Neurodevelopmental origins of abnormal cortical morphology in dissociative identity disorder


Objective: To examine the two constitutes of cortical volume (CV), that is, cortical thickness (CT) and surface area (SA), in individuals with dissociative identity disorder (DID) with the view of gaining important novel insights into the underlying neurobiological mechanisms mediating DID.

Methods: This study included 32 female patients with DID and 43 matched healthy controls. Between-group differences in CV, thickness, and SA, the degree of spatial overlap between differences in CT and SA, and their relative contribution to differences in regional CV were assessed using a novel spatially unbiased vertex-wise approach. Whole-brain correlation analyses were performed between measures of cortical anatomy and dissociative symptoms and traumatization.

Results: Individuals with DID differed from controls in CV, CT, and SA, with significantly decreased CT in the insula, anterior cingulate, and parietal regions and reduced cortical SA in temporal and orbitofrontal cortices. Abnormalities in CT and SA shared only about 3% of all significantly different cerebral surface locations and involved distinct contributions to the abnormality of CV in DID. Significant negative associations between abnormal brain morphology (SA and CV) and dissociative symptoms and early childhood traumatization (0 and 3 years of age) were found.

Conclusions: In DID, neuroanatomical areas with decreased CT and SA are in different locations in the brain. As CT and SA have distinct genetic and developmental origins, our findings may indicate that different neurobiological mechanisms and environmental factors impact on cortical morphology in DID, such as early childhood traumatization.

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Key words: childhood trauma; dissociation; MRI; neuroimaging; post-traumatic stress disorder

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Significant outcomes

- This multicenter case–control study in 75 participants revealed that dissociative identity disorder is associated with significant abnormal cortical volume and with distinct abnormalities of cortical thickness and cortical surface area.
- Because cortical thickness and cortical surface area have distinct genetic and developmental origins, different neurobiological mechanisms and environmental factors may impact differently on brain morphology in dissociative identity disorder.
Limitations

- Only female individuals with dissociative identity disorder volunteered to participate in the study.
- We were not able to perform a regression analysis with post-traumatic stress disorder severity.

Introduction

Dissociative identity disorder (DID) is considered an early-onset and chronic interpersonal trauma-related disorder (1–6). For early-onset interpersonal trauma-related disorders, it is currently unknown how early traumatization affects the development of the brain and what particular aspect of the cortical neuroanatomy is most affected. Altered stress reactivity following childhood trauma is related to altered gene expression (7), thus suggesting that early life stressors may have long-lasting detrimental effects on neurobiology and foster development of trauma-related psychopathology (8) such as DID. A novel spatially unbiased vertex-wise method that examines regional differences in cortical volume (CV) on the basis of its two different neurodevelopmentally driven constituent components, cortical thickness (CT) and surface area (SA), has become available (9). Examining the brain in DID using this method may therefore provide important new insights into the neurobiological development in early-onset trauma-related disorders.

Dissociative identity disorder is a psychiatric disorder involving two or more dissociative personality states, recurrent gaps in the recall of everyday events or important personal information, and/or traumatic events that are inconsistent with ordinary forgetting, which is not related to substance abuse or general medication (10). Prevalence of DID is approximately 1% among women in the general population (11) and 6% in psychiatric out-patients (12). Nevertheless, few neuroimaging studies have examined the neuroanatomical correlates of DID. Previous studies examining neuroanatomical alterations in DID mostly focused on subcortical regions (3, 13–15). However, a recent study by our group (4) has also investigated brain abnormalities in DID on the cortical level using an exploratory approach in a set of 68 predefined cortical areas across the cortex and reported that individuals with DID have significantly reduced gray matter volume in the medial and dorsolateral prefrontal cortex, the anterior cingulate, the insular cortex, inferior parietal areas, and in several regions within the temporal lobe (4). A high degree of overlap was found between these neuroanatomical aberrations and dissociative personality state-dependent brain functioning during emotion regulation, which showed predominantly activation in the parietal regions, insula and limbic(prefrontal circuitry (16, 17). The parietal and insular regions, and the limbic-prefrontal circuitry of the brain are therefore of pivotal interest in the investigation of brain function and structure in DID.

Moreover, previous studies examining neuroanatomical abnormalities in DID were mostly based on a priori defined regions of interests and were based on traditional measures of regional or brain volumes. However, CV is by definition a product of CT and SA, which represent distinct aspects of the cortical architecture (18), are mediated by different genetic determinants (19), and have a contrasting phylogeny (20) and distinct developmental trajectories (21). It is thus crucial for our understanding of the effects that early-onset and chronic interpersonal traumatization has on the brain, and which particular aspects of the cortical architecture are most vulnerable. Last, only few studies to date have investigated the relationship between dissociative symptoms and measures of structural brain morphology (4, 22–24), and the neurobiological correlates of dissociative symptoms therefore remain poorly understood.

