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Hippocampal atrophy in recurrent major depression

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ABSTRACT **Hippocampal volumes of subjects with a history of major depressive episodes but currently in remission and with no known medical comorbidity were compared to matched normal controls by using volumetric magnetic resonance images. Subjects with a history of major depression had significantly smaller left and right hippocampal volumes with no differences in total cerebral volumes. The degree of hippocampal volume reduction correlated with total duration of major depression. In addition, large (diameter ≥ 4.5 mm)-hippocampal low signal foci (LSF) were found within the hippocampus, and their number also correlated with the total number of days depressed. These results suggest that depression is associated with hippocampal atrophy, perhaps due to a progressive process mediated by glucocorticoid neurotoxicity.**

Dysregulation of the hypothalamic–pituitary–adrenal axis resulting in hypercortisolemia has been studied for many years as a biological characteristic of acute major depression (1). Young *et al.* (2) have shown that depression is accompanied by dysregulation in the fast-feedback control of cortisol secretion, possibly at the level of the hippocampus. Work in experimental systems suggests that this disinhibition can be induced by chronic corticosteroid exposure or by stress alone (3, 4).

The precise mechanisms by which stress or depression disturb hippocampal regulation of cortisol function are unknown, but recent studies have raised the possibility that neurotoxic tissue damage is involved. The work of Sapolsky *et al.* (3, 5, 6) has demonstrated that rats injected repeatedly with glucocorticoids develop hippocampal neuronal loss, perhaps due to enhanced neuronal vulnerability to glutamate neurotoxicity (7). Rats exposed to stress (8) or exposed relatively briefly to glucocorticoids (daily injection for 3 weeks) (9) have shortening and atrophy of hippocampal dendritic processes.

These experimental studies raise the possibility that humans experiencing recurrent depressive episodes and elevated levels of glucocorticoids might also sustain neurotoxic damage to hippocampal neurons. While adequate pathological studies have not been conducted to test this hypothesis in affective disorders (10), a radiologic hallmark of such neurotoxic damage might be hippocampal volume loss. Supporting this idea, a recent volumetric magnetic resonance image (MRI) study has demonstrated right-sided hippocampal volume decrease in combat-related posttraumatic stress disorder (11). To date, however, no evidence of hippocampal volume loss has been found in association with major depression (12), although MRI abnormalities in hippocampal spin-lattice relaxation time (T1) characteristics have been reported (13).

The present study evaluated hippocampal volume in older women with recurrent major depression by using high-resolution MRI and stereological measurement. Based on the glucocorticoid hypothesis described above, we hypothesized that hippocampal volume loss related to depression would be age– and duration-dependent. To reduce the influence of extraneous factors that may affect brain volume, subjects were screened to exclude medical disorders other than depression.

METHODS

Subject Selection. Subjects were recruited from the Memory and Aging Project of the Alzheimer's Disease Research Center and the outpatient psychiatry service at the Washington University School of Medicine. Subjects, ranging in age from 51 to 86 years old (mean = 68; median = 68), were all female and right-handed. The choice was made to select all women because it eliminated brain differences due to gender (14, 15), decreased the possibility of hypertension and occult cardiovascular disease, and increased the ability to obtain subjects, although at the cost of generalizability. Each depressed subject was matched using a case-control design for age and educational level, and the groups were matched overall for height, since this variable is a predictor of overall brain size (16). Potential subjects were screened by questionnaire, medical history, review of medical records, and physical exam to exclude those with medical problems potentially affecting the central nervous system, such as a current or past neurological disorder, head trauma, hypertension, myocardial infarction or ischemia, diabetes, Cushings disease, steroid use, or drug/alcohol abuse. These exclusionary criteria were consistent with routine Alzheimer's Disease Research Center screening criteria (17). In addition, subjects who had received more than three courses of electroconvulsive therapy (ECT) were excluded. Three subjects included in the study had received ECT previously during the course of their treatment, and the time elapsed since last ECT treatment was 34, 30, and 14 years. All subjects gave informed consent.

