

## Similar cortical but not subcortical gray matter abnormalities in women with posttraumatic stress disorder with versus without dissociative identity disorder



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### ABSTRACT

Neuroanatomical evidence on the relationship between posttraumatic stress disorder (PTSD) and dissociative disorders is still lacking. We acquired brain structural magnetic resonance imaging (MRI) scans from 17 patients with dissociative identity disorder (DID) and co-morbid PTSD (DID-PTSD) and 16 patients with PTSD but without DID (PTSD-only), and 32 healthy controls (HC), and compared their whole-brain cortical and subcortical gray matter (GM) morphological measurements. Associations between GM measurements and severity of dissociative and depersonalization/derealization symptoms or lifetime traumatizing events were evaluated in the patient groups. DID-PTSD and PTSD-only patients, compared with HC, had similarly smaller cortical GM volumes of the whole brain and of frontal, temporal and insular cortices. DID-PTSD patients additionally showed smaller hippocampal and larger pallidum volumes relative to HC, and larger putamen and pallidum volumes relative to PTSD-only. Severity of lifetime traumatizing events and volume of the hippocampus were negatively correlated. Severity of dissociative and depersonalization/derealization symptoms correlated positively with volume of the putamen and pallidum, and negatively with volume of the inferior parietal cortex. Shared abnormal brain structures in DID-PTSD and PTSD-only, small hippocampal volume in DID-PTSD, more severe lifetime traumatizing events in DID-PTSD compared with PTSD-only, and negative correlations between lifetime traumatizing events and hippocampal volume suggest a trauma-related etiology for DID. Our results provide neurobiological evidence for the side-by-side nosological classification of PTSD and DID in the DSM-5.

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### 1. Introduction

A proportion of individuals develop posttraumatic stress disorder (PTSD) following potentially traumatizing events. Confronted with reminders of these events, many individuals with PTSD become hyperaroused, experience flashbacks and relive their traumatic experiences (Lanius et al., 2010). These symptoms have also been referred to as 'positive' dissociative symptoms (Nijenhuis and van der

Hart, 2011). However, some individuals become hypoaroused, emotionally numb, and experience depersonalization and derealization (Lanius et al., 2010). These symptoms have been referred to as 'negative' dissociative symptoms (Nijenhuis and van der Hart, 2011). The latter pattern would particularly characterize PTSD patients who have experienced prolonged traumatizing events such as chronic childhood physical and psychological abuse. Whereas some predominantly respond with hyperarousal and others with hypoarousal, still others alternate between the two (Van der Hart et al., 2006; Lanius et al., 2010). Although several imaging studies have investigated the neuroanatomical correlates of PTSD (Bremner et al., 2003; Geuze et al., 2008; Kasai et al., 2008; Woodward et al., 2009), the neuroanatomical correlates of dissociative symptoms in relation to lifetime potentially traumatizing events remain unclear.

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The recent nosological classification in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5; American Psychiatric Association, 2013) has placed PTSD in the trauma- and stressor-related disorders (TSRD) category, right before the dissociative disorders (DD) category “to indicate the close relationship between them” (Spiegel et al., 2013). Among dissociative disorders, dissociative identity disorder (DID) is the most severe one, and it shares many of the features described for PTSD. DID is further characterized by a disruption of identity by two or more distinct “personality states”, a discontinuity in the sense of self, impaired recall of everyday events or important personal information, and/or traumatizing events that are inconsistent with ordinary forgetting. In individuals with DID, symptoms such as dissociative amnesia, depersonalization/derealization, and sensorimotor negative dissociative symptoms can cause clinically significant distress or impairment in social, occupational, or other important areas of functioning. Interestingly, PTSD has been conceptualized as a “simple dissociative disorder” (Van der Hart et al., 2006), and DID as a severe childhood-onset PTSD (Boon and Draijer, 1993a, 1993b; Putnam, 1997; Van der Hart et al., 2006; Spiegel et al., 2013). However, empirical neurobiological evidence for such an intimate relationship is lacking.

Abundant clinical observations and retrospective correlational research suggest that DID is related to a history of severe and chronic childhood traumatization (Chu and Dill, 1990; Boon and Draijer, 1993b; Mulder et al., 1998; Draijer and Langeland, 1999; Van der Hart et al., 2006; Nijenhuis and Den Boer, 2009). However, there is still an ongoing debate about the etiology of DID (Dalenberg et al., 2012, 2014; Paris, 2012; Brand et al., 2013; Martinez-Taboas et al., 2013; Lynn et al., 2014). Two competing models concerning the etiology of DID have been put forward (Dalenberg et al., 2012; Reinders et al., 2012). The *trauma-related* model indicates that DID is causally related to early childhood traumatization by a combination of factors such as disorganized attachment, lack of affect regulation by caregivers, and chronic and severe neglect and abuse (Boon and Draijer, 1993a; Van der Hart et al., 2006). In this model, DID is comprehended as a childhood onset posttraumatic disorder. This model accommodates the fact that more than 90% of the DID patients meet the criteria for PTSD (Rodewald et al., 2011). Conversely, the *non-trauma-related* model (Lilienfeld et al., 1999; Merckelbach and Muris, 2001; Piper and Merskey, 2004; Giesbrecht et al., 2008), which is also referred to as the sociocognitive (Spanos, 1996) or fantasy model (Dalenberg et al., 2012), assumes that DID is due to simulation, suggestive psychotherapy and/or sociocultural influences and is mediated by high fantasy proneness. Neurobiological research testing these models has been called for by proponents of both models (Brand, 2012; Paris, 2012) as it can help clarify the etiology and nature of DID, which will eventually help diagnoses and treatment of these patients.

So far, there are only a few studies on brain morphological abnormalities in DID which investigated gray matter (GM) volumetric abnormalities in only a small number of *a-priori* hypothesized regions. Compared with healthy controls (HC), patients with DID had smaller volumes of the parahippocampal cortex (Ehling et al., 2008), hippocampus (Tsai et al., 1999; Vermetten et al., 2006; Ehling et al., 2008; Irle et al., 2009) and amygdala (Vermetten et al., 2006; Ehling et al., 2008; Irle et al., 2009). To our knowledge, no neuroimaging study has yet assessed whole-brain morphology in DID. The neuroanatomical correlates of PTSD mainly point to smaller GM volume of the hippocampal formation and insula, frontal (including anterior cingulate, medial and lateral prefrontal, orbitofrontal, superior, middle and inferior frontal) cortices and temporal (including superior temporal and parahippocampal) cortices (Bremner et al., 2003; Geuze et al., 2008; Kasai et al., 2008; Weniger et al., 2008; Woodward et al., 2009; Nardo et al., 2010, 2013; Kuo et al., 2012). Furthermore, previous literature investigating the relationships between brain morphology and severity of lifetime traumatizing events, dissociative and depersonalization/derealization symptoms in both DID and PTSD patients

have reported mixed findings (Stein et al., 1997; Bremner et al., 2003; Ehling et al., 2008; Nardo et al., 2010, 2013). Therefore, these relationships need to be explored further, preferably in larger samples of DID and PTSD patients than were included to date.

The current study investigated, for the first time, whole-brain cortical and subcortical GM morphological features in patients with DID and co-morbid PTSD and compared them to those of gender, education and age-matched HC and patients with PTSD. It also explored the relationship between the morphological features and severity of lifetime traumatizing events, and dissociative, and depersonalization/derealization symptoms.

We hypothesized that (1) patients with DID and co-morbid PTSD and patients with PTSD only would show GM reductions compared to controls, in the frontal cortices (including anterior cingulate, medial and lateral prefrontal, orbitofrontal, superior, middle and inferior frontal) (Geuze et al., 2008; Woodward et al., 2009; Nardo et al., 2013) and insular cortex (Kasai et al., 2008) as well as in the hippocampus and amygdala (Vermetten et al., 2006; Ehling et al., 2008); (2) Differences in GM abnormalities between the two patient groups were expected in the inferior parietal cortex (Simeon et al., 2000; Reinders et al., 2003, 2006, 2012, 2014) and the dorsal striatum (Reinders et al., 2014). Finally, (3) we expected that volume of the GM regions sensitive to the effects of stress, such as the hippocampus, would show negative correlations with severity of the lifetime traumatizing events. Furthermore, correlations with severity of dissociative symptoms were expected in the parietal cortices and the striatum, but with unknown directionality due to heterogeneity of previous findings.

## 2. Methods

### 2.1. Subjects

Sixty-five women underwent magnetic resonance imaging (MRI): 17 with a diagnosis of DID and co-morbid PTSD, 16 with a diagnosis of PTSD only and 32 HC. Participants were Caucasian and were all matched for gender, age, number of years of education (Table 1). DID patients and PTSD patients with a history of interpersonal traumatizing events were recruited via mental healthcare institutions and internet advertisements.

