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Childhood Trauma Associated With Smaller Hippocampal Volume in Women With Major Depression

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Abstract

Objective—Smaller hippocampal volume has been reported only in some but not all studies of unipolar major depressive disorder. Severe stress early in life has also been associated with smaller hippocampal volume and with persistent changes in the hypothalamic-pituitary-adrenal axis. However, prior hippocampal morphometric studies in depressed patients have neither reported nor controlled for a history of early childhood trauma. In this study, the volumes of the hippocampus and of control brain regions were measured in depressed women with and without childhood abuse and in healthy nonabused comparison subjects.

Method—Study participants were 32 women with current unipolar major depressive disorder—21 with a history of prepubertal physical and/or sexual abuse and 11 without a history of prepubertal abuse—and 14 healthy nonabused female volunteers. The volumes of the whole hippocampus, temporal lobe, and whole brain were measured on coronal MRI scans by a single rater who was blind to the subjects' diagnoses.

Results—The depressed subjects with childhood abuse had an 18% smaller mean left hippocampal volume than the nonabused depressed subjects and a 15% smaller mean left hippocampal volume than the healthy subjects. Right hippocampal volume was similar across the three groups. The right and left hippocampal volumes in the depressed women without abuse were similar to those in the healthy subjects.

Conclusions—A smaller hippocampal volume in adult women with major depressive disorder was observed exclusively in those who had a history of severe and prolonged physical and/or sexual abuse in childhood. An unreported history of childhood abuse in depressed subjects could in part explain the inconsistencies in hippocampal volume findings in prior studies in major depressive disorder.

Stressful life events are frequently associated with the onset of episodes of major depression (1, 2). Elevated levels of plasma cortisol (3, 4) and deficits in declarative memory mediated by the hippocampus (5–7) have also been reported in subgroups of patients with unipolar major depressive disorder. Preclinical studies have confirmed that chronic psychosocial stress and cortisol administration inhibit neurogenesis in the dentate gyrus (8–10) and cause atrophy or remodeling of the apical dendrites of the pyramidal neurons in the CA3 region of the hippocampus (reviewed in references 11–13).

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Morphometric techniques based on magnetic resonance imaging have been used to determine whether these preclinical findings of hippocampal damage can be extended to patients with major depression and other stress-related disorders. Over the last 5 years, several groups have confirmed smaller than normal volumes of the left hippocampus (14, 15) and of the left and right hippocampus (5, 16, 17) in unipolar major depressive disorder. A smaller hippocampal volume was correlated with the total duration of depression (5, 16). Other groups, however, have not found significant differences in hippocampal volume between patients with unipolar major depressive disorder and healthy subjects (18–23). Reports on hippocampal volume in bipolar disorder are also mixed, with reports of larger (24) and smaller (25) hippocampal volumes, as well as no difference in volume between bipolar disorder patients and normal subjects (26).

In addition to methodological issues such as slice thickness and definition of hippocampal landmarks, several clinical and biological factors may help explain these disparate findings in hippocampal morphometry in major depressive disorder. A parallel corpus of studies in adults with a history of childhood abuse has confirmed the presence of smaller hippocampal volumes using similar morphometric magnetic resonance imaging (MRI) techniques. Patients with posttraumatic stress disorder (PTSD) associated with severe and repeated physical and/or sexual abuse in childhood have been shown to have significantly smaller left hippocampal volumes (27, 28). Adult women with a history of childhood abuse have smaller left hippocampal volumes despite different psychiatric diagnoses (28). Women with borderline personality disorder and a history of childhood trauma also have been reported to have smaller hippocampal volumes, compared to healthy women (29).

According to the most recent data from the National Child Abuse and Neglect Data System, an estimated 826,000 cases of child maltreatment were reported in the United States in 1999 (30). Half of these cases were instances of neglect, 21% were instances of physical abuse, and 11% were instances of sexual abuse. Comorbid major depressive disorder occurs in approximately 40%–50% of patients with PTSD (31, 32). Despite preclinical and clinical evidence suggesting that severe stress early in life is associated with persistent hypothalamic-pituitary-adrenal (HPA) axis abnormalities and a reduction of hippocampal volume in adulthood, morphometric studies in major depressive disorder have neither reported nor controlled for a history of early childhood trauma. The inconsistent findings on hippocampal volume in major depressive disorder therefore may be partly due to the uncontrolled and variable inclusion of women with a history of childhood trauma.

The present study measured the volumes of the whole hippocampus and of control brain regions in depressed subjects and healthy comparison subjects for whom a detailed evaluation of childhood history of physical and/or sexual abuse was obtained. In view of the aforementioned preclinical and clinical literature showing persistent brain changes after adverse experiences early in life, we hypothesized that depressed patients with a history of early childhood abuse would have smaller hippocampal volumes, compared to depressed subjects and healthy subjects without a history of childhood trauma.

Method

Subjects

Forty-six women were recruited through newspaper advertisements and flyers and were admitted as inpatients to the Emory University Hospital General Clinical Research Center. The protocol was approved by both the Emory University Institutional Review Board (the Human Investigators Committee) and the General Clinical Research Center Human Subjects Committee. All subjects provided written informed consent before participation. Twenty-one subjects who fulfilled criteria for childhood physical and/or sexual abuse and major

depressive disorder, 11 patients who fulfilled criteria for current major depressive disorder but had not experienced childhood abuse, and 14 healthy subjects without early trauma history were included in the study. All subjects received monetary compensation for participation.

Depressed patients were included if they fulfilled criteria for major depressive disorder on the basis of the Structured Clinical Interview for DSM-IV Axis I Disorders (33). Severity of depression was measured with the 17-item Hamilton Depression Rating Scale (34) and the Zung Depression Scale (35).

