Available online at www.sciencedirect.com
ScienceDirect
Neuroscience and Biobehavioral Reviews 30 (2006) 1004–1031
NEUROSCIENCE AND BIOBEHAVIORAL REVIEWS
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Review

A meta-analysis of structural brain abnormalities in PTSD

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Received 20 October 2005; received in revised form 16 March 2006; accepted 21 March 2006

Abstract

This series of meta-analyses examined structural abnormalities of the hippocampus and other brain regions in persons with PTSD compared to trauma-exposed and non-exposed control groups. The findings were significantly smaller hippocampal volumes in persons with PTSD compared to controls with and without trauma exposure, but group differences were moderated by MRI methodology, PTSD severity, medication, age and gender. Trauma-exposed persons without PTSD also showed significantly smaller bilateral hippocampal compared to non-exposed controls. Meta-analyses also found significantly smaller left amygdala volumes in adults with PTSD compared to both healthy and trauma-exposed controls, and significantly smaller anterior cingulate cortex compared to trauma-exposed controls. Pediatric samples with PTSD exhibited significantly smaller corpus callosum and frontal lobe volumes compared to controls, but there were no group differences in hippocampal volume. The overall findings suggested a dimensional, developmental psychopathology systems model in which: (1) hippocampal volumetric differences covary with PTSD severity; (2) hippocampal volumetric differences do not become apparent until adulthood; and (3) PTSD is associated with abnormalities in multiple frontal–limbic system structures.

Keywords: Meta-analysis; PTSD; Hippocampus; MRI; Plasticity; Memory

Contents

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doi:10.1016/j.neubiorev.2006.03.004

1. Introduction

Exposure to trauma can precipitate the development of posttraumatic stress disorder (PTSD), a complex syndrome comprising re-experiencing symptoms (e.g., nightmares, flashbacks) hyperarousal symptoms (e.g., insomnia), numbing symptoms (e.g., restricted affect, anhedonia), and avoidance symptoms (e.g., avoiding trauma-related stimuli) (DSM-IV, American Psychiatric Association, 1994) in addition to poor concentration and difficulty explicitly recalling aspects of the traumatic event (DSM-IV, American Psychiatric Association, 1994). PTSD may be accompanied by other types of mild cognitive impairment, such as relatively impoverished autobiographic memory for positive events (Harvey et al., 1998; McNally et al., 1995) as well as problems with attention, working memory (Vasterling et al., 1998, 2002), and learning novel word associations (Golier et al., 2002). Studies of electroencephalographic activity (Karl et al., 2006) have found that PTSD is associated with enhanced processing of trauma-related stimuli and reduced processing of neutral stimuli. Converging evidence from neuroimaging research suggests that this altered information processing is associated with differential functional neuroanatomical activity in PTSD (Bremner et al., 1999b, 2003b; Clark et al., 2003; Matsuo et al., 2003; Rauch et al., 1996; Shaw et al., 2002; Shin et al., 2004a, b).

Studies of structural brain abnormalities in PTSD have focused in particular on the hippocampus, a grey matter structure in the limbic system that is critically involved in explicit (declarative) memory, working memory (O'Keefe and Nadel, 1978; Squire, 1992), and memory for episodic events (Eldridge et al., 2000; Tulving, 1985; Wheeler and Buckner, 2004). The hippocampus also has an important role in the regulation of stress (Jacobson and Sapolsky, 1991), and findings from animal research suggest that chronic stress may affect the hippocampus through excess release of glucocorticoids (Sapolsky et al., 1990), corticotropin-releasing hormone (Brunson et al., 2001), and glutamate (Moghaddam, 2002; Moghaddam and Bolinao, 1994), inhibition of neurogenesis (Gould et al., 1997); impaired long-term potentiation induction (Li et al., 2005); inhibition of brain-derived neurotrophic factor (BDNF, Duric and McCarson, 2005) and altered serotonergic receptor function (Harvey et al., 2003).

Because of its critical role in learning and memory as well as stress regulation, alterations in the hippocampus have been proposed as contributing to the etiology of PTSD (Bremner, 2001; Sapolsky, 2000). However, findings from PTSD neuroimaging research are equivocal (Jelicic and Merckelbach, 2004). Some cross-sectional studies find reduced hippocampal volumes (e.g., Bremner et al., 1995; Gurvits et al., 1996; Stein et al., 1997) in PTSD but others do not (e.g., Pederson et al., 2004; Schuff et al., 2001). Right-sided (Bremner et al., 1995), left-sided (Gurvits et al., 1996) as well as bilateral (Bremner et al., 2003a) volumetric reductions have been reported. One longitudinal study failed to find reduced hippocampal volume at 6 months post-trauma (Bonne et al., 2001), but the sample in this study experienced only a single incident trauma rather than chronic trauma exposure. Smaller hippocampal volumes have been associated with longer time since trauma (Villarreal et al., 2002) as well as trauma severity (Bremner et al., 1997; Gurvits et al., 1996; Winter and Irle, 2004) but there are negative findings as well (Stein et al., 1997). Winter and colleagues (Winter and Irle, 2004) found reduced hippocampal volumes in burn survivors with and without PTSD, compared to non-exposed healthy controls, which suggests that trauma exposure may produce reductions in hippocampal volumes in the absence of a PTSD diagnosis. In contrast, in Gilbertson et al.'s (2002) twin study, smaller hippocampal volumes were only found in combat veterans with more severe PTSD compared to non-exposed controls, with no significant differences when

veterans with less severe PTSD were included in the analyses. Perhaps most critically, they found no significant difference in hippocampal volumes between monozygotic twin pairs with and without PTSD, and concluded that smaller hippocampal volume is a premorbid risk factor for severe and chronic PTSD, rather than a consequence of PTSD or trauma exposure.

In their critical review, Jelicic and Merckelbach (2004) noted that PTSD hippocampus volumetric studies are beset by a number of limitations, including small study sample sizes and low statistical power, methodological heterogeneity (e.g., neuroimaging measurements, type of control sample), and sample heterogeneity (e.g., type and severity of trauma exposure, comorbid psychopathology, medication use). Meta-analysis is a technique that can address some of these limitations, and the results of two recent meta-analyses have provided further evidence of hippocampal volumentric reduction in PTSD. Smith (2005) meta-analyzed 13 studies of adult patients with PTSD and found that persons with PTSD had left and right hippocampal volumes that were 7.2% and 7.0% smaller, respectively, than those of non-exposed controls, and 4.3% and 4.5% smaller, respectively, than those of trauma-exposed controls. Kitayama and associates (2005) also found smaller bilateral hippocampal volume in PTSD compared to both trauma-exposed and non-exposed controls in a meta-analysis of nine studies of adult patients, the majority of whom had chronic trauma exposure (combat veterans and adult survivors of childhood abuse).

The objective of the research that we present in this paper was to quantitatively integrate the literature through a comprehensive series of meta-analyses of structural abnormalities in PTSD. We expanded upon the results of the two previous meta-analyses (Kitayama et al., 2005; Smith, 2005) in the following ways. As recommended by Glass et al. (1981) we did not restrict the study sample to only those studies with the best methodology, which yielded a larger and more inclusive sample of studies. We then used empirical methods to identify sample heterogeneity and to construct homogenous groups for analyses. To examine whether volumetric reductions were specific to PTSD, we also meta-analyzed comparisons of trauma-exposed samples without PTSD versus healthy controls. To address method and sample variance, we conducted an extensive series of analyses examining the effects of moderator variables, including MRI methodology, gender, age and age of trauma exposure, PTSD severity and duration, comorbid disorders, and medication. To examine whether volumetric reductions were restricted to the hippocampus, we meta-analyzed PTSD volumetric studies of other brain regions. For ease of apprehension, we have organized the series of meta-analyses into separate sections punctuated by summaries. In the discussion we summarize the overall results and explicate their implications for the formulation of comprehensive neurobiological models of PTSD.

2. Methods

2.1. Studies/samples

Fifty English language candidate studies (23 hippocampus studies; 27 studies of other brain areas) were l ocated through electronic indexes (Medline, PsychInfo; keywords: PTSD and MRI, hippocampal volume, amygdala volume, ACC, corpus callosum) and through perusing relevant journals from 1990 to 2005 (e.g., Neuroimage, Nature Neuroscience, Hippocampus, Biological Psychiatry, Biological Psychology). To address the "file drawer problem" (Hunter and Schmidt, 1990),[1] citations and conference abstract bands (Society for Neuroscience, Human Brain Mapping) were also examined.

Candidate studies were classified according to their methodology and region examined (including brain hemisphere), and those with similar methods were included in the present meta-analysis. The meta-analysis study inclusion criteria were: (1) inclusion of a PTSD group based on DSM-III-R or DSM IV diagnostic criteria and a comparison group (either a non-PTSD trauma-exposed, or non-exposed controls); (2) sufficient methodological specification (e.g. sample size, MRI methodology); and (3) sufficient reporting of statistics. Twenty-one hippocampus studies, 11 amygdala studies and 18 studies reporting other structural brain measures were included in the meta-analyses. (See Appendices A, C and D). Two studies were not included because the study did not provide statistical information (Neylan et al., 2004b) or did not report right and left hippocampal/amygdala volume (Carrion et al., 2001).

2.2. Statistical procedures

Meta-analyses were computed based on the single effect size (ES) r, the Pearson product–moment correlation, a standardized form of the size of the observed effect. ES r values were calculated by the transformation of M and SD, t, F, or χ^2 values into r to obtain unitary ESs (Kraemer and Thiemann, 1987), using the Meta-analysis Program version 5.3 software by Schwarzer (1989). Only one ES per construct, per study was included in the meta-analysis (Rosenthal, 1995).

The meta-analysis was based on the more conservative random-effects model (Hedges and Olkin, 1985), in which both the within-study variance (used in the fixed-effects

[1]Among the general limitations of meta-analysis is the "file drawer problem": studies that find null or difficult-to-interpret results and are therefore unpublished. Although we attempted to address this problem, we obviously would not have access to unpublished papers and all conference presentations. On the other hand, the topic itself may be somewhat protected against this problem. Because of its relative novelty there may have been a strong motivation (in both the investigators and the editors) to publish all sorts of results.

model) and the between-study variance (τ^2) are incorporated in the variance component used to calculate weights (Field, 2001). ES *r*-values were weighted according to study sample size (Hedges and Olkin, 1985; Hedges and Vevea, 1998) and converted into the common metric of Fisher's *z* transformation of *r* (Rosenthal, 1995). The mean of *z* and 95% confidence interval (CI) were calculated for each set of ERP components (k = number of studies; Rosenthal, 1995). Mean ESs and CI were then converted back to *r* for ease of interpretation. If the 95% CI did not include zero, the null hypothesis could be rejected at a α level of .05. Cohen's (1988) guidelines for interpreting the ES of sample–weighted average correlations were used: small = .10, medium = .30, and large = .50.

Sample heterogeneity was determined according to procedures proposed by Hedges and associates (1985, 1998) and (2001), in which heterogeneity is present if the between trials variance (τ^2) is greater than zero and/or the within-trials variance test (χ^2) is significant. To address the file drawer problem, Orwin's fail safe *N* (Orwin, 1983) was computed. For a specified critical *r* value, for example, .10, the fail safe *N* is the number of studies with an ES of zero required to reduce the mean population ES to that critical value, i.e., .10.

2.2.1. Moderator variables

Moderator variables, which can account for sources of sample heterogeneity, were tested three ways. In analyses of MRI methodological moderators, we grouped studies according to common methodology, and then conducted meta-analyses of volumetric differences followed by tests (ANOVA, χ^2) of group differences in hypothetical moderator variables. For sample-related (individual differences) variables, we used disjoint cluster analysis (Hedges and Olkin, 1985; Mullen and Rosenthal, 1985) to identify homogenous subsets of studies. Disjoint cluster analysis yields non-overlapping clusters of study effect sizes through a rank-ordering of effect sizes and a comparison of their differences to critical values at a .01 α level. For the analysis, *r*-values are transformed into Fisher's *z*-values, and *z*-values are then multiplied by the square root of the sample size. The resulting value (u) is rank-ordered and the gap between each pair of consecutive *u*-values is compared to a predetermined critical value (i.e., .01 α level, Schwarzer, 1989). We conducted two series of disjoint cluster analyses. In the first, we cluster analyzed all studies to derive homogenous clusters, and followed this with meta-analyses of volumetric differences and tests (ANOVA, χ^2) of group differences in hypothetical moderator variables, with Bonferroni-corrected α levels to adjust for multiple comparisons. In the second, we used disjoint cluster analysis to identify studies that were homogenous for a particular moderator variable and then meta-analyzed volumetric differences in the homogenous clusters.

3. Results

3.1. Analyses 1: hippocampal volumetric studies

Studies were grouped according to type of control group: trauma-exposed (non-PTSD) or non-trauma exposed healthy controls (HC); and by hippocampal hemisphere.

PTSD vs. HC: The meta-analysis included 15 studies (Studies # 1–4, 8, 9, 11, 12, 14–17, 25, 26, 35 in Appendix A), $N = 562$. Persons with PTSD had significantly smaller bilateral hippocampal volume; see Table 1 and Fig. 1.

