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Smaller head of the hippocampus in Gulf War-related posttraumatic stress disorder

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Abstract

Reductions in hippocampal volume and impairment in short-term verbal memory have been reported in Vietnam combat veterans with posttraumatic stress disorder (PTSD) and in women with abuse-related PTSD. The present investigation evaluated hippocampal volume and memory in Gulf War veterans. This research is timely given the ongoing war in Iraq and the anticipated high rates of PTSD among returning combat soldiers. Fourteen veterans with PTSD related to traumatic experiences during the Gulf War (1990–1991), 23 deployed veterans without PTSD, 22 non-deployed reservists and 29 healthy civilians were studied. Volumes of the hippocampus, temporal lobe, and whole brain were measured on coronal MRI scans, and hippocampal mediated memory function was evaluated. The head of the hippocampus was the only subregion that was significantly smaller in Gulf War veterans with PTSD than in healthy civilians. Deployed veterans with PTSD, deployed veterans without PTSD, and non-deployed reservists had significantly smaller whole hippocampal volume and lower scores on immediate and delayed verbal and visual retrieval compared with healthy civilians.

Keywords: PTSD; Combat; Stress; Magnetic resonance imaging; Memory

1. Introduction

The finding of smaller hippocampal volume in individuals with posttraumatic stress disorder (PTSD)

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has generated interest and controversy in the field of psychological trauma. PTSD as a result of combat-related trauma experiences during the Vietnam War has been associated with smaller right (Bremner et al., 1995) and left and right hippocampal volume (Gurvits et al., 1996; Hedges et al., 2003; Villarreal et al., 2002). Reduced hippocampal volume has also been reported in civilian survivors of sexual and/or physical abuse (Bremner et al., 1997, 2003b; Stein et al., 1997), mixed trauma (Villarreal et al., 2002) with recent PTSD (Wignall et al., 2004), and policeman with PTSD (Lindauer et al., 2004). However, not all published studies found smaller hippocampal volume in subjects with PTSD (Bonne et al., 2001; De Bellis et al., 1999, 2001; Fennema-Notestine et al., 2002; Pederson et al., 2004; Schuff et al., 1997, 2001; Winter and Irle, 2004).

Possible explanations for discrepant findings regarding hippocampal volume include differences in imaging methodology, differences in comparison groups, variability in intensity and duration of trauma exposure, chronicity of PTSD symptomatology, and presence of co-morbid psychiatric disorders associated with reduced hippocampal volume. It is also possible that discrepant findings in PTSD volumetric studies could, in part, be related to differences in the subregions of the hippocampus. Schizophrenia is associated with focal abnormalities in the head of the hippocampus in the absence of a generalized decrease in hippocampal volume (Csernansky et al., 2002). Focal abnormalities in the subiculum have also been recently reported in major depression (Posener et al., 2003). To date, morphometry of the subregions of the hippocampus has not been evaluated in subjects with PTSD or in veterans of the Gulf War.

There are several possible explanations for smaller hippocampal volume in PTSD (reviewed in Pitman, 2001). A pre-existing smaller hippocampal volume could predispose traumatized subjects to develop PTSD (Gilbertson et al., 2002). Alternatively, small hippocampal volume could be a result of comorbid conditions such as alcohol dependence (Agartz et al., 1999; Caetano et al., 2004) and major depression (Caetano et al., 2004; Sheline et al., 1999; Videbech and Ravnkilde, 2004); could be secondary to trauma exposure; or could be due to the chronic stress of PTSD. The aim of the present study was to measure the volume of the hippocampus and its subregions, including the head and body, in veterans of the Gulf War and to relate these findings to hippocampal mediated neuropsychological testing. Gulf War veterans with PTSD were compared with deployed veterans who did not develop PTSD and non-deployed reservists. History of early childhood abuse and presence of co-morbid major depression and/or substance abuse were assessed thoroughly, as these variables have previously been associated with reduced hippocampal volume (Agartz et al., 1999; Bremner et al., 1997; MacQueen et al., 2003; Sheline et al., 1999, 1996; Stein et al., 1997; Vythilingam et al., 2002). Because the reservists had greater rates of major depressive disorder (MDD), alcohol abuse and childhood trauma than anticipated, healthy controls without military service and who did not meet criteria for any past or present psychiatric disorders were included as an additional control group. All groups were imaged using the same scanner and identical scan sequence.

