Reduced Anterior and Posterior Cingulate Gray Matter in Borderline Personality Disorder


Background: Structural abnormalities in prefrontal and cingulate gyrus regions—important in affective processing, impulse control and cognition may contribute to the psychopathology of borderline personality disorder (BPD). Previous MRI studies examining volume have reported that compared with healthy controls, BPD patients have decreases in right anterior cingulate, no differences in dorsolateral prefrontal cortex, and mixed findings for prefrontal cortex. We extended this investigation by examining gray and white matter volume of frontal and cingulate gyrus Brodmann areas (BAs) in a large group of patients and healthy controls.

Methods: MRI scans were acquired in 50 BPD patients (n = 13 with comorbid diagnosis of BPD and Schizotypal Personality Disorder (SPD) and n = 37 without SPD) and 50 healthy controls, and gray/white matter volume in cingulate gyrus and frontal lobe BAs were assessed. Normal BPD and BPD subgroup comparisons were conducted.

Results: Compared with controls, BPD patients showed reduced gray matter volume in BA 24 and 31 of the cingulate. BPD patients without comorbid SPD had isolated gray matter volume loss in BA 24, but were spared for BA 31 in contrast to BPD patients with SPD. There were no group differences in whole cingulate or frontal lobe volume.

Conclusions: The finding of more pervasive cingulate shrinkage in the patients with BPD and SPD comorbidity resembles recent observations with the same methods in patients with schizophrenia. The pattern of reduced anterior and posterior cingulate gray matter volume in BPD patients, particularly those comorbid for SPD is consistent with the affective and attentional deficits observed in these personality disorders.

Key Words: Borderline personality disorder, schizotypal personality disorder, magnetic resonance imaging, cingulate, gray matter volume, white matter volume

Borderline personality disorder (BPD) is associated with affective instability, impulsivity, and cognitive distortions accompanying emotional distress. Since subcomponents of the cingulate cortex have been shown to subserve an array of functions including emotional and attentional processing (Devinsky et al 1995; Drevets 1998; Vogt et al 1992), it is a candidate structure for dysfunction in BPD. The affective subdivision of the cingulate (Brodmann area (BA) 24, 25, and 32) is connected to the amygdala and orbitofrontal cortex, among other regions and assesses the salience of emotional and motivational information and the regulation of emotional responses (Bush et al 2000). Humans with lesions within the anterior cingulate (subgenual region-BA 25) show abnormal autonomic responses to emotionally provocative stimuli and inability to experience emotion related to concepts that ordinarily evoke emotion (Damasio et al 1990). However, relatively few studies have examined brain structure and function in BPD and none have examined gray and white matter volume within BAs in the anterior and posterior cingulate gyrus.

Most magnetic resonance imaging (MRI) studies examining limbic volumes found smaller volumes in BPD in the hippocampus and amygdala (Driessen et al 2000; Irlé et al 2005; Rusch et al 2003; Schmahl et al 2003b; Tebartz van Elst et al 2003) or amygdala alone (Brambilla et al 2004). Significant volume reduction has been reported with manually traced assessment of the right anterior cingulate (BA 24) and left orbitofrontal cortex (Tebartz van Elst et al 2003) but this was not confirmed in a larger sample using voxel-based morphometry (Rusch et al 2003). Other tracing studies showed smaller total frontal lobe volumes without examining subdivisions (Lyoo et al 1998) and no dorsolateral frontal reduction without examining orbitofrontal cortex (Brambilla et al 2004).

Positron emission tomography (PET)-18F-deoxyglucose studies showed healthy volunteers having greater relative glucose metabolism compared with BPD patients during rest in anterior cingulate gyrus (De La Fuente et al 1997), posterior cingulate gyrus (BA 31 and 29)(New et al 2002), medial and orbital regions (including BA 10-11 bilaterally)(Soloff et al 2000). Others have reported BPD patients show increased resting rGMR in frontal and anterior cingulate regions (Jungling et al 2003) and increases during a go/nogo task (Vollm et al 2004). In response to abandonment scripts, female BPD patients showed higher activation than nonborderline women in BA 9 and 10 bilaterally and decreased activation in right medial frontal regions (BA 24 and 32) (Schmahl et al 2003a, 2004). Pharmacological challenge studies indicate that healthy controls show increased relative glucose metabolism in the anterior cingulate gyrus and orbitofrontal cortex following serotonergic stimulation, while BPD patients show decreased metabolism in these areas (New et al 2002; Soloff et al 2000). These studies suggest that anterior cingulate and adjacent regions which normally exert an inhibitory influence, perhaps through a serotonergic mechanism, are dysfunctional in BPD patients.

