Progress in Neuro-Psychopharmacology & Biological Psychiatry 34 (2010) 1181–1188

Contents lists available at ScienceDirect

Progress in Neuro-Psychopharmacology & Biological Psychiatry

journal homepage: www.elsevier.com/locate/pnp

Review article

Hippocampal volume deficits associated with exposure to psychological trauma and posttraumatic stress disorder in adults: A meta-analysis

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ARTICLE INFO

Article history:
Received 13 February 2010
Received in revised form 30 May 2010
Accepted 16 June 2010
Available online 21 June 2010

Keywords:
Brain
Hippocampus
Magnetic resonance imaging (MRI)
Neuroimaging
Posttraumatic stress disorder (PTSD)
Trauma

ABSTRACT

Trauma exposure itself in the absence of posttraumatic stress disorder (PTSD) may be associated with hippocampal volume deficits. We meta-analytically compared hippocampal volumes in PTSD subjects, in trauma-exposed subjects without PTSD, and in trauma-unexposed subjects. Using the words and phrases *PTSD*, *neuroimaging*, *hippocampus*, *brain*, *violence*, *trauma*, *abuse*, *rape*, *war*, *combat*, *accident*, and *disaster*, we searched major computerized databases to obtain candidate studies through 2008 for inclusion. We identified 39 hippocampal volumetric studies in adults with PTSD compared to control groups consisting of either trauma-exposed controls without PTSD or trauma-unexposed controls, or both. We meta-analytically compared left, right, and total hippocampal volumes between 1) PTSD subjects and a trauma-unexposed group, 2) PTSD subjects and a trauma-exposed group without PTSD, and 3) a trauma-unexposed group and a trauma-exposed group without PTSD. Hippocampal volumes were smaller in the PTSD group and trauma-exposed group without PTSD compared to the trauma-unexposed group. Further, the right hippocampus was smaller in the PTSD group compared to the trauma-exposed group without PTSD. Additionally, the right hippocampus was larger than the left in the PTSD and trauma-unexposed groups but not in the trauma-exposed group without PTSD. Hippocampal volume reduction is associated with trauma exposure independent of PTSD diagnosis, albeit additional hippocampal reduction was found in PTSD compared to the trauma-exposed group without PTSD.

Contents

1. Introduction

Occurring in certain people after exposure to trauma, posttraumatic stress disorder (PTSD) is characterized by a sense of reexperiencing the trauma, avoidance of situations reminiscent of the trauma, numbing, and increased arousal (American Psychiatric Association, 2000). Further, PTSD appears to be associated with abnormalities in brain structure (Hedges and Woon, 2007). Indeed, numerous neuroimaging studies of PTSD have focused on the hippocampus, a brain region of particular interest in PTSD given its extensive involvement in declarative, episodic, contextual, and spatial learning and memory (Brewin et al., 2007; Burgess et al., 2002; Eichenbaum et al., 1992; Phillips and LeDoux, 1992; Squire et al., 2004) and its regulation of the hypothalamic-pituitary-adrenocortical axis (Buchanan et al., 2004). Moreover, the hippocampus is capable of considerable structural reorganization (McEwen, 2007).

Abbreviations: PTSD, posttraumatic stress disorder; DSM-IV, Diagnostic and Statistical Manual IV; MRI, magnetic resonance imaging.

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doi:10.1016/j.pnpbp.2010.06.016

Bremner et al. (1995) reported the intriguing finding of volume reduction in the hippocampus in combat-related PTSD compared to controls, igniting intense interest in brain-imaging studies of patients with PTSD. Since then, several additional studies have reported volume reduction not only in combat-related PTSD, but also in adult PTSD associated with childhood sexual abuse and other forms of trauma (Bonne et al., 2008; Bossini et al., 2008; Bremner et al., 1997, 2003; Emdad et al., 2006; Gurvits et al., 1996; Hedges et al., 2003; Li et al., 2006; Lindauer et al., 2005; Shin et al., 2004; Villarreal et al., 2002; Vythilingam et al., 2005). In contrast, some researchers have not found hippocampal volume reduction in PTSD (Fennema-Notestine et al., 2002; Freeman et al., 2006; Golier et al., 2005; Jatzko et al., 2006; Pederson et al., 2004; Schuff et al., 2001; Yehuda et al., 2007). Further clarifying the relationship between PTSD and hippocampal volume are the results of three meta-analyses. In one meta-analysis, Kitayama et al. (2005) studied nine reports from 1995 to 2003 that included a total of 133 PTSD patients and concluded that both right and left hippocampal volumes were smaller in PTSD patients compared to controls. In a second meta-analysis, Smith (2005) evaluated 215 PTSD patients and 325 controls from 13 studies of hippocampal volume in adult PTSD and found smaller left and right hippocampal volumes in PTSD subjects compared to controls. Of particular relevance is Smith's observation that the differences in hippocampal volume were smaller when PTSD subjects were compared to trauma-exposed controls without PTSD than when compared to trauma-unexposed controls, although the two control groups did not significantly differ in hippocampal volume. More recently, Karl et al.'s (2006) meta-analysis of 15 studies comparing PTSD subjects to trauma-unexposed controls and 12 studies comparing PTSD subjects to trauma-exposed controls without PTSD found that 1) left and right hippocampal volumes were smaller in PTSD subjects compared to the trauma-unexposed controls and 2) the left hippocampus was smaller in the PTSD group compared to trauma-exposed controls without PTSD.

