Abnormal Hippocampal Morphology in Dissociative Identity Disorder and Posttraumatic Stress Disorder Correlates with Childhood Trauma and Dissociative Symptoms

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Abstract

Smaller hippocampal volume has been reported in individuals with posttraumatic stress disorder (PTSD) and dissociative identity disorder (DID), but the regional specificity of hippocampal volume reductions and the association with severity of dissociative symptoms and/or childhood traumatization are still unclear. Brain structural MRI scans were analyzed for 33 outpatients (17 with DID and 16 with PTSD only) and 28 healthy controls (HC), all matched for age, sex, and education. DID patients met criteria for PTSD (PTSD-DID). Hippocampal global and subfield volumes and shape measurements were extracted. We found that global hippocampal volume was significantly smaller in all 33 patients (left: 6.75%; right: 8.33%) compared to HC. PTSD-DID (left: 10.19%; right: 11.37%) and PTSD-only with a history of childhood traumatization (left: 7.11%; right: 7.31%) had significantly smaller global hippocampal volume relative to HC. PTSD-DID had abnormal shape and significantly smaller volume in the CA2-3, CA4-DG and

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(pre)subiculum compared to HC. In the patient groups, smaller global and subfield hippocampal volumes significantly correlated with higher severity of childhood traumatization and dissociative symptoms. These findings support a childhood trauma-related etiology for abnormal hippocampal morphology in both PTSD and DID and can further the understanding of neurobiological mechanisms involved in these disorders.

Keywords

Dissociative disorders; Stress; Neuroimaging; Hippocampal volume; Childhood abuse; Gray matter

Introduction

Recent epidemiological and neurobiological research in trauma-related disorders has focused on the relationship between childhood and chronic trauma and dissociation. This has led to the recent nosological inclusion of a dissociative subtype of Posttraumatic Stress Disorder (PTSD)[Lanius et al., 2010] in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5)[American Psychiatric Association, 2013]. The dissociative disorders category has also recently been placed next to the trauma- and stress-related disorders category "to indicate the close relationship between them" [Spiegel et al., 2013]. However, neurobiological evidence for a close relationship between PTSD and dissociative disorders is lacking. Furthermore, to date, the link between neuroanatomical abnormalities and childhood traumatization and/or dissociative symptoms in PTSD and dissociative disorders remains unclear.

A smaller hippocampal volume is the most consistently reported neuroanatomical finding in individuals with a history of childhood adversity, with or without psychiatric disorders [Andersen et al., 2008; Bremner et al., 2003; Dannlowski et al., 2012; Samplin et al., 2013; Stein et al., 1997; Thomaes et al., 2010]. Relevant to our study, a meta-analysis of structural brain imaging studies in childhood-related PTSD has revealed significantly smaller hippocampal volume in adults, but not children, with PTSD compared to healthy controls (HC)[Woon and Hedges, 2008]. However, none of these PTSD studies has investigated hippocampal shape or the regional specificity of hippocampal volume reductions in this disorder. The relation between hippocampal morphology and childhood adversity also remains unknown. Furthermore, evidence relating hippocampal structural abnormality to the severity of dissociative symptoms in PTSD is mixed. While some PTSD studies have reported a negative correlation between global hippocampal volume and severity of dissociative symptoms [Bremner et al., 2003; Stein et al., 1997], others reported no significant association [Bremner et al., 1995; Nardo et al., 2013].Therefore, the relationship between hippocampal morphology, childhood maltreatment and dissociative symptoms in a sufficiently large sample of PTSD patients is still open to test.

So far, only few structural imaging studies have investigated hippocampal volume in dissociative disorders [Ehling et al., 2008; Irle et al., 2009; Stein et al., 1997; Tsai et al., 1999; Vermetten et al., 2006; Weniger et al., 2008]. Studies in patients with dissociative disorders and co-morbid PTSD [Ehling et al., 2008; Irle et al., 2009; Stein et al., 1997; Tsai

et al., 1999; Vermetten et al., 2006] have found smaller hippocampal volume in these individuals relative to HC, and only one study [Ehling et al., 2008] reported a negative correlation between hippocampal volume and severity of life-time traumatizing experience and dissociative symptoms in individuals with Dissociative Identity Disorder (DID). DID is the most severe dissociative disorder, and has been conceptualized as a severe childhood-onset PTSD [Van der Hart et al., 2006]. Interestingly, hippocampal volume has been reported as preserved in patients with dissociative disorders without co-morbid PTSD [Weniger et al., 2008]. Unfortunately, these studies suffered from several limitations: small sample sizes; inclusion of patients with mixed diagnoses of dissociative disorders without differentiating these groups within the analyses (DID, dissociative amnesia, dissociative disorder-not otherwise specified); and age differences between patients and controls [Ehling et al., 2008; Irle et al., 2009; Stein et al., 1997; Tsai et al., 1999; Vermetten et al., 2006; Weniger et al., 2008].

