Reduced Hippocampal Volume and Total White Matter Volume in Posttraumatic Stress Disorder

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Background: *Reduced hippocampal volumes in posttraumatic stress disorder (PTSD) patients are thought to reflect specific changes of this structure. Previous magnetic resonance imaging (MRI) studies have not consistently examined indices of overall brain atrophy, therefore it cannot be completely ruled out that hippocampal changes are explained by whole-brain atrophy. The purpose of this study was to assess hippocampal and whole-brain volume in civilian PTSD.*

Methods: *Twelve subjects with PTSD and 10 control subjects underwent brain MRI. Hippocampal volumes were visually quantified using a computerized volumetric program. Whole-brain volumes were obtained with automated k-means-based segmentation.*

Results: *No differences were found in intracranial volumes (ICV). Subjects with PTSD had higher cerebrospinal fluid (CSF)/ICV ratios and lower white matter/ICV ratios, consistent with generalized white matter (WM) atrophy. The effect of age on CSF/ICV was more pronounced in the PTSD group. Subjects with PTSD had smaller absolute and normalized bilateral hippocampal volumes. These differences persisted after adjusting for lifetime weeks of alcohol intoxication. Posttraumatic stress disorder and depression scores correlated negatively with left hippocampal volume, but PTSD scores were a better predictor of hippocampal volumes.*

Conclusions: *Our results replicate previous findings of reduced hippocampal volume in PTSD but also suggest independent, generalized, white matter atrophy.* Biol Psychiatry 2002;52:119–125

Key Words: Hippocampus, posttraumatic stress disorder, magnetic resonance imaging, white matter, segmentation

Introduction

Previous magnetic resonance imaging (MRI) studies report reduced hippocampal volumes in adult patients with posttraumatic stress disorder (PTSD) related to combat exposure or childhood sexual abuse (Bremner et al 1995, 1997; Gurvits et al 1996; Stein et al 1997). Two prospective studies have failed to document hippocampal changes in PTSD. A report in adults studied after traumatic events and at a 6-month follow-up found no hippocampal changes in subjects who developed PTSD (Bonne et al 2001). Pediatric subjects with PTSD did not show hippocampal changes at baseline or follow-up at least 2 years later (De Bellis et al 2001).

The cause of these volumetric changes is currently debated. Several explanations of reduced hippocampal volumes have been put forward and can be summarized as follows: 1) The smaller hippocampal size is a preexisting condition that predisposes individuals to experience events as traumatic or increases vulnerability to develop PTSD following trauma; 2) traumatic experiences and/or subsequent PTSD causes hippocampal damage; and 3) PTSD leads to complications (such as alcohol abuse) that damage the hippocampus (discussed in Pitman 2001). Findings from current prospective PTSD studies (Bonne et al 2001; De Bellis et al 2001) do not support hippocampal damage or preexisting hippocampal abnormalities in PTSD; longer studies are needed.

Bremner (1999) has proposed that reduced hippocampal volumes are a result of neurotoxic effects related to traumatic events/PTSD, in a process similar to hippocampal damage in animal models of stress. Studies in nonhuman primates and rodents demonstrate specific hippocampal neuronal atrophy resulting from chronic psychosocial stress (Magarinos et al 1996; McEwen and Magarinos 1997; Uno et al 1989). Mounting evidence indicates that hippocampal neuronal injury in these animal models of stress is due to an interaction of elevated glucocorticoids and excitatory neurotransmiters (Armanini et al 1990; Magarinos et al 1996). This is considered a specific effect on the hippocampus, owing to its high concentration of glucocorticoid receptors (reviewed in McEwen and Magarinos 1997); however, there is some

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Received October 25, 2001; revised February 1, 2002; accepted February 11, 2002.

