The stress connection: Neuroimaging studies of emotion circuits in social stress, personality, and stress-related psychopathology

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CHAPTER 6

Evidence for focal right amygdala volume reductions in posttraumatic stress disorder following childhood trauma

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ABSTRACT

Hippocampus and amygdala volumes in posttraumatic stress disorder (PTSD) related to childhood trauma are relatively understudied, albeit the potential importance to the disorder. Whereas a few studies reported hippocampal volume reductions, no evidence was found for abnormal amygdala volumes. Further reasearch is thus warranted. Here we investigated hippocampus and amygdala volumes and shapes in an adult sample of PTSD patients related to childhood trauma. T_1-weighted magnetic resonance images were acquired from 12 female PTSD patients with trauma related to physical, sexual, and/or emotional abuse before age 18, and 12 age- and education-matched healthy female controls. Automated segmentation of the hippocampus and amygdala was carried out, and volumes were calculated and corrected for total intracranial volume. Additionally, a shape analysis was done on the surface of the structures to explore abnormalities in specific subnuclei. Decreased right amygdala volumes were found in PTSD patients as compared with controls. Volume reductions appeared to be specifically located in the basolateral and superficial nuclei groups. Severity of sexual abuse during childhood was negatively correlated with the size of the amygdala. No difference in hippocampal volumes was found. Although our results are not conclusive, we hypothesize that traumatic events in childhood might impede normal development of the amygdala, which could render a person more vulnerable to develop PTSD later in life.

INTRODUCTION

Patients suffering posttraumatic stress disorder (PTSD) experience negatively arousing intrusions, often reliving the traumatic experience that shaped the disorder. Key roles in the neuropathology of PTSD and its symptomatology have been attributed to the amygdala and hippocampus (Pitman et al., 2012). At the functional level, abnormal hippocampus activity has mainly been associated with trauma-related memory (Astur et al., 2006; Bremner, Vythilingam, Vermetten, Southwick, McGlashan, Staib, et al., 2003b; Brohawn et al., 2010; Shin et al., 2004; Thomaes et al., 2009), while the amygdala often has been found hyperresponsive to trauma or threat-related stimuli in PTSD (Bryant et al., 2008; Protopopescu et al., 2005; Shin et al., 2005). Abnormal function of these subcortical brain structures might be explained by an underlying compromised anatomical integrity.

Indeed, the hippocampus has frequently been found to be smaller in PTSD patients or traumatized subjects without PTSD compared with healthy controls (Apfel et al., 2011; Bossini et al., 2008; Villarreal et al., 2002; Vythilingam et al., 2005; Wang et al., 2010; Wignall et al., 2004), though not always (Fennema-Notestine, Stein, Kennedy, Archibald, & Jernigan, 2002; Golier et al., 2005; Pederson et al., 2004). Nevertheless, bilateral hippocampus volume decreases appeared to be consistent in recent meta-analyses (Karl et al., 2006; Woon et al., 2010; Woon & Hedges, 2011). Volumetric studies of the amygdala, in contrast, mostly failed to show differences (Bonne et al., 2001; Bremner et al., 1997; Fennema-Notestine et al., 2002; Gilbertson et al., 2002; Gurvits et al., 1996; Lindauer et al., 2004; 2005; Wignall et al., 2004), though decreases have been reported (Matsuoka, Yamawaki, Inagaki, Akechi, & Uchitomi, 2003; Goran Pavlisa, Papa, Pavić, & Pavlisa, 2006). Nevertheless, recent meta-analyses do offer evidence for decreased right (Karl et al., 2006) and left amygdala volumes in the disorder (Karl et al., 2006; Woon & Hedges, 2009), though the effect sizes are low.