Most studies on the effects of early stress on the hippocampus, including those on PTSD or DID, have only examined differences in global hippocampal volume. However, the hippocampus consists of several histologically distinct subfields, each with distinct structural and functional connections with the cortex, specialized functional properties, and different developmental trajectories [Wang et al., 2010]. In individuals from the general community, childhood traumatization (assessed using the Childhood Trauma Questionnaire (CTQ)[Bernstein et al., 1994]) is specifically associated with relatively small volume within the CA2-3 (CA: cornu ammonis), CA4-DG (DG: dentate gyrus), subiculum, and to a lesser extent with smaller volume of the CA1 hippocampal subfields, revealing a relationship between childhood adversity maltreatment and small hippocampal subfield volumes [Teicher et al., 2012]. So far, only two studies evaluated hippocampal subfield volumes in PTSD patients [Bonne et al., 2008; Wang et al., 2010]. These studies found smaller volume of the CA3/DG and posterior regions in PTSD patients compared to controls. However, these studies did not investigate the association with childhood traumatization or dissociative symptoms. Indeed, regional hippocampal volume and shape abnormalities have never been investigated in dissociative disorders.

The current study is the first to investigate hippocampal morphological correlates of childhood traumatization and dissociative symptoms in both DID and PTSD patients. To this end, we obtained structural MRI scans from HC and patients with DID and/or PTSD. All participants were carefully matched for age, sex, and education. We investigated global hippocampal volume, subfield volumes, as well as hippocampal regional shape deformations. In the patient samples, we examined the association between hippocampal volume and severity of self-reported early childhood traumatization, that is physical maltreatment, sexual and emotional abuse, and emotional neglect, and severity of dissociative symptoms. We tested three *a priori* hypotheses: 1) both DID and PTSD patients, as compared to HC, would have smaller global hippocampal volume, regional volumetric abnormalities, and shape deformations in various hippocampal subfields; 2) global hippocampal volume, as well as, regional volume in the CA4-DG, CA2-3 and subiculum subfields would be negatively associated with the severity of childhood

traumatization; and 3) global hippocampal and regional volumes would be negatively associated with dissociative symptoms.

Materials and Methods

Subjects

Sixty-five women (only female patients with DID volunteered to participate in this study) underwent magnetic resonance imaging (MRI): 17 with a diagnosis of DID, 16 with a diagnosis of PTSD and 32 HC. Four HC were excluded from the demographic and morphological analyses due to the presence of artifacts in the MRI scans. Participants were matched for sex, age, years of education (Table I) and Western European ancestry. PTSD patients with a history of interpersonal traumatizing events and DID patients were recruited via mental healthcare institutions and internet advertisements.

The diagnosis of DID was confirmed by one of two DID experts (E.N. or N.D.) using the Structural Clinical Interview for DSM-IV Dissociative Disorders (SCID-D) [Boon and Draijer, 1993; Steinberg, 1993], during which PTSD co-morbidity was assessed as well. The evaluation revealed that all DID patients met criteria for either current co-morbid PTSD (82.35%) or PTSD in remission (17.65%). Therefore, we refer to this sample as "PTSD-DID". The personal therapists of the patients with PTSD-DID 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 phobias (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 catalepsy (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. Depersonalization symptoms were evaluated using the Cambridge Depersonalization Scale (CDS)[Sierra and Berrios, 2000]. Severity of Lifetime traumatizing events were assessed with the Traumatic Experiences Checklist (TEC)[Nijenhuis et al., 2002]. PTSD-DID patients completed these questionnaires in their predominant identity state and all of them reported experiencing severe traumatizing events starting from their childhood and extended into their adult life including severe emotional neglect and abuse, physical maltreatment or extreme physical punishments, and sexual abuse. Childhood maltreatment was retrospectively assessed using the CTQ [Bernstein et al., 1994]. The CTQ is a retrospective 28-item self-report inventory that measures the severity of five different types of childhood traumatization (i.e. emotional abuse and neglect, physical abuse and neglect and sexual abuse) with scores ranging from 5 to 25 for each trauma type. Total childhood traumatization is calculated as the sum of all the five subscores. In PTSD-DID, CTQ scores were obtained from a trauma-conscious state.

In the sixteen PTSD 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 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 5 PTSD patients reported traumatizing events only during adult life. Two PTSD patients scored high on the DES/SDQ-20 and therefore underwent a SCID-D interview and DID was excluded. Hence, we refer to this patient group as "PTSD-only". As both PTSD-DID and PTSD-only groups shared the diagnosis of PTSD, we further merged them into one larger group, referred to as "All-PTSD", in order to investigate the common morphological features of PTSD.

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, respectively), 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. 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 medications usage are provided in Table I.

After complete description of the study to the subjects, written informed consent was obtained according to procedures approved by the Medical Ethical Committee (METc) of the University Medical Center Groningen (UMCG) and of the Amsterdam Medical Center (AMC).

Image acquisition

T1-weighted anatomical MR scans (MPRAGE, TR=9.95ms, TE=5.6ms, flip-angle=8°, 1×1×1mm voxels, number of slices=160, total scan-time=10m 14s) were acquired on two (UMCG and AMC) 3T MR scanners (Philips Medical Systems, Best, NL) in The Netherlands after a reproducibility study determined one optimized structural MRI protocol for the two centers [Chalavi et al., 2012]. All-PTSD patients and their matched HC were scanned interleaved within a short time interval and the samples were balanced over the two centers: twenty All-PTSD patients (ten PTSD-DID, ten PTSD-only) and nineteen HC were scanned at UMCG (See supplementary material 1 for more details).