We hypothesized that deployed Gulf War veterans with PTSD would have smaller volumes of the head, body and whole hippocampus and poorer hippocampal mediated memory function than deployed Gulf War veterans without PTSD, reservists and healthy civilians.

2. Methods

2.1. Subjects

Eighty-eight subjects were assigned to one of four groups based upon their deployment status and presence of combat-related PTSD. Fourteen subjects (8 men, 6 women; mean age 35 ± 9 years) had PTSD related to trauma [Gulf War (1990–1991)], 23 (15 men, 8 women; mean age 35 ± 7 years) had been deployed to the Gulf but did not develop PTSD and did not have a lifetime history of PTSD, 22 (9 men, 13 women; mean age 39 ± 7 years) were non-deployed reservists, and 29 (9 men, 20 women; mean age 34 ± 10 years) were healthy civilians. Veterans were recruited through the Veterans' Administration (VA), veteran centers, newspapers, and fliers. Healthy civilians were recruited through advertisements and fliers. This research was approved by the Department of Defense, West Haven VA Medical Center and Yale

University School of Medicine Human Investigations Committee. Subjects provided written informed consent before participation and received monetary compensation for participation.

Subjects were included in the PTSD group based on the Structured Clinical Interview for DSM-IV (First et al., 1996) and if specific combat-related events led to the development of PTSD. Subjects were classified as deployed non-PTSD if they had been deployed to the Gulf but did not develop PTSD. Reservists served in the military at the time of the Gulf War but were not deployed to the Gulf. Healthy civilians had never served in the military and had no history of psychiatric or illness and were healthy.

The Combat Exposure Scale (CES) was administered to all subjects who were deployed to the Gulf. Severity of PTSD was measured with the Mississippi Scale for Combat-Related Posttraumatic Stress Disorder (Keane et al., 1988). The Clinician Early Trauma Inventory (ETI) (Bremner et al., 2000) was administered to assess non-combat-relatedtrauma. The ETI assesses the number, frequency, duration, and subjective impact of different types of traumatic experiences (physical, sexual, and emotional abuse traumas).

Subjects were excluded from the study if they were more than 60 years old, had other major Axis I disorders (e.g. schizophrenia and bipolar disorder), had PTSD unrelated to military service, or had a major medical illness. However, patients with comorbid dysthymia, panic attacks, and MDD were included. Were excluded if they had a history of significant head trauma, irregular menses, treatment with electroconvulsive therapy (ECT), exposure to oral or intravenous steroids, Cushing's disease, current history of alcohol or substance dependence or abuse, contraindication for an MRI, or IQ below 90.

Consensus diagnosis for PTSD was made by two board-certified psychiatrists (MV and SS).

2.2. MRI

2.2.1. MRI acquisition and processing

Subjects were imaged with a 1.5-Tesla General Electric Signa Device using a tilted coronal 3D volume Spoiled Gradient Recoil (SPGR) sequence with TR=25 ms, TE=5 ms, NEX (number of excitations)=2, matrix=256×192, and field of view=24 cm. This resulted in 60 coronal 1.5-mm contiguous slices through the hippocampus. Images were transferred via computer network to a Sun Sparc Ultra 80 workstation. Regions of interest were traced manually with a mouse-driven cursor using the ANALYZE program (Mayo Foundation, Rochester, MN). An initial sagittal localizing sequence was obtained to determine the long axis of the hippocampus, and axial images through the brain were also obtained.

