Hippocampal Volumes in Patients With Chronic Combat-Related Posttraumatic Stress Disorder: A Systematic Review

Jason E. Childress, B.S.
Emily J. McDowell, B.A.
Venkata Vijaya K. Dalai, M.B.B.S.
Saivivek R. Bogale, B.A.
Chethan Ramamurthy, B.A.
Ali Jawaid, M.B.B.S.
Mark E. Kunik, M.D., M.P.H.
Salah U. Qureshi, M.D.
Paul E. Schulz, M.D.

The authors and others have recently demonstrated that veterans with chronic combat-related PTSD (CR-PTSD) have a twofold increased risk of dementia. To understand this increased incidence, they performed a systematic review of the literature on neuroanatomical differences between veterans with chronic CR-PTSD and control subjects (22 included studies). The hippocampus was most commonly and consistently reported to differ between groups, thereby suggesting the hypothesis that PTSD is associated with smaller hippocampi, which increases the risk for dementia. However, an alternate hypothesis is that smaller hippocampal volumes are a preexisting risk factor for PTSD and dementia. Studies are clearly needed to differentiate between these important possibilities.

(The Journal of Neuropsychiatry and Clinical Neurosciences 2013; 25:12–25)

Posttraumatic stress disorder (PTSD) is a psychiatric illness that affects individuals exposed to a life-threatening event or trauma.[1] The lifetime prevalence of PTSD is approximately 6.8% in the general United States population,[2] but has been estimated to be 19% in Vietnam veterans, with 9% suffering from PTSD symptoms more than 10 years post-war experience.[3] Similarly, PTSD rates in soldiers returning from the Iraq and Afghanistan conflicts have been estimated at 22%.[4] PTSD is associated with a great deal of suffering from psychiatric and physical comorbidities,[5] and it is likely to become an extremely pressing public health concern as more soldiers return from continuing operations.

Received January 5, 2012; revised April 4, 2012; accepted April 16, 2012. From the Dept. of Neurology, University of Texas Health Science Center at Houston, Houston, TX; Baylor College of Medicine, Houston, TX; University Hospital Zurich, Institute of Neuropathology, Zurich, Switzerland; Houston HSR&D Center of Excellence, Michael E. DeBakey VA Medical Center, Houston, TX; VA South Central Mental Illness Research, Education and Clinical Center; and Mischer Neuroscience Institute and Memorial Hermann Hospital, Houston, TX. Send correspondence to Paul E. Schulz, M.D. (Paul.E.Schulz@uth.tmc.edu)

In addition to the three core PTSD symptom clusters (intrusive recollections, avoidant/numbing symptoms, and hyper-arousal symptoms[1]), investigators have shown that 1) PTSD results in neurocognitive deficits;[6–10] and 2) PTSD symptom severity is positively associated with degree of cognitive impairment.[11] Also, a meta-analysis revealed that verbal memory deficits are the most consistent cognitive impairment in PTSD patients,[12] just as memory impairment is the first notable symptom in Alzheimer disease (AD) patients.[13]

These observations led us to examine the prevalence of dementia in veterans with chronic combat-related PTSD (CR-PTSD). In that study,[14] we examined a large veteran cohort of patients with PTSD but no Purple Heart (PTSD+/PH−, N=3,660); those without PTSD but with a Purple Heart (PTSD−/PH+, N=1,503); those with PTSD and a Purple Heart (PTSD+/PH+, N=153); and those without PTSD or a Purple Heart (PTSD−/PH−, N=5,165). The incidence of dementia during the 9-year follow-up period was 2.2-fold higher ($p<0.001$) in the PTSD+/PH− group than the PTSD−/PH− group and 1.7-fold higher ($p<0.001$) than the PTSD−/PH+ group even after accounting for age, sex, race, number of primary care visits, and multiple comorbid illnesses (diabetes mellitus, dyslipidemia, hypertension, coronary artery disease, stroke, traumatic brain injury, alcohol abuse and dependence, and drug abuse and dependence). Notably, a second study also found a similar twofold increased risk of dementia in PTSD veterans as compared with veterans without PTSD.[15] The reasons for this association were unclear. We wondered whether neuroanatomical changes associated with PTSD might put these veterans at greater risk for dementia.

We found no systematic reviews of structural neuroanatomy in veterans with chronic CR-PTSD. Although past reviews of imaging in PTSD have been published,[16,17] none have focused on how these brain features may relate to the PTSD/dementia association, and each has combined veteran and civilian populations in their analyses. To understand our clinical finding of an elevated prevalence of dementia, we have performed a systematic review of volumetric neuroanatomy in veterans with chronic CR-PTSD.

METHODS

We used the PubMed database to search for the term PTSD in combination with any of the following terms: physical changes, neuroanatomical, frontal, parietal, temporal, hippocampal, cortical, prefrontal, amygdala, and locus coeruleus. The literature search extended to 08/11/2011 (range: earliest returned article, 1966 – latest returned article, 2011), and the articles produced for each of the above search combinations were merged to form a catalog of 1,084 articles. This initial query was filtered by including only human adult (age 19+ years) studies published in English (488 articles).

The resulting collection of articles was then reviewed for focus, demographics, and duration of PTSD by researcher personnel (JC). Each study had to 1) be an original study; 2) investigate structural neuroanatomy; 3) use veterans with chronic CR-PTSD, defined as PTSD of ≥6 months' duration resulting from trauma in combat; and 4) compare the veteran group with a control group. This process produced 22 articles[18–39] that covered 21 cross-sectional studies[18–38] and one longitudinal study.[39] The bibliographies of these 22 articles were searched to identify relevant studies not captured by our search net, but none were identified (Figure 1).