Image analysis

Manual measures of global volume and shape analysis of the hippocampus—
After preprocessing the MR images the hippocampi were manually traced using MultiTracer by a single rater (SC), who was blind to all demographic variables and was trained by an expert (JHC) according to an established protocol [Thompson et al., 2004] (details in supplementary material 1). Hippocampal global volumes obtained from these tracings were statistically analyzed. To assess the shape deformations of different hippocampal subfields, an anatomical surface mesh modeling method was applied according to standard procedures [Thompson et al., 2004]. In brief: Localized gray matter contractions and expansions of the hippocampal surface were established corresponding to the CA1, CA2-3 and subiculum. In each individual, the medial core, a central 3D curve threading down the long axis of the structure, was computed and from each point on the hippocampal surface, a radial distance measure was derived to the medial core. Statistical comparisons were made at each

hippocampal surface point between the groups to index contrasts on a local scale. Probability values from these statistical comparisons were mapped onto an average hippocampal shape for the entire sample to generate a 3D representation of the structural differences between the groups. The approximate overlay of the hippocampal subfields was defined based on the Duvernoy atlas ([Duvernoy, 1988], Figure 1.a).

Automated extraction of hippocampal global and subfield volumes—We used FreeSurfer v5.1 (http://surfer.nmr.mgh.harvard.edu) to segment all images into tissue classes and to extract estimates of hippocampal subfield volumes (CA1, CA2-CA3, CA4-DG, subiculum, presubiculum and fimbria) [Van Leemput et al., 2009]. An estimate of parenchymal volume (total gray matter (GM) + total white matter (WM)) was also obtained using FreeSurfer and was used in subsequent statistical analyses to correct for whole-brain size.

Statistical analysis

The effect of PTSD diagnosis was first investigated on the global hippocampal and subfield volumes by comparing volumetric measurements between All-PTSD and HC. To this end, a repeated-measures analysis of covariance (ANCOVA) was used with hemisphere (left or right) as the repeated measure and age and parenchymal volume as covariates. The analysis was then followed by pairwise *t*-tests to compare left and right hippocampal volumes separately between: 1) PTSD-DID vs. HC, 2) PTSD-DID vs. PTSD-only, and 3) PTSD-only vs. HC.

To assess regional hippocampal shape deformations, statistical regression analyses, with age and parenchymal volume as covariates, were conducted at each hippocampal surface point to map the associations between group and radial distance, a measure of local hippocampal shape. The resulting statistical maps (*P*-map) of group differences (uncorrected) were displayed on the hippocampal surface template, which was created by averaging hippocampal shapes from the entire sample. Furthermore, permutation tests with 10,000 iterations and a threshold of p<0.05 were run to obtain an omnibus corrected *p*-value for each *P*-map.

In the All-PTSD group, we tested the association of severity of childhood traumatizing events with global hippocampal and subfield volumes using partial correlations while controlling for age and parenchymal volume. Furthermore, a possible link between global and subfield hippocampal volumes and severity of dissociative symptoms was tested.

Results

Hippocampal global and subfield volumes

We found a significant main effect of PTSD on global hippocampal volumes (F(2,54)=6.65, p=0.003) which was independent of hemisphere (group × side) (Wilks' Lambda=0.97, F(1,57)=1.69, p=0.20). We also found a significant main effect of PTSD diagnosis on hippocampal subfield volumes (F(12,44)=3.19, p=0.002), also independent of hemisphere (group × side: Wilks' Lambda=0.99, F(1,55)=0.052, p=0.82).

Bilateral global hippocampal volumes were significantly smaller (left: 6.75%; right 8.33%) in All-PTSD compared to HC (Table II). Further pairwise *t*-tests (Table II) showed that PTSD-DID had significantly smaller bilateral hippocampal volumes as compared to PTSD-only (left: 7.25%; right: 6.58%) and to HC groups (left: 10.19%; right: 11.37%). We also found a trend for a smaller right hippocampal volume in PTSD-only as compared to HC (right: 5.13%; p=0.067). *Post hoc* analyses (see supplementary material 3) revealed that bilateral hippocampal volumes were only significantly smaller in those PTSD-only patients with childhood onset traumatizing events (left: 7.11%; right: 7.31%)(see Figure 2).

Compared to HC, the All-PTSD group had significantly smaller volume in the bilateral CA2-3, right CA4-DG, and left presubiculum, and, at trend level, also in the right CA1, left CA4-DG and bilateral subiculum. Pairwise *t*-tests revealed that PTSD-DID patients had significantly smaller right CA1, bilateral CA2-3, CA4-DG and subiculum, and left presubiculum volumes than HC. Furthermore, the PTSD-DID group showed significantly smaller left CA4-DG and subiculum volumes than the PTSD-only group. In contrast, hippocampal subfield volumes of the PTSD-only group were not different from those of HC.

Hippocampal shape analysis

As compared to HC, All-PTSD (Figure 1.b) as well as both PTSD-DID (Figure 1.c) and PTSD-only (Figure 1.e) showed deformations in the CA1, CA2-3 and subiculum. Direct comparison of shape measures between PTSD-DID and PTSD-only showed relative contractions in the CA1, CA2-3 and subiculum in PTSD-DID (Figure 1.d). The results of these shape analyses did not survive multiple comparison correction with permutations. Uncorrected shape deformation results are presented for exploratory purposes because they support and inform on the significant volumetric results.