2.2.2. Measurement of hippocampal volume

Anatomical guidelines for the hippocampus were based on the work of Watson et al. (1992) and Duvernoy (Bronen, 1992; Bronen and Cheung, 1991a,b,c; Duvernoy, 1998) and were modified in consultation with a neuroradiologist who is an expert in hippocampal anatomy (Bronen, 1992; Bronen and Cheung, 1991a,b,c). After extensive training in hippocampal anatomy, a single rater without knowledge of the subjects' diagnoses traced the hippocampal boundaries of the patients and the healthy comparison subjects. Structures included in the hippocampal volume were the gray matter of the hippocampus proper, dentate gyrus, subicular complex, alveus, and fimbria. The parahippocampal gyrus, tail of the caudate, fornix, amygdala, and cerebrospinal fluid (CSF) around the hippocampus were excluded. Posteriorly, the first slice was defined as the slice 3 mm anterior to where the crura of the fornix separated from the hippocampus. The CSF of the temporal horn of the lateral ventricle and white matter tracts identified the lateral and inferior boundaries, respectively. Anteriorly, the hippocampus was reliably differentiated from the amygdala by using the criteria of Watson et al. (1992). The CSF in the uncal recess of the temporal horn, when visible, was the most reliable boundary between the hippocampal head and the amygdala. In instances where the uncal recess was not visible, the alveus was used as the boundary to separate the hippocampus and amygdala. If neither the uncal recess nor the alveus was obvious, a straight line was drawn connecting the plane of the inferior horn of the lateral ventricle with the surface of the uncus. The average number of slices traced for each hippocampus was 24 (S.D.=2).

The hippocampus was segmented into the head, body, and tail to evaluate subregional differences in hippocampal volume between groups. The body (mid-

hippocampal segment) included ten 15-mm coronal slices between the superior colliculus and the bifurcation of the basilar artery, with the first slice anterior to superior colliculus (Bremner et al., 1995, 1997; Bronen and Cheung, 1991a). The tail was defined as all slices posterior to the end slice of the body.

2.2.3. Interrater reliability

Two raters (MV and TL), without knowledge of subject identity and diagnosis, traced the hippocampus in a subgroup of 12 randomly selected scans, and the interrater correlation coefficients were calculated. Interrater reliability was determined with the intraclass correlation coefficient (ICC) and one-way analysis of variance for volumetric assessments of the hippocampus by two raters. The ICCs were 0.9 for the left hippocampus and 0.8 for the right hippocampus.

2.3. Neuropsychological testing

Intelligence and verbal and visual memory was evaluated using the Wechsler Adult Intelligence Scale-Revised (WAIS-R), Wechsler Memory Scale-Revised (WMS-R), and Verbal and Visual Selective Reminding Test (SRT). All neuropsychological tests employed in this study (with the exception of alternate form for WMS-R Logical Memory) were standardized clinical measures (reviewed in Lezak, 1995; Spreen and Strauss, 1998).

2.4. Statistical analysis

Group differences between continuous demographic variables were analyzed using analysis of variance. Significant omnibus main effects and interactions were evaluated with Bonferroni-adjusted simple effects tests. When distributions deviated significantly from normal as reviewed with Shapiro–Wilk's test ($P<0.01$), the Kruskal–Wallis H test was used. Groups were compared on volumetric measures using analysis of covariance with whole brain, age, past alcohol dependence, and severity of early childhood trauma as covariates. For neuropsychological measures, covariates included age and years of alcohol abuse. Where noted, current or past depression was used as an additional covariate. Categorical variables were examined using chi-square tests. Given various distribution concerns, correlations were performed using Spearman's rho. Linear regression was used to understand the unique relationships between various demographic factors and hippocampal volume, where all relevant demographic factors were entered simultaneously to predict hippocampal volume.

3. Results

3.1. Subject characteristics (Table 1)

Table 1 presents the sociodemographic and clinical characteristics of the subjects. PTSD subjects had significantly greater rates of current MDD than other subjects. PTSD, deployed non-PTSD, and reservists had rates of past MDD that were significantly greater than healthy civilians, but only PTSD and deployed non-PTSD subjects had greater rates of past alcohol abuse and dependence than healthy civilians.

As expected, subjects with PTSD had significantly greater scores on the Mississippi Scale for Combat-Related Posttraumatic Stress Disorder and the Combat Exposure Scale (CES) ($P<0.03$) compared with the deployed non-PTSD group. Subjects with PTSD also had significantly higher scores than the other three groups on the Early Trauma Inventory (ETI) in the Total Clinician Report, as well as the physical and emotional trauma subscales.

Although performance scores on the WAIS-R were not significantly different between the four groups, healthy civilians had higher scores on the full scale and the verbal subtests than did subjects with PTSD, deployed non-PTSD, and reservists.