All subjects were assessed clinically by a psychiatrist (Y.I.S.) experienced in the use of the diagnostic interview for genetic studies (DIGS), a structured interview with high reliability (18). The DIGS was used to make the diagnosis of recurrent major depression by American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) criteria and to exclude other psychiatric diagnoses. Only depressive episodes that met full criteria for major depression were included. Time elapsed (months) since last depressed was determined. One subject with a single episode of major depression was included. In addition, the DIGS was used to score each depressive episode for duration (in days) and number of symptoms, which were identical to those used to make the diagnosis of major depression by DSM-IV criteria. The average number of depressive symptoms over the course of the total depressive episodes was determined. This was determined by averaging the number of symptoms occurring in each depressive episode (a minimum of five symptoms was required to qualify for the diagnosis of major depression and the maximum number of symptoms was nine). Subjects with current acute depression were excluded from the study to eliminate potential confounds related to

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Abbreviations: MRI, magnetic resonance image; LSF, low signal foci; DIGS, diagnostic interview for genetic studies; ECT, electroconvulsive therapy; CE, coefficient of error; HRSD, Hamilton rating scale for depression.

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state-dependent changes (e.g., hypercortisolemia) in MRI volumetric measurements, and none of the subjects had been acutely depressed within the past 6 months. Eight of the 10 depressed subjects were receiving antidepressants: selective serotonin reuptake inhibitors in three cases, tricyclic antidepressants in three cases, and maprotiline and trazodone in one case each. Antidepressant status and doseage in milligrams were determined. Two patients had previously been treated with neuroleptics, one with chlorpromazine and one with haloperidol. In both cases the duration of treatment was brief, and neither patient was psychotic at the time of treatment. Patients and controls were also assessed using the Hamilton rating scale for depression (HRSD) (19) to determine the presence and severity of any current symptoms.

Cortisol Measurement. Blood samples were obtained to measure cortisol concentrations at 8:00 a.m. on the day before (baseline) and the day following oral administration of 1 mg dexamethasone at 11:00 p.m. (dexamethasone suppression test). Plasma was obtained within 1 hr of obtaining each sample by centrifuging the sample at $\approx 1000 \times g$ for 15 min. All plasma samples were stored at -20°C before assay by using a commercially available kit (ICN).

Magnetic Resonance Scan Parameters. MRI scans were obtained using a Magnetom SP-4000 1.5T imaging system (Siemens, Iselin, NJ) and a standard Siemens 30-cm circularly polarized rf head coil. Anatomic images, consisting of 128 contiguous 1.25-mm thick sagittal slices, were acquired using magnetization prepared rapid gradient echo (MPRAGE), a fast gradient echo magnetic resonance acquisition. No sedation was used during scanning. Specific MPRAGE scanning parameters were TR = 10 ms, TE = 4 ms, inversion time = 300 ms, flip angle = 8, matrix = 256 × 256 pixels, voxel size = 1 × 1 × 1.25 mm, and slice thickness = 1.25 mm.

Preprocessing of Images. Image processing was done on a graphics workstation (Sun Sparcstation 20; Sun Microsystems, Mountain View, CA) using ANALYZE software (Biomedical Imaging Resource, Mayo Foundation) (20). First, images were interpolated from 1.25-mm sections to 0.5-mm sections. Next, images were reoriented to the anterior commissure–posterior commissure plane (21) for standard alignment. To minimize inter-scan variations, MRIs underwent gray scale normalization as described (22). Gray scale histograms of cylindrical regions-of-interest subvolumes inclusive of the hippocampus were generated to aid in tissue classification. These subvolumes were analyzed using PEAKFIT software (Jandel Scientific, San Rafael, CA) by the Marquardt–Levenberg algorithm for nonlinear curve fitting (23, 24) as described (22). Trilinear scaling of magnetic resonance data to 8-bit gray scale resolution was performed using these calculated thresholds to generate data sets with high contrast between gray and white matter. To save image loading time and memory and to increase the regions-of-interest volume occupied by the hippocampus, left and right medial temporal lobe cubical subvolumes were interactively defined by an expert observer (Fig. 1*a*).

Stereologic Method and Reliability. Two raters (Y.I.S. and P.W.W.) measured unilateral hippocampal gray matter volumes after extensive training and assessment standardization with a neuroradiologist expert in hippocampal anatomy (M.G.). Volume determination was based on stereologic estimation methods, which have been used with precision in microscopy and magnetic resonance volumetry (25, 26). From three-dimensional MRI cubical subvolumes composed of 0.5 × 0.5 × 0.5-mm voxels, coronal slices were sampled every 1.5 mm from a randomly chosen start slice. A 7 × 7-mm^2 rigid grid of points, with random starting position and angle of deviation from horizontal, was then superimposed on the images. Grid points falling within the hippocampal gray matter (see definition of hippocampus below) were counted. The ANALYZE program allows viewing of grid points simultaneously in three orthogonal perspectives: sagittal, axial, and coronal (Fig. 1*b*).

