CNS Spectrums (2017), **22**, 363–372. © Cambridge University Press 2016
doi:10.1017/S1092852916000833

ORIGINAL RESEARCH

Posttraumatic stress disorder symptom severity is associated with left hippocampal volume reduction: a meta-analytic study

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Objective. Many studies have reported hippocampal volume reductions associated with posttraumatic stress disorder (PTSD), while others have not. Here we provide an updated meta-analysis of such reductions associated with PTSD and evaluate the association between symptom severity and hippocampal volume.

Methods. A total of 37 studies met the criteria for inclusion in the meta-analysis. Mean effect sizes (Hedges' *g*) and 95% confidence intervals ($CI_{95\%}$) were computed for each study and then averaged to obtain an overall mean effect size across studies. Meta-regression was employed to examine the relationship between PTSD symptom severity and hippocampal volume.

Results. Results showed that PTSD is associated with significant bilateral reduction of the hippocampus (left hippocampus effect size = –0.400, $p < 0.001$, 5.24% reduction; right hippocampus effect size = –0.462, $p < 0.001$, 5.23% reduction). Symptom severity, as measured by the Clinician-Administered PTSD Scale (CAPS), was significantly associated with decreased left, but not right, hippocampal volume.

Conclusions. PTSD was associated with significant bilateral volume reduction of the hippocampus. Increased symptom severity was significantly associated with reduced left hippocampal volume. This finding is consistent with the hypothesis that PTSD is more neurotoxic to the left hippocampus than to the right. However, whether the association between PTSD and lower hippocampal volume reflects a consequence of or a predisposition to PTSD remains unclear. More prospective studies are needed in this area.

Received 28 June 2016; Accepted 26 October 2016; First published online 19 December 2016

Key words: Posttraumatic stress disorder, hippocampus, magnetic resonance imaging, meta-analysis, symptom severity.

Introduction

Posttraumatic stress disorder (PTSD) is a severe and debilitating mental illness that may develop after experiencing a traumatic event. The *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) defines a traumatic event as an experience that possesses the threat of death or serious injury to the self or others.[1] The event also induces feelings of intense fear, helplessness, or terror. Some events that frequently precede PTSD include physical assault, sexual assault, motor vehicle accidents, and combat experience.[2] PTSD is characterized by symptoms of increased arousal, intrusive reexperiencing, avoidant behaviors, and negative changes in mood and/or cognition.[1] The National Comorbidity Survey Replication (NCS-R) estimated lifetime prevalence of PTSD among U.S. adults to be 6.8%.[3] Current PTSD prevalence (within 12 months) was estimated at 3.5%.[4]

Improving technology has caused a surge of interest in studying the neuroanatomic correlates of PTSD using magnetic resonance imaging (MRI). One structure that has received substantial research is the hippocampus. It has been shown to play a role in learning, memory storage, and retrieval.[5–7] Furthermore, the hippocampus specifically facilitates emotional memory storage and recall.[8] As a result, it is likely a significant component involved in remembering traumatic memories and events. Moreover, PTSD has been linked to a variety of memory disturbances, such as an increased ability or an

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inability to recall aspects of a traumatic event. Meta-analytic studies of memory function in PTSD show impairments in both verbal[9,10] and visual memory.[9] These disruptions may result from hippocampal pathology.[11–14] Indeed, hippocampal volume has been shown to be inversely correlated with verbal memory in PTSD.[15–17] In a recent study, bilateral hippocampal volume reduction was significantly associated with overgeneralization of negative contexts in an associative learning paradigm,[18] which could be related to the triggering of intrusive "flashbacks" in this population. Moreover, the hippocampus and ventromedial prefrontal cortex (vmPFC) have been implicated in conditioned fear extinction,[19,20] which is abnormal in this population.[20]

It has been theorized that dysregulation of the hypothalamus–pituitary–adrenal (HPA) axis may contribute to hippocampal pathology.[14,21] For example, it has been proposed that changes in hippocampal structure and function might result from chronic exposure to corticosteroids and glutamate (stress-related chemicals).[22] Furthermore, decreased hippocampal volume might stem from a reduction in hippocampal activity following a traumatic event.[23] This decreased activity may result from, and further potentiate, diminished neuron density, reduced neuron branching, and the degeneration of neurons at synaptic terminals.[24] Additionally, PTSD is associated with decreased hippocampal *N*-acetylaspartate:creatine (NAA/Cr) ratios,[25–28] thought to reflect neuronal integrity. These findings suggest a link between responses to traumatic stress and structural changes in the hippocampus.