BPD may overlap with other personality disorders; the presence of cognitive distortions under stress sometimes results in a comorbid diagnosis of schizotypal personality disorder (SPD). The diagnoses of BPD and SPD arose from two different research approaches, although there was significant diagnostic overlap between the two groups as assessed by DSM-III. This overlap was diminished by the introduction of the borderline criterion for...
paranoid ideation under stress in DSM-III-R. The diagnosis “borderline personality organization” (Kernberg 1977) and its more specific description as borderline personality disorder (Gunderson and Singer 1975), characterized by intense affect, usually hostile or depressed, impulsive behavior, and defective relationships, led to the development of criteria for BPD in DSM-III. The landmark Danish adoption studies of schizophrenia (Kety et al 1975; Rosenthal et al 1971) found a continuum of disorder in relatives of patients with schizophrenia – a borderline schizophrenia – and based on their studies, this became “schizotypal personality disorder” in DSM-III. While initial studies suggested “borderline schizophrenia,” which included some symptoms related to current conceptions of BPD, is genetically related to schizophrenia at the time of DSM-III (review by Siever and Gunderson 1979), changes in DSM-IV criteria for BPD and newer studies of the genetics of schizophrenia do not support a genetic relationship between BPD and chronic schizophrenia. However, there continues to be modest clinical comorbidity and some apparent overlap in relatives of schizophrenic patients (Fanous et al 2001) which may represent true comorbidity of two independent diagnoses or BPD patients with substantial cognitive/perceptual abnormalities. In a sample of 668 personality disorder patients, reasonable discriminant validity was shown for BPD and SPD diagnoses (Grilo et al 2001). Because BPD patients show symptoms of dysregulation of affective tone and impulse control as well as cognitive control under stress – key functions of the cingulate gyrus – and because cingulate gyrus volume loss has been widely observed in the schizophrenia spectrum, we focused on cingulate gyrus volume in BPD and secondarily evaluated the effects of a comorbid diagnosis of SPD.

The main goal of the present study was to examine both gray and white matter volume within BAs of the cingulate gyrus and frontal lobe in a large group of BPD patients and healthy controls ($n = 50$ in each group) and to examine comorbidity by subgrouping the BPD patients: those with SPD—the prototypic schizophrenia spectrum disorder ($n = 13$) – and those without SPD ($n = 37$). We also explored the association between volume of frontal BAs and clinical symptomatology.

Methods and Materials

Participants

We assessed $50$ patients meeting DSM-III-R criteria for BPD and $50$ age and sex-matched healthy controls (see Tables 1–2). Participants provided written informed consent approved by Mount Sinai and Bronx Veterans Affairs Medical Center institutional review boards.

Participants completed psychometric self-report measures of aggression (Buss-Durkee Hostility Inventory, BDHI (Buss and Durkee 1957), impulsivity (Barratt Impulsivity Scale, BIS) (Barratt 1965), affective lability (Affective Lability Scale, ALS) (Harvey et al 1989), and affective intensity (Affective Intensity Measure, AIM) (Larsen and Diener 1985).

MRI Acquisition

All participants received a T1-weighted MRI (repetition time = 24 msec, echo time = 5 msec, flip angle = 40°, slice thickness = 1.2 mm, pixel matrix = $256 \times 256$, field of view = 23 cm, slices = 128) and images were resectioned to standard (Talairach and Tournox 1988) position.

Brodman Area Measurements and Tissue Type Quantification

An analysis of the BAs of the frontal lobe was conducted on coronal MRI slices (Buchbaum et al 2002; Mitelman et al 2003) using a digitized version of a histologically-based atlas (Perry et al, personal communication, 1991) that includes $33$ coronal slice maps of BAs defined by microscopic examination of one entire post-mortem brain. Coronal slices perpendicular to the anterior commissure-posterior commissure line were divided into $20$ radial sectors on each hemisphere surface and $10$ midline sectors. BAs were then assessed for the gray and white matter pixels within all sectors identified in each BA. For quantification, the coronal images were segmented into gray matter, white matter, and cerebrospinal fluid (CSF) using cutoff values individually determined in each subject by examining the within-brain-edge histogram of axial MRI values as validated and assessed for reliability earlier (Mitelman et al 2003). Every sector was assigned a BA according to the same radial sector division applied to Perry’s drawing of the BA margins. Volume measures were obtained by computing relative size as the ratio of (area of ROI)/(volume of brain) $\times 1000$. The assessment of the reliability across $16$ subjects who were imaged twice, one month apart (intra-class correlation coefficient = $0.88 - 0.75$ for frontal BAs $44$, $45$, and $46$, inter-tracer histogram cutoff reliability ($0.99 - 0.92$), and validation of the gray-white matter segmentation have been reported elsewhere (Buchbaum et al 2002).

Statistical Methods

Our histological atlas program obtained data from the $15$ BAs within the prefrontal cortex and cingulate gyrus identified by Perry (8-9-10-11-12, 23-24-25, 29, 31-32, 44-45-46-47). Subgroups of these variables developed on a theoretical and anatomical basis were entered into a series of mixed-design multivariate analyses of variance (MANOVAs; reporting Wilk’s $F$, Statistica, Statsoft, Inc., Tulsa, Oklahoma, 1999). Diagnostic group (Healthy controls vs. BPD patients) was the between-group factor. We also conducted parallel 3-group analyses (Controls vs. BPD patients without SPD comorbidity (termed BPD$^{S+P-}$) vs. BPD patients with SPD (termed BPD$^{S+P+}$)). For cingulate analyses, repeated measures included anteroposterior BAs within the cingulate gyrus (BA 25, 24, 31, 23, 29), tissue or matter type (gray, white), and hemisphere (left, right). For the prefrontal cortex analysis, repeated measures included region (anterior, medial, orbital, and dorsolateral), selected sets of BAs nested within each region (anterior: BA 8, 9, 10; medial: BA 32, 25, 24; orbital: BA 11, 12, 47, and dorsolateral: BA 44, 45, 46), matter type (gray, white), and hemisphere (left, right). This approach, which provided tests of hypothesized group differences, can help minimize Type I statistical error involved with $t$-tests for each group contrast, area, and hemisphere. Fisher’s least significant difference (Fisher LSD) tests were used post-hoc to follow-up significant interaction effects which included diagnostic group.