In this study, we therefore employed a spatially unbiased, that is vertex-wise, approach to investigate cortical morphology in a large sample of adult females with DID as compared to healthy controls (HC) in order to disentangle differences in CT and SA and their relative contribution to observed differences in CV. We hypothesized that individuals with DID would show neuroanatomical differences in all three parameters predominantly in parietal and insular regions, and the limbic-prefrontal circuitry of the brain. These differences are expected to correlate negatively with the severity of dissociative symptoms and traumatic experiences. We further hypothesized that differences in CT and SA would be largely non-overlapping, given the non-specific, that is non-genetic, etiology of DID, and hence reflecting different phylogenetic processes under the influence of early life stress.
Aims of the study

Traditional volumetric measures of brain anatomy are highly unspecific as cortical volume is—by definition—a product of the two distinct parameters cortical thickness (CT) and cortical surface area (SA). We aimed to not only investigate whether dissociative identity disorder (DID) is associated with volumetric differences in brain morphology, but also to disentangle the relative contribution of CT and SA to regional abnormalities in cortical volume in order to elucidate the neurobiological underpinnings of DID. Furthermore, we aimed to investigate whether abnormalities in cortical morphology are associated with dissociative symptoms and/or (early) traumatization. Ultimately, we aimed to provide new insights into neurobiological mechanisms involved in the development of abnormal cortical morphology in DID.

Material and methods

Participants

Overall, data from 75 participants (32 women with DID, 43 female HC) were included in this study from three centers: the University Medical Centre in Groningen (UMCG, the Netherlands), the Amsterdam Medical Centre (AMC, the Netherlands), and the University Hospital in Zurich (USH, Switzerland). Sample details have been published previously [see Chalavi et al. (3, 4) for the Dutch sample and Schlumpf et al. (25, 26) for the Swiss/German sample]. In sum, all women with DID were recruited from private practitioners of psychiatry and psychotherapy and psychiatric outpatient departments and initially diagnosed according to DSM-IV criteria. The clinical diagnosis was subsequently confirmed by independent experts using the Structural Clinical Interview for DSM-IV Dissociative Disorders (SCID-D) (27, 28). Psychoform dissociative symptoms were measured with the Dissociative Experiences Scale (DES Ref. 29), and somatoform dissociative symptoms with the Somatoform Dissociation Questionnaire (SDQ-20 Ref. 30). Depersonalization symptoms were assessed using the Cambridge Depersonalization Scale (CDS Ref. 31). Potentially traumatizing events were measured with the Traumatic Experiences Checklist (TEC Ref. 32). For the five categories emotional neglect, emotional abuse, physical abuse, sexual abuse, and sexual harassment, the TEC total scores as well as TEC scores from different stages in childhood were calculated, that is for 0–6 years, 7–12 years, and 13–18 years. In addition, using a set of paired $t$-tests, the five TEC categories were statistically compared between the three different childhood age ranges: 0–6 vs. 7–12, 0–6 vs. 13–18, and 7–12 vs. 13–18.

Out of 32 DID individuals, 29 individuals had comorbid post-traumatic stress disorder (PTSD), and three individuals had PTSD in remission. The following information concerning other comorbid disorders was obtained based on DSM-IV classification (American Psychiatric Association, 1994) from the participants and/or their personal therapists ($N = 29$): no other comorbid disorders ($N = 13$), somatoform disorder ($N = 2$), depression (chronic $N = 1$, recurrent $N = 10$), dystymic disorder ($N = 1$), specific phobias ($N = 3$), panic disorder ($N = 3$), anxiety disorder ($N = 1$), obsessive-compulsive disorder ($N = 1$), personality disorders [not otherwise specified ($N = 2$), mixed ($N = 2$), borderline personality disorder ($N = 5$), dependent and histrionic ($N = 1$), eating disorder ($N = 3$), sleeping disorder ($N = 2$), catalepsy ($N = 1$), psychogenic seizures ($N = 1$), and attention deficit disorder ($N = 1$).

The DID and control group were carefully matched for demographics including age, gender, years of education, and Western European ancestry (see Table 1). All HC were free of medication and psychiatric disorders. They scored below a critical cutoff of 25 on the DES and 29 on the SDQ-20. We had excluded HC with potentially traumatizing experiences as measured by the TEC from participation. All participants gave informed written consent in accordance with ethics approval by the Declaration of Helsinki.