While many structural MRI studies have found smaller hippocampal volumes in participants with PTSD,[2,15,18,29–45] others have not.[27,46–59] However, previous meta-analyses on the neuroanatomic correlates of PTSD demonstrate that it is associated with reduced volume of the hippocampus bilaterally in adults.[60–66]

The severity of PTSD symptoms is often assessed using the Clinician-Administered Posttraumatic Stress Disorder Scale (CAPS),[67] which has three subscales: reexperiencing (CAPS-B), avoidance (CAPS-C), and hyperarousal (CAPS-D). Some data suggest that PTSD symptom severity may moderate the relationship between PTSD and reduced hippocampal volume.[62] For example, hippocampal volume has been found to vary inversely with intrusive reexperiencing[36,68] and total PTSD symptoms.[2,28,29,31,69,70] However, others found no such relationships.[15,27,29]

Meta-analysis provides a systematic quantitative method for integrating results across studies. This not only dramatically increases sample size (and therefore statistical power) but also allows the researcher to specify moderator variables that may help account for differences in results between studies. When assessing volumetric differences in brain structures between groups, the mean volumes and standard deviations for each group are used to compute an effect size (Cohen's *d*, for example), which is the difference between group means divided by the pooled standard deviation. Values of Cohen's *d* of 0.20 are considered small, 0.50 medium, and 0.80 large.[71] Here we provide an updated meta-analysis regarding hippocampal volume deficits in PTSD and evaluate the relationship between symptom severity and hippocampal volume by conducting a meta-regression with symptom severity (total CAPS score) as a continuous moderator variable.

Methods

Study selection

Searches for the terms "posttraumatic stress disorder," "stress," "hippocampus," "hippocampal volume," "MRI," and "magnetic resonance imaging" were entered into the PsycINFO, MEDLINE, and ProQuest databases. Cited reference searches (both forward and backward) for relevant articles were performed using the Web of Science. The reference sections of previous meta-analyses were also examined. From these results, 89 articles published between 1995 and 2016 were retrieved. To be included in the meta-analysis, studies must have (1) used human adults (minimum age $\geq$ 18 years) as participants, (2) a group diagnosed with PTSD, (3) a non-PTSD comparison group, (4) reported means and standard deviations for left and right hippocampal volumes separately, (5) not included participants from another study used in the meta-analysis, and (6) reported a mean CAPS score of 45 or greater (if the CAPS was employed). The last criterion was utilized because a psychometric study found that a total CAPS score of 45 represents a reasonable threshold for PTSD diagnosis.[72] From the initial group of studies, 37 studies met the inclusion criteria. Mean volumetric data from Wang and colleagues[57] were obtained from the corresponding author. One study[26] reported volume for the right hippocampus only. When studies reported volumes for both traumatized and nontraumatized control groups, data from the nontraumatized control group were utilized in the interest of sample homogeneity. If a study reported volumes separately for PTSD participants with and without comorbidities, volumes for the PTSD-only (no comorbidity) group were used.

Meta-analytic techniques

All meta-analyses were performed using Comprehensive Meta-Analysis version 2.2.064 (Biostat, Englewood, New Jersey), a commercially available software package designed for meta-analysis and meta-regression. Hippocampal mean volumes and standard deviations from each

https://doi.org/10.1017/S1092852916000833 Published online by Cambridge University Press

study were entered directly into the software, which then computed Cohen's *d*, which in this context is the mean difference between patient and control hippocampal volumes divided by the pooled within-group standard deviation. Cohen's *d* was then transformed to Hedges' *g* with correction for potential bias due to sample size.[73] Hedges' *g* and 95 percent confidence intervals ($CI_{95\%}$) were then computed for each study. A mean effect size across studies was then calculated, with each study weighted inversely according to its variance.[73] A random-effects model was used for all analyses. Meta-regression is conceptually similar to multiple regression, except that the study becomes the unit of analysis. The reader interested in further details regarding meta-analysis is referred to the work of Borenstein and colleagues,[73] Hedges and Olkin,[74] and Cooper and coworkers.[75]

Results

After the initial meta-analyses, two studies[34,35] were identified as outliers, as they had very large effect sizes, high standard errors, and small sample sizes. Therefore, they were excluded from further consideration. Demographic information from the remaining 35 studies is provided in Table 1. Mean hippocampal volumes are given in Table 2. Total *n* for the left hippocampus was 1354 (PTSD = 654, controls = 700) and 1368 for the right hippocampus (PTSD = 661, controls = 707). The results of the overall meta-analysis showed significant

TABLE 1. Demographic information for PTSD and control participants in studies that reported mean hippocampal volumes.