PTSD vs. non-PTSD: The meta-analysis included 12 studies (# 2, 4–7, 10, 13–15, 18, 25, 35 Appendix A), $N = 379$. The meta-analysis for the right hippocampus was not significant; but as shown in Table 1 and Fig. 1, the PTSD group had significantly smaller left hippocampal volumes. As shown by τ^2 and χ^2 values in Table 1, analyses of sample heterogeneity were significant for all four of these meta-analyses, and therefore we analyzed potential moderators in Analyses 2 and 3 below.

Non-PTSD vs. HC: The meta-analysis included six studies (# 2, 4, 14, 15, 25, 35, Appendix A), $N = 175$. As shown in Table 1 and Fig. 1, the meta-analysis revealed significantly smaller hippocampal volumes bilaterally in the non-PTSD group as compared to the HC. The analysis for sample heterogeneity was significant for the right hippocampus, and therefore disjoint cluster analysis was used to identify a homogenous cluster of four studies (# 2, 15, 25, 35, Appendix A), $N = 119$. The meta-analysis of these studies found significantly smaller right hippocampal volume in the Non-PTSD group, with a medium effect size (ES).

Summary: When comparing PTSD vs. HC and also non-PTSD vs. HC, meta-analyses found significantly smaller bilateral hippocampal volume in PTSD. Meta-analyses of PTSD vs. non-PTSD were significant only for smaller left hippocampal volume. However, significant sample heterogeneity may have influenced the findings and therefore a series of moderator analyses was performed for MRI and volumetry methods (Analyses 2) as well as sample-related variables (Analyses 3). Due to the small number of studies comparing Non-PTSD vs. HC, moderator analyses were not performed for these studies.

3.2. Analyses 2: moderator analyses, MRI and volumetry methods

Two sets of analyses were performed: (a) one in which studies were grouped according to MRI acquisition protocols; and (b) one in which studies were grouped according to the anatomical borders employed.

3.2.1. MRI acquisition protocols

Appendix B presents MRI methodology for the studies. As shown, all but one study (#10) used whole body scanners operating at 1.5 T. Most laboratories employed three-dimensional T1-weighted spoiled gradient echo tech-

Table 1
Meta-analysis of studies comparing hippocampal volume (PTSD vs. controls): MRI and volumetry methods

Side	Moderator/analysis	PTSD vs.	*k*	*N*	r_w	CI_w		τ	χ^2	Orwin's fail safe *N*
PTSD vs. *healthy controls* (*no trauma*)										
Right	No moderator/all studies	Healthy controls (HC)	15	562	−.28[a]	−.42	−.13	.05[b]	38.15[b]	6
	MRI acquisition	HC, WBV + high resolution	9	355	−.36[a]	−.55	−.13	.09[b]	31.88[b]	7
		HC, other corr. + low resolution	6	207	−.20[a]	−.35	−.04	.01[b]	6.09[b]	0
	Volumetry method	HC, alveus–fornix	5	123	−.48[a]	−.61	−.32	0	3.48	7
		HC, mammillary bodies–fornix	5	274	−.17	−.42	.11	.07[b]	16.08[b]	−1
		HC, hippocampal body	3	103	−.32[a]	−.52	−.09	.01[b]	2.64	2
Left	No moderator/all studies	HC	15	562	−.29[a]	−.43	−.14	.06[b]	39.56[b]	7
	MRI acquisition	HC, WBV + high resolution	9	355	−.34[a]	−.54	−.10	.10[b]	35.27[b]	6
		HC, other corr. + low resolution	6	207	−.25[a]	−.38	−.11	0	4.07	1
	Volumetry method	HC, alveus–fornix	5	123	−.39[a]	−.54	−.22	.001	4.11	5
		HC, mammillary bodies–fornix	5	274	−.25	−.53	.09	.12[b]	25.69[b]	1
		HC, hippocampal body	3	103	−.32[a]	−.51	−.10	.01[b]	2.49	2
PTSD vs. *non-PTSD* (*exposed to index trauma*)										
Right	No moderator/all studies	Non-PTSD	12	379	−.15	−.29	.001	.03[b]	21.50[b]	−3
	MRI acquisition	Non-PTSD, WBV + high resolution	9	301	−.17[a]	−.32	−.01	.02[b]	13.71[b]	−1
		Non-PTSD, other corr. + low resolution	3	78	−.07	−.49	.38	.12[b]	7.87[b]	−2
	Volumetry method	Non-PTSD, alveus–fornix	5	186	−.07	−.22	.08	0	3.76	−3
		Non-PTSD, mammillary bodies–fornix	3	80	−.31	−.65	.13	.11[b]	6.85[b]	2
Left	No moderator/all studies	Non-PTSD	12	379	−.22[a]	−.39	−.04	.07[b]	33.23[b]	1
	MRI acquisition	Non-PTSD, WBV + high resolution	9	301	−.26[a]	−.46	−.04	.08[b]	27.51[b]	3
		Non-PTSD, other corr. + low resolution	3	78	−.09	−.42	.26	.06	4.44	−2
	Volumetry method	Non-PTSD, alveus–fornix	5	186	−.14	−.28	.01	0	3.44	−2
		Non-PTSD, mammillary bodies–fornix	3	80	−.53	−.88	.19	.43[b]	20.70[b]	5
Non-PTSD vs. *HC*										
Right	No moderator/all studies	Non-PTSD/HC	6	174	−.32[a]	−.47	−.15	.01[b]	6.26[b]	4
		Subset	4	119	−.42[a]	−.56	−.25	0	1.26	4
Left	No moderator/all studies	Non-PTSD/HC	6	174	−.23[a]	−.38	−.08	0	1.82	0

Note: k = number of studies, r_w = weighted r, CI_w = 95% confidence interval for weighted r, τ^2 = between trials variance; χ^2 = within trials variance; non-PTSD trauma exposed refers to those exposed to the study index trauma, but without PTSD.

[a] $p < .05$.

[b] Heterogeneity.

niques with echo times in the range of 4–6 ms and repetition times of 15–35 ms. In the majority of studies, volume estimation was done by manual tracings (rather than automated methods) that were typically rated by two or three experts; inter-rater reliability coefficients ranged from .61 to .99. Intra-rater reliability coefficients ranged from .82 to .97; however, three of the eight studies that reported this analyzed ratings from only one expert. Most studies employed algorithms correcting hippocampal volume for either body height or whole brain volume (WBV) that was typically determined by semi-automated tissue segmentation algorithms.

For the meta-analyses, studies were grouped according to the following two acquisition methods: (1) WBV correction and high spatial resolution (PTSD/HC Studies # 1, 3, 11, 15–17, 25, 26, 35, $N = 355$; PTSD/non-PTSD Studies # 5, 6, 7, 10, 13, 15, 18, 25, 35, $N = 301$) and (2) other/no correction and lower resolution (PTSD/HC Studies # 2, 4, 8, 9, 12, 14, $N = 207$; PTSD/non-PTSD Studies # 2, 4, 14, $N = 78$).

PTSD vs. HC: As shown in Table 1, both the meta-analysis of studies employing WBV correction/high resolution as well as that for studies using other/no correction and lower resolution revealed significantly smaller hippocampal volume on bilaterally.

PTSD vs. non-PTSD: The meta-analysis for studies employing WBV correction/high resolution found significantly smaller hippocampal volume bilaterally, but the meta-analysis of studies that used other/no correction and lower resolution was not significant. However, as shown in Table 1 (τ^2 and χ^2), analyses of sample heterogeneity were significant for all four of these meta-analyses. χ^2 tests found that samples in studies that used other/no correction methods and lower resolution had a significantly greater proportion of females, $\chi^2(2) = 11.87$; $p = .003$; and there was a trend for samples in WBV correction/high-resolution studies to have a greater proportion of children and older adults, $\chi^2(2) = 5.71$; $p = .06$.

3.2.2. Delineation of hippocampal anatomical boundaries

As shown in Appendix B, the majority of studies determined hippocampal volume in contiguous coronal slices using the landmark method for the determination of anatomical boundaries, and mostly included the entire hippocampus, with the exception of three studies (# 8, 9, 14) that determined only the mid-hippocampal segment

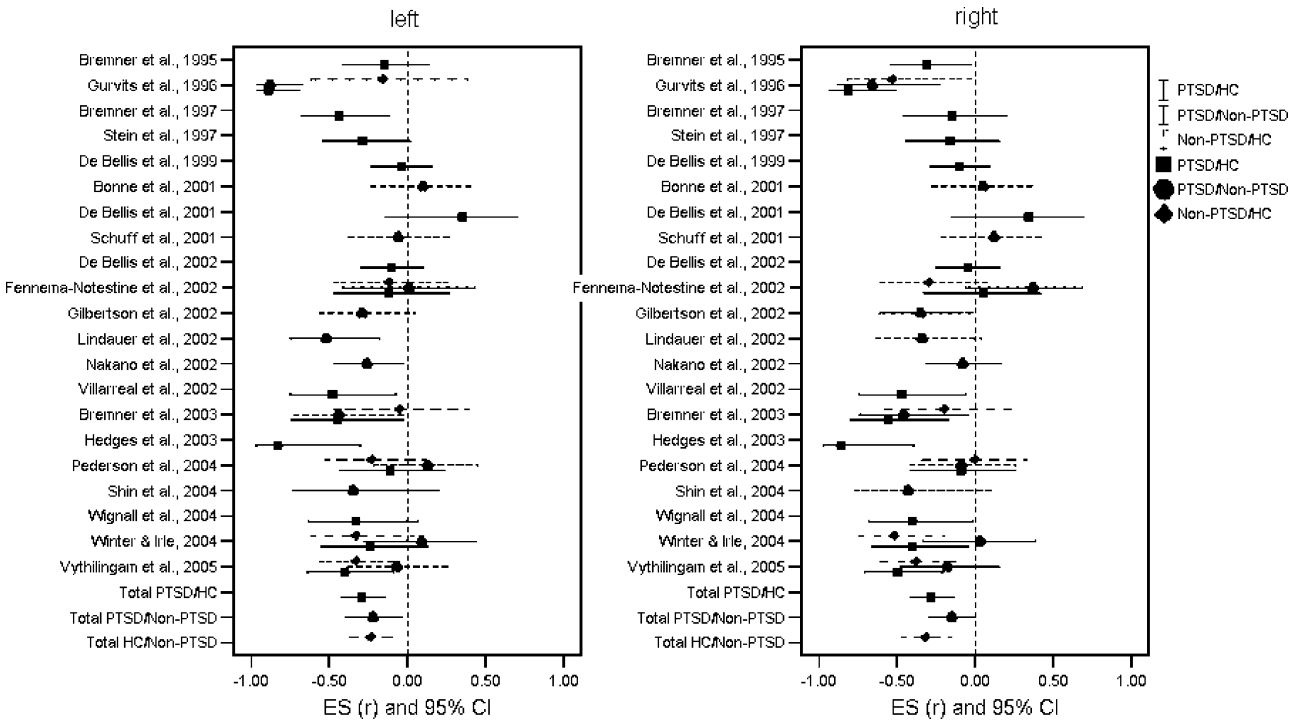

Fig. 1. *Effect of PTSD:* Hippocampal volume effect sizes (ES) and 95% confidence intervals (CI) for comparisons of PTSD and control groups (squares and circles) and, *Effect of Trauma:* Hippocampal volume effect sizes (ES) and 95% confidence intervals (CI) for comparison of Non-PTSD and HC (rhombus), plotted per hemisphere (left panel: left hippocampal volume ES, right panel: right hippocampal volume ES). Negative ESs indicate smaller hippocampal volume in PTSD respectively trauma-exposed groups. Non-PTSD = exposed to index trauma, but no PTSD; HC = non-exposed healthy controls.

(hippocampal body). Studies varied in the landmarks/ anatomical borderlines employed to delineate the hippocampus. For the most anterior slice, several studies employed landmarks such as the first appearance of the mammillary bodies (# 7, 10, 11, 12, 15–17) or the superior colliculi (# 8, 9, 14). More recent studies (# 1, 3, 5, 18, 25, 26) used the appearance of the alveus/ uncal recess to delineate the border between the hippocampus and amygdala. Most studies used the crus of the fornix to determine the posterior slice, but three (# 8, 9, 14) used the slice that showed a bifurcation of the basilar artery as posterior boundary.

For the analyses, studies were grouped according to hippocampal anatomical boundaries as follows. For PTSD vs. HC, the groups of studies were: (1) uncal recess/ alveus–crus of fornix (alveus/fornix), five studies (# 1, 3, 25, 26, 35), $N = 123$; (2) mammillary bodies–crus of fornix (mammillary bodies/fornix), five studies (# 11, 12, 15, 16, 17), $N = 274$; and (3) superior colliculi–bifurcation of basilar artery (hippocampal body),[2] three studies (# 8, 9, 14), $N = 103$. For PTSD vs. non-PTSD the groups of studies were: (1) uncal recess/alveus—crus of fornix (alveus/fornix), five studies (# 5, 6, 18, 25, 35), $N = 186$; (2) mammillary bodies–crus of fornix (mammillary bodies/ fornix), three studies (# 7, 10, 15), $N = 80$.

PTSD vs. HC: As shown in Table 1, meta-analyses for studies employing alveus/fornix and those employing superior colliculi/basilar artery found that persons with PTSD had significantly smaller hippocampal volume bilaterally, with medium effect sizes. No significant effects were found for studies employing the mammillary bodies/ fornix as boundaries.