The selection and composition of patient and control groups in meta-analyses examining hippocampal volume in PTSD is important in that subjects having diagnoses in addition to PTSD associated with both PTSD (an exposure variable) and hippocampal volume (the outcome) may confound the association between PTSD and hippocampal volume (Hedges and Woon, 2007). In addition, some of the earlier meta-analytic studies included primary studies in which only a subset of the PTSD group had PTSD at the time of the study. Further, some meta-analyses contained primary studies in which PTSD was only of secondary interest and associated with another serious medical (e.g., cancer) or another DSM-IV Axis-II disorder (e.g., dissociative identity disorder) that could affect the association between hippocampal volume and PTSD (Dietrich et al., 2008; Sar and Ross, 2006).

Despite theoretical and clinical interest in the relation between PTSD and the hippocampus, the etiology and timing of the putative hippocampal volume deficits in PTSD remains unknown, although several causes have been proposed. First, trauma exposure or PTSD itself may be toxic to the hippocampus (Bremner, 1999), an effect possibly mediated by cortisol. Cortisol can alter hippocampal anatomy (Sapolsky, 2000), consistent with observations that hypercortisolemia reduces hippocampal volume reduction in human studies and animal models (McEwen, 2007). Of note, however, chronic PTSD is associated with low but not elevated cortisol concentrations (Yehuda, 2006) even though exposure to trauma is associated with elevations in cortisol concentration (Bremner, 2006).

A second hypothesis concerning the hippocampal volume deficits associated with PTSD suggests that a small premorbid hippocampus may be a risk factor for PTSD. Making a strong case for this hypothesis, Gilbertson et al. (2002) found that in identical twins discordant for combat exposure, PTSD twin pairs (combat-exposed twin with PTSD and combat-unexposed twin without PTSD) had smaller hippocampal volumes compared to non-PTSD twin pairs (combat-exposed twin without PTSD and combat-unexposed twin without PTSD), suggesting that a small hippocampus may predispose to PTSD after exposure to trauma. Similarly, Gurvits et al. (2006) found neurological soft signs in both twins with PTSD associated with combat exposure and their twins with no PTSD and no combat exposure, further implying that premorbid neurological dysfunction is a risk factor for PTSD after trauma exposure.

The availability of two distinct control groups consisting of either trauma-exposed subjects without PTSD and or trauma-unexposed subjects without PTSD could provide insight into the source of the hippocampal volume deficits associated with PTSD. If a history of trauma exposure without the presence of PTSD is associated with deficits in hippocampal volume, trauma exposure itself independent of PTSD could be a possible cause of hippocampal volume deficits, an observation that would provide indirect evidence supporting the hypothesis that at least part of the hippocampal volume deficits associated with PTSD may occur after trauma exposure. Further, a comparison of hippocampal volume between groups with PTSD and groups with a history of trauma exposure without PTSD could help determine whether PTSD affects hippocampal volume independent of trauma exposure alone.

Some primary studies included in previous meta-analyses have used a heterogeneous control group containing both trauma-unexposed subjects and trauma-exposed subjects without PTSD. The use of a heterogeneous PTSD patient or control group precludes conclusions as to whether trauma exposure alone, trauma exposure coupled with PTSD, or other nonspecific variables are associated with hippocampal volume deficits. Further, since the publication of earlier meta-analyses of hippocampal volume in PTSD, additional studies on the relationships between the hippocampal volume, PTSD, and trauma exposure without PTSD have been published. Given the uncertainty about the cause of the hippocampal volume deficits associated with PTSD and the availability of studies not yet subjected to meta-analysis, our aim in this study was to further investigate the relationship between PTSD, trauma exposure, and hippocampal volume by meta-analytically comparing 1) PTSD subjects to a trauma-unexposed group, 2) PTSD subjects to a trauma-exposed group without PTSD, and 3) a trauma-unexposed group to a trauma-exposed group without PTSD. Based on existing studies, we hypothesized that we would find a smaller hippocampus in PTSD subjects and trauma-exposed subjects without PTSD compared to trauma-unexposed subjects and that additional reduction in the hippocampal volume would be seen in the PTSD subjects compared to the trauma-exposed subjects without PTSD.

2. Methods

2.1. Search strategy and selection of studies

We included all published papers reporting adult hippocampal volume in PTSD and control groups assessed by MRI. Using the words and phrases *posttraumatic stress disorder*, *post-traumatic stress disorder*, *PTSD*, *brain imaging*, *neuroimaging*, *magnetic resonance imaging*, *amygdala*, *hippocampus*, *brain anatomy*, *brain structure*, *rape*, *crime*, *violence*, *trauma*, *abuse*, *interpersonal violence*, *assault*, *war*, *combat*, *accident*, and *disaster*, we searched computerized databases including the National Library of Medicine's PubMed, EMBASE, the Cochrane Library, the Journal Storage Archive, Dissertations and Theses (ProQuest), PsycINFO, the PILOTS database of the National Center for PTSD, and the Social Sciences Citation Index to obtain candidate studies through the last part of 2008 for inclusion. In addition, we searched the text and reference lists of all identified studies for additional, relevant articles. Because the neuroanatomy associated with PTSD appears to differ in children compared to adults (Hedges and Woon, 2007), we restricted our analysis to MRI studies of adults (age greater than or equal to 18 years, without upper age limit)

according to the following inclusion criteria: 1) studies in which all PTSD subjects in the source studies at the time of brain imaging were diagnosed according to the criteria in the Diagnostic and Statistical Manual-III-R (American Psychiatric Association, 1987), the Diagnostic and Statistical Manual-IV-TR (American Psychiatric Association, 2000), or the International Classification of Diseases-10 (World Health Organization, 2004) with one or more explicitly defined non-PTSD control groups, which could include either trauma-unexposed controls or trauma-exposed controls without PTSD, or both control groups, and 2) studies containing absolute hippocampal volume data including mean and standard deviation (or standard error of the mean).