The diagnosis of DID was assessed by one of two DID experts (E.N. or N.D.) using the Structured Clinical Interview for DSM-IV Dissociative Disorders (SCID-D) (Boon and Draijer, 1993a; Steinberg, 1993) during which a possible PTSD comorbidity was assessed as well. Of the DID patients, 82.35% ( $n=14$ ) met criteria for PTSD. The remaining 17.65% ( $n=3$ ) had PTSD symptoms, but these had become reduced with psychotherapy at the time of the MRI measurements. These three individuals were thus cases of PTSD in remission. We refer to this sample of 17 patients as “DID-PTSD”. The personal therapists of the patients with DID-PTSD reported the following co-morbid disorders, based on DSM-IV classification (American Psychiatric Association, 1994): somatoform disorder ( $n=2$ ), recurrent major depression ( $n=4$ ), dysthymic disorder ( $n=1$ ), trauma-related specific phobia ( $n=2$ ), personality disorder-not otherwise specified ( $n=2$ ), mixed personality disorders ( $n=2$ ), borderline personality disorder symptoms ( $n=3$ ), dependent personality disorder symptoms ( $n=1$ ), histrionic personality disorder symptoms ( $n=1$ ), eating disorder ( $n=2$ ), sleeping disorder ( $n=2$ ), and epilepsy ( $n=1$ ).

Severity of psychoform and somatoform dissociative symptoms were evaluated using the Dissociative Experiences Scale (DES: Bernstein and Putnam (1986)) and Somatoform Dissociation Questionnaire (SDQ-20: Nijenhuis et al. (1996)), respectively. The DES is a 28-item self-report screening questionnaire on which participants indicate which percentage of time (0–100%) each statement of psychoform dissociation applies to them. The overall DES score is the average of all the item scores and ranges from 0 to 100. The SDQ-20 is a 20-item questionnaire whose items range from 1 to 5 and pertain to negative (e.g., analgesia) and positive somatoform dissociative phenomena (e.g., site-specific pain) and the total score ranges from 20 to 100. The five-item SDQ-5 (total score range: 5–25) was derived from the SDQ-20. These five items as a group discriminate best between patients with and without a dissociative disorder (Nijenhuis et al., 1997, 1998). The cut-off scores that we used for the DES and SDQ-5 were 25 and 7, respectively (Boon and Draijer, 1993b; Nijenhuis et al., 1997). Depersonalization symptoms were evaluated using the Cambridge Depersonalization Scale (CDS: Sierra and Berrios (2000)), which is a 29-item self-report measure of depersonalization experiences and is designed to explore the “frequency” (range 0–4) and “duration” (range 0–6) of depersonalization symptoms over the last 6 months. To obtain a total score, the

**Table 1**

Demographic and clinical characteristics of the participants.

	Mean (S.D.) [Range]			Post hoc tests: P values		
	DID-PTSD (n=17)	PTSD-only (n=16)	HC (n=28)	DID-PTSD vs. HC	DID-PTSD vs. PTSD-only	PTSD-only vs. HC
<b>Demographics</b>						
Age, years	43.82 (9.85) [26–63]	40.75 (12.05) [18–58]	41.75 (12.29) [22–62]	0.56	0.45	0.78
Education, years	14.88 (0.99) [12–16]	14.94 (0.85) [14–16]	15.04 (1.20) [10–16]	0.64	0.88	0.77
Handedness, n (%right)	14 (87.50%)	15 (93.75%)	27 (96.43%)	0.54	0.99	0.99
<b>Medication history</b>						
Antipsychotics: n (typical, atypical)	Past:2(1,1) Current:8(2,6) <sup>a</sup>	Past: 0 Current: 0	Past: 0 Current: 0			
Anti-epileptics: n	Past:1 Current:3	Past: 0 Current: 0	Past: 0 Current: 0			
Antidepressant: n	Past: 2 Current:10	Past: 0 Current: 2	Past: 0 Current: 0			
<b>Clinical measures <sup>b</sup></b>						
Depersonalization (CDS)						
Frequency	1.91 (0.51) [0.93–2.86]	0.85 (0.44) [0.24–2.07]	0.26 (0.30) [0–0.52]	< 0.001*	< 0.001*	< 0.001*
Duration	2.73 (0.70) [1.48–3.62]	1.37 (0.72) [0.31–3.03]	0.44 (0.47) [0–1.24]	< 0.001*	< 0.001*	< 0.001*
Total score	134.77 (33.46) [70–183]	64.56 (32.70) [16–148]	20.57 (21.31) [0–45]	< 0.001*	< 0.001*	< 0.001*
Dissociation						
Psychoform (DES)	54.41 (16.18) [24.29–78.57]	22.18 (13.83) [3.21–48.93]	5.02 (3.10) [0.36–14.64]	< 0.001*	< 0.001*	< 0.001*
Somatoform (SDQ-20)	57.06 (17.26) [31–80]	32.69 (13.43) [20–74]	22.04 (2.21) [20–27]	< 0.001*	< 0.001*	< 0.001*
Traumatic Experience Checklist (TEC)						
Emotional neglect	12.23 (3.15) [0–13]	7.50 (5.82) [0–13]	1.67 (3.61) [0–10]	< 0.001*	0.002*	< 0.001*
Emotional abuse	11.06 (4.11) [0–13]	6.81 (5.36) [0–13]	0.37 (1.36) [0–6]	< 0.001*	0.001*	< 0.001*
Physical abuse	10.76 (4.56) [0–13]	3.69 (4.19) [0–13]	0.52 (2.04) [0–10]	< 0.001*	< 0.001*	0.006*
Sexual harassment	8.76 (5.32) [0–13]	2.56 (2.58) [0–8]	0.44 (1.25) [0–6]	< 0.001*	< 0.001*	0.042*
Sexual abuse	9.18 (5.14) [0–13]	2.37 (3.07) [0–9]	0.07 (0.38) [0–2]	< 0.001*	< 0.001*	0.025*
Total trauma score	17.53 (4.08) [11–26]	11.06 (4.01) [4–16]	1.96 (1.93) [0–7]	< 0.001*	< 0.001*	< 0.001*

Abbreviations: PTSD-only=patients with only posttraumatic stress disorder; DID-PTSD=patients with dissociative identity disorder and co-morbid PTSD; HC=healthy controls.

<sup>a</sup> One DID-PTSD patient used typical antipsychotics in the past but stopped and was using atypical antipsychotics at the time of the MRI scan. Another DID-PTSD patient used atypical antipsychotics in the past but was not using any antipsychotics at the time of the MRI scan.

<sup>b</sup> CDS, DES, SDQ and TEC data were not available for one HC.

\* P-value ≤ 0.05.

frequency and duration of all items are added up (range 0–290). Severity of lifetime traumatizing events was assessed with the Traumatic Experiences Checklist (TEC: Nijenhuis et al. (2002)). The TEC is a self-report measure inquiring about 29 types of potentially traumatizing events. Different scores can be calculated from the TEC including a cumulative score, and scores for emotional neglect, emotional abuse, physical abuse, sexual harassment, and sexual abuse. The TEC total score ranges from 0 to 29. DID patients completed these questionnaires in their most predominant identity state.

In the 16 PTSD-only patients, symptom severity was assessed using the Clinician Administered PTSD Scale (CAPS) interview (Blake et al., 1995) conducted by researchers E.V. and M.G. Eleven of the PTSD-only patients reported multiple types of interpersonal traumatizing events during childhood ( $n=6$ ) or starting from childhood and continuing into adult life ( $n=5$ ). The remaining five PTSD-only patients reported traumatizing events only during adult life. Two PTSD-only patients scored high on the DES/SDQ-5 (both reported DES > 25 and one of them also reported SDQ-5 > 7) and consequently underwent a SCID-D interview in which a DSM-IV/5 dissociative disorder was excluded. Hence, we refer to this patient group as "PTSD-only". As both DID-PTSD and PTSD-only groups shared the diagnosis of PTSD, we created one larger group, referred to as "All-PTSD", in order to investigate the common morphological features of PTSD. The results are reported in the *Supplementary Material 1*.

Exclusion criteria for all participants were age outside the range of 18–65, pregnancy, systemic or neurological illness, claustrophobia, presence of metal implants in the body and alcohol/drug abuse. Details of psychotropic medication usage are provided in Table 1 and *Supplementary Material 3*. HC were recruited through advertisements in local newspapers. Additional exclusion criteria for HC were a high score of (psychoform/somatoform) dissociative symptoms (evaluated with the DES and SDQ-20/SDQ-5), a psychiatric disorder in the past or at present, or a high score on the TEC. All HC were free of present and past psychiatric medication. All participants were given a complete description of the study and gave written informed consent according to procedures approved by the Medical Ethical Committee (METC) of the University Medical Center Groningen (UMCG) and of the Amsterdam Medical Center (AMC).

## 2.2. Image acquisition

All participants were scanned on a 3T MRI scanner (Philips Medical Systems, Best, NL) in one of two participating centers in The Netherlands (UMCG and AMC). To ensure image comparability, a reproducibility study was conducted that resulted in an optimized structural MRI protocol with a high reproducibility between the two centers (Chalavi et al., 2012). At both centers, T1-weighted anatomical MR scans were acquired (MPRAGE, repetition time=9.95 ms, echo time=5.6 ms, flip-angle=8°,  $1 \times 1 \times 1 \text{ mm}^3$  voxels, number of slices=160, total scan-time=10 m, 14 s). DID-PTSD patients and their matched PTSD-only patients and HC were scanned in an interleaved order within a short time interval. The samples were equally distributed over the two centers: 20 patients (10 with DID-PTSD, 10 with PTSD-only) and 19 HC were scanned at UMCG. Four scans (all from HC) were excluded due to technical or quality problems, leaving artifact-free data from 33 patients and 28 HC for demographic and volumetric analyses.