Whereas most studies have focused on patients that have been exposed to trauma in adulthood, volumetric data on the hippocampus and amygdala are still sparse in adult PTSD patient samples with a history of childhood maltreatment

(Bremner et al., 1997; Bremner, Vythilingam, Vermetten, Southwick, McGlashan, Nazeer, et al., 2003a; Pederson et al., 2004; Stein, Koverola, Hanna, Torchia, & McClarty, 1997). It seems especially relevant to study the detrimental effects of traumatic experiences during childhood, since these may cause a change in the normal developmental trajectory (i.e., increase in volume) of the hippocampus and amygdala throughout adolescence into adulthood (Giedd et al., 1999; Guo et al., 2007; Østby et al., 2009). Consequently, such abnormal trajectory could render the brain more vulnerable to develop affective psychopathology later in life.

A recent meta-analysis in PTSD patients with a history of childhood trauma (Woon & Hedges, 2008) indicated that bilateral hippocampal volume reductions actually might not become evident until the disorder manifests itself during adulthood, since studies investigating childhood PTSD did not report volumetric differences in this structure (Carrion et al., 2001; De Bellis, Hall, Boring, Frustaci, & Moritz, 2001; De Bellis et al., 1999; 2002). As such, this could be taken as evidence for a deviant neurodevelopmental trajectory of the hippocampus in the pathogenesis of adult PTSD. No differences in amygdala volumes were found between PTSD patients with a history of childhood maltreatment and controls, neither when studied in children or in adults (Woon & Hedges, 2008). Surprisingly, however, only one study investigated amygdala volumes in an adult sample with PTSD related to childhood trauma to date (Bremner et al., 1997). Replication of previous results and further investigation of this specific group of patients is thus warranted, especially given the current standard of higher field strength data acquisition and availability of more advanced segmentation algorithms.

To this end, we studied the volumes of the hippocampus and amygdala in a group of adult female PTSD patients who suffered childhood trauma and compared these to age and education matched healthy control females with no history of trauma. Additionally, we were interested whether potential volume increases or reductions could be observed in specific subnuclei of the hippocampus or amygdala, which would provide further specificity with respect to functional subdivisions of these structures in the disorder. Therefore, a shape analysis was employed on the segmented structures to determine local morphological changes. Given the previously reported studies in

PTSD following trauma experienced in either childhood or adulthood, we expected smaller hippocampus and amygdala volumes in our PTSD group compared with healthy controls.

METHODS

PARTICIPANTS

Twenty-four females participated in the current study, 12 patients diagnosed with PTSD (mean age 28.08 ± 7.2) and 12 healthy control participants (mean age 26.83 ± 6.55). Patients were recruited within primary mental health care institutions (de Voorde, Leiden and Trauma center, PsyQ, The Hague) in the vicinity of the Leiden University Medical Center, where this study was conducted. Control participants were recruited by means of advertisements, and were matched to the patients for age and years of education followed.

Inclusion criteria for the patient group were: 1) PTSD diagnosis according to the MINI-International Neuropsychiatric Interview (Sheehan, Lecrubier, & Sheehan, 1998), administered by a trained clinical research assistant; 2) Interpersonal trauma related to emotional abuse, emotional neglect, sexual, and/or physical abuse during childhood or adolescence (< 18 years old), as determined by the Traumatic Experiences Checklist (TEC) (Nijenhuis, Van der Hart, & Kruger, 2002). Exclusion criteria were: 1) Repetitive psychotic episodes; 2) Use of antipsychotic medication. However, other stable use of psychotropic medication was allowed (use of citalopram (n = 2), duloxetine (n = 1), fluoxetine (n = 1), venlafaxine (n = 1), and methylphenidate (n = 1). In addition, several patients fulfilled additional diagnostic criteria for comorbid major depression (n = 5), social anxiety disorder (n = 4), panic disorder (n = 2), and obsessive-compulsive disorder (n = 1). Of note, some patients fulfilled criteria for multiple comorbid disorders. In the current study, comorbid personality disorders were not assessed.

Healthy controls were screened for absence of current or past psychiatric disorders, as determined by the MINI. Additionally, controls had to score low (< 145,

Table 6.1 Study sample demographics and psychometrics.

