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Reduced Posterior Hippocampal Volume in Posttraumatic Stress Disorder

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Abstract

Objective—Hippocampal volume is reduced in posttraumatic stress disorder (PTSD). In the present study, we sought to determine whether volume loss is homogenously distributed or confined to certain part of the structure.

Method—Twenty-two adult outpatients with PTSD (11 after prolonged prepubertal trauma and 11 after single adult trauma) and 22 matched healthy subjects were scanned at the National Institute of Mental Health using high-resolution 3T magnetic resonance imaging between September 2003 and August 2004. PTSD diagnosis was conferred using the Structured Clinical Interview for DSM-IV. Volumes of whole, anterior, and posterior hippocampus and subiculum were compared between groups.

Results—Total hippocampal volume was lower in patients with PTSD ($p = .2$), with a significant diagnosis by hippocampal-subregion interaction ($p = .2$). Post hoc analysis revealed significantly smaller posterior hippocampi in PTSD ($p = .006$), with no difference in the volumes of anterior hippocampus or subiculum. No volume differences were found between PTSD participants with prolonged childhood abuse compared to single adult trauma exposure.

Conclusions—The posterior hippocampus has been associated with storage, processing, and retrieval of spatiotemporal memories, central to the protective function of fear conditioning. Volume deficit in the posterior hippocampus may indicate malfunction in this faculty, leading to the exaggerated conditioned fear response observed in PTSD.

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Drug name: fluoxetine (Prozac and others).

A large body evidence suggests that hippocampal volume is reduced in posttraumatic stress disorder (PTSD), although this finding is not universal.^{1,2} Moreover, the exact role of the hippocampus in the pathophysiology of the disorder, and in the origin of volume reduction and its precise localization, are still unknown. With few exceptions,³⁻⁵ most previous structural neuroimaging studies in PTSD measured volume of the whole hippocampus. Thus, it is currently unknown whether hippocampal volume reduction in PTSD, if at all, is homogeneously distributed or if the decrease in volume is predominantly localized to a certain part of this structure. Should volume deficit be limited to a discrete region within the hippocampus, this could tentatively explain the seeming contradictions between studies reporting on the presence or absence of whole hippocampus volume reduction in PTSD. Using high-resolution 3T magnetic resonance imaging (MRI), the current study examined the volume of the whole hippocampus and the volumes of the anterior, posterior, and subiculum subregions of the hippocampus in a group of patients with PTSD consequent to either prolonged childhood abuse or a single traumatic episode and in a group of nontraumatized healthy controls.

METHOD AND MATERIALS

Twenty-two unmedicated outpatients with PTSD (mean $\pm$ SD age = 36.0 ± 10.4 years; 19 female) and 22 age- and gender-matched, never traumatized, healthy subjects (mean $\pm$ SD age = 35.8 ± 10.4 years; 19 female) participated in the study. PTSD status and severity were determined by the Clinician-Administered PTSD Scale (CAPS).⁶ A minimal CAPS score of 50 was required for inclusion (mean $\pm$ SD score = 78.0 ± 16.8). Eleven PTSD subjects suffered prolonged prepubertal trauma: sexual (N = 6) or physical/emotional (N = 5) abuse. Eleven PTSD subjects underwent single adult trauma: sexual assault (N = 4), motor vehicle accident (N = 4), and assault/robbery (N = 3). Patients all had long-standing PTSD, although in many cases there was no formal diagnosis of the disorder until recently. Time that had elapsed from exposure to trauma (mean $\pm$ SD) was 9.3 ± 8.0 years in the adult single trauma group and 26.0 ± 4.0 years in patients who underwent prolonged prepubertal trauma. Healthy control subjects and adult single-trauma PTSD patients had no childhood history of physical or sexual abuse.

The Structured Clinical Interview for DSM-IV⁷ evaluated concurrent and lifetime DSM-IV Axis I disorders. The Early Trauma Inventory⁸ was used to exclude or document childhood trauma. Patients with current or past diagnoses of anxiety or major depressive disorder (MDD) were included, provided diagnosis of PTSD preceded the comorbid condition. Nine patients had concurrent and 3 patients had past diagnoses of MDD. One patient had generalized anxiety, and another had specific phobia. No patient had a history of or a current habit of severe alcohol ingestion (this may be related to the low number of men in our cohort). Depression symptoms were rated using the Inventory of Depressive Symptomatology,⁹ with mean $\pm$ SD scores of 20.4 ± 14.6 and 5.4 ± 2.8 ($p = .003$) for PTSD and healthy subjects, respectively, and anxiety symptoms were assessed using the Hamilton Rating Scale for Anxiety,¹⁰ with mean $\pm$ SD scores of 10.2 ± 6.6 and 4.75 ± 1.91 ($p = .001$) for PTSD and healthy subjects, respectively. Intelligence was evaluated using The Wechsler Abbreviated Scales of Intelligence.¹¹ Patients were not treated with psychotropic drugs 3 weeks before scanning (6 weeks for fluoxetine). Written informed consent was obtained from all participants. The study was conducted at the National Institute of Mental Health and was approved by its institutional review board.