## 2.3. Image analysis

FreeSurfer (v5.0) (<http://freesurfer.net/>) was used to extract subcortical GM volume ( $\text{mm}^3$ ) and three cortical measures: cortical volume ( $\text{mm}^3$ ), cortical surface area ( $\text{mm}^2$ ), and cortical thickness (mm) from the brain scans. All the images were analyzed using the same version of FreeSurfer to avoid a bias due to cross-version differences (Gronenschild et al., 2012). Technical particulars of FreeSurfer have been described in details by the developers (Fischl and Dale, 2000). To summarize: image processing included motion correction, skull stripping, Talairach transformation, segmentation of the subcortical white matter (WM) and deep GM structures, intensity normalization, tessellation of the GM/WM boundary and finally, surface deformation following intensity gradients to optimally place the GM/WM and GM/cerebrospinal fluid (CSF) borders at the location where the greatest shift in intensity defines the transition to the other tissue class. Once the cortical models were completed, a refinement procedure was applied to obtain a representation of

the GM/WM boundary. This surface was subsequently deformed outward to obtain an explicit representation of the pial surface, which was then divided into distinct cortical regions. The parcellation labeled cortical sulci and gyri, and cortical surface area and cortical thickness values were calculated in the 34 regions per hemisphere. Cortical surface area was calculated as the sum of the areas of each tessellation falling within each region. Cortical thickness was calculated as the average distance between the GM/WM boundary and the GM/CSF boundary within each region. Cortical thickness and surface area are genetically independent, emerge through different neurobiological events during development, and have different sensitivities to various clinical conditions and therefore they can provide complementary information (Panizzon et al., 2009). Cortical volume, which is by definition the product of thickness and surface area, combines the morphological properties of both cortical surface area and cortical thickness (Panizzon et al., 2009). Each subcortical voxel was assigned one of 39 labels by the automatic subcortical segmentation, after which volume of each subcortical structure were extracted (Dale et al., 1999; Fischl and Dale, 2000; Fischl et al., 2004).

#### 2.4. Cortical measures and subcortical volume

FreeSurfer extracts 68 cortical and 39 subcortical brain regions from each brain image. To provide robust protection against type-I error and to satisfy assumptions for multivariate analysis of variance, which states that the number of cases in each category must be larger than the number of dependent variables, the number of cortical and subcortical brain regions were reduced in dimensionality as follows: for cortical measurements, left, right and total (sum of left and right), so-called superparcels (Woodward et al., 2009) were defined for the frontal, parietal, temporal, occipital and insular cortices and whole-brain cortex. Subsequently, cortical measurements of each superparcel were calculated by summing the corresponding cortical measurements of the individual cortices within the superparcel. In this approach, the superparcels represent lobar regions of the cortex and of the whole cortex and therefore GM morphological abnormalities of each superparcel can indicate the cumulative GM morphological abnormalities of its individual parcels. For subcortical volumes, left, right and total (sum of left and right) volumes of all the segmented GM subcortical structures, that is thalamus, caudate, putamen, pallidum, hippocampus, amygdala, nucleus accumbens and ventral diencephalon, were extracted. Whole-brain subcortical GM volume was defined as the sum of the volumes of all the above-mentioned GM subcortical structures. This approach allows for a whole-brain comparison between groups.

#### 2.5. Statistical analyses

All statistical analyses were performed using SPSS 18.0. Demographic and clinical data were compared between the groups using analysis of variance (ANOVA) followed by two-sample *t*-tests. With regard to the neuroanatomical measures, first an *F*-test was conducted to assess the main effect of group on the total measures (Omnibus test). Then, for each superparcel and subcortical GM region pairwise *t*-tests were performed on the total measures for (i) DID-PTSD vs. HC, (ii) DID-PTSD vs. PTSD-only, and (iii) PTSD-only vs. HC. Post hoc and pairwise *t*-tests were performed on the left and right volumetric measurements. In all these analyses, group and scanning center were used as categorical predictors, and age and parenchymal volume (total GM+total WM) as continuous covariates. To protect against type-I error, multiple comparisons correction was applied using Bonferroni-Holm for both the Omnibus test (to correct for number of measurements) and pairwise comparisons (to correct for the number of groups) and for each morphological measurement separately. In a set of exploratory analyses, individual regions within the superparcels were also compared between groups and are reported in *Supplementary Material 2*.

#### 2.6. Correlation analyses

One of the aims of this study was to investigate the clinical relevance of morphological abnormalities of brain GM regions in DID-PTSD and PTSD-only patients. The clinical measures of interest were (i) severity of lifetime traumatizing events (including emotional neglect, emotional abuse, physical abuse, sexual harassment and sexual abuse and total lifetime trauma as assessed by the TEC and (ii) somatoform and psychoform dissociative symptoms (assessed using SDQ-20 and DES, respectively) and frequency, duration and total depersonalization/derealization symptoms (assessed using CDS). First, the intercorrelations between the total scores of these clinical measures were calculated using Pearson's correlations. We expected to find a high level of correlations between these 11 clinical variables. In order to reduce the dimensionality of these clinical variables and retain the components that best describe the variance in the data, we performed principal component analysis (PCA) with the oblique rotation (promax) method using a threshold of one for the eigenvalues. This led to the generation of two principal components, resulting in a cumulative explained variance of 74.83%. These two principal components, which are intrinsically orthogonal, were associated with the dissociative symptoms (explaining 57.08% of the variance and labeled as the *dissociative* component) and with lifetime potentially traumatizing

events (explaining 17.75% of the variance, labeled as the *lifetime traumatizing events* component), respectively. Partial correlation analyses were conducted between the dissociative and lifetime traumatizing events components and volumes of *a priori* hypothesized GM regions. *A priori* hypothesized regions were the hippocampus and amygdala (Vermetten et al., 2006; Ehling et al., 2008) and the areas included in the neurobiological model for DID (Reinders et al., 2014), namely the middle and superior and inferior frontal, (anterior) cingulate, insula and inferior and superior parietal and precuneus cortices, and the dorsal striatum (caudate, putamen and pallidum). To this end, subcortical structures and the individual cortical regions within the frontal and parietal superparcels were explored (from *Supplementary eTables 3 (frontal)* and *4 (parietal)*) for significant group differences ( $p < 0.05$ , uncorrected). These correlations were conducted only on the GM volumes and were controlled for age and parenchymal volume.

### 3. Results

#### 3.1. Whole-brain neuroanatomical measurement

There was no group  $\times$  MRI-center interaction for the cortical volume, surface area and thickness and subcortical volume measurements.

##### 3.1.1. Cortical volume

A significant main effect of group was found for the cortical volumes of the whole-brain, frontal, temporal and insula superparcels (Table 2a and Fig. 1). Pairwise *t*-tests revealed that in comparison with HC, DID-PTSD patients had significantly smaller cortical volume of the whole-brain, both hemispheres, and total and bilateral frontal and temporal, left parietal, and total and left insula superparcels. PTSD-only patients, in comparison with HC, had significantly smaller cortical volume of the whole-brain, both hemispheres, and total and bilateral frontal and temporal and total and left insula superparcels. However, there was no significant difference in cortical volumes in any of the superparcels between DID-PTSD and PTSD-only patients.

##### 3.1.2. Cortical surface area

Significant differences between all the groups (omnibus test) were found in cortical surface area of the frontal and insula superparcels. Pairwise *t*-tests revealed that all the cortical regions with significant cortical surface area differences between groups also showed the above described significant cortical volume differences (for details see Table 2b).

##### 3.1.3. Cortical thickness

The omnibus tests and the pairwise tests did not show any significant effect of group on cortical thickness measurements (Table 2c).

##### 3.1.4. Subcortical volumes

Volumes of the hippocampus, putamen and pallidum differed significantly between the groups (Table 3). DID-PTSD patients had larger total and right pallidum volumes relative to HC and larger total, left and right putamen and total and right pallidum volumes than PTSD-only patients. Pairwise *t*-tests showed significantly smaller total, left and right hippocampal volumes in DID-PTSD patients as compared with HC. The PTSD-only and HC groups did not differ significantly on the subcortical measurements. This was a reason to conduct *post hoc* pairwise tests on the hippocampal volume using only a subset of PTSD-only patients with a history of (multiple) traumatizing events starting in their childhood ( $n=11$ ). In this small subgroup, we observed smaller, albeit only at trend level, total ( $p=0.085$ ) and left ( $p=0.092$ ) hippocampal volume as compared with HC.