MRI data acquisition

Data were obtained on 3-T Philips whole-body MRI scanners (Philips Medical Systems, Best, NL, USA). An optimized structural MRI protocol with highly reproducible anatomical measures between centers was used (33) at all three centers, and T1-weighted anatomical MR scans were acquired (3D MPRAGE, $TR = 9.95 \text{ ms}$, $TE = 5.6 \text{ ms}$, flip-angle = $8^\circ$, $1 \times 1 \times 1 \text{ mm}^3$ voxels, number of slices = 160, total scan-time = 10m 14s). Approximately equal ratios of patients to controls were acquired in an interleaved manner within centers (10 : 17 at the UMCG, 7 : 11 at the AMC, 15 : 15 in Zurich; patients: controls respectively). The number of participants in each group did not differ across centers (chi-square = 1.01, $P = 0.603$).

Cortical surface reconstruction using Freesurfer

The Freesurfer analysis suite (vFS5.3.0 release, http://surfer.nmr.mgh.harvard.edu/) was used to...
derive models of the cortical surface in each T1-weighted image. These well-validated and fully automated procedures have been extensively described elsewhere (34–37). In brief, a single filled white matter volume was generated for each hemisphere after intensity normalization, skull stripping, and image segmentation using a connected components algorithm. Then, a surface tessellation was generated for each white matter volume by fitting a deformable template. This resulted in a triangular cortical mesh for gray and white matter surfaces consisting of approximately 150,000 vertices (i.e., points) per hemisphere. Following standard FReeSurfer preprocessing, each reconstructed surface was then visually inspected for reconstruction errors.

A spatially unbiased vertex-wise approach provides measures of CT, SA, and CV at several thousand points, that is, vertices, across the cortical surface. Measures of CT were computed as the closest distance from the gray and white matter boundary to the gray matter and cerebrospinal fluid boundary at each vertex on the tessellated surface and vertex-based estimates of SA were derived (38). Vertex-wise estimates of CV were derived as the product of CT and SA at each cerebral vertex. We also computed mean CT, total SA, and total CV (across hemispheres) for each participant. To improve the ability to detect population changes, each parameter was smoothed using a 13-mm surface-based smoothing kernel. Of note, this cortical surface reconstruction method does not include subcortical and (para)hippocampal regions.

**Statistical analysis**

We first examined between-group differences in global brain measures (i.e., total gray and white matter volume, total SA, and mean CT) using a multivariate general linear model (GLM) with diagnostic group and site as categorical fixed-effects factors and age as continuous covariate (P < 0.05, two-tailed). To examine the relative contribution of differences in CT and SA to regional differences in CV, a vertex-wise statistical analysis was subsequently conducted using the SurfStat toolbox (http://www.math.mcgill.ca/keith/surfstat/) for MATLAB (MATLAB Release 2014a; The MathWorks, Inc., Natick, MA, USA). Parameter estimates for vertex-based measures of CT, SA, and CV were estimated by performing a linear regression at each vertex with subject j, with (1) group and site as categorical fixed-effects factors; and (2) age as continuous covariates, so that

\[
Y_i = \beta_0 + \beta_1 \text{Group}_j + \beta_2 \text{Site}_j + \beta_3 \text{Age}_j + \epsilon_i.
\]

Between-group differences were estimated from the fixed-effect coefficient \(\beta_1\) normalized by the corresponding standard error. Corrections for multiple comparisons across the whole brain were performed using random-field theory (RFT)-based cluster-corrected analysis for non-isotropic images using a \(P < 0.05\) (two-tailed) cluster-significance
threshold (39). Between-group differences in global brain measures were examined using the same GLM as formalized above. To compare frequencies of unique or overlapping differences in each morphometric parameter, the resulting spatially distributed binary patterns of differences unique to CT and/or SA, as well as their overlap regardless of the sign (i.e., based on their statistical threshold), were then compared using a chi-square test (i.e., contingency table) testing the null hypothesis that differences in CT and SA are equally distributed. Furthermore, a simulation strategy was used to assess whether the observed degree of overlap between differences in CT and SA is consistent with the idea of two spatially independent patterns. This hypothesis was tested on the basis of \( N = 5000 \) randomly generated difference maps (i.e., maps containing random \( t \) values, thresholded at \( P < 0.05 \)) for CT and SA. The extent of overlap between groups (i.e., number of vertices with differences in CT and SA) was then assessed in each of the 5000 overlapping patterns to derive a probability value of obtaining a given percentage of overlap on the basis of randomly varying patterns of differences.