The clinician-rated Early Trauma Inventory (36) was administered to determine the presence of early life trauma and to evaluate the extent of the trauma. The Early Trauma Inventory assesses the number, frequency, duration, and subjective impact of different types of traumatic experiences (physical, sexual, and emotional abuse and general traumas) and has been shown to be a valid and reliable measure of early trauma. Considerable effort was made to obtain independent validation of abuse from court, social service, and/or medical records and from family members or friends. Independent verification was possible for 11 (52%) of 21 subjects. The Clinician-Administered PTSD Scale (37) was also administered to confirm the presence of PTSD symptoms and evaluate their severity.

Since traumatic experiences early in childhood (and not peripubertal/postpubertal trauma) have been consistently associated with persistent HPA axis and hippocampal structural abnormalities and an increased risk for adulthood disorders (38), we restricted this study to women with a history of prepubertal physical and/or sexual abuse. Stringent criteria for physical and/or sexual abuse were used to reduce variability related to differences in types of trauma. Depressed women with a history of childhood abuse were included if the abuse occurred before the subject's first menstrual period at a frequency of at least once a month for more than a year. Sexual abuse was defined as having been forced to touch another person's intimate parts, having been touched in intimate parts, or attempted or completed vaginal, oral, or anal intercourse. Physical abuse was defined as having been spanked, hit, kicked, or choked in a way that left bruises or injuries; having been attacked with a weapon; or having been tied up or locked in a room or a closet (39). Women with major depressive disorder and healthy women without a history of childhood physical and/or sexual abuse, parental loss, or exposure to other traumatic events formed the comparison group.

The healthy women had no current or past history of psychiatric illness, including alcohol or other substance abuse or dependence. Subjects were excluded from the study if they had a major medical illness, significant head trauma, irregular menses, or any other axis I disorder, including bipolar disorder, schizophrenia, and schizoaffective disorder. Those with a contraindication for an MRI, including having a cardiac pacemaker, were excluded.

The subjects were free of hormonal (except for oral contraceptives) or psychotropic medication at the time of the study. The subjects were part of a larger project on the neurobiology of early trauma (39, 40).

MRI

MRI acquisition—Subjects were imaged with a 1.5-T General Electric Signa device (General Electric, Milwaukee) by using a tilted coronal three-dimensional volume spoiled gradient recoil sequence with TR=25 msec, TE=5 msec, NEX (number of excitations)=2, matrix 256×256, and field of view=22 cm. This resulted in 124 axial 1.5-mm contiguous slices.

MRI processing—Images were transferred through the computer network to a Sun Sparc Ultra 80 workstation (Sun Microsystems, Santa Clara, Calif.). All images were resliced from axial images into 1-mm isometric voxel coronal images that were perpendicular to the long axis of the hippocampus. The boundaries of the hippocampus were traced manually with a mouse-driven cursor by using the ANALYZE program (Mayo Foundation, Rochester, Minn.).

Measurement of hippocampal volume—Anatomic guidelines for the hippocampus were based on the work of Watson et al. (41) and Duvernoy (42) and were modified in consultation with a neuroradiologist who is an expert in hippocampal anatomy (43–46). After extensive training in hippocampal anatomy, a single rater who was blind to the subjects' diagnoses (M.V.) traced the hippocampal boundaries of the patients and the healthy comparison subjects (Figure 1). 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 CSF around the hippocampus were excluded. Posteriorly, the start slice was defined as the slice 3 mm anterior to where the crura of the fornix separate 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. (41). 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 (SD=2).

The hippocampus was segmented into the head, body, and tail to evaluate regional differences in hippocampal volume between the groups and to allow comparison of the results of this study with those of previous studies that measured only the hippocampal body (14, 47). The body (mid-hippocampal segment) included 10 15-mm coronal slices between the superior colliculus and the bifurcation of the basilar artery, with the first slice anterior to superior colliculus (27, 45, 47). The tail was defined as all slices posterior to the end slice of the body.

The region-of-interest module of the ANALYZE software package calculated volumes for each slice based on the cross-sectional area measure multiplied by the slice thickness. The final volumes of the right and left whole, head, body, and tail of the hippocampus were calculated by summing the volumes of the individual slices for each region.

Measurement of control brain regions—The temporal lobe of subjects was measured by using previously described methods (48). The whole brain volume was assessed by using the auto-trace mode in the ANALYZE program and included the gray matter, white matter, and CSF of both cerebral hemispheres, the cerebellum, and the brainstem above the level of the pons.

Interrater reliability—Two raters traced the hippocampus in a subgroup of 12 randomly selected subjects, and the interrater correlation coefficients were calculated. Interrater reliability was determined with the intraclass correlation coefficient (ICC) and one-way analysis of variance (ANOVA) 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.

Statistical Analysis

Group differences between continuous variables such as age and weight were analyzed by using ANOVA. Categorical variables, including race, handedness, and presence or absence of PTSD and alcohol and other substance abuse or dependence, were evaluated by using chi-square tests. Psychometric scale score differences among the three groups were evaluated by using the Kruskal-Wallis nonparametric multiple comparisons test. Comparisons of volumetric measures were conducted by using multivariate analysis of covariance, with whole brain volume, age, race, education, presence of PTSD, and presence of alcohol and other substance abuse or dependence as covariates. Spearman's rho correlations were used to analyze the relationship between hippocampal volume and the clinical variables.

Results

Subject Characteristics

The sociodemographic and clinical characteristics of subjects are given in Table 1. PTSD was more prevalent in the abused group with major depressive disorder than in the major depressive disorder and healthy subject groups (χ^2=22.28, df=2, p<0.001). Of the 21 subjects with depression and childhood abuse, five (24%) had current PTSD, nine (43%) had both a current and lifetime diagnosis of PTSD, one (<1%) had only a past history of PTSD, and six (29%) had neither a current nor a lifetime diagnosis of PTSD.