Studies that included subjects with another serious medical (e.g., cancer) or a unique psychiatric disorders (dissociative identity disorder) were excluded. Because the primary aim was to compare hippocampal volumes in PTSD subjects to trauma-unexposed controls and trauma-exposed controls without PTSD, studies that contained a control group composed of both trauma-exposed controls and trauma-unexposed controls without PTSD were excluded. Further, in cases in which two studies contained data for the same, or part of the same, PTSD group, we excluded the study with the smaller number of subjects, unless the larger study resulted in significant study heterogeneity, in which case we included only the smaller study.

2.2. Analysis

Right, left, and total hippocampal volumes were compared between patients with PTSD and both types of control groups and between trauma-unexposed controls and trauma-exposed controls without PTSD when data from at least four source studies were available. In addition, we compared right and left hippocampal volumes within each group to determine any laterality effect on hippocampal volume.

For all meta-analysis calculations, we used Comprehensive Meta-Analysis 2.0 (Biostat, Englewood, New Jersey) based upon the random-effects model by Hedges and Olkin (1985), which calculates more conservative effect sizes than fixed-effects models by assuming that the source studies estimate different effects that are distributed according to a particular pattern. In the random-effects model, each source study is weighted according to its sample size (Hedges and Olkin, 1985).

Means, standard deviations, and sample sizes were used to calculate standardized differences between hippocampal volumes for PTSD subjects and controls in each study by dividing the difference in hippocampal volumes between two groups by the pooled standard deviation. To correct for sample size, the standardized difference was then multiplied by the J correction factor $[1-(3/4*(\text{degrees of freedom}-1)]$, where degrees of freedom is equal to the total number of subjects minus 2 (Hedges and Olkin, 1985). Overall effect sizes and corresponding 95% confidence intervals were then generated comparing PTSD subjects to trauma-unexposed controls and trauma-exposed controls without PTSD. In computing overall effect sizes, only one effect size per each source study was used (Rosenthal, 1979) to obtain a pooled effect size indicating the magnitude of association across studies (Hedges and Olkin, 1985). In this study, negative effect sizes indicated a smaller hippocampal volume in 1) PTSD subjects compared to controls or 2) trauma-exposed controls without PTSD compared to trauma-unexposed controls. In analyses of laterality differences in hippocampal volume within each group, negative effect sizes indicated a greater left than right hippocampal volume, and positive effect sizes indicated a greater right than left hippocampal volume. Mean effect sizes were considered significant ($p<.05$) if the 95% confidence interval did not include zero. According to Cohen (1988), effect sizes of .20, .50, and .80 indicate weak, moderate, and strong effects, respectively.

Study homogeneity was assessed using the chi-square test to generate Q values (Hunter et al., 1982; Whitehead, 2002). The null hypothesis for this test is that the source samples are homogenous and that it is appropriate to pool the effect sizes from the source studies. In contrast, a significant Q value ($p<.05$) indicates heterogeneity among source studies and precludes appropriate pooling. When the Q value was significant, we excluded outlying studies identified by a funnel-plot analysis and the between-studies variance test (I-squared test) (Higgins and Thompson, 2002) until the Q value became nonsignificant.

To estimate the extent to which unpublished null results could reduce the estimated effect sizes in cases in which overall differences in effect sizes were significant, we calculated the classic (Rosenthal, 1979) and Orwin's (1983) failsafe-N analyses to estimate the number of additional null studies needed to make the results nonsignificant (Rosenthal, 1979) and the number of studies with an effect size of zero required to move the initially calculated effect size to a smaller predetermined effect size (Orwin, 1983), respectively. In addition, we did a Trim-and-Fill calculation, a procedure that estimates a new effect size after adjusting for the numbers of missing studies and the most extreme positive, small study. A small difference between the initial and final effect sizes indicates a more accurate initial effect size (Duval and Tweedie, 2000).

3. Findings

We identified 39 articles published in English between 1995 and 2008 that potentially met inclusion criteria and contained right, left, and total hippocampal volumetric data in adults that had been formally assessed for PTSD. In cases in which it was not clear what type of control group was used, the primary author was contacted via e-mail to clarify the specific type of control groups used. One study (Bonne et al., 2001) reported right and left hippocampal volume data obtained at baseline and again six months later. In this case, we used only data from the six-month point. In one study reporting hippocampal volume data from both before and after psychotherapy (Lindauer et al., 2005), only pretreatment data were included. Woodward, Kaloupek, Streeter, Kimble et al. (2006) reported data from not only combat-exposed subjects and controls, but also categorized subjects according to a history of alcohol use; as such, we treated the results from this study as essentially two studies and calculated two effect sizes. We included the alcohol group because while alcohol appears to contribute to hippocampal volume deficits in PTSD, the results of a meta-analysis suggest that PTSD is associated with hippocampal volume deficits independent of alcoholism (Hedges and Woon, 2010a). Gilbertson et al. (2002) reported hippocampal volume data on identical twin discordant for combat exposure. Because the two combat-unexposed groups contained data from either subjects whose cotwins had PTSD (and who had hippocampal volume deficits themselves) or from twins whose cotwins did not have PTSD (and who had normal hippocampal volume themselves), the two combat-unexposed groups differed from each other. As such, we used only the combat-related PTSD group and the combat-exposed group without PTSD in our analysis.