PTSD vs. non-PTSD: Only studies employing alveus/ fornix and mammillary bodies/fornix could be tested, and neither meta-analysis was significant. However, as shown in Table 1 (τ^2 and χ^2), analyses of sample heterogeneity were significant for two these meta-analyses, and also for the PTSD vs. HC meta-analyses. A χ^2 test found a trend for samples in the PTSD vs. HC studies that used the alveus/fornix and the superior colliculi/basilar artery to have a greater proportion of adults compared to studies that used mammillary bodies/fornix to determine boundaries, $\chi^2(4) = 7.89$; $p = .096$.

Summary: Meta-analyses found significantly smaller bilateral hippocampal volume in PTSD vs. HC, regardless of the type of correction method used, or level of spatial resolution. However, when comparing PTSD to trauma-exposed non-PTSD, significantly smaller bilateral hippocampal volumes were found only in those studies that used WBV correction and high spatial resolution. The results

[2]One study (Vythilingam et al., 2005) also reported hippocampal body size with a zero result. However, this study was not included in the meta-analysis because the whole hippocampus ES of that study was already included in anatomical group 1 and we followed the recommendations by (Rosenthal, 1995) that only one ES per study is to be included in the same meta-analysis.

suggest that subtle volumetric differences between PTSD and non-PTSD samples may not be revealed without WBV correction and high spatial resolution. However, studies that used these methods also had significantly fewer females, which suggests that gender may have moderated these effects. Meta-analyses of studies that used the alveus/fornix and superior colliculi/basilar artery to determine hippocampal volume found significantly smaller bilateral hippocampal volume in PTSD compared to HC, whereas the meta-analyses of studies that used the mammillary bodies/fornix as boundaries were not significant. However, samples were heterogeneous, and there was a trend for studies that used the alveus/fornix and superior colliculi/basilar artery as boundaries to have a greater proportion of adults. Meta-analyses of studies comparing PTSD vs. non-PTSD were not significant, regardless of the anatomical boundaries used, but samples were heterogeneous. The overall results point towards the moderating effects of methodology, but we were unable to definitively parse these from the effects of gender and age, which were examined (along with other potential moderators) below.

3.3. Analyses 3: moderator analyses, sample-related variables

Appendix A describes sample characteristics for each study. We first present the cluster analyses of all studies, followed by the meta-analyses of volumetric differences. This is followed by tests of group differences in potential moderators and meta-analyses of volumetric differences in clusters that were homogenous for a particular moderator variable.

3.3.1. Disjoint cluster analysis of all studies

3.3.1.1. PTSD vs. HC. Right hippocampal volume: Disjoint cluster analysis identified three homogenous clusters. *Cluster 1* consisted of seven studies (#2, 4, 9, 11, 12, 16, 17 in Appendix A), $N = 355$. All but one study (#9) reported PTSD severity level, which was in the moderate range for all six studies (e.g. CAPS[2] = 40–60). Three studies had pediatric samples and four had samples of young adult (24–40 year-old) females. As shown in Table 2, the meta-analysis found no significant groups difference in hippocampal volume. *Cluster 2* consisted of six studies (#1, 8,14, 25, 26, 35), $N = 184$. Five had male (#8, 25) or mixed gender (#1, 26, 35) samples; one used a sample of females (#14). As shown in Table 2, the meta-analysis found significantly smaller right hippocampal volume in persons with PTSD, with a moderate ES. *Cluster 3* consisted of two studies (#3, 15), $N = 23$, with older male combat veterans with severe PTSD (e.g. CAPS[3] > 60). As shown in Table 2, the meta-analysis for Cluster 3 found significantly smaller right hippocampal volumes in persons with PTSD, with a large ES.

[3]Symptoms score from Clinician-Administered PTSD Scale (CAPS (Blake et al., 1990).

Left hippocampal volume: Disjoint cluster analysis also identified three homogenous clusters. *Cluster 1* consisted of six of the seven studies (all but #12) that were in Cluster 1 for analyses of the right side of hippocampus, $N = 327$. The meta-analysis did not find significant group differences in hippocampal volume. *Cluster 2* consisted of all six studies that were in Cluster 2 for analyses of the right side of hippocampus, plus Study #12, $N = 212$. As shown in Table 2, the meta-analyses found significantly smaller hippocampal volumes in PTSD, with a medium ES. *Cluster 3* was the same as that for analyses of the right side of hippocampus. The meta-analysis again found significantly smaller hippocampal volume in PTSD, with a large ES as shown in Table 2.

3.3.1.2. PTSD vs. non-PTSD. Right hippocampal volume: Disjoint cluster analysis identified two homogenous clusters. *Cluster 1* consisted of seven studies (# 2, 4, 5, 10, 18, 25, 35 in Appendix A), $N = 264$, with moderate levels of PTSD. The meta-analysis did not find significant differences in hippocampal volume. *Cluster 2* consisted of five studies (# 6, 7, 13, 14, 15), $N = 115$, of unmedicated samples with severe PTSD. As shown in Table 2, this meta-analysis revealed significantly reduced hippocampal volumes in PTSD, with medium ES. *Left hippocampal volume:* Disjoint cluster analysis also identified two homogenous clusters. *Cluster 1* consisted of six of the seven studies (all but # 18) that were in Cluster 1 for analyses of the right side of hippocampus, $N = 197$, and the meta-analyses was did not find significant group differences. *Cluster 2*[4] consisted of four of the five studies (all but # 15) that were in Cluster 2 for analyses of the right side of hippocampus, plus Study #18, $N = 167$. As shown in Table 2, this meta-analysis again found significantly smaller volumes in PTSD, with medium ES.

3.3.2. Effects of moderator variables

3.3.2.1. Age. Comparison of cluster differences:

Right hippocamal volume in PTSD vs. HC: The clusters differed significantly in age, $F(2, 12) = 8.04$; $p = .006$. Post-hoc tests revealed that Cluster 1 was significantly younger than Clusters 2 ($p = .02$) and 3 ($p = .02$), with no significant difference between Clusters 2 and 3. As shown in Fig. 2, age was negatively correlated with ES, $r = -.74$; $p = .001$. Results remained significant when studies with pediatric samples (# 11, 16, 17) were excluded, $F(2, 9) = 4.88$; $p = .04$; $r = -.64$; $p = .02$).

Left hippocamal volume in PTSD vs. *HC:* Results were again significant, $F(2, 12) = 5.96$; $p = .02$. Again, post-hoc tests revealed that Cluster 1 was significantly younger than

[4]In subsequent comparisons of between-cluster differences in moderator variables, one study (#15) that was included in Cluster 3 in the PTSD vs. HC analyses was included in Cluster 2 in the PTSD vs. non-PTSD analyses because it differed from other studies in Cluster 2 only by virtue of a larger ES.

Table 2
Meta-analysis of studies comparing hippocampal volume (PTSD vs. controls): homogenuos clusters and sociodemographical and clinical moderators

Side	Moderator/analysis	PTSD vs.	*k*	*N*	r_w	CI_w		τ	χ^2	Orwin's fail safe *N*
PTSD vs. *healthy controls* (*no trauma*)										
Right	CA/all studies	HC: Cluster 1	7	355	−.07	−.17	.04	0	3.72	−5
		HC: Cluster 2	6	184	−.42[a]	−.54	−.29	0	1.79	7
		HC: Cluster 3	2	23	−.83[a]	−.93	−.60	0	.09	6
	Age	HC, Age 40–55	7	183	−.46[a]	−.62	−.25	.05[b]	12.63[b]	9
		HC, Age 40–55 1	5	160	−.33[a]	−.47	−.18	0	2.02	3
		HC, Age 40–55 2	2	23	−.83[a]	−.93	−.60	0	.10	6
	PTSD severity	Moderate PTSD vs. HC	5	160	−.22[a]	−.37	−.06	0	1.22	1
		Severe PTSD vs. HC	6	151	−.55[a]	−.70	−.36	.04[b]	9.27[b]	11
		Severe PTSD vs. HC 1	4	128	−.44[a]	−.57	−.28	0	1.72	5
		Severe PTSD vs. HC 2	2	23	−.83[a]	−.93	−.60	0	.10	6
	Gender	Male	4	101	−.59[a]	−.80	−.25	.21[b]	9.45[b]	8
		Male 1	2	23	−.83[a]	−.93	−.60	0	.10	6
		Male 2	2	78	−.34[a]	−.53	−.13	0	.18	1
		Mixed adult	3	85	−.46[a]	−.62	−.27	0	.22	4
	Time since trauma	Time since trauma: >10 yrs	8	239	−.41[a]	−.58	−.20	.07[b]	19.19[b]	8
		Time since trauma: >10 yrs 1	3	44	−.73[a]	−.87	−.48	0	2.68	8
		Time since trauma: >10 yrs 2	5	195	−.25[a]	−.40	−.10	0	4.65	1
Left	CA/all studies	HC: Cluster 1	6	327	−.07	−.18	.04	0	3.43	−4
		HC: Cluster 2	7	212	−.37[a]	−.48	−.24	0	1.69	6
		HC: Cluster 3	2	23	−.88[a]	−.95	−.70	0	.19	7
	Age	HC, Age 20–39	5	162	−.27[a]	−.41	−.12	0	3.00	2
		HC, Age 40–55	7	183	−.49[a]	−.68	−.24	.10[b]	19.50[b]	10
		HC, Age 40–55 1	5	160	−.31[a]	−.45	−.15	0	2.94	3
		HC, Age 40–55 2	2	23	−.88[a]	−.95	−.70	0	.19	7
	PTSD Severity	Moderate PTSD vs. HC	5	160	−.20[a]	−.36	−.03	0	4.50	0
		Severe PTSD vs. HC	6	151	−.55[a]	−.75	−.26	.13[b]	18.16[b]	10
		Severe PTSD vs. HC 1	4	128	−.33[a]	−.48	−.16	.01	2.85	3
		Severe PTSD vs. HC 2	2	23	−.88[a]	−.95	−.70	0	.19	7
	Gender	Male	4	101	−.59[a]	−.85	−.09	.29[b]	19.07[b]	8
		Male 1 3,15	2	23	−.88[a]	−.95	−.70	0	.19	7
		Female	5	159	−.28[a]	−.42	−.12	0	3.43	2
		Mixed adults	3	85	−.40[a]	−.57	−.20	0	.34	3
	Time since trauma	Time since trauma: >10 yrs	8	239	−.44[a]	−.62	−.22	.08[b]	21.68[b]	10
		Time since trauma: >10 2	6	216	−.29[a]	−.41	−.16	0	4.16	3
		Time since trauma: >10 1	2	23	−.88[a]	−.95	−.70	0	.19	7
PTSD vs. *non-PTSD* (*exposed to index trauma*)										
Right	CA/all studies	Non-PTSD: Cluster 1	7	264	−.001	−.13	.13	0	5.26	−7
		Non-PTSD: Cluster 2	5	115	−.42[a]	−.57	−.25	0	1.91	6
	PTSD Severity	Severe PTSD vs. Non-PTSD	4	109	−.37[a]	−.55	−.17	0	3.64	3
	Medication	Medication no	6	132	−.25[a]	−.52	−.07	.11[b]	15.26[b]	3
		Medication no 1	4	80	−.45[a]	−.62	−.25	0	1.57	5
		Medication yes	2	71	.02	−.22	.26	0	.72	−2
Left	CA/all studies	Non-PTSD: Cluster 1	6	197	.03	−.11	.18	0	1.20	−5
		Non-PTSD: Cluster 2	5	167	−.34[a]	−.48	−.20	0	2.09	4
	Medication	Medication no	6	132	−.40[a]	−.67	−.04	.18[b]	21.86[b]	7
		Medication no 1	3	65	−.46[a]	−.64	−.23	0	3.80	4
		Medication yes	2	71	.03	−.21	.27	0	.59	−2

Note: k = number of studies, r_w = weighted r, CI_w = 95% confidence interval for weighted r, τ^2 = between trials variance; χ^2 = within trials variance; non-PTSD trauma exposed refers to those exposed to the study index trauma, but without PTSD.

[a] $p < .05$.

[b] Heterogeneity.

Cluster 3 ($p = .03$) and there was a trend for it to be younger than Cluster 2 ($p = .05$); with no significant difference between Clusters 2 and 3. As shown in Fig. 2, age was significantly correlated with ES ($r = -.74$; $p = .002$). However, group differences were no longer significant when studies with pediatric samples (# 11, 16, 17) were excluded, and the correlation between age and ES dropped to a trend ($r = -.57$; $p = .05$).

PTSD vs. *non-PTSD:* There were no significant between-cluster differences in age, and age was not correlated with ES (right hippocampus, $r = -.15$; NS; left hippocampus, $r = -.30$; NS).