0006-3223/02/$22.00
PII S0006-3223(02)01359-8

Table 1. Clinical Information on the PTSD Sample

Age/gender	Trauma	Comorbid diagnoses	Medications
36/M	Childhood sexual abuse	2° MDD in remission	None
35/F	Assault	2° Major depression	Imipramine, Lorazepam
50/M	Combat exposure	2° Major depression	Nortryptyline
41/F	Childhood sexual abuse, assault	2° MDD in remission	None
57/F	Witnessed son's death in a fire	2° MDD in remission	Imipramine, Lorazepam
41/F	Childhood sexual abuse, rape, assault	2° Major depression	Serzone
48/F	Childhood sexual/physical abuse	2° Major depression, panic disorder	Trazodone, Alprazolam
39/F	Rape	2° MDD	None
52/F	Childhood sexual/physical abuse	2° MDD in remission	Nefazodone
25/F	Car accident	2° MDD in remission	None
36/F	Threatened with a weapon	2° MDD in remission, panic disorder	Doxepin, Alprazolam
53/F	Childhood sexual abuse	2° MDD partial remission ETOH abuse in remission for 32 years	Paroxetine, Lorazepam Risperidone

PTSD, posttraumatic stress disorder; M, male; F, female; MDD, major depressive disorder; 2°, secondary; ETOH, alcohol.

evidence of decreased hippocampal glucocorticoid receptors in primates (Sanchez et al 2000). Furthermore, there is also evidence of genetic variability in hippocampal volumes (Lyons et al 2001).

Volumetric studies in PTSD have typically measured control brain regions to test how specific hippocampal changes are, but they have not examined whole-brain volumes (Bremner et al 1995, 1997; Stein et al 1997). Only one study assessed whole-brain volumes, but it had a small *n* of 7 subjects per group and no matched control subjects (Gurvits et al 1996). To our knowledge, no study has examined total volumes of white matter (WM), gray matter (GM), and cerebrospinal fluid (CSF) in PTSD. Furthermore, reports in pediatric PTSD failed to replicate changes in hippocampal volumes and instead found smaller brain volumes (Carrion et al 2001; De Bellis et al 1999), enlarged ventricles, and decreased area of the corpus callosum (De Bellis et al 1999). These findings are consistent with impaired brain development or generalized atrophy in pediatric PTSD. It is therefore important to examine indices of brain atrophy in adult PTSD.

The aim of this study was to investigate the specificity of hippocampal volumetric changes in a sample of civilian PTSD patients by measuring hippocampal volumes and whole-brain GM, WM, and CSF volumes. Because hippocampal atrophy is thought to be a very specific effect, we hypothesized that 1) PTSD patients have smaller hippocampal volumes; and 2) PTSD patients do not have evidence of whole-brain atrophy.

Methods and Materials

Patients

This study was conducted at the Department of Psychiatry and the Clinical and Magnetic Resonance Research Center (CMRRC), University of New Mexico (UNM) Health Sciences Center. Subjects with PTSD were recruited form psychiatric outpatient clinics, referred by clinicians, or self-referred. After explaining study procedures, all participants signed an informed consent approved by the institutional review board.

Twelve subjects with PTSD (10 women) diagnosed with the Clinician-Administered PTSD Scale (CAPS; Blake et al 1995) were included. All patients had scores of 60 or higher (mean ± SD, 87 ± 15) on the CAPS. Time since trauma was 270 ± 163 months and duration of illness 138 ± 81 months. The Structured Clinical Interview for DSM-IV Axis I Disorders, patient version (SCID-I/P; First et al 1996) was also administered. See Table 1. for detailed information about the patient group including gender, age, type of trauma, and medications.

Ten control subjects (female) who were free of current major axis I diagnosis on the SCID-I/NP (nonpatient version) were recruited. They were matched as closely as possible to patients by age, gender, race, height, years of education, estimated intelligence quotient (assessed by the Kaufman Brief Intelligence Test, Kaufman and Kaufman 1990), handedness (assessed by the Crovitz handedness questionnaire, Crovitz and Zener 1962) and lifetime weeks of alcohol intoxication. A week of alcohol intoxication was defined as alcohol use to the point of intoxication at least one day of the index week. Both groups also completed the Beck Depression Inventory (BDI) and the Beck Anxiety Inventory (BAI).