3.2. Brain volumetric results (Table 2)

The volume of the left, right and mean head of the hippocampus was significantly smaller in Gulf War veterans with PTSD than in healthy civilians (Fig. 1). Additionally, the left and the mean whole hippocampal volumes were significantly larger in healthy civilians compared with the three military groups. Healthy civilians had a larger right hippocampal volume compared with PTSD and deployed non-PTSD subjects. There were no significant differences in right or left hippocampal volume between the military groups (Table 2).

Table 1
Sociodemographic data and clinical characteristics in PTSD, deployed non-PTSD, non-deployed reservists and healthy civilians

	PTSD ($n=14$)	Deployed non-PTSD ($n=23$)	Reservists ($n=22$)	Healthy civilians ($n=29$)	F	df	P
	Mean ± S.D. (or n)	Mean ± S.D. (or n)	Mean ± S.D. (or n)	Mean ± S.D. (or n)			
Mean age (years)	35 ± 9	35 ± 7	39 ± 7	34 ± 10	1.72	3,84	0.17
Height (in.)	67 ± 3	69 ± 5	66 ± 3	67 ± 4	2.44	3,77	0.07
Weight (lbs.)	171 ± 29	180 ± 42	155 ± 36	155 ± 36	2.47	3,77	0.07
Education (years)	14 ± 2	15 ± 2	16 ± 3	16 ± 2	7.60[K]	3	0.06
					χ^2	df	P
Gender: male/female	8/6	15/8	9/13	9/20	6.94	3	0.07
Race: Caucasian/African American/other	10/3/1	19/3/1	15/4/3	27/1/1	6.70	6	0.35
Handedness: right/left/no preference	11/1/2	22/0/1	17/3/2	24/5/0	8.67	6	0.19
Psychiatric comorbidity							
MDD current	7	0	0	0	40.20	3	<0.01[a]
MDD past	11	8	7	0	28.68	3	<0.01[b]
Substance and alcohol abuse							
Alcohol abuse past	6	6	3	0	14.07	3	<0.01[c]
Years alcohol abuse	2.5 ± 2.9	1.2 ± 2.1	1.0 ± 2.0	0 ± 0	6.12[f]	3,84	<0.01[d]
Alcohol dependence past	2	7	4	0	9.71	3	0.02[e]
Years alcohol dependence	1.3 ± 3.5	1.8 ± 3.8	1.0 ± 2.3	0 ± 0	9.05[K]	3	0.03[e]
Substance abuse past	3	1	2	0	7.09	3	0.08
Substance dependence past	1	1	0	0	2.98	3	0.40
					F	df	P
Mississippi Scale for Combat-Related PTSD	103 ± 25	63 ± 17	NA	NA	32.51	1,34	<0.01
Combat Exposure Scale	15 ± 10	9 ± 7	NA	NA	5.00	1,34	0.03
Early Trauma Inventory (ETI) (clinician)							
Total clinician report ETI	776 ± 950	258 ± 424	292 ± 348	146 ± 337	4.65	3,78	0.01[a]
General trauma subscale	36 ± 57	22 ± 24	37 ± 44	4 ± 6	4.06	3,78	0.01[g]
Physical trauma subscale	275 ± 369	72 ± 132	60 ± 55	27 ± 38	6.90	3,78	<0.01[a]
Emotional trauma subscale	409 ± 486	163 ± 312	190 ± 320	113 ± 339	15.49[K]	3	<0.01[h]
Sexual trauma subscale	56 ± 128	1 ± 3	5 ± 16	1 ± 4	7.11[K]	3	0.07

K=Kruskal–Wallace χ^2 .
[a] PTSD > deployed non-PTSD, non-deployed, healthy ($P<0.04$).
[b] PTSD > deployed non-PTSD > healthy ($P<0.01$).
[c] PTSD, deployed non-PTSD > healthy, PTSD > non-deployed ($P<0.05$).
[d] PTSD > healthy ($P<0.01$).
[e] PTSD, deployed non-PTSD > healthy ($P<0.04$).
[f] PTSD > deployed non-PTSD ($P<0.01$).
[g] Non-deployed > healthy ($P<0.02$).
[h] PTSD > non-deployed > healthy, PTSD > deployed non-PTSD ($P<0.04$).