	PTSD group				Control group	
Study and year	M/F	Mean age	Total CAPS score	Diagnostic criteria	M/F	Mean age
Bonne *et al.*, 2001[46]	3/7	33.7	57.9	DSM–IV	15/12	29.8
Bossini *et al.*, 2008[29]	13/21	37.97	74.4	DSM–IV, SCID	13/21	37.82
Bremner *et al.*, 1995[15]	26/0	46	NR	DSM–III–R	22/0	44.5
Bremner *et al.*, 1997[30]	12/5	40.1	NR	DSM–III–R	12/5	42.4
Bremner *et al.*, 2003[31]	0/10	35	NR	SCID	0/7	38
Chalavi *et al.*, 2015[32]	0/16	40.75	NR	CAPS	0/28	41.75
Eckart *et al.*, 2012[47]	20/0	36.1	68.9	CAPS	11/0	30.2
Emdad *et al.*, 2006[33]	23/0	38.65	NR	CAPS	17/0	37.88
Fennema-Notestine *et al.*, 2002[48]	0/11	33.5	58	SCID, CAPS	0/17	35.3
Freeman *et al.*, 2006[49]	10/0	79.6	53.3	CAPS	6/0	80.8
Gilbertson *et al.*, 2002[50]	17/0	53.1	72.2	M–PTSD	17/0	53.1
Golier *et al.*, 2005[51]	5/9	70.5	73.1	CAPS	13/7	71.4
Hara *et al.*, 2008[52]	0/15	44.8	NR	SCID	0/15	44.9
Jatzko *et al.*, 2006[53]	13/2	48.2	59	DSM–IV	13/2	47.9
Landré *et al.*, 2010[54]	0/17	24.9	73.4	CAPS	0/17	24.7
Levy-Gigi *et al.*, 2014[18]	9/17	35.46	58.57	SCID	8/14	38
Lindauer *et al.*, 2004[36]	8/6	35.4	NR	SI–PTSD	8/6	36.9
Morey *et al.*, 2012[37]	79/20	38.4	NR	CA–S, DTS	86/16	37.5
Pavić *et al.*, 2007[38]	15/0	41	NR	ICD–10, DSM–IV	15/0	41
Pederson *et al.*, 2004[55]	0/17	24.8	53.7	CAPS	0/17	23.8
Schmahl *et al.*, 2009[39]	0/10	28.5	NR	SCID	0/25	32.84
Schuff *et al.*, 1997[26]	6/1	48	NR	SCID	7*	42.4
Schuff *et al.*, 2001[27]	18/0	51.2	63.1	CAPS	19/0	51.8
Shin *et al.*, 2004[40]	7/1	50.5	52.6	CAPS	8/0	43.5
Shu *et al.*, 2013[28]	2/9	36.3	84.9	DSM–IV	2/9	35.27
Starčević *et al.*, 2014[56]	49/0	46.47	NR	ICD–10	30/0	46.87
Starčević *et al.*, 2015[41]	25/0	47.08	NR	ICD–10	25/0	45.36
Villarreal *et al.*, 2002[2]	2/10	43	87	CAPS	0/13	44
Vythilingam *et al.*, 2005[42]	8/6	35	NR	SCID	9/20	34
Wang *et al.*, 2010[57]	17/0	41	61	SCID, CAPS	19/0	38
Weniger *et al.*, 2008[43]	0/10	32	NR	SCID	0/25	33
Wignall *et al.*, 2004[44]	9/6	43	55.33	CAPS	9/2	29
Winter & Irle, 2004[45]	15/0	42	NR	SCID	15/0	41
Yehuda *et al.*, 2007[58]	17/0	60.6	45.4	CAPS	16/0	65.1
Yehuda *et al.*, 2010[59]	8*	45.25	67.83	CAPS	12*	41.42

* Gender breakdown not reported. CAPS = Clinician-Administered PTSD Scale; DSM = *Diagnostic and Statistical Manual of Mental Disorders*; DTS = Davidson Trauma Scale; F = number of female participants; ICD = International Classification of Diseases; M = number of male participants; M–PTSD = Mississippi Scale for Combat-Related PTSD; NR = not reported; SCID = Structured Clinical Interview for DSM–IV; SI–PTSD = Structured Interview for Posttraumatic Stress Disorder.

https://doi.org/10.1017/S1092852916000833 Published online by Cambridge University Press

TABLE 2. Hippocampal means (*M*)/standard deviations (*SD*), and scanning parameters for studies included in the meta-analysis