Review Process

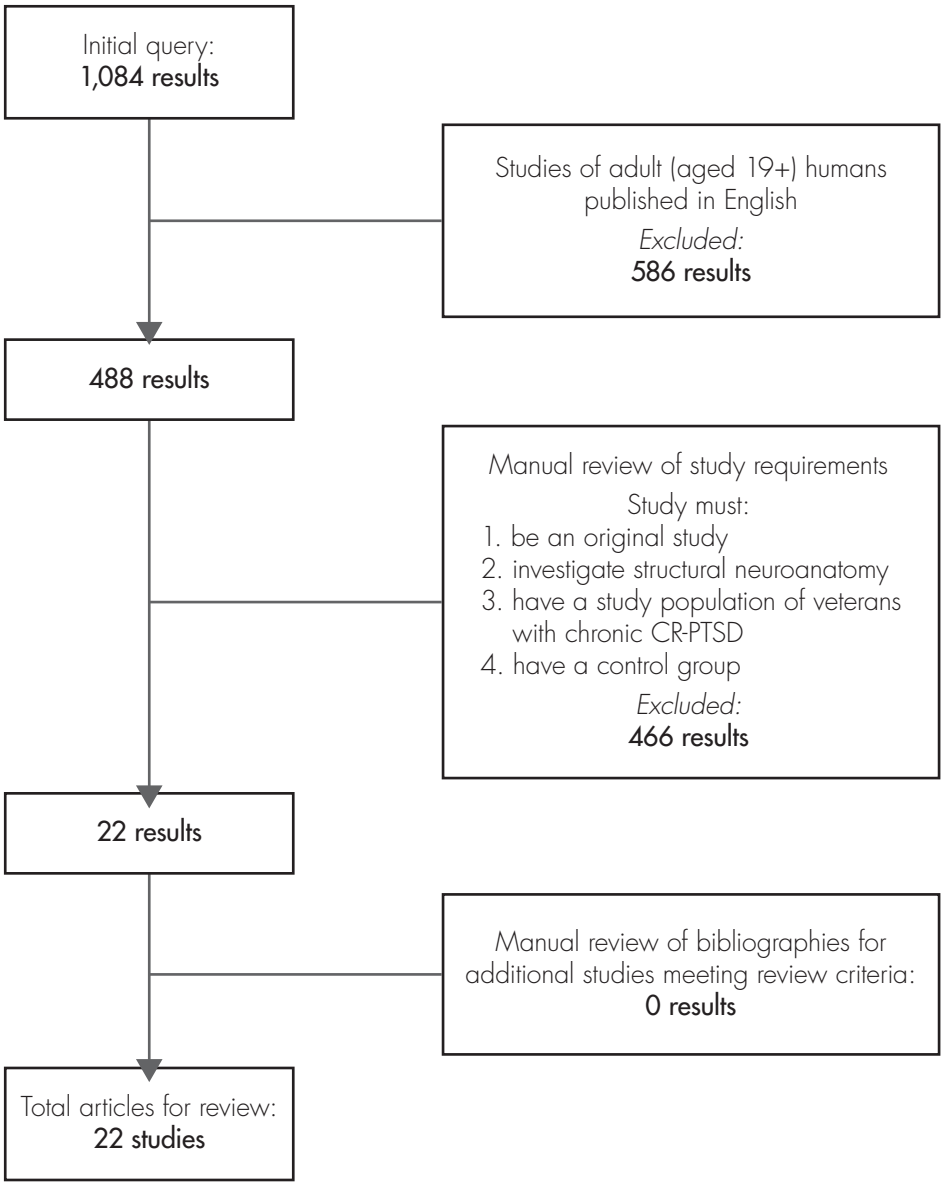
Two authors (EM, JC) independently rated the quality of the selected 22 articles, using a scale developed for this study. The scale assigned each paper a score between 0 and 4, giving 1 point each for 1) having 10+ participants in the CR-PTSD group, based on guidelines for meta-analyses on imaging literature;[40] 2) using a valid PTSD diagnostic tool (e.g., the Clinician-Administered PTSD Scale [CAPS], Mississippi Scale for Combat-Related PTSD); 3) using a combat-exposed control group without PTSD; and 4) accounting for substance abuse, given its prevalence in PTSD and association with brain atrophy.[41] In our opinion, higher-quality scores represent a stronger methodology for the purposes of this review.

Results were generated by abstracting all data related to structural neuroanatomy associated with PTSD. Specifically, we examined all statistical analyses that compared neuroanatomical volumes between chronic CR-PTSD veterans and a control group. For a finding to be considered positive, the reporting study had to demonstrate a significance level of ≤0.05.

RESULTS

Of the 1,084 articles initially reviewed, 22 studies[18–39] were found to meet all of our inclusion criteria and were

FIGURE 1. Flow Chart of Study Identification Process



assigned a quality score (QS). These resulting articles were all magnetic resonance imaging (MRI) studies. All significant results were then sorted by QS and included in the attached tables. See Table 1 for a list of brain regions and QS differences between positive and negative studies. Table 2, Table 3, Table 4, and Table 5 include the significant results pertaining to specific brain anatomical regions.

Hippocampal Differences (see Table 2)

One of our main areas of interest in this review was the hippocampus, because of its strong association with dementia.[42–44] Of the 12 cross-sectional studies examining the hippocampus in veterans with chronic CR-PTSD, 9 found a significantly smaller volume in either or both hippocampi,[18,21–23,25,30,33,34,36] and 3 found no significant volume differences.[24,29,32] Studies that found a smaller total or right hippocampus were more numerous and of higher quality than those that did not (see Table 1). The positive studies were generally of greater size than the negative studies (average for positive findings: N=53.7; average for negative findings: N=15.7), and eight of the nine controlled for alcohol abuse. Two of the three

TABLE 1. Quantity and Quality of Cross-Sectional Anatomical Findings by Brain Area

Brain Area	(N) Positive Studies[a] (p≤0.05)	(+) Total QS	(+) Mean QS	(N) Negative Studies (p>0.05)	(−) Total QS	(−) Mean QS
Hippocampus	(9) Bremner et al;[18] Gilbertson et al;[9] Gurvits et al;[22] Hedges et al;[23] Kasai et al;[25] Pavić et al;[30] Vythilingam et al;[33] Wang et al;[34] Woodward et al[36]	30	3.33	(3) Hedges et al;[24] Neylan et al;[29] Schuff et al[32]	6	2.00
Mean/total hippocampus	(6) Gilbertson et al;[9] Gurvits et al;[22] Hedges et al;[23] Vythilingam et al;[33] Wang et al;[34] Woodward et al[36]	20	3.33	(4) Bremner et al;[18] Hedges et al;[24] Neylan et al;[29] Pavić et al[30]	12	3.00
L hippocampus	(3) Gurvits et al;[22] Hedges et al;[23] Vythilingam et al[33]	9	3.00	(6) Bremner et al;[18] Gilbertson et al;[9] Hedges et al;[24] Kasai et al;[25] Neylan et al;[29] Pavić et al[30]	20	3.33
R hippocampus	(6) Bremner et al;[18] Gilbertson et al;[9] Hedges et al;[23] Kasai et al;[25] Pavić et al;[30] Vythilingam et al[33]	20	3.33	(4) Gurvits et al;[22] Hedges et al;[24] Neylan et al;[29] Schuff et al[32]	9	2.25
Frontal lobe cortex	(2) Geuze et al;[20] Woodward et al[38]	7	3.50	(1) Hedges et al[24]	2	2.00
Temporal lobe cortex	(2) Geuze et al;[20] Woodward et al[38]	7	3.50	(3) Bremner et al;[18] Hedges et al;[24] Vythilingam et al[33]	9	3.00
Parietal lobe cortex	(0)	NA	NA	(1) Woodward et al[38]	4	4.00
Occipital lobe cortex	(0)	NA	NA	(1) Woodward et al[38]	4	4.00
Paralimbic cortex	(3) Kasai et al;[25] Woodward et al;[35] Woodward et al[38]	12	4.00	(1) Hedges et al[24]	2	2.00
ACC	(3) Kasai et al;[25] Woodward et al;[35] Woodward et al[38]	12	4.00	(0)	NA	NA
Non-ACC	(2) Kasai et al;[25] Woodward et al[38]	8	4.00	(1) Hedges et al[24]	2	2.00
Amygdala	(1) Pavliša et al[31]	3	3.00	(3) Gilbertson et al;[9] Gurvits et al;[22] Hedges et al[24]	9	3.00
Cerebellum	(1) Levitt et al[26]	4	4.00	(0)	NA	NA
White matter	(2) Canive et al;[19] Hedges et al[24]	4	2.00	(1) Hedges et al[23]	2	2.00
Septum pellucidum	(2) May et al;[27] Myslobodsky et al[28]	6	3.00	(0)	NA	NA

QS: quality score; ACC: anterior cingulate cortex; NA: not applicable.
The longitudinal study by Cardenas et al.[39] is not included.
[a]Positive studies have at least one significant finding in a subfield of the brain area; negative studies have no such findings.

