Corpus callosum abnormalities in women with borderline personality disorder and comorbid attention-deficit hyperactivity disorder

Nicolas Rüsch, MD; Eileen Luders, PhD; Klaus Lieb, MD; Roland Zahn, MD; Dieter Ebert, MD; Paul M. Thompson, PhD; Arthur W. Toga, PhD; Ludger Tebartz van Elst, MD

Rüsch, Zahn, Ebert, Tebartz van Elst — Department of Psychiatry and Psychotherapy, University of Freiburg, and the South German Brain Imaging Center, Freiburg, Germany; Luders, Thompson, Toga — Laboratory of Neuro Imaging, Department of Neurology, UCLA School of Medicine, Los Angeles, Calif.; Lieb — Department of Psychiatry, University of Mainz, Germany.

Objective: Decreased brain volumes in prefrontal, limbic and parietal areas have been found in women with borderline personality disorder (BPD). Recent models suggest impaired structural and functional connectivity in this condition. To investigate this, we studied the thickness of the corpus callosum, the largest connecting fibre bundle in the human brain. Methods: We acquired magnetic resonance imaging scans from 20 healthy women and 20 women with BPD and comorbid attention-deficit hyperactivity disorder. A novel computational mesh-based method was applied to measure callosal thickness at high spatial resolution. Results: Women with BPD had a thinner isthmus of the corpus callosum, compared with healthy women. In the patient group, a history of childhood sexual abuse was associated with a thinner posterior body of the corpus callosum. Conclusion: Interhemispheric structural connectivity involving parietal and temporal areas may be impaired in women with BPD and comorbid attention-deficit hyperactivity disorder.

Introduction

Structural neuroimaging studies have shown volume reductions in frontolimbic and parietal areas in women with borderline personality disorder (BPD). In addition, recent models suggest that the complex symptomatology of BPD is related not only to alterations in separate brain regions but also to impaired connectivity. Finally, a diffusion tensor imaging study found that impaired inferior frontal white matter microstructure, an index of reduced structural connectivity, was associated with dysfunctional affect regulation, anger–hostility, dissociative symptoms and general psychopathology among women with BPD.

Against this background, we hypothesized that the corpus callosum might be impaired in women with BPD and comorbid attention-deficit hyperactivity disorder.

Correspondence to: Dr. Nicolas Rüsch, Joint Research Programs in Psychiatric Rehabilitation, Illinois Institute of Technology, 3424 S. State St., Chicago IL 60616; fax 312 567-6753; nicolas.ruesch@uniklinik-freiburg.de

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callosum, the largest connecting fibre bundle in the human brain, is structurally altered in people with BPD. Callosal fibres are organized topographically, where callosal subdivisions also correspond to cortical regions and functional boundaries. Given that previous BPD studies revealed reductions in such frontal regions as the orbitofrontal and anterior cingulate cortex and in parietal and temporal regions, we hypothesized that callosal fibres connecting these regions are affected in people with BPD. More specifically, we expected a reduced thickness in the genu, the posterior body and the isthmus of the corpus callosum, assuming that callosal thickness is an indicator of the degree of myelination or the number of crossing axons, or both, and thus a structural marker of interhemispheric connectivity.

In addition, childhood sexual abuse is common in BPD and has been shown to be associated with decreased callosal size. For example, Teicher and colleagues detected significant reductions of the callosal body in adolescent female survivors of sexual abuse. We therefore set out to contrast callosal thickness in BPD subgroups and compare women with a history of sexual abuse with women without such a history. We hypothesized a reduced thickness of the body of the corpus callosum in women with BPD and childhood sexual abuse. To test our hypotheses, we applied a novel and well-validated computational mesh-based method to measure callosal thickness at high spatial resolution. This method provides greater spatial detail and localization power than traditional approaches that parcellate the corpus callosum into different segments at geometrical boundaries of controversial structural and functional validity.