When current or past depression was included as a covariate, the volume of the hippocampal head was smaller among veterans with PTSD compared with healthy civilians. Right and mean whole hippocampal volume was smaller in PTSD and deployed non-PTSD subjects than in healthy civilians. The left hippocampal volume was smaller in the deployed non-PTSD subjects than in healthy civilians. There were no significant differences in the whole brain or temporal lobe volume between the four groups before or after correcting for depression.

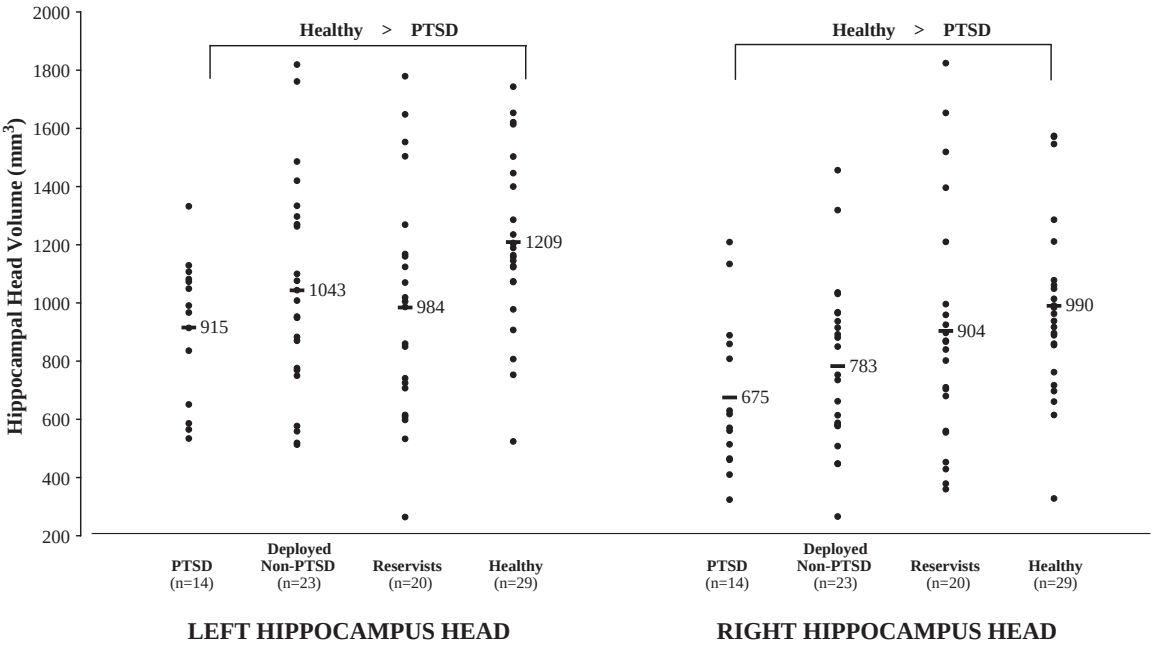

Fig. 1. Hippocampal head volume in patients with combat-related PTSD, deployed without PTSD, reservists, and healthy civilians.

3.3. Neuropsychological findings (Table 3)

There were significant differences between the groups for immediate and delayed memory on the verbal subtest of the WMS-R and immediate, delayed, and % retention on the visual subtest. Veterans with PTSD, deployed non-PTSD veterans and reservists performed significantly worse on the immediate and delayed retrieval on the verbal and visual subtests compared with healthy civilians. However, deployed non-PTSD subjects had greater values on visual percent retention compared with healthy civilians (Table 3).

There was a significant difference between the four groups for consistent long-term retrieval (CLTR) ($P=0.02$) and trend differences for long-term retrieval (LTR) ($P=0.05$) on the verbal SRT. Reservists had higher scores than healthy civilians for verbal CLTR ($P=0.03$). Significant differences were also observed for long-term storage (LTS), LTR and CLTR on the visual SRT. Deployed non-PTSD veterans and reservists had significantly higher scores compared with healthy civilians on the visual subtests for LTR and CLTR. Only deployed non-PTSD subjects had significantly higher scores than healthy civilians on the visual LTS.