Nine (43%) of the 21 subjects with abuse and depression had a past history of alcohol dependence, and one subject had a past history of alcohol abuse. In contrast, three (27%) of the 11 patients with major depression alone had a past history of alcohol abuse, and none had dependence. None of the subjects in the healthy comparison group had either alcohol abuse or dependence. The prevalence of a past history of alcohol abuse or dependence was significantly different across the three groups (χ^2=9.40, df=2, p=0.009), with higher rates in the depressed women with a history of childhood abuse compared to the healthy subjects (p=0.002, Fisher's exact test) and similar rates in the depressed women with and those without a history of abuse. Data on other current and lifetime comorbid psychiatric diagnoses in the patient group are presented in Table 2.

Brain Volumetrics Results

Left hippocampal volume was significantly different between the abused women with current major depression, the nonabused women with current major depression, and the healthy comparison subjects after age, race, presence of PTSD, presence of alcohol and other substance abuse or dependence, and whole brain volume were co-varied (F=5.45, df=2, 39, p=0.009) (Table 3 and Figure 2). The subjects with childhood sexual and/or physical abuse and current major depressive disorder had an 18% smaller mean left hippocampal volume than the depressed subjects without abuse (corrected mean volume=2705 mm^3, SE=106, compared with 3292 mm^3, SE=116, for the nonabused depressed subjects) (p=0.007, Tukey) and a 15% smaller mean left hippocampal volume than the healthy subjects (corrected mean volume=2705 mm^3, SE=106, compared with 3179 mm^3, SE=123, for the healthy subjects) (p=0.06, Tukey). There was no significant difference in the left hippocampal volume between the depressed women without abuse and the healthy subjects (corrected mean volume=3292 mm^3, SE=116, compared with 3179 mm^3, SE=123, for the healthy subjects) (p=0.85, Tukey).

The right hippocampus volume was similar in all three groups (F=2.07, df=2, 36, p=0.14).

In all groups combined, there was a strong positive correlation between volumes for the hippocampal body and the whole hippocampus (left hippocampal body: r_s=0.62, df=44,

p<0.001; right hippocampal body: r_s=0.59, df=44, p<0.001), as well as between volumes for the head of the hippocampus and the whole hippocampus (left-head: r_s=0.80, df=44, p<0.001; right head: r_s=0.84, df=44 p<0.001). The positive correlation was also preserved when individual subgroups were examined.

There was a significant difference in the volume of the left hippocampal head and a nearly significant difference in the volume of the left hippocampal body across the three groups (left hippocampal head: F=3.64, df=2, 36, p=0.04; left hippocampal body: F=2.83, df=2, 36, p=0.07) (Table 3 and Figure 2). There were no significant differences in the volume of the whole brain or of the temporal lobe between the depressed women with and without abuse and the healthy subjects.

Correlations Between Severity of Depression, Trauma, and Hippocampal Volume

There were no significant correlations between right and left hippocampal volumes and any clinical variables, including a history of alcohol abuse. After significance levels were corrected for multiple comparisons, no significant correlations were found between hippocampal volume and the Early Trauma Inventory total score or the physical, sexual, and emotional subscale scores.

Discussion

This study demonstrates that adult women with major depressive disorder and a history of severe and repeated physical and/or sexual abuse in childhood had smaller left hippocampal volumes, compared to depressed women without a history of abuse and compared to healthy subjects. Hippocampal volumes in depressed women without a history of childhood abuse were similar to those of healthy women with neither an abuse history nor psychiatric illness.

The findings may explain both positive and negative findings in previous studies of hippocampal volume in major depressive disorder. The finding of smaller hippocampal volumes in depressed women with abuse in this study is similar to reports of smaller hippocampal volumes in some studies of patients with major depressive disorder (5, 14–17). The normal hippocampal volume in depressed women without abuse in this study is similar to reported negative findings in earlier studies (18–20, 22, 23). Close examination of the MRI studies of patients with major depressive disorder suggests that hippocampal structural abnormalities may be restricted to subjects with treatment-resistant depression (15, 49), older women with major depressive disorder (5, 16), women with treatment-resistant depression (18), and elderly depressed patients (16, 17), with some exceptions (14, 19, 20). Patients with depression and comorbid illnesses such as PTSD are known to have a poorer response to antidepressants, compared to patients with depression alone. Findings of smaller hippocampal volumes in depressed women and in patients with treatment-resistant depression but not in mixed groups of patients with treatment-responsive depression raise the possibility that prepubertal childhood physical and/or sexual abuse could be associated with poor antidepressant response as well as with morphological abnormalities in the hippocampus in adulthood. Because, to our knowledge, no previous studies of hippocampal volume in major depressive disorder have documented the presence or absence of childhood physical and/or sexual abuse, it is possible that varying trauma histories may have contributed to the disparate findings in hippocampal morphometry. Hippocampal abnormalities could be a direct consequence of severe childhood trauma or could occur as a result of interaction with other factors, such as depression, alcohol use, or medical illness. In this study, however, significant differences in hippocampal volumes between depressed subjects with childhood trauma and comparison subjects were found after controlling for a past history of alcohol and other substance abuse.

The findings of this study are similar to those of a study by Stein et al. (28) reporting smaller left hippocampal volumes in women with childhood sexual abuse, although the magnitude of the difference in hippocampal volume was greater in the present study (18% smaller mean volume versus 5% smaller mean volume than in normal comparison subjects). Because Stein et al. (28) did not include a depressed group without abuse and only a third of the 21 subjects in the current study had childhood abuse and current major depression, definitive conclusions regarding the contribution of early trauma to hippocampal volume in depressed adults could not be drawn. Smaller hippocampi have been reported in adult subjects with PTSD secondary to combat (47, 50) and to childhood physical and/or sexual abuse (27). In contrast, similar smaller hippocampal volumes have not been found in children with PTSD secondary to sexual abuse (51, 52) and in adults with PTSD after a motor vehicle accident (53). Taken together, MRI studies in PTSD suggest that the severity, duration, frequency, and kind of trauma as well as the subject's age during exposure to trauma and comorbid alcohol use (54) could contribute to the contradictory findings about hippocampal volume in this disorder. We attempted to reduce variability in the study group by restricting inclusion to women with a history of severe, recurrent, and prolonged abuse that occurred before puberty. The volume of the left hippocampus was smaller than normal in this study as well as in prior studies that evaluated brain changes related to childhood trauma (27, 28). In contrast, smaller right hippocampal volumes were seen in subjects with postpubertal traumatic experiences (46, 49). The possibility that traumatic experiences before puberty may differentially affect the developing left hippocampus, particularly the head, needs to be examined.