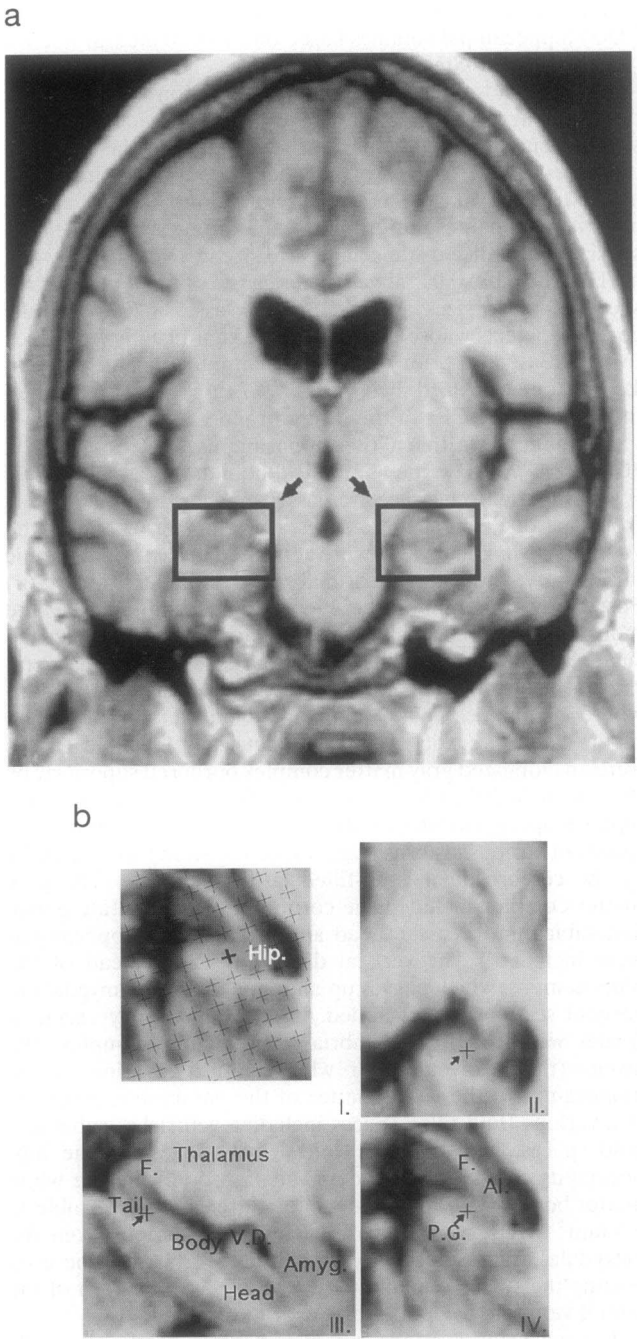

FIG. 1. (*a*) Coronal section through the hippocampus. Cubic volumes containing the hippocampus were sectioned out from the total brain volume. (*bI*) A randomly placed 7 × 7-mm^2 grid overlying the hippocampus. Horizontal (*II*), sagittal (*III*), and coronal (*IV*) views simultaneously showing bolded crosshair in *I*. F, fimbria; V.D., vertical digitation of the hippocampus; Amyg., amygdala; Hip., hippocampus (tail, body, head); Al., alveus; P.G., parahippocampal gyrus.

This provided greater clarity of anatomic localization. Based on the number of selected grid points, a volume estimate was extrapolated by ANALYZE. Raters were blind to subject identity and clinical characteristics. Raters measured left and right hippocampi separately. Mean volumes were determined from the average of four measurements of each volume, two measurements each by two independent raters. The Spearman–Brown prediction formula was used to determine intra-rater and inter-rater reliability (27). Intra-rater correlation coefficients were calculated for left (0.96 and 0.95) and right (0.89 and 0.95) hippocampal gray matter volumes volumes. The overall coefficient of error (CE) was 0.02. Inter-rater corre-

lation coefficients were calculated for left (0.94) and right (0.95) hippocampal volumes based on 17 of 20 measurements.

