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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 some studies reported smaller hippocampal volumes, little evidence was found for abnormal amygdala volumes. Here we investigated hippocampus and amygdala volumes and shapes in an adult sample of PTSD patients related to childhood trauma. T1-weighted MR images were acquired from 12 female PTSD patients with trauma related to physical, sexual, and/or emotional abuse before age 18, and from 12 matched controls. Hippocampus and amygdala were segmented, and volumes were calculated and corrected for the total intracranial volume. Additionally, a shape analysis was done on the surface of the structures to explore abnormalities in specific subnuclei. Smaller right amygdala volumes were found in PTSD patients as compared with the controls. This difference appeared to be located specifically 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, traumatic events in childhood might impede normal development of the amygdala, which could render a person more vulnerable to develop PTSD later in life.

1. Introduction

Patients suffering from posttraumatic stress disorder (PTSD) experience negatively arousing intrusions, often reliving the traumatic experience that shaped the disorder, avoid distressing trauma-related stimuli, demonstrate negative alterations in cognition and mood, and demonstrate alterations in arousal and reactivity (American Psychiatric Association, 2013). 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 (Bremner et al., 2003b; Shin et al., 2004; Astur et al., 2006; Thomaes et al., 2009; Brohawn et al., 2010), while the amygdala often has been found hyperresponsive to trauma or threat-related stimuli in PTSD (Protopopescu et al., 2005; Shin et al., 2005; Bryant et al., 2008). Abnormal function of these subcortical brain structures may be related to an underlying compromised anatomical integrity (Shin et al., 2006).

Indeed, the hippocampus has frequently been found to be smaller in PTSD patients or traumatized subjects without PTSD, compared with healthy controls (Villarreal et al., 2002; Wignall et al., 2004; Vythilingam et al., 2005; Bossini et al., 2008; Wang et al., 2010; Apfel et al., 2011), though not always (Fennema-Notestine et al., 2002; Pederson et al., 2004; Golier et al., 2005). Nevertheless, smaller bilateral hippocampus volumes appeared to be found consistently, as indicated by recent meta-analyses (Karl et al., 2006; Woon et al., 2010; Woon and Hedges, 2011). Volumetric studies of the amygdala, in contrast, mostly failed to show

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differences (Gurvits et al., 1996; Bremner et al., 1997; Bonne et al., 2001; Fennema-Notestine et al., 2002; Gilbertson et al., 2002; Lindauer et al., 2004; Wignall et al., 2004; Lindauer et al., 2005; Schmahl et al., 2009), though both smaller (Matsuoka et al., 2003; Pavlisa et al., 2006; Vermetten et al., 2006; Weniger et al., 2008, 2009; Irle et al., 2009; Morey et al., 2012;) and larger (Kuo et al., 2012) volumes have been reported. Nevertheless, recent meta-analyses do offer evidence for smaller right or left amygdala volumes in the disorder (Karl et al., 2006; Woon and Hedges, 2009), though the effect sizes reported are small.

Whereas most studies have focused on patients that have been exposed to trauma in adulthood, few have investigated hippocampus and amygdala volumes in adult PTSD patients (either as primary or comorbid diagnosis) with a history of childhood maltreatment (Bremner et al., 1997, 2003a; Stein et al., 1997; Pederson et al., 2004; Vermetten et al., 2006; Weniger et al., 2008, 2009; Irle et al., 2009; Schmahl et al., 2009). A recent meta-analysis in PTSD patients with a history of childhood trauma (Woon and Hedges, 2008) indicated that smaller hippocampal and amygdala volumes actually might not become evident until the disorder manifests itself during adulthood, since studies investigating childhood PTSD did not report volumetric differences in these structures (De Bellis et al., 1999, 2001, 2002; Carrion et al., 2001). As such, this could be taken as evidence for a deviant neurodevelopmental trajectory of the hippocampus and amygdala in the pathogenesis of adult PTSD.