The absence of a comparison group with early childhood trauma without current major depressive disorder or PTSD limits our ability to determine whether having a smaller left hippocampus is a risk factor for developing major depressive disorder or a consequence of abuse. Numerous preclinical studies support the possibility that morphological changes in the hippocampus are a consequence of stress. Exposure to chronic psychosocial stress and administration of hydrocortisone alter the morphology of apical dendrites and the synaptic structure of hippocampal neurons (reviewed in references 12, 55). Psychosocial stress, as well as glucocorticoids, inhibits neurogenesis in the dentate gyrus of the hippocampus (9, 56). Recent preclinical evidence supports the possibility that exposure to elevated levels of corticotropin releasing hormone (CRH) early in development results in progressive loss of hippocampal CA3 neurons (57). Increased levels of CSF CRH seen in rats after maternal separation (58–60), in nonhuman primates exposed to variable foraging demand (61), and in humans with PTSD (62, 63) raise the possibility that elevated CRH levels could have a direct neurotoxic effect on hippocampus neurons in stress-related disorders.

Human studies have replicated increased HPA axis sensitization after childhood abuse. Women with current depression and a history of childhood physical and/or sexual abuse had greater increases in plasma cortisol and ACTH in response to the Trier Social Stress Test (39). The importance of childhood abuse is further supported by the finding that subjects with major depressive disorder and without a history of childhood abuse had a normal cortisol response to a psychological stress paradigm (39, 64, unpublished 2002 manuscript of M. Vythilingam et al.). A similar enhancement of pituitary response to an endocrine challenge test—the CRH stimulation test—was seen in depressed children with ongoing abuse (65) and in women with childhood abuse (40), suggesting that persistent abnormalities in the HPA axis occur relatively early in life. Thus, increased levels of CRH and cortisol during repeated childhood abuse together with persistent hyperactivity and sensitization of the HPA axis in adulthood could damage hippocampal neurons in adult women with major depressive disorder. The lack of a smaller hippocampal volume in depressed women without a history of abuse in this study as well as in an independent sample of depressed subjects

recruited at a different center (unpublished 2002 manuscript of M. Vythilingam, et al.) further highlights the deleterious effects of childhood abuse on brain development.

Smaller hippocampal volume could also be a risk factor for developing psychiatric disorders after exposure to overwhelming stress. Recent studies in humans and in nonhuman primates confirmed that about 40%–54% of the variance in hippocampal volume is genetically determined (66, 67). Morphological changes in the hippocampus have not been consistently observed subsequent to psychosocial stress or hydrocortisone administration (68, 69). Gilbertson et al. (70) observed smaller hippocampal volume both in non-combat-exposed and in combat-exposed identical co-twins with PTSD and concluded that smaller hippocampi increase the vulnerability for developing PTSD in individuals exposed to trauma. Similar twin studies or prospective studies in high-risk populations will help resolve whether smaller hippocampal volume predisposes traumatized individuals to developing depression.

We demonstrated that smaller left hippocampal volume in women with major depressive disorder can be attributed to severe and repetitive physical and/or sexual abuse in childhood. Given the high prevalence of abuse in childhood, future studies evaluating hippocampal structure and function in depressed subjects should treat subjects with and without childhood abuse as separate groups. This strategy will help to increase homogeneity among subjects and to enhance reproducibility of biological findings in psychiatric illnesses. Future research should also focus on developing strategies to prevent and reverse structural brain changes after exposure to traumatic experiences in childhood.

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References

1. Kendler KS, Thornton LM, Gardner CO. Stressful life events and previous episodes in the etiology of major depression in women: an evaluation of the “kindling” hypothesis. Am J Psychiatry. 2000; 157:1243–1251. [PubMed: 10910786]
2. Maciejewski PK, Prigerson HG, Mazure CM. Sex differences in event-related risk for major depression. Psychol Med. 2001; 31:593–604. [PubMed: 11352362]
3. Wirz-Justice, A. Biological rhythms in affective disorders, in Psychopharmacology: The Fourth Generation of Progress. Bloom, FE.; Kupfer, DJ., editors. New York: Raven Press; 1995. p. 999-1017.
4. Young EA, Carlson NE, Brown MB. Twenty-four-hour ACTH and cortisol pulsatility in depressed women. Neuropsychopharmacology. 2001; 25:267–276. [PubMed: 11425510]
5. Sheline YI, Sanghavi M, Mintun MA, Gado MH. Depression duration but not age predicts hippocampal volume loss in medically healthy women with recurrent major depression. J Neurosci. 1999; 19:5034–5043. [PubMed: 10366636]
6. Bemelmans KJ, Goekoop JG, van Kempen GM. Recall performance in acutely depressed patients and plasma cortisol. Biol Psychiatry. 1996; 39:750–752. [PubMed: 8731465]
7. Rubinow DR, Post RM, Savard R, Gold PW. Cortisol hypersecretion and cognitive impairment in depression. Arch Gen Psychiatry. 1984; 41:279–283. [PubMed: 6703846]
8. Czeh B, Michaelis T, Watanabe T, Frahm J, de Biurrun G, van Kampen M, Bartolomucci A, Fuchs E. Stress-induced changes in cerebral metabolites, hippocampal volume, and cell proliferation are

prevented by antidepressant treatment with tianeptine. Proc Natl Acad Sci USA. 2001; 98:12796–12801. [PubMed: 11675510]