Hippocampal volume and severity of childhood traumatization

Bilateral global hippocampal volumes were significantly, or at a trend level, negatively correlated with severity of childhood emotional neglect, sexual abuse and total traumatization (Table III and Figure 3). Subfield volumes of the left CA1, CA2-3, CA4-DG and (pre)subiculum, also showed correlations with severity of childhood traumatizing events. The strongest correlations were observed between left presubiculum volume and total childhood trauma (r=-0.64, p<0.001).

Hippocampal volume and dissociative symptoms

Significant negative correlations were found between severity of dissociative symptoms and the volumes of the left subiculum and presubiculum (Table III).

Discussion

This study is the first to investigate clinical correlates of global and regional morphological abnormalities of the hippocampus in DID and PTSD patients. As hypothesized, we found that in all patients with PTSD and patients with DID, relative to healthy controls, global hippocampal volume is smaller and regional volumetric abnormalities are localized in the subfields CA2-3, CA4-DG and subiculum. Furthermore, these findings are supported by

evidence of hippocampal surface contractions in the subfields CA1, CA2-3 and subiculum. Another important finding is that within our patient sample, the severity of childhood traumatizing events, in particular emotional neglect and sexual abuse, was negatively correlated with global and subfield hippocampal volumes. However, severity of dissociative symptoms (psychoform or somatoform) was negatively associated with the volumes of the left presubiculum and subiculum only. These findings support a link between hippocampal morphological abnormalities and childhood traumatization in both DID and PTSD patients.

The subgroup with DID, who all had co-morbid PTSD (PTSD-DID), had significantly smaller global volumes as compared to HC (left: 10.19%; right: 11.37%) as well as compared to PTSD patients without DID (PTSD-only) (left: 7.25%; right: 6.58%). The PTSD-only group showed a trend level difference in the right global hippocampal volume when compared to HC (right: 5.13%; p=0.067), and *post hoc* analyses (see supplementary material 3) revealed that bilateral hippocampi were significantly smaller in those PTSD-only patients with a history of childhood onset traumatizing events (left: 7.11%; right: 7.31%), suggesting again that childhood traumatization is an important factor in the hippocampal abnormalities. These findings concur with prior neuroimaging studies in adult victims of childhood adversity, with or without PTSD [Andersen et al., 2008; Bremner et al., 2003] and in DID patients [Ehling et al., 2008; Irle et al., 2009; Stein et al., 1997; Tsai et al., 1999; Vermetten et al., 2006]. Also, our findings support and advance a previous report of smaller hippocampal volume in DID patients with co-morbid PTSD [Vermetten et al., 2006] which was limited by the unmatched characteristics of their control group [Vermetten, 2006], an issue we did not have in this study.

Smaller hippocampal volumes were particularly located in the subfields CA1, CA2-3, CA4-DG, and (pre)subiculum, a finding also supported by shape analysis results. The subiculum has specifically been associated with memory retrieval, whereas regions corresponding to CA2-3 are involved in the encoding of episodic information [Eldridge et al., 2005]. The role of CA1 in encoding and retrieval of contextual memory has been reported in animal studies [Daumas et al., 2005]. Therefore, abnormalities of any of these subfields could result in memory abnormalities and the localized deformations and gray matter loss in different hippocampal subfields observed in PTSD-DID and PTSD-only patients could underlie memory alterations reported in DID patients [Dorahy, 2001] and the impaired (non-)declarative memory often reported in PTSD patients (for review see [Samuelson, 2011])). Our study opens avenues to investigate the cognitive correlates of hippocampal abnormalities and we suggest that future research investigate the relationship between memory performance and hippocampal abnormalities in DID and PTSD with childhood traumatizing events.

Our findings of smaller volume and deformed shape of the hippocampal subfields in PTSD patients with childhood adversity and in DID patients are consistent with evidence of a relationship between stress and/or elevated level of glucocorticoids (the main stress-related hormones) and morphological alteration of the hippocampal CA1, CA2-3, CA4-DG and (pre)subiculum subfields [Teicher et al., 2012; Wang et al., 2010]. Elevated levels of stress hormones can result in reduced branching of dendrites, reduced synaptic plasticity, neuronal loss or suppression of neurogenesis [Sapolsky, 1993]. The CA2-3 and subiculum subfields

have the highest density of glucocorticoid receptors [Sarrieau et al., 1986] and hence are the most susceptible subfields to the adverse effect of stress. The CA1 neurons in the anterior hippocampus in humans project to the medial prefrontal cortex [Small et al., 2011]. The morphological abnormalities of this subfield could perhaps indicate a potential disturbance in the prefrontal-limbic system, including in the regulation of the hypothalamic-pituitary-adrenal (HPA) axis during stress [Herman et al., 2005]. Therefore, they could possibly be, at least in part, related to the HPA axis dysfunction reported in the patients with PTSD (for a review see de Kloet et al. [2006]) or with a dissociative disorder [Simeon et al., 2007]. The dentate gyrus is involved in neurogenesis and it has been suggested that childhood traumatization can suppress neurogenesis and hence result in smaller CA4-dentate gyrus subfield [Teicher et al., 2012]. This is of course conjecture and the direct relationship between hippocampal morphometric abnormalities and these stress hormone pathways and neuronal properties would need to be confirmed experimentally.