	PTSD Group		Control group		MRI scanning parameters	
Study and year	L hippocampal volume, *M* (*SD*)	R hippocampal volume, *M* (*SD*)	L hippocampal volume, *M* (*SD*)	R hippocampal volume, *M* (*SD*)	Magnet strength	Slice width
Bonne *et al.*, 2001[46]	3910 mm^3 (430)	3950 mm^3 (420)	3800 mm^3 (490)	3840 mm^3 (420)	2.0 T	3.0 mm
Bossini *et al.*, 2008[29]	2884.6 mm^3 (418.8)	3089.9 mm^3 (391.5)	3271.7 mm^3 (351.9)	3384.7 mm^3 (396.3)	1.5 T	1.0 mm
Bremner *et al.*, 1995[15]	1186 mm^3 (138)	1184 mm^3 (142)	1233 mm^3 (163)	1286 mm^3 (175)	1.5 T	3.0 mm
Bremner *et al.*, 1997[30]	1050 mm^3 (152)	1062 mm^3 (169)	1193 mm^3 (142)	1116 mm^3 (190)	1.5 T	3.0 mm
Bremner *et al.*, 2003[31]	973 mm^3 (162)	915 mm^3 (179)	1160 mm^3 (205)	1180 mm^3 (213)	1.5 T	3.0 mm
Chalavi *et al.*, 2015[32]	2166 mm^3 (228)	2220 mm^3 (202)	2237 mm^3 (196)	2340 mm^3 (205)	3.0 T	1.0 mm
Eckart *et al.*, 2012[47]	1800 mm^3 (180)	1870 mm^3 (190)	1830 mm^3 (250)	1910 mm^3 (270)	3.0 T	1.0 mm
Emdad *et al.*, 2006[33]	2870 mm^3 (370)	3060 mm^3 (450)	3190 mm^3 (560)	3340 mm^3 (500)	1.5 T	5.0 mm
Fennema-Notestine *et al.*, 2002[48]	1431 voxels (192)	1498 voxels (158)	1474 voxels (153)	1480 voxels (206)	NR	1.2 mm
Freeman *et al.*, 2006[49]	2640.7 mm^3 (433.1)	2746 mm^3 (677.9)	2866.4 mm^3 (351.2)	2955.2 mm^3 (531.1)	1.5 T	3.0 mm
Gilbertson *et al.*, 2002[50]	3340 mm^3 (460)	3320 mm^3 (590)	3490 mm^3 (570)	3260 mm^3 (390)	1.5 T	3.0 mm
Golier *et al.*, 2005[51]	1780 mm^3 (260)	1890 mm^3 (260)	1780 mm^3 (250)	1890 mm^3 (270)	1.5 T	1.3 mm
Hara *et al.*, 2008[52]	2240 mm^3 (170)	2310 mm^3 (180)	2110 mm^3 (180)	2210 mm^3 (180)	1.5 T	1.5 mm
Jatzko *et al.*, 2006[53]	3700 mm^3 (400)	3700 mm^3 (500)	3500 mm^3 (400)	3600 mm^3 (400)	1.5 T	1.0 mm
Landré *et al.*, 2010[54]	3702 mm^3 (356)	3890 mm^3 (378)	3621 mm^3 (281)	3783 mm^3 (319)	1.5 T	NR
Levy-Gigi *et al.*, 2014[18]	4604.35 mm^3 (264.7)	4626.35 mm^3 (286.08)	4789.09 mm^3 (184.26)	4836.82 mm^3 (193.89)	3.0 T	1.0 mm
Lindauer *et al.*, 2004[36]	2030 mm^3 (280)	2180 mm^3 (220)	2340 mm^3 (220)	2370 mm^3 (300)	1.5 T	1.0 mm
Morey *et al.*, 2012[37]	4067 mm^3 (421)	4129 mm^3 (415)	4180 mm^3 (505)	4188 mm^3 (469)	3.0 T	1.0 mm
Pavić *et al.*, 2007[38]	4390 mm^3 (537)	4070 mm^3 (513)	4440 mm^3 (562)	4620 mm^3 (623)	2.0 T	1.1 mm
Pederson *et al.*, 2004[55]	2874 mm^3 (370)	3071 mm^3 (352)	2956 mm^3 (377)	3137 mm^3 (345)	1.5 T	1.0 mm
Schmahl *et al.*, 2009[39]	2870 mm^3 (470)	3012 mm^3 (488)	3084 mm^3 (393)	3224 mm^3 (410)	1.5 T	1.0 mm
Schuff *et al.*, 1997[26]	NR	3279 mm^3 (128)	NR	3488 mm^3 (95)	1.5 T	1.4 mm
Schuff *et al.*, 2001[27]	3240 mm^3 (417)	3460 mm^3 (424)	3292 mm^3 (399)	3364 mm^3 (384)	1.5 T	1.4 mm
Shin *et al.*, 2004[40]	3880 mm^3 (490)	3930 mm^3 (430)	4210 mm^3 (370)	4380 mm^3 (510)	1.5 T	1.0 mm
Shu *et al.*, 2013[28]	3331.69 mm^3 (273.36)	3250.80 mm^3 (195.81)	3566.93 mm^3 (215.95)	3399.52 mm^3 (209.77)	1.5 T	5.0 mm
Starčević *et al.*, 2014[56]	3562 mm^3 (712)	3570 mm^3 (.702)	3664 mm^3 (159)	3696 mm^3 (159)	3.0 T	1.2 mm
Starčević *et al.*, 2015[41]	3247 mm^3 (594)	3313 mm^3 (587)	3854 mm^3 (594)	3809 mm^3 (722)	3.0 T	1.2 mm
Villarreal *et al.*, 2002[2]	2950 mm^3 (310)	3010 mm^3 (290)	3380 mm^3 (490)	3350 mm^3 (370)	1.5 T	1.5 mm
Vythilingam *et al.*, 2005[42]	2938 mm^3 (309)	2726 mm^3 (323)	3274 mm^3 (413)	3185 mm^3 (423)	1.5 T	1.5 mm
Wang *et al.*, 2010[57]	4165 mm^3 (487)	4176 mm^3 (524)	4336 mm^3 (340)	4324 mm^3 (414)	4.0 T	2.0 mm
Weniger *et al.*, 2008[43]	2490 mm^3 (410)	2540 mm^3 (460)	2950 mm^3 (430)	3160 mm^3 (350)	1.5 T	1.3 mm
Wignall *et al.*, 2004[44]	1474 mm^3 (325)	1567 mm^3 (278)	1703 mm^3 (328)	1835 mm^3 (345)	1.5 T	1.0 mm
Winter & Irle, 2004[45]	3560 mm^3 (550)	3590 mm^3 (690)	3800 mm^3 (390)	4100 mm^3 (450)	1.5 T	1.3 mm
Yehuda *et al.*, 2007[58]	3860 mm^3 (80)	4030 mm^3 (80)	3790 mm^3 (90)	4090 mm^3 (90)	3.0 T	.82 mm
Yehuda *et al.*, 2010[59]	2086.42 mm^3 (351.56)	2129.08 mm^3 (370.23)	2235.75 mm^3 (231.17)	2179.75 mm^3 (192.96)	3.0 T	.82 mm