**Table 2a**Statistical results for cortical volume ( $\text{mm}^3$ ).

Superparcel	Total/side	Omnibus test	Mean (S.D.)			Group comparisons: P value (effect size <sup>a</sup> )		
			DID-PTSD (n=17)	PTSD-only (n=16)	HC (n=28)	DID-PTSD vs. HC	DID-PTSD vs. PTSD-only	PTSD-only vs. HC
Whole brain <sup>b</sup>	Total	<b>0.002**</b>	446,401 (37,257)	452,332 (37,169)	468,430 (28,543)	<b>0.003**</b> (-0.67)	0.98 (-0.16)	<b>0.003**</b> (-0.49)
	Left		222,674 (18,165)	225,741 (18,497)	234,336 (14,676)	<b>0.001**</b> (-0.71)	0.91 (-0.17)	<b>0.001**</b> (-0.52)
	Right		223,727 (19,168)	226,591 (18,820)	234,094 (14,003)	<b>0.009**</b> (-0.63)	0.99 (-0.15)	<b>0.011**</b> (-0.46)
Frontal <sup>c</sup>	Total	<b>0.003**</b>	167,141 (16,312)	169,937 (17,707)	176,665 (10,572)	<b>0.002**</b> (-0.71)	0.79 (-0.16)	<b>0.007**</b> (-0.48)
	Left		83,709 (7489)	85,356 (8528)	88,555 (5548)	<b>0.001**</b> (-0.74)	0.74 (-0.21)	<b>0.005**</b> (-0.45)
	Right		83,431 (8863)	84,581 (9253)	88,110 (5173)	<b>0.006**</b> (-0.67)	0.85 (-0.13)	<b>0.012**</b> (-0.49)
Parietal <sup>d</sup>	Total	0.19	121,424 (8372)	124,058 (8490)	126,517 (9795)	0.084 (-0.56)	0.62 (-0.31)	0.24 (-0.27)
	Left		60,021 (3960)	61,775 (4731)	63,019 (5287)	0.041 (-0.65)	0.43 (-0.40)	0.24 (-0.25)
	Right		61,403 (4545)	62,283 (3926)	63,497 (4702)	0.20 (-0.45)	0.88 (-0.21)	0.28 (-0.28)
Temporal <sup>e</sup>	Total	<b>0.016**</b>	100,784 (9853)	101,619 (8226)	105,858 (7498)	<b>0.031*</b> (-0.58)	0.65 (-0.09)	<b>0.010**</b> (-0.54)
	Left		50,669 (5019)	50,664 (4021)	53,209 (3967)	<b>0.038*</b> (-0.57)	0.36 (0.00)	<b>0.003**</b> (-0.64)
	Right		50,114 (4873)	50,955 (4315)	52,648 (3719)	<b>0.039*</b> (-0.59)	0.95 (-0.18)	<b>0.050*</b> (-0.42)
Occipital <sup>f</sup>	Total	0.39	43,885 (4534)	43,524 (4401)	45,340 (4850)	0.51 (-0.31)	0.50 (0.08)	0.17 (-0.39)
	Left		21,900 (2596)	21,569 (2068)	22,552 (2541)	0.69 (-0.25)	0.36 (0.14)	0.16 (-0.43)
	Right		21,985 (2062)	21,955 (2449)	22,788 (2513)	0.41 (-0.35)	0.72 (0.01)	0.24 (-0.34)
Insula	Total	<b>0.002**</b>	13,165 (1000)	13,192 (1068)	14,047 (1042)	<b>0.010**</b> (-0.86)	0.45 (-0.03)	<b>0.001**</b> (-0.81)
	Left		6373 (579)	6376 (523)	6999 (446)	<0.001** (-1.22)	0.66 (-0.01)	<0.001** (-1.29)
	Right		6792 (526)	6816 (661)	7048 (704)	0.51 (-0.42)	0.41 (-0.04)	0.12 (-0.34)

Abbreviations: PTSD-only = patients with only posttraumatic stress disorder; DID-PTSD = patients with dissociative identity disorder and co-morbid PTSD; HC = healthy controls.

\* Uncorrected for multiple comparisons ( $P$ -value  $\leq 0.05$ ).

\*\* Corrected for multiple comparison.

<sup>a</sup> Cohen's  $d$  effect size.

<sup>b</sup> Sum of the cortical measurements of the five superparcels (Frontal, Parietal, Temporal, Occipital, and Insula).

<sup>c</sup> Sum of the cortical measurements of the caudal and rostral middle frontal, lateral and medial orbitofrontal, pars opercularis, pars triangularis and pars orbitalis of the inferior frontal, paracentral, precentral, superior frontal, frontal pole, and caudal and rostral anterior cingulate.

<sup>d</sup> Sum of the cortical measurements of the superior and inferior parietal, postcentral, precuneus, isthmus and posterior cingulate, and supramarginal.

<sup>e</sup> Sum of the cortical measurements of the superior, middle and inferior temporal, temporal pole, transverse temporal, banks of the superior temporal sulcus, parahippocampal, entorhinal, and fusiform.

<sup>f</sup> Sum of the cortical measurements of the lateral occipital, cuneus, lingual, and peri-calcarine.

### 3.2. Clinical measures and their correlation with GM volume

#### 3.2.1. Clinical measures

Psychoform and somatoform dissociative symptoms were significantly (all  $p < 0.001$ ) higher in DID-PTSD patients compared with HC and PTSD-only patients, and in PTSD-only patients compared with HC. The DID-PTSD and PTSD-only groups had experienced significantly more severe lifetime traumatizing events than the HC group ( $p < 0.05$ ). Individuals with DID-PTSD had experienced more severe lifetime traumatizing events than individuals with PTSD-only ( $p < 0.001$ ) (see Table 1). In the patient groups, significant intercorrelations were found between all the clinical measures. That is, correlations between the dissociation predictors were significant between total DES score and total SDQ-20 score ( $\rho=0.835$ ,  $p < 0.001$ ), between total DES score and total CDS score ( $\rho=0.699$ ,  $p < 0.001$ ), and between total SDQ-20 score and total CDS score ( $\rho=0.752$ ,  $p < 0.001$ ). Moreover, the between predictor correlations were significant between total TEC and total DES score ( $\rho=0.709$ ,  $p < 0.001$ ), between total TEC and total SDQ-20 score ( $\rho=0.657$ ,  $p < 0.001$ ), and between total TEC and total CDS scores ( $\rho=0.694$ ,  $p < 0.001$ ).

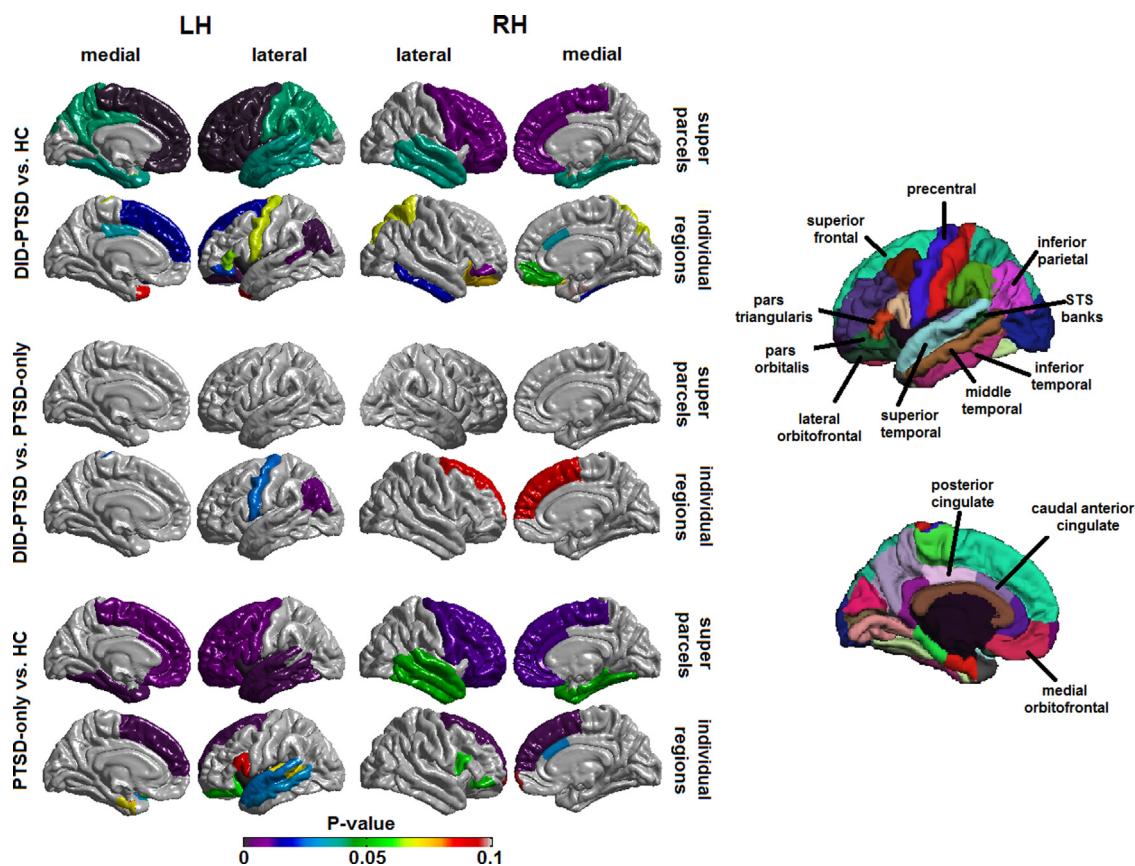
#### 3.2.2. Correlation analyses

Results of the partial correlation analyses between the dissociative component or the lifetime traumatizing events component and volume of the *a priori* GM regions are presented in Table 4. We found that the dissociative component was positively correlated with volume of the bilateral putamen, right pallidum and right superior frontal cortex and was negatively correlated with the cortical volume of the left pars orbitalis, precentral and inferior

parietal cortices (see Fig. 2). Furthermore, the lifetime traumatizing events component was negatively correlated with volume of the left pars orbitalis and precentral cortices and the bilateral hippocampus, and positively correlated with volume of the right pallidum (see Fig. 3). Results of the partial correlations between the *a priori* GM regions and each clinical measure are listed in Supplementary eTable 20 for the interested reader.