TABLE 2. Hippocampal Differences Between Posttraumatic Stress Disorder (PTSD) Cohorts and Control Subjects

QS	Study	WBA or ROI β (T) / Slice Thickness (mm)	Subject Groups	Description	N M/F	Mean Age (SD)	Brain Area(s)	Main Findings
4	Gilbertson et al[21]	ROI 1.5 T / 1.5 mm	Cohort PTSD+ veterans	Vietnam veterans with severe combat-related PTSD (CAPS >65)	12 12/0	53.1 (3.3)	Total hippocampus	↓ volume in PTSD+ twin pair vs. PTSD− twin pair (p=0.004); volume difference within twin pairs: NS
			Control 1 Twins of PTSD+	Twin siblings of PTSD+ veterans	12 12/0	53.1 (3.3)		
			Control 2 PTSD− veterans	Vietnam combat veterans without PTSD	23 23/0	51.8 (2.3)	R hippocampus	↓ volume in PTSD+ twin pair vs. PTSD− twin pair (p=0.003); volume difference within twin pairs: NS
			Control 3 Twins of PTSD−	Twin siblings of PTSD− veterans	23 23/0	51.8 (2.3)		
4	Vythilingam et al[33]	ROI 1.5 T / 1.5 mm	Cohort	Gulf War veterans with combat-related PTSD	14 8/6	35 (9)	Mean hippocampal head	↓ volume in cohort versus civilian control (p<0.04); difference between cohort and reservist or combat controls: NS
			Control 1 Vietnam	Gulf War combat veterans without PTSD	23 15/8	35 (7)	Left hippocampal head	↓ volume in cohort vs. civilian control (p<0.04); difference between cohort and reservist or combat controls: NS
			Control 2 Reservist	Non-deployed reservists without PTSD	22 9/13	39 (7)	Right hippocampal head	↓ volume in cohort vs. civilian control (p<0.04); difference between cohort and reservist or combat controls: NS
			Control 3 Civilian	Healthy civilians without PTSD	29 9/20	34 (10)		
4	Woodward et al[36]	ROI 1.5 T / 1.5–1.7 mm	Cohort 1 Vietnam	Vietnam veterans with combat-related PTSD	38 38/0	53.5 (2.6)	Hippocampus	9% smaller in PTSD+/Alcohol+ subgroup vs. PTSD−/Alcohol+ subgroup (p=0.002); inversely correlated with Combat Exposure Scale score in Vietnam cohort vs. Vietnam control (p<0.03).
			Cohort 2 Gulf War	Gulf War veterans with combat-related PTSD	13 13/0	37.0 (5.7)		
			Control 1 Vietnam	Vietnam veterans without PTSD	25 25/0	56.0 (3.5)		
			Control 2 Gulf War	Gulf War veterans without PTSD	23 19/4	36.7 (3.9)		
3	Bremner et al[18]	ROI 1.5 T / 3 mm	Cohort	Vietnam veterans with combat-related PTSD	26 26/0	46.0 (1.8)	R hippocampus	8.0% smaller in cohort vs. control (p=0.03)
			Control	Civilians without PTSD; matched for age, sex, race, handedness, height, weight, education, socioeconomic level, and years of Alcohol abuse	22 22/0	44.5 (7.3)		
3	Gurvits et al[22]	ROI 1.5 T / 1.5 mm	Cohort	Vietnam veterans with combat-related PTSD	7 7/0	44.4 (1.7)	Total hippocampus	Volume correlated with ↑ CAPS score (p=0.001) and ↑ M-PTSD score (p=0.03), both measures of PTSD severity
			Control 1 Veteran	Vietnam combat veterans without PTSD	7 7/0	47.6 (2.9)	L hippocampus	↓ volume in cohort vs. veteran and civilian control (p<0.001); finding significant after controlling for months of Alcohol abuse and Combat Exposure Scale score (p=0.02)
			Control 2 Civilian	Civilians without PTSD	8 8/0	38.1 (10.0)	R hippocampus	↓ volume in cohort vs. veteran and civilian controls (p<0.001); finding NS after controlling for months of Alcohol abuse and Combat Exposure Scale score

TABLE 2. Hippocampal Differences Between Posttraumatic Stress Disorder (PTSD) Cohorts and Control Subjects (Continued)

QS	Study	WBA or ROI β (T) / Slice Thickness (mm)	Subject Groups	Description	N M/F	Mean Age (SD)	Brain Area(s)	Main Findings
3	Pavić et al[30]	ROI 2.0 T / 1.1 mm	Cohort	Croatian War veterans with combat-related PTSD; 9 years post-traumatic event	15 15/0	41.0 (5.37)	R hippocampus	↓ volume in cohort vs. control ($p<0.05$)
			Control	Civilian controls; matched for age, sex, handedness, education, and socioeconomic level	15 15/0			
3	Wang et al[34]	ROI 4.0 T / 1 mm	Cohort	Veterans with combat-related PTSD	17 17/0	41 (12)	Total hippocampus	↓ volume in cohort vs. control ($p=0.05$); PTSD diagnosis explains 31% of variance; age explains 56% of variance
			Control	Veterans without PTSD; matched for age	19 19/0	38 (15)	CA3 / dentate gyrus	11.4% (1.5% SD) smaller in cohort vs. control ($p=0.02$)
2	Hedges et al[23]	ROI 1.5 T / 1 mm	Cohort	Vietnam veterans with combat-related PTSD	4 4/0	54.5 (6.02)	L hippocampus	↓ volume in cohort vs. control ($p=0.029$)
			Control	Civilians without PTSD; matched for age and total intracranial volume	4 4/0	54.3 (7.09)	R hippocampus	↓ volume in cohort vs. control ($p=0.029$)

SD: standard deviation; QS: quality score; WBA: whole-brain analysis; ROI: region-of-interest analysis; β: magnetic field strength; NS: not significant.

negative studies controlled for alcohol abuse, and one study had a QS of 0. Findings regarding the left hippocampus do not currently support a significant difference between CR-PTSD and control subjects; of the six high-quality studies (average QS: 3.33) reporting a positive finding in the Right hippocampus, five reported a negative finding for the Left hippocampus.

Paralimbic Differences (See Table 3)

In addition to the hippocampus, other limbic areas are involved in dementing illnesses, and it was important to examine these nonhippocampal abnormalities within the limbic region. For the purposes of this review, studies identifying changes in the amygdala, anterior cingulate cortex (ACC), and parahippocampal gyrus were defined as paralimbic. Three studies[25,35,38] identified reduced volumes in either regions of the ACC or the ACC in general. One study[31] found smaller amygdala volumes, and one study[38] found smaller parahippocampal gyrus in veterans with CR-PTSD.