Of the 14 nonoverlapping studies that met inclusion criteria for total hippocampal volume, 8 studies contained a trauma-exposed group without PTSD, and 10 contained a trauma-unexposed group (Table 1). Four studies used both a trauma-exposed group without PTSD and a trauma-unexposed group. Of the 24 studies reporting data for right hippocampal volumes, 14 studies used a trauma-exposed group without PTSD, 18 studies used a trauma-unexposed group, and 8 studies used both types of controls (Table 2). Twenty-three studies reported data for left hippocampal volumes, with 14 studies containing data for a trauma-exposed group without, 17 studies for a trauma-unexposed group, and 8 studies for both types of controls.

Table 1
Summary of studies containing total hippocampal volume data for subjects with PTSD, trauma-exposed controls without PTSD, and trauma-unexposed controls.

Study and year	Adults with PTSD			Trauma-exposed controls without PTSD			Trauma-unexposed controls		
	M/F	Mean ± SD		M/F	Mean ± SD		M/F	Mean ± SD	
		Age	Total volume		Age	Total volume		Age	Total volume
Bonne et al. (2008)	3/19	36 ± 10.4	3300 ± 460	–	–	–	3/19	35.8 ± 10.4	3640 ± 410
Emdad et al. (2006)	23/0	38.65 ± 6.23	5930 ± 790	–	–	–	17/0	37.88 ± 8.58	6530 ± 100
Fennema-Notestine et al. (2002)	0/11	33.5 ± 10.3	2929 ± 310	0/11	35.4 ± 9.6	2774 ± 440	0/17	35.3 ± 12.5	2954 ± 301
Gilbertson et al. (2002)[a]	12/0	NR[b]	6660 ± 830	23/0	51.8 ± 2.3	7410 ± 930	–	–	–
Hedges et al. (2003)	4/0	54.5 ± 6.02	2920 ± 435.6	–	–	–	4/0	54.3 ± 7.09	4242.5 ± 347.7
Jatzko et al. (2006)	13/2	48.2 ± 12.2	7300 ± 900	–	–	–	13/2	47.9 ± 12.9	7100 ± 700
Lindauer et al. (2004)[c]	8/6	35.4 ± 11.2	4210 ± 480	8/6	36.9 ± 10.1	4710 ± 500	–	–	
Lindauer et al. (2005)[c]	8/10	39.6 ± 9	4060 ± 520	8/6	36.9 ± 10.1	4710 ± 500	–	–	–
Pavic et al. (2007)	15/0	32 ± 5.44	8326 ± 1073	–	–	–	15/0	41 ± 5.37	9110 ± 1085
Pederson et al. (2004)	0/17	24.8 ± 5.2	5946 ± 637	0/17	26.8 ± 6.6	5903 ± 713	0/17	23.8 ± 5.6	6093 ± 616
Vythilingam et al. (2005)	8/6	35 ± 9	2832 ± 311	15/8	35 ± 7	2924 ± 371	9/20[d]	34 ± 10[c]	3230 ± 407[c]
Wignall et al. (2004)	9/6	43 ± 9	3041 ± 589	–	–	–	9/2	29 ± 10	3539 ± 646
Winter and Irle (2004)	15/0	42 ± 10	7150 ± 120	15/0	41 ± 11	7050 ± 800	15/0	41 ± 17	7900 ± 800
Woodward, Kaloupek, Streeter, Kimble, Reiss, Eliez et al. (2006)[e]	24[f]	NR[f]	8720 ± 880	20[f]	NR[f]	9510 ± 1100	–	–	–
Woodward, Kaloupek, Streeter, Kimble, Reiss, Eliez et al. (2006)[g]	27[f]	NR[f]	8970 ± 760	28[f]	NR[f]	9260 ± 1130	–	–	–

M = male; F = female.
[a] Data were extracted for combat-exposed veterans with PTSD and combat-exposed veterans without PTSD with a Clinician-Administered PTSD Scale (CAPS) score>65.
[b] Mean age for this subgroup of veterans with a Clinician-Administered PTSD Scale (CAPS) score>65 was not reported.
[c] Lindauer et al. (2005) was entered in the meta-analysis in lieu of Lindauer et al. (2004) when the former did not contribute to significant study heterogeneity.
[d] Data for "healthy civilians" were extracted.
[e] Data for alcoholic subgroup were extracted.
[f] Gender and mean age for this subgroup of veterans with or without alcoholism were not reported.
[g] Data for nonalcoholic subgroup were extracted.