Results

Cingulate Gyrus

Two-Group Cingulate Gyrus Analysis: Healthy Controls versus BPD.

Compared with healthy controls, BPD patients had less gray matter in BAs 24 and 31 and greater white matter in BA 24, 31, and 23. BA 25 and 29 volumes did not differ between groups. This was confirmed with MANOVA and follow-up post-hoc tests (Figure 1).
Compared with controls, BPDSPD− patients had significantly less gray matter in BA 24, 31, and 23 and greater white matter in BA 24 and 31. In contrast, the BPDSPD+ group only showed gray matter reduction in BA 24, while greater white matter was observed in BA 24, 31, and 23 (Figure 2).

Table 1. Borderline Personality Disorder Patients

<table>
<thead>
<tr>
<th>Patient No./Sex/Age</th>
<th>Axis I Disorders</th>
<th>Axis II Disorders</th>
</tr>
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<tbody>
<tr>
<td>1/F/37 MDD past, GAD, Hx ETOH</td>
<td>BPD, PPD</td>
<td></td>
</tr>
<tr>
<td>2/M/28 MDD past, Hx ETOH, Hx Polysub</td>
<td>BPD, PPD</td>
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<td>BPD, HPD, PAPD, PPD</td>
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</tr>
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</tr>
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<td></td>
</tr>
<tr>
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<td>BPD, PPD, SPD</td>
<td></td>
</tr>
<tr>
<td>8/M/31 MDD past</td>
<td>BPD, DPD, OCPD</td>
<td></td>
</tr>
<tr>
<td>9/M/18 MDD past</td>
<td>BPD, NPD</td>
<td></td>
</tr>
<tr>
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</tr>
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</tr>
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<td>BPD, NPD, PAPD</td>
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<tr>
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<td>32/M/21 MDD past</td>
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<td>37/F/34 Hx ETOH</td>
<td>BPD</td>
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<tr>
<td>38/F/40 MDD past</td>
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<tr>
<td>39/M/31</td>
<td>BPD, HPD</td>
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</tr>
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<td>BPD, ASPD</td>
<td></td>
</tr>
<tr>
<td>41/M/35 MDD past</td>
<td>BPD, ASPD, OCPD, PPD</td>
<td></td>
</tr>
<tr>
<td>42/F/24 MDD past</td>
<td>BPD, APD</td>
<td></td>
</tr>
<tr>
<td>43/M/50 MDD past, Hx ETOH</td>
<td>BPD, APD</td>
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<td>44/M/36 MDD past, OCD, Hx ETOH</td>
<td>BPD</td>
<td></td>
</tr>
<tr>
<td>45/F/39 MDD past</td>
<td>BPD, OCPD, PAPD, SPD</td>
<td></td>
</tr>
<tr>
<td>46/F/37 MDD past, Hx Polysub</td>
<td>BPD</td>
<td></td>
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<td>47/F/23 MDD past</td>
<td>BPD, OCPD</td>
<td></td>
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<tr>
<td>48/M/36 MDD past, GAD</td>
<td>BPD, APD, ASPD, NPD, OCPD, PAPD, PPD, SPD</td>
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</tr>
<tr>
<td>49/M/33 MDD past</td>
<td>BPD, DPD, HPD, NPD, PAPD, PPD</td>
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<td>50/M/29 MDD past, GAD, PTSD, Hx ETOH</td>
<td>BPD, APD, PPD, SPD</td>
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</table>

ASPD, antisocial personality disorder; APD, avoidant personality disorder; BPD, borderline personality disorder; DPD, dependent personality disorder; HPD, histrionic personality disorder; NPD, narcissistic personality disorder; OCPD, obsessive-compulsive personality disorder; PAPD, passive-aggressive personality disorder; PPD, paranoid personality disorder; SPD, schizotypal personality disorder; GAD, generalized anxiety disorder; Hx ETOH, history of alcohol abuse; Hx Polysub, history of polysubstance abuse; MDD past, history of major depressive disorder; PTSD, post-traumatic stress disorder.
Table 2. Demographics on Study Participants

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Men/Women</th>
<th>Age</th>
<th>SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy Controls</td>
<td>50</td>
<td>30M/20W</td>
<td>31.5</td>
<td>9.9</td>
<td>20–58</td>
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<tr>
<td>BPD Patients</td>
<td>50</td>
<td>27M/23W</td>
<td>33.2</td>
<td>8.5</td>
<td>18–52</td>
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<tr>
<td>BPD Subgroup without SPD</td>
<td>37</td>
<td>20M/17W</td>
<td>32.8</td>
<td>8.8</td>
<td>18–52</td>
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<tr>
<td>BPD Subgroup with SPD</td>
<td>13</td>
<td>10M/3W</td>
<td>34.2</td>
<td>7.6</td>
<td>21–48</td>
</tr>
</tbody>
</table>

BPD, borderline personality disorder; SPD, schizotypal personality disorder.

Correlations Between Prefrontal Gray and Self-Report Measures

Pearson product-moment correlations for the entire group of BPD patients revealed that in anterior cingulate gyrus, smaller left gray matter volume in BA 25 was associated with higher ratings of impulsivity as measured by the BIS (r = -0.30, n = 45, p = 0.048). There were no correlations with BA 24.

In posterior cingulate (BA 23), smaller right white matter volume was associated with higher ratings of impulsivity (BIS, r = -0.33, n = 45, p = 0.03) and smaller left white matter volume was associated with higher ratings of irritability-assaultiveness as measured by the BDHI Irritability-Assaultiveness (I-A) Subscale (r = -0.32, n = 47, p = 0.03). There were no correlations with BA 31 or 29.