Cortical and Frontal/Temporal Lobe Differences (See Table 4)

Additional, nonlimbic areas are also involved in certain dementia types. In order to group together the significant results, any cortical, insular, frontal, or temporal lobe abnormalities were combined in a single table. Of the reviewed studies, one[25] found a difference in insular densities; two[20,38] found altered frontal or temporal gyri; and two found reduced cortical volumes.[19,38]

Other Regional Differences (See Table 5)

Of the remaining studies, significant results were found in regions that, although less directly linked to dementia, may provide some understanding of the PTSD disease process. One study[26] identified reduced cerebellar volumes; two studies[27,28] found an increased presence of septum pellucidum; and two studies[19,24] found white-matter abnormalities.

Longitudinal Study

Only one of the included studies was of a longitudinal design, and, as such, was not included in the tables. In this study,[39] which spanned 24+ months between baseline and follow-up assessments, only baseline age was significantly associated with longitudinal hippocampal atrophy. No associations were found between atrophy rate and either baseline CAPS score or change in PTSD symptoms (Improved: 15+ decrease on CAPS;

TABLE 3. Paralimbic Differences Between Posttraumatic Stress Disorder (PTSD) Cohorts and Control Subjects

QS	Study	WBA or ROI β (T) / Slice Thickness (mm)	Subject Groups	Description	N M/F	Mean Age (SD)	Brain Areas(s)	Main Finding(s)
4	Kasai et al[25]	ROI 1.5 T / 1.5 mm	Cohort PTSD+ veterans	Vietnam veterans with severe combat-related PTSD	18 18/0	52.8 (3.4)	Pregenual ACC	↓ gray-matter density in PTSD+ veterans vs. PTSD- veterans (p=0.004); ↓ gray-matter density in PTSD+ veterans vs. all controls (p=0.02); significant correlation with symptom cluster B (re-experiencing; p=0.008)
			Control 1 Twins of PTSD+	Twin siblings of PTSD+ veterans	18 18/0	52.8 (3.4)		
			Control 2 *PTSD−* veterans	Vietnam combat veterans w/o PTSD	23 23/0	51.8 (2.3)		
			Control 3 Twins of PTSD−	Twin siblings of PTSD− veterans	23 23/0	51.8 (2.3)		
4	Woodward et al[35]	ROI 1.5 T / 1.5–1.7 mm	Cohort 1 Vietnam	Vietnam veterans with combat-related PTSD	38 38/0	53.5 (2.6)	ACC	↓ volume in both cohorts vs. both controls (p=0.001); still significant in Alcohol− subgroups (p=0.012); volume inversely correlated with total CAPS score (p<0.001) and total M-PTSD score (p<0.001)
			Cohort 2 Gulf War	Gulf War veterans with combat-related PTSD	13 10/3	37.0 (5.7)		
			Control 1 Vietnam	Vietnam veterans without PTSD	25 25/0	56.0 (3.5)		
			Control 2 Gulf War	Gulf War veterans without PTSD	23 19/4	36.7 (3.9)		
4	Woodward et al[38] (All results adjusted for stature and cerebral white-matter volume.)	WBA 1.5 T / 1.5–1.7 mm	Cohort 1 Alcohol+	Alcohol+ veterans with combat-related PTSD	24 NR	50.3 (2.6)	Parahippocampal gyrus	↓ volume associated with PTSD (p<0.001)
			Cohort 2 Alcohol−	Alcohol− veterans with combat-related PTSD	26 NR	48.3 (9.0)		
			Control 1 Alcohol+	Alcohol+ combat veterans without PTSD	19 NR	47.1 (11.1)	Rostral (pregenual) ACC	↓ volume associated with PTSD (p<0.03)
			Control 2 Alcohol−	Alcohol− combat veterans without PTSD	28 NR	45.9 (9.5)	Caudal (dorsal) ACC	↓ volume associated with PTSD (p<0.01)
3	Pavliša et al[31]	ROI 2.0 T / 1.1 mm	Cohort	Croatian War veterans with combat-related PTSD	11 11/0	40.0 (5.44)	Amygdala	R smaller than L in cohort (p=0.031); ↓ R-to-L ratio in cohort versus *Szabo* control (p<0.0001); ↓ R-to-L ratio in cohort versus *Bower* control (p=0.0005)
			Control 1 Szabo	Healthy, alcohol-free civilian comparison group from Szabo et al., matched for sex and handedness	9 9/0	27 (NR)		
			Control 2 Bower	Healthy, alcohol-free civilian comparison group without past head injury, medical or psychiatric history, from Bower et al., matched for sex and handedness	31 31/0	NR		

SD: standard deviation; QS: quality score; WBA: whole-brain analysis; ROI: region-of-interest analysis; β: magnetic field strength; NR: not reported; ACC: anterior cingulate cortex.

TABLE 4. Cortical and Frontal/Temporal Lobe Differences Between Posttraumatic Stress Disorder (PTSD) Cohorts and Control Subjects

QS	Study	WBA or ROI β (T) / Slice Thickness (mm)	Subject Groups	Description	N M/F	Mean Age (SD)	Brain Area(s)	Main Finding(s)
4	Woodward et al[38] (All results adjusted for stature and cerebral white-matter volume.)	WBA 1.5 T / 1.5–1.7 mm	Cohort 1 Alcohol+	Alcohol+ veterans with combat-related PTSD	24 NR	50.3 (2.6)	Total cortex Parcellated cortex	PTSD associated with ↓ volume ($p<0.001$), ↓ thickness ($p=0.03$) ↓ volume associated with PTSD ($p<0.001$)
			Cohort 2 Alcohol−	Alcohol−veterans with combat-related PTSD	26 NR	48.3 (9.0)	Superior and transverse temporal cortex	↓ volume associated with PTSD ($p<0.001$), ↓ thickness ($p=0.04$), ↓ area ($p=0.003$)
			Control 1 Alcohol+	Alcohol+combat veterans without PTSD	19 NR	47.1 (11.1)	Lateral division of orbital frontal cortex	↓ volume associated with PTSD ($p=0.001$)
			Control 2 Alcohol−	Alcohol−combat veterans without PTSD	28 NR	45.9 (9.5)	Pars orbitalis of inferior frontal gyrus	↓ volume associated with PTSD ($p=0.002$)
4	Kasai et al[25]	ROI 1.5 T / 1.5 mm	Cohort PTSD+ veterans	Vietnam veterans with severe combat-related PTSD	18 18/0	52.8 (3.4)	R midinsula	↓ gray-matter density in PTSD+ veterans vs. PTSD− veterans ($p=0.001$); significant correlation with symptom cluster B (re-experiencing; $p=0.006$)
			Control 1 Twins of PTSD+ veterans	Twin siblings of PTSD+ veterans	18 18/0	52.8 (3.4)	L anterior insula	↓ gray-matter density in PTSD+ veterans vs. PTSD− veterans ($p=0.005$); significant correlation with symptom cluster B (re-experiencing; $p=0.013$)
			Control 2 PTSD− veterans	Vietnam combat veterans w/o PTSD	23 23/0	51.8 (2.3)		
			Control 3 Twins of PTSD+ veterans	Twin siblings of PTSD-veterans	23 23/0	51.8 (2.3)		
3	Geuze et al[20]	ROI 1.5 T / 1.2 mm	Cohort	Dutch veterans with combat-related PTSD	25 25/0	35.08 (4.44)	L superior frontal gyrus L middle frontal gyrus L inferior temporal gyrus	↓ cortical thickness in cohort vs. control ($p=0.001$) ↓ cortical thickness in cohort vs. control ($p=0.004$) ↓ cortical thickness in cohort vs. control ($p=0.012$)
			Control	Dutch combat veterans without PTSD; matched for age, sex, time since trauma, year, and country of development.	25 25/0	34.01 (5.61)	L superior temporal gyrus R superior frontal gyrus R middle frontal gyrus	↓ cortical thickness in cohort versus control ($p=0.032$) ↓ cortical thickness in cohort vs. control ($p=0.018$) ↓ cortical thickness in cohort vs. control ($p=0.026$)
2	Canive et al[19]	WBA NR	Cohort	Veterans with combat-related PTSD	42 42/0	NR	Cortex	↑ incidence of cortical atrophy in cohort vs. control (p value NR)
			Control	Civilians without PTSD, matched for average age (±5 years)	20 20/0	NR		

SD: standard deviation; QS: quality score; WBA: whole-brain analysis; ROI: region-of-interest analysis; β: magnetic field strength; NR: not reported.