9. Gould E, McEwen BS, Tanapat P, Galea LA, Fuchs E. Neurogenesis in the dentate gyrus of the adult tree shrew is regulated by psychosocial stress and NMDA receptor activation. J Neurosci. 1997; 17:2492–2498. [PubMed: 9065509]
10. Gould E, Tanapat P, McEwen BS, Flugge G, Fuchs E. Proliferation of granule cell precursors in the dentate gyrus of adult monkeys is diminished by stress. Proc Natl Acad Sci USA. 1998; 95:3168–3171. [PubMed: 9501234]
11. Sapolsky RM. Stress hormones: good and bad. Neurobiol Dis. 2000; 7:540–542. [PubMed: 11042072]
12. McEwen BS. Effects of adverse experiences for brain structure and function. Biol Psychiatry. 2000; 48:721–731. [PubMed: 11063969]
13. Sapolsky RM. Stress, glucocorticoids, and damage to the nervous system: the current state of confusion. Stress. 1996; 1:1–19. [PubMed: 9807058]
14. Bremner JD, Narayan M, Anderson ER, Staib LH, Miller HL, Charney DS. Hippocampal volume reduction in major depression. Am J Psychiatry. 2000; 157:115–117. [PubMed: 10618023]
15. Mervaala E, Fohr J, Kononen M, Valkonen-Korhonen M, Vainio P, Partanen K, Partanen J, Tiihonen J, Viinamaki H, Karjalainen AK, Lehtonen J. Quantitative MRI of the hippocampus and amygdala in severe depression. Psychol Med. 2000; 30:117–125. [PubMed: 10722182]
16. Sheline YI, Wang PW, Gado MH, Csernansky JG, Vannier MW. Hippocampal atrophy in recurrent major depression. Proc Natl Acad Sci USA. 1996; 93:3908–3913. [PubMed: 8632988]
17. Steffens DC, Byrum CE, McQuoid DR, Greenberg DL, Payne ME, Blitchington TF, MacFall JR, Krishnan KR. Hippocampal volume in geriatric depression. Biol Psychiatry. 2000; 48:301–309. [PubMed: 10960161]
18. Vakili K, Pillay SS, Lafer B, Fava M, Renshaw PF, Bonello-Cintron CM, Yurgelun-Todd DA. Hippocampal volume in primary unipolar major depression: a magnetic resonance imaging study. Biol Psychiatry. 2000; 47:1087–1090. [PubMed: 10862809]
19. Ashtari M, Greenwald BS, Kramer-Ginsberg E, Hu J, Wu H, Patel M, Aupperle P, Pollack S. Hippocampal/amygdala volumes in geriatric depression. Psychol Med. 1999; 29:629–638. [PubMed: 10405084]
20. Pantel J, Schroder J, Essig M, Popp D, Dech H, Knopp MV, Schad LR, Eysenbach K, Backenstrass M, Friedlinger M. Quantitative magnetic resonance imaging in geriatric depression and primary degenerative dementia. J Affect Disord. 1997; 42:69–83. [PubMed: 9089060]
21. Coffey CE, Wilkinson WE, Weiner RD, Parashos IA, Djang WT, Webb MC, Figiel GS, Spritzer CE. Quantitative cerebral anatomy in depression: a controlled magnetic resonance imaging study. Arch Gen Psychiatry. 1993; 50:7–16. [PubMed: 8422224]
22. Axelson DA, Doraiswamy PM, McDonald WM, Boyko OB, Tupler LA, Patterson LJ, Nemeroff CB, Ellinwood EH Jr, Krishnan KR. Hypercortisolemia and hippocampal changes in depression. Psychiatry Res. 1993; 47:163–173. [PubMed: 8341769]
23. Rusch BD, Abercrombie HC, Oakes TR, Schaefer SM, Davidson RJ. Hippocampal morphometry in depressed patients and control subjects: relations to anxiety symptoms. Biol Psychiatry. 2001; 50:960–964. [PubMed: 11750892]
24. Kemmerer M, Nasrallah H, Sharma S, Olson S, Martin R, Lynn M. Increased hippocampal volume in bipolar disorder (abstract). Biol Psychiatry. 1994; 35:626.
25. Swayze VW II, Andreasen NC, Alliger RJ, Yuh WT, Ehrhardt JC. Subcortical and temporal structures in affective disorder and schizophrenia: a magnetic resonance imaging study. Biol Psychiatry. 1992; 31:221–240. [PubMed: 1547297]
26. Hauser P, Altshuler LL, Berrettini W, Dauphinais ID, Gelernter J, Post RM. Temporal lobe measurement in primary affective disorder by magnetic resonance imaging. J Neuropsychiatry Clin Neurosci. 1989; 1:128–134. [PubMed: 2521053]
27. Bremner JD, Randall P, Vermetten E, Staib L, Bronen RA, Mazure C, Capelli S, McCarthy G, Innis RB, Charney DS. Magnetic resonance imaging-based measurement of hippocampal volume in posttraumatic stress disorder related to childhood physical and sexual abuse—a preliminary report. Biol Psychiatry. 1997; 41:23–32. [PubMed: 8988792]