Exclusion criteria for both groups included lifetime history of major medical or psychiatric diagnoses: schizophrenia, bipolar disorder, mental retardation, organic brain syndrome, obsessive-compulsive disorder, head trauma with loss of consciousness, seizures, neurologic disorder, and standard MRI exclusion criteria. We excluded patients with histories of substance or alcohol *dependence*. Two subjects with a distant history of alcohol *abuse* were included (one patient and one control subject).

Magnetic Resonance Imaging

Studies were completed at 1.5 Tesla (Signa, GE Medical Systems, Waukesha, WI). The imaging protocol included a T1-weighted coronal series (fast-spoiled grass [fast-SPGR], echo time = 6.9 msec, repetition time = 17.7 msec, flip angle = 250, 1.5-mm thickness, 0-mm gap, 256 × 192 matrix) that covered the whole brain.

Hippocampal Volumetric Analysis

Volumetric determinations of the hippocampus were performed with MEASURE (Institute of Psychiatric Neuroimaging, Johns Hopkins University) (Barta et al 1997), which allows the region of measurement to be displayed in sagittal, coronal, and axial formats simultaneously. Head tilt was corrected along the anterior commissure-posterior commissure (AC–PC) line and intrahemispheric fissure before measurement. The hippocampal region measured included the subicular complex, hippocampus proper, dentate gyrus, alveus, and fimbria, and was traced anterior to posterior on coronal slices according to anatomic boundaries described by Watson et al (1992). The first anterior slice was selected according to one of the following guidelines: 1) when the inferior horn of the lateral ventricle separating the amygdala from the hippocampus was visible; 2) if the alveus was visible, the superior alveus separated the hippocampus from the amygdala; 3) if the ventricle medial to the cortical surface could not be followed, then a line was drawn extending the most medial visible portion of the ventricle to the deepest part of the semilunar gyrus; or 4) if the preceding rules could not be followed, a straight line was drawn from the most inferior part of the ventricle to the surface of the temporal lobe. The last posterior slice used for measurement was the one where the crux of the fornix separated from the hippocampus. The hippocampi were delineated in the coronal plane using a mouse-driven cursor and simultaneously using axial and sagittal planes for verification. The volumes were then reviewed (and edited if necessary) from the entire sequence of reconstructed axial and sagittal images. Volumes were obtained by two raters who were blind to each subject's diagnosis. The intraclass correlation coefficients for hippocampal volume determinations were 0.9841 for the right side and 0.9846 for the left side. The mean value of the two raters was used for analysis.

Total Brain Volumetric Analysis

The image of the brain was extracted from the cranium using the program BET (FMRIB Image Analysis Group, Oxford University, Oxford, UK [http://www.fmrib.ox.ac.uk/fsl]). Automated k-means-based segmentation of the cerebrum (excluding the cerebellum) was used to determine the volumes of GM, WM, and CSF, as previously described (Petropoulos et al 1999) Figure 1. is a typical MRI image showing the automated segmentation. Pixels that could not be assigned to CSF or GM exclusively were considered partial volume (PV). Half of the PV was assigned to GM and half to CSF. Intracranial volume (ICV) was calculated as PV + GM + WM + CSF. Total parenchyma was calculated as (PV/2) + GM + WM. The following ratios were used for statistical comparisons: GM/ICV, WM/ICV, and CSF/ICV, a sensitive measure of atrophy (Petropoulos et al 1999).

Statistical Analysis

Demographic and clinical variables were compared with two-tailed, unpaired *t* tests for continuous variables and Fisher's Exact Test for categorical variables. Brain volumes were compared with two-tailed, unpaired *t* tests. Analysis of covariance (ANCOVA) was conducted to compare hippocampal volume/total parenchyma ratios using weeks of lifetime problematic alcohol use as covariate. Correlations between clinical and volumetric variables were assessed with Pearson Product–Moment correlation coefficient.