TABLE 5. Other Regional Differences Between Posttraumatic Stress Disorder (PTSD) Cohorts and Control Subjects

QS	Study	WBA or ROI β (T) / Slice Thickness (mm)	Subject Groups	Description	N M/F	Mean Age (SD)	Brain Area(s)	Main Finding(s)
4	Levitt et al[26]	ROI 1.5 T / 1.5 mm	Cohort PTSD+ veterans	Vietnam veterans with severe combat-related PTSD	18 18/0	52.5 (3.2)	Anterior superior cerebellar vermis	Volume correlated between twins ($p<0.0001$); volume difference in PTSD+ veterans and their twins vs. PTSD− veterans and their twins: NS
			Control 1 Twins of PTSD+	Twin siblings of PTSD+ veterans	20 20/0	52.8 (3.2)	Posterior superior cerebellar vermis	Volume correlated between twins ($p=0.003$); volume difference in PTSD+ veterans and their twins vs. PTSD− veterans and their twins: NS
			Control 2 *PTSD−* veterans	Vietnam combat veterans without PTSD	22 22/0	51.7 (2.3)	Inferior posterior cerebellar vermis	Volume correlated between twins ($p=0.001$); volume difference in PTSD+ veterans and their twins vs. PTSD− veterans and their twins: NS
			Control 3 Twins of *PTSD−*	Twin siblings of PTSD− veterans	23 23/0	51.8 (2.3)	Total cerebellar vermis	Volume correlated between twins ($p<0.001$); volume difference in PTSD+ veterans and their twins vs. PTSD− veterans and their twins: NS
4	Woodward et al[37]	ROI 1.5 T / 1.5–1.7 mm	Cohort 1 Vietnam	Vietnam veterans with combat-related PTSD	38 38/0	53.5 (2.6)	Sulcal CSF	↓ volume in Vietnam cohort vs. Vietnam control, Alcohol− only ($p<0.01$); ↓ volume in Gulf War cohort vs. Gulf War control, no Alcohol interaction ($p<0.01$); ↓ volume in both cohorts vs. both controls, no Alcohol interaction ($p<0.01$)
			Cohort 2 Gulf War	Gulf War veterans with combat-related PTSD	13 10/3	37.0 (5.7)		
			Control 1 Vietnam	Vietnam veterans without PTSD	25 25/0	56.0 (3.5)	Total cranium	↓ volume in Vietnam cohort vs. Vietnam control, no Alcohol interaction ($p<0.01$); ↓ volume in Gulf War cohort vs. Gulf War control ($p<0.01$), with ↓ volume in Gulf War Alcohol+ versus Gulf War Alcohol− ($p<0.01$); in all subjects; ↓ volume associated with PTSD+ ($p<0.001$), Alcohol+ ($p<0.05$), Gulf War veterans ($p<0.001$)
			Control 2 Gulf War	Gulf War veterans without PTSD	23 19/4	36.7 (3.9)		
3	May et al[27]	ROI 1.5 T / 1.5 mm	Cohort PTSD+ veterans	Vietnam veterans with severe combat-related PTSD	20 20/0	52.3 (3.3)	Septum pellucidum	Presence of cavum septum pellucidum significantly correlated between twins ($p=0.01$); correlation based on PTSD diagnosis: NS; correlation based on PTSD diagnosis × combat exposure: NS
			Control 1 Twins of PTSD+	Twin siblings of PTSD+ veterans	23 23/0	52.7 (3.2)		
			Control 2 PTSD− veterans	Vietnam combat veterans without PTSD	23 23/0	51.8 (2.3)		
			Control 3 Twins of PTSD−	Twin siblings of PTSD− veterans	24 24/0	51.8 (2.3)		

TABLE 5. Other Regional Differences Between Posttraumatic Stress Disorder (PTSD) Cohorts and Control Subjects (Continued)

QS	Study	WBA or ROI β (T) / Slice Thickness (mm)	Subject Groups	Description	N M/F	Mean Age (SD)	Brain Area(s)	Main Finding(s)
3	Myslobodsky et al[28]	WBA 0.5 T / 4.7 mm	Cohort	Veterans with combat-related PTSD	10 NR	33 (7.3)	Septum pellucidum	Presence of cavum septum pellucidum more frequent in cohort versus normal control (p=0.04); 0/10 combat controls with cavum septum pellucidum (p value NR).
			Control 1 Normal	Normal controls without PTSD, matched for age (subgroup of 10 veterans with combat experience)	21 NR	31 (6.7)		
			Control 2 PCS	Patients with post-concussion syndrome (PCS)	7 NR	Range 20–35		
2	Canive et al[19]	WBA NR	Cohort	Veterans with combat-related PTSD	42 42/0	NR	White matter	↑ incidence of white-matter lesions in cohort versus control (p value NR)
			Control	Civilians without PTSD; matched for age (±5 years)	20 20/0	NR		
2	Hedges et al[24]	ROI 1.5 T / 1.2 mm	Cohort	Vietnam veterans with combat-related PTSD	6 6/0	55.5 (1.87)	R temporal lobe white matter	↓ volume in cohort vs. control (p=0.0164)
			Control	Vietnam veterans without combat-related PTSD	5 5/0	55.0 (2.55)		

SD: standard deviation; QS: quality score; WBA: whole-brain analysis; ROI: region-of-interest analysis; β: magnetic field strength; NR: not reported; NS: not significant; CSF: cerebrospinal fluid.

Not-Improved: 2+ increase on CAPS). The investigators hypothesized that the smaller hippocampal volumes found in other studies may have pre-dated the traumatic event or occurred within an acute post-trauma time-frame, with no subsequent atrophy. Although this study is generally of very high methodological quality, it should be noted that it did not use combat-exposed control subjects for its comparisons.

