on medications. Compared with controls, the BPD group showed reduced cortical thickness, surface area, mean curvature, depth of sulcus, and metric distortion in the right medial OFC. In the left medial OFC, the BPD group had reduced cortical thickness and mean curvature, but increased metric distortion. This study confirmed the utility of surface-based analysis in the study of BPD cortical structures. In addition, we observed extensive structural abnormalities in the medial OFC of female subjects with BPD, findings that were most pronounced in the right OFC, with preliminary data suggesting hemispheric asymmetry.

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1. Introduction

Borderline personality disorder (BPD) is a devastating condition that affects 1–2% of the population and causes an intense disruption of patients' lives and relationships (Minzenberg et al., 2007, 2008). BPD patients often exhibit emotional instability, impulsive

behavior, rapid mood changes, and a propensity toward intense negative emotional states like anger, anxiety and dysphoria (Lis et al., 2007; Silbersweig et al., 2007).

The orbitofrontal cortex (OFC) is involved in high-level aspects of cognition and emotional behavior (Elliott et al., 2000; Ongur and Price, 2000). OFC lesions result in emotional dysregulation, along with impulsivity and socially inappropriate behavior (Malloy et al., 1993). In patients with BPD, functional neuroimaging studies have consistently identified abnormal findings in the OFC (Soloff et al., 2000, 2003, 2005; New et al., 2007, 2009). To date, however, structural magnetic resonance imaging (MRI) investigations

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have yielded mixed results, with few studies showing reduced OFC volume (Tebartz van Elst et al., 2003; Chanen et al., 2008; Vollm et al., 2009; Brunner et al., 2010), while others failed to replicate similar findings (Rüsch et al., 2003; Goodman et al., 2011). Several factors could have contributed to the discrepant results, including the following: (1) differences in the image-processing methods used in the various MRI studies, a factor that is especially important in the context of data indicating a differential effect of BPD on white vs. gray matter or right vs. left hemisphere. (2) Given the putative functional distinction between subregions of the OFC (e.g. medial for emotional processing vs. lateral for cognitive processing) (Elliott et al., 2000; Ongur and Price, 2000), subregions differences might have confounded region-of-interest analyses. (3) All previously studied MRI cohorts were carried out in BPD patients with a high level of comorbidity with several other psychiatric disorders.

To contribute to the understanding of such discrepancies between the above-mentioned volume-based preliminary findings, we used a well-validated surface-based processing method to measure five geometric parameters of the OFC in a homogeneous group of female BPD patients without psychiatric comorbidities. We hypothesized that the BPD group would present significant OFC alterations, mainly OFC reductions, of all morphometric parameters in comparison with controls. In addition, an exploratory analysis of the morphometrics of the OFC in relationship to the severity of the disorder was also conducted.

2. Methods

2.1. Participants and study design

BPD patients and healthy controls, aged 18–45, were enrolled in this cross-sectional, case-control neuroimaging study. Participants enrolled were recruited from 137 BPD patients at an outpatient clinic at a tertiary center (Department of Psychiatry of the Universidade Federal de São Paulo, Brazil). Out of 137 screened subjects, 25 BPD (18.2%) and 25 healthy subjects met the study criteria. The Ethics Committee of the Universidade Federal de São Paulo, Brazil, approved all study procedures. Before enrollment, informed consent was obtained from all subjects. A comprehensive medical and psychiatric evaluation was performed to determine eligibility. The Structured Clinical Interview for DSM-IV Axis I & II Disorders (SCID-I and SCID-II) was used to confirm diagnoses (Spitzer et al., 1989; First et al., 1998; American Psychiatric Association, 2004). In addition, the Clinical Global Impression scale (CGI) was used to document severity – on a scale that ranges from 1 (less severe) to 7 (more severe) (Guy, 1976). For the patients group, inclusion criteria were (1) female gender; (2) BPD diagnosis, as determined by SCID-II; (3) absence of other current psychiatric comorbidities, as determined by SCID-I and SCID-II; (4) no MRI contraindications; (5) medically stable; and (6) treatment on our unit for at least 6 months. A total of 25 females with BPD, and 25 age- and gender-matched healthy subjects completed all study procedures, including evaluations and MRI protocols.