Methods

Participants

Twenty women with BPD and comorbid attention-deficit hyperactivity disorder (ADHD) were recruited by the Department of Psychiatry and Psychotherapy, University of Freiburg, Germany. The sample investigated in the study reported here, including healthy control subjects, is identical to the subjects of the above-mentioned diffusion tensor imaging study. All subjects were free of psychotropic medication for at least 2 weeks before image acquisition. All women with BPD met diagnostic criteria for BPD according to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV), as assessed by the Structured Clinical Interview for DSM-IV Axis II Personality Disorders, and fulfilled DSM-IV criteria for ADHD. Axis I comorbidity was assessed with the Mini-International Neuropsychiatric Interview. We studied women with BPD and ADHD as a representative and more homogeneous subgroup within the heterogeneous BPD syndrome because ADHD symptoms are common in BPD (about 60% of adults with BPD have a lifetime history of ADHD) and show considerable overlap with BPD features such as emotional instability and impulsivity.

Comorbid psychiatric disorders are frequent in BPD and should be considered carefully to maintain the external and internal validity of studies in this condition. Therefore, to limit sample heterogeneity, we excluded subjects with the following comorbid conditions: current major depression at the time of scanning, lifetime substance dependence and any substance abuse in the 6 months before image acquisition. Further, we excluded subjects with a lifetime diagnosis of schizophrenia, bipolar I disorder, traumatic brain injury or any medical disorder that might affect brain structure. Only women were studied to minimize possible variance due to sex differences and to reflect the greater prevalence of BPD among women.

Women with BPD had a history of about 2 suicide attempts, with a mean of 2.2 (standard deviation [SD] 2.5); about 2 previous psychiatric hospitalizations, with a mean of 2.3 (SD 2.0); and about 3 self-injurious behaviours per month during the past half year, with a mean of 2.9 (SD 5.1). Of all 20 participants with BPD, 7 had a current eating disorder, 20 participants with BPD, 7 had a current eating disorder,
and 14 had previously had a major depression. One-half of the patients had suffered from sexual abuse in childhood, and of those 10, 5 had current posttraumatic stress disorder.

Twenty healthy female control subjects were group-matched with the patients for age, school education and premorbid intelligence as measured by the Mehrfachwahl-Wortschatz-Intelligenz-Test19 (Table 1). We assessed general psychopathology with the Symptom Check List-revised.21 The level of ADHD symptomatology was retrospectively assessed by a 25-item version of the Wender Utah Rating Scale.22 Dissociative symptoms were assessed by the 44-item German version23 of the Dissociative Experience Scale,24 which has a total mean score between 0 and 100. All 40 subjects in this study were right-handed women between 18 and 45 years of age who had completed at least 9 years of school education. The study was approved by the Ethics Committee of the University Hospital Freiburg, and all participants gave written informed consent after the procedures had been fully explained.

**MRI acquisition and data preprocessing**

On a 3 Tesla Magnetom Trio MRI scanner (Siemens Medical Systems, Erlangen, Germany), we acquired high-resolution $T_1$-weighted images with a magnetization-prepared ultrafast gradient-echo sequence and the following parameters: field of view (FOV) 240 mm (FOV phase 100%), 1 slab; 160 slices; 30% slice oversampling; repetition time (TR) 2300; inversion time (TI) 1100; echo time (TE) 3.68; flip angle 12°; bandwidth 140 Hz/pixel; voxel size $1 \times 1 \times 1$ mm. Radiofrequency bias field corrections were applied to all images to eliminate intensity drifts due to magnetic field inhomogeneities; this was followed by the manual repositioning of each image volume to horizontally reorient the anterior–posterior commissure line.

**Callosal thickness and area measurements**

A systematic overview of the basic steps in the measurement of callosal thickness is provided elsewhere.23 Briefly, one rater (E.L.), who was blind to group status, identified the corpus callosum in the midsagittal section of each brain and delineated the upper (top) and lower (bottom) callosal boundaries and then computed the spatial mean curve (medial curve) from homologous surface points representing top and bottom. Pointwise distances from the medial curve to callosal top and bottom curves were calculated at 100 points across the corpus callosum. These callosal distances were compared between groups by applying independent sample Student’s $t$ tests at each distance measure. Because we had predicted a priori that thickness is decreased in certain callosal subregions — in the genu, posterior body and isthmus for women with BPD, compared with healthy women; and in the callosal body for women with BPD and childhood sexual abuse, compared with women with BPD but without childhood sexual abuse — we did not correct for multiple comparisons.