The longitudinal study also found an increased atrophy rate of the left lateral parietal region in the PTSD Improved group when compared with controls. Furthermore, the PTSD Not-Improved group was associated with greater atrophy rates in many gray-matter areas, as compared with controls, including gray-matter areas in the frontal lobe (dorsolateral prefrontal cortex), temporal lobe (anterior cortex), ACC, insula, occipital lobe (extra-striate cortex), and cerebellum. Likewise, frontal and temporal white-matter atrophy rates were accelerated in the PTSD Not-Improved group, as compared with controls. Again, it is important to note this study did not use combat-exposed controls, but it is interesting to consider the possibility of global cortical atrophy as part of the PTSD disease process. Importantly, increasing atrophy rates were associated with greater rates of both verbal memory decline and delayed facial recognition, which suggests that a more substantial disease course could potentially result in either increased or accelerated cognitive decline.

DISCUSSION

In the 22 studies reviewed, the most frequently cited neuroanatomical differences found in patients with chronic CR-PTSD were in the hippocampus, involving either smaller total or right hippocampal volumes. Although volumetric differences were reported in other regions, including the frontal cortex, temporal cortex, and ACC, the findings for these areas were less conclusive and preclude a firm conclusion.

The reductions in hippocampal volume observed in these studies offer a potential explanation for the increased rates of dementia we and others observe in veterans with chronic CR-PTSD.[14,15] Dementia is a loss of cognitive faculties in a person who was previously cognitively normal. Its etiologies include neurodegenerative disorders such as AD and Lewy-body dementia. AD, in particular, is associated with reduced hippocampal volumes. In a metaanalysis of potential

neurostructural predictors for the progression from mild cognitive impairment (MCI) to AD, volume reductions in the hippocampus and parahippocampal gyrus were the most consistent predictors of conversion from MCI to AD.[45] One could hypothesize that the smaller hippocampal volumes in chronic CR-PTSD noted in the studies reviewed here would put patients at greater risk for AD.

However, two of the reviewed studies suggest a different interpretation. The sole longitudinal study[39] did not find increased hippocampal atrophy rates in PTSD patients, suggesting that the PTSD disease process does not lead to reduced hippocampal volumes. Accordingly, it is possible that smaller hippocampal volumes pre-dated the traumatic event, in which case reduced hippocampal volume could, in fact, be a risk for PTSD. Indeed, a twin study on CR-PTSD appears to also support this interpretation. Gilbertson et al.[21] compared two types of monozygotic twin pairs: 1) combat veterans with CR-PTSD and their non-combat twins; and 2) combat veterans without PTSD and their non-combat twins. Hippocampal size correlated well between twin brothers; moreover, both the CR-PTSD veterans and their twins had smaller hippocampi than the combat veterans who never developed PTSD. This study, too, suggests that smaller hippocampi may be a risk factor for CR-PTSD. Together, these findings support the hypothesis that reduced hippocampal volumes are a risk factor for PTSD and AD, rather than one causing the other.

Nevertheless, these data are not definitive because other potential mechanisms may play a role. In one study, the hippocampal volumes of recent trauma-exposed individuals (within 1 week) did not differ in those who would subsequently develop PTSD at a 6-month follow-up assessment, as compared with those who would not develop such symptoms.[46] Also, if the hippocampal volumes were entirely determined by genetic predisposition, the Gilbertson et al.[21] data should show hippocampal differences between the CR-PTSD+ and CR-PTSD− veterans mirroring the differences between the non-combat individuals. In fact, whereas the difference in total hippocampal volume was significant between the veteran groups, the difference between the non-veteran groups was not significant, which suggests that an additional environmental factor may play a role in the volumetric differences.

Concerning the negative studies included in this review, two reported no significant results in their respective regions of interest.[29,32] One study[32] found slightly reduced, but nonsignificant, right hippocampal volume reductions in PTSD veterans versus normal controls; however, they did show reduced N-acetylaspartate (NAA) levels, a marker of neuronal integrity, in the right hippocampus nearly meeting significance levels (p=0.06). Importantly, the small sample size (N: 7 PTSD+; N: 7 PTSD−) represents a notable limitation in this study, and the study received a QS rating of 0 for the purposes of this review. Similarly, a second study[29] found no differences between veterans with PTSD and veterans without PTSD in hippocampal or entorhinal cortical volumes, but did find significant bilateral reductions in NAA density (Left: p=0.019; Right: p=0.012) in the PTSD cohort. Notably, in their linear-regression models, further accounting for left hippocampal and entorhinal cortical volumes accounted for 15.3% of incremental variance (p=0.023). Although these two studies failed to report associations between PTSD and reduced hippocampal volumes, they do provide evidence that PTSD effects on hippocampal neuronal integrity represent either a plausible risk factor or potential modifier for subsequent dementia.

Clearly, more longitudinal studies are needed to differentiate between these hypotheses and to determine whether treating PTSD reduces the risk of subsequent dementia. If reduced hippocampal volume is a risk for both, then treating PTSD will not prevent dementia. Clinicians would instead focus on early detection and treatment of dementia in those with PTSD.

Our review has certain limitations. Like all reviews, our results are limited by the "file-drawer" problem, the idea that researchers may not report or publish negative results.[47] Also, we only examined studies that were published in English, which reduces the number of studies meeting our methodological criteria. The imaging methodologies of the studies included (e.g., strength of the MRI field, thickness of structural slices, interrater reliability for morphometry, preprocessing/enhancement of images, and delineation of anatomical landmarks) were not consistent, and, in general, studies were inconsistent with regard to the quality of their confirmation of PTSD diagnosis and exclusion/inclusion criteria, as well as types and severity of both the severity of the experienced trauma and PTSD symptomatology. Moreover, there may be differences between studies in the veterans' experiences of war and combat-related trauma, such as differences related to the particular combat in which they were involved and the evolution of warfare. Most studies also

differed with regard to controlling for associated disorders, such as severe depression and alcohol abuse, both of which are frequently concomitant with PTSD and have been shown to reduce hippocampal volume.[48–52] Some studies were also performed by the same authors over time, which could potentially introduce bias. Certain premorbid factors, such as previous trauma exposure, including both adult and early-life stress, or preexisting psychiatric/neurological disorders, may influence PTSD development[53–55] but were not consistently controlled for in the studies reviewed. Also, this review was unable to control for presence of traumatic brain injury (TBI). Over 40% of returning U.S. Iraqi veterans with mild TBI met PTSD criteria,[56] whereas lower, but still significant, correlations appear between PTSD and severe TBI.[57,58] These associations are significant, as TBI has also been shown to be a risk factor for dementia in two large veteran cohorts.[59,60] Finally, this review focused on studies evaluating veterans with combat-related PTSD, including studies primarily or exclusively using male subjects; therefore, these results may not be directly applicable to female veterans with PTSD or civilian PTSD populations.

Future Research

Whether the chronic PTSD disease process results in reduced hippocampal (or other brain region) volumes, or these reduced volumes represent pre-existing variation, still needs to be investigated. Therefore, there is an urgent need for further studies of trauma, and both volumetric and functional neuroimaging will provide important data. For case–control studies, fully identifying the type and severity of trauma as well as the duration and severity of the PTSD symptoms is paramount. In order to provide significant evidence regarding the neuroanatomical changes associated with PTSD, our recommendations are that future studies be 1) performed longitudinally; 2) consist of two separate matched controls: trauma-exposed and trauma-naïve; 3) consist of multiple MRI acquisitions, preferably pre-trauma, immediately post-trauma, and at subsequent follow-up assessments; 4) account for relevant PTSD risk factors,[53,54] such as the number of previous stressful events or pre-existing anxiety/depression; 5) document the type, duration, and severity of the physical trauma; and 6) provide empirical data on PTSD severity and duration.