3.4. Correlations

Immediate and delayed verbal memory was positively correlated with left, right and mean hippocampal volume (immediate: $r=0.32$, $P=0.003$; $r=0.39$, $P<0.001$; $r=0.35$, $P=0.001$; delayed: $r=0.35$, $P=0.001$; $r=0.42$, $P<0.001$; $r=0.38$, $P<0.001$, respectively). Immediate visual memory was correlated with the left, right and mean hippocampal volume ($r=0.34$, $P=0.002$; $r=0.35$, $P=0.001$; $r=0.36$, $P=0.001$, respectively). A significant positive correlation was also seen between the WAIS full-scale score and the left, right, and mean hippocampal volume in the combined sample ($r=0.40$, $P<0.001$; $r=0.44$, $P<0.001$; $r=0.42$, $P<0.001$, respectively). The clinician ETI score had small, but significant, negative correlations with the left, right and mean hippocampal volume ($r=-0.28$, $P=0.012$; $r=-0.26$, $P=0.02$; $r=-0.28$, $P=0.01$, respectively). Correlations with the hippocampal head were similar to the whole hippocampus except for delayed visual memory.

Table 2
Volume (mm^3) of the hippocampus, whole brain and temporal lobe in PTSD, deployed non-PTSD, non-deployed reservists and healthy civilians

	PTSD ($n=14$)	Deployed non-PTSD ($n=23$)	Reservists ($n=22$)	Healthy civilians ($n=23$)	F	P
	Mean ± S.D.	Mean ± S.D.	Mean ± S.D.	Mean ± S.D.		
Hippocampus whole						
Left	2938 ± 309	2988 ± 392	2879 ± 526	3274 ± 413	5.68	<0.01[a]
Right	2726 ± 323	2860 ± 377	2834 ± 466	3185 ± 423	6.47	<0.01[b]
Mean	2832 ± 311	2924 ± 371	2856 ± 489	3230 ± 407	6.42	<0.01[a]
Hippocampus body						
Left	1289 ± 175	1173 ± 151	1143 ± 172	1220 ± 147	1.94	0.13
Right	1288 ± 151	1259 ± 111	1179 ± 183	1279 ± 134	1.60	0.20
Mean	1289 ± 147	1216 ± 121	1161 ± 170	1249 ± 132	1.69	0.18
Hippocampus head						
Left	915 ± 246	1043 ± 371	990 ± 392	1215 ± 298	3.49	0.02[c]
Right	675 ± 268	783 ± 284	890 ± 409	1012 ± 258	3.71	0.02[c]
Mean	795 ± 231	913 ± 309	940 ± 384	1113 ± 259	3.96	0.01[c]
Whole brain	1 268 950 ± 102 532	1 272 513 ± 104 901	1 207 953 ± 123 647	1 243 514 ± 131 343	1.80	0.15
Temporal lobe						
Left	16 955 ± 1447	17 499 ± 1970	16 801 ± 2725	17 040 ± 1917	0.51	0.67
Right	16 544 ± 1304	16 875 ± 1526	16 805 ± 2214	17 414 ± 2624	2.48	0.07
Mean	16 750 ± 1113	17 187 ± 1638	16 803 ± 2382	17 227 ± 2062	1.52	0.22

Covariates: age, alcohol dependence, whole brain, and Total Clinician Report ETI.
$df=3, 74$; for whole brain comparison 3, 75.
[a] Healthy > PTSD, deployed non-PTSD, non-deployed ($P<0.05$).
[b] Healthy > PTSD, deployed non-PTSD ($P<0.01$).
[c] Healthy > PTSD ($P<0.04$).

To understand the unique contributions of various factors, group, full-scale WAIS-R score, history of child abuse, major depression, and alcohol abuse were entered into a linear regression to predict whole hippocampal volume. Only the WAIS-R full-scale score was a significant independent predictor, explaining 6% of the variance.