Rationale for Stereologic Parameters. The coronal orientation was chosen as the primary orientation because prior research suggested that optimal efficiency is achieved with slices oriented perpendicular to the long axis of the structure of interest (28). However, orthogonal slices could be inspected as needed (see above). A voxel size of 0.5 mm^3 was chosen to achieve maximal resolution while maintaining a workable data set size. Inter-slice distance and grid size were chosen to yield a CE in the 0.02–0.04 range. Selecting the optimal numbers of slices and grid sizes are essential for assessing structurally complex objects whose profiles change significantly from slice to slice. Based on prior studies (22), an inter-slice distance of 1.5 mm, or every third slice, and a 7×7-mm^2 grid size resulted in volumes with CEs in the desired range.

Anatomic Definition of the Hippocampus. Specific rules (29, 30) were used to define anatomical boundaries as follows. (*i*) Every third coronal slice was assessed, beginning randomly from one of the first three slices at the posterior end of the volume. Orthogonal views were consulted in cases of anatomic uncertainty, though the coronal view retained priority. (*ii*) Posteriorly, the tail of the hippocampus continues as the indusium griseum, a thin strip of gray matter overlying the surface of the corpus callosum. For purposes of measurement, the posterior-most slice for volumetry was defined as the slice where the hippocampus first appeared adjacent to the trigone of the lateral ventricle. (*iii*) Volumetrically included tissues were an elongated gray matter complex bordered superiorly by the fornix-fimbria white matter junction, inferiorly by parahippocampal gyrus white matter, medially by the subarachnoid spaces of various cisterns (e.g., ambient cistern), and laterally by the cerebrospinal fluid-filled lateral ventricle. The gray matter complex included the cornu ammonis, dentate gyrus, and subiculum (i.e., the head and body of the hippocampus were included). The vertical digitation of the head of the hippocampus, which curves up and medial to the amygdala in coronal sections was included. (*iv*) Volumetrically excluded tissues were the fornix-fimbria white matter complex; the alveus (the intraventricular white matter covering of the hippocampus); the white matter of the parahippocampal gyrus; various fluid-filled spaces including ventricles, subarachnoid spaces, and sporadic fluid-density spaces in the hippocampus complex; and the amygdala proper and the white matter border with it (a thin white matter line, discernible in 0.5-mm^3 MRIs, which separated the hippocampus from the amygdala). When necessary, we used an arbitrary line connecting the sulcus semiannularis and the inferior horn of the lateral ventricle to define this separation (31).

The subiculum is a long stretch of tissue, extending medially from the cornu ammonis~. The superior component of the cornu ammonis does not extend medially far enough to aid in demarcating the border of the hippocampus, and the inferior component of the cornu ammonis is in direct continuity with the subiculum. Therefore, no clear gross anatomic separation exists among the hippocampus, subiculum, presubiculum, or parasubiculum. For practical purposes, we adopted a precedence to include the subiculum in the measured volume called "hippocampus" (30).

Total Cerebral Volume. Total cerebral volume, defined as all brain tissue of the cerebral hemispheres (both gray and white matter), included the midbrain superior to the pons. The superior border of the pons was chosen as the point of demarcation because it is easily recognizable. This volume measurement was also made by using stereological methods as described above. The intra-rater correlation coefficients were calculated and were 0.96 and 0.96 for rater 1 and rater 2, respectively. The inter-rater correlation coefficient was 0.90, based on 17 out of 20 measurements. The overall CE was 0.01.

Estimation of Total Time Depressed. Using the DIGS as described above, the number of symptoms and duration (days) of each episode were determined (see above). Only the portion of a depressive episode which met full DSM-IV criteria (32) for major depression was included in this determination. For example, if a subject had symptoms that qualified for a diagnosis of dysthymia, or residual depression during some number of the days, that portion of the episode was not included. The total cumulative duration of major depression was then calculated, summing over all episodes (Table 1). Hippocampal gray matter volumes were obtained as described above. Then for each depressed subject the hippocampal gray matter volume was regressed against total days depressed. A limitation of the present study is the use of retrospective data to identify past episodes of depression. Rigorous diagnostic criteria were used to establish each episode, and, whenever possible, corroborating information was obtained from family members or treating psychiatrists. In depressed populations, self-reporting may underestimate the duration of earlier episodes, but this has been shown to be no more likely in older than in younger subjects (33). Furthermore, patients with more severe histories of depression, such as those in the current study, have been previously shown to have greater stability of diagnosis (34).