28. Stein MB, Koverola C, Hanna C, Torchia MG, McClarty B. Hippocampal volume in women victimized by childhood sexual abuse. Psychol Med. 1997; 27:951–959. [PubMed: 9234472]
29. Driessen M, Herrmann J, Stahl K, Zwaan M, Meier S, Hill A, Osterheider M, Petersen D. Magnetic resonance imaging volumes of the hippocampus and the amygdala in women with borderline personality disorder and early traumatization. Arch Gen Psychiatry. 2000; 57:1115–1122. [PubMed: 11115325]
30. US Department of Health and Human Services. Washington, DC: US Government Printing Office; 2001. Administration on Children, Youth and Families: Child Maltreatment 1999.
31. Breslau N, Davis GC, Andreski P, Peterson E. Traumatic events and posttraumatic stress disorder in an urban population of young adults. Arch Gen Psychiatry. 1991; 48:216–222. [PubMed: 1996917]
32. Kessler RC, Sonnega A, Bromet E, Hughes M, Nelson CB. Posttraumatic stress disorder in the National Comorbidity Survey. Arch Gen Psychiatry. 1995; 52:1048–1060. [PubMed: 7492257]
33. First, MB.; Spitzer, RL.; Gibbon, M.; Williams, JBW. Structured Clinical Interview for DSM-IV Axis I Disorders, Patient Edition (SCID-P), version 2. New York: New York State Psychiatric Institute, Biometrics Research; 1996.
34. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry. 1960; 23:56–62. [PubMed: 14399272]
35. Zung WWK. A self-rating depression scale. Arch Gen Psychiatry. 1965; 12:63–70. [PubMed: 14221692]
36. Bremner JD, Vermetten E, Mazure CM. Development and preliminary psychometric properties of an instrument for the measurement of childhood trauma: the Early Trauma Inventory. Depress Anxiety. 2000; 12:1–12. [PubMed: 10999240]
37. Blake DD, Weathers FW, Nagy LM, Kaloupek DG, Gusman FD, Charney DS, Keane TM. The development of a clinician-administered PTSD scale. J Trauma Stress. 1995; 8:75–90. [PubMed: 7712061]
38. Heim C, Nemeroff CB. The role of childhood trauma in the neurobiology of mood and anxiety disorders: preclinical and clinical studies. Biol Psychiatry. 2001; 49:1023–1039. [PubMed: 11430844]
39. Heim C, Newport DJ, Heit S, Graham YP, Wilcox M, Bonsall R, Miller AH, Nemeroff CB. Pituitary-adrenal and autonomic responses to stress in women after sexual and physical abuse in childhood. JAMA. 2000; 284:592–597. [PubMed: 10918705]
40. Heim C, Newport DJ, Bonsall R, Miller AH, Nemeroff CB. Altered pituitary-adrenal axis responses to provocative challenge tests in adult survivors of childhood abuse. Am J Psychiatry. 2001; 158:575–581. [PubMed: 11282691]
41. Watson C, Andermann F, Gloor P, Jones-Gotman M, Peters T, Evans A, Olivier A, Melanson D, Leroux G. Anatomic basis of amygdaloid and hippocampal volume measurement by magnetic resonance imaging. Neurology. 1992; 42:1743–1750. [PubMed: 1513464]
42. Duvernoy, HM. The Human Hippocampus: An Atlas of Applied Anatomy. Munich, JF: Bergmann Verlag; 1988.
43. Bronen RA. Hippocampal and limbic terminology. AJNR Am J Neuroradiol. 1992; 13:943–945. [PubMed: 1590195]
44. Bronen RA, Cheung G. MRI of the temporal lobe: normal variations, with special reference toward epilepsy. Magn Reson Imaging. 1991; 9:501–507. [PubMed: 1779721]
45. Bronen RA, Cheung G. MRI of the normal hippocampus. Magn Reson Imaging. 1991; 9:497–500. [PubMed: 1779720]
46. Bronen RA, Cheung G. Relationship of hippocampus and amygdala to coronal MRI landmarks. Magn Reson Imaging. 1991; 9:449–457. [PubMed: 1881265]
47. Bremner JD, Randall P, Scott TM, Bronen RA, Seibyl JP, Southwick SM, Delaney RC, McCarthy G, Charney DS, Innis RB. MRI-based measurement of hippocampal volume in patients with combat-related posttraumatic stress disorder. Am J Psychiatry. 1995; 152:973–981. [PubMed: 7793467]