High-resolution images through the temporal lobes were acquired using a GE 3T MRI scanner (General Electric, Milwaukee, Wis.) as previously described.¹² Hippocampal structures were manually segmented by one rater (S.W.), blind to diagnosis, in coronal planes using Medx 3.4.1 (Sensor Systems, Sterling, Va.). Hippocampus was delimited from amygdala either by the temporal horn of the lateral ventricle or the alveus. The anterior subiculum/ventral CA1 region was defined on all coronal slices passing through the anterior hippocampus, delimited from the posterior hippocampus by the coronal plane in which the hippocampal head separated

from the body. The ventral boundary of the subiculum was defined by white matter of the parahippocampal gyrus, the dorsal boundary by white matter lining the uncus sulcus, the medial boundary by vertical line drawn from the dorsomedial tip of the parahippocampal gyrus white matter, and the lateral boundary by a horizontal line extending from the tip of the uncus sulcus. The remainder of the *anterior* hippocampus was segmented through the same range of slices to lying dorsal to the uncus sulcus.¹³ The *posterior* hippocampus consisted of the body, tail, and portion of the head of the hippocampus, situated posterior to the coronal plane in which the hippocampal head separated from the body. The body and tail were bounded ventrally and medially by the parahippocampal gyral white matter, and laterally and dorsally by the temporal horn of the lateral ventricle and the fimbria. In the posterior-most sections, the hippocampal tail was specifically delimited from the pulvinar and caudate tail.

Intrater reliabilities were assessed by computing intraclass correlation coefficients (ICC) between 2 volume measures obtained from the same image on separate days. Measures were tightly correlated, with ICC values of $r = 0.990$ and $r = 0.952$ for left and right anterior hippocampus, $r = 0.997$ and $r = 0.993$ for the left and right posterior hippocampus, $r = 0.826$ and $r = 0.820$ for left and right anterior subiculum, $r = 0.998$ and $r = 0.994$ for left and right whole hippocampus, and $r = 0.999$ for whole brain.

Data were analyzed using analysis of covariance with diagnosis as a between-subjects factor and laterality and hippocampal subregion as within-subjects factors. Total cerebral volume and age served as covariates. Pairwise comparisons were performed with significant tests from the omnibus analysis, with Bonferroni corrections for multiple comparisons.

RESULTS

Whole brain volume did not differ between patients and controls (Table 1; $t = 0.55$, $df = 42$, $p = .58$). Total hippocampal volume was significantly lower in patients with PTSD ($t = 5.78$, $df = 1.40$; $p = .02$), with a significant diagnosis by hippocampal-subregion interaction ($F = 4.96$, $df = 1.4, 57.5$; $p = .02$). Post hoc analysis revealed significantly smaller posterior hippocampi in PTSD ($t = 2.91$, $df = 42$, $p = .006$), with no difference in anterior hippocampus ($t = 1.01$, $df = 42$, $p = .32$) or subiculum ($t = 0.14$, $df = 42$, $p = .89$). Since diagnosis by side interaction was not significant, results are presented together for both sides. Since our cohort comprised mainly women, we performed the analysis without men and found no major difference relative to the above findings.

No differences in brain volume, behavioral measures, or intelligence were found between patients whose PTSD resulted from prolonged childhood abuse compared to patients whose PTSD resulted from single trauma. No differences in intelligence were found between patients with PTSD and healthy controls. No correlations were found between brain volume measures and severity or duration of PTSD, severity of depressive and anxiety symptoms, or intelligence.

DISCUSSION

Our findings suggest that hippocampal volume loss in PTSD is largely attributable to decrease in posterior hippocampal tissue and is not associated with age at traumatization, trauma type, illness duration, or comorbid depression. Not many studies sought an association between mental disorders and subdivisions of the hippocampus. Yehuda et al.⁵ and Golier et al.¹⁴ divided the hippocampus into 4 quadrants in comparing combat veterans⁵ and holocaust survivors¹⁴ with healthy controls. No volume difference was found between groups for the whole hippocampus as well as in all quadrants. In a group of patients with recurrent MDD in full remission, some drug naive and others previously medicated, Neumeister et al.¹⁵ found a reduction in hippocampal volume that was most pronounced in the posterior hippocampus. A

recent study¹⁶ looking at healthy monozygotic twins discordant for the risk of incurring anxiety or depression found lower gray matter volumes in the left posterior hippocampus of high-risk twins. The reduction in posterior hippocampal volume was clearly attributable to the effect of environmental stressors. Thus, while vulnerability to PTSD may be at least partly genetically determined and related to premorbid hippocampal volume,¹⁷ the role of environmental stressors in bringing about the disorder and altering cerebral structure cannot be easily dismissed.