Hippocampal Low Signal Foci (LSF). During stereological volumetric measurements LSF were found within the hippocampal formation. Areas of low signal appear dark on T1-weighted images and appeared to be indistinguishable from cerebrospinal fluid spaces in these scans. Gray scale values were sampled for these areas and were found to be similar to neighboring cerebrospinal fluid spaces. The number and size of these LSF in the hippocampus were measured by defining a threshold value determined by sampling gray scale values of the LSF in all scans. The mean gray scale value was 155 ± 22. This thresholding algorithm was then applied to all scans. The resulting scans had LSF ranging in size from <0.1 mm to ≈ 10 mm in diameter. LSF were counted in each scan and classified as "large" LSF if they were ≥ 4.5 mm in diameter (see Fig. 4).

Data Analysis. Two-tailed paired *t* tests were used to compare depressed and control subjects on all demographic and MRI measures. With the exception of correlations involving LSF, the Pearson correlation (35) was used to determine

Table 1. Comparison of depressed subjects and matched controls

	Depressed subjects (n = 10)		Matched controls (n = 10)		Paired t test	
Variable	Mean	SD	Mean	SD	t	p
Age, yr	68.5	10.4	68.0	9.5	0.7	0.52
Education, yr	14.3	2.9	13.6	2.9	1.1	0.31
Height, cm	161.2	5.6	162.1	6.1	0.5	0.73
Cortisol, μg/liter						
Baseline	20.8	10.2	23.8	9.5	0.6	0.55
DST	2.7	1.2	2.0	0.9	0.8	0.44
HRSD	6.0	5.4	1.9	1.7	2.8	0.02
Days depressed	1293	1067	—	—	—	—
Race, no.						
White	9	(90%)	10	(100%)	—	—
Black	1	(10%)	0	(0%)	—	—
Hippocampal gray matter volume, mm^3						
Left	2159	301	2544	333	4.1	0.003
Right	2283	324	2577	259	2.8	0.02
Total cerebral volume, $mm^3 \times 10^3$						
	1167	133	1159	104	0.2	0.83
Number of LSF in hippocampus						
Left large* LSF	22	14	6	7	3.3	0.01
Right large* LSF	23	16	9	9	2.4	0.04

LSF, low signal foci; DST, dexamethasone suppression test (see text).
*Large defined as ≥4.5 mm diameter.

Table 2. Clinical data and hippocampal volumes for depressed subjects

No.	Left hipp. volume, mm³	Right hipp. volume, mm³	Days dep.	Time since depressed, months	ECT status, days	Current antidepressant, (daily dose in mg)	Dep. severity
S-02	2049	2233	252	10	12	Amitriptyline (100)	5.00
S-03	2237	2637	196	24	0	Trazodone (50)	5.00
S-04	1690	1851	2065	8	20	Maprotiline (200)	8.00
S-09	1897	2109	3752	10	0	Fluoxetine (20)	7.75
S-10	1842	1977	3276	36	0	Amitriptyline (100)	9.00
S-11	2081	2021	210	6	0	Doxepin (100)	5.25
S-13	2265	2269	2160	6	9	Sertraline (100)	8.50
S-14	2485	2301	21	524	0	None	8.00
S-15	2407	2536	980	36	0	None	7.67
S-18	2632	2894	119	168	0	Paroxetine (20)	5.50

hipp., Hippocampus; dep., depression.

the significance of correlations among MRI measures, and between MRI measures and total cumulative duration of depression. The data on numbers of LSF were not normally distributed; therefore, a Spearman rank correlation (36) was used for correlations involving these data.

RESULTS

Demographics. Table 1 summarizes demographic and other characteristics for depressed subjects and normal controls. The lack of hypercortisolemia, either baseline or after administration of dexamethasone, and HRSD scores are consistent with the absence of acute current depression. While the groups differ in HRSD score, a score of ≤ 7 would indicate that a subject was asymptomatic (37). Depressed subjects had a mean of 4.5 lifetime episodes of major depression (range, 1–18), accounting for a lifetime mean of 1303 days depressed (range, 21–3752; median, 616). Table 2 displays data on individual depressed subjects, including duration of depression, time since last depressed, ECT status (number of days of ECT treatment), current daily antidepressant dose in milligrams, average number of depressive symptoms over all depressive episodes, and left and right hippocampal volumes.