48. Vythilingam M, Anderson ER, Goddard A, Woods SW, Staib LH, Charney DS, Bremner JD. Temporal lobe volume in panic disorder—a quantitative magnetic resonance imaging study. Psychiatry Res. 2000; 99:75–82. [PubMed: 10963983]
49. Shah PJ, Ebmeier KP, Glabus MF, Goodwin GM. Cortical grey matter reductions associated with treatment-resistant chronic unipolar depression: controlled magnetic resonance imaging study. Br J Psychiatry. 1998; 172:527–532. [PubMed: 9828995]
50. Gurvits TV, Shenton ME, Hokama H, Ohta H, Lasko NB, Gilbertson MW, Orr SP, Kikinis R, Jolesz FA, McCarley RW, Pitman RK. Magnetic resonance imaging study of hippocampal volume in chronic, combat-related posttraumatic stress disorder. Biol Psychiatry. 1996; 40:1091–1099. [PubMed: 8931911]
51. De Bellis MD, Keshavan MS, Clark DB, Casey BJ, Giedd JN, Boring AM, Frustaci K, Ryan ND. AE Bennett Research Award. Developmental traumatology, part II: brain development. Biol Psychiatry. 1999; 45:1271–1284. [PubMed: 10349033]
52. De Bellis MD, Hall J, Boring AM, Frustaci K, Moritz G. A pilot longitudinal study of hippocampal volumes in pediatric maltreatment-related posttraumatic stress disorder. Biol Psychiatry. 2001; 50:305–309. [PubMed: 11522266]
53. Bonne O, Brandes D, Gilboa A, Gomori JM, Shenton ME, Pitman RK, Shalev AY. Longitudinal MRI study of hippocampal volume in trauma survivors with PTSD. Am J Psychiatry. 2001; 158:1248–1251. [PubMed: 11481158]
54. Agartz I, Momenan R, Rawlings RR, Kerich MJ, Hommer DW. Hippocampal volume in patients with alcohol dependence. Arch Gen Psychiatry. 1999; 56:356–363. [PubMed: 10197833]
55. McEwen BS, Sapolsky RM. Stress and cognitive function. Curr Opin Neurobiol. 1995; 5:205–216. [PubMed: 7620309]
56. Gould E, Tanapat P. Stress and hippocampal neurogenesis. Biol Psychiatry. 1999; 46:1472–1479. [PubMed: 10599477]
57. Brunson KL, Eghbal-Ahmadi M, Bender R, Chen Y, Baram TZ. Long-term, progressive hippocampal cell loss and dysfunction induced by early-life administration of corticotropin-releasing hormone reproduce the effects of early-life stress. Proc Natl Acad Sci USA. 2001; 95:279–283.
58. Dent GW, Okimoto DK, Smith MA, Levine S. Stress-induced alterations in corticotropin-releasing hormone and vasopressin gene expression in the paraventricular nucleus during ontogeny. Neuroendocrinology. 2000; 71:333–342. [PubMed: 10878495]
59. Pihoker C, Owens MJ, Kuhn CM, Schanberg SM, Nemeroff CB. Maternal separation in neonatal rats elicits activation of the hypothalamic-pituitary-adrenocortical axis: a putative role for corticotropin-releasing factor. Psychoneuroendocrinology. 1993; 18:485–493. [PubMed: 8265736]
60. Fahlke C, Lorenz JG, Long J, Champoux M, Suomi SJ, Higley JD. Rearing experiences and stress-induced plasma cortisol as early risk factors for excessive alcohol consumption in nonhuman primates. Alcohol Clin Exp Res. 2000; 24:644–650. [PubMed: 10832905]
61. Coplan JD, Andrews MW, Rosenblum LA, Owens MJ, Friedman S, Gorman JM, Nemeroff CB. Persistent elevations of cerebrospinal fluid concentrations of corticotropin-releasing factor in adult nonhuman primates exposed to early-life stressors: implications for the pathophysiology of mood and anxiety disorders. Proc Natl Acad Sci USA. 1996; 93:1619–1623. [PubMed: 8643680]
62. Bremner JD, Licinio J, Darnell A, Krystal JH, Owens MJ, Southwick SM, Nemeroff CB, Charney DS. Elevated CSF corticotropin-releasing factor concentrations in posttraumatic stress disorder. Am J Psychiatry. 1997; 154:624–629. [PubMed: 9137116]
63. Baker DG, West SA, Nicholson WE, Ekhator NN, Kasckow JW, Hill KK, Bruce AB, Orth DN, Geracioti TD Jr. Serial CSF corticotropin-releasing hormone levels and adrenocortical activity in combat veterans with posttraumatic stress disorder. Am J Psychiatry. 1999; 156:585–588. correction, 156:986. [PubMed: 10200738]
64. Young EA, Lopez JF, Murphy-Weinberg V, Watson SJ, Akil H. Hormonal evidence for altered responsiveness to social stress in major depression. Neuropsychopharmacology. 2000; 23:411–418. [PubMed: 10989268]

65. Kaufman J, Birmaher B, Perel J, Dahl RE, Moreci P, Nelson B, Wells W, Ryan ND. The corticotropin-releasing hormone challenge in depressed abused, depressed nonabused, and normal control children. Biol Psychiatry. 1997; 42:669–679. [PubMed: 9325560]

66. Sullivan EV, Pfefferbaum A, Swan GE, Carmelli D. Heritability of hippocampal size in elderly twin men: equivalent influence from genes and environment. Hippocampus. 2001; 11:754–762. [PubMed: 11811670]

67. Lyons DM, Yang C, Sawyer-Glover AM, Moseley ME, Schatzberg AF. Early life stress and inherited variation in monkey hippocampal volumes. Arch Gen Psychiatry. 2001; 58:1145–1151. [PubMed: 11735843]

68. Sanchez MM, Hearn EF, Do D, Rilling JK, Herndon JG. Differential rearing affects corpus callosum size and cognitive function of rhesus monkeys. Brain Res. 1998; 812:38–49. [PubMed: 9813233]

69. Leverenz JB, Wilkinson CW, Wamble M, Corbin S, Grabber JE, Raskind MA, Peskind ER. Effect of chronic high-dose exogenous cortisol on hippocampal neuronal number in aged nonhuman primates. J Neurosci. 1999; 19:2356–2361. [PubMed: 10066285]

70. Gilbertson MW, Shenton ME, Ciszewski A, Kasai K, Lasko NB, Orr SP, Pitman RK. Smaller hippocampal volume predicts pathologic vulnerability to psychological trauma. Nat Neurosci. 2002; 5:1242–1247. [PubMed: 12379862]

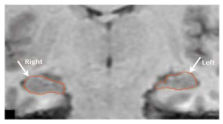

FIGURE 1. Representative MRI Showing Tracing of the Boundaries of the Right and Left Hippocampus in a Study of Hippocampal Volume and Childhood Physical and/or Sexual Abuse History in Women With Major Depressive Disordera

[a] Structures included in the hippocampal volume were the gray matter of the hippocampus proper, the dentate gyrus, the subicular complex, the alveus, and the fimbria.

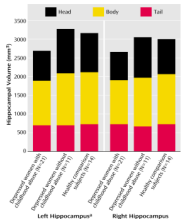

FIGURE 2. Volume of the Left and Right Hippocampal Head, Body, and Tail in Depressed Women With and Without a History of Childhood Physical and/or Sexual Abuse and in Healthy Comparison Subjectsa

[a] For the whole left hippocampus volume, significant difference among groups (F=5.45, df=2, 36, p=0.009), between depressed women with and without a history of abuse (p=0.007, Tukey), and between depressed women with a history of abuse and healthy women (p=0.06, Tukey).