To further clarify the relationship between PTSD and dementia, long-term prospective studies that follow trauma-exposed individuals for extended time-frames are required. Also, twin studies would also be informative, as twins discordant for combat exposure should provide compelling evidence regarding whether combat exposure and/or PTSD causes an increased risk of dementia.

Another important research objective would be to determine the effects of timely PTSD treatment methods and subsequent reductions in PTSD symptoms, both duration and severity, and the rates of other disease processes that may be mediated by a chronic PTSD disease course.

Clinically, multiple studies have shown that PTSD may produce long-term negative physical[5] consequences and neurocognitive deficits.[12] Although this review concludes that PTSD is associated with reduced hippocampal volumes, a causative relationship cannot be determined. However, as PTSD has been associated with an increase in vascular risk factors[61] and reduced cognitive ability,[62] it is imperative that proper PTSD treatment regimens be implemented as soon as possible to prevent any further potential damage. In addition to both pharmacological and psychological PTSD therapies, vascular risk factors and relevant behavioral modifications (e.g., increased alcohol or nicotine dependence) should be closely monitored in this population, while preventive measures such as increased physical activity should be stressed.

CONCLUSIONS

Most studies reviewed suggest that the hippocampi are smaller in veterans with chronic CR-PTSD. However, it is unclear whether smaller hippocampi are a risk factor for the development of PTSD or they are the result of chronic PTSD. In either event, smaller hippocampi may explain the increase in dementia that we and others have observed in chronic CR-PTSD.[14,15]

The implications are important: if smaller hippocampi are a pre-existing risk factor for PTSD, imaging them could serve as an important tool in identifying military personnel vulnerable to developing PTSD after combat exposure. Perhaps their combat experiences could be tailored to prevent PTSD. Moreover, smaller hippocampi would suggest that older veterans with PTSD should be screened more regularly for cognitive changes.

This work was partially supported by the VA HSR&D Center of Excellence (Houston Center for Quality of Care & Utilization Studies, HFP-90-020), Houston, TX.

The views expressed reflect those of the authors and do not necessarily represent those of the Department of Veterans Affairs, Baylor College of Medicine, and/or UTHealth.

The authors report no financial or commercial involvements that may be deemed conflicts of interest in connection with this manuscript.

References

1. American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorder, 4th Edition (DSM-IV-TR). Washington, DC, American Psychiatric Association, 2000; accessed online, 1/4/2012 from *STAT!RefOnline Electronic Medical Library*. http://online.statref.com/document.asp?fxid=37&docid=230
2. Kessler RC, Chiu WT, Demler O, et al: Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry 2005; 62:617–627
3. Dohrenwend BP, Turner JB, Turse NA, et al: The psychological risks of Vietnam for U.S. veterans: a revisit with new data and methods. Science 2006; 313:979–982
4. Seal KH, Metzler TJ, Gima KS, et al: Trends and risk factors for mental health diagnoses among Iraq and Afghanistan veterans using Department of Veterans Affairs health care, 2002–2008. Am J Public Health 2009; 99:1651–1658
5. Qureshi SU, Pyne JM, Magruder KM, et al: The link between post-traumatic stress disorder and physical comorbidities: a systematic review. Psychiatr Q 2009; 80:87–97
6. Vasterling JJ, Duke LM, Brailey K, et al: Attention, learning, and memory performances and intellectual resources in Vietnam veterans: PTSD and no disorder comparisons. Neuropsychology 2002; 16:5–14
7. Yehuda R, Golier JA, Halligan SL, et al: Learning and memory in Holocaust survivors with posttraumatic stress disorder. Biol Psychiatry 2004; 55:291–295
8. Jelinek L, Jacobsen D, Kellner M, et al: Verbal and nonverbal memory functioning in posttraumatic stress disorder (PTSD). J Clin Exp Neuropsychol 2006; 28:940–948
9. Gilbertson MW, Paulus LA, Williston SK, et al: Neurocognitive function in monozygotic twins discordant for combat exposure: relationship to posttraumatic stress disorder. J Abnorm Psychol 2006; 115:484–495
10. Samuelson KW, Neylan TC, Metzler TJ, et al: Neuropsychological functioning in posttraumatic stress disorder and alcohol abuse. Neuropsychology 2006; 20:716–726
11. Qureshi SU, Long ME, Bradshaw MR, et al: Does PTSD impair cognition beyond the effect of trauma? J Neuropsychiatry Clin Neurosci 2011; 23:16–28
12. Johnsen GE, Asbjørnsen AE: Consistent impaired verbal memory in PTSD: a meta-analysis. J Affect Disord 2008; 111:74–82
13. Grober E, Hall CB, Lipton RB, et al: Memory impairment, executive dysfunction, and intellectual decline in preclinical Alzheimer's disease. J Int Neuropsychol Soc 2008; 14:266–278
14. Qureshi SU, Kimbrell T, Pyne JM, et al: Greater prevalence and incidence of dementia in older veterans with posttraumatic stress disorder. J Am Geriatr Soc 2010; 58:1627–1633
15. Yaffe K, Vittinghoff E, Lindquist K, et al: Posttraumatic stress disorder and risk of dementia among US veterans. Arch Gen Psychiatry 2010; 67:608–613
16. Hull AM: Neuroimaging findings in post-traumatic stress disorder: systematic review. Br J Psychiatry. J Ment Sci 2002; 181:102–110
17. Smith ME: Bilateral hippocampal volume reduction in adults with post-traumatic stress disorder: a meta-analysis of structural MRI studies. Hippocampus 2005; 15:798–807
18. Bremner JD, Randall P, Scott TM, et al: MRI-based measurement of hippocampal volume in patients with combat-related posttraumatic stress disorder. Am J Psychiatry 1995; 152:973–981
19. Canive JM, Lewine JD, Orrison WW Jr, et al: MRI reveals gross structural abnormalities in PTSD. Ann N Y Acad Sci 1997; 821:512–515
20. Geuze E, Westenberg HGM, Heinecke A, et al: Thinner prefrontal cortex in veterans with posttraumatic stress disorder. Neuroimage 2008; 41:675–681
21. Gilbertson MW, Shenton ME, Ciszewski A, et al: Smaller hippocampal volume predicts pathologic vulnerability to psychological trauma. Nat Neurosci 2002; 5:1242–1247
22. Gurvits TV, Shenton ME, Hokama H, et al: Magnetic resonance imaging study of hippocampal volume in chronic, combat-related posttraumatic stress disorder. Biol Psychiatry 1996; 40:1091–1099
23. Hedges DW, Allen S, Tate DF, et al: Reduced hippocampal volume in alcohol and substance naïve Vietnam combat veterans with posttraumatic stress disorder. Cogn Behav Neurol 2003; 16:219–224
24. Hedges DW, Thatcher GW, Bennett PJ, et al: Brain integrity and cerebral atrophy in Vietnam combat veterans with and without posttraumatic stress disorder. Neurocase 2007; 13: 402–410
25. Kasai K, Yamasue H, Gilbertson MW, et al: Evidence for acquired pregenual anterior cingulate gray matter loss from a twin study of combat-related posttraumatic stress disorder. Biol Psychiatry 2008; 63:550–556
26. Levitt JJ, Chen QC, May FS, et al: Volume of cerebellar vermis in monozygotic twins discordant for combat exposure: lack of relationship to post-traumatic stress disorder. Psychiatry Res 2006; 148:143–149
27. May FS, Chen QC, Gilbertson MW, et al: Cavum septum pellucidum in monozygotic twins discordant for combat exposure: relationship to posttraumatic stress disorder. Biol Psychiatry 2004; 55:656–658
28. Myslobodsky MS, Glicksohn J, Singer J, et al: Changes of brain anatomy in patients with posttraumatic stress disorder: a pilot magnetic resonance imaging study. Psychiatry Res 1995; 58:259–264
29. Neylan TC, Schuff N, Lenoci M, et al: Cortisol levels are positively correlated with hippocampal N-acetylaspartate. Biol Psychiatry 2003; 54:1118–1121
30. Pavić L, Gregurek R, Rados M, et al: Smaller right hippocampus in war veterans with posttraumatic stress disorder. Psychiatry Res 2007; 154:191–198
31. Pavliša G, Papa J, Pavić L, et al: Bilateral MR volumetry of the amygdala in chronic PTSD patients. Coll Antropol 2006; 30:565–568