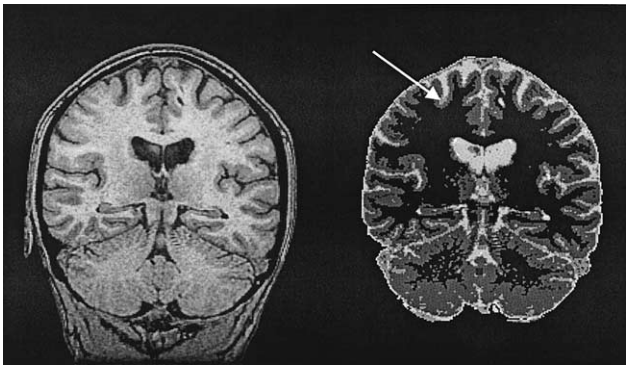

Figure 1. Left image is a T1-weighted coronal slice from a posttraumatic stress disorder patient. Right image shows the segmentation of extracted brain into white matter, gray matter, cerebrospinal fluid (CSF), and gray matter/CSF partial volume (arrow).

Results

The following comorbid diagnoses were present in the 12 PTSD patients: current secondary (beginning after PTSD) major depressive (MD) episode in 4 (33%), MD in remission in 6 (50%), MD in partial remission in 1 (8%), alcohol abuse in remission for 32 years in 1 (8%). Of the 12 patients, 8 (67%) were taking medications (see Table 1). See Table 2. for detailed information on clinical and demographic variables of both groups. Because we matched control subjects by lifetime history of alcohol intoxication, one control (10%) met criteria for alcohol abuse in remission for 18 years.

Means (SD) for volumetric measures are shown on Table 3. Subjects with PTSD had smaller absolute right (10%) and left (13%) hippocampal volumes, smaller left and right hippocampal/total parenchyma ratios (hippocampal volumes normalized to total brain tissue), smaller WM/ICV ratios, and larger CSF/ICV ratios. There were no differences in total parenchyma, ICV, or GM/ICV ratios between groups.

We conducted an analysis of covariance (ANCOVA) for left and right hippocampal/total parenchyma ratios in PTSD versus control subjects, adjusting for weeks of lifetime alcohol intoxication. We found hippocampal/total parenchyma ratios to be smaller in PTSD subjects on both the left side [$F(1,19) = 8.77$, $p < .01$] and the right side [$F(1,19) = 8.42$, $p < .01$].

The following significant correlations were found in the PTSD group: total CAPS score and left hippocampus ($r = -0.66$, $n = 12$, $p = .02$); CAPS intrusion and left

Table 2. Demographic and Clinical Variables

Variable	PTSD (n = 12) Mean	PTSD (n = 12) SD	Controls (n = 10) Mean	Controls (n = 10) SD	p^a
Age (y)	43	9.3	44	11.4	.75
Education (y)	16	3.7	16	4.5	.68
Height (inches)	65	5.4	66	4.0	.3853
Estimated IQ[b]	108	14.5	107	12.4	.89
Weeks of lifetime alcohol intoxication	44	82	23	37.5	.45
Beck Anxiety Inventory	21	10.6	2	1.8	<.01
Beck Depression Inventory	18	11.5	2	1.7	<.01
	n	%	*n*	%	p^c
Handedness					
Right	9	66.6	9	89	.6
Left	3	33.3	1	11	
Gender					
Female	10	83.3	8	80	1
Male	2	16.6	2	20	1

PTSD, posttraumatic stress disorder.
[a]Unpaired, two-tailed *t* tests.
[b]Intelligence quotient by The Kaufmann Brief Intelligence Test.
[c]Fisher's Exact Test.