	PTSD	Healthy Controls
Age	28.08 (±7.2)	26.83 (±6.55)
Education (years)	7.58 (±2.19)	8.25 (±1.91)
Harvard Trauma Questionnaire	73.08 (±11.56)**	32.83 (±2.92)
Traumatic Experiences Checklist	39.83 (±17.95)**	3.5 (±4.36)
Emotional neglect	5.33 (±4.27)*	0.67 (±1.23)
Emotional abuse	5 (±4.33)*	0.17 (±0.58)
Physical abuse	8.36 (±4.18)**	0.42 (±1)
Sexual abuse	7.25 (±5.38)**	0
Dissociative Experience Scale	27.86 (±13.65)**	8.36 (±8.29)
Beck Depression Inventory	32.17 (±11.32)**	2.17 (±2.76)
Symptom Check List 90	223.67 (±49.69)**	101.08 (±7.04)
State-Trait Anxiety Inventory (trait)	62.5 (±6.88)**	31.25 (±6.65)
State-Trait Anxiety Inventory (state)	45.5 (±10.79)**	29.25 (±4.96)

Note: values represent mean ± standard deviation; * PTSD > Healthy Controls ($p < .005$); ** PTSD > Healthy Controls ($p < .001$); all participants were female and right-handed.

according to norm scores of a healthy population) on the Symptom Checklist (SCL-90) (Arrindell & Ettema, 1986), assessing levels of psychoneuroticism. Exclusion criteria for all participants were: 1) Presence or history of a major internal or neurological illness; 2) MINI diagnosis of substance abuse and/or addiction (alcohol and drugs); 3) Pregnancy; 4) General MRI contraindications. Lastly, all participants were required to: 1) Be right-handed; 2) Understand and speak Dutch sufficiently to complete each element of the study; 3) Have a body mass index between 19 and 26 kg/m^2.

On the day of the scan session, all participants were assessed with the Harvard Trauma Questionnaire (Mollica et al., 1992), the Dutch version of the Beck Depression Inventory (Bouman et al., 1985), the Dissociative Experience Scale (Bernstein & Putnam, 1986), and the State-Trait Anxiety Inventory (Spielberger, 1983). All demographic and clinical details of the final study sample are provided in **Table 6.1**.

The Medical Ethical Committee of the Leiden University Medical Center approved the study, and all participants gave written informed consent.

MATERIALS

MRI data acquisition

Imaging data were acquired on a Philips 3T Achieva MRI scanner using an eight-channel SENSE head coil for radiofrequency reception (Philips Healthcare, Best, The Netherlands). A high-resolution anatomical image (3D T_1-weighted ultra-fast gradient-echo acquisition; TR = 9.75 ms; TE = 4.59 ms; flip angle = 8°; 140 axial slices; FOV = 224 × 224 mm; in-plane resolution 0.875 × 0.875 mm; slice thickness = 1.2 mm) was acquired for segmentation of the amygdala and hippocampus.

Demographic and psychometric data analysis

Demographic and psychometric data were all compared between groups using independent samples *t*-tests using SPSS Version 18.0 (IBM), with the significance threshold set at $p = .05$.

Segmentation of the amygdala and hippocampus

Prior to analysis, all T_1-weighted images were submitted to a visual quality control check to ensure that no gross artifacts were present in the data. Next, data were analyzed using FSL Version 4.1.3 (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl) (Smith et al., 2004) using the FIRST tool for automated model-based registration and segmentation of subcortical structures (Patenaude, Smith, Kennedy, & Jenkinson, 2011). The following processing steps were employed: 1) Affine registration of the T_1-weighted images to the MNI-152 1 mm isotropic standard space template (Montreal Neurological Institute, Montreal, QC, Canada). 2) Second stage affine registration using an MNI-152 subcortical mask to exclude voxels outside the subcortical regions. 3) Automated segmentation of the bilateral amygdala and hippocampus. The segmentation procedure is informed by shape and intensity information of anatomical models of these structures that were constructed from manually segmented images provided by the Center for Morphometric Analysis (CMA), MGH, Boston. 4) Boundary correction to ameliorate partial volume effects using tissue classification information based on FSL's FAST segmentation tool. For more information and a

detailed description of the method we refer to Patenaude et al. (2011). All registration and segmentation results were visually checked for errors by an experienced neuroscientist (I.V.).