The relationship between cortical thickness, surface area, and dissociative symptoms and traumatization.

General linear model analyses were performed to investigate associations between neuroanatomical features and composite clinical scores, that is, dissociative symptoms and traumatization respectively. Corrections for multiple comparisons across the whole brain were performed using RFT-based cluster-corrected analysis for non-isotropic images using a \( P < 0.05 \) (two-tailed) cluster-significance threshold (39). Correlations between neuroanatomical features and measures of dissociative symptom severity (see Table 1) were explored using composite clinical dissociation scores because the three questionnaires are closely related. To this end, the SDQ-20, DES, and CDS scores were subjected to a principal component analysis (PCA) (4) and an eigenvalue of 1 was used as the cutoff (16, 40–42). This resulted in one principal component explaining 71.5% of the variance in clinical measures of dissociation, which was used in the analyses. Correlations between neuroanatomical features and measures of traumatic experiences (see Tables 1 and 2) were explored using composite clinical scores of the three developmental periods, that is for 0–6, 7–12, and 13–19, in three separate analyses.

**Results**

Participant demographics and total brain measures.

Overall, the DID and control groups did not differ significantly in age (\( t_{73} = 0.08, P = 0.608 \)) or years of education (\( t_{73} = -1.23, P = 0.220 \)). As expected, individuals with DID differed significantly from controls in depersonalization and psychoform as well as somatoform dissociative symptom scores, which were significantly higher in the DID group as compared to the HC group (\( P < 0.001 \)) (see Table 1). DID patients scored significantly higher compared to HC on all five adverse event categories, namely emotional neglect, emotional abuse, physical abuse, sexual abuse, and sexual harassment (see Table 2). This was the case for the total TEC scores as well as for the three childhood age ranges 0–6, 7–12, and 13–18 years. Notably, TEC scores for none of the five categories were significantly different between the childhood age ranges 7–12 and 13–18. On the other hand, TEC scores from the age range 0–6 differed significantly on all five categories when compared to both older age ranges. These results are indicative of early childhood traumatization.

Individuals with DID had significantly reduced total gray matter volume relative to HC (\( F_{1} = 6.169, P = 0.015 \)). There were no significant between-group differences in total SA (\( F_{1} = 3.18, P = 0.079 \)) or average CT (\( F_{1} = 1.71, P = 0.196 \)).

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### Table 2. Experience trauma scores during different stages of childhood in dissociative identity disorder (DID) patients

<table>
<thead>
<tr>
<th>DID (n = 28)</th>
<th>Mean (SD)</th>
<th>Paired ( t )-test comparisons: ( P )-values</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Age 0–6</td>
<td>Age 7–12</td>
</tr>
<tr>
<td>Emotional neglect</td>
<td>5.00 (0.00)</td>
<td>4.00 (0.00)</td>
</tr>
<tr>
<td>Emotional abuse</td>
<td>4.75 (0.97)</td>
<td>3.79 (0.79)</td>
</tr>
<tr>
<td>Physical abuse</td>
<td>4.75 (1.00)</td>
<td>3.82 (0.86)</td>
</tr>
<tr>
<td>Sexual harassment</td>
<td>3.57 (1.97)</td>
<td>2.79 (1.57)</td>
</tr>
<tr>
<td>Sexual abuse</td>
<td>4.36 (1.57)</td>
<td>3.21 (1.55)</td>
</tr>
</tbody>
</table>

\( x \) = Paired \( t \)-test was not calculated since standard deviation of the two variables was zero.

*\( P \)-value < .05.
Between-group differences in cortical thickness

We initially examined vertex-wise between-group differences in CT. Individuals with DID had significantly decreased CT ($P < 0.05$) in several spatially distributed clusters across the cortex, see Table 3 and Fig. 1a. The clusters included (1) the left insular cortex, extending into the dorsolateral orbitofrontal cortex [Brodmann area (BA) 44/45/47], (2) the cingulate cortex, (3) the left temporoparietal junction (BA 19/39), (4 & 5) the left pre/postcentral gyrus, and (6) the right temporal lobe. There were no brain regions where individuals with DID had significantly increased CT relative to HC.

Between-group differences in surface area

Individuals with DID had significantly reduced SA ($P < 0.05$) in the left superior temporal sulcus (STS), the cingulate sulcus, extending into the medial superior frontal lobe (BA 6/8), and in the right dorsolateral orbital prefrontal cortex. Statistical details for regions of significantly between-group differences are listed in Table 3 and depicted in Fig. 1b. We did not observe any clusters of significantly increased SA in DID as compared to controls.