In contrast with our findings and the ones listed above, Vythilingam et al.³ reported a reduction in the volumes of whole and *anterior* hippocampus in military veterans with PTSD compared with healthy, nontraumatized civilian controls. No difference in hippocampal volume was found between deployed veterans with PTSD, deployed veterans without PTSD, and nondeployed reservists. The absence of PTSD or trauma exposure–related difference in size of the hippocampus among 3 groups of military personnel is opposed to the findings of most structural neuroimaging studies published to date.^{1,2} Still, this should be considered a robust finding of the Vythilingam et al. study³ given that these constitute optimal comparison groups. Regarding the differences between military personnel and healthy controls, military veterans with PTSD differed from healthy controls in gender ($p = .07$) and significantly differed from healthy controls in education, early trauma, and intelligence.³ While mean IQ for each of the 3 military groups was in the average range, mean IQ for the healthy civilian group was nearly 2 standard deviations above the mean for the normal population. Andreasen et al.¹⁸ reported that hippocampal volume is related to full-scale IQ. Therefore, since hippocampal volume and IQ for the entire sample were significantly and positively correlated, it is possible that the difference in hippocampal volume between nontraumatized healthy controls and military personnel results from a larger than normal hippocampus in supranormal healthy controls no less than from a smaller hippocampal volume in military personnel.

Furthermore, smaller hippocampal volume in the 3 military groups may be related to a history of child abuse, major depression, and alcohol dependence, each of which were present in some members of the military groups but not in healthy controls.³ It may also be argued that the prevalence of personality types among military personnel does not fully correspond to that found in the general population. Since personality type has also been associated with hippocampal volume,¹⁹ this could be an additional confounding factor related to the difference in hippocampal volume found between military personnel and healthy controls. All things considered, results of the Vythilingam et al. study³ are not readily comparable with our own.

No differences in hippocampal volume were found between subjects exposed to trauma 9.3 years before the study and those traumatized 26.0 years prior to the study. Given emerging knowledge about memory reconsolidation,²⁰ both time periods may be considered quite comparable in terms of their chronicity. Furthermore, a recent study has shown that hypothalamic-pituitary-adrenocortical (HPA) axis activity in subjects with long-term PTSD is lower than that in healthy subjects, and that there is an inverse correlation between time since exposure to trauma and HPA axis activity.²¹ Thus, while HPA axis activity levels in recently exposed patients with PTSD are higher than in normal subjects, as time progresses, HPA axis activity declines to levels lower than normal. The exact time point when the “switch” between increased and decreased HPA axis activity occurs has not yet been defined, but both 9.3 and 26.0 years since trauma belong well within the low HPA axis activity region.

Hippocampal function is in many respects region-specific.²² The posterior hippocampus contains the main afferent and efferent connections between the hippocampus and the rest of temporal lobe.²³ It is activated by presentation of familiar items that possess behavioral relevance and require processing on the basis of meaning, in contrast with anterior hippocampus that is activated in response to the presentation of perceptually novel items.²⁴

The posterior (dorsal in animals) hippocampus has also been associated with processing, storage, and retrieval of spatiotemporal information.²⁵ Thus, posterior hippocampus volume in London taxi drivers was greater than in age-matched controls.²⁶ Interestingly, posterior hippocampus volume in London taxi drivers was even greater than that of London bus drivers, who were matched for driving experience and levels of stress, but differed in that they follow a constrained set of routes.²⁷ This increase is interpreted as an occupation-related, acquired increase reflecting the continued need to acquire and update spatial representations. In animals, acquisition of a conditioned contextual fear response is dependent on *N*-methyl-D-aspartate (NMDA) receptor-mediated mechanisms in the dorsal hippocampus (DH).²⁸ Injection of anisomycin, interleukin-1B (IL-1B), and muscimol into the DH disrupts this process.²⁹ Contextual learning increases levels of brain-derived neurotrophic factor in the DH, whereas exposure to stress or injection of IL-1B reduce it.^{30,31}