Volume analysis

For the boundary corrected segmentations of the amygdala and hippocampus, left and right side separately, volumes in mm^3 were calculated using the FSL command line tool *fslstats*. Each volume was normalized for differences in total intracranial volume. Volume differences between groups were then analyzed using a multivariate analysis of variance (MANOVA) in SPPS statistics 18.0 (IBM), setting the significance threshold at $p = .05$. Effect sizes (ω^2) of the between-groups effects were calculated additionally. Additionally, paired *t*-tests were carried out within each group to test for effects of lateralization. Last, correlations were calculated between structures that differed in volume between the two groups and scores on the HTQ, the TEC total, and TEC subscales Emotional Neglect, Emotional Abuse, Physical Abuse, and Sexual Abuse. Taking the mutual correlation between the six (subscales of the) questionnaires into account (average $r = 0.4$), the Bonferroni corrected significance threshold is $p < .017$ (as calculated with SISA, an online statistics calculator; www.quantitativeskills.com/sisa/)

Shape analysis

We opted to investigate whether the amygdala and hippocampus differed between patients and controls in local shape and size to reveal a possible predisposition for subregions to show volume increases or reductions. To this end, surface meshes were created from the individual segmentations of both structures in native space. Each mesh is composed of a set of triangles. The apex of neighboring triangles is called a vertex. The number of vertices is fixed for each subcortical structure to ascertain comparability both across and between participants. Surface meshes from the FIRST models that were used to aid segmentation were used as a common template to which each individual surface mesh was aligned. For each of the four structures comparisons between the two groups were carried out using non-parametric permutation based

statistics (FSL Randomise tool), with the height of each of the vertices entered as dependent variables (Patenaude et al., 2011; Zarei et al., 2010). Per vertex a null distribution of *F*-values was derived for the between group contrast by performing 5000 random permutations (Nichols & Holmes, 2002). The resulting statistical maps were cluster corrected for multiple comparisons, using an initial cluster forming threshold of $F(1, 22) > 4.3$ ($p < .05$), and a corrected $p < .05$. Localization of effects was carried out using the Juelich histological atlas, provided in FSL's image viewer.

PROCEDURE

Upon arrival on the day of the scan session participants were first instructed about the proceedings of the day and then filled out several questionnaires (HTQ, DES, BDI, and STAI). Afterwards, participants were brought to the scanner. Before participants entered the scanner, and after the scanning protocol was completed, a 10-point Likert scale was used to inquire about the perceived levels of stress, anxiety, concentration, and intrusions. Before and after the scan protocol, outside the scanner, participants also rated the four items of the short Dissociation Tension Scale (Stiglmayr, Schmahl, Bremner, Bohus, & Ebner-Priemer, 2009). An exit-interview and extensive debriefing followed at the end of the experiment. Subsequently, participants were thanked and paid for their participation in the study.

RESULTS

Behavioral results

Patients and controls did not differ on age and years of education (both $p > .05$). As expected, patients scored higher ($p < .005$) on all clinical scales (see **Table 6.1** for means and standard deviations) compared to controls.

Table 6.2 Amygdala and hippocampus volumetry results.

	PTSD	Healthy Controls
Left amygdala	1498.52 (±353.34)	1567.91 (±322.91)
Right amygdala	1356.3 (±332.99)*	1667.55 (±264.45)
Left hippocampus	5095.85 (±931.51)	5275.52 (±617.11)
Right hippocampus	5197.27 (±474.75)	5347.99 (±420.98)

Note: values are in mm^3 and represent mean volumes ± standard deviation, normalized for intracranial volume; * PTSD < Healthy Controls (p = .019).