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. Moreover, as volumetric studies in adult PTSD related to childhood trauma are still sparse, further investigation of this specific group of patients is needed. 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 differences 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 differences. 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.

2. Methods and materials

2.1. Participants

Twenty-four females participated in the current study, 12 patients diagnosed with PTSD (mean age 28.08 ± 7.2 y/o) and 12 healthy controls (mean age 26.83 ± 6.55 y/o). 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. Female controls 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 by a board-certified psychiatrist at one of the participating institutions, and confirmation of the diagnosis upon inclusion by the MINI-International Neuropsychiatric Interview (Sheehan et al., 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 y/o), as determined by the Traumatic Experiences Checklist (TEC) (Nijenhuis et al., 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, according to norm scores of a healthy population) on the Symptom Checklist (SCL-90) (Arrindell and 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 and Putnam, 1986), and the State-Trait Anxiety Inventory (Spielberger, 1983). Lastly, the WAIS-III subscales Picture Completion, Arithmetic, Information, and Block Design were administered after scanning to estimate total IQ (TIQ; Wechsler 1997). Test data from two controls were incomplete, and could not be used to assess TIQ. All demographic and clinical details of the final study sample are provided in Table 1.

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

3. MRI data acquisition

Imaging data were acquired on a Philips 3.0-T Achieva MRI scanner using an eight-channel SENSE head coil for radio-frequency 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.

3.1. 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 $p=0.05$ (two-tailed).

Table 1
Study sample demographics and psychometrics.

	PTSD	Healthy controls
Age	28.08 (± 7.2)	26.83 (± 6.55)
Education (years)	13.6 (± 2.19)	14.25 (± 1.91)
WAIS total IQ[†]	106.92 (± 15.75)	108.8 (± 11.32)
Harvard Trauma Questionnaire	73.08 (± 11.56)[1]	32.83 (± 2.92)
Traumatic Experiences Checklist	39.83 (± 17.95)[1]	3.5 (± 4.36)
Emotional neglect	5.33 (± 4.27)[2]	0.67 (± 1.23)
Emotional abuse	5 (± 4.33)[2]	0.17 (± 0.58)
Physical abuse	8.36 (± 4.18)[1]	0.42 (± 1)
Sexual abuse	7.25 (± 5.38)[1]	0
Dissociative Experience Scale	27.86 (± 13.65)[1]	8.36 (± 8.29)
Beck Depression Inventory	32.17 (± 11.32)[1]	2.17 (± 2.76)
Symptom Check List 90	223.67 (± 49.69)[1]	101.08 (± 7.04)
State-Trait Anxiety Inventory (trait)	62.5 (± 6.88)[1]	31.25 (± 6.65)
State-Trait Anxiety Inventory (state)	45.5 (± 10.79)[1]	29.25 (± 4.96)

Note: Values represent mean ± standard deviation; All participants were female and right-handed.

[†] Approximated by WAIS subtests Picture Completion, Arithmetic, Information, and Block Design; All participants were female and right-handed.

[1] PTSD > Healthy controls ($p < 0.001$).

[2] PTSD > Healthy controls ($p < 0.005$).

3.2. Segmentation of the amygdala and hippocampus

Prior to analysis, all T1-weighted images were screened for (clinically relevant) anatomical abnormalities by a board-certified neuroradiologist, and checked for gross image acquisition artefacts by an experienced neuroscientist (I.V.). None were reported. Next, data were analyzed using FSL Version 4.1.3 (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl/fslwiki; Smith et al., 2004) using the FIRST tool for automated model-based registration and segmentation of subcortical structures (Patenaude et al., 2011). The following processing steps were employed: (1) Affine registration of the T_1-weighted images to the MNI152 1 mm isotropic standard space template (Montreal Neurological Institute, Montreal, QC, Canada). (2) Second stage affine registration using an MNI152 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 (author I.V.).