Our finding of a relationship between abnormalities of global and subfield hippocampal volume and severity of childhood traumatizing events in DID, provides a first neuroanatomical support for the hypothesis that the pathophysiology of DID is related to childhood traumatization [Van der Hart et al., 2006; Reinders et al., 2003; Reinders et al., 2006; Reinders et al., 2012]. Although, the present findings need to be confirmed by other neuroanatomical studies, they are in line with the negative correlations previously reported between severity of childhood traumatizing events and hippocampal global [Andersen et al., 2008; Dannlowski et al., 2012; Samplin et al., 2013] and subfield [Teicher et al., 2012] volumes in adults from the general community with a history of early-life adversity. However, as the current study is a cross-sectional study we could not examine direct or indirect links between these measures and hence longitudinal studies are needed to further explore these.

In the two patient groups, severity of dissociative symptom was negatively correlated with the volume of presubiculum and the subiculum, but not with global hippocampal volumes. So far, limited studies have investigated this relationship in traumatized individuals and some studies reported a negative relationship consistent with our results [Bremner et al., 2003; Ehling et al., 2008; Stein et al., 1997], but other studies did not find any significant association [Bremner et al., 1995; Nardo et al., 2013]. While it is possible that the hippocampal morphological abnormalities in our patient samples were at least, in part, involved in the dissociative symptoms, it can be speculated that the associations between morphological measures and dissociative symptoms are actually mediated by childhood traumatization. Future studies can explore this relationship by including individuals with dissociative symptoms but without childhood traumatization.

Some strengths and limitations: although our sample size of 17 PTSD-DID and 16 PTSD-only patients can be considered as modest, it is in fact the largest sample of individuals with DID in which hippocampal morphology has been studied. PTSD severity was evaluated differently across the two patient groups limiting us to investigate the morphological correlates of PTSD severity. Our findings of more pronounced morphological abnormalities in DID might be due to an interaction between (co-morbid) PTSD severity and childhood traumatization [Van Voorhees et al., 2012]. Medication effects were tested (see

supplementary material 2) and showed that the smaller hippocampal volume in PTSD-DID as compared to HC is a robust finding. However, the shape analyses did not survive multiple comparison correction, which is likely due to insufficient statistical power for conducting multiple tests across the hippocampal surface. Nevertheless, permutation testing can be considered too conservative in this context, as all the tests are treated independently, when in fact many of the surface points are highly related.

In conclusion, we provide novel evidence that smaller hippocampal global and subfield volumes and contractions of hippocampal surface in PTSD patients, with or without DID, are related to the severity of childhood traumatizing events and dissociative symptoms. Our findings are in line with the clinical observation that DID is related to chronic childhood abuse and neglect. These findings can help to understand the neurobiological mechanisms involved in PTSD and DID.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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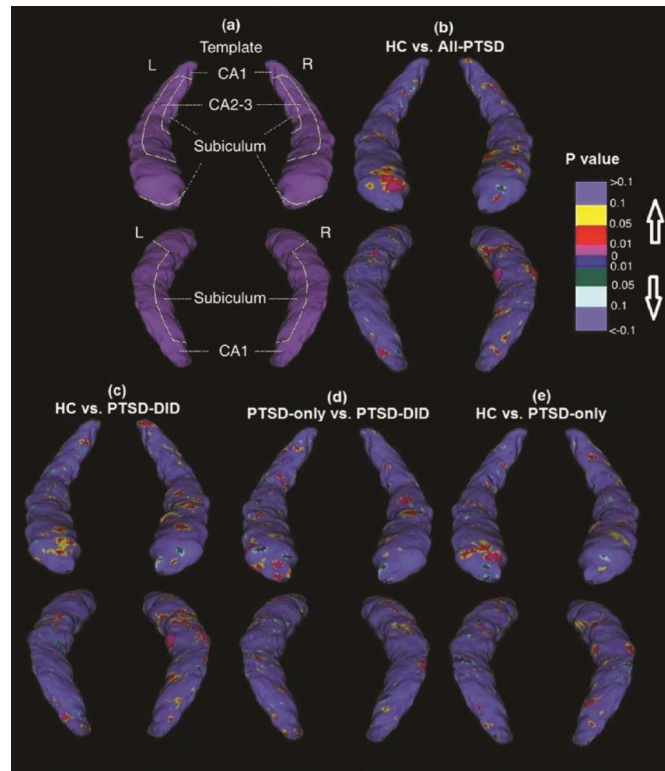
Figure 1.
(a) A schematic representation of the hippocampal subfields mapped onto a representative hippocampal surface obtained by averaging the surface from all the participants. In addition, 3D maps of regional hippocampal shape differences (uncorrected) are shown comparing (b) All-PTSD vs. HC, (c) PTSD-DID vs. HC, (d) PTSD-DID vs. PTSD-only and (e) PTSD-only vs. HC. Upper rows represent anterior view and lower rows represent posterior view. Abbreviations: PTSD-only = patients with only posttraumatic stress disorder; PTSD-DID= patients with PTSD and dissociative identity disorder; All-PTSD= includes both PTSD-only and PTSD-DID patient groups. HC= healthy controls.
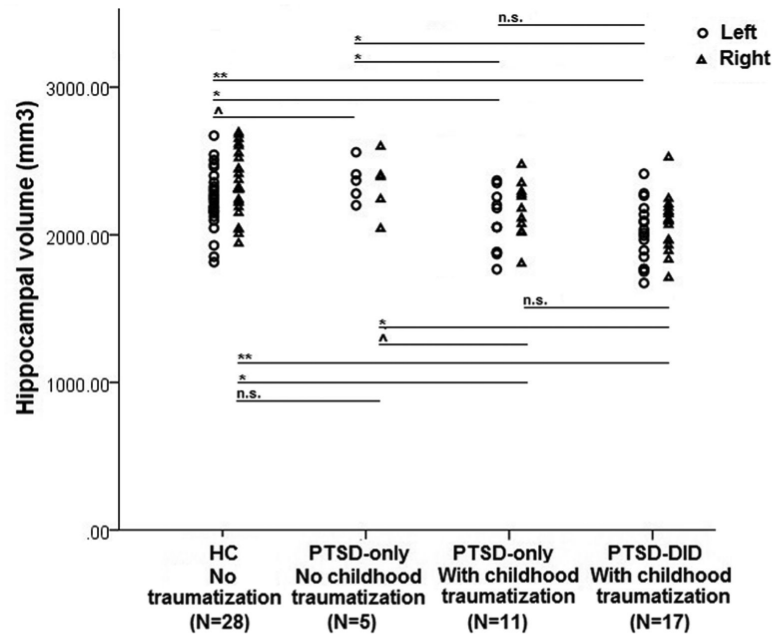
Figure 2.
Left and right hippocampal volumes in different diagnosis groups (** *P*-value<=0.001; * *P*-value <=0.05; ^ 0.05<*P*-value<0.1; n.s.: not significant).