In anterior prefrontal regions, smaller left gray matter volume in BA 10 was associated with higher ratings of impulsivity (r = -0.38, n = 45, p = 0.01). No correlations were significant for BA 8 or 9. In orbitofrontal regions, greater left white matter volume in BA 47 was associated with higher ratings of impulsivity and irritability-assaultiveness (n = 47, r = 0.29, p = 0.04 and r = 0.35, p = 0.02, respectively). There were no correlations with BA 11 or 12.

Lastly, in dorsolateral regions, greater white matter volume in both left and right BA 44 was associated with higher ratings of hostility and irritability-assaultiveness (n = 47, BDHI: left: r =

**Figure 1.** Gray and white matter cingulate gyrus volume changes in borderline personality disorder. As can be seen, BPD patients (n = 50) had less gray matter and more white matter in the cingulate compared with healthy controls (n = 50). Group × BA × Matter interaction, F(4,95) = 3.31, p = 0.014. Post-hoc follow-up tests revealed that BPD patients had significantly reduced gray matter in BA 24 and 31, and greater white matter in BA 24, 31, and 23 compared with healthy controls (all p < 0.01, Fisher LSD tests are indicated by an asterisk in figure). BA 22 and 29 did not differ between groups. BPD patients had less total cingulate gray matter and more total white matter compared with healthy individuals (Group × Matter interaction, F(1,98) = 12.86, p = 0.001; Mean Gray matter: Controls: 4.47, SD: 0.56; BPD: 4.27, SD: 0.54; Mean White matter: Controls: 4.17, SD: 0.55; BPD: 4.47, SD: 0.58). Follow-up comparisons for these gray/white mean values were significant (both p < 0.001). The BPD patients showed a pattern of reduced gray and increased white matter more in the right cingulate than in the left, although all values were significantly different between groups (all p < 0.05) (Group × Matter × Hemisphere, F(1,98) = 5.27, p = 0.024; Mean difference from normal: right cingulate: gray matter = -0.25, white matter = 0.35; left cingulate: gray matter = -0.15, white matter = 0.26). The two groups did not differ in total cingulate volume (averaged across the five BAs, both hemispheres, and gray and white matter within the cingulate); main effect of Group and all other interactions with group were not significant. BPD, borderline personality disorder; BA, Brodmann’s area.

**Figure 2.** Graph showing the mean difference from normal for the entire group in the anterior, medial, and orbitofrontal regions. As can be seen, BPD patients (n = 50) had less gray matter and more white matter in these regions compared with healthy controls (n = 50). Group × Region × Matter interaction, F(6,93) = 3.47, p = 0.004. There were no correlations with BA 24, Fisher LSD, p = 0.018, while none of the other BAs were significantly different (Group × Region × BA × Matter interaction, F(6,93) = 3.47, p = 0.004). BPD patients showed a pattern of decreased volumes in anterior, medial, and orbital regions and decreased volumes in dorsolateral regions compared with controls, especially on the left, although none of the post-hoc Fisher LSD tests were significant (Group × Region × BA × Hemisphere interaction, F(6,93) = 2.66, p = 0.020). Compared with controls, the BPD patients had less gray and more white matter volume in the medial regions (Group × Region × Matter interaction, F(3,96) = 2.78, p = 0.045; post-hoc comparison for the medial region (BA 32, 25, and 24 combined) white matter was significant, p = 0.02.) There were no between-group differences in total prefrontal cortex volume (averaged across the 12 BAs in each hemisphere; main effect of Group was not significant) and none of the other interactions with group were significant.

**Figure 3.** Graph showing the mean difference from normal for the entire group in the anterior, medial, and orbitofrontal regions. As can be seen, BPD patients (n = 50) had less gray matter and more white matter in these regions compared with healthy controls (n = 50). Group × Region × Matter interaction, F(6,93) = 3.47, p = 0.004. There were no correlations with BA 24, Fisher LSD, p = 0.018, while none of the other BAs were significantly different (Group × Region × BA × Matter interaction, F(6,93) = 3.47, p = 0.004). BPD patients showed a pattern of decreased volumes in anterior, medial, and orbital regions and decreased volumes in dorsolateral regions compared with controls, especially on the left, although none of the post-hoc Fisher LSD tests were significant (Group × Region × BA × Hemisphere interaction, F(6,93) = 2.66, p = 0.020). Compared with controls, the BPD patients had less gray and more white matter volume in the medial regions (Group × Region × Matter interaction, F(3,96) = 2.78, p = 0.045; post-hoc comparison for the medial region (BA 32, 25, and 24 combined) white matter was significant, p = 0.02.) There were no between-group differences in total prefrontal cortex volume (averaged across the 12 BAs in each hemisphere; main effect of Group was not significant) and none of the other interactions with group were significant.
Diagnostic Comorbidity in Borderline Personality Disorder

Comorbidity of Past Major Depressive Disorder.

BPD patients with a current MDD (during last 6 months) were excluded from this study. However, because there is substantial comorbidity between depression and BPD, many of our patients had a past history of MDD (occurring > 6 months from time of MRI). In order to address whether our main findings in the cingulate could be explained by this comorbidity issue, we compared patients with a past history of depression (n = 12). This 2-group MANOVA failed to show a main effect of Group or any interaction with group indicating that these two BPD subgroups did not differ from each other in whole cingulate volume, gray/white volume, or volume of BAs within the cingulate (Group × BA × Matter interaction, p = .50).