### 4. Discussion

This study examined, for the first time, whole-brain GM morphology, including cortical volume, cortical surface area, cortical thickness and subcortical volume, in a relatively large sample of individuals with DID and co-morbid PTSD and individuals with PTSD-only. We also investigated the association between the previously reported GM abnormalities and severity of traumatizing events or dissociative symptoms in these patient groups. We found that patients with DID and co-morbid PTSD and patients with PTSD-only jointly differed from HC with respect to whole-brain, frontal, temporal and insular cortical volumes. Furthermore, we found, as compared with HC, larger striatal volume in patients with DID and co-morbid PTSD (DID-PTSD) and smaller hippocampal volume in both DID-PTSD patients and in the PTSD-only patients with a history of traumatizing events during childhood. Importantly, our findings further revealed that PTSD-only does not differ significantly from DID-PTSD with regard to lobar GM cortical measurements, while these two groups differ significantly in putamen and pallidum volumes. Our other major finding is that bilateral hippocampal volume correlated significantly with the severity of lifetime traumatizing events, whereas volume of the GM regions that differed



**Fig. 1.** Cortical maps displaying superparcels and individual cortical regions where significant cortical volume differences were observed between DID-PTSD and HC, PTSD-only and HC and DID-PTSD and PTSD-only. Individual cortical parcels driving the cortical volume differences ( $p \leq 0.05$ , uncorrected) in the superparcels are DID-PTSD vs. HC: left lateral orbitofrontal, right medial orbitofrontal, left and right pars orbitalis, left superior frontal, and right caudal anterior cingulate cortices in the frontal superparcel; left inferior parietal and left posterior cingulate cortices in the parietal superparcel; right inferior temporal, and left STS banks in the temporal superparcel. DID-PTSD vs. PTSD-only: left precentral cortex in the frontal superparcel; left inferior parietal cortex in the parietal superparcel. PTSD-only vs. HC: left and right superior frontal and right caudal anterior cingulate cortices in the frontal superparcel; left superior and middle temporal cortices in the temporal superparcel. Abbreviations: LH=left hemisphere; RH=right hemisphere; DID-PTSD=dissociative identity disorder individuals with co-morbid posttraumatic stress disorder; PTSD-only=posttraumatic stress disorder patients without dissociative identity disorder; HC=healthy controls.

between the two PTSD groups, i.e., putamen and pallidum, correlated significantly with the severity of dissociative and depersonalization/derealization measures. This latter finding suggests that these differences in GM morphology between PTSD-only and DID-PTSD patients might be specific to the severity of dissociative symptoms.

Cortical volume, and to a lesser extent cortical surface area, of the whole-brain, frontal, temporal and insular cortices were smaller in both DID-PTSD and PTSD-only groups as compared with HC. These findings are in line with previous reports of smaller GM of the whole brain (Woodward et al., 2009), frontal (Geuze et al., 2008; Kasai et al., 2008; Nardo et al., 2013), temporal (Geuze et al., 2008; Woodward et al., 2009) and insular (Kasai et al., 2008) cortices in PTSD patients. Our findings show that DID-PTSD patients did not significantly differ from the PTSD-only patients with respect to cortical volumetric measurements. Taken together, these findings suggest similar cortical morphological abnormalities in the two patient groups. Although, compared with HC, cortical thinning was observed in a few cortical regions namely the left frontal and parietal cortices in DID-PTSD and left temporal in PTSD-only, the total cortical volume abnormalities in DID-PTSD and PTSD-only relative to HC were mainly driven by surface area differences. These differences could reflect influences of genetic (Panizzon et al., 2009; Yoon et al., 2012) as well as gene-environmental factors in the etiology of DID and PTSD. In the remainder of the manuscript we discuss cortical volume findings only as this measurement includes both cortical surface area and cortical thickness (Panizzon et al., 2009).

Cortical volume of the right insula was smaller in the DID-PTSD and PTSD-only groups as compared with the HC group. Furthermore, exploratory analyses (see Supplementary eTable 3) revealed that the smaller cortical GM of the frontal superparcel was mainly driven by the smaller left lateral orbitofrontal, right medial orbitofrontal and anterior cingulate and bilateral pars orbitalis, and superior frontal cortices. These findings are in line with prior studies in PTSD (Geuze et al., 2008; Woodward et al., 2009; Nardo et al., 2013). Prefrontal and insular cortices have been implicated in dissociative reactions in the proposed neurobiological models for PTSD (Lanius et al., 2010) and for DID (Reinders et al., 2014). Our study extends these functional neuroimaging studies by showing that these areas are also structurally affected. Furthermore, the orbitofrontal cortex is crucial in affective and social imprinting in the first two years of life (Schore, 1996) and may therefore be involved in the etiology of DID (Forrest, 2001). This idea is consistent with abnormal activity of the orbitofrontal cortex in DID patients (Sar et al., 2001, 2007).

We found smaller hippocampal volume in DID-PTSD and PTSD-only with childhood onset traumatizing events (albeit only at trend level for PTSD-only) as compared with HC. These findings are in line with previous neuroimaging reports in both DID and PTSD patients (Tsai et al., 1999; Bremner et al., 2003; Vermetten et al., 2006; Ehling et al., 2008; Irle et al., 2009). Excluding PTSD-only patients with only adult traumatizing events resulted in higher significant group differences in hippocampal volume. This may indicate that severity, early onset, frequency and type of traumatizing events are

**Table 2b**Statistical results for cortical surface area ( $\text{mm}^2$ ).

Superparcel	Total/side	Omnibus test	Mean (S.D.)			Group comparisons: P value (effect size <sup>a</sup> )		
			DID-PTSD (n=17)	PTSD-only (n=16)	HC (n=28)	DID-PTSD vs. HC	DID-PTSD vs. PTSD-only	PTSD-only vs. HC
Whole brain <sup>b</sup>	Total	0.091	162,433 (12,472)	162,318 (11,870)	166,157 (11,612)	0.15 (-0.31)	0.49 (0.01)	0.042 (-0.33)
	Left		81,060 (6187)	81,138 (5922)	82,813 (5722)	0.16 (-0.79)	0.52 (-0.30)	0.050 (-0.48)
	Right		81,372 (6320)	81,180 (5965)	83,344 (5917)	0.14 (-0.05)	0.47 (-0.04)	0.035 (-0.01)
Frontal <sup>c</sup>	Total	<b>0.019*</b>	59,526 (5360)	59,487 (5105)	61,592 (4019)	<b>0.048*</b> (-0.44)	0.46 (0.01)	<b>0.010**</b> (-0.46)
	Left		29,732 (2649)	29,820 (2443)	29,794 (2736)	0.072 (-0.39)	0.57 (-0.03)	<b>0.025*</b> (-0.37)
	Right		29,794 (2736)	30,939 (2039)	29,666 (2678)	<b>0.034*</b> (-0.48)	0.38 (0.05)	<b>0.005**</b> (-0.54)
Parietal <sup>d</sup>	Total	0.54	46,110 (3080)	46,595 (3098)	46,828 (3688)	0.31 (-0.21)	0.89 (-0.16)	0.44 (-0.07)
	Left		22,705 (1426)	23,085 (1622)	23,132 (1855)	0.21 (-0.26)	0.78 (-0.25)	0.41 (-0.03)
	Right		23,404 (1690)	23,509 (1542)	23,695 (1893)	0.45 (-0.16)	0.99 (-0.07)	0.50 (-0.11)
Temporal <sup>e</sup>	Total	0.072	31,819 (2786)	31,570 (2608)	32,474 (2418)	0.28 (-0.25)	0.23 (0.09)	0.024 (-0.36)
	Left		16,160 (1399)	15,999 (1409)	16,409 (1268)	0.47 (-0.19)	0.22 (0.11)	0.046 (-0.31)
	Right		15,658 (1419)	15,570 (1237)	16,065 (1199)	0.16 (-0.31)	0.28 (0.07)	0.015 (-0.41)
Occipital <sup>f</sup>	Total	0.55	20,536 (1962)	20,258 (1914)	20,669 (2489)	0.74 (-0.06)	0.50 (0.14)	0.30 (-0.19)
	Left		10,300 (1075)	10,111 (948)	10,314 (1270)	0.91 (-0.01)	0.44 (0.19)	0.34 (-0.18)
	Right		10,235 (940)	10,147 (999)	10,354 (1278)	0.60 (-0.11)	0.59 (0.09)	0.29 (-0.18)
Insula	Total	<b>0.035*</b>	4442 (272)	4406 (257)	4593 (366)	0.12 (-0.47)	0.32 (0.13)	<b>0.013**</b> (-0.60)
	Left		2162 (173)	2120 (104)	2304 (185)	<b>0.005**</b> (-0.79)	0.39 (-0.30)	<b>0.001**</b> (-0.48)
	Right		2279 (131)	2286 (214)	2288 (230)	0.99 (-0.05)	0.38 (-0.04)	0.32 (-0.01)

Abbreviations: PTSD-only=patients with only posttraumatic stress disorder; DID-PTSD= patients with dissociative identity disorder and co-morbid PTSD; HC=healthy controls.

\* Uncorrected for multiple comparisons ( $P$ -value  $\leq 0.05$ ).

\*\* Corrected for multiple comparison.