Volumetric results

Table 6.2 lists the volumes of the left and right amygdala and hippocampus. All four structures met the criteria of homogeneity of variance and normality to justify parametric statistics. The multivariate test revealed a trend for the independent variable Group, $F(4, 19) = 2.33$, $p = .093$, though with an observed power of .56. Subsequent univariate tests showed that right amygdala volumes were smaller in the PTSD patients (mean ± *SD*: 1365.3 ± 332.99) than in the healthy controls (mean ± *SD*: 1667.55 ± 264.45), $F(1, 22) = 6.43$, $p = .019$, $\omega^2 = .19$, reflecting a medium to strong effect size, and a moderate observed power of .68. No differences were found for the left amygdala or the left and right hippocampus (all $p > .25$). Paired t-tests did not reveal volumetric asymmetry between the left and right side of the amygdala and hippocampus within both groups ($p > .2$). Last, right amygdala volumes correlated negatively with the Traumatic Experiences Checklist subscale Sexual Abuse ($r = -.64$, $p = .013$, one-tailed).

Shape results

The vertex analysis revealed focal volume reduction in PTSD patients compared with healthy controls on the surface of the right amygdala (**Figure 6.1a**). The affected area showed good overlap with two main groups of subnuclei of the amygdala: the basolateral (red), and the superficial or cortical (light blue) group (Amunts et al., 2005). The effects encompassed 18.8 % and 14.6 % of the amygdala surface, respectively. Although volumes of the left amygdala and bilateral hippocampus did not differ between the two groups, it could still be possible that shape differences are observed

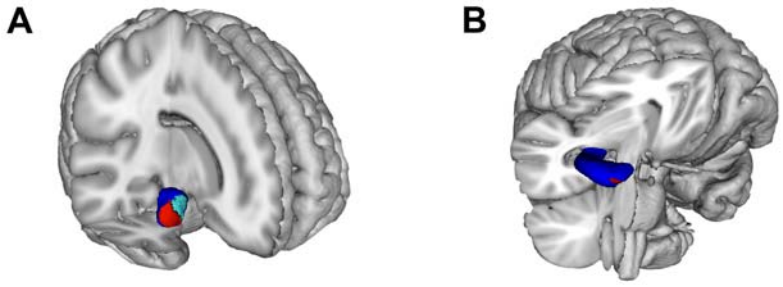

Figure 6.1 Shape analysis results, revealing loci of decreased volume in PTSD compared with controls on the surface of the amygdala and hippocampus (dark blue). (**A**) Volume reductions are found specifically in parts of the basolateral (red) and superficial (light blue) groups of the right amygdala ($p < .05$, corrected). (**B**) A small trend for volume decrease was found in the anterior subiculum of the right hippocampus ($p < .05$, uncorrected). All subgroups were identified using the Juelich Histological Atlas, incorporated in FSL.

in these structures (e.g., existence of focal increases as well as decreases, which on average yield volumes similar to the control group). However, at a lenient uncorrected threshold of $p < .05$ the vertex analysis only revealed a marginal decreased volume of the anterior subiculum of the right hippocampus in PTSD patients compared with healthy controls (**Figure 6.1b**).

DISCUSSION

Up to now, surprisingly little research has been done on amygdala volumes in PTSD, especially not in patients that have been exposure to childhood trauma. In this study we investigated whether volume and shape of the amygdala and hippocampus differed between adult female PTSD patients that have been exposed to childhood maltreatment, and a group of age and education matched healthy control women. Whereas no differences were observed in the volumes of the bilateral hippocampus and left amygdala, we did find smaller right amygdala volumes in the PTSD group compared to controls. Moreover, the difference was mainly located at the surface of the basolat-

eral and superficial nuclei groups. This is the first study to report on amygdala volume reductions in an adult sample with PTSD associated with childhood maltreatment, together with evidence for this reduction to occur in specific amygdala subregions. Moreover, volume reductions were associated with severity of sexual abuse during childhood. Our results provide new insights on how adverse events during childhood could render the brain vulnerable to develop PTSD later in life.