Further, in order to determine whether these BPD subgroups of patients with and without a past history of MDD (MDD+ vs. MDD-) differed from normal, we conducted a 3-group MANOVA.

Figure 2. Gray and white matter changes in cingulate gyrus volume in borderline personality disorder patient subgroups. The BPDSPD+ patients had significantly less gray matter in BA 24, 31, and 23, and greater white matter in BA 24 and 31 (all p < .04). In contrast, the BPDSPD- group only showed gray matter reduction in BA 24 (p = .01) while greater white matter was observed in BA 24, 31, and 23 (p < .03). Group × Cingulate BA × Matter interaction is shown for 3-group analysis (Healthy controls vs. BPDSPD+ vs. BPDSPD-). F(8,188) = 2.28, p = .024. Significant Fisher LSD tests for post-hoc comparisons with healthy controls are marked with an asterisk and significant comparisons of BPDSPD+ vs. BPDSPD- are marked with “+”.

Two-group follow-up MANOVA with controls vs. BPDSPD+: F(4,82) = 2.20, p = .077 (trend) and 2-group with controls vs. BPDSPD+: F(4,58) = 2.99, p = .026. The BPDSPD+ group had the most reduced gray matter and increased white matter volume from normal and the BPDSPD- group was intermediate (Group × Matter interaction 3-groups: F(2,97) = 7.32, p = .001; post-hoc 2-group with normal vs. BPDSPD+: F(1,85) = 7.31, p = .008; 2-group with controls vs. BPDSPD+: F(1,61) = 12.03, p = .001). Mean Gray matter: Controls = 4.47, SD = 1.34; BPDSPD+ = 4.33, SD = 1.33; BPDSPD- = 4.09, SD = 1.33; Mean White matter: Controls = 4.17, SD = 1.20; BPDSPD+ = 4.46, SD = 1.16, BPDSPD- = 4.51, SD = 1.15). Post-hoc comparisons for these gray and white matter values indicated that both patient groups differed significantly from normal (p < .05). Compared with the BPDSPD+ group, the BPDSPD- group had significantly less gray matter volume (p = .006), but not white matter volume in the cingulate. The three groups did not differ in total cingulate gyrus volume (averaged across the five BAs, both gray and white matter within the cingulate); main effect of Group and all other interactions with group were not significant. BPD, borderline personality disorder; BA, Brodmann’s area; MANOVA, multivariate analysis of variance; LSD, least significant difference test.

Figure 3. Mean differences from normal in gray and white matter frontal lobe Brodmann area volume in BPD patient subgroups. Differences from normal were confirmed with the Group × Region (Anterior: BA 8, 9, 10; Medial: BA 32, 25, 24; Orbital: BA 11, 12, 47; Dorsolateral: BA 44, 45, 46) × BA × Matter interaction, F(12,184) = 2.02, p = .025. Post-hoc tests indicated that the BPD without SPD group had significantly greater white matter volume in BA 9 (Fisher LSD, p = .018) and BA 24 (Fisher LSD, p = .031) compared with the controls (colored red in row 2). None of the other between-group post-hoc tests contrasting the three groups were significant. The Group × Region × Matter interaction was also significant (F(6,190) = 2.28, p = .038) and indicated that compared with the controls, the BPDSPD+ group showed a widespread pattern of small frontal gray reductions and white matter increases in volume and the BPDSPD- group was in between. Post-hoc comparisons indicated that compared with the controls, the BPDSPD+ groups had significantly greater white matter volumes in anterior (p = .042) and medial (p = .048) frontal regions. None of the other post-hoc tests were significant. BPD, borderline personality disorder; BA, Brodmann’s area; SPD, schizotypal personality disorder; LSD, least significant difference test.
Table 3. Self-Report Ratings in Healthy Controls and Borderline Personality Disorder Patients

<table>
<thead>
<tr>
<th>Scale</th>
<th>Healthy Controls</th>
<th>Borderline PD Patients</th>
<th>Borderline PD&lt;sub&gt;SPD&lt;/sub&gt;</th>
<th>Borderline PD&lt;sub&gt;PD+&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Mean</td>
<td>SD</td>
<td>n</td>
</tr>
<tr>
<td>Affective Liability Scale</td>
<td>42</td>
<td>.4</td>
<td>.3</td>
<td>39</td>
</tr>
<tr>
<td>Buss Durkee Hostility Inventory (BDHI Total)</td>
<td>43</td>
<td>19.3</td>
<td>8.7</td>
<td>47</td>
</tr>
<tr>
<td>BDHI: Irritability-Assaultiveness Subscale</td>
<td>43</td>
<td>5.3</td>
<td>3.5</td>
<td>47</td>
</tr>
<tr>
<td>Barratt Impulsivity Scale</td>
<td>42</td>
<td>39.9</td>
<td>18.2</td>
<td>45</td>
</tr>
<tr>
<td>Affective Intensity Measure</td>
<td>42</td>
<td>3.3</td>
<td>.5</td>
<td>43</td>
</tr>
</tbody>
</table>

PD, personality disorder; SPD, schizotypal personality disorder.
<sup>a</sup>Significantly different from healthy controls, t-test, p < .05.