<sup>a</sup> Cohen's  $d$  effect size.

<sup>b</sup> Sum of the cortical measurements of the five superparcels (Frontal, Parietal, Temporal, Occipital, and Insula).

<sup>c</sup> Sum of the cortical measurements of the caudal and rostral middle frontal, lateral and medial orbitofrontal, pars opercularis, pars triangularis and pars orbitalis of the inferior frontal, paracentral, precentral, superior frontal, frontal pole, and caudal and rostral anterior cingulate.

<sup>d</sup> Sum of the cortical measurements of the superior and inferior parietal, postcentral, precuneus, isthmus and posterior cingulate, and supramarginal.

<sup>e</sup> Sum of the cortical measurements of the superior, middle and inferior temporal, temporal pole, transverse temporal, banks of the superior temporal sulcus, parahippocampal, entorhinal, and fusiform.

<sup>f</sup> Sum of the cortical measurements of the lateral occipital, cuneus, lingual, and peri-calcarine.

important determinants for hippocampal size. In fact, this is supported by the significant negative correlation between severity of lifetime traumatizing events and volume of the bilateral hippocampi. This is in line with the reports that prolonged exposure to stress has detrimental impacts on the hippocampal morphology which may be due to high density of glucocorticoid receptors in the hippocampus (Sapolsky, 1993). Smaller hippocampal volume has previously been reported in patients with dissociative disorders and co-morbid PTSD (Irle et al., 2009), but hippocampal volume was preserved in patients with dissociative disorders or dissociative amnesia (DA) without co-morbid PTSD (Weniger et al., 2008). Although the numbers of actual DID patients in the two latter studies were very small ( $n=2$  and 4, respectively), the authors suggested that smaller hippocampal volume in DID may be due to the co-occurrence of PTSD. As all DID patients in our sample had co-morbid PTSD, we could not test this idea. Still, our correlation analyses showing a relationship between hippocampal volume and severity of traumatizing events but not with dissociative symptoms provide indirect support to this hypothesis.

Contrary to our *a priori* hypothesis, we found preserved amygdalar volumes in both patient groups relative to the HC group. Although amygdala hyperactivity has been previously reported in DID patients (Reinders et al., 2003, 2006, 2012), and in PTSD patients (Lanius et al., 2010), findings regarding amygdalar volume have been inconsistent. While some studies have reported smaller amygdalar volume in DID (Vermetten et al., 2006; Ehling et al., 2008) and PTSD (Weniger et al., 2008), reports of preserved or larger amygdalar volume in DID (Weniger et al., 2008) or PTSD (Weniger et al., 2008; Kuo et al., 2012) also exist. Preserved amygdalar volume does not, however, rule out the possibility of amygdalar dysfunction.

The DID-PTSD group had larger putamen and pallidum volumes as compared with the PTSD-only group. We considered whether this could be related to exposure to antipsychotics, as this can result in enlargement of striatal volume (see Supplementary Material 3). However, excluding the DID-PTSD patients with a history of typical antipsychotics increased the significance level of the morphological differences, suggesting that abnormalities of these structures are DID-specific. The dorsal striatum has been reported to activate differently across different dissociative identity states (Reinders et al., 2006, 2012, 2014; Schlumpf et al., 2013). Furthermore, this structure seems to play an important role in the recurrent alternation ("switching") between different dissociative identity states (Tsai et al., 1999), their self-stabilization for a period of time (Reinders et al., 2006, 2012, 2014; Schlumpf et al., 2013), the dominance of trauma-related procedural memory in trauma-related dissociative identity states (Quirarte et al., 2009; Schwabe and Wolf, 2012) and also in pain processing and dissociation reaction (Mickleborough et al., 2011). Furthermore, larger volumes of the putamen and pallidum in DID-PTSD were associated with more severe (psychoform/somatoform) dissociative and depersonalization/derealization symptoms. The latter finding is in contrast with a previous report of a negative correlation between the putamen GM intensity and dissociative symptoms in a sample of traumatized individuals with or without PTSD (Nardo et al., 2013). This discrepancy between our finding and those of Nardo et al. may be due to the differences in the characteristics of the patient samples. Although similar to our study, Nardo et al. (2013) investigated neural correlates of dissociative symptoms in traumatized individuals, their sample had much lower dissociative symptom scores (DES range: 3.93–31.07 for PTSD and 1.79–30.36 for non-PTSD) than the patients in our sample (DES

**Table 2c**

Statistical results for cortical thickness (mm).

Superparcel	Total/ side	Omnibus test	Mean (S.D.)			t-test: P value (effect size <sup>a</sup> )		
			DID-PTSD (n=17)	PTSD-only (n=16)	HC (n=28)	DID-PTSD vs. HC	DID-PTSD vs. PTSD-only	PTSD-only vs. HC
Whole brain <sup>b</sup>	Total	0.159	167.68 (5.87)	170.23 (7.74)	171.38 (6.55)	0.057 (-0.60)	0.38 (-0.37)	0.41 (-0.16)
	Left		82.51 (2.93)	83.57 (3.65)	84.62 (3.33)	0.021 (-0.67)	0.50 (-0.32)	0.14 (-0.30)
	Right		85.17 (3.14)	86.66 (4.19)	86.75 (3.40)	0.15 (-0.48)	0.31 (-0.41)	0.83 (-0.02)
Frontal <sup>c</sup>	Total	0.186	64.85 (2.02)	66.40 (3.75)	66.24 (2.72)	0.081 (-0.59)	0.16 (-0.54)	0.91 (0.05)
	Left		32.61 (1.08)	33.46 (1.81)	32.76 (1.37)	0.025 (-0.12)	0.14 (-0.58)	0.60 (0.44)
	Right		32.23 (1.11)	32.94 (1.99)	33.48 (1.46)	0.26 (-0.97)	0.22 (-0.45)	0.78 (-0.31)
Parietal <sup>d</sup>	Total	0.176	33.24 (1.21)	33.83 (1.71)	34.09 (1.56)	0.066 (-0.61)	0.43 (-0.40)	0.38 (-0.16)
	Left		16.72 (0.55)	17.02 (0.81)	17.21 (0.82)	0.027 (-0.72)	0.42 (-0.45)	0.22 (-0.23)
	Right		16.53 (0.71)	16.81 (0.94)	16.88 (0.80)	0.17 (-0.46)	0.48 (-0.34)	0.61 (-0.08)
Temporal <sup>e</sup>	Total	0.258	51.10 (2.13)	51.44 (1.96)	52.06 (2.31)	0.13 (-0.44)	0.75 (-0.17)	0.27 (-0.29)
	Left		25.30 (1.06)	25.17 (1.04)	25.79 (1.18)	0.11 (-0.44)	0.58 (0.13)	0.039 (-0.56)
	Right		25.80 (1.27)	26.28 (1.00)	26.28 (1.31)	0.21 (-0.37)	0.31 (-0.43)	0.96 (0.00)
Occipital <sup>f</sup>	Total	0.247	15.19 (0.81)	15.18 (0.68)	15.55 (0.72)	0.17 (-0.48)	0.92 (0.01)	0.17 (-0.53)
	Left		7.52 (0.44)	7.52 (0.28)	7.74 (0.37)	0.090 (-0.54)	0.99 (-0.01)	0.11 (-0.67)
	Right		7.67 (0.40)	7.66 (0.43)	7.81 (0.38)	0.35 (-0.36)	0.86 (0.02)	0.29 (-0.37)
Insula	Total	0.222	5.85 (0.27)	5.96 (0.28)	6.03 (0.34)	0.087 (-0.58)	0.47 (-0.41)	0.41 (-0.21)
	Left		2.90 (0.15)	2.99 (0.15)	3.00 (0.19)	0.13 (-0.55)	0.26 (-0.53)	0.85 (-0.08)
	Right		2.94 (0.17)	2.97 (0.15)	3.02 (0.17)	0.13 (-0.50)	0.92 (-0.21)	0.19 (-0.32)

Abbreviations: PTSD-only=patients with only posttraumatic stress disorder; DID-PTSD= patients with dissociative identity disorder and co-morbid PTSD; HC=healthy controls.

<sup>a</sup> Cohen's *d* effect size.

<sup>b</sup> Sum of the cortical measurements of the five superparcels (Frontal, Parietal, Temporal, Occipital, and Insula).

<sup>c</sup> Sum of the cortical measurements of the caudal and rostral middle frontal, lateral and medial orbitofrontal, pars opercularis, pars triangularis and pars orbitalis of the inferior frontal, paracentral, precentral, superior frontal, frontal pole, and caudal and rostral anterior cingulate.

<sup>d</sup> Sum of the cortical measurements of the superior and inferior parietal, postcentral, precuneus, isthmus and posterior cingulate, and supramarginal.

<sup>e</sup> Sum of the cortical measurements of the superior, middle and inferior temporal, temporal pole, transverse temporal, banks of the superior temporal sulcus, parahippocampal, entorhinal, and fusiform.

<sup>f</sup> Sum of the cortical measurements of the lateral occipital, cuneus, lingual, and peri-calcarine.

range: 24.29–78.57 for DID-PTSD and 3.21–48.93 for the PTSD-only (see Table 1)). In fact Nardo et al. considered their sample as “subclinically dissociated” whereas our sample of individuals with DID and co-morbid PTSD reported severe dissociative symptoms. Taken together, our positive correlation findings along with the results of larger striatal volume in DID-PTSD as compared with both PTSD-only and HC suggest that the striatum is an important brain region in the neurobiology of dissociation and DID.