4. Discussion

In the present study, volume of the head of the hippocampus was smaller in subjects with Gulf War-related PTSD compared with healthy civilians. It is possible that hippocampal structural abnormalities in PTSD are restricted to subregions of the hippocampus, and measurement of the whole structure could miss the detection of subtle, but important, differences that have functional significance in PTSD. The head or the anterior part of the hippocampus has reciprocal connections with the prefrontal cortex (Barbas and Blatt, 1995; Carmichael and Price, 1995), and it is important in the encoding of associative memories (Sperling et al., 2003). Preclinical studies suggest that lesions in the hippocampal formation early in development result in behavioral abnormalities consistent with frontal lobe dysfunction in adulthood (Lipska et al., 1993), while removal of an abnormal hippocampus improves prefrontal cortical function (Hermann et al., 1988). Decreased volume of the anterior hippocampus has been correlated with lower scores on tests of executive function in schizophrenia (Bilder et al., 1995), while larger volume of the anterior hippocampus has been positively correlated with prefrontal cortical activation (Weinberger et al., 1992), suggesting that a smaller anterior hippocampus predicts dysfunction of the prefrontal cortex.

The head of the hippocampus is a densely vascular structure (Huang and Okudera, 1997) and consists of CA1 neurons that are particularly sensitive to stress and

Table 3
Scores on neuropsychological test battery in PTSD, deployed non-PTSD, non-deployed reservists and healthy civilians

	PTSD ($n=14$)	Deployed non-PTSD ($n=23$)	Reservists ($n=22$)	Healthy civilians ($n=28$)	F	df	P
	Mean ± S.D.	Mean ± S.D.	Mean ± S.D.	Mean ± S.D.			
WAIS-R							
WAIS-Full	97.64 ± 10.38	102.74 ± 8.45	107.41 ± 16.38	119.61 ± 17.79	7.99	3,81	<0.01[a]
WAIS-Verbal	96.93 ± 9.17	100.96 ± 8.50	105.00 ± 13.63	119.75 ± 13.65	13.52	3,81	<0.01[a]
WAIS-Performance	100.36 ± 12.16	105.87 ± 13.40	107.95 ± 18.61	111.96 ± 22.05	1.28	3,81	0.29
Wechsler Memory Scale							
Verbal							
Immediate	22.64 ± 5.85	23.35 ± 5.64	26.50 ± 6.12	32.00 ± 5.56	12.59	3,79	<0.01[a]
Delayed	18.29 ± 5.78	20.61 ± 5.64	23.73 ± 6.98	29.07 ± 6.39	11.61	3,81	<0.01[a]
% Retention	80.50 ± 11.44	87.78 ± 11.64	88.59 ± 9.47	89.08 ± 11.16	2.15	3,79	0.10
Visual							
Immediate	19.86 ± 5.07	20.74 ± 4.34	19.73 ± 4.17	34.44 ± 5.17	47.46	3,78	<0.01[a]
Delayed	18.29 ± 5.21	20.57 ± 4.01	19.32 ± 4.36	29.58 ± 9.67	12.14	3,79	<0.01[a]
% Retention	93.57 ± 19.07	100.17 ± 13.52	98.09 ± 10.99	83.60 ± 22.14	3.41	3,78	0.02[b]
Selective Reminding Test							
Verbal							
Long-term retrieval	104.29 ± 23.37	110.09 ± 20.17	120.00 ± 13.80	107.05 ± 17.83	2.82	3,68	0.05
Delayed retrieval	10.00 ± 2.60	10.23 ± 2.29	10.79 ± 1.18	10.11 ± 1.88	0.72	3,68	0.54
Long-term storage	110.29 ± 20.96	114.82 ± 18.35	123.21 ± 12.42	113.74 ± 13.67	2.47	3,68	0.07
Consistent long-term retrieval	88.29 ± 31.86	95.00 ± 29.59	112.11 ± 22.07	86.00 ± 32.30	3.56	3,68	0.02[c]
Visual							
Long-term retrieval	130.71 ± 12.54	132.05 ± 10.76	132.95 ± 5.93	120.11 ± 20.58	4.23	3,68	<0.01[d]
Delayed retrieval	11.64 ± 0.63	11.68 ± 0.65	11.84 ± 0.38	11.63 ± 0.60	0.86	3,68	0.46
Long-term storage	132.14 ± 10.49	133.27 ± 8.20	133.53 ± 5.43	122.89 ± 17.63	3.99	3,68	0.01[d]
Consistent long-term retrieval	127.21 ± 18.46	129.05 ± 16.90	131.53 ± 7.19	110.84 ± 31.34	4.78	3,68	<0.01[d]