Meta-analyses of homogenous groups:

Right hippocamal volume in PTSD vs. HC: As shown in Table 2, the overall meta-analysis revealed sample heterogeneity. Disjoint cluster analysis identified two homogenous

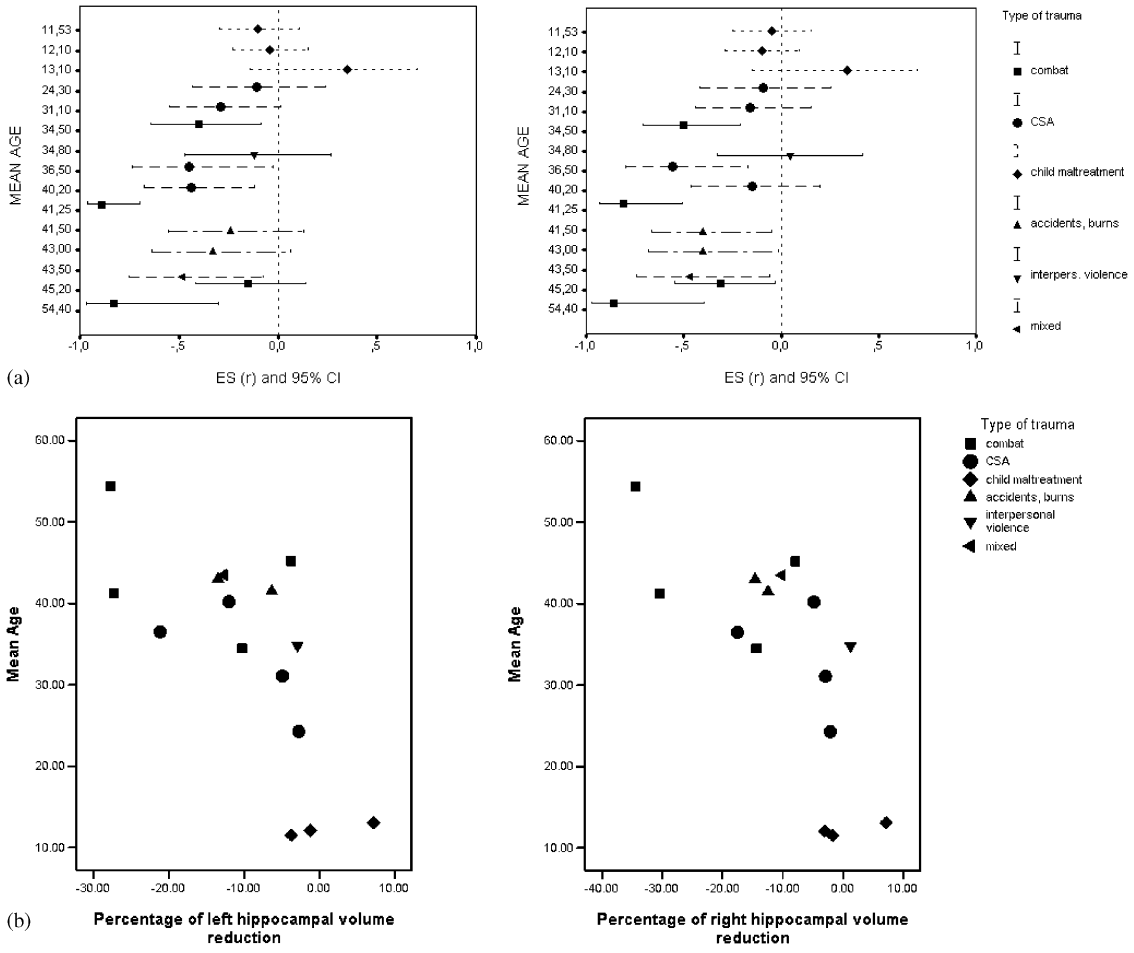

Fig. 2. Relationship between mean age of the study subjects and (a) hippocampal volume ES for comparisons of PTSD vs. HC and (b) percentage of volume loss in PTSD as compared to HC as a function of trauma type (left panel: left hippocampal volume ES resp. percentage reduction, right panel: right hippocampal volume ES resp. percentage reduction). A negative percentage value indicates volume reduction, a positive value indicates increase.

subsets with older (40–55-year-old) adults: Group 1 (Studies # 1, 8, 9, 25, 26 in Appendix A), $N = 160$; and Group 2 (# 3, 15), $N = 23$. As shown in Table 2 and Fig. 2, meta-analyses found significantly smaller hippocampal volume in PTSD in all three groups, with medium to large ES.

Left hippocamal volume in PTSD vs. HC: Disjoint cluster analysis identified the same two homogenous subsets as for the right hippocampus, plus an additional third cluster of younger (20–39-year-old) adults (Studies # 2, 4, 12, 14, 35 in Appendix A), $N = 162$. Meta-analyses found significantly smaller hippocampal volumes in all three clusters, with a small ES for the younger adult cluster and medium to large ES for the other clusters.

PTSD vs. non-PTSD: Disjoint cluster analysis failed to identify age-homogenous groups due to the variability in ES across the studies.

3.3.2.2. Age of trauma exposure. Comparison of cluster differences:

Right hippocamal volume in PTSD vs. HC: There was a trend ($\chi^2(4) = 9.18$; $p = .06$) for cluster differences in the age of trauma exposure (childhood vs. adulthood), suggesting a higher prevalence of childhood trauma in Cluster 1. The χ^2 comparing Cluster 1 vs. Clusters 2 and 3 combined was significant, $\chi^2(2) = 8.11$; $p = .02$, but when studies with pediatric samples (#11, 16, 17) were excluded, the effect dropped to a trend $\chi^2(2) = 4.77$; $p = .09$.

Left hippocampal volume in PTSD vs. HC: χ^2 tests were not significant.

PTSD vs. non-PTSD: χ^2 tests were not significant.

Meta-analyses of homogenous groups: Disjoint cluster analyses failed to identify homogenous groups for PTSD vs. HC or PTSD vs. Non-PTSD.

3.3.2.3. Gender. Comparison of cluster differences:

Right hippocamal volume in PTSD vs. HC: The χ^2 comparing the three clusters found a trend, $\chi^2(4) = 9.32$; $p = .05$, suggesting a lower prevalence of males in Cluster 1. The χ^2 comparing Cluster 1 to Clusters 2 and 3 combined also found a trend, $\chi^2(2) = 5.76$; $p = .06$), but was significant when studies with pediatric samples (#11, 16, 17) were excluded, $\chi^2(2) = 8.40$; $p = .02$.

Left hippocamal volume in PTSD vs. HC: χ^2 tests were not significant.

PTSD vs. non-PTSD: χ^2 tests were not significant.

Meta-analyses of homogenous groups:

Right hippocamal volume in PTSD vs. HC: Disjoint cluster analysis identified three homogenous groups. Two groups were composed of male samples: Group 1 (# 3, 15), $N = 23$; and Group 2 (# 8, 25), $N = 78$. Group 4 had both males and females (# 1, 26, 35), $N = 85$. As shown in Table 2, meta-analyses for all four groups found significantly smaller hippocampal volumes in PTSD, with medium to large ES.

Left hippocamal volume in PTSD vs. HC: Disjoint cluster analysis also identified three homogenous groups. Two of these were the same as those for the right hippocampus: Groups 1 and 2, and the mixed gender group. The third group contained only females, (Studies # 9, 12, 14 in Appendix A), $N = 159$. As shown in Table 2, meta-analyses for all four groups found significantly smaller left hippocampal volumes in PTSD. The group with females had a small ES, whereas the other three groups again had medium to large ES. *PTSD* vs. *Non-PTSD:* Disjoint cluster analyses failed to identify homogenous groups for analyses.

3.3.2.4. PTSD severity. Comparison of cluster differences:

Right hippocamal volume in PTSD vs. HC: The clusters differed significantly in PTSD severity, $\chi^2(4) = 11.10$, $p = .03$: Cluster 1 had a lower prevalence of subjects with severe PTSD than Cluster 2 and Cluster 3, with no significant difference between Clusters 2 and 3. This effect remained significant when Clusters 2 and 3 were combined and compared to Cluster 1, $\chi^2(2) = 10.18$; $p = .006$ and when studies with pediatric samples (#11, 16, 17) were excluded, $\chi^2(2) = 6.60$, $p = .04$.

Left hippocamal volume in PTSD vs. HC: χ^2 tests were not significant.

PTSD vs. non-PTSD: χ^2 tests were not significant.

Meta-analyses of homogenous groups:

Right and left hippocamal volume in PTSD vs. HC: Disjoint cluster analysis identified three clusters for both sides of the hippocampus. One group had moderate PTSD, (Studies # 2, 4, 12, 25, 26 in Appendix A), $N = 160$; and the other two groups had severe PTSD, Group 1, (# 1, 8, 14, 35), $N = 128$; and Group 2 (# 3, 15), $N = 23$. As shown in Table 2, meta-analyses for all three groups revealed significantly smaller hippocampal volume in PTSD, with small ES ($r = -.20, -.22$) for the moderate PTSD group and medium to large ES for the other three groups.

PTSD vs. non-PTSD: Disjoint cluster analysis identified one homogenous group with severe PTSD for the right side of the hippocampus only (Studies # 13, 14, 15, 35 in Appendix A), $N = 109$. As shown in Table 2, the meta-analysis found significantly smaller hippocampal volumes in persons with PTSD, with a medium ES.

3.3.2.5. PTSD duration. Comparison of cluster differences: There were no significant cluster differences in either PTSD vs. HC or PTSD vs. Non-PTSD.

Meta-analyses of homogenous groups:

Right hippocamal volume in PTSD vs. HC: Disjoint cluster analysis identified two groups, each of which contained samples that were at least 10 years post-exposure, Group 1 (Studies # 3, 14, 15), $N = 44$; Group 3 (# 4, 8, 9, 12, 35), $N = 195$.

Left hippocamal volume in PTSD vs. HC: Disjoint cluster analysis identified two groups. Group 1 (# 4, 8, 9, 12, 35), $N = 216$ and Group 2 (# 3, 15), $N = 23$ also had samples that were at least 10 years post-exposure. As shown in Table 2, meta-analyses revealed significantly smaller hippocampal volumes bilaterally in each of the three groups.

PTSD vs. non-PTSD: Disjoint cluster analyses failed to identify homogenous groups for analyses.

3.3.2.6. Comorbid alcohol use and axis I disorders. As shown in Appendix A, few studies had samples that were not comorbid for one or more of these conditions, and some studies did not report comorbidity. For analyses of *PTSD vs. HC and non-PTSD,* there were no significant cluster differences in comorbid disorders, and disjoint cluster analyses failed to identify homogenous groups for further analyses.

3.3.2.7. Psychotropic medication. Comparison of cluster differences: There were no significant cluster differences in either PTSD vs. HC or PTSD vs. Non-PTSD.

Meta-analyses of homogenous groups:

PTSD vs. HC: Disjoint cluster analyses failed to identify homogenous groups for analyses.

Right hippocamal volume in PTSD vs. non-PTSD: Disjoint cluster analysis identified two groups, one with un-medicated samples (# 6, 7, 14, 15), $N = 80$; and one with medicated samples, (# 4, 5), $N = 71$.

Left hippocamal volume in PTSD vs. non-PTSD: Group 1 also contained un-medicated samples (Studies # 6, 7, 14 in Appendix A), $N = 65$. As shown in Table 2, meta-analyses revealed significantly smaller hippocampal volumes bilaterally only in groups with un-medicated samples, with non-significant findings for groups with medicated samples.

Summary: Meta-analyses comparing hippocampal volumes in *PTSD vs. HC* in the three clusters identified by disjoint cluster analysis found significantly smaller bilateral volumes in PTSD in Clusters 2 and 3 only. Cluster 1 differed from these two clusters in having less males and more samples with moderate levels of PTSD. Cluster differences in gender and PTSD severity were significant only for the right side of the hippocampus. The effects of gender and severity were confirmed in analyses of gender- and severity-homogenous groups, with male and severe PTSD samples showing larger effect sizes (for both sides of the hippocampus) than mixed gender and moderate PTSD samples, respectively. However females with PTSD also

showed significantly smaller volumes compared to HC, and findings for moderate PTSD samples were significant for both sides of the hippocampus. The findings suggest that gender and PTSD severity moderate volumes bilaterally, but that the effects are more pronounced in the right hemisphere.

Cluster 1 also had the youngest samples, and we found a significant negative correlation between age and effect sizes, indicating the largest group differences in volume for the oldest samples. Like gender and severity, the effects of age were stronger for the right side of the hippocampus. Meta-analyses of age-homogenous groups showed significantly smaller volumes bilaterally in samples at least 40 years old, and significantly smaller volumes of the left side for younger adults, with a smaller effect size than the older samples. However, because cluster analysis did not identify a homogenous young adult cluster for the right side of the hippocampus, smaller right-sided volumes in younger adults cannot be disconfirmed. We found no significant cluster differences in time since trauma, but the clusters were heterogenous. Because disjoint cluster analyses only identified PTSD duration-homogenous groups that were at least 10 years post-exposure, (each of which showed significantly smaller hippocampal volumes bilaterally in PTSD vs. HC), we cannot rule out significantly smaller volumes in less chronic PTSD. Age of trauma exposure did not appear to be a significant moderator. Cluster differences appeared to be more related to sample age rather than age of exposure, but we were unable to identify more homogenous clusters for additional analyses. We also found no significant cluster differences in medication and comorbid disorders, but again were unable to identify homogenous clusters for analyses.

In meta-analyses of PTSD vs. non-PTSD, the only significant moderators we identified were PTSD severity and medication use. Disjoint cluster analysis identified two clusters with apparent differences in these variables and significant volume reductions were found only in the cluster of un-medicated samples with severe PTSD. These effects were substantiated in meta-analyses of medication- and severity-homogenous groups. Although un-medicated samples showed significantly smaller hippocampal volumes bilaterally, meta-analyses with medicated groups were not significant. Disjoint cluster analysis identified one severity-homogenous group for the right side of the hippocampus only, which showed significantly smaller volumes in the PTSD group, with a smaller effect size than those of PTSD vs. HC analyses.