hippocampus ($r = -0.61$, $n = 12$, $p = .03$); BDI and left hippocampus ($r = -0.63$, $n = 12$, $p = .03$). Figure 2. shows a scatter plot of total CAPS scores versus left hippocampal volumes. The following correlations were also significant in the PTSD group: time since trauma and CSF/ICV ($r = .84$, $n = 12$, $p = .001$); duration of illness and CSF/ICV($r = .67$, $n = 10$, $p = .034$); age and CSF/ICV ($r = .86$, $n = 12$, $p < .01$). Duration of illness correlated with time since trauma ($n = 11$, $r = .84$, $p = .001$), and age correlated with time since trauma ($n = 11$, $r = .75$, $p = .004$). Hippocampal volumes did not correlate with time since trauma, duration of illness, or age. In the whole sample, BDI scores correlated negatively with WM/ICV, ($r = -0.48$, $n = 22$, $p = .024$) and positively with CSF/ICV ($r = .49$, $n = 22$, $p = .021$).

Because both CAPS and BDI scores correlated with hippocampal volumes, a multivariate analysis was used. Stepwise regression indicated that CAPS score was the better predictor of left hippocampal volume in the PTSD group ($p = .03$). Also, a stepwise regression with CSF/ICV ratio as dependent variable and age, time since trauma, and duration of illness as independent variables revealed that age was the best model to predict CSF/ICV volumes in the PTSD group ($p = .002$). A general linear model with group, age, and their interaction as predictors and CSF/ICV as dependent variable revealed that the effect of age was greater in PTSD than in control subjects (interaction, $p = .03$). Figure 3. is a scatter plot of CSF/ICV versus age in PTSD and control subjects.

Table 3. Comparison of Brain Volumes between PTSD and Matched Control Subjects

Variable	Patients (n = 12) Mean (SD)	Control Subjects (n = 12) Mean (SD)	p^a
Right hippocampus (cc)	3.01 (.29)	3.35 (.37)	.024
Left hippocampus (cc)	2.95 (.31)	3.38 (.49)	.044
Right hippocampus/total parenchyma	.0025 (.0003)	.0028 (.0002)	.01
Left hippocampus/total parenchyma	.00264 (.00027)	.00294 (.00029)	.01
Intracranial volume (cc)	1385 (112)	1367 (134)	.73
Gray matter/ICV	.47 (.03)	.47 (.01)	.91
White matter/ICV	.33 (.04)	.36 (.03)	.039
CSF/Intracranial volume	.19 (.02)	.15 (.02)	.008
Total parenchyma (cc)[b]	1121 (107)	1150 (111)	.73

ICV, intracranial volume; CSF, cerebrospinal fluid; PTSD, posttraumatic stress disorder.
[a]Two-tailed, unpaired *t* tests.
[b]Total parenchyma: ½ partial volume + gray matter volume + white matter volume.

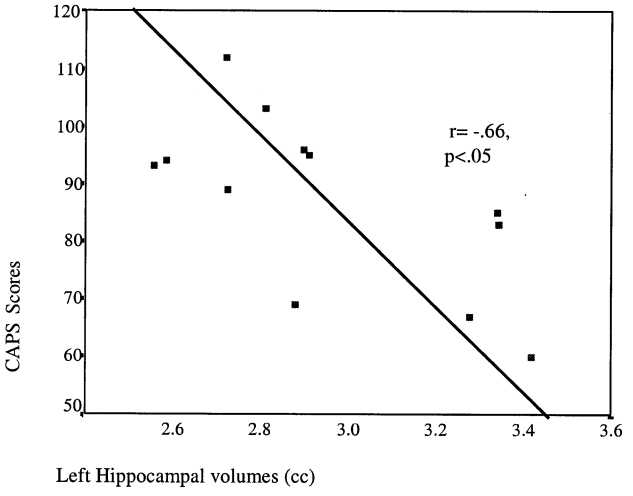

Figure 2. Scatter plot of Clinician-Administered PTSD Scale (CAPS) scores versus left hippocampal volumes in civilian PTSD ($n = 12$).