Abbreviations: PTSD-only = patients with only posttraumatic stress disorder; PTSD-DID= patients with PTSD and dissociative identity disorder; HC= healthy controls.
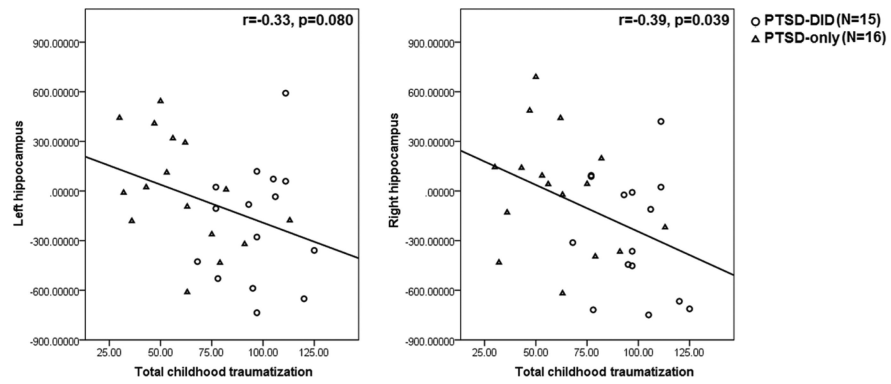
Figure 3.
Scatter plots of the residual values of bilateral global hippocampal volumes from PTSD-DID and PTSD-only groups after regressing out the effect of age and parenchymal volume. The lines represent linear correlations between the residual values and total childhood trauma scores.

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

Table I

Demographic and clinical characteristics of the participants

| | All-PTSD to HC comparison | | | Different group comparisons | | | | |
| | Mean (SD) | | t-test: P Value | Mean (SD) | | t-test: P Value | | |
	All-PTSD (n=33)	HC (n=28)	All-PTSD vs. HC	PTSD-DID (n=17)	PTSD-only (n=16)	PTSD-DID vs. HC	PTSD-DID vs. PTSD-only	PTSD-only vs. HC
Demographics								
Age, years	42.33 (10.91)	41.75 (12.29)	0.85	43.82 (9.85)	40.75 (12.05)	0.56	0.45	0.78
Education, years	14.91 (0.91)	15.04 (1.20)	0.64	14.88 (0.99)	14.94 (0.85)	0.64	0.88	0.77
Handedness, n (%right)	29 (90.63%)	27 (96.43%)	0.37	14 (87.50%)	15 (93.75%)	0.54	0.99	0.99
Medication history								
Antipsychotics:	past:2(1,1)	past: 0	-	past:2(1,1)	past: 0	-	-	-
n (typical, atypical)	current:8(2,6)[1]	current: 0		current:8(2,6)[a]	current: 0			
Anti-epileptics: n	past:1	past: 0	-	past:1	past: 0	-	-	-
	current:3	current: 0		current:3	current: 0			
Antidepressant: n	past: 2	past: 0	-	past: 2	past: 0	-	-	-
	current:12	current: 0		current:10	current: 2			
Clinical measures								
Dissociative symptoms								
Psychoform (DES)	38.79 (22.09)	5.02 (3.10)	<0.001*	54.41 (16.18)	22.18 (13.83)	<0.001*	<0.001*	<0.001*
Somatoform (SDQ-20)	45.24 (19.65)	22.04 (2.21)	<0.001*	57.06 (17.26)	32.69 (13.43)	<0.001*	<0.001*	<0.001*
Traumatic experience checklist (TEC)								
Total lifetime trauma	14.40 (5.16)	1.96 (1.93)	<0.001*	17.53 (4.08)	11.06 (4.01)	<0.001*	<0.001*	<0.001*
Childhood Trauma Questionnaire (CTQ)[2]								
emotional neglect	19.90 (5.69)	10.36(4.14)	<0.001*	23.40 (2.26)	16.63 (6.02)	<0.001*	<0.001*	<0.001*
physical neglect	13.87 (5.22)	7.42 (2.28)	<0.001*	17.47 (3.87)	10.50 (3.93)	<0.001*	<0.001*	0.020*
emotional abuse	18.48 (6.56)	7.50 (2.56)	<0.001*	22.80 (3.30)	14.44 (6.31)	<0.001*	<0.001*	<0.001*
physical abuse	12.35 (5.94)	5.43 (1.34)	<0.001*	15.60 (5.37)	9.31 (4.84)	<0.001*	<0.001*	0.018*
sexual abuse	13.84 (7.69)	5.29 (0.73)	<0.001*	17.87 (7.32)	10.06 (6.06)	<0.001*	<0.001*	0.024*