3.4. Analyses 3: structural abnormalities in other brain areas

3.4.1. Amydgala

Studies that reported amygdala volumes are shown in Appendix C. The meta-analysis of PTSD vs. HC included seven studies, (# 2, 9, 11, 15, 16, 17, 26 in Appendix C), $N = 320$ and the meta-analysis of PTSD vs. non-PTSD included six studies, (# 2, 7, 10, 13, 15, 24), $N = 213$. As shown in Table 3, *meta-analyses of the right amygdala* were not significant for PTSD vs. HC and non-PTSD. However, sample heterogeneity was significant for both of these analyses. Disjoint cluster analyses did not identify homogenous groups of studies for further analyses of PTSD vs. HC studies, but identified a homogenous group of three PTSD vs. non-PTSD studies (# 7, 10, 24), $N = 141$. As shown in Table 3, this meta-analysis was significant, with a small ES. *Meta-analyses of the left amygdala* were significant for PTSD vs. both HC and non-PTSD, but sample heterogeneity was significant for both analyses. Disjoint cluster analyses identified a homogenous group of five PTSD vs. HC studies that excluded studies #15 and #17, $N = 211$ and a homogenous group of four PTSD vs. non-PTSD studies that excluded studies #2 and #15, $N = 176$. As shown in Table 3, meta-analyses of these homogenous groups found significantly smaller left amyg-

Table 3
Metaanalyses volume of other brain structures

Brain structure	Side	*PTSD compared with (type of control)*	*k*	*N*	r_w	CI_w		τ	χ^2	Orwin's fail safe *N*
Amygdala	Right	HC	7	320	−.07	−.21	.07	.01[b]	8.20[b]	−5
	Left	HC	7	320	−.14[a]	−.26	−.004	.005	7.24[b]	−2
		Ex 15 17	5	211	−.23[a]	−.36	−.09	0	1.23	1
Amygdala	Right	Non-PTSD	6	213	−.05	−.22	.12	.01[b]	6.78[b]	−4
		Incl. 7,10, 24	3	141	−.18[a]	−.34	−.01	0	.35	0
	Left	Non-PTSD	6	213	−.13	−.28	.03	.01[b]	6.32[b]	−2
		Ex 2 15	4	176	−.22[a]	−.36	−.07	0	.29	0
Corpus callosum		HC	3	221	−.29[a]	−.41	−.16	0	.22	1
Caudate		HC	4	281	−.06	−.17	.06	0	2.94	−3
ACC		Non-PTSD	5	161	−.33[a]	−.47	−.18	0	1.06	3
Prefrontal/frontal lobe		Mixed	2	223	−.25[a]	−.37	−.12	0	.27	1
CSP		Mixed	2	63	−.11	−.35	.15	0	.21	−1

Note: k = number of studies, r_w = weighted r, CI_w = 95% confidence interval for weighted r, τ^2 = between trials variance; χ^2 = within trials variance; non-PTSD trauma exposed refers to those exposed to the study index trauma, but without PTSD.

[a] $p < .05$.

[b] Heterogeneity, ACC = anterior cingulate cortex, CSP = cavum septum pellucidum.

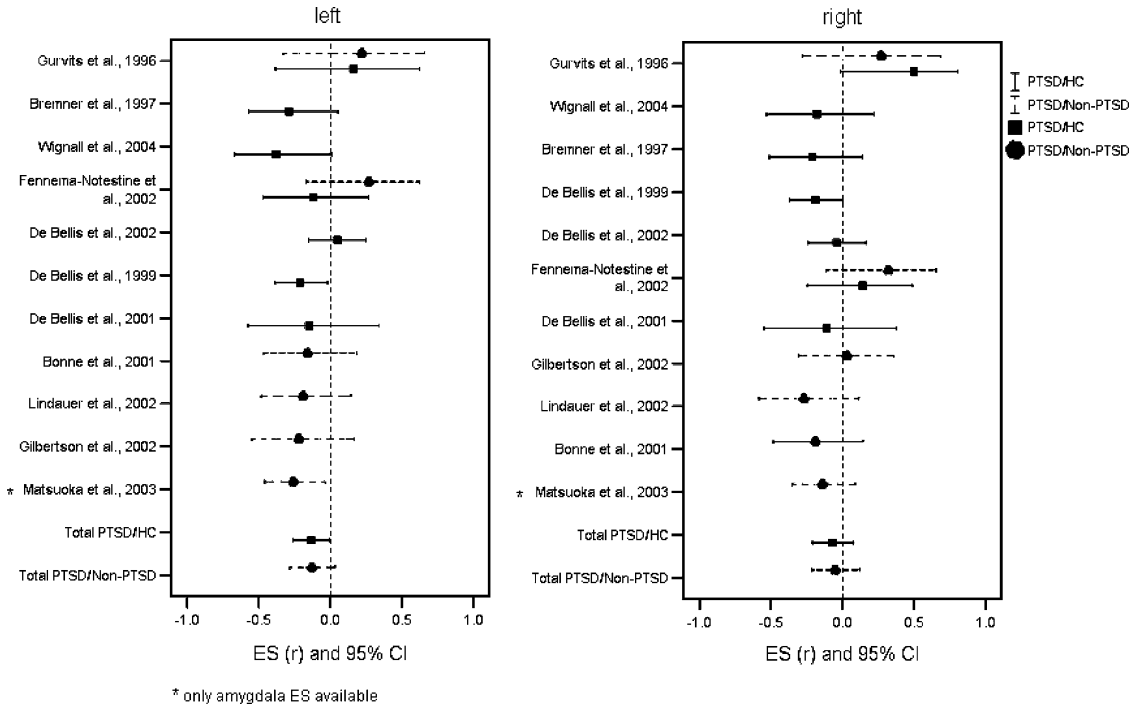

Fig. 3. Amygdala volume effect sizes (ES) and 95% confidence intervals (CI) for comparisons of PTSD and control groups, plotted per hemisphere (left panel: left hippocampal volume ES, right panel: right hippocampal volume ES) sorted by hippocampal ES starting from the highest negative ES (for Matsuoka et al., 2003 no hippocampal ES was available). Negative ESs indicate smaller amygdala volume in PTSD groups. Non-PTSD = exposed to index trauma, but no PTSD; HC = non-exposed healthy controls.

dala volumes in PTSD vs. both HC and non-PTSD, with a small ES that was further attenuated in the PTSD vs. non-PTSD analysis (See Fig. 3 for ES).

For studies that examined both hippocampal and amgdala volumes, (PTSD vs. HC: Studies # 2, 9, 11, 15, 16, 17, 26 in Appendix C, $N = 320$; PTSD vs. non-PTSD: Studies # 2, 7, 10, 13, 15 in Appendix C, $N = 137$), correlations between the right and left hippocampal volume reduction ES and right and left amygdala volume reduction ES were computed.

PTSD vs. HC: All four correlations were not significant, with the largest correlation found between left hippocampus and left amygdala, $r = -.19$, n.s.

PTSD vs. non-PTSD: All four correlations were also not significant. However, correlations were *negative* and the largest correlation was between the left hippocampus ES and right amygdala ES ($r = -.60$).

3.4.2. Other structures

The few volumetry studies of other brain structures in PTSD are shown in Appendix D. As shown in Table 3, for *PTSD vs. HC* meta-analyses were possible for the corpus callosum (CC), which included studies # 16, 17 (primarily children and adolescents) and #27 (adults) in Appendix D, $N = 221$; and the caudate (a basal ganglia structure), Studies # 8, 9, 16, 17, $N = 281$, mixed sample of children, adolescents, and adults). Meta-analyses revealed significantly smaller CC in the primarily pediatric sample with PTSD with a medium ES; see Fig. 4 for ES. There were no group differences in caudate volumes. As shown in Table 3, for *PTSD vs. non-PTSD,* meta-analysis was possible only for the anterior cingulate cortex (ACC), Studies # 28, 29, 34, 40 and 41 in Appendix D, $N = 161$ adults. The meta-analysis found significantly smaller ACC in PTSD, with a medium ES (Table 3 and Fig. 4). For prefrontal/frontal lobes and the cavum septum pellucidum (CSP), meta-analyses comparing PTSD vs. a mixed control sample of HC and non-PTSD were possible. For the prefrontal/frontal lobes, the meta-analysis of two studies (# 16, 17, 31 in Appendix D, $N = 223$ children and adolescents) revealed significantly smaller volumes in PTSD, with a small ES (Table 3 and Fig. 4). The meta-analysis of the CSP (# 32, 33, $N = 63$, mixed sample of adults and children) revealed no significant effects.

Summary: Meta-analyses revealed significantly smaller left amygdala volumes in PTSD compared to both trauma-exposed and unexposed controls (in a homogenous subsample), with small effect sizes. For the right amygdala, the meta-analysis was not significant for heterogeneous samples of PTSD vs. HC and non-PTSD studies. We could not identify a homogenous subsample of PTSD vs. HC studies, but found significantly smaller right anygdala volumes in PTSD vs. non-PTSD, in a homogenous subsample of studies. Correlations between effects sizes for hippocampal and amygdala volume reductions were not significant. However, the large (−.60) correlation between left amygdala and right hippocampus effects sizes suggests that this null finding may have been due to low

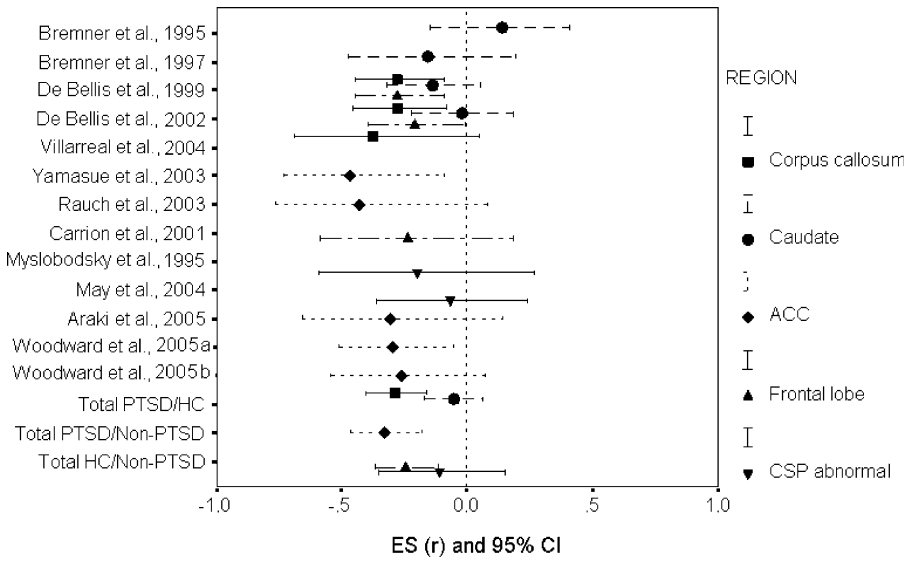

Fig. 4. Different brain structures' volume effect sizes (ES) and 95% confidence intervals (CI) for comparisons of PTSD and control groups. Negative ESs indicate smaller volume in PTSD groups. Non-PTSD = exposed to index trauma, but no PTSD; HC = non-exposed healthy controls.

statistical power. Adults with PTSD also showed significantly smaller ACC compared to trauma-exposed controls, with a medium ES. In pediatric samples, children with PTSD showed significantly smaller CC compared to healthy controls, and significantly smaller prefrontal/frontal lobe volumes compared to a mixed control group of healthy and trauma-exposed controls. There were no significant group differences in caudate volumes and CSP. Although effect sizes were smaller than those associated with differences in hippocampal volume, the results suggest that PTSD is accompanied by smaller volumes in multiple frontal lobe and limbic system structures.

4. Discussion

The main findings of the meta-analyses were as follows. Compared to control groups with no trauma exposure, samples with PTSD and trauma-exposed samples without PTSD showed significantly smaller hippocampal volume bilaterally. Compared to trauma-exposed controls, persons with PTSD reliably exhibited significantly smaller hippocampal volumes bilaterally only in samples with severe PTSD. MRI methodology differentially moderated results, depending upon the type of method and type of control group. Medication moderated the results of analyses with PTSD samples and trauma-exposed controls, whereas demographic variables such as age and gender were significant moderators in comparisons of PTSD samples and controls without trauma exposure.

Volumetric abnormalities were not restricted to the hippocampus. Compared to trauma-exposed controls, adults with PTSD showed significantly smaller anterior cingulate cortex, and in analyses with homogenous subsamples, significantly smaller amygdala volumes bilaterally. Adults with PTSD also had significantly smaller left amygdala volumes compared to non-exposed controls. Effect sizes were small and attenuated relative to those associated with hippocampal volumetric differences; and effects sizes associated with hippocampal and amygdala between-group volumetric differences were not reliably correlated with each other. Analysis of mainly pediatric samples showed significantly smaller corpus callosum and prefrontal/frontal lobe volumes compared to a mixed control group sample as well. There were no group differences in caudate and cavum septum pellucidum volumes, and meta-analyses of the cluster with the pediatric samples (Cluster 1) found no significant diagnostic group differences in hippocampal volumes.