To measure brain size as a possible confounding variable, we manually delineated total brain volume, including the cerebrum, cerebellum and brainstem superior to the pons, as was done for earlier publications by our group.2 Total brain volume did not differ significantly between healthy women and women with BPD, nor did it differ between women with BPD with and without childhood sexual abuse (Table 1 and Table 2). We therefore analyzed data without including brain volume as a covariate. To visualize group differences in callosal thickness, we generated 2 sets of colour-coded maps illustrating statistically significant regions: first, between women with BPD ($n = 20$) and healthy women ($n = 20$); and second, within the BPD group, between subjects with a history of childhood sexual abuse ($n = 10$) and subjects without such history ($n = 10$) (Fig. 1, left panel). To clarify results of the pointwise $t$ tests in those areas in which the group

<table>
<thead>
<tr>
<th>Group; mean (and SD)</th>
<th>Women with BPD and childhood sexual abuse ($n = 10$)</th>
<th>Women with BPD but without childhood sexual abuse ($n = 10$)</th>
<th>df</th>
<th>$t$ value*</th>
<th>$p$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>30.6 (6.7)</td>
<td>25.3 (3.7)</td>
<td>18</td>
<td>$-2.16$</td>
<td>0.042</td>
</tr>
<tr>
<td>Education, yr</td>
<td>10.5 (1.9)</td>
<td>11.0 (2.1)</td>
<td>18</td>
<td>0.061</td>
<td>0.55</td>
</tr>
<tr>
<td>Premorbid intelligence (MWT-B)</td>
<td>27.4 (3.9)</td>
<td>28.8 (5.6)</td>
<td>18</td>
<td>0.65</td>
<td>0.53</td>
</tr>
<tr>
<td>ADHD symptoms (WURS)</td>
<td>57.6 (15.5)</td>
<td>53.8 (20.4)</td>
<td>18</td>
<td>$-0.47$</td>
<td>0.65</td>
</tr>
<tr>
<td>General psychopathology (SCL-90-R)</td>
<td>1.3 (0.7)</td>
<td>1.2 (0.7)</td>
<td>18</td>
<td>$-0.43$</td>
<td>0.68</td>
</tr>
<tr>
<td>Dissociative symptoms (DES)</td>
<td>13.1 (8.1)</td>
<td>17.8 (11.8)</td>
<td>18</td>
<td>1.04</td>
<td>0.31</td>
</tr>
<tr>
<td>Anterior third area, mm$^2$</td>
<td>246.6 (55.3)</td>
<td>259.8 (41.5)</td>
<td>18</td>
<td>$-0.60$</td>
<td>0.56</td>
</tr>
<tr>
<td>Anterior body area, mm$^2$</td>
<td>68.1 (13.1)</td>
<td>77.2 (10.0)</td>
<td>18</td>
<td>$-1.75$</td>
<td>0.098</td>
</tr>
<tr>
<td>Posterior body area, mm$^2$</td>
<td>54.0 (8.5)</td>
<td>63.4 (8.9)</td>
<td>18</td>
<td>$-2.44$</td>
<td>0.025</td>
</tr>
<tr>
<td>Isthmus area, mm$^2$</td>
<td>45.0 (6.3)</td>
<td>54.4 (12.8)</td>
<td>18</td>
<td>$-2.09$</td>
<td>0.051</td>
</tr>
<tr>
<td>Splenium area, mm$^2$</td>
<td>169.4 (24.4)</td>
<td>172.5 (23.0)</td>
<td>18</td>
<td>$-0.29$</td>
<td>0.78</td>
</tr>
<tr>
<td>Total brain volume, cm$^3$</td>
<td>1203 (79)</td>
<td>1236 (132)</td>
<td>18</td>
<td>0.68</td>
<td>0.50</td>
</tr>
</tbody>
</table>

BPD = borderline personality disorder; SD = standard deviation; df = degrees of freedom; MWT-B = Mehrfachwahl-Wortschatz-Intelligenz-Test; ADHD = attention-deficit hyperactivity disorder; WURS = Wender Utah Rating Scale; SCL-90-R = Symptom Check List-90-revised; DES = Dissociative Experience Scale. German version.*

*Comparisons are 2-tailed $t$ tests for means across each row.
comparisons did not reach significance, we further included maps showing the respective t values for both comparisons (Fig. 1, right panel).