Discussion

Our findings of decreased absolute and normalized hippocampal volumes are consistent with previous reports (Bremner et al 1995, 1997; Gurvits et al 1996; Stein et al 1997) and support our primary hypothesis of reduced hippocampal volume in PTSD. Hippocampal volumes in PTSD were also smaller after controlling for lifetime weeks of alcohol intoxication. This suggests that hippocampal volumetric changes are not explained by the effects of alcohol, which is associated with hippocampal atrophy (Agartz et al 1999; Laakso et al 2000; Sullivan et al 1995). The cross-sectional nature of the study does not allow causal inferences regarding the origin of these hippocampal changes.

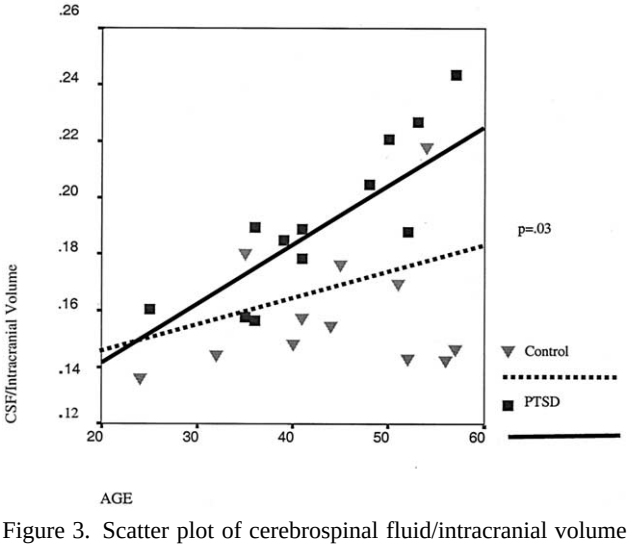

Figure 3. Scatter plot of cerebrospinal fluid/intracranial volume ratio versus age in posttraumatic stress disorder and normal control subjects. The slope is significantly different between groups ($p = .03$). CSF, cerebrospinal fluid; PTSD, posttraumatic stress disorder.

We found negative correlations between total CAPS scores and left hippocampal volumes and between re-experiencing subscale of the CAPS and left hippocampal volumes, indicating an association between current severity of PTSD symptoms and loss of left hippocampal volume. A negative correlation was also noted between BDI and left hippocampal volume, indicating that severity of current depressive symptoms is also associated with loss of hippocampal volume; however, a stepwise regression revealed that CAPS scores were better predictors of left hippocampal volume than BDI scores, suggesting that severity of PTSD symptoms has a greater impact on hippocampal volume than severity of depression.

We found high levels of anxiety in the PTSD sample, which are probably related to hyperarousal symptoms; however, BAI did not correlate with total CAPS scores or hyperarousal subscores.

Our results in the PTSD group of increased CSF to ICV ratio (CSF/ICV) and decreased WM to ICV ratio are consistent with loss of WM in PTSD. This suggests a process of WM loss leading to increased CSF volume. This is contrary to our secondary hypothesis of specific hippocampal changes. White matter loss however, does not explain hippocampal differences, because normalized hippocampal volumes (divided by total parenchyma or brain tissue) were also smaller in PTSD. These findings indicate that generalized WM atrophy in PTSD does not explain the reductions in hippocampal volume. In other words, this is consistent with specific hippocampal atrophy, independent of generalized WM atrophy.

Canive et al (1997) reported increased number of WM lesions in PTSD subjects compared to matched control subjects. These lesions were most apparent using a fluid attenuated inversion recovery (FLAIR) pulse sequence, than with standard T1- and T2-weighted images, suggesting WM pathology in PTSD subjects. We did not acquire T2 or FLAIR sequences; therefore we cannot rule out an increase in this type of WM lesions. Our findings, however, do suggest WM pathology in PTSD. The reports in pediatric PTSD of decreased brain volume (Carrion et al 2001; De Bellis et al 1999) and increased ventricular volume (De Bellis et al 1999) suggest generalized atrophy or impaired brain development. Interestingly, the finding of smaller area of the corpus callosum in this population (De Bellis et al 1999) is consistent with decreased WM matter volume.