4.1. Methodological moderating variables

The most significant moderator we identified was type of correction method and level of spatial resolution. When comparing PTSD to trauma-exposed non-PTSD, significantly smaller bilateral hippocampal volumes were found only in those studies that used WBV correction and high spatial resolution. Because age and gender were not found to be significant moderators in PTSD vs. non-PTSD comparisons, this finding did not appear to be due to the moderating effects of these variables. Our results are consistent with the finding that applying a correction method to standardize volumetric estimates provides more reliable data than working with uncorrected sizes (Buckner et al., 2004; Free et al., 1995). However, our findings suggest that correction methods differ in their suitability, and that the common procedure of using controls matched according to height and weight, based on demonstrated correlations of these variables and brain size (Van Petten,

2004), may be less preferable than referencing based on whole brain volume (Peters et al., 1998; Raz et al., 2004). Methods that yield high spatial resolution are also recommended. An optimal voxel dimension should be homogenous and in the range of $1 \times 1 \times 1\,mm^3$, whereas slice thicknesses of 3 mm or greater may be less well suited for the estimation of small volumina like the hippocampus or amygdala.

The majority of studies we reviewed also used manual tracing in their MRI acquisition protocols rather than automated algorithms. Method variance can be introduced by the use of different software packages to trace the target structures (Geuze et al., 2005). Research also suggests that applying multiple methods may yield the most accurate results (Miyahira et al., 2004; Testa et al., 2004). Voxel-based morphometry (VBM) utilizes a voxel-wise comparison of multiple brain images (Ashburner and Friston, 2000) to analyze regional differences in grey matter density throughout the brain, with no a priori regions of interest (ROI). Miyahira et al. (2004) and Testa et al. (2004) found that a combination of VBM and ROI-based volumetry of the hippocampus was the most reliable method for the identification of brain atrophy. VBM may have greater utility in estimating whole brain volumes for correction standardization, while software-based ROI analysis of experienced neuroanatoms may be preferable for the calculation of small volumina (Miyahira et al., 2004; Testa et al., 2004).

We also found that the type of anatomical boundaries employed to determine hippocampal volume moderated the results in comparisons of persons with PTSD and controls not exposed to trauma, but did not moderate the results of meta-analyses of PTSD groups compared to trauma-exposed controls. Results were significant for the samples of studies that used the alveus/fornix and superior colliculi/basilar artery as boundaries, but non-significant for the sample that used the mammillary bodies/fornix as boundaries. Although we found only a trend for studies that used the alveus/fornix and superior colliculi/basilar artery to have more adults, because age and gender were identified as significant moderators in comparisons of PTSD and non-exposed controls, these findings should be interpreted with some caution.

However, the results suggest that techniques used to delineate boundaries may be a source of method variance in volumetric research. This may be especially important if hippocampal volumetric abnormalities in PTSD are found only in specific regions of the hippocampus, such as the head and the tail (Vythilingam et al., 2005).

A related issue in hippocampal volumetry is the exact separation of the amygdala from the hippocampus, which is especially problematic when two-dimensional analysis software programs are used, due to a lateral shifting of these structures. The majority of studies we reviewed determined hippocampal volume in contiguous coronal slices. However, it is preferable to employ all three spatial dimensions and cross-validate the segmentation in different planes (Bartzokis et al., 1998, 1993; Pruessner et al., 2000). The use of 3D software programs (e.g. MEASURE, AMIRA, ANALYZE) that allow the simultaneous employment of sagittal, coronal and transverse images for visualization and segmentation of structures, especially those with tilted and shifted demarcation, is also recommended. An exact reformatting (Winter and Irle, 2004) may also be preferable because Bartzokis et al. (1993, 1998) found that reformatted 3D images showed significantly less scan-rescan variability than non-reformatted images. Although such variability does not necessarily affect volume estimates, it is crucial for estimating sample sizes needed when designing studies and should also be taken into account when comparing results from different research groups (Pruessner et al., 2000).

In summary, the overall results of our analyses of methodological moderators highlight the need for standardization in volumetry methods. Our findings suggest that method variance has contributed to some of the inconsistent findings in PTSD neuroimaging research. Standardized protocols, continued technological refinements, and combining structural and functional neuroimaging techniques might help to further elucidate the nature of abnormalities in the hippocampus as well as other brain regions in PTSD.

4.2. Sample-related moderating variables

Between-group volumetric differences and effect sizes varied according to whether control groups were exposed to trauma or not, with the largest effect sizes for bilateral differences found in comparisons of PTSD and non-exposed controls. For comparisons of PTSD and trauma-exposed persons without PTSD, severity was an important moderator. Group differences reliably emerged only in samples with severe PTSD, with medium effect sizes. However, although the largest effect sizes are associated with severe PTSD, we also found that, compared to unexposed controls, trauma-exposed persons without PTSD also showed smaller right-sided volumes with a medium effect size, and smaller left-sided volumes with a small effect size. Therefore the overall findings suggest that either (1) trauma-exposed populations, regardless of diagnostic status, may have smaller premorbid hippocampal volumes relative to unexposed samples, with the smallest volumes associated with the most severe PTSD; or that (2) regardless of diagnostic status, trauma exposure itself is associated with reduced hippocampal volume, but that the volume reductions occur along a PTSD severity continuum.

The volumetric differences between samples with severe PTSD and trauma-exposed controls could also reflect the deleterious long-term effects of severe PTSD itself. This interpretation is concordant with our finding of significant between-group volumetric differences only in samples that were not taking psychotropic medication. We previously found that differential activity of cortical neurons in PTSD (as measured by evoked potentials) was less pronounced in

medicated samples (Karl et al., 2006). Vermetten and colleagues (2003) found that long-term administration of antidepressant medication was associated with increased hippocampal volume as well as improvements in PTSD symptoms and memory performance, and suggested that such treatment effects seemed unlikely if smaller hippocampal volumes in PTSD were due solely to genetic factors. However, their results (and ours) do not rule out the possibility that chronic antidepressant administration could compensate for some sort of congenital biochemical abnormality that moderates hippocampal volume in adulthood. Moreover, combat veterans and sexually abused adult females with PTSD exhibit greater premorbid histories of neurodevelopmental abnormalties such as attention deficits and hyperactivity, learning problems, and enuresis compared to trauma-exposed controls without PTSD, which points towards premorbid differences between these two groups (Gurvits et al., 1993, 2000). The answer to whether smaller hippocampal volume is a result of premorbid vulnerabilities or their interaction with the effects of singular and/or cumulative trauma exposure awaits further research. However, the association between medication use and hippocampal volume underscores the plastictity and dynamic nature of brain morphology.

Our finding that age and gender were significant moderators only for comparisons of persons with PTSD and non-exposed controls supports the hypothesis of premorbid differences in these populations. However, because these variables did not appear to moderate the results of comparisons with trauma-exposed controls, the overall results again suggest that if group differences are premorbid, then they appear to be found in trauma-exposed samples regardless of diagnostic status. Vythilingam and associates (2005) found no hippocampal volumetric differences in combat-exposed and non-exposed veterans with and without PTSD and non-deployed reservists, but found that non-exposed controls (recruited from a university town setting) had significantly larger hippocampal volumes and higher full scale IQs than all three military groups. The three military groups also more closely resembled each other in history of depression, alcohol abuse, and early life traumatic events. Familial depression, history of conduct disorder, and history of substance dependence have also been associated with an increased risk of trauma exposure in veteran samples (Koenen et al., 2002).

We also found that age was negatively correlated with ES in comparisons of PTSD samples with unexposed (but not trauma-exposed) controls. Vythilingam and associates (2005) found PTSD-related volumetric abnormalities primarily in the head and the tail, the same regions associated with age-related atrophy (Pruessner et al., 2001). Pruessner et al. (2001) also found that hippocampal volumes were related to age in middle-aged males but not females; and we found that volumetric differences were less pronounced in younger female subjects. These findings are consistent with research demonstrating that estrogen protects the hippocampus from age-related atrophy (e.g., Eberling et al., 2003).

McEwen (2001) has suggested that genetic predispositions and early adverse events may interact to influence hippocampal volume changes that emerge later in life as a result of the cumulative effects of ongoing neural and endocrine activity and life experiences. Chronic dysregulation of the hypothalamic–pituitary axis (HPA) can lead to subsequent dysfunction in dependent systems, including disinhibition of inflammatory mechanisms of the immune system (McEwen and Stellar, 1993). Both chronic stress and peripheral chronic inflammation have been associated with down-regulation of hippocampal BDNF expression (Duric and McCarson, 2005). Inflammatory mediators also foster atherosclerotic processes in blood vessels (Ross, 1999). Wiseman et al. (2004), who found associations between chronic hypertension and smaller hippocampal volumes and brain-wide white matter lesions, and between abnormal diastolic blood pressure and volumetric alterations in hippocampus and amygdala, has suggested that nitric oxide-mediated cell damage could be one of the mechanisms involved in volumetric changes. In addition to our findings of smaller volumes in the hippocampus and amygdala, PTSD has also been associated with increased white matter lesions (Canive et al., 1997) and decreased white matter volumes (Villarreal et al., 2002) as well as alterations in the immune system (Rohleder et al., 2004) and cardiovascular functioning (Buckley and Kaloupek, 2001). The overall findings suggest a confluence of HPA axis-related changes in central and peripheral systems that may interact to influence age-related volumetric changes. Future longitudinal studies should investigate whether the relationship between altered central and peripheral immune system functioning in traumatized persons with and without PTSD is associated with greater age-related volumetric reductions in these populations.

We did not identify any additional moderating variables. Age of trauma exposure was not a reliable moderator, which may reflect the similarity of volumetric differences of adults with PTSD secondary to childhood abuse and combat veterans, the two most common types of adult trauma samples. It may also reflect the lack of significant hippocampal volumetric differences in the cluster with pediatric samples (Cluster 1) with PTSD. Meta-analyses of homogenous groups at least ten year post-trauma found significantly smaller volumes in persons with PTSD compared to non-exposed controls. However, because sample heterogeneity precluded analyses of homogenous groups with fewer years post-exposure, we cannot rule out significant volumetric differences in trauma populations with less chronic PTSD. Comorbid disorders (including alcohol) did not emerge as significant moderators, but again we were unable to identify homogenous groups for further analyses.

4.3. Implications for future research

The finding that trauma-exposed persons with and without PTSD show smaller hippocampal volumes relative to unexposed control samples suggests the presence of premorbid vulnerabilities that appear to be more related to trauma exposure than diagnostic status, and also underscores the need to utilize well-match comparison samples in PSTD research. However, these findings could also reflect that regardless of diagnostic status, trauma exposure may be associated with some reduction in hippocampal volumes, with the smallest volumes associated with the greatest risk of PTSD following exposure. The findings of volumetric differences between persons with PTSD and trauma-exposed controls, as well as the moderating effects of PTSD severity, also suggest that volumetric differences occur along a PTSD severity continuum. Considered along with the finding of a moderating effect of medication on volumetric differences in comparisons of persons with PTSD and trauma-exposed controls, the possibility also remains that volumentric differences could occur as a result of the progressive effects of chronic PTSD. Our analyses were not designed to test the hypothesis that several factors could interact to produce the volumetric differences found in trauma-exposed persons with and without PTSD, including premorbid morphology (Gilbertson et al., 2002), severity of trauma exposure (Bremner et al., 1997; Gurvits et al., 1996; Winter and Irle, 2004), and the cumulative effects of lifetime trauma exposure and chronic stress (e.g., the effects of "allostatic load," see McEwen, 1998; McEwen and Stellar, 1993) which is a known risk factor for PTSD (e.g. Neuner et al., 2004). However, a variety of future research designs could help to tease apart the influence of these factors: twin and familial volumetric studies; behavioral genetic research; treatment research that examines changes in brain morphology and functioning; and longitudinal research. The finding of differential volumetric abnormalities in pediatric and adult samples highlights the need for long-term studies that follow trauma-exposed pediatric samples through adulthood.

Another important research objective is to understand the relationship between structural abnormalities and PTSD symptomology. PTSD severity has been positively correlated with hippocampal volume in some studies (Bremner et al., 2003a; Gilbertson et al., 2002; Gurvits et al., 1996; Winter and Irle, 2004) but not in others (Bonne et al., 2001; Bremner et al., 1995; Pederson et al., 2004; Schuff et al., 2001; Wignall et al., 2004). PTSD re-experiencing symptoms were correlated with hippocampal volume in two studies (Lindauer et al., 2004; Villarreal et al., 2002), but not in a third (Nakano et al., 2002). There are two reports of significant correlations between symptoms of dissociation and left hippocampal volume (Bremner et al., 2003a; Stein et al., 1997), and no findings of a relationship between hippocampal volume and avoidance, numbing, or hyperarousal symptoms.

Research has also not consistently found significant correlations between hippocampal volume and memory impairment in PTSD. Of eight studies that have examined this, two found significant (positive) correlations (Bremner et al., 1995; Gurvits et al., 1996), but the rest found non-significant results (Nakano et al., 2002; Neylan et al., 2004a; Pederson et al., 2004; Stein et al., 1997; Winter and Irle, 2004). Although Vermetten et al. (2003) found improvement in PTSD symptoms as well as verbal memory performance, neither of these were correlated with volumetric increases. In functional neuroimaging studies, memory performance has not been associated with either differential hippocampal volume or activity (Bremner et al., 2003b; Shin et al., 2004b). The inconsistent results resemble those of research with general population samples, leading some to question the relationship between hippocampal volume and performance (Van Petten, 2004). Animal research (Zola and Squire, 2001) suggests that a certain threshold of reduction may be necessary in order to observe impairment; the two studies that found significant volume–performance correlations reported volume reductions of 8% (Bremner et al., 1995) and 26% (Gurvits et al., 1996). It is also important to note that memory is not localized and appears to involve interactions between several medial temporal structures and the neocortex (Aggleton and Brown, 1999), with greater deficits associated with more extensive medial temporal lobe damage (Rempel-Clower et al., 1996). Moreover, some authors have suggested that apparent memory deficits in PTSD may be due to impairment in attention and concentration and possible frontal lobe, rather than hippocampal, dysfunction (Matsuo et al., 2003; Vasterling et al., 1998, 2002).