To render our results comparable to previous findings in the literature, we also examined areas of 5 predefined callosal subdivisions according to well-known conventional parcellation schemes.24–26 For this purpose, the callosal renderings were reoriented to maximize callosal length and divided vertically into 5 partitions representing the splenium, isthmus, posterior midbody, anterior midbody and anterior third, as described previously.12 Area measures were acquired in mm² for each segment and compared between groups by applying independent sample Student’s t tests.

Results

Group comparison of women with BPD and healthy women

As demonstrated in Figure 1 (top panel, left), the isthmus of the corpus callosum was significantly thinner in women with BPD than in healthy women. Conversely, control subjects did not show significantly reduced callosal thickness, relative to patients, in any area of the corpus callosum (map not shown). In comparison, the subarea comparison according to the traditional parcellation scheme indicated only trends for reduced isthmus and posterior body areas among women with BPD (Table 1).
Subgroup comparison of women with BPD with and without childhood sexual abuse

As further displayed in Figure 1 (middle panel, left), when we compared the 2 patient subgroups that differed with respect to childhood sexual abuse, we found a thinner posterior callosal body in women with BPD and a history of sexual abuse. We did not find regions of significantly increased callosal thickness in patients with a history of sexual abuse, compared with patients without such a history (map not shown). Since women with BPD and childhood sexual abuse were older than those with BPD alone (Table 2), we repeated the callosal thickness analysis, controlling for age as covariate of no interest. The subgroup difference remained significant, and women without sexual abuse had an increased callosal thickness, compared with women with sexual abuse. Nevertheless, regions of increased callosal thickness were less widespread (Fig. 1, lower panel, left).

When we compared subareas of predefined callosal sections, the posterior body was significantly reduced in women with BPD and childhood sexual abuse. In addition, there was a trend for reduced anterior body and isthmus areas in women with BPD and childhood sexual abuse (Table 2). After controlling for age in an analysis of covariance, the significant differences in the area of the posterior callosal body turned into a nonsignificant trend \(F_{1,17} = 3.81, p = 0.068\), whereas subgroup differences in the area of the isthmus remained a trend \(F_{1,17} = 3.78, p = 0.069\) and anterior body differences were nonsignificant \(F_{1,17} = 1.34, p = 0.26\).

Discussion

We found a thinner isthmus of the corpus callosum in women with BPD and comorbid ADHD. Reduced callosal thickness may result from disturbed myelination or a reduced number of callosal fibres, or both; it may therefore be a structural marker of disturbed interhemispheric structural connectivity. Thus our results offer empirical support for impaired structural interhemispheric connectivity in BPD. This parallels our finding in the same sample that impaired structural connectivity in bilateral inferior frontal white matter is linked to key symptoms of BPD, such as dysfunctional affect regulation and anger–hostility.

Despite previous findings of frontal volume reductions in BPD,\(^7\)\(^\text{10}\) we did not find reduced thickness of the genu (the anterior section of the corpus callosum). Interestingly, a recent study\(^2\) detected reduced grey matter in the anterior cingulate in BPD but increased underlying white matter, whereas overall prefrontal volume did not differ from that in control subjects. Thus one could speculate that these structural alterations may outweigh each other in their effect on callosal thickness and area in the genu and thus lead to similar callosal measurements in BPD and control subjects. However, this issue clearly needs further investigation because many previous morphometric studies failed, unlike that of Hazlett and colleagues,\(^2\) to differentiate between grey and white matter volume. Further, continued development of the frontal cortex until early adulthood may explain the lack of significant group differences in anterior sections of the corpus callosum.