3.3. 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 raw volume was multiplied by a scaling factor to obtain the volumes normalized for total intracranial volume. This scaling factor was determined by an affine registration of the T1 image to MNI152 space (using the skull image to determine the registration scaling), using FSL's SIENAX toolbox. Volume differences between groups were then analyzed using independent samples *t*-tests in SPPS statistics 18.0 (IBM), using a Bonferroni corrected significance threshold of $p=0.0125$. Importantly, all between groups comparisons were tested one-sided given our a priori expectations of smaller amygdala and hippocampus volumes in PTSD patients compared to controls. In addition, 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 $p<0.017$ (as calculated with SISA; www.quantitativeskills.com/sisa/).

3.4. Shape analysis

Volume differences between the two groups do not necessarily have to occur across the structure in an equal fashion. Instead, differences could be specific only to part of the structure. As both the amygdala and hippocampus consist of several functionally distinct subregions, we investigated local shape and size of these structures to determine whether there would indeed be a topological preference for volume differences to occur. 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 Randomize tool), with the height of each of the vertices entered as dependent variables (Zarei et al., 2010; Patenaude et al., 2011). Per vertex a null distribution of *F*-values was derived for the between group contrast by performing 5000 random permutations (Nichols and Holmes, 2002). The resulting statistical maps were cluster corrected for multiple comparisons, using an initial cluster forming threshold of $F(1, 22)>4.3$ ($p<0.05$), and a corrected $p<0.05$. Localization of effects was carried out using the Juelich histological atlas, provided in FSL's image viewer.

3.5. 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. 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.

4. Results

4.1. Behavioral results

See Table 1 for means and standard deviations. Using independent samples *t*-tests, no evidence was found for patients and controls to differ on age, $t(22)=0.445$, $p=0.661$, years of education, $t(22)=-0.794$, $p=0.436$, and total IQ, $t(20)=-0.316$, $p=0.756$. As expected, patients scored higher on each of the clinical scales compared to controls, all $t(22)>3.637$, $p<0.005$.

4.2. Volumetric results

Table 2 lists the volumes of the left and right amygdala and hippocampus, normalized for intracranial volume. Of note, an independent samples *t*-test did not show a difference in total intracranial volume between the groups, $t(22)=0.668$, $p=0.511$. For all four structures the homogeneity of variance (Levene's test) and normality (Kolmogorov–Smirnov test) criteria were met, thereby justifying the use of parametric statistics. The independent samples *t*-tests showed that right amygdala volumes were smaller in the PTSD patients (mean $\pm$ *SD*: 1365.3 $\pm$ 332.99) than in the healthy controls (mean $\pm$ *SD*: 1667.55 $\pm$ 264.45), $t(22)=-2.54$, $p=0.01$, one-tailed, $\omega^2=0.19$, reflecting a medium to strong effect size, and a moderate observed power of 0.68 (see Fig. 1a). No differences were found for the left amygdala or the left and right hippocampus (all $p>0.13$, one-tailed). Of note, the inclusion of age, education, and total IQ as covariates, using analysis of covariance (ANCOVA), yielded the same result for the right amygdala, $F(1, 17)=6.67$, $p=0.01$, (one-tailed). Paired *t*-tests did not reveal volumetric asymmetry between the left and right side of the amygdala and hippocampus within both groups ($p>0.2$). Last, right amygdala volumes correlated negatively with the Traumatic Experiences Checklist subscale Sexual Abuse, $r(12)=-0.64$, $p=0.013$, one-tailed (see Fig. 1b). Importantly, although the volumes of the left amygdala did not show differences between the two groups, the same negative correlation was found within the PTSD group: $r(12)=-0.60$, $p=0.019$, one-tailed.

Table 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)[1]	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.

[1] PTSD < Healthy controls ($p = 0.01$, one-tailed).

4.3. Shape results

The vertex analysis revealed a specific location for the smaller volume on the surface of the right amygdala of PTSD patients compared with healthy controls (Fig. 2a). The area affected 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 can be observed in these structures (e.g., existence of focal differences, which on average yield volumes similar to the control group). However, at a lenient uncorrected threshold of $p < 0.05$ the vertex analysis only revealed a marginally smaller volume of the anterior subiculum of the right hippocampus in PTSD patients compared with healthy controls (Fig. 2b).