Our findings of reduced volumes in the amygdala also suggest the need to consider the role of abnormalities in other brain regions in PTSD. Individual PTSD amygdala volumetric studies have typically reported null findings (e.g., Bonne et al., 2001; Bremner et al., 1997; Fennema-Notestine et al., 2002; Gurvits et al., 1996; Wignall et al., 2004), which could be due to a combination of small effect sizes and small samples, as well as difficulty in differentiating the hippocampus and amgdala (discussed above). However, the role of amygdala volume change in psychiatric disorders is not well understood. Early onset depression has been associated with enlargement, (Lange and Irle, 2004), whereas reduced, or non-altered volume has been associated with chronic depression (Sheline et al., 1998). Thus, our findings of reduced volumes could reflect PTSD chronicity. However, Lange and Irle (2004) also found smaller hippocampi in the presence of enlarged amygdala in depression, whereas in our analyses volume reduction effect sizes for these structures were not significantly correlated. Therefore common effects across the disorders should not be assumed. Given the small effect sizes, future PTSD studies with adequate sample sizes are clearly needed to more fully explore whether amygdala

volumetric abnormalities are reliably associated with PTSD.

Our findings of altered volumes in the amygdala, anterior cingulated cortex, and prefrontal cortical regions are consistent with the results of functional neuroimaging research that has found altered activity in these regions in persons with PTSD (e.g., Bremner et al., 1999a, 2003a, 2004; Clark et al., 2003; Matsuo et al., 2003; Rauch et al., 1996; Shin et al., 1999, 2004a, 2001). The results are also consistent with reports of increased neurodevelopmental abnormalities and neurological "soft signs" in persons with PTSD (Gurvits et al., 1993, 2000). The hippocampus may have a key role in the neuropathology of PTSD, because of its importance in stress regulation, its proximity to the amygdala, and its manifold neuronal connection to frontal and parietal association cortices. However, the collected findings suggest that PTSD is a condition that may be associated with altered structure and function in several brain regions rather than focal abnormalities in one selected brain area. Because abnormalities in similar brain regions have been reported for other disorders such as depression (e.g., Campbell et al., 2004; Lange and Irle, 2004; Sheline et al., 1998; Videbech and Ravnkilde, 2004), a question of continued importance is whether they represent distinct etiological factors that produce common morphological and functional changes across disorders, or a non-specific predispositional factor.

4.4. Limitations

Although we attempted to be as inclusive as possible, this series of meta-analyses is limited by the relatively small number of studies included in some of the meta-analyses, and especially in some of the moderator analyses. As is the case with all meta-analyses, ours are limited by the "file drawer[1]" problem. Moreover, because most studies compared one group of subjects with PTSD to two types of control groups (trauma-exposed and non-exposed controls), sample generalizability may be limited. In particular, several studies used samples with very chronic PTSD, such as combat veterans or adult survivors of childhood abuse, and we were unable to examine homogenous samples with less chronic PTSD. In some instances we were unable to identify homogenous groups of studies for analyses of certain potential moderators (such as comorbidity) or analyze other potential moderators (such as handedness) due to sample characteristics. In addition, we were unable to definitely isolate the effects of MRI methodological moderators from sample-related moderators, and vice-versa. A general disadvantage of meta-analyses is the necessity to categorize and quantify variables, which may lead to a neglect of the qualitative aspects of individual studies.

4.5. Conclusions

The results of our study provide reliable evidence that: (1) trauma exposure (regardless of diagnostic status) is associated with smaller hippocampal volumes that appear to be moderated by age and gender; (2) in comparisons with trauma exposed controls, severe PTSD in unmedicated, adult samples is associated with smaller hippocampal volumes; (3) for all comparisons, effect sizes increase with PTSD severity; (4) volumetric differences are not restricted to the hippocampus; and (5) adults and minors exhibit different types of structural abnormalities. Our findings emphasize the need for: (1) methodological standardization and use of well-matched control samples; (2) further comparisons of trauma-exposed persons with PTSD and trauma-exposed controls, and comparisons of trauma-exposed persons without PTSD and unexposed controls to parse apart the effects of singular and cumulative trauma exposure from those of premorbid vulnerabilities; and (3) neurodevelopmental longitudinal research, with further examination of abnormalities in frontal-limbic system structures to clarify the role of structural and functional brain abnormalities in the etiology and/or maintenance of PTSD.

Acknowledgements

Our current research on PTSD is supported by the Deutsche Forschungsgemeinschaft (KA1476/3). Denise Dörfel was awarded a scholarship by the G.A. Lienert Foundation.

Appendix A

Hippocampal volume studies: Sociodemographic and clinical characteristics are shown in Table A1.

Appendix B

See Table B1 for comparison of methodical aspects (MRI protocols, analysis software, correction algorithms, anatomical borderlines).

Appendix C

Amygdala volume studies are shown in Table C1.

Appendix D

Volume studies of other brain areas are shown in Table D1.

Table A1

	Study	Included in MA	Age	Handedness	Gender	PTSD	Control	Trauma type	Time since trauma	Axis1	Medication	Alcohol	PTSD severity
1	Villarreal et al. (2002)	P-HC	43.5	Mixed	F/M	12	10	Mixed	> 2 yrs	Yes	Yes	Yes	Severe
2	Fennema-Notestine et al. (2002)	P-HC,	34.8;	Mixed	F	11	17	IPV	NR	NR	No	No	Moderate
		P-NPTSD, HC-NPTSD	34.4;			11	11						
			35.4;			17	11						
3	Hedges et al. (2003)	P-HC	54.4	NR	M	4	4	COM	>10 yrs	No	Yes	No	Severe
4	Pederson et al. (2004)	P-HC,	24.3	NR	F	17	17	CSA	>10 yrs	Yes	Yes	NR	Moderate
		P-NPTSD, HC-NPTSD	25.8			17	17						
			25.3			17	17						
5	Schuff et al. (2001)	P-NPTSD	51.5	NR	M	18	19	COM	NR	Yes	Yes	Yes	Moderate
6	Shin et al. (2004b)	P-NPTSD	47	Right	F/M	8	7	FF	NR	Yes	No	NR	Moderate
7	Lindauer et al. (2004)	P-NPTSD	36.2	NR	F/M	14	14	POL	NR	Yes	No	NR	Moderate
8	Bremner et al. (1995)	P-HC	45.2	Mixed	M	26	22	COM	>10 yrs	Yes	NR	Yes	Severe
9	Bremner et al. (1997)	P-HC	40.2	Mixed	F	17	17	CSA	>10 yrs	Yes	NR	Yes	NR
10	Bonne et al. (2001)	P-NPTSD	NR	NR	F/M	10	27	NR	0–2 yrs	NR	NR	NR	Moderate
11	De Bellis et al. (2001)	P-HC	13.1	NR	F/M	9	9	CM	>2 yrs	Yes	Yes	No	NR
12	Stein et al. (1997)	P-HC	31.1	Mixed	F	21	21	CSA	>10 yrs	NR	NR	NR	Moderate
13	Gilbertson et al. (2002)	P-NPTSD	52.4	NR	M	12	23	COM	>10 yrs	Yes	NR	Yes	Severe
14	Bremner et al. (2003a)	P-HC,	36.5	Right	F	10	11	CSA	>10 yrs	Yes	No	No	Severe
		P-NPTSD, HC-NPTSD	33.5			10	12						
			35			12	11						
15	Gurvits et al. (1996)	P-HC,	41.25	Mixed	M	7	8	COM	>10 yrs	Yes	No	No	Severe
		P-NPTSD, HC-NPTSD	46			7	7						
			42.8			7	8						
16	De Bellis et al. (1999)	P-HC	12.1	Mixed	F/M	44	61	CM	>2 yrs	Yes	Yes	Yes	NR
17	De Bellis et al. (2002)	P-HC	11.53	Mixed	F/M	28	66	CM	>2 yrs	Yes	No	NR	NR
18	Nakano et al. (2002)	P-NPTSD	48.5	NR	F	28	39	CAN	>2 yrs	Yes	NR	NR	Only Re-experiencing
19	Winter and Irle (2004)	P-HC,	41.50	NR	M	15	15	BS	< 2 yrs.	No	No	No	Moderate
		P-NPTSD, HC-NPTSD	41.50			15	15						
			41.5			15	15						
20	Wignall et al. (2004)	P-HC	43.00	Mixed	F/M	15	11	Acc	< 2 yrs.	No	No	NR	Moderate
21	Vythilingam et al. (2005)	P-HC,	34.5	Mixed	F/M	14	23	COM	>10 yrs	Yes	NR	Yes	Severe
		P-NPTSD, HC-NPTSD	35.0			14	23						
			34.5			23	23						

IPV = intimate partner violence, COM = combat, CSA = childhood sexual abuse, CM = childhood maltreatment, BS = burn survivors, Acc = accident, FF = fire fighters, POL = police officers, NR = not reported, CAN = cancer survivors, POW = prisoners of war, PA = poison attack, P-HC = PTSD vs. HC, P-NPTSD = PTSD vs. non-PTSD, HC-NPTSD = HC vs. non-PTSD.

Table B1

	Study	B_0-strength sequence TE/TR (ms) resolution (mm^3)	Manual/autom. post-processing software volume correction	Number of raters reliability intraclass-correl. IR = INTER/ IA = INTRA)	Anatomical boundaries					Additional method. Info/ comment
					Most anterior	Most posterior	Medial border	Lateral border	Inferior border	
1	Villarreal et al. (2002)	1,5 T General Electric (GE) T1-w. fast spoiled GRASS 6.9/17.7 1 × 1.5 × 1.5	Manual tracing in sagittal, coronal and axial slices MEASURE (3D) yes (WBV)	2 0.98/NR	CSF in uncal recess of temporal horn or (when not visible) the alveus	When crura of fornices are seen in full profile	Mesial edge of temporal lobe	Temporal horn of lateral ventricle	Incl. subicular complex and uncal cleft with the border separating the subicular complex from the parahippo-campal gyrus	(Watson et al., 1992) Subicular complex, dentate gyrus, alveus and fimbria included
2	Fennema-Notestine et al. (2002)	1,5 T G E T1-w. spoiled GRASS 5/24 NR × NR × 4	Semi-automated tissue segmentation manual ROI analysis in coronal slices NR	2 0.85–0.99/NR	Where temporal pole is separated from frontal lobe by lateral sulcus	Fornix	NR	NR	NR	Subiculum included Slice thickness of 4 mm
3	Hedges et al. (2003)	1,5 T GE Dual spin echo technique NR 1 × 1 × 1	ROI-segmentation-based routines in coronal and sagittal slices ANALYZE (3D) Yes (WBV)	2 > 0.9/NR	Anterior aspect of the hippocampus or uncal recess separating amygdala from hippocampus	Two of four criteria: presence of superior colliculi, presence of medial pulvinar, visibility of oblong position of hippocampus at crura of fornices, presence of a distinct separation of the temporal horn from atria	Anterior choroidal artery or point at which boundaries of ambient cistern/ choroidal fissure are most readily identified	Medial wall of the temoral horn	NR	(Bigler et al., 1997)
4	Pederson et al. (2004)	1.5 T Siemens T1-weighted sequence 1 × 1 × 1	Manual tracing in sagittal slices 2D yes (body-height)	1 (3 times) NR	White matter lamina or implicit curve of hippocampal head	NR	CSF from temporal horn	CSF of lateral ventricle and parahippo-campal gyrus	NR	correction of brain size with body height (−), only sagittal slices for volumetry
5	Schuff et al. (2001)	1.5 T Siemens T1-w double spin echo MPRAGE 4/10 1 × 1 × 1.4	Manual tracing in sagittal, coronal and axial slices MEASURE (3D) yes (WBV)	2 0.98/NR	CSF in uncal recess of temporal horn or (when not visible) the alveus	When crura of fornices are seen in full profile	Mesial edge of temporal lobe	Temporal horn of lateral ventricle	Incl. subicular complex and uncal cleft with the border separating the subicular complex from the	(Watson et al., 1992) Subicular complex, dentate gyrus, alveus and fimbria included