2.2. MRI data acquisition

All MRI studies were conducted on a 1.5 T (Magnetom Sonata [Maestro Class] – Siemens AG, Medical Solutions, Erlangen, Germany) with an eight-channel head coil. To minimize variation, the same investigator positioned all subjects using the orbito-metal line as landmark. The following two conventional sequences were performed: (a) Axial T2-weighted FLAIR (fluid-attenuated inversion recovery) in a plane parallel to the anterior commissure–posterior commissure (AC–PC) line [TR=8500 ms, TE=107 ms, IT=2500 ms, slice thickness=5.0 mm, slice interval=1.5 mm, field of view=240 mm, matrix size=256 × 256, number of excitations=1]; (b) Sagittal T1-gradient echo volumetric acquisition for multiplanar reconstruction (TR=2000 ms, TE=3.42 ms, flip angle=15°, field of view=245 mm, 1.0-mm slice thickness with no gaps, totaling 160 slices per slab, matrix size=256 × 256, number of excitations=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.

2.3. Images processing

Structural images were processed using the recon-all pipeline of the Freesurfer package, which is documented and freely available for download online (surfer.

nmr.mgh.harvard.edu). The main steps of this pipeline are gray/white matter segmentation, pial and white matter surface modeling, transformation of the cortical surface to spherical coordinates, nonlinear surface registration based on curvature (gyrus and sulcus) allowing for analysis of multiple subjects and automated parcellation of cortical areas. Technical details of such procedures are described in the pivotal studies (Dale et al., 1999; Fischl et al., 1999, 2004; Fischl and Dale, 2000).

The following five morphometric parameters (per vertex) were extracted using Freesurfer: average convexity (depth of sulcus), mean radial curvature, metric distortion (Jacobian), cortical thickness, and surface area. The average convexity is a measure of the primary folding of a surface. Mean radial curvature is used to quantify small secondary and tertiary folds. Metric distortion measures the deformation of individual cortical surfaces when registered to the Freesurfer template (fsaverage). Cortical thickness is the distance between white matter and pial surfaces. Surface area reflects the area of the pial surface. Since this is a hypothesis-driven investigation focusing on OFC characterization, the results were masked to include only the surface vertices within the segmented lateral and medial portions of the OFC. The delineation of medial and lateral OFC of each individual was defined using the automated parcellation described in Fischl et al. (2004) using the Desikan–Killiany Atlas (Desikan et al., 2006). Additional information about Freesurfer cortical parcellation can be found at surfer.nmr.mgh.harvard.edu/fswiki/CorticalParcellation. Further technical details of these parameters are also described in prior publications (Dale et al., 1999; Fischl et al., 1999, 2004; Fischl and Dale, 2000).

2.4. Statistical analyses

Clinical and demographic data were presented as mean ± standard deviation. Before analyses were performed, measures were examined for normality using the Shapiro–Wilk test. The level of significance was set at $p < 0.05$, two-tailed. Age and handedness matching between patients and controls was evaluated using independent sample *t*-tests and chi-square tests. Statistical difference maps between BPD and controls were constructed, in Freesurfer, using a GLM (generalized linear model) vertex-by-vertex analysis and assuming a significance level of $p \leq 0.05$; corrected for multiple comparisons using false discovery rate (FDR).

3. Results

3.1. Demographic and clinical data

Table 1 presents demographic information for the BPD ($n=25$) and the healthy ($n=25$) groups; the two groups showed no significant demographic differences. Among BPD patients, the mean (\pm S.D.) duration of the disorder was 16.6 ± 9.5 years and the mean CGI score (an indicator of the severity of psychiatric disorders) was 3.3 ± 1.8 (range 3–6). Although clinically stable and without fulfilling complete criteria for any current psychiatric comorbidity at the time of the study, all BPD patients had a past psychiatric history, mainly mood disorders (19 patients; 76%). Among them, 13 patients had the diagnosis of major depressive disorder and 6 of bipolar disorder. Other diagnoses were alcohol and drug abuse/dependence (13; 52%) and nonspecific psychotic disorders (9; 36%). Twelve BPD patients (48%) had a history of two or more psychiatric comorbidities. 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 patients were taking a mood stabilizer, while 18 were taking antidepressants and 10 were using antipsychotics. Six patients were on monotherapy, 13 were taking two medications, and six were on three medications.

3.2. Morphometrics of the OFC

A vertex-by-vertex surface-based analysis showed that patients with BPD, compared with controls, had a significant reduction of cortical thickness and metric distortion, but an increase in curvature ($p < 0.05$, corrected for multiple comparisons) in the left medial OFC (Fig. 1). In addition, a significant reduction of cortical thickness, curvature, depth of sulcus, surface area and metric distortion in the right medial OFC of BPD group as compared with

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