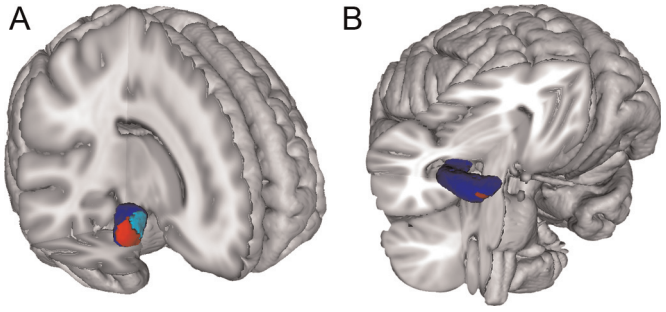

Fig. 2. Shape analysis results, revealing loci of smaller volume in PTSD compared with controls on the surface of the amygdala and hippocampus (dark blue). (A) Smaller volumes are found specifically in parts of the basolateral (red) and superficial (light blue) groups of the right amygdala ($p < 0.05$, corrected). (B) A weak trend for a smaller volume was found in the anterior subiculum of the right hippocampus in patients ($p < 0.05$, uncorrected). All subgroups were identified using the Juelich Histological Atlas, incorporated in FSL. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

5. 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, thereby corroborating previous reports of smaller amygdala volumes in the disorder (Matsuoka et al., 2003; Pavlisa et al., 2006; Vermetten et al., 2006; Weniger et al., 2008, 2009; Irle et al., 2009; Morey et al., 2012). Moreover, the difference was mainly located at the surface of the basolateral and superficial nuclei groups. Lastly, amygdala volumes were associated with severity of sexual abuse during childhood. Our results provide new insights on how adverse events during childhood may render the brain vulnerable to develop PTSD later in life.

Increased dendritic branching and greater spine density of amygdala neurons have been reported in rodents after chronic restraint stress (Vyas et al., 2002; Mitra et al., 2009; Roozendaal et al., 2009), 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 (Mehta et al., 2009; Tottenham et al., 2010; Lupien et al., 2011), although smaller medial temporal lobe volumes were found as well (Hanson et al., 2015). In adulthood, however, limited evidence was found for a difference in amygdala volumes between PTSD patients who were exposed to childhood maltreatment and controls in a small meta-analysis (Woon and Hedges, 2008), though smaller volumes have been reported in other studies (Vermetten et al., 2006; Weniger et al., 2008, 2009; Irle et al., 2009), as well as in adult borderline patients with a history of childhood abuse (Driessen et al., 2000; Schmahl et al., 2003), which is in line with our current results.

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 at first increase the sensitivity of the amygdala through dendritic growth and synaptic connectivity, as is found in rodents (Roozendaal et al., 2009), which may result in a larger total volume. While this process may be beneficial to increase chances of