We found that the left inferior parietal cortical volume was smaller in DID-PTSD compared with HC and with PTSD-only. Furthermore, there was a negative correlation between volume of the inferior parietal cortex and severity of dissociative symptoms. The parietal cortex is an association area integrating sensory information from different modalities and it is involved in visuospatial processing. Alterations in this brain region may therefore affect the integration of somatosensory, visual and auditory, vestibular cues. Electrophysiological studies have reported inducing out of body/ depersonalization experience after the application of electrical stimulation on the inferior parietal region in human subjects. Experiencing dissociation of self from the body might thus relate to failure to integrate complex somatosensory and vestibular cues (Blanke et al., 2002; Blanke and Arzy, 2005; De Ridder et al., 2007). In line with this idea, the involvement of the parietal regions has previously been indicated in functional neuroimaging studies in DID (Reinders et al., 2003, 2006, 2012, 2014; Schlumpf et al., 2014) and depersonalization disorder (Simeon et al., 2000). Altogether, our findings along with previous reports suggest that the inferior parietal cortex plays a role in the neurobiology of dissociative and depersonalization symptoms in DID and PTSD.

An important strength of our study is that the DID diagnosis was established by one of two independent experts in this field, limiting

the chance of including false positive cases (Draijer and Boon, 1999). Several limitations need to be considered. The first limitation of this study is the sample size. Although our sample size of 17 DID and 16 PTSD patients constitutes the largest volumetric study of DID to date, it is still a modest sample size. Because the limited statistical power may have led to type-2 errors, particularly for the DID-PTSD vs. PTSD-only comparisons, the study needs to be replicated with a larger sample size. That said, the findings of the present study can guide future research. Another limitation is that due to the relatively small sample, we introduced cortical superparcels (Woodward et al., 2009) to satisfy the assumption for multivariate analysis of variance. These superparcels provided us with lobar cortical findings and importantly allowed us to conduct multiple comparison correction. The comparisons of volumetric measurements of each individual cortical region across groups were nevertheless presented as exploratory analyses only. The documented morphological abnormalities of these individual cortical regions and their associations with clinical measures are in line with prior findings as well as the neurobiological model for DID (Reinders et al., 2014). A final limitation is that we did not structurally assess the co-morbidities in DID patients but relied on the co-morbidity reports from the DID patients' personal therapists. However, these clinical assessments were mostly based on structural interviews for axis-I and axis-II diagnoses. As the PTSD comorbidity was evaluated differently across the two patient groups we could not investigate the morphological correlates of PTSD severity. Therefore, it might be speculated that more pronounced morphological abnormalities in DID-PTSD compared with PTSD-only are not related to distinct features of DID, but to higher PTSD severity and/or more severe lifetime traumatizing events. However, we found neuroanatomical abnormalities specific to the DID-PTSD group, that correlated with severity of dissociative and depersonalization/

**Table 3**Statistical results for subcortical volume (mm<sup>3</sup>).

Subcortical structure	Total/side	Omnibus test	Mean (S.D.)			Group comparisons: P value (effect size <sup>a</sup> )		
			DID-PTSD (n=17)	PTSD-only (n=16)	HC (n=28)	DID-PTSD vs. HC	DID-PTSD vs. PTSD-only	PTSD-only vs. HC
Whole brain	Total	0.22	54,297 (3897)	53,597 (4691)	54,373 (2956)	0.27 (-0.02)	0.087 (0.16)	0.40 (-0.20)
	Left		27,162 (2052)	26,827 (2396)	27,207 (1571)	0.29 (-0.02)	0.10 (0.15)	0.41 (-0.19)
	Right		27,134 (1886)	26,769 (2322)	27,165 (1448)	0.27 (-0.02)	0.094 (0.17)	0.43 (-0.21)
Hippocampus	Total	<b>0.030*</b>	7404 (789)	7804 (723)	8016 (709)	<b>0.008**</b> (-0.82)	0.12 (-0.53)	0.38 (-0.30)
	Left		3700 (428)	3866 (355)	3951 (387)	<b>0.040*</b> (-0.62)	0.24 (-0.42)	0.47 (-0.23)
	Right		3704 (400)	3938 (391)	4065 (353)	<b>0.003**</b> (-0.96)	0.070 (-0.59)	0.33 (-0.34)
Amygdala	Total	0.99	3092 (346)	3134 (328)	3150 (371)	0.96 (-0.16)	0.99 (-0.12)	0.97 (-0.05)
	Left		1544 (175)	1561 (180)	1584 (198)	0.71 (-0.21)	0.84 (-0.10)	0.56 (-0.12)
	Right		1548 (205)	1573 (170)	1565 (184)	0.79 (-0.09)	0.84 (-0.13)	0.64 (0.05)
Caudate	Total	0.082	7385 (849)	7037 (1005)	7071 (632)	0.031 (0.42)	0.095 (0.38)	0.79 (-0.04)
	Left		3601 (406)	3441 (500)	3439 (323)	0.024 (0.44)	0.092 (0.35)	0.73 (0.00)
	Right		3783 (462)	3596 (518)	3631 (328)	0.052 (0.38)	0.11 (0.38)	0.86 (-0.08)
Putamen	Total	<b>0.039*</b>	10,891 (1120)	10,408 (1379)	10,764 (933)	0.17 (0.12)	<b>0.011**</b> (0.39)	0.12 (-0.31)
	Left		5542 (621)	5313 (702)	5513 (469)	0.27 (0.05)	<b>0.016**</b> (0.35)	0.098 (-0.34)
	Right		5349 (544)	5095 (694)	5251 (504)	0.13 (0.19)	<b>0.018*</b> (0.41)	0.21 (-0.26)
Pallidum	Total	<b>0.033*</b>	3247 (306)	3072 (408)	3128 (301)	<b>0.034*</b> (0.39)	<b>0.015**</b> (0.49)	0.50 (-0.16)
	Left		1771 (189)	1704 (253)	1740 (181)	0.21 (0.17)	0.083 (0.30)	0.45 (-0.17)
	Right		1475 (148)	1368 (161)	1387 (146)	<b>0.003**</b> (0.60)	<b>0.003**</b> (0.69)	0.67 (-0.12)
Nucleus accumbens	Total	0.26	1248 (190)	1230 (202)	1323 (159)	0.19 (-0.43)	0.88 (0.09)	0.16 (-0.52)
	Left		588 (103)	584 (86)	647 (101)	0.060 (-0.58)	0.90 (0.04)	0.088 (-0.67)
	Right		660 (99)	646 (131)	676 (86)	0.76 (-0.17)	0.68 (0.12)	0.46 (-0.28)
Thalamus	Total	0.32	12,930 (973)	12,735 (1229)	12,791 (1047)	0.15 (0.14)	0.24 (0.18)	0.92 (-0.05)
	Left		6365 (501)	6303 (686)	6318 (556)	0.18 (0.09)	0.38 (0.10)	0.74 (-0.02)
	Right		6565 (486)	6431 (567)	6473 (540)	0.15 (0.18)	0.17 (0.25)	0.89 (-0.08)
Ventral diencephalon	Total	0.91	8097 (876)	8172 (656)	8127 (520)	0.66 (-0.04)	0.88 (-0.10)	0.80 (0.08)
	Left		4048 (474)	4118 (360)	4115 (312)	0.30 (0.11)	0.54 (-0.01)	0.74 (0.15)
	Right		4049 (424)	4054 (327)	4012 (241)	0.86 (-0.17)	0.78 (-0.17)	0.89 (0.01)

Abbreviations: PTSD-only=patients with only posttraumatic stress disorder; DID-PTSD=patients with dissociative identity disorder and co-morbid PTSD; HC=healthy controls.

\* Uncorrected for multiple comparisons (*P*-value ≤ 0.05).

\*\* Corrected for multiple comparisons.

<sup>a</sup> Cohen's *d* effect size.

**Table 4**

Correlations between cortical or subcortical volumes and severity of dissociative symptoms or lifetime traumatizing events components in the DID-PTSD and PTSD-only groups (*n*=33).