Here, the MDD subgroups did not differ from each other, but they both differed from normal, Group × BA × Matter interaction, F(8,188) = 2.05, p = .04. Follow-up post-hoc tests confirmed the MDD+ and MDD- subgroups did not significantly differ from each other and of greatest importance, both had significantly less gray matter volume in BA 24 and BA 31 compared with the healthy controls (similar to Figure 1; Fisher LSD tests p < .03). Both the MDD+ and MDD- subgroups also had significantly more white matter in BA 24 compared with healthy controls (both p < .01), but only the MDD- subgroup had significantly more white matter in BA 31 and BA 23 compared with controls (both p < .02).

**Comorbidity of Personality Disorders.** A subgroup of our BPD patients (n = 10) had no other personality disorder. In order to determine whether our main findings in the cingulate could be explained by the issue of comorbidity of personality disorders, we compared these BPD patients (n = 10) to those with BPD and at least one other personality disorder (n = 40). The 2-group MANOVA showed no main effect of Group and no interactions with group indicating that these two subgroups did not significantly differ in total or regional cingulate volume (Group × BA × Matter interaction was p = .20).

Both patients with BPD only and BPD plus other PD differed from normal but did not differ from each other (3 Group × BA × Matter interaction, F(8,188) = 2.46, p = .01). Post-hoc tests confirmed that the BPD only and BPD plus other PD subgroups had significantly less gray matter and more white matter volume in BA 24 compared with the healthy controls (p = .05 for BPD only subgroup, all other comparisons were p < .01). In BA 31, the BPD only subgroup did not differ from normal for either gray or white matter volume while the BPD plus other PD subgroup had significantly less gray and more white matter (both p < .01). Lastly, only the BPD plus other PD subgroup had significantly more white matter in BA 23 compared with controls (p < .02).

**Comorbidity of Substance Abuse.** While the majority of our BPD patients did not have a lifetime history of substance abuse, we compared patients with a past history of substance abuse (n = 14) to those without such a history (n = 36). This 2-group MANOVA showed no significant main effect of Group nor significant interactions with group indicating that these two BPD subgroups did not significantly differ from each other in whole cingulate volume, gray/white volume, or volume of BAs within the cingulate (Group × BA × Matter interaction was p = .37).

In order to determine whether these BPD subgroups differed from normal in the cingulate, we conducted a 3-group MANOVA. While the substance abuse subgroups did not differ significantly from each other, they both differed from normal, Group × BA × Matter interaction, F(8,188) = 2.06, p = .04. Post-hoc tests confirmed that both these BPD subgroups with and without a history of substance abuse had significantly less gray and more white matter volume in BAs 24 and 31 compared with the healthy controls (all p < .03). In BA 23, patients with no history of substance abuse (n = 36) had significantly more white matter compared with healthy controls (p < .01), while those with a positive history (n = 14) did not differ from normal.

**Discussion**

The main findings of our study are: (1) the BPD patients showed reduced cingulate gray and increased white matter volume in BA 24 and 31 compared with the healthy controls; (2) the subgroup of BPD patients without SPD comorbidity showed this same gray/white matter volume abnormality in BA 24 compared with healthy controls, but gray matter reduction in BA 31 was spared. In contrast, the subgroup of BPD patients with SPD had reduced gray matter volume in both BA 24 and 31 of the cingulate. Moreover, gray matter volume loss in BA 31 was significantly greater in the BPD patients with SPD than the BPD patients without SPD; (3) the whole BPD group as well as the BPD subgroups did not differ from normal in whole prefrontal brain volume or whole cingulate volume.

Our cingulate findings of smaller volumes of gray matter in the cingulate extend results from an MRI study (Tebartz van Elst et al 2003) which reported right anterior cingulate volume reductions in 8 BPD patients in a few ways. First, we studied a larger sample of BPD patients (n = 50) which allowed us to conduct subgroup analyses on patients with and without a comorbid diagnosis of SPD, lifetime history of MDD, and lifetime history of substance abuse. Second, our findings indicate for the first time that BPD patients do not differ from normal in overall cingulate volume, instead they differ in gray and white matter volume in discrete BAs which subserve different functions.

Our finding of volumetric abnormality in the cingulate is consistent with functional studies in BPD which have demonstrated baseline decreases and abnormalities in activation and pharmacological response. These volumetric decreases should not be interpreted merely as the artifactual partial volume explanation of functional changes observed in functional studies of the cingulate. First, these BAs are relatively large, more than 20 times larger than scanner full-width half-maximum resolution or fMRI resolution, so the volume change cannot be implicated in metabolic rate or blood flow reduction. Second, functional studies widely identify the cingulate as abnormal in BPD, but depending on the behavioral task may show both increases and decreases. Thus, cingulate volume changes appear to be associated with compromised or abnormal function, or even disturbances in efficiency of processing requiring greater than normal metabolic activity rather than contributing to functional effects on the pure basis of imaging physics. Third, we evaluated the

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correlation between gray and white matter volumes and relative metabolic rate in a separate sample of 70 healthy subjects. The correlations between gray matter volume and relative metabolic rate for BA 25, 24, 31, 23, and 29 were –.12, –.17, –.11, –.31, and .14 respectively, indicating that volume and activity variation are relatively independent in a sample of normal individuals and thus, not consistent with an artifactual relationship between BA volume and relative metabolic rate.