Interestingly, as far as functional connectivity is concerned, an electroencephalographic study\(^4\) found impaired posterior synchrony in BPD, which agrees well with the posterior localization of the callosal abnormalities in our study. Possibly, impaired structural interhemispheric connectivity leads to poor integration of neural networks that, in turn, is linked to dissociative symptoms, impulsivity and cognitive impairments in BPD.\(^7\) The posterior localization of our finding further connects well to recent reports of reduced parietal volume among women with BPD.\(^7\)

Because women with BPD in this study also had ADHD symptoms, research on ADHD should be considered in the interpretation of our findings. Recent data suggest impaired structural and functional networks, particularly interhemispheric networks, in ADHD.\(^2\)\(^7\)\(^\text{20}\) The posterior localization of our finding corroborates previous reports of parietal cortical thinning in adults with ADHD.\(^7\) It also corroborates reports of structural abnormalities that were found particularly in posterior regions of the corpus callosum in children with ADHD.\(^2\) Moreover, a recent neuronal network model suggests that ADHD is associated with impaired interhemispheric connectivity that may be structurally evident as reduced callosal thickness.\(^8\) Considering these previous and our current findings, it may be worthwhile for future research to investigate neurobiological similarities between BPD and ADHD in addition to the well-known clinical similarities.\(^15\)

We found a thinner callosal posterior body among women with BPD and childhood sexual abuse. Similarly, a previous study\(^11\) investigating callosal size in children who had experienced various types of abuse and neglect revealed a significant effect of sexual abuse on the thickness of the callosal body only in girls, not in boys. Although both studies are in agreement, our finding of callosal thinning related to childhood sexual abuse in this population should be considered preliminary; it needs to be confirmed in future investigations for the following reasons: First, both of our subgroups were small, albeit larger than some previous samples.\(^5\) Second, women with BPD and childhood sexual abuse were slightly older than the comparison subgroup, and after controlling for age, subgroup differences were less widespread, making age a confound in our analysis. Third, one-half of the sexually abused BPD subgroup suffered from current comorbid posttraumatic stress disorder. Sexual abuse history and posttraumatic stress disorder very frequently cooccur in women with BPD, but of course, this overlap is a possible confound in this subgroup comparison.

This initial study has some further limitations. Although we defined inclusion and exclusion criteria carefully to strike a reasonable balance between external and internal validity with respect to psychiatric comorbidity and clinical history, confounding influences of comorbid conditions cannot be ruled out. Future studies of larger samples should include comparisons of subgroups with different comorbidities and should also include subjects with ADHD alone (that is, without comorbid BPD). We did not assess Axis II comorbidity;
therefore, the possible influence of comorbid personality disorders on brain morphology could not be examined. Because we studied a female sample with ADHD comorbidity, our findings cannot be generalized to men or to people with BPD but without comorbid ADHD. Finally, longitudinal studies should investigate whether reduced callosal thickness is a cause or consequence of BPD.

Methodologically, our study underlines the advantage of assessing callosal thickness at high spatial resolution as compared with area measurements in several callosal subregions parcellated at well-established but arbitrary geometrical boundaries. The pattern of callosal area reductions in the parcellated at well-established but arbitrary geometrical boundaries. The pattern of callosal area reductions in the 2 group comparisons reflected regional findings of callosal thinning and thus supported the plausible association between callosal thickness and area. Comparisons of callosal subareas, however, were clearly less sensitive and had much lower localization power than pointwise thickness measurements.

In summary, we found reduced thickness in the callosal isthmus among women with BPD and comorbid ADHD. This suggests impaired structural interhemispheric connectivity affecting especially posterior regions, which is consistent with previous reports of altered morphology in the parietal and temporal lobes. Further, a thinner callosal posterior body was associated with childhood sexual abuse among women with BPD and comorbid ADHD.

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Competing interests: None declared.

Contributors: Drs. Rüsch, Ebert and Tebartz van Elst designed the study. Dr. Rüsch acquired the data, which all authors analyzed. Drs. Rüsch, Luders, Zahn, Thompson and Toga wrote the article, and all authors revised it. All authors gave final approval for the article to be published.

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