Spatial overlap between differences in surface area and cortical thickness

Table 4 lists significant spatial overlap between differences in CT and SA, which are presented in Fig. 1c. Across both hemispheres, the largest proportion of all between-group differences (either CT or SA or both) resulted from differences in CT only (66.80%), while vertices with a significant reduction in SA only explained about 29.47% overall. Thus, there were two times as many differences in CT only as there were in SA only (66.80% vs. 29.47%, $\chi^2_{df=2} = 27.45$, $P < 0.001$).

The patterns of significant differences in CT and SA were largely non-overlapping and shared only 3.53% of all different spatial locations on the cerebral surface. The probability of any one vertex displaying a difference in both CT and SA was therefore very low. Simulations revealed that the probability of obtaining the same degree of overlap of 3.53% or lower by chance is >99%. The observed percentage of overlap is hence consistent with the hypothesis that differences in CT and SA are spatially independent, and may contribute in a unique way to between-group differences in CV.

Between-group differences in vertex-wise estimates of cortical volume

Individuals with DID had extensive volumetric reductions ($P < 0.05$) in regional gray matter across the cerebral hemispheres (see Table 3 and Fig. 2a). Significant clusters of between-group differences in CV were found in (1 and 2) the left and right insula extending to the dorsolateral and orbitofrontal prefrontal cortex (BA 11/45/47), (3) the left superior and inferior temporal lobe, (4) the left cingulate sulcus, (5) the right medial superior frontal cortex, (6) the left postcentral gyrus, (7) the right anterior cingulate cortex, and (8) the right fusiform gyrus. There were no clusters of significantly increased CV in DID as compared to controls.

Contribution of cortical thickness and surface area to volumetric differences

Only 44.05% of the differences in CV could be explained by significant differences in CT, SA, or both (see Table 4 and Fig. 2b). There was also no statistical difference between the contribution of CT (24.45%) and SA differences (17.35%) to the observed differences in CV. The remaining differences in CV (55.94%) could not be explained by differences in either SA or CT or both and must therefore be due to a combination of subthreshold variations in both of these features.

Correlations between cortical thickness, surface area and cortical volume, and dissociative symptoms and traumatization

In many regions with a significant between-group difference in SA and/or CV, we also found a significant negative correlation between neuroanatomical deficits and measures of dissociative symptom severity. These are listed in Table S1 and depicted in Figure S1. Significant correlations were predominantly observed in bilateral frontal lobe regions for both SA and CV, including the orbitofrontal cortex, and in the right posterior temporal lobe and precuneus for measures of CV. There were no clusters of significant correlations between clinical composite scores and measure of CT.

The regression analyses of CT, SA, and CV with the total trauma composite scores per developmental period, that is, for 0–6, 7–12, and 13–18, did not provide any significant results. Lowering the threshold to explore uncorrected significance levels did not reveal any neuroanatomical correlates of traumatization for any of the three developmental periods.
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Cluster</th>
<th>Region labels*</th>
<th>Side</th>
<th>BA (t_{max})</th>
<th>No vertices</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>t_{max}</th>
<th>(p_{cluster})</th>
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<td>2</td>
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<td>23/24</td>
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<td>Angular gyrus, inferior parietal cortex, lateral occipital cortex</td>
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<td>-20</td>
<td>34</td>
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<td>3205</td>
<td>37</td>
<td>1</td>
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<td>10</td>
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<td>6899</td>
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<td>-4.35</td>
<td>4.31 \times 10^{-2}</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>Fusiform gyrus, inferior temporal gyrus</td>
<td>R</td>
<td>36/37</td>
<td>2619</td>
<td>46</td>
<td>-60</td>
<td>-2</td>
<td>-4.44</td>
<td>4.88 \times 10^{-3}</td>
</tr>
</tbody>
</table>

**Table 3.** Clusters of significant reductions in CT, SA, and CV in DID individuals relative to controls

BA, Brodmann area; \(t_{max}\), maximum absolute t-value (corrected for multiple comparisons); x, y, z: Talairach coordinates at \(t_{max}\); \(p_{cluster}\): cluster probability; DID, dissociative identity disorder; R, right; L, left; CT, cortical thickness; CV, cortical volume; SA, surface area; STS, superior temporal sulcus.