Significant heterogeneity was found in left, right, and total hippocampal volumes in the analysis of the PTSD group compared to the trauma-unexposed group. After excluding two studies with the smallest samples of PTSD subjects (Gurvits et al., 1996; Hedges et al., 2003), however, heterogeneity was reduced to a nonsignificant level. Significant reductions in left ($g = -.499$, $p = .001$), right ($g = -.555$, $p = .001$), and total hippocampal ($g = -.622$, $p = .001$) volumes were found in the PTSD group compared to the trauma-unexposed group (Table 3). Further, large classic and Orwin's failsafe-N values ranging from 20 to 144 studies and a negligible decrease in Trim-and-Fill effect sizes lends support for the findings from all three meta-analyses (Table 3).

In the analysis of PTSD group compared to the trauma-exposed group without PTSD, significant heterogeneity existed in the left, right, and total hippocampal volumes. The funnel-plot analyses and *I*-squared test identified extreme effect sizes in the negative direction in the left hippocampus in two studies (Gurvits et al., 1996; Lindauer et al., 2005) and in total hippocampal volume in one study (Lindauer et al., 2005). Two studies (Fennema-Notestine et al., 2002; Golier et al., 2005) reported an extreme effect size in the positive direction in the right hippocampal volume. After excluding these outlying studies, significant reduction was found in right hippocampal volume ($g = -.483$, $p = .001$) in the PTSD group compared to the trauma-exposed group without PTSD (Table 3). The classic and Orwin's failsafe-N analyses were 41 and 14, respectively, indicating that the finding would be relatively unlikely to be overturned by unpublished null results. Left ($g = -.204$, $p = .145$) and total ($g = -.247$, $p = .133$) hippocampal volumes did not differ significantly between groups (Table 3). Further, a small reduction in Trim-and-Fill effect sizes from the initial effect sizes suggests that the findings are unlikely to be susceptible to bias (Table 3).

A significant reduction was found in the left ($g = -.403$; $p = .002$), right ($g = -.575$; $p = .001$), and total hippocampal ($g = -.642$; $p = .001$) volumes in the trauma-exposed group without PTSD compared with the trauma-unexposed group (Table 3). These analyses produced a range of 10 to 31 studies in the classic and Orwin's failsafe-N analyses with a minute shift in Trim-and-Fill effect sizes, suggesting little bias.

A significantly greater right than left hippocampal volume was found in the PTSD group ($g = .180$, $p = .013$) and the trauma-unexposed group ($g = .164$, $p = .039$), but not in the trauma-exposed group without PTSD ($g = .169$, $p = .143$, Table 4). Analyses of heterogeneity showed *I*-squared indices to be minimally dispersed with 0 to 19 failsafe-N analyses in all three meta-analyses. A negligible difference between the initial and final effect sizes, as calculated with the Trim-and-Fill procedure, indicates a rather accurate initial effect size.

4. Discussion

In this study, the results of a series of meta-analyses comparing hippocampal volumes among the PTSD group, trauma-exposed control group without PTSD, and trauma-unexposed control group contain several main findings. First, left, right, and total hippocampal volumes in PTSD subjects and in trauma-exposed controls without PTSD are reduced compared with trauma-unexposed controls, consistent with the findings reported by Karl et al. (2006), Smith (2005), and Kitayama et al. (2005). Further, similar to the findings of Smith and Karl et al. (2006), the finding of reduced hippocampal volume in trauma-exposed controls without PTSD compared to trauma-unexposed controls supports our hypothesis that trauma exposure itself, even in the absence of PTSD, may be associated with hippocampal volume deficits. A study of healthy monozygotic twins discordant for risk for anxiety found reduced left hippocampal volumes in high-risk twins, providing evidence for the effect of environmental stressors on hippocampal volume (de Geus et al., 2007) that is broadly consistent with our findings of reduced hippocampal volume in not only the PTSD group compared to trauma-unexposed controls, but also in the trauma-exposed controls without PTSD compared to trauma-unexposed controls.

While hippocampal volume deficits may be a risk factor for either trauma exposure or the development of PTSD after trauma exposure (Gilbertson et al., 2002), Sullivan et al. (2001) found in a study of monozygotic and dizygotic twins in combat that only 40% of the variance in hippocampal volume could be attributed to direct genetic

Table 2
Summary of studies containing right and left hippocampal volume data for subjects with PTSD, trauma-exposed controls without PTSD, and trauma-unexposed controls.