Our finding of reduced BA 24 volume in BPD patients compared with healthy controls is consistent with affective and attentional abnormalities observed in BPD. BA 24 which showed reduced gray matter volume in BPD patients is involved in the recognition of affective states and execution of affect-related operations. The caudal part of BA 24 is involved in the response selection to cognitively demanding tasks (Devinsky et al 1995) such as sustained attention (Johannsen et al 1999). BPD patients show abnormal performance on an attention network test which evaluates conflict resolution (Posner et al 2002) and parallel neuroimaging work in healthy subjects indicates that an important part of this conflict network involves the anterior cingulate (Fan et al 2003). Other neuroimaging work has shown that conscious self-regulation of emotion (Beauregard et al 2001) and degree of sadness during emotional film excerpts (Levesque et al 2003) activates BA 24. Adjacent medial frontal BA 10 showed greater activation in patients with BPD in comparison with normal controls (Herpertz et al 2001). Both affective and attentional abnormalities are seen in autism, a group which has reduced metabolic rates in BA 24 (Hazlett et al 2004; Haznedar et al 1997). It is important to note that our comorbidity analyses examining patients with BPD alone, patients without MDD, and patients without a lifetime history of substance abuse continue to implicate BA 24. It is possible that SPD symptoms may reflect severity of cognitive dysfunction in some BPD subjects. Indeed, our data suggest that the subgroup of BPD patients with SPD comorbidity showed more pervasive shrinkage of gray matter in the cingulate than the BPD alone subgroup.

In contrast to anterior cingulate, the posterior cingulate gyrus is involved in working memory, visuospatial behaviors (Olson 1993; Sutherland and Hoesing 1993), and processing of emotional stimuli (Maddock et al 2003b). The posterior division of the cingulate cortex consists of BA 23, 29, 30, 31 and 36 and is reciprocally connected to the anterior cingulate; has thalamic, associative temporal, mediotemporal and orbitofrontal connections (Bentivoglio et al 1993; Vogt et al 1992). Our finding of reduced gray matter volume of BA 31 in the BPD patients compared with healthy controls lends support to the idea that the posterior cingulate cortex has a role in emotional processing as suggested by others (Vogt et al 2000). The posterior cingulate cortex is activated when healthy individuals make valence judgments of emotionally-salient stimuli, including threat-related words (Maddock et al 2003b) and panic-disorder patients exhibit an increased response in this same region (Maddock et al 2003a). The finding that activation of areas 23/31 appears to be associated with alternate nongrammatical strategies for processing grammatically complex sentences in elderly subjects, with cognitive difficulty, perhaps as compensation for normal prefrontal activation (Grossman et al 2002) is intriguing; deficits in this area used in cognitive compensation strategies might be especially disadvantageous to individuals who have frontal deficits. The current results suggest that reduced volume of posterior cingulate gray matter (BA 31) may contribute to the emotional/affective instability observed in BPD. It should be noted that the reduction in BA 31 we observed is not entirely inconsistent with the reduced parietal lobe volumes observed in BPD recently (Irle et al 2005) since our atlas does not depend on sulcal markings and could include parts of BA 4 and 7. However, activation of BA 31 with the Stroop test (Salgado-Pineda et al 2002) suggests its involvement in a variety of cognitive and perceptual tasks as well.

A novel finding in our study is that BA 31 gray matter volume is significantly more reduced in the BPDSPD+ subgroup compared with the BPD SPD- subgroup which did not differ from controls. This Brodmann area has rather distinct cytopology (Vogt et al 2001) and may possibly have distinct functions. This finding of posterior cingulate shrinkage in BA 31 in the BPDSPD+ group is consistent with previous work published from our group (Mitropoulou et al 2002; Roitman et al 2000) that shows that SPD patients (regardless of BPD comorbidity) exhibit working memory impairment compared with healthy controls. The sparing of BA 31 may reflect the lesser severity of BPD without SPD or a characteristic distinguishing BPD with comorbid SPD marked by greater loss of cognitive control of affective processing from BPD without SPD. The lack of dorsolateral gray loss in BPD without SPD also separates BPD from the schizophrenic disorders where prefrontal gray loss is often observed (reviewed by Molina et al 2004). In BA 23, the BPDSPD+ subgroup also showed decreased gray matter volume compared with controls, while the BPDSPD- subgroup only showed increased white matter volume. SPD is genetically-related to schizophrenia while BPD and schizoprenia appear not to be related (Siever and Gunderson 1979). Our finding may either mean that patients with more severe psychopathology (i.e. having two comorbid personality disorders) have more structural changes in the cingulate or it may indicate a more specific, possibly genetic relationship in the BPDSPD+ patients to schizophrenia. Schizophrenia patients have reduced posterior cingulate gray matter size (Hulshoff Pol et al 2001; Sowell et al 2000) and functional impairment as seen in failure to activate the posterior cingulate during verbal encoding (Hofer et al 2003). We have recently shown that poor-outcome schizophrenia patients have less gray matter volume in BA 31 compared with both good-outcome patients and healthy controls (Mittal et al 2005), suggesting that the schizophrenia-spectrum dimension in our patients may be the source of BA 31 change. Interestingly, patients with schizophrenia had significantly increased 6-[18F]-fluoro-L-DOPA PET uptake in the posterior cingulate compared with normal control subjects (Elkashef et al 2000) although N-acetylaspartate was unchanged in the posterior cingulate (Blasi et al 2004). It should be noted that our analysis of 10 BPD patients with no other personality disorder also confirmed sparing of BA 31 compared with the controls. However, the remaining 40 BPD patients with at least one other personality disorder showed significantly less gray and more white matter in BA 31, also resembling the finding in the BPDSPD+ subgroup. Further investigation of posterior cingulate gyrus volume and function is warranted and SPD and BPD patients without overlapping comorbidity will be needed to fully resolve the issue of specificity.