*First area listed belongs to \(t_{max}\) and cluster extends into following areas listed.
Fig. 1. Between-group differences for measures of cortical thickness (CT) and surface area (SA). (a) Clusters with significantly reduced CT [random-field theory (RFT)-based, cluster-corrected, \( P < 0.05 \)] in dissociative identity disorder (DID) compared to controls while controlling for the effects of site and age. (b) Clusters with significantly reduced SA (RFT-based, cluster-corrected, \( P < 0.05 \)) in DID compared to controls. (c) Percentage overlap between differences in CT and SA, where orange denotes significant differences in both CT and SA, green denotes significant differences in CT only, and cyan denotes a significant difference in SA only. [Colour figure can be viewed at wileyonlinelibrary.com]
Cortical morphology in DID

Table 4. Spatial overlap between differences in CT and SA, and relative contribution of differences in CT and SA to differences in cortical volume

<table>
<thead>
<tr>
<th>Measure</th>
<th>Left hemisphere</th>
<th>Right hemisphere</th>
<th>Across hemispheres</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overlap CT and SA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CT only</td>
<td>20954 (67.35)</td>
<td>9095 (65.58)</td>
<td>30049 (66.80)</td>
</tr>
<tr>
<td>SA only</td>
<td>8703 (27.96)</td>
<td>4554 (33.04)</td>
<td>13257 (29.47)</td>
</tr>
<tr>
<td>CT &amp; SA</td>
<td>1454 (4.67)</td>
<td>135 (0.98)</td>
<td>1589 (3.53)</td>
</tr>
<tr>
<td>Total†</td>
<td>31111 (100)</td>
<td>13784 (100)</td>
<td>44895 (100)</td>
</tr>
<tr>
<td>Contribution of CT and SA to CV</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CV</td>
<td>43040 (100)</td>
<td>26059 (100)</td>
<td>69099 (100)</td>
</tr>
<tr>
<td>CT only</td>
<td>13330 (30.97)</td>
<td>3567 (13.68)</td>
<td>16897 (24.45)</td>
</tr>
<tr>
<td>SA only</td>
<td>7965 (18.55)</td>
<td>4064 (15.36)</td>
<td>11989 (17.35)</td>
</tr>
<tr>
<td>CT &amp; SA</td>
<td>1423 (3.30)</td>
<td>135 (0.51)</td>
<td>1558 (2.25)</td>
</tr>
<tr>
<td>CV explained</td>
<td>22738 (52.82)</td>
<td>7706 (29.57)</td>
<td>30444 (44.05)</td>
</tr>
<tr>
<td>CV unexplained</td>
<td>20302 (47.17)</td>
<td>18353 (70.42)</td>
<td>38655 (55.94)</td>
</tr>
</tbody>
</table>

CT, cortical thickness; SA, surface area; CV, cortical volume.

*All vertices with significant difference in CT or SA.
†Total number of vertices with significant difference in either CT or SA.

Discussion

This is the first study, to our knowledge, to examine regional differences in CT and SA, the two components of CV, in a large sample of women with DID, using a novel spatially unbiased vertex-wise approach. We found that, relative to HC, women with DID presented distributed neuroanatomical changes in cortical morphology. Women with DID showed significant and extensive volumetric reductions of regional gray matter in the insula, the cingulate cortex, the dorsolateral, superior, medial, and orbitofrontal prefrontal cortex, and the superior and inferior temporal lobe. Furthermore, differences in CT and SA were largely non-overlapping and CT and SA contributed differently to differences in CV. These findings are important from a neurodevelopmental perspective as CT and SA represent distinct aspects of cortical architecture, which are likely modulated by distinct epigenetic and neurobiological mechanisms.

Spatially distributed differences in CT and SA were virtually non-overlapping. This finding is consistent with the notion that variations in CT and SA are spatially independent, and reflect independent sources of neuroanatomical variability (9) and possibly different phylogenetic processes, which could be affected by early life stress. Our findings also concur with reports suggesting that CT and SA are distinct neuroanatomical features that are mediated by different sets of genes (19) and—in the mature brain—reflect distinct aspects of the cortical architecture (18). For instance, the radial unit hypothesis [RUH (43)] links the size of the cortical surface to the number of radial units (or mini-columns) in the brain, while CT is more closely related to the number of cells within mini-columns (18). CT and SA may therefore result from distinct neurodevelopmental trajectories (21) that are possibly modulated by different neurobiological mechanisms under the influence of the early life environment (8, 44).