Increased dendritic branching and spine density of amygdala neurons has been reported in rodents after chronic restraint stress (Mitra, Ferguson, & Sapolsky, 2009; Roozendaal et al., 2009; Vyas, Mitra, Shankaranarayana Rao, & Chattarji, 2002), as well as increased myelination after maternal separation (Ono et al., 2008), which was accompanied by higher levels of anxious behavior. Similarly, several human studies have shown that early life adversity, such as prolonged orphanage rearing or poor care due to maternal depression, is related to larger amygdala volumes in adolescence compared to their peers, as well as an increased risk to develop affective psychopathology (Lupien et al., 2011; Mehta et al., 2009; Tottenham et al., 2010). In adulthood, however, no evidence was found for a difference in amygdala volumes between PTSD patients who were exposed to childhood maltreatment and controls (Woon & Hedges, 2008). Nonetheless, *decreased* volumes have been reported in adult borderline patients with a history of childhood abuse (Driessen et al., 2000; Schmahl, Vermetten, Elzinga, & Douglas Bremner, 2003), which is in line with the current finding.

With respect to the apparent discrepancy in amygdala volume differences between childhood and adulthood samples, the following could be hypothesized: Severe adversity during childhood could increase the sensitivity of the amygdala through dendritic growth and synaptic connectivity (Roozendaal et al., 2009), resulting in a larger total volume. While this process could be beneficial to increase chances of survival in a hostile environment by amplification of threatening cues, it could eventually come with a cost: repetitive activation of the amygdala could ultimately result in wear and tear (cf. "neurotoxicity hypothesis") (Lupien et al., 2009; Sapolsky, Krey, & McEwen, 1986), which would be manifested as volume reductions in adulthood. Some support for this idea is lent by studies showing larger amygdala volumes in first

episode depression, which seem to normalize to the size of controls after recurrent depressive episodes (Frodl et al., 2003; Lange & Irle, 2004; Tottenham et al., 2010). On the other hand, the recent meta-analysis by Woon and Hedges (2008) did not find any evidence for altered amygdala volumes in children with maltreatment-related PTSD. Given that the amygdala continue to develop during adolescence (Giedd et al., 1999; Guo et al., 2007; Østby et al., 2009), alternatively it could be hypothesized that severe adversity puts a break on normal maturation of the amygdala. As such, a difference in volume would not become apparent until adulthood.

The volume reductions found in this study appeared to be localized in the basolateral and superficial (or cortical) nuclei groups of the amygdala, as was determined by the shape analysis. These two groups together form the ventral portion of the human amygdala and receive major input and feedback projections from sensory and prefrontal brain regions (Sah, Faber, Lopez De Armentia, & Power, 2003). The role of the basolateral group has been described extensively in the literature, assigning it a crucial role in promoting emotional memory formation (Roozendaal et al., 2009), as well as fear conditioning (LeDoux, 2000). In addition, it has been shown that stress hormones are important modulators within the basolateral amygdala in creating memory traces for emotionally salient events (McGaugh, 2004; Roozendaal et al., 2009). Moreover, induced stress may facilitate this process. As such, exposure to severe stress can lead to enhanced fear conditioning and traumatic memory formation, which lies at the heart of the symptomatology of PTSD. Reduced volumes of these specific groups of nuclei specifically may therefore reflect wear and tear due to repetitive activation of the traumatic memory traces and conditioned fear responses in PTSD.