Study and year	Adults with PTSD				Trauma-exposed controls without PTSD				Trauma-unexposed controls			
	M/F	Mean ± SD			M/F	Mean ± SD			M/F	Mean ± SD		
		Age	Hippocampus			Age	Hippocampus			Age	Hippocampus	
			Right	Left			Right	Left			Right	Left
Bonne et al. (2001)[a]	3/7	36 ± 10.4	3980 ± 420	3930 ± 540	15/12	29.8 ± 10.1	3940 ± 330	3810 ± 540	–	–	–	–
Bossini et al. (2008)	13/21	38 ± 10.5	3089.9 ± 391.5	2884.6 ± 418.8	–	–	–	–	13/21	37.8 ± 10.7	3384.7 ± 396.3	3271.7 ± 351.9
Bremner et al. (1995)	26/0	46 ± 1.8	1184 ± 142	1186 ± 138	–	–	–	–	22/0	44.5 ± 7.3	1286 ± 175	1233 ± 163
Bremner et al. (1997)	12/5	40.1 ± 5.7	1062 ± 169	1050 ± 152	–	–	–	–	12/5	40.4 ± 7.3	1116 ± 190	1193 ± 142
Bremner et al. (2003)	0/10	35 ± 6	915 ± 179	1050 ± 152	0/12	32 ± 8	1101 ± 174	1150 ± 189	0/11	38 ± 7	1180 ± 213	1160 ± 205
Emdad et al. (2006)	23/0	38.7 ± 6.2	3060 ± 450	2870 ± 370	–	–	–	–	17/0	37.88 ± 8.5	3340 ± 500	3190 ± 560
Fennema-Notestine et al. (2002)	0/11	33.5 ± 10	1498 ± 158	1431 ± 192	0/11	35.4 ± 9.6	1346 ± 217	1428 ± 231	0/17	35.3 ± 12.5	1480 ± 206	1474 ± 153
Freeman et al. (2006)	10/0	79.6 ± 3.2	2746 ± 677.9	2640.7 ± 433.1	10/0	79.8 ± 2.8	2841.9 ± 273.5	2715.9 ± 296.9	6/0	80.8 ± 3.5	2955.1 ± 531.1	2866.4 ± 351.2
Gilbertson et al. (2002)[b]	12/0	NR[c]	3320 ± 590	3340 ± 460	23/0	51.8 ± 2.3	3760 ± 540	3650 ± 500	–	–	–	–
Golier et al. (2005)	5/9	70.5 ± 5.6	1890 ± 260	1780 ± 260	6/7	68.5 ± 7.3	1800 ± 220	1760 ± 240	13/7	71.4 ± 6.4	1890 ± 270	1780 ± 250
Gurvits et al. (1996)	7/0	44.4 ± 1.7	3200 ± 600	3200 ± 300	7/0	47.6 ± 2.9	4100 ± 400	4300 ± 300	8/0	38.1 ± 10	4600 ± 400	4400 ± 300
Hedges et al. (2003)	4/0	54.5 ± 6	1442.5 ± 254	1477.5 ± 175.9	–	–	–	–	4/0	54.3 ± 7.09	2197.5 ± 174.6	2045 ± 198.4
Jatzko et al. (2006)	13/2	48.2 ± 12	3700 ± 500	3700 ± 400	–	–	–	–	13/2	47.9 ± 12.9	3600 ± 400	3500 ± 400
Lindauer et al. (2004)[d]	8/6	35.4 ± 11.2	2180 ± 220	2030 ± 280	8/6	36.9 ± 10.1	2370 ± 300	2340 ± 200	–	–	–	–
Lindauer et al. (2005)[d]	8/10	39.6 ± 9	2050 ± 270	2010 ± 270	8/6	36.9 ± 10.1	2370 ± 300	2340 ± 200	–	–	–	–
Pavic et al. (2007)	15/0	32 ± 5.44	4070 ± 513	4390 ± 537	–	–	–	–	15/0	41 ± 5.37	4620 ± 623	4440 ± 562
Pederson et al. (2004)	0/17	24.8 ± 5.2	3071 ± 352	2874 ± 370	0/17	26.8 ± 6.6	3134 ± 375	2769 ± 413	0/17	23.8 ± 5.6	3137 ± 345	2956 ± 377
Schuff et al. (1997)	6/1	48 ± 2	3279 ± 336	–	–	–	–	–	NR	42.4 ± 6	3488 ± 251	–
Shin et al. (2004)	7/1	50.5 ± 10	3930 ± 430	3880 ± 490	8/0	43.5 ± 8.8	4380 ± 510	4210 ± 370	–	–	–	–
Villarreal et al. (2002)	10/2	43 ± 9.3	3010 ± 290	2950 ± 310	–	–	–	–	8/2	44 ± 11.4	3350 ± 370	3380 ± 490
Vythilingam et al. (2005)	8/6	35 ± 9	2726 ± 323	2938 ± 309	15/8	35 ± 7	2860 ± 377	2988 ± 392	9/20[e]	34 ± 10[e]	3185 ± 423[e]	3274 ± 413[e]
Wignall et al. (2004)	9/6	43 ± 9	1567 ± 278	1474 ± 325	–	–	–	–	9/2	29 ± 10	1835 ± 345	1703 ± 328
Winter and Irle (2004)	15/0	42 ± 10	3590 ± 690	3560 ± 550	15/0	41 ± 11	3560 ± 440	3490 ± 500	15/0	41 ± 17	4100 ± 450	3800 ± 390
Yehuda et al. (2007)	17/0	60.6 ± 7	4030 ± 329.85	3860 ± 329.85	16/0	65.1 ± 9.9	4090 ± 360	3790 ± 360	–	–	–	–

M = male; F = female.
NR = not reported.
[a] Data at six-month follow-up were extracted.
[b] Data were extracted for combat-exposed veterans with PTSD and combat-exposed veterans without PTSD with a Clinician-Administered PTSD Scale (CAPS) score > 65.
[c] Mean age for this subgroup of veterans with a Clinician-Administered PTSD Scale (CAPS) score > 65 was not reported.
[d] Lindauer et al. (2005) was entered in the meta-analysis in lieu of Lindauer et al. (2004) when the former did not contribute to significant study heterogeneity.
[e] Data for "healthy civilians" were extracted.