Volumes not originally reported in mm^3 have been converted to mm^3 for ease of comparison, with the exception of one study[48] for which this was not possible, as voxel dimensions were not reported. mm = millimeter; mm^3 = cubic millimeter; NR = not reported; T = tesla.

volumetric reductions for both the left (g = -0.400; $CI_{95\%}$ = [-0.563, -0.237]; $p < 0.001$; see Figure 1) and right (g = -0.462; $CI_{95\%}$ = [-0.621, -0.302]; $p < 0.001$; see Figure 2) hippocampi in participants with PTSD compared to non-PTSD controls. These results correspond to a volumetric reduction of 5.24% for the left hippocampus and 5.23% for the right hippocampus. Secondary meta-analyses conducted only on those studies that reported CAPS scores again showed significant, but smaller, reductions in both the left (g = -0.307; $CI_{95\%}$ = [-0.546, -0.069]; p = 0.012) and right hippocampus (g = -0.243; $CI_{95\%}$ =[-0.465, -0.022]; p = 0.031). These results correspond to a volumetric reduction of 4.02% for the left hippocampus and 2.55% for the right hippocampus. However, only 19 studies reported CAPS scores (see Table 1). The meta-regression of CAPS scores on Hedges' g for the left hippocampus (slope = -0.024; intercept = 1.20; Z = -2.92, $p < 0.004$; see Figure 3) was significant, but the meta-regression for the right hippocampus (slope = -0.010; intercept = 0.38; Z = -1.26, $p < 0.21$; see Figure 4) was not. In other words, increased symptom severity was significantly associated with decreased volume of the left, but not the right, hippocampus.

Discussion

This meta-analytic study produced two main findings. First, PTSD in adults was associated with significant

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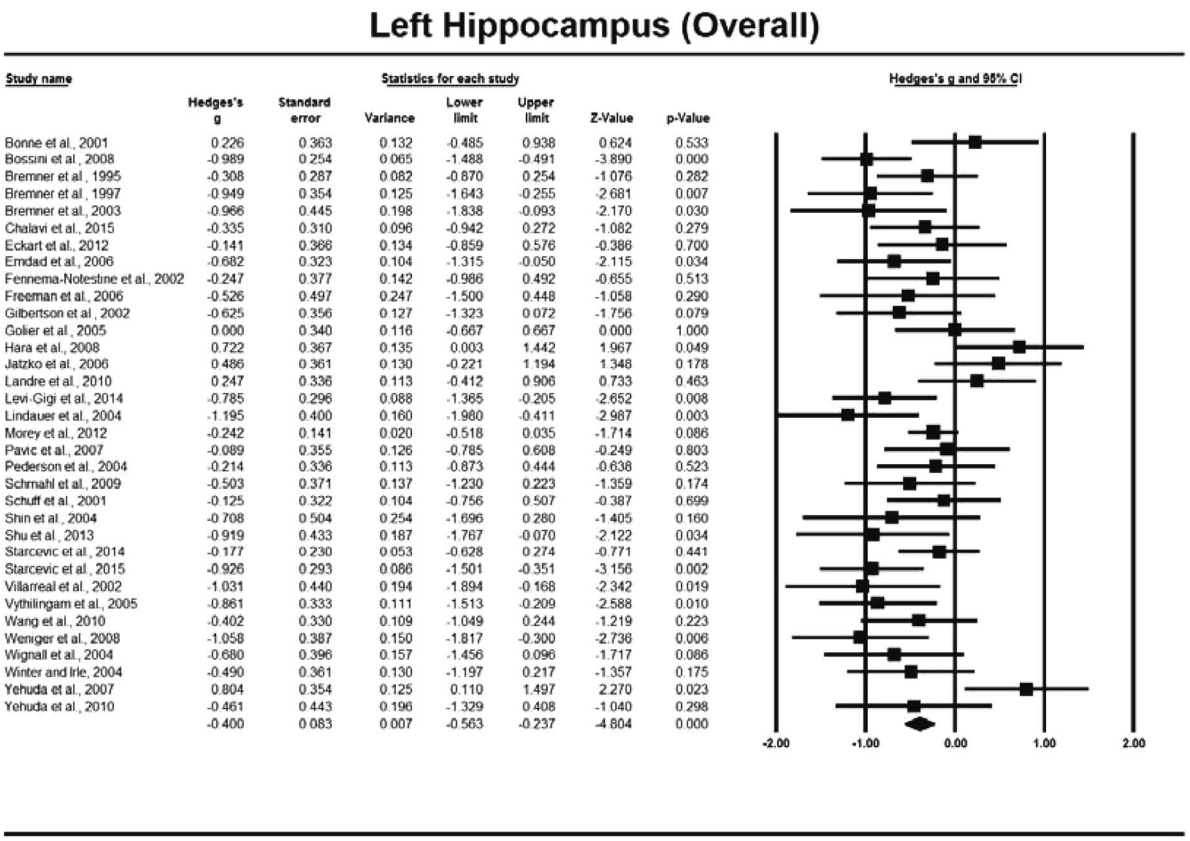