A negative correlation was found between the sexual abuse subscale of the Traumatic Experience Checklist and right amygdala volume in the PTSD group, indicating smaller volumes when sexual abuse was more severe during childhood. While this could point at the particularly devastating effects of childhood sexual abuse, the association should be interpreted with caution: As small group sizes are especially prone to spurious correlations, replication in a larger group of patients is certainly warranted.

Irrespective of the type of trauma encountered, previous studies have reported hippocampal volume reductions rather consistently (Karl et al., 2006; Woon et al., 2010; Woon & Hedges, 2011). While our patient group seemed to have smaller hippocampus volumes on average, the difference failed to reach significance. A potential explanation for this null finding, however, could be the large standard deviations observed for this structure, in combination with the small sample size.

The current study suffers several limitations. First, our sample size is small (n = 12), yet comparable in size with the four studies discussed by Woon and Hedges (Woon & Hedges, 2008) on volumetric differences in adult PTSD associated with childhood maltreatment, which included 16.25 patients (SD = 4.57) on average. Nevertheless, even within our small group of patients, we found a significant reduction of right amygdala volume compared to controls, with a concurrent medium to strong effect size. The observed power, however, was moderate, indicating that for replication of our findings, future studies should use a larger sample size.

Second, in the current study we did not include a group of PTSD patients with trauma originating in adulthood, so we cannot infer whether the volume reduction of the right amygdala is specific to childhood trauma. Nonetheless, recent meta-analyses in adult PTSD samples predominantly related to adulthood trauma only showed a tendency towards smaller amygdala volumes or no differences at all between patients and controls (Karl et al., 2006; Woon & Hedges, 2009), possibly indicating that our findings might indeed be specific to childhood trauma. Clearly, longitudinal studies are needed to further elucidate the time course of amygdala volume changes in PTSD associated with childhood trauma to draw conclusions on the developmental trajectory of the amygdala following childhood trauma.

Third, most of the patients included in the current study suffered from comorbid psychopathology, which is typical for patients with PTSD, and half of the patients used psychotropic medication. We therefore cannot disentangle whether our findings reflect a PTSD endophenotype per se or are rather related to complex psychopathology, while it remains unclear to what extent medication might have influenced these volumetric differences.

Fourth, our PTSD sample comprised female patients only. Although the number of traumatic events encountered, irrespective of the type of event, is similar or even higher in males than in females, females approximately do have a twofold higher risk to develop PTSD (Breslau, Chilcoat, Kessler, Peterson, & Lucia, 1999; de Vries & Olff, 2009; Kessler, Sonnega, Bromet, Hughes, & Nelson, 1995). In addition, a recent Dutch prevalence study reported that females are confronted with physical and sexual abuse, two of our inclusion criteria, more frequently in childhood than males (de Vries & Olff, 2009).

Conversely, our study has several strengths. All studies on volumetric differences of the hippocampus and amygdala were done on 1.5 Tesla data. In comparison, the 3T MR scanner used in the current study allows for an increase in the signal to noise ratio, which should facilitate easier and more precise segmentation of the structures under scrutiny. Second, the recent emergence of advanced imaging processing software permitted us to study shape differences alongside the volumetric measures. Here we show that such a tool might offer important information on which groups of subnuclei are affected specifically. Last, the scores of the clinical scales indicate that our patient group was severely affected, which was also reflected by the high comorbidity rate. Conceivably, the differences found in the current study might have emerged specifically due to the severely affected nature of the patient group.

In sum, we found smaller right amygdala volumes in PTSD patients compared with controls, whereas the left amygdala and bilateral hippocampus did not differ between the two groups. In addition, this volume reduction appeared to originate in the basolateral and centromedial nuclei groups of the right amygdala. Although our results are not conclusive, we hypothesize that traumatic events in childhood might impede normal development of the amygdala, rendering a person more vulnerable to develop PTSD, or psychopathology in general, later in life. Future longitudinal studies are needed, however, to test this hypothesis, and to shed more light on the detrimental effects of childhood trauma on both structure and function of the brain, and its relation to the pathogenesis of PTSD.