Furthermore, we found that CT and SA contributed similarly to the differences we observed in CV (Table 4, bottom part). Moreover, given a cluster-threshold of \( P < 0.05, 56\% \) of vertices within the cluster(s) of significant differences in CV could not be explained by (i.e., did not overlap with) vertices within clusters of significant differences in SA and/or CT (or both). While this finding limits the interpretability of our results in terms of identifying a specific neural mechanism for the volumetric structural abnormalities associated in DID, it remains a very important finding suggesting that non-genetic, environmental factors affect multiple aspects of brain development in DID that cannot be linked unaniomously to a specific molecular and/or developmental pathway. DID is thus unlike other neurodevelopmental conditions that are associated with specific neuroanatomical abnormalities. For example, autism spectrum disorder (ASD), a neurodevelopmental condition, has been shown to be associated with an accelerated expansion of the cortical surface, rather than an increase in CT (45). In the future, it will therefore be important to link specific neuroanatomical alterations to specific neurodevelopmental mechanisms and their respective sets of genes (21), patterns of gene expression (7), and/or altered stress reactivity following childhood trauma in DID.

As expected, the areas affected included parietal and insular regions as well as the limbic-frontal circuitry of the brain, previously shown to be implicated in emotion regulation in DID (16). DID is considered an early-onset form of PTSD (1–5), and therefore, one could reasonably expect to find similarities in abnormality of cortical morphology. In fact, PTSD is accompanied by abnormalities in brain anatomy and connectivity, which are correlated with symptom severity (46, 47). A meta-analysis showed that PTSD is related to decreased regional GM volume in the anterior cingulate cortex, the ventromedial prefrontal cortex, and the left temporal pole/middle temporal gyrus compared to individuals who lived adverse events but who did not have PTSD (48), or relative to HC (49). The present study revealed neuroanatomical alterations in similar regions in DID: spatially distributed reductions in CT and/or SA in a variety of cortical regions, including the anterior and posterior cingulate cortex, dorsolateral, and medial prefrontal regions (DLPFC, MPFC), as well as the STS and the temporo-parietal junctions. In many
of these regions, there also was reduction in regional cortical gray matter volume (CV) relative to HC. These similarities support the notion that DID is a severe form of PTSD. This needs empirical confirmation as we could not directly compare DID with PTSD, but the indications that DID overlaps with PTSD and the involvement of early life trauma in developing DID can help tailor treatment of individuals suffering from this disorder.

Whole-brain correlation analyses revealed significant associations between dissociative symptoms in SA and CV in several cortical regions, but not CT, including the bilateral prefrontal cortex, specifically the orbitofrontal cortex. This area has a pivotal role in the ‘orbitofrontal model’ (50) of DID, which proposes the involvement of the orbitofrontal cortex in the development of DID based on the maturation of the orbitofrontal cortex in an early abusive environment. It is also important to note that the orbitofrontal cortex plays an important role in the excitatory and inhibitory mechanisms of the limbic system (51). Our results suggest that early childhood traumatization alters brain anatomy targeting the prefrontal cortex and the maturation of the limbic system (52), which might be mediated by gene expression in the adult prefrontal cortex (7). We speculate that in DID, the orbitofrontal cortex has matured differently under the influence of an abusive environment which consequently affects emotion regulation in the limbic system (16, 53). In sum, considering the orbitofrontal cortex’s role in emotion processing and regulation, the SA reduction in this region and negative association with dissociative symptoms provide clinically relevant implications for the treatment of DID.

Other studies have reported positive correlations between dissociative phenomenology and gray
Cortical morphology in DID

matter volume. A voxel-based morphometry (VBM) study reported a significant positive correlation between dissociation severity [depersonalization/derealization as measured by items 29 and 30 of the Clinician Administered PTSD Scale (CAPS)] and gray matter volume in the right middle frontal gyrus but did not report any significant negative correlation (23). However, this study is different in several aspects from our study, namely in the relatively low number of individuals with dissociative PTSD (n = 15), dissociative symptom severity, only including depersonalization/derealization as a dissociative symptom, and data analysis methodology. Another study applying a region-of-interest approach found a positive correlation between depersonalization and the dorsal anterior cingulate cortex (dACC) in child maltreatment-related PTSD (24). However, in the latter study, the dACC thickness did not differ between patients and controls, and only 16 patients with PTSD were included.