ANOVA with age and years of alcohol dependence.
[a] Healthy > PTSD, non-PTSD combat controls, non-deployed ($P<0.05$).
[b] Deployed non-PTSD > healthy ($P<0.03$).
[c] Non-deployed > healthy ($P<0.03$).
[d] Deployed non-PTSD, non-deployed > healthy ($P<0.04$).

glucocorticoids (Yusim et al., 2000). Menon et al. (2004) reported anterior hippocampal dysfunction in veterans with Gulf War syndrome using magnetic resonance spectroscopy, and postulated that this region could be vulnerable to circulating toxins. Alternative causes for smaller volume of the head of the hippocampus include preeexisting genetic factors that increase the risk for developing PTSD in traumatized subjects (Gilbertson et al., 2002), comorbid illness including depression and alcoholism, or trauma exposure per se (Pitman, 2001). Recent studies have also demonstrated impaired prefrontal cortical function and structure in PTSD (Clark et al., 2003; Matsuo et al., 2003; Rauch et al., 2003). Although the present study did not evaluate structural functional abnormalities in the prefrontal cortex, it is possible that an initial abnormality in the CA1 neurons and dentate gyrus in the head of the hippocampus could lead to secondary abnormalities in the prefrontal cortex.

The mean whole hippocampal volume was significantly smaller in all three military groups (deployed PTSD, deployed non-PTSD and reservists) compared with healthy civilians. The military groups also had significantly lower scores on immediate and delayed verbal and visual recall subscales of the WMS-R compared with the healthy subject group.

The present study is similar to several recent studies that have not found selective impairment in hippocampal mediated memory (reviewed in Danckwerts and Leathem, 2003; Vasterling et al., 1998). Deployed

non-PTSD veterans and reservists performed better than the healthy civilians in the long-term visual storage, retrieval and verbal CLTR, respectively. It is possible that differences between the WMS-R (paragraph recall) and the SRT (word list recall) could partly explain the discrepancy in these findings. Significantly higher IQ scores in the healthy civilians could be explained by a selection bias caused by recruiting healthy subjects from a university town setting.

There are a number of potential explanations for the similarities in whole hippocampal volume and neuropsychological test performance among the three military groups and differences with healthy civilians. First, differences in IQ, or some factor related to IQ, may have contributed to differences in hippocampal volume between the healthy civilian group and the three military groups. Andreasen et al. (1993) found that hippocampal volume is correlated with full-scale IQ in healthy volunteers. While mean IQ for each of the three military groups was in the average range, mean IQ for the healthy civilian group was significantly higher and nearly two standard deviations above the mean for the normal population. Since hippocampal volume and IQ for the entire subject sample were significantly and positively correlated, and since IQ accounted for 6% of the variance in a model with other demographic factors, it is possible that IQ or some related factor may help explain the differences between hippocampal volume in the healthy civilians compared with all three military groups. Second, smaller hippocampal volume and neuropsychological deficits in the three military groups may have been related to histories of child abuse (Bremner et al., 2003a; Stein et al., 1997), major depression (MacQueen et al., 2003; Sheline et al., 1999) and alcohol dependence (Agartz et al., 1999), each of which were present in some members of all three military groups. Third, shorter duration of traumatic exposure in the Gulf and limited exposure to traditional combat may have contributed to the present findings. In previous studies, subjects with chronic PTSD of many years' duration had reduced hippocampal volume (Bremner et al., 1995, 1997, 2003b; Gurvits et al., 1996; Stein et al., 1997), but not subjects with recent PTSD (Bonne et al., 2001; De Bellis et al., 2001). This study was limited by a small number of veterans with PTSD and was conducted approximately 5 years after the Gulf War. It is possible that with the passage of time these veterans could experience a progressive loss of hippocampal volume, as has been reported in preclinical studies (Brunson et al., 2001).

The present study underlines the importance of selecting appropriate control subjects matched on sociodemographic and clinical variables, including IQ. It is possible that the focal hippocampal abnormality in PTSD is related to brain differences that existed before the trauma. Future studies should prospectively evaluate hippocampal and prefrontal cortical structure and function in subjects with PTSD as well as in well-matched controls.

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