| | All-PTSD to HC comparison | | | Different group comparisons | | | |
| | Mean (SD) | | t-test: *P* Value | Mean (SD) | | t-test: *P* Value | |
	All-PTSD (n=33)	HC (n=28)	All-PTSD vs. HC	PTSD-DID (n=17)	PTSD-only (n=16)	PTSD-DID vs. HC	PTSD-DID vs. PTSD-only	PTSD-only vs. HC
Total trauma	78.45 (26.92)	36.00 (8.00)	<0.001 *	97.13 (16.63)	60.94 (22.70)	<0.001 *	<0.001 *	<0.001 *

PTSD-only = patients with only posttraumatic stress disorder; PTSD-DID= patients with PTSD and dissociative identity disorder; All-PTSD= includes both PTSD-only and PTSD-DID patient groups. HC= healthy controls.

[1] one PTSD-DID patient used typical antipsychotics in the past but stopped and was using atypical antipsychotics at the time of the MRI scan. Another PTSD-DID patient was using atypical antipsychotics in the past but was not using any antipsychotics at the time of the MRI scan.

[2] CTQ data was available for 15 PTSD-DID, 16 PTSD-only and 14 HC

*
P-value<0.05

Table II

Statistical analyses of parenchymal (cm³), hippocampal global (mm³) and subfields (0.5 mm³) volumes.

Measurement	All-PTSD to HC comparison			Different group comparisons				
	Mean (SD)		t-test: *P* Value (change%)	Mean (SD)		t-test: *P* Value (change%)		
	All-PTSD (n=33)	HC (n=28)	All-PTSD vs. HC	PTSD-DID (n=17)	PTSD-only (n=16)	PTSD-DID vs. HC	PTSD-DID vs. PTSD-only	PTSD-only vs. HC
Parenchymal	1072 (779)	1084 (599)	0.69 (−1.11)	1068 (819)	1075 (759)	0.48 (−1.48)	0.78 (−0.65)	0.70 (−0.83)
Global volume								
Left hippocampus	2086 (229)	2237 (196)	0.012 * (−6.75)	2009 (208)	2166 (228)	0.001 * (−10.19)	0.046 * (−7.25)	0.30 (−3.17)
Right hippocampus	2145 (204)	2340 (205)	0.001 * (−8.33)	2074 (185)	2220 (202)	<0.001 * (−11.37)	0.047 * (−6.58)	0.067 ^ (−5.13)
Subfield volumes								
Left CA1	2436 (321)	2421 (304)	0.56 (0.62)	2366 (330)	2511 (302)	0.78 (−2.28)	0.16 (−5.77)	0.20 (3.70)
Right CA1	2425 (300)	2551 (265)	0.090 ^ (−4.94)	2382 (258)	2471 (341)	0.024 * (−6.62)	0.12 (−3.61)	0.60 (−3.12)
Left CA2-3	6789 (857)	7284 (832)	0.031 * (−6.80)	6578 (995)	7012 (640)	0.009 * (−9.70)	0.12 (−6.19)	0.38 (−3.73)
Right CA2-3	7303 (930)	7778 (851)	0.043 * (−6.11)	7074 (838)	7547 (986)	0.006 * (−9.06)	0.052 ^ (−6.26)	0.57 (−2.98)
Left CA4-DG	3836 (506)	4094 (462)	0.053 ^ (−6.30)	3680 (580)	4003 (361)	0.007 * (−10.12)	0.046 * (−8.07)	0.66 (−2.22)
Right CA4-DG	4032 (464)	4361 (468)	0.009 * (−7.54)	3942 (455)	4128 (470)	0.003 * (−9.61)	0.13 (−4.50)	0.19 (−5.34)
Left presubiculum	3521 (361)	3721 (364)	0.027 * (−5.37)	3413 (361)	3635 (336)	0.007 * (−8.28)	0.11 (−6.09)	0.35 (−2.32)
Right presubiculum	3413 (350)	3591 (377)	0.12 (−4.96)	3430 (344)	3396 (368)	0.30 (−4.48)	0.64 (1.00)	0.13 (−5.43)
Left subiculum	4680 (561)	4919 (439)	0.082 ^ (−4.86)	4476 (567)	4896 (482)	0.007 * (−9.00)	0.022 * (−8.57)	0.89 (−0.46)
Right subiculum	4694 (435)	4905 (442)	0.085 ^ (−4.30)	4613 (412)	4780 (455)	0.020 * (−5.95)	0.10 (−3.49)	0.63 (−2.54)
Left fimbria	498 (104)	498 (164)	0.90 (0.00)	491 (115)	507 (95)	0.83 (−1.58)	0.85 (−3.20)	0.99 (1.67)
Right fimbria	503 (90)	471 (158)	0.25 (6.79)	521 (92)	485 (87)	0.11 (10.59)	0.24 (7.48)	0.80 (2.89)