Cortical/subcortical volume	Region/structure	Left/right	Partial correlation coefficients <sup>a</sup>		
			Dissociative component	Lifetime traumatizing events component	
Cortical volume	Lateral orbitofrontal	Left	-0.249		-0.158
	Medial orbitofrontal	Right	-0.080		-0.230
	Pars orbitalis	Left	-0.334 <sup>^</sup>		<b>-0.461**</b>
	Pars orbitalis	Right	-0.107		-0.181
	Precentral	Left	-0.312 <sup>^</sup>		-0.346 <sup>^</sup>
	Superior frontal	Left	-0.106		-0.038
	Superior frontal	Right	0.313 <sup>^</sup>		0.290
	Caudal anterior cingulate	Right	0.044		0.230
	Inferior parietal	Left	<b>-0.363*</b>		-0.272
	Posterior cingulate	Left	0.186		-0.096
Subcortical volume	Insula	Left	-0.030		-0.114
	Hippocampus	Left	-0.128		<b>-0.440*</b>
	Hippocampus	Right	-0.270		<b>-0.417*</b>
	Putamen	Left	<b>0.522**</b>		0.286
	Putamen	Right	<b>0.562**</b>		0.227
	Pallidum	Right	<b>0.487**</b>		0.301 <sup>^</sup>

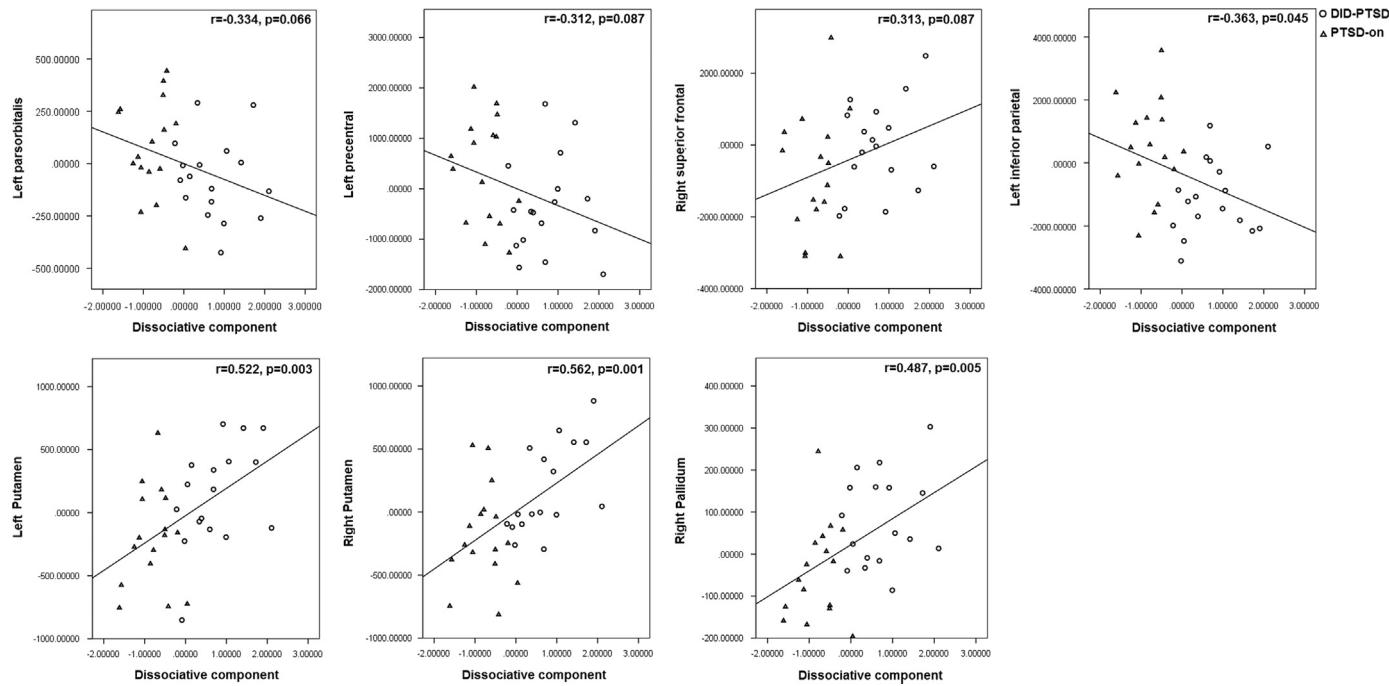
Abbreviations: PTSD-only=patients with only posttraumatic stress disorder; PTSD-DID=patients with dissociative identity disorder and co-morbid PTSD.

\* *P*-value ≤ 0.05.

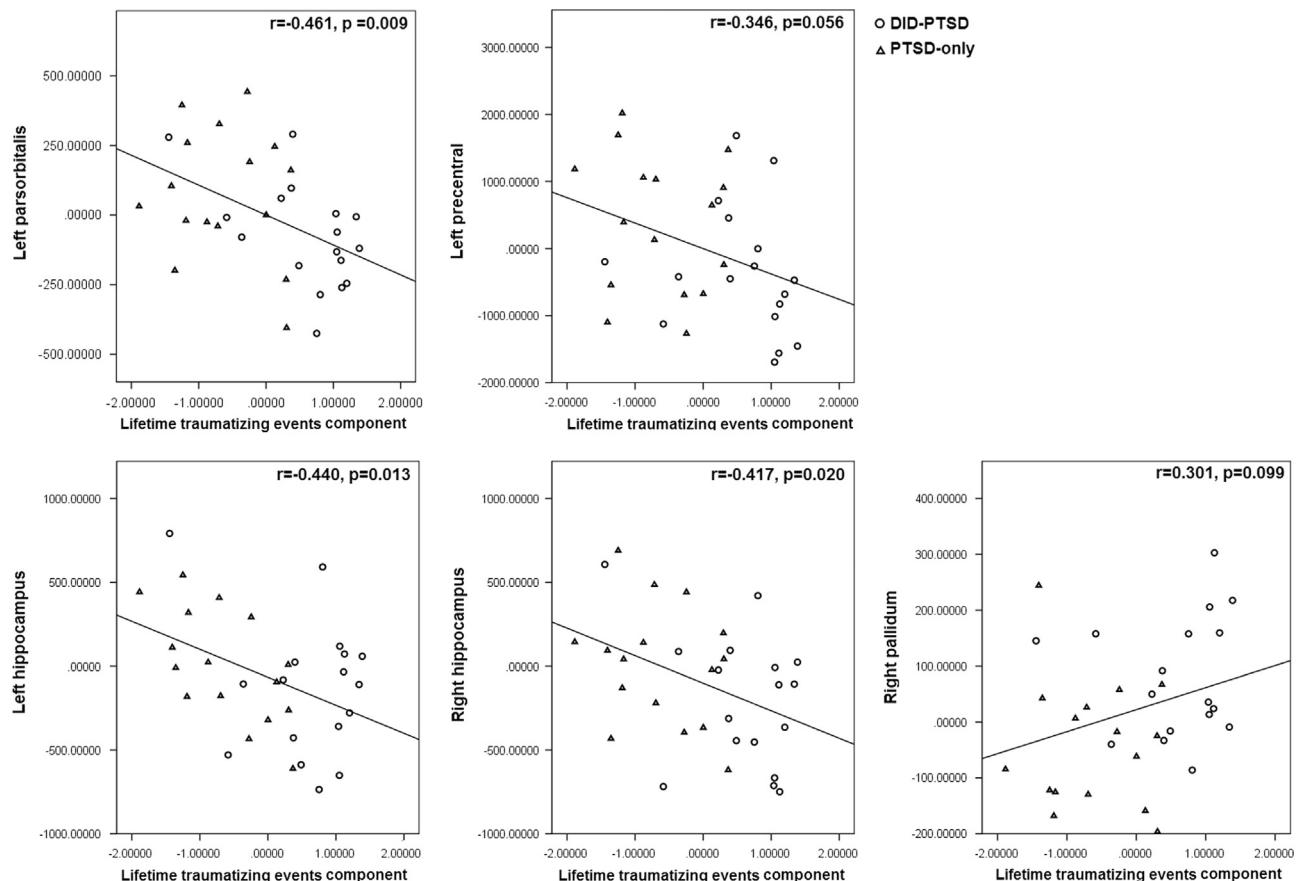
\*\* *P*-value ≤ 0.01.

<sup>^</sup> 0.05 < *P*-value < 0.1.

<sup>a</sup> Controlled for age and parenchymal volume.



**Fig. 2.** Scatter plots of the *a priori* GM regions that showed significant or marginally significant correlations with dissociative component. The values in the x and y axes are adjusted for the age and parenchymal volume. Abbreviations: PTSD-only=patients with only posttraumatic stress disorder; DID-PTSD=patients with dissociative identity disorder and co-morbid PTSD.



**Fig. 3.** Scatter plots of the *a priori* GM regions that showed significant or marginally significant correlations with lifetime traumatizing events component. The values in the x and y axes are adjusted for the age and parenchymal volume. Abbreviations: PTSD-only=patients with only posttraumatic stress disorder; DID-PTSD=patients with dissociative identity disorder and co-morbid PTSD.

derealization symptoms. These findings might indicate the presence of disorder-specific neuroanatomical abnormalities. We thus conclude that our findings support the differential nosological categorization in the DSM-5 of these two patient groups.

In conclusion, the present study provides evidence of abnormalities of cortical and subcortical GM morphology in individuals with DID and co-morbid PTSD and individuals with PTSD only. It documents similar as well as dissimilar (sub)cortical GM morphological abnormalities in these patients groups and therewith satisfies aims of the National Institute of Mental Health (NIMH) Research Domain Criteria (RDoC) (Cuthbert and Insel, 2010), which is to create a neuroscience-based nosological framework for future research on psychopathology. DID-specific abnormalities involved the inferior parietal cortex, putamen and pallidum, which were associated with dissociative and depersonalization/derealization symptoms and can be considered neurobiological markers for DID. Our findings support trauma-related models of DID (Boon and Draijer, 1993b; Van der Hart et al., 2006; Dalenberg et al., 2012; Reinders et al., 2012). PTSD and DID, thus, impress as closely related, yet also different disorders, each with profound roots in traumatizing life events. Therefore, our findings of a close relationship between PTSD and DID justify the side-by-side nosological classification in the DSM-5 (Spiegel et al., 2013).

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## Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at <http://dx.doi.org/10.1016/j.psychresns.2015.01.014>.

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