influences. In fact, neuroendocrinological investigations in animal studies have provided valuable insights into the effect of stress exposure on hippocampal structure. Specifically, stress-induced release of glucocorticoids can alter hippocampal microarchitecture and cell number (Alfarez et al., 2003; McEwen et al., 1993; Neylan et al., 2003; Sapolsky et al., 2000; Yehuda, 2001). Further, stress-induced excitotoxicity can reduce neurogenesis in the dentate gyrus of the hippocampus (Nagata et al., 2008) and increase neuronal death in the CA3 subregion of the hippocampus (Zhao et al., 2007). The findings that only 40% of the variance in hippocampal volume is directly due to genetic influences and that stress exposure in animals affects hippocampal structure are consistent with our results that trauma exposure alone in the absence of clinically recognizable PTSD is associated with hippocampal volume deficits. The findings that a small premorbid hippocampus may be a risk factor for PTSD (Gilbertson et al., 2002) and that environmental factors such as trauma exposure may affect hippocampal volume suggest that both genetic and environmental factors may ultimately interact to determine hippocampal volume.

We also found significant differences in hippocampal volume between PTSD subjects and trauma-exposed controls without PTSD in the right hippocampus but not in the left hippocampus or in total hippocampal volume. This difference in right hippocampal volume may be associated with PTSD itself and reflect an additional

Table 3
Meta-analysis of left, right, and total hippocampal volumes in a) adults with PTSD compared to trauma-unexposed controls, b) adults with PTSD compared to trauma-exposed controls without PTSD, and c) trauma-exposed controls without PTSD compared to trauma-unexposed controls.

Group	Laterality	*k*	*N*	*ES* (95% CI)	Classic failsafe N	Orwin's failsafe N	Trim-and-Fill ES (*k* trimmed)	χ^2	I^2	*p*
Adults with PTSD compared to trauma-unexposed controls	Left	15	504	−.499 (−.725, −.274)	103	24	−.412 (2)	22.071	36.569	.001*
	Right	16	518	−.555 (−.769, −.342)	144	29	−.521 (1)	21.681	30.816	.001*
	Total	9	305	−.622 (−.940, −.304)	57	20	−.622 (0)	15.113	47.067	.001*
Adults with PTSD compared to trauma-exposed controls without PTSD	Left	12	341	−.204 (−.480, .071)	0	0	−.204 (0)	18.008	38.915	.145
	Right	11	310	−.483 (−.780, −.185)	41	14	−.318 (2)	16.677	40.038	.001*
	Total	7	257	−.247 (−.570, .075)	0	3	−.247 (0)	10.155	40.917	.133
Trauma-exposed controls without PTSD compared to trauma-unexposed controls	Left	8	231	−.403 (−.659, −.146)	10	9	−.443 (1)	3.525	0	.002*
	Right	8	231	−.575 (−.859, −.290)	31	15	−.575 (0)	8.178	14.403	.001*
	Total	4	144	−.642 (−.973, −.310)	11	9	−.642 (0)	2.604	0	.001*

PTSD = posttraumatic stress disorder; *k* = number of studies; *N* = total number of subjects; *ES* = weighted effect size; CI = Confidence Interval; χ^2 = Homogeneity *Q* test; I^2 = *I*-squared test (between-group variance); * = alpha level < .05. Negative effect sizes indicate reduced hippocampal volume in the primary group of interest compared to the comparison group.

neuropathological process beyond that associated with trauma exposure without the occurrence of PTSD. The reduced right hippocampal volume in the PTSD sample compared with trauma-exposed controls without PTSD is consistent with a magnetic resonance spectroscopy study that found a decrease in the N-acetyl-L-aspartic acid/creatine ratio, which is thought to reflect neuronal density, in right-sided medial temporal structures in patients with combat-related PTSD compared to trauma-exposed controls without PTSD (Freeman et al., 1998). In contrast, in his meta-analyses Smith (2005) found reduced left and right hippocampal volumes and Karl et al. (2006) found a smaller left hippocampal volume in PTSD subjects compared to trauma-exposed controls without PTSD. The inconsistencies between their findings and ours may be due to several factors. First, Karl and colleagues found the difference in hippocampal volume only in studies that corrected for whole-brain volume and had used high spatial resolution, a finding that could mean that hippocampal volume differences between PTSD and trauma-exposed groups without PTSD may be more subtle than hippocampal volume differences between PTSD and trauma-unexposed groups (Hedges and Woon, 2007). Second, some of the differences between our findings and those of Smith and Karl and colleagues might be due to additional source studies were included in our study since the last published meta-analysis (Karl et al., 2006). We also included only primary studies in which all PTSD subjects were diagnosed with PTSD at the time the study was done and excluded studies that used a heterogeneous control group combining both trauma-exposed controls and trauma-unexposed controls within the same group. Nevertheless, in a broader sense, the findings of volume differences between PTSD subjects and trauma-exposed subjects without PTSD in our study and the previous meta-analyses raise the possibility that the development of PTSD entails pathophysiology beyond the effects of exposure to stress alone.