PTSD-only = patients with only posttraumatic stress disorder; PTSD-DID= patients with PTSD and dissociative identity disorder; All-PTSD= includes both PTSD-only and PTSD-DID patient groups. HC= healthy controls.

*
P-value<0.05

^
0.05<P-value<0.1 (a trend)

Table III

Correlations between hippocampal global and subfield volumes and severity of dissociative symptoms or childhood traumatizing events in the patients.

| | | | Partial correlation r(P-value)[1] | | | | | |
| | | | Childhood trauma questionnaire (CTQ) | | | | | |
	DES	SDQ-20	emotional neglect	physical neglect	emotional abuse	physical abuse	sexual abuse	Total trauma
Global volume								
Left hippocampus	0.009(0.96)	−0.04(0.84)	−0.43(**0.021**)*	−0.26(0.17)	−0.27(0.16)	−0.17(0.39)	−0.32(0.090)^	−0.33(0.080)^
Right hippocampus	−0.21(0.25)	−0.17(0.36)	−0.35(0.061)^	−0.26(0.17)	−0.28(0.15)	−0.27(0.16)	−0.47(**0.010**)*	−0.39(**0.039**)*
Subfield volumes								
Left CA1	−0.26(0.15)	−0.15(0.42)	−0.30(0.11)	−0.13(0.49)	−0.25(0.19)	−0.22(0.24)	−0.41(**0.029**)*	−0.32(0.094)^
Right CA1	−0.15(0.43)	0.001(0.99)	−0.25(0.18)	−0.25(0.19)	−0.12(0.54)	−0.05(0.79)	−0.25(0.19)	−0.21(0.27)
Left CA2-3	−0.21(0.25)	−0.20(0.28)	−0.35(0.064)^	−0.19(0.32)	−0.36(0.057)^	−0.24(0.20)	−0.44(**0.018**)*	−0.38(**0.044**)*
Right CA2-3	−0.14(0.44)	0.05(0.79)	−0.34(0.069)^	−0.30(0.11)	−0.27(0.15)	−0.15(0.45)	−0.35(0.059)^	−0.33(0.081)^
Left CA4-DG	−0.25(0.17)	−0.25(0.17)	−0.37(0.051)^	−0.26(0.16)	−0.38(**0.044**)*	−0.31(0.10)	−0.42(**0.022**)*	−0.41(**0.027**)*
Right CA4-DG	−0.09(0.63)	−0.05(0.77)	−0.29(0.12)	−0.27(0.15)	−0.25(0.18)	−0.13(0.50)	−0.30(0.12)	−0.29(0.13)
Left presubiculum	−0.39(**0.031**)*	−0.49(**0.005**)*	−0.46(**0.012**)*	−0.60(**0.001**)*	−0.56(**0.002**)*	−0.59(**0.001**)*	−0.54(**0.003**)*	−0.64(**<0.001**)*
Right presubiculum	0.02(0.90)	−0.21(0.25)	−0.13(0.51)	−0.17(0.37)	−0.27(0.15)	−0.26(0.18)	−0.14(0.45)	−0.22(0.24)
Left subiculum	−0.37(**0.040**)*	−0.31(0.086)^	−0.46(**0.013**)*	−0.38(**0.041**)*	−0.45(**0.013**)*	−0.46(**0.013**)*	−0.56(**0.001**)*	−0.54(**0.002**)*
Right subiculum	−0.17(0.35)	−0.19(0.31)	−0.33(0.081)^	−0.31(0.11)	−0.21(0.26)	−0.12(0.52)	−0.35(0.060)^	−0.31(0.10)
Left fimbria	−0.03(0.87)	0.20(0.28)	−0.06(0.72)	0.006(0.98)	0.02(0.90)	0.01(0.95)	0.004(0.98)	−0.002(0.99)
Right fimbria	0.20(0.27)	0.19(0.31)	0.10(0.96)	0.17(0.37)	0.08(0.69)	0.09(0.63)	0.14(0.45)	0.12(0.54)

CTQ= childhood trauma questionnaire; DES= dissociative experience scale; SDQ= somatoform dissociative questionnaire; PTSD= posttraumatic stress disorder.

[1] Controlled for age and parenchymal volume

* P-value<0.05

^ 0.05<P-value<0.1 (a trend)