FIGURE 1. Forest plot showing overall left hippocampal volume effect sizes (Hedges' *g*) and 95% confidence intervals (*CI 95%*) for comparisons of PTSD and control groups. Negative effect sizes (Hedges' *g*) indicate smaller hippocampal volume in the PTSD participant group. Square size indicates relative study weight in the meta-analysis. Mean effect size and confidence interval across studies are indicated by the solid diamond.

bilateral volumetric reduction of the hippocampus, as has been reported in previous meta-analyses.[60–66] Second, increased PTSD symptom severity was associated with decreased left hippocampal volume. No association was found between symptom severity and right hippocampal volume. This conclusion, however, must be viewed with caution, as studies that reported CAPS scores had lower mean effect sizes than those in the overall meta-analysis. Therefore, the relationship between symptom severity and right hippocampal volume may have been underestimated.

Because of the cross-sectional nature of the studies reviewed here, the observed volume differences in the overall meta-analysis could either indicate that PTSD produces hippocampal volume deficits or that they are a predisposing factor. A recent model of PTSD suggests that a hyperresponsive amygdala and dorsal anterior cingulate cortex (dACC) are predisposing factors to the development of the disorder, while reduced hippocampal connectivity with the vmPFC is a consequence of it.[69] Additional research demonstrates that current, but not lifetime, PTSD symptomatology predicts hippocampal volume deficits.[70] If smaller hippocampal volume were a predisposing factor to PTSD, one would expect that both current and lifetime symptom severity would be associated with volumetric deficits.[70] Furthermore, in an 18-month prospective study of Israeli Defense Force soldiers pre- and postcombat, increased PTSD symptomatology postcombat was associated with reduced hippocampal volume.[76] Additionally, in a study of veterans with brain lesions, the vmPFC and amygdala were found to be critical in the etiology of PTSD, while the hippocampus was not.[77] These findings suggest that the hippocampal volume changes observed in PTSD are a result of the disease rather than its cause. However, a study of monozygotic twins (one with and one without PTSD) found that PTSD symptom severity in the affected twin was inversely associated with hippocampal volume in both PTSD and non-PTSD twins.[50] This suggests that reduced hippocampal volume constitutes a predisposition to PTSD.[50] A more recent study also suggested that left hippocampal volume reduction is a risk factor for the persistence of PTSD.[78] Clearly, more prospective studies are necessary to determine the reasons for these hippocampal volume differences.

The finding that left hippocampal volume was significantly and inversely associated with symptom severity is consistent with the results of several previous