Our finding of increased white matter volume in anterior and posterior cingulate regions in the BPD group and BPD subgroups suggests that white matter connections in limbic circuitry may be inefficient and this could play a role in the pathophysiology of BPD. Other investigators who reported increased white matter volume in the corpus callosum in antisocial personality disorder patients interpreted their finding as a deficiency in axonal pruning or increased white matter myelination (Raine et al 2003). White matter volume increases in men but not women with
Schizophrenia were observed by Highley and coworkers (Highley et al 2003) and were attributed to cell adhesion molecule genes on the Y chromosome.

Our study has important limitations. Studies with larger sample sizes would ensure more power to detect differences between BPD subgroups with and without comorbid diagnoses and could determine if greater white matter in some BAs within the cingulate serves as a protective factor. We also lack sufficient patients with generalized anxiety disorder and PTSD to examine the contribution of these potentially important comorbidity diagnoses. We did not present data on the other 24 BAs because our main hypotheses concerned the prefrontal and cingulate cortex, but we do note that whole prefrontal volume and whole cingulate volume do not differentiate the groups, giving some specificity to our BA 24 findings. Other hypotheses, such as a cortical cytoarchitectural type vulnerability, could be tested using all 39 BAs, but Type I error possibilities led us to focus on prefrontal/cingulate regions. Other limitations of our study include the assignment of white matter to the overlying and stereotaxically defined gray matter; this may be more accurate for cingulate regions but prefrontal white matter areas may include fasciculi containing fibers from several prefrontal areas. Our segmentation of gray and white, while based on individually chosen intensity thresholds and a MRI sequence selected for equal values in all regions of the field of view as well as gray/white differentiation, is none the less vulnerable to noise variation. However, this would tend to diminish statistical power to differentiate groups, rather than find spurious between-group differences. Further, since there were no between-group whole prefrontal volume differences, only medial frontal and cingulate effects, it seems unlikely that some group segmentation artifact is responsible for the differences. Our grouping of BAs also deserves comment. Vogt et al (1995) define BA 32 as cingulo-frontal transition cortex as it has the histological characteristics of more of the prefrontal cortex than the cingulate. Accordingly, we did not include BA 32 in our cingulate MANOVA but included it as a medial-frontal area. Lastly, the family history, especially of Axis I disorders, might help to differentiate schizophrenia spectrum, affective spectrum or even bipolar spectrum concepts from personality disorder distinctions, but even our relatively large sample of 50 patients is small for such analyses.

We did not find any significant differences between BPD and healthy controls in dorsolateral regions (BA 44, 45, 46), replicating the findings of previous MRI studies (Brambilla et al 2004; Tebartz van Elst et al 2003). While we did observe a pattern of reduced gray matter volume and increased white matter volume in orbitofrontal regions (BA 11, 12, 47; significant Group × Region × BA × Matter interaction) in BPD patients compared with controls, none of the between-group post-hoc tests were significant. In contrast, a preliminary study which did not separate gray and white matter reported smaller left orbitofrontal volume in BPD (Tebartz van Elst et al 2003). We and others have previously reported increased glucose metabolism in orbitofrontal cortex and anterior cingulate gyrus in normal individuals following serotonergic stimulation and decreased metabolism in these regions in BPD patients that were impulsive aggressive (New et al 2002; Soloff et al 2003). It may be that anterior cingulate abnormalities are more robust in BPD and therefore present in both structural and functional imaging, while orbitofrontal abnormalities are less robust and only consistently found in functional imaging studies.

The correlations between anatomical measures and self-report ratings in the BPD patients must be treated as exploratory as many were done and only a few were significant. Among the BPD patients, smaller gray and white matter volume in the cingulate (anterior: BA 25; posterior: BA 23) and smaller gray matter volume in anterior prefrontal regions (BA 10) was associated with greater impulsivity as measured by the Barratt Impulsivity Scale. In contrast to our cingulate correlations, patients with larger white matter volume in orbit (BA 47) and dorsolateral prefrontal regions (BA 44) had greater irritability-assaultiveness. Prefrontal cortex, particularly anterior cingulate and orbitofrontal regions, appears to play a central role in the regulation of aggression, and white matter damage in dorsolateral prefrontal regions has been associated with aggression and impulsivity (Anderson et al 1999). Our correlational findings suggest that the structural integrity of gray and white matter in discrete prefrontal and cingulate areas may be related to borderline symptoms such as impulsivity and irritability-assaultiveness.

In conclusion, we found smaller BA 24 volumes in patients with BPD alone while patients with both BPD and SPD also had smaller BA 31. Neither past history of MDD or substance abuse explained smaller BA 24 in patients. The structural integrity of discrete prefrontal and cingulate areas was related to key borderline symptoms. Future studies comparing BPD and SPD patients will be important in achieving a better understanding of volumetric abnormalities and symptom correlates in personality disorders.

This work was supported in part by an Independent Investigator Award from National Alliance for Research on Schizophrenia and Depression to Dr. Hazlett, National Institute of Mental Health (NIMH) grants to Dr. Buchsbaum (MH40071 and MH56489), a Veterans Affairs Merit Award and NIMH grant (MH56606) to Dr. Siever, a grant from the National Center for Research Resources (MO1-RR00071) awarded to the General Clinical Research Center, Mount Sinai School of Medicine, and a Mental Illness Research, Education and Clinical Center (MIRECC) Veterans Integrated Service Network 3 award.


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