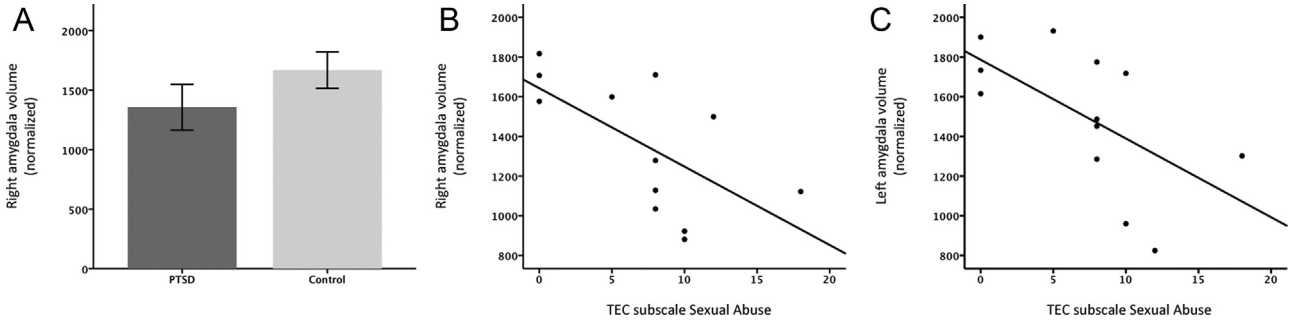

Fig. 1. Volumetry results for the right amygdala. (A) Bar graph depicting the difference in right amygdala volume between the two groups, corrected for total intracranial volume; Error bars represent 2 standard errors of the mean. (B) and (C) Scatter plots illustrating the association between normalized right and left amygdala volume, respectively, and the subscale Sexual Abuse of the Traumatic Experiences Checklist.

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, as is, for example, observed in the hippocampus and medial prefrontal cortex under influence of prolonged and excessive exposure to glucocorticoids (cf. "neurotoxicity hypothesis"; Sapolsky et al., 1986; Lupien et al., 2009). A similar mechanism may, in turn, lead to smaller amygdala volumes in adulthood. Although provisional, 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 and Irle, 2004; Tottenham et al., 2010), although this may have been a consequence of medication as well. 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), it could be hypothesized alternatively 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 smaller volume 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 et al., 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 in 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). As such, exposure to severe stress could lead to enhanced fear conditioning and traumatic memory formation, which lies at the heart of the symptomatology of PTSD. Smaller volumes of these specific groups of nuclei may, as such, reflect wear and tear due to repetitive activation of the traumatic memory traces and conditioned fear responses in PTSD. It is important to note, however, that allocation of the volume differences to specific amygdala subnuclei should be taken provisionally, as the localization is based on correspondence to a probabilistic atlas, which is constructed from averaged cytoarchitectonic post-mortem brain segmentations.

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 smaller hippocampal volume rather consistently (Karl et al., 2006; Woon et al., 2010; Woon and 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 ($n=12$), though quite comparable in size with previous studies on volumetric differences in adult PTSD associated with childhood maltreatment, which included 13.33 patients ($SD=4.24$) on average. Nevertheless, even within our small group of patients, we found a significant smaller right amygdala volume than 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. It is important to note that small sample sizes also render a study susceptible to Type II errors, because of the reduced power. In addition, not finding a significant difference, as was the case for the left amygdala and bilateral hippocampus in the current study, should not be taken as evidence for an absence of a difference. Second, in the current study we did not include a group of PTSD patients with trauma originating in adulthood, nor did we assess recent trauma in our patient group. Therefore, we cannot infer whether the smaller right amygdala volume 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 and Hedges, 2009), possibly indicating that our findings might indeed be specific to childhood trauma. In addition, a recent study demonstrated smaller amygdala and hippocampus volumes in children that were exposed to early life stress (Hanson et al., 2015), while such an association was only found for the hippocampus in adults (Dannlowski et al., 2012). 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. This is perhaps not too surprising as females approximately have a twofold higher risk to develop PTSD, although the number of traumatic events encountered, irrespective of the type of event, is similar or even higher in males than in females (Kessler et al., 1995; Breslau et al., 1999; De Vries, Olff, 2009). 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). Nevertheless, it remains to be confirmed whether the current results will generalize to male PTSD patients with similar types of childhood trauma as well.

Conversely, our study has several strengths. Most studies on volumetric differences of the hippocampus and amygdala in PTSD related to childhood trauma were done on 1.5 T data. In comparison, the 3 T 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 no differences were observed for the left amygdala and bilateral hippocampus between the two groups. In addition, the smaller volume 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.

6. Financial disclosure

All authors declare not to have any financial interests or potential conflicts of interest in having the results presented in this article being published.

7. Contributors

I.V., N.O., M.B., P.S., B.E., S.R. designed research; I.V., N.O. acquired and analyzed the data; I.V., N.O., M.B., P.S., B.M., S.R. wrote the manuscript.

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