32. Schuff N, Marmar CR, Weiss DS, et al: Reduced hippocampal volume and N-acetyl aspartate in posttraumatic stress disorder. Ann N Y Acad Sci 1997; 821:516–520
33. Vythilingam M, Luckenbaugh DA, Lam T, et al: Smaller head of the hippocampus in Gulf War-related posttraumatic stress disorder. Psychiatry Res 2005; 139:89–99
34. Wang Z, Neylan TC, Mueller SG, et al: Magnetic resonance imaging of hippocampal subfields in posttraumatic stress disorder. Arch Gen Psychiatry 2010; 67:296–303
35. Woodward SH, Kaloupek DG, Streeter CC, et al: Decreased anterior cingulate volume in combat-related PTSD. Biol Psychiatry 2006; 59:582–587
36. Woodward SH, Kaloupek DG, Streeter CC, et al: Hippocampal volume, PTSD, and alcoholism in combat veterans. Am J Psychiatry 2006; 163:674–681
37. Woodward SH, Kaloupek DG, Streeter CC, et al: Brain, skull, and cerebrospinal fluid volumes in adult posttraumatic stress disorder. J Trauma Stress 2007; 20:763–774
38. Woodward SH, Schaer M, Kaloupek DG, et al: Smaller global and regional cortical volume in combat-related posttraumatic stress disorder. Arch Gen Psychiatry 2009; 66:1373–1382
39. Cardenas VA, Samuelson K, Lenoci M, et al: Changes in brain anatomy during the course of posttraumatic stress disorder. Psychiatry Res 2011; 193:93–100
40. Hedges LV, Olkin I: Statistical Methods for Meta-Analysis. Orlando, FL, Academic Press, 1985
41. Bjork JM, Grant SJ, Hommer DW: Cross-sectional volumetric analysis of brain atrophy in alcohol dependence: effects of drinking history and comorbid substance use disorder. Am J Psychiatry 2003; 160:2038–2045
42. Bouchard TP, Malykhin N, Martin WR, et al: Age- and dementia-associated atrophy predominates in the hippocampal head and amygdala in Parkinson's disease. Neurobiol Aging 2008; 29:1027–1039
43. Apostolova L, Alves G, Hwang KS, et al: Hippocampal and ventricular changes in Parkinson's disease mild cognitive impairment. Neurobiol Aging 2011; [e-pub ahead of print]
44. Barber R, Ballard C, McKeith IG, et al: MRI volumetric study of dementia with Lewy bodies: a comparison with AD and vascular dementia. Neurology 2000; 54:1304–1309
45. Ferreira LK, Diniz BS, Forlenza OV, et al: Neurostructural predictors of Alzheimer's disease: a meta-analysis of VBM studies. Neurobiol Aging 2011; 32:1733–1741
46. Bonne O, Brandes D, Gilboa A, et al: Longitudinal MRI study of hippocampal volume in trauma survivors with PTSD. Am J Psychiatry 2001; 158:1248–1251
47. Easterbrook PJ, Berlin JA, Gopalan R, et al: Publication bias in clinical research. Lancet 1991; 337:867–872
48. Koolschijn PCMP, van Haren NEM, Lensvelt-Mulders GJLM, et al: Brain volume abnormalities in major depressive disorder: a meta-analysis of magnetic resonance imaging studies. Hum Brain Mapp 2009; 30:3719–3735
49. Kronmüller KT, Schröder J, Köhler S, et al: Hippocampal volume in first-episode and recurrent depression. Psychiatry Res 2009; 174:62–66
50. Agartz I, Momenan R, Rawlings RR, et al: Hippocampal volume in patients with alcohol dependence. Arch Gen Psychiatry 1999; 56:356–363
51. Beresford TP, Arciniegas DB, Alfers J, et al: Hippocampus volume loss due to chronic heavy drinking. Alcohol Clin Exp Res 2006; 30:1866–1870
52. Nagel BJ, Schweinsburg AD, Phan V, et al: Reduced hippocampal volume among adolescents with alcohol use disorders without psychiatric comorbidity. Psychiatry Res 2005; 139:181–190
53. Brewin CR, Andrews B, Valentine JD: Meta-analysis of risk factors for posttraumatic stress disorder in trauma-exposed adults. J Consult Clin Psychol 2000; 68:748–766
54. Ozer EJ, Best SR, Lipsey TL, et al: Predictors of posttraumatic stress disorder and symptoms in adults: a meta-analysis. Psychol Bull 2003; 129:52–73
55. Woon FL, Hedges DW: Hippocampal and amygdala volumes in children and adults with childhood maltreatment-related posttraumatic stress disorder: a meta-analysis. Hippocampus 2008; 18:729–736
56. Hoge CW, McGurk D, Thomas JL, et al: Mild traumatic brain injury in U.S. soldiers returning from Iraq. N Engl J Med 2008; 358:453–463
57. Williams WH, Evans JJ, Wilson BA, et al: Brief report: prevalence of post-traumatic stress disorder symptoms after severe traumatic brain injury in a representative community sample. Brain Inj 2002; 16:673–679
58. Bryant RA, Marosszeky JE, Crooks J, et al: Posttraumatic stress disorder after severe traumatic brain injury. Am J Psychiatry 2000; 157:629–631
59. Kalkonde YV, Jawaid A, Qureshi SU, et al: Medical and environmental risk factors associated with frontotemporal dementia: a case–control study in a veteran population. Alz Dement 2011; (in press) 10.1016/j.jalz.2011.03.011
60. Plassman BL, Havlik RJ, Steffens DC, et al: Documented head injury in early adulthood and risk of Alzheimer's disease and other dementias. Neurology 2000; 55:1158–1166
61. Coughlin SS: Post-traumatic stress disorder and cardiovascular disease. Open Cardiovasc Med J 2011; 5:164–170
62. McNally RJ: Cognitive abnormalities in post-traumatic stress disorder. Trends Cogn Sci 2006; 10:271–277