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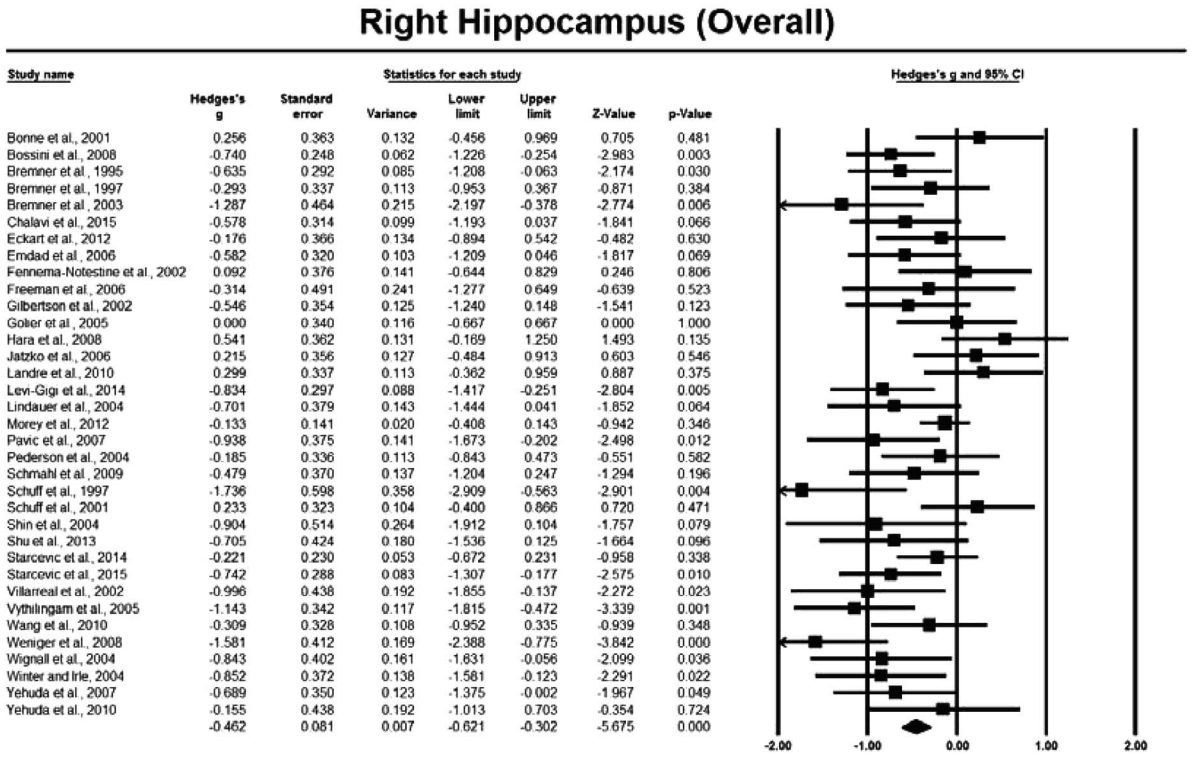

FIGURE 2. Forest plot showing overall right hippocampal volume effect sizes (Hedges' *g*) and 95% confidence intervals ($CI_{95\%}$) for comparisons of PTSD and control groups. Negative effect sizes (Hedges' *g*) indicate smaller hippocampal volume in the PTSD participant group. Square size indicates relative study weight in the meta-analysis. Mean effect size and confidence interval across studies is indicated by the solid diamond.

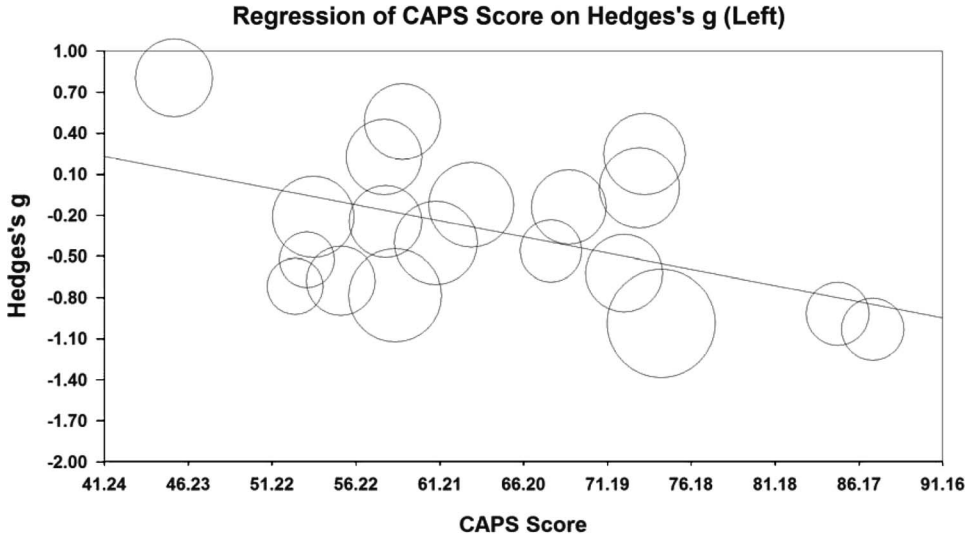

FIGURE 3. Meta-regression of participants' CAPS scores on Hedges' *g* for the left hippocampus. Circle size indicates relative study weight in the meta-regression. Slope = –0.024; intercept = 1.20; $Z = -2.92$, $p < 0.004$.

studies. For example, total CAPS score and CAPS-B score significantly predicted left hippocampal volume deficits in a civilian PTSD sample, while time since trauma, illness duration, and age did not.[2] Another study also found a significant correlation between CAPS total and CAPS-C score and left, but not right, hippocampal volume.[28] Additionally, CAPS-B score was inversely correlated with left hippocampal volume in a sample of Dutch police officers.[36,68] Furthermore, in a study of survivors of a Chinese coal-mining disaster using both voxel-based morphometry (VBM) and region of interest (ROI) approaches, reduced gray matter volume in the left