6	Shin et al. (2004b)	1.5 T Siemens 3D MPRAGE 3/7.25 1 × 1 × 1.3	Semi-automated gray matter-white matter-segmentation of hippocampus manual tracing in coronal slices NR	NR	Lateral ventricle tip of temporal horn	Segmented as a continuous gray matter mass in the primary segmental fornix	Segmented as a continuous gray matter	Segmented as a continuous gray matter	parahippo-campal gyrus Segmented as a continuous gray matter	Excluding parahippocampal gyrus (Makris et al., 1999)
7	Lindauer et al. (2004)	1.5 T Siemens 3D MPRAGE 4/7.4 1 × 1 × 1	Manual tracing in coronal slices (HC) MRICRO FAST (brain extraction tool) for WB Yes (WBV)	2 0.96/ 0.95 (left HC) 0.98/ 0.96 (right HC)	When oval shape of mammillary bodies was first visible	When fornix was visible as a continuous tract	NR	NR	NR	Border of hippocampus defined by its gray matter
8	Bremner et al. (1995)	1,5 T GE T1-w spoiled GRASS 5/25 0.6 × 0.6 × 3	Manual tracing in coronal slices MIND yes (body-height)	2 0.78/0.75 (HC mean)	First slice anterior to the superior colliculus	Proceed 5 contiguous 3 mm slices to bifurcation of basillary artery	Mesial edge of the temporal lobe	Temporal horn of the lateral ventricle	Incl. subicular complex and uncal cleft	Only hippocampal body, slice thickness 3 mm (−) correction of brain size with body height (−)
9	Bremner et al. (1997)	1,5 T GE T1-w spoiled GRASS 5/25 0.6 × 0.6 × 3	Manual tracing in coronal slices ROI analyze yes (body-height)	2 0.61/NR (left HC) 0.79/NR (right HC)	First slice anterior to the superior colliculus	Proceed 5 contiguous 3 mm slices to bifurcation of basillary artery	Mesial edge of the temporal lobe	Temporal horn of the lateral ventricle	Incl. subicular complex and uncal cleft	Only hippocampal body, slice thickness 3 mm (−) correction of brain size with body height (−)
10	Bonne et al. (2001)	2 T Elscint Double -echo-sequence 30; 80/ 3000 0.9 × 0.9 × 1.5	Semi-automated (clustering/ connectivity algorithm) manual tracing in coronal slices yes (WBV)	2 0.89/ NR (HC mean)	First appearance of mammillary bodies	Last appearance of fibers coursing crux of fornix,	NR	NR	NR	28 contiguous 1,5 mm slices (Gurvits et al., 1996)
11	De Bellis et al. (2001)	1,5 T GE 3D T1-w spoiled GRASS 5/25 1.1 × 1.1 × 1.5	Manual tracing in coronal slices landmark method NR	2 0.98/ NR (left HC) 0.96/ NR (right HC)	Coronal slice containing the most anterior portions of the mammillary bodies	When fibers of fornix still visible	NR	NR	NR	incl. Cornu ammonis, dentate gyrus, subiculum correction of brain size (Giedd et al., 1996)
12	Stein et al. (1997)	1,5 T Siemens T2-w Turbo Spinecho 90/4000 0.5 × 0.5 × 4	Manual tracing in coronal slices ALLEGRO Yes (WBV)	1 (2x) NA/ 0.67 (left HC) NA/ 0.71 (right HC)	First slice posterior mammillary bodies	7 slices posterior up to fornix	NR	NR	NR	Standardized brain volume on first index slice slice thickness 4 mm (−)
13	Gilbertson et al. (2002)	1,5 T GE 3D T1-w spoiled GRASS 5/35 0.9 × 0.9 × 1.5	Semi-automated (clustering/ connectivity algorithm)	2 0.96/ NR (right HC), 0.92/ NR (left HC)	White matter tract linking the temporal lobe with rest of brain	Slice in which fibers of fornix are still visible	NR	NR	NR	Mammillary bodies used to separate amygdala and

Table B1 (*continued*)

	Study	B_0-strength sequence TE/TR (ms) resolution (mm^3)	Manual/autom. post-processing software volume correction	Number of raters reliability intraclass-correl. IR = INTER/ IA = INTRA)	Anatomical boundaries					Additional method. Info/ comment
					Most anterior	Most posterior	Medial border	Lateral border	Inferior border	
			manual tracing in coronal slices yes (WBV)							hippocampus (Shenton et al., 1992)
14	Bremner et al. (2003a)	1,5 T GE T1-w spoiled GRASS 5/25 $0.6 \times 0.6 \times 3$	Manual tracing in coronal slices MIND yes (body-height)	2 0.78/ 0.75 (HC mean)	First slice anterior to the superior colliculus	Proceed 5 contiguous 3 mm slices to bifurcation of basillary artery	Mesial edge of the temporal lobe	Temporal horn of the lateral ventricle	Incl. subicular complex and uncal cleft	Only hippocampal body, slice thickness 3 mm (−) correction of brain size with body height (−)
15	Gurvits et al. (1996)	1,5 T GE 3D T1-w spoiled GRASS 5/35 $0.9 \times 0.9 \times 1.5$	S emi-automated (clustering/ connectivity algorithm) manual tracing in coronal slices yes (WBV)	3 0.78/ NR (HC/ AG complex mean)	First appearance of mammillary bodies	Last appearance of fibers coursing crux of fornix,	NR	NR	NR	28 contiguous 1,5 mm slices mammillary bodies to divide hippocampal and amygdala complex
16	De Bellis et al. (1999)	1,5 T GE 3D T1-w spoiled GRASS 5/25 $0.9 \times 1.5 \times 1.5$	Semi-automated (WB) manual tracing (HC) in coronal slices IMAGE Yes (WBV)	2 0.99/NR (left HC/AG complex) 0.97/ NR (right HC/ AG complex)	Coronal slice containing the most anterior portions of the mammillary bodies	When fibers of fornix still visible	NR	NR	NR	incl. cornu ammonis, dentate gyrus, subiculum correction of brain size ?? (Giedd et al., 1996)
17	De Bellis et al. (2002)	1,5 T GE 3D T1-w spoiled GRASS 5/25 $0.9 \times 1.5 \times 1.5$	Manual tracing (HC) IMAGE Yes (WBV)	2 0.96/ 0.98 (HC mean)	Coronal slice containing the most anterior portions of the mammillary bodies	When fibers of fornix still visible	NR	NR	NR	incl. cornu ammonis, dentate gyrus, subiculum correction of brain size ?? (Giedd et al., 1996)
18	Nakano et al. (2002)	1.5 T GE 3D-T1w spoiled GRASS 5/25 $0.8 \times 0.8 \times 1.5$	Manual tracing in coronal slices (HC) semi-automated (WB) ANALYZE yes (age, IQ)	1 (2 times) NA/ 0.97	Where white alveus surrounds remainings of hippocampal head	Where hippocampus tail was defined as the slice in which crus of fornix is longest	NR	NR	NR	CA, dentate gyrus, fimbria subiculum
19	Winter and Irle, 2004)	1,5 T Philips 3D T1-weighted sequence 6/24 $1 \times 1 \times 1.3$	Manual tracing in coronal, sagittal and horizontal slices	1 NA/ 0.94 (HC mean)	Emergence of uncal recess and alveus (one	Crus of fornix (gray matter attached to TLV)				Tail, body and head of hippocampus included: dentate

		reformatted to $1 \times 1 \times 1$	(HC) semiautomated (WB) CURRY (3D) Yes (WBV)		additional row of pixels anterior)					gyrus, CA, alveus, fimbria, fasciolar gyrus adjacent to CA region (Pruessner et al., 2000)
20	Wignall et al. (2004)	1,5 T Philips T1-w spoiled Gradientecho 4.4/15 $1 \times 1 \times 1$	Manual tracing in coronal slices ANALYZE (HC) SPM 99 (WB) Yes (WBV)	2 IR: 0.82/ 0.82 (mean HC)	When lighter band of cells forming alveus not distinguishable as border between hippocampus and amygdala	When crus of fornix was seen in continuity with the body of hippocampus and where hippocampus seen as distinct globular structure	NR	NR	NR	Hippocampus, subiculum and dentate gyrus
21	Vythilingam et al. (2005)	1.5 T GE 3D SPGR 5/25 $0.9 \times 1.2 \times 1.5$	Manual tracing in coronal slices ANALYZE yes (body-height)	2 0.90/ NR (right HC), 0.80/ NR (left HC)	CSF in uncal recess of temporal horn or (when not visible) the alveus	3 mm anterior to where crura of fornix separated from hippocampus	Mesial edge of temporal lobe	CSF of temporal horn of lateral ventricle	white matter tracts	(Watson et al., 1992) gray matter of hippocampus proper, dentate gyrus, subicular complex, alveus and fimbria included

WB = whole brain, WBV = whole brain volume, HC = hippocampus, NR = not reported, NA = not applicable, CA = cornu ammonis.

Table C1

	Study	Included in MA	Age	Handedness	Gender	PTSD	Control	Trauma type	Time since trauma (years)	Axis1	Medication	Alcohol	PTSD severity
1	Fennema-Notestine et al. (2002)	P-HC;	34.8	Mixed	F	11	17	IPV	NR	NR	No	No	Moderate
		P-NPTSD	34.4			11	11						
2	Lindauer et al. (2004)	P-NPTSD	36.2	NR	F/M	14	14	POL	NR	Yes	No	NR	Moderate
3	Bremner et al. (1997)	P-HC	40.2	Mixed	F	17	17	CSA	>10	Yes	NR	Yes	NR
4	Bonne et al. (2001)	P-NPTSD	NR	NR	F/M	10	27	COM	0–2	NR	NR	NR	Moderate
5	De Bellis et al. (2001)	P-HC	13.1	NR	F/M	9	9	CM	>2	Yes	Yes	No	NR
6	Gilbertson et al. (2002)	P-NPTSD	52.4	NR	M	12	23	COM	>10	Yes	NR	Yes	Severe
7	Gurvits et al. (1996)	P-HC;	41.25	Mixed	M	7	8	COM	>10	Yes	No	No	Severe
		P-NPTSD	46			7	7						
8	De Bellis et al. (1999)	P-HC	12.1	Mixed	F/M	44	61	CM	>2	Yes	Yes	Yes	NR
9	De Bellis et al. (2002)	P-HC	11.53	Mixed	F/M	28	66	CM	>2	Yes	No	NR	NR
10	Wignall et al. (2004)	P-HC	43.00	Mixed	F/M	15	11	Acc	< 2	No	No	NR	Moderate
11	Matsuo et al. (2003)	P-NPTSD	48.6	Mixed	F	35	41	CAN	< 2	Yes	Yes	NR	Only re-experiencing

IPV = intimate partner violence, COM = combat, CSA = childhood sexual abuse, CM = childhood maltreatment, BS = burn survivors, Acc = Accident, FF = fire fighters, POL = police officers, NR = not reported, CAN = cancer survivors, POW = prisoners of war, PA = poison attack, P-HC = PTSD vs. HC, P-NPTSD = PTSD vs. Non-PTSD, HC-NPTSD = HC vs. Non-PTSD.

Table D1

	Study	Type of control	Age	Handed-ness	Gender	PTSD	Control	Trauma type	Time since trauma (years)	Axis1	Medication	Alcohol	PTSD severity
	Caudate												
1	Bremner et al. (1995)	HC	45.2	Mixed	M	26	22	COM	>10	Yes	NR	Yes	Severe
2	Bremner et al. (1997)	HC	40.2	Mixed	F	17	17	CSA	>10	Yes	NR	Yes	NR
3	De Bellis et al. (2001)	HC	13.1	NR	F/M	9	9	CM	>2	Yes	Yes	No	NR
4	De Bellis et al. (1999)	HC	12.1	Mixed	F/M	44	61	CM	>2	Yes	Yes	Yes	NR
5	De Bellis et al. (2002)	HC	11.53	Mixed	F/M	28	66	CM	>2	Yes	no	NR	NR
	Corpus callosum												
6	De Bellis et al. (1999)	HC	12.1	Mixed	F/M	44	61	CM	>2	Yes	Yes	Yes	NR
7	De Bellis et al. (2002	HC	11.53	Mixed	F/M	28	66	CM	>2	Yes	No	NR	NR
8	Villarreal et al. (2004)	HC	43.50	Mixed	F/M	12	10	Mixed	< 2	Yes	Yes	Yes	Severe
	Anterior cingulate												
9	Yamasue et al. (2003)	Non-PTSD	44.50	Mixed	M	9	16	PA	>5	Yes	Yes	No	Severe
10	Rauch et al. (2003)	Non-PTSD	51.80	Mixed	M	9	9	COM nurses	>10	Yes	No	No	Severe
11	Araki et al. (2005)	Non-PTSD	47.10	Right	F/M	8	13	PA	>5	No	No	No	Mild
12	Woodward et al. (2005a)	Non-PTSD	54.80	NR	M	38	25	COM	>10	Yes	NR	Yes	Severe
13	Woodward et al. (2005b)	Non-PTSD	36.80	NR	F/M	13	23	COM	>10	Yes	NR	Yes	Severe
	Prefrontal/frontal lobe												
14	De Bellis et al. (1999)	HC	12.1	Mixed	F/M	44	61	CM	>2	Yes	Yes	Yes	NR
15	De Bellis et al. (2002)	HC	11.53	Mixed	F/M	28	66	CM	>2	Yes	No	NR	NR
16	Carrion et al. (2001)	NR	11.00	Mixed	F/M	12	12	NR	>2	Yes	Yes	NR	NR
	Cavum septum pellucidum												
17	Myslobodsky et al. (1995)	HC	33.00	NR	M	10	10	COM	>10	NR	No	No	Severe
18	May et al. (2004)	HC	52.00	NR	M	20	23		NR	NR	NR	NR	Severe

IPV = intimate partner violence, COM = combat, CSA = childhood sexual abuse, CM = childhood maltreatment, BS = burn survivors, Acc = accident, FF = fire fighters, POL = police officers, NR = not reported, CAN = cancer survivors, POW = prisoners of war, PA = poison attack, P-HC = PTSD vs. HC, P-NPTSD = PTSD vs. non-PTSD, HC-NPTSD = HC vs. non-PTSD.

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