We also found significantly larger rightward hippocampal asymmetry in PTSD subjects and trauma-unexposed controls, but not in trauma-exposed controls without PTSD. Consistent with findings of hippocampal asymmetry are the results of a study of hippocampal volume in 3564 healthy participants, which reported significantly greater right than left hippocampal volume (Pedraza et al., 2004), similar to our findings of a larger right than left hippocampus in the PTSD and trauma-unexposed groups. The absence of asymmetry in our trauma-exposed subjects without PTSD suggests the possibility of a differential hippocampal response to trauma with the right hippocampal volume possible being more vulnerable to the effects of trauma than left hippocampal volume. The reason for the asymmetry in the PTSD group, however, is unclear, but it does indicate hippocampal volume differences between PTSD subjects and trauma-exposed subjects without PTSD. Language ability and localization and handedness could be factors possibly accounting for the asymmetry in the PTSD group, although lack of systematic data about handedness and language function in source studies precludes further meta-analytic investigation at this time.

Even though childhood exposure to trauma is not associated with hippocampal volume reduction in children, exposure to trauma in childhood eventually may affect adult hippocampal volume (Woon and Hedges, 2008). Similarly, early-life stress is associated with later abnormalities in hippocampal development in animal models (Andersen and Teicher, 2004). While exposure to trauma in adulthood was well documented in the source studies we used for the meta-analysis reported herein, there was less systematic documentation of the presence or absence of childhood trauma exposure in the subjects composing the source studies we used. As such, a limitation of our study is that we were unable to determine the contributions that any trauma exposure in childhood may have had on adult hippocampal volume. As may be the case with genetic predisposition and experience both contributing to hippocampal volume, there may be an interaction between exposure to trauma in childhood and subsequent exposure to trauma during adulthood on adult hippocampal volume, although we were unable to test this hypothesis in this study. Longitudinal or case–control studies evaluating trauma exposure in childhood, trauma exposure in adulthood, and hippocampal volume in adulthood are required to more fully elucidate any potential interaction between childhood trauma exposure and trauma exposure in adulthood on adult hippocampal volume. A second factor affecting the interpretation of our findings is our focus on the hippocampus, when, in fact, volume abnormalities in other brain regions such as the anterior cingulate (Woodward, Kaloupek, Streeter, Martinez et al., 2006), septum pellucidum, insular cortex, corpus callosum (Hedges and Woon,

Table 4
Meta-analysis of hippocampal lateralization in adults with PTSD, trauma-exposed controls without PTSD, and trauma-unexposed controls.

Group	*k*	*N*	*ES* (95% CI)	Classic failsafe N	Orwin's failsafe N	Trim-and-Fill ES (*k* trimmed)	χ^2	I^2	*p*
Adults with PTSD	25	368	.180 (.0038, .321)	5	0	.180 (0)	19.568	0	.013*
Trauma-exposed controls without PTSD	13	196	.169 (−.057, .396)	0	0	.169 (0)	15.818	24.139	.143
Trauma-unexposed controls	19	303	.164 (.008, .321)	19	0	.116 (3)	14.767	0	.039*

PTSD = posttraumatic stress disorder; *k* = number of studies; *N* = total number of subjects; *ES* = weighted effect size; CI = Confidence Interval; χ^2 = Homogeneity *Q* test; I^2 = *I*-squared test (between-group variance); * = alpha level < .05. Positive effect sizes indicate greater right than left hippocampal volume.

2007) and even in total brain volume (Hedges and Woon, 2010b) may exist. As such, the finding of reduced hippocampal volume in subjects with PTSD and exposure to trauma should be considered as only a part of other potential volumetric abnormalities associated with PTSD and perhaps trauma exposure without PTSD.

Several additional limitations may preclude generalization of the findings reported herein to all people exposed to trauma or who have PTSD. Because of our primary focus on the effects of trauma exposure even in the absence of PTSD, we did not examine other factors that may moderate the effects of trauma exposure and PTSD on hippocampal volume. Karl et al. (2006) found that a smaller hippocampal volume in PTSD was moderated by MRI methodology, age, PTSD severity, medication, and gender. Other possible moderating factors include age at the time of trauma exposure, length of trauma exposure (e.g., one-time or repetitive exposure), time since the onset of PTSD, handedness, comorbid disorders, types of trauma, and history of alcohol use (Hedges and Woon, 2007), all of which may be crucial in understanding the effects of trauma exposure on hippocampal volume. Nevertheless, compared to trauma-unexposed subjects, Bossini et al. (2008) found reduced hippocampal volumes in subjects with PTSD who did not have comorbidity, were exposed to a single traumatic event, and had no lifetime history of psychotropic medication use. Further, the results of a meta-analysis found that PTSD in the absence of alcoholism is associated with hippocampal volume deficits, although alcoholism in addition to PTSD was associated with greater hippocampal volume deficits (Hedges and Woon, 2010a). Our study was not designed to investigate the relationships between hippocampal subregions, trauma exposure, and PTSD, the importance of which is emphasized by the findings of selectively reduced posterior (Bonne et al., 2008), anterior, and total hippocampal volumes (Vythilingam et al., 2005). Hippocampal subregional distinctions provide the basis for more directed investigations of hippocampal volume in trauma exposure and PTSD with high-resolution MRI methods.

5. Conclusion

The results of this meta-analysis suggest that trauma exposure independent of PTSD is associated with hippocampal volume reduction compared to trauma-unexposed subjects. Further, PTSD subjects have a smaller right hippocampal volume compared to trauma-exposed controls without PTSD. We found a larger right than left hippocampal volume in the trauma-unexposed group and the PTSD group but not in the trauma-exposed group without PTSD. Trauma exposure even in the absence of PTSD may be associated with hippocampal volume deficits, although further hippocampal volume deficit was seen in PTSD.

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