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TABLE 1

Characteristics of Subjects in a Study of Hippocampal Volume and Childhood Physical and/or Sexual Abuse History in Women With Major Depressive Disorder

Characteristic	**Group 1: Women With Major Depressive Disorder and Childhood Abuse (N=21)**		**Group 2: Women With Major Depressive Disorder and No Childhood Abuse (N=11)**		**Group 3: Healthy Women With No Childhood Abuse (N=14)**		**Analysis**			
	Mean	SD	Mean	SD	Mean	SD	F	df	p	Significant Post Hoc Comparisons[a]
Age (years)	33	6	34	8	27	5	4.67	2, 43	0.02	1>3, p=0.04; 2>3, p=0.02
Weight (lb)	172	51	153	28	142	35	1.95	2, 39	0.16	
	N		N		N		χ^2	df	p	
Race							1.22	2	0.54	
Caucasian	17		8		9					
African American	4		3		5					
Handedness[b]							1.95	2	0.38	
Right	19		9		12					
Left	1		0		2					
	Mean	SD	Mean	SD	Mean	SD	Kruskal-Wallis χ^2	df	p	Significant Post Hoc Comparisons[a]
Clinical measures										
17-item Hamilton Depression Rating Scale score	18	6	19	2	2	1	28.76	2	<0.001	1>3, p<0.001; 2>3, p<0.001
Hamilton Anxiety Rating Scale score	19	9	21	6	2	1	25.98	2	<0.001	1>3, p<0.001; 2>3, p<0.001
Clinician-Administered PTSD Scale score	52	19	3	8	2	5	36.24	2	<0.001	1>3, p<0.001; 1>2, p<0.001
Early Trauma Inventory (clinician-rated) score Total	803	574	130	118	65	92	29.37	2	<0.001	1>3, p<0.001; 1>2, p<0.001
General trauma	116	137	19	43	34	88	13.62	2	<0.001	1>3, p=0.002
Physical trauma	131	117	36	52	7	9	20.37	2	<0.001	1>3, p=0.009; 2>3; p=0.09
Emotional trauma	468	395	73	77	24	52	27.25	2	<0.001	1>3, p<0.001; 1>2, p<0.001; 2>3, p=0.05
Sexual trauma	89	159	1	2	0	0	23.75	2	<0.001	1>3, p<0.001; 1>2, p<0.001

[a] Tukey test.

[b]Data on handedness missing for one subject in group 1 and two subjects in group 2.

TABLE 2

Current and Lifetime Comorbid Psychiatric Diagnoses of Depressed Women With and Without a History of Childhood Physical and/or Sexual Abuse

	Depressed Women With Childhood Abuse (N=21)		Depressed Women With No Childhood Abuse (N=11)	
Diagnosis	**N**	**%**	**N**	**%**
Dysthymia				
Current	2	10	1	9
Lifetime	0	0	0	0
Posttraumatic stress disorder				
Current	14	66	0	0
Lifetime	10	48	0	0
Panic disorder with agoraphobia				
Current	2	10	0	0
Lifetime	1	5	0	0
Panic disorder without agoraphobia				
Current	2	10	0	0
Lifetime	3	15	1	9
Social phobia				
Current	4	19	1	9
Lifetime	4	19	0	0
Specific phobia				
Current	1	5	0	0
Lifetime	1	5	0	0
Generalized anxiety disorder				
Current	2	10	1	9
Lifetime	1	5	0	0
Obsessive-compulsive disorder				
Current	2	10	0	0
Lifetime	2	5	0	0
Somatoform disorder				
Current	1	5	1	9
Lifetime	2	10	0	0
Hypochondriasis				
Current	2	10	0	0
Lifetime	1	5	0	0
Anorexia nervosa (lifetime)	1	5	0	0
Bulimia nervosa (lifetime)	2	10	0	0
Cannabis abuse (lifetime)	0	0	2	18
Cannabis dependence (lifetime)	2	10	1	9
Cocaine abuse (lifetime)	1	5	0	0

	Depressed Women With Childhood Abuse (N=21)		Depressed Women With No Childhood Abuse (N=11)	
Diagnosis	**N**	**%**	**N**	**%**
Cocaine dependence (lifetime)	2	10	0	0

TABLE 3

Hippocampal, Temporal Lobe, and Whole Brain Volumes in Depressed Women With and Without a History of Childhood Physical and/or Sexual Abuse and in Healthy Comparison Subjects[a]

	Volume (mm^3)							
	Women With Major Depressive Disorder and Childhood Abuse (N=21)		Women With Major Depressive Disorder and No Childhood Abuse (N=11)		Healthy Women With No Childhood Abuse (N=14)		Analysis	
Brain Area	Mean	SE	Mean	SE	Mean	SE	F (df=2, 36)	p
Hippocampus								
Whole								
Left[b]	2,705	106	3,292	116	3,179	123	5.45	0.009
Right	2,690	115	3,078	126	3,037	134	2.07	0.14
Body								
Left[c]	1,193	51	1,386	56	1,393	59	2.83	0.07
Right	1,189	47	1,312	51	1,344	54	1.73	0.19
Head[d]								
Left	807	84	1,187	93	1,041	98	3.64	0.04
Right	761	96	1,074	105	935	112	1.97	0.15
Temporal lobe								
Left	15,631	462	17,014	508	16,524	538	1.59	0.22
Right	15,635	513	17,021	565	16,664	598	1.28	0.29
							F (df=2, 37)	p
Whole brain	1,121,827	23,672	1,102,606	22,643	1,115,389	32,400	0.31	0.74

[a] Analyses of hippocampal volume used age, race, presence of posttraumatic stress disorder, presence of alcohol and other substance use, and whole brain volume as covariates.

[b] Significant difference between depressed women with and without a history of abuse (p=0.007, Tukey); nonsignificant difference between depressed women with a history of abuse and healthy women (p=0.06, Tukey).

[c] Nonsignificant difference between depressed women with and without a history of abuse (p=0.09, Tukey).

[d] Significant difference between depressed women with and without a history of abuse (p=0.03, Tukey).