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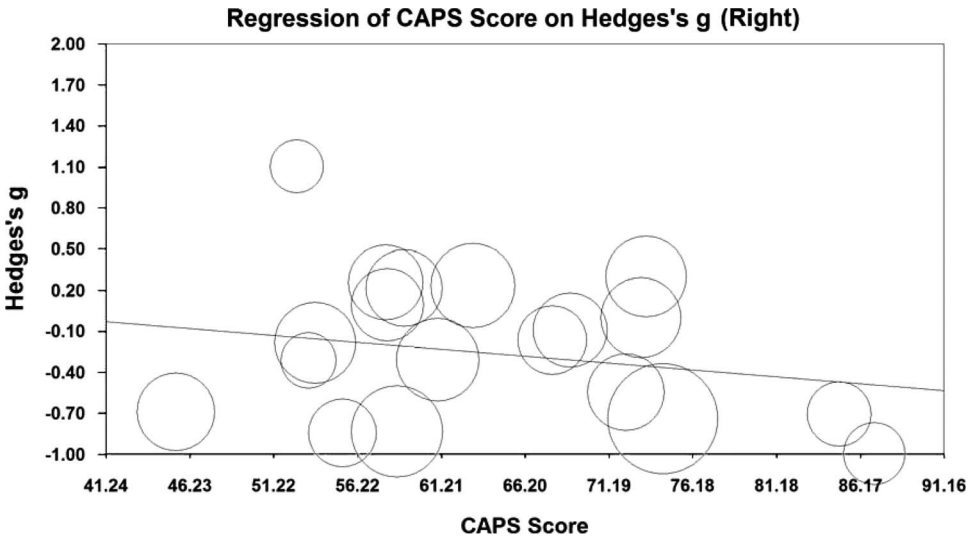

FIGURE 4. Meta-regression of participants' CAPS scores on Hedges' *g* for the right hippocampus. Circle size indicates relative study weight in the meta-regression. Slope = –0.010; intercept = 0.38; $Z = -1.26$, $p < 0.21$.

hippocampus and left parahippocampal gyrus were observed.[79] There was also reduced gray matter density in the left hippocampus. While there was no correlation between left hippocampal volume and total CAPS score, a significant inverse correlation ($r = -0.49$) was found between left hippocampal gray matter density and total CAPS score.[79] These findings suggest that increased PTSD symptom severity may be associated with hippocampal pathology in ways that are not always observable using traditional volumetric MRI techniques. Similarly, in a study of civilians with recent-onset PTSD, significant inverse correlations were found between left hippocampus NAA/Cr ratio and total CAPS ($r = -0.939$), CAPS-B ($r = -0.829$), CAPS-C ($r = -0.743$), and CAPS-D ($r = -0.635$) scores.[28] No such relationships between NAA/Cr ratio and symptom severity were observed for the right hippocampus.[28] However, other studies examining the effects of PTSD on the hippocampus have not found any effects of symptom severity on hippocampal volume.[15,27,29] Taken together with the current results, these findings suggest that PTSD damages the left hippocampus more than the right hippocampus and that this relationship may manifest itself in additional ways other than those observable with MRI volumetry.

Study limitations

There are several factors that limited this study. Not all studies investigating hippocampal volume reduction in PTSD reported mean CAPS scores, and those that did had smaller effect sizes than those that did not. This may have led to the underestimation of the relationship between symptom severity and hippocampal volume, especially for the right hippocampus. Furthermore, we were unable to account for some potentially important moderator variables, such as illness duration (only seven studies in this sample reported illness duration), psychiatric comorbidity (which is high in this population), MRI scanning parameters, and substance abuse, all of which may affect reported hippocampal volume. There was also substantial variance in the anatomical boundaries used to delineate the hippocampus. This variance may at least partially explain the wide range in hippocampal volumes reported in the studies included in this meta-analysis. Finally, as the majority of studies examined were cross-sectional designs, rather than longitudinal, we cannot unequivocally state whether or not the observed differences in hippocampal volume were consequences of the disorder or predisposing factors.

Conclusions

In conclusion, the studies reviewed in this meta-analysis indicate that PTSD is associated with moderate bilateral volumetric reduction of the hippocampal formation in adults. Increased symptom severity appears to be associated with reduced left, but not right, hippocampal volume in this group of studies. More prospective studies are needed to clarify the etiology of the differences in hippocampal volume associated with PTSD.

Acknowledgments

The authors wish to thank Anna Marie Medina, PhD, and Gary L. Thorne, PhD, for helpful comments concerning this manuscript, and Norbert Schuff, PhD, for providing hippocampal volumes not included in a published article.

Disclosures

Michael Nelson and Alecia Tumpap hereby state that they have no conflicts of interest to disclose.

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