We did not find any significant bivariate correlations between measures of traumatization and morphometric features for any of the three developmental periods. This is most likely due to the lack of sufficient variance in the TEC scores, which precludes the examination of significant associations (see Table 2). However, as it is important to link our main results to early traumatization, we proceeded with a post hoc exploratory analysis. We further reduced the earliest developmental period to a period from 0 to 3 years. Importantly, this did increase the variance in the data [emotional neglect (M = 4.11, SD = 1.95), emotional abuse (M = 3.64, SD = 2.16), physical abuse (M = 3.50, SD = 2.28), sexual harassment (M = 1.82, SD = 2.33), and sexual abuse (M = 3.25, SD = 2.30)]. After performing regression analyses with this earliest developmental period we did not find any significances following corrections for multiple comparisons. However, we did find significant neuroanatomical correlates of early childhood trauma at an uncorrected, vertex-wise threshold of P < 0.02 (two-tailed). These results are now presented in Table S2 and Figure S2. While these results need to be interpreted with care due to uncorrected significance levels, it is important to note that the neuroanatomical correlates of very early traumatization overlap with many brain areas previously noted in many functional MRI studies examining atypical brain functioning in dissociative personality state during emotion regulation, such as parietal regions and prefrontal regions (16, 17), as well as with previously found neuroanatomical aberrations (4).

Future research should detail the environmental risk factors associated with abnormal brain development in DID, determine the neural mechanisms that underlie the involved anatomical deficits, and establish epigenetic markers that identify interindividual differences in susceptibility to severe and chronic adversity starting in early life. Our study includes several limitations. First, findings suggest that the neuroanatomical differences of DID resemble the neural substrates underlying common PTSD, which is not surprising because all patients met criteria for PTSD, past or current. Unfortunately, we were not able to perform a regression analysis with PTSD severity as we did not have CAPS scores for the overall sample. Approximately half of the participants did not report any other comorbid disorders. Depression was the second most reported comorbidity with one participant reporting chronic depression, and 10 participants reported recurrent depression. Some overlap between our findings and atypical cortical gray matter in depression seems to be present (54), and future studies are therefore required to establish whether—and to what degree—dissociative symptoms contribute to findings in studies including depressed participants and vice versa. Dissociative symptoms are also present in other psychiatric disorders, such as depression (55–57), borderline personality disorder (58), and PTSD (53). We thus recommend that it is crucial to assess dissociative symptoms across psychiatric disorders to aid cross-diagnostic comparison of the neural correlates of dissociative symptoms. Second, we employed a multicenter acquisition protocol to overcome single-site recruitment limitations. However, the MRI acquisition parameters were matched across sites using a study optimized scanning sequence (33). We also accounted for intersite effects in the statistical model. The detected between-group differences thus cannot fully be explained by this limitation. Third, while there was no significant between-group difference in total SA or average CT, we did observe a significant reduction in total gray matter volume in DID. However, as the purpose of our study was to determine what drives the volumetric differences in the brain in DID (i.e., differences in CT and/or SA), it was essential to utilize the same GLM consistently across morphometric features. We therefore did not covary for total gray matter volume in the vertex-wise analysis. Notably, we were not able to recruit males with DID as part of the study. Although we suspect similar results in males with DID, it will be crucial to replicate out findings in an independent sample of males with DID in the future. However, by focusing on females exclusively, our study design also minimized the neuroanatomical and clinical heterogeneity that could
have been introduced by analyzing data across gender categories.

In summary, DID is accompanied by neuroanatomical deficits in both CT and SA, which—in turn—lead to significant reductions in regional and total brain volume. Whole-brain correlation analyses revealed significant associations between abnormal brain morphology, dissociative symptoms and early traumatization in SA and CV, but not CT. The spatially largely non-overlapping distributed patterns for CT and SA indicate distinct neurodevelopmental pathways that are likely modulated by different neurobiological mechanisms and environmental factors, such as childhood traumatization.

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Declaration of interest

None.

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Cortical morphology in DID


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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. (a) Clusters with significant negative correlations between measures of SA and the severity of DID symptoms as...
obtained via principal component analysis (RFT-based, cluster-corrected, $P < 0.05$). (b) Clusters of significant negative
correlations between measures of CV and the severity of DID
symptoms as assessed using principal component analysis
(RFT-based, cluster-corrected, $P < 0.05$).

Figure S2. (a) Clusters of negative and positive correlations
between measures of SA and the severity of early traumatization
between the age of 0 and 3, using a composite score. (b)

Clusters of negative and positive correlations between measures of CV and the severity of early traumatization between
the age of 0 and 3, using a composite score.

Table S1. Clusters with significant negative correlations
between measures of SA and CV, and dissociative symptoms.

Table S2. Clusters with negative or positive correlations
between measures of SA and CV, and early traumatization
between the age of 0 and 3, using a composite score.