The neurobiological mechanism of WM atrophy is unclear. Alcohol is an unlikely cause: we excluded subjects with alcohol dependence and we did not find a correlation between lifetime weeks of alcohol intoxication

with WM volume, nor were lifetime weeks of alcohol intoxication significantly different between groups. Interestingly, WM changes have been described in depression (reviewed in Sheline 2000). All our PTSD subjects had current or past depression, and BDI scores correlated negatively with WM/ICV and positively with CSF/ICV, suggesting an association between severity of depressive symptoms and WM atrophy.

Late-onset depression (typically beginning after age 60) is associated with structural findings of cortical atrophy and WM hyperintensities. These WM changes are thought to be secondary to medical and neurologic comorbidities (Sheline 2000). In contrast, brain structural findings in early-onset recurrent depression (EORD) include hippocampal abnormalities (see below) and reductions in frontal lobe volume (Coffey et al 1993; Drevets et al 1997). Our PTSD sample was more similar to EORD than late-onset depression, because all subjects were under 60 years of age, and neurologic conditions were excluded. Therefore, it is unlikely that the WM changes observed were related to medical comorbidities, although we cannot completely rule out another underlying pathologic process, such as asymptomatic artheroesclerotic changes in the PTSD group. To our knowledge, reductions in total WM volume has not been reported in EORD. Because we did not conduct separate segmentation for the different cortical regions, we cannot rule out specific involvement of the frontal lobe as studies in depression have. Future PTSD studies should conduct tissue segmentation of the whole brain as well as of different cortical and subcortical regions to explore generalized and specific WM and GM changes.

We also found a greater effect of age on CSF/ICV increase in PTSD subjects compared to control subjects. Previous studies have shown that aging in normal volunteers is associated with a rapid increase in CSF (Jernigan et al 2001). Normal volunteers also have WM loss that appears later in life and is ultimately greater than GM loss (Jernigan et al 2001). Our findings suggest acceleration of this normal age-related WM atrophy in PTSD subjects.

A number of limitations of the current study should be mentioned. First, PTSD was related to different types of traumas, and therefore was more heterogeneous than in previous studies. At the same time, we think this PTSD group was more similar to a clinical sample. Second, psychotropic medications were used in 8 of 12 (67%) PTSD subjects; therefore we cannot exclude medication effects (we do not have enough numbers to compare patients with and without medications). Third, this was a cross-sectional study and therefore cannot establish causality. Fourth, we controlled for history of alcohol intoxication, but we are aware that it is difficult to make a retrospective assessment of alcohol use. Fifth, the majority of PTSD subjects had either current major depression or major depression in remission. This is an inherent difficulty in the PTSD literature, owing to the high comorbidity with depression and overlap in diagnostic criteria. The brain imaging literature in depression is conflicting, with some studies reporting smaller hippocampal volumes (Bremner et al 2000; Sheline et al 1996, 1999), whereas others, typically using lower resolution scanners, do not (Ashtari et al 1999; Axelson et al 1993; Dupont et al 1995). We cannot completely exclude the effects of chronic depression on brain structure. Because all patients had either current or past depression, PTSD and depression were confounded; therefore, it was not possible to determine the effect of depression as a covariate.

Future studies should compare subjects with PTSD with subjects with major depression, matching for severity and chronicity of depressive symptoms. In this way, the independent effects on brain structure of depression and PTSD could be examined.

Despite the above limitations, the current findings in civilian PTSD replicate findings of reduced hippocampal volumes that are not explained by the WM atrophy that was also observed. Clearly our findings need replication. Future studies in PTSD should consistently measure indices of overall brain atrophy as well as hippocampal atrophy. Specifically, WM volume and area of the corpus callosum should be examined in PTSD patients. Moreover, other measurements of WM, such as lesion analysis and magnetic resonance spectroscopy, should be employed.

This project was supported in part by the dedicated funds of the University of New Mexico School of Medicine.

The authors thank Clifford Qualls, Ph.D., for his assistance with the statistical analysis.

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