Fear conditioning is a protective and adaptive mechanism, optimizing response to hazard, ensuring vigilance, and preventing diffusion of attention to meaningless stimuli. Its proper function depends on the integration of content and context information.³² In PTSD, fear conditioning loses its protective faculty. Patients fail to discriminate between threat- and non-threat-related stimuli³³ and repeatedly experience intense and unpredictable fear responses, a condition resembling “inescapable stress” leading to “learned helplessness-like” behavior: avoidance, emotional numbing, loss of interest, and withdrawal. In animals, facilitation of serotonergic neurotransmission in DH after exposure to inescapable stress prevents development of learned helplessness³⁴ and inhibition of hippocampal cell proliferation.³⁵ Repeated exposure to an inescapable stressor results in a cascade of regionally selective changes in the expression of mineralocorticoid and glucocorticoid receptors in the DH, abolished by lesions to the 5-HT fibers from the median raphe nucleus.³⁶

The mechanism responsible for the selective posterior hippocampal damage in PTSD is unclear. The dorsal hippocampus, especially the CA1 pyramidal cells of this subregion, is particularly sensitive to transient ischemia.³⁷ A 5-minute period of ischemia caused delayed death in almost all CA1 pyramidal cell neurons with no effect on other neuronal cell populations.³⁸ During reperfusion after ischemia, cerebral blood flow is greater in the ventral than in the dorsal hippocampus.³⁹ Induction of transient ischemia is associated with long-lasting spatial learning deficits and neurodegeneration in DH CA1 cells.⁴⁰ The vulnerability to insult in the DH may be related to the high density of NMDA receptors within this region. Neurologic insult involves an excess of glutamate accumulating in the synapse, which, at sufficiently high concentration, functions as an “excitotoxin.” Excess cytosolic calcium is mobilized, producing overactivity of calcium-dependent enzymes. This produces cytoskeletal degradation, protein misfolding, and oxygen radical generation, collectively leading to neuronal death.⁴¹ Adrenal steroids are important mediators of remodeling of hippocampal neurons.⁴² The role of adrenal steroids involves interactions with neurochemical systems in the hippocampus, including serotonin, γ -aminobutyric acid, and excitatory amino acids. Probably the most important interactions are those with excitatory amino acids such as glutamate. Posttraumatic stress disorder is associated with glucocorticoid receptor hypersensitivity.⁴³ This may enhance the neurotoxic glucocorticoid effect of impairing glutamate removal from the synapse, calcium extrusion from the postsynaptic cytoplasm, and blunting the compensatory increase in antioxidant enzyme activity during insult.⁴⁰

Our study has several limitations. First, our healthy control group comprised nontraumatized subjects. Since smaller hippocampal volume was also noted in trauma-exposed individuals without PTSD compared with nonexposed healthy controls,² our findings may be at least partly related to trauma exposure rather than exclusively to PTSD. Second, the likelihood of exposure to traumatic events is at least partly related to constitution, in that individuals who are inclined to seek to seek novelty or take risks are more prone to undergo trauma. Since it has recently

been shown that hippocampal volume is related to such personality traits,⁴⁴ the between-group differences in hippocampal volume found in our study may even reflect pretrauma vulnerability factors. The relative contribution of PTSD and/or trauma exposure to our findings should be explored in future studies comprising non trauma exposed, non PTSD trauma exposed, and PTSD patient groups. Third, since it has been suggested that smaller hippocampal volume may be a pretrauma vulnerability factor toward the acquisition of PTSD,¹⁷ it is not possible to determine whether smaller posterior hippocampal volume is a premorbid or an acquired deficit. Last, our PTSD sample is predominantly female, with only 3 male subjects. While an analysis of the 19 female PTSD subjects and the 19 female controls gave identical results, in light of the small number of male subjects in our cohort it can be argued that our findings may only be applicable to female individuals with PTSD.

In conclusion, we have shown that hippocampal volume reduction in PTSD may be largely attributable to smaller posterior hippocampal volume. Volume deficit in the posterior hippocampus in PTSD may be associated with functional impairment in region-specific mechanisms vital to adaptive coping with severe stress.

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Table 1

Whole Brain, Whole Hippocampus, and Hippocampal Subregion Mean Volume (left and right hemisphere) in Patients With PTSD and Healthy Control Subjects (N = 22 in each group)

Brain Region	PTSD, Mean $\pm$ SE	Controls, Mean $\pm$ SE	Significance
Whole brain, volume, L	1.15 $\pm$ 0.10	1.17 $\pm$ 0.12	NS
Whole hippocampus, volume, mL	3.30 $\pm$ 0.46	3.64 $\pm$ 0.41	p = .022
Hippocampal subregion, volume, mL			
Subiculum	0.437 $\pm$ 0.082	0.457 $\pm$ 0.077	NS
Anterior	1.08 $\pm$ 0.22	1.13 $\pm$ 0.21	NS
Posterior	1.86 $\pm$ 0.28	2.05 $\pm$ 0.26	p = .006

Abbreviations: NS = not significant, PTSD = posttraumatic stress disorder.