Neuromorphometric Measures. Table 1 and Fig. 2 show that left and right hippocampal gray matter volumes were smaller and the number of large LSF in left and right hippocampus were larger in depressed subjects than in normal controls. Mean total cerebral volumes did not differ. Correlations between number of large LSF and hippocampal gray matter volumes were determined. For left hippocampal gray matter volumes, the correlation with left large LSF was $\rho = -0.56$ ($P = 0.01$). The correlation between right hippocampal gray matter volumes and large LSF was $\rho = -0.53$ ($P = 0.02$).

Correlations Between Hippocampal Gray Matter Volumes and Total Time Depressed. There was a significant correlation between total days depressed and left hippocampal gray matter volume ($r = -0.65$; $P = 0.04$) (Fig. 3). There was also a trend toward a relationship between right hippocampal gray matter volume and total days depressed ($r = -0.59$; $P = 0.10$). In addition, the correlation between hippocampal LSF and total days depressed was determined (Fig. 4). The number of large LSF in left ($\rho = 0.76$, $P = 0.02$) and right ($\rho = 0.66$, $P = 0.05$) hippocampus were significantly correlated with total number of days depressed.

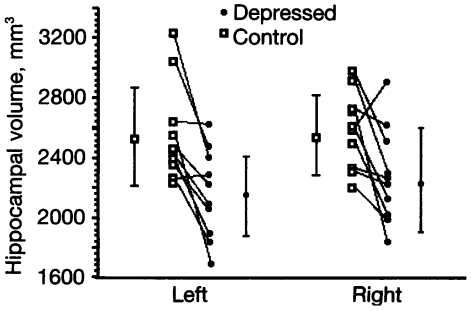

FIG. 2. Left and right hippocampal volumes for each subject pair of depressed subject and the age, gender, education, and height-matched case control; the mean and SD for each group are also shown.

DISCUSSION

The major finding of the present study is that patients with a history of recurrent major depression, but with no current depression or history of medical comorbidity, had smaller hippocampal gray matter volumes than a group of pair-wise matched normal controls. This reduction was not a result of overall brain atrophy; total cerebral volumes did not differ between the groups. In examining the left and right hippocampus individually, both differed significantly between depressed patients and controls.

Present data contrast with those obtained by a previous study that found no hippocampal volume differences between depressed patients and controls (12). This discrepancy may be explained by methodological differences. We achieved higher spatial resolution examining 0.5-mm slices rather than the 5-mm slices used by Axelson *et al.* (12), and we isolated hippocampal gray matter volume rather than assessing combined gray and white matter volume of the combined hippocampus-amygdala complex. These technical differences may have enhanced our ability to detect small differences specific to hippocampal gray matter volume.

An important aspect of this study design is that the depressed individuals were not currently suffering from depression. Therefore, the results reported are not likely due to the acute effects of corticosteroids, but rather appear to be a con-

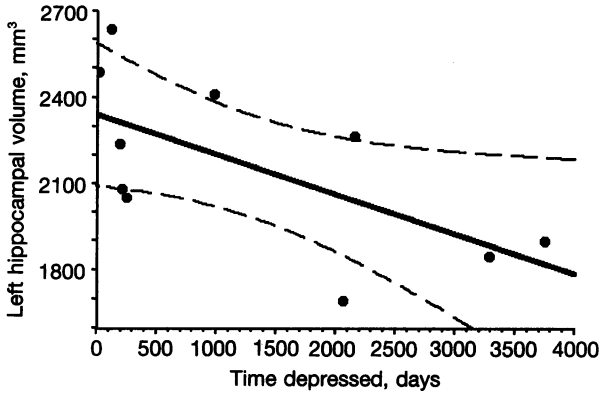

FIG. 3. Correlation between left hippocampal gray matter volumes and total days of major depression.

sequence of the cumulative depression history. This study is limited by its retrospective nature, and we were unable to correlate hypercortisolism with hippocampal atrophy. However, it is interesting to note that both combat and depression are stressors, and both appear to be associated with hippocampal atrophy (11), even in the absence of hypercortisolism (38) after the acute stress has resolved. In fact, posttraumatic stress disorder is associated with decreased urinary cortisol excretion which can continue for decades after the initial trauma (39). Evidence for the neurotoxic effects of corticosteroids in humans is also provided by the finding that patients with Cushings syndrome have selective hippocampal atrophy, which is correlated with plasma cortisol levels (40) and memory dysfunction.

Our finding that MRI cerebral volumes in depressed patients and controls were not significantly different is consistent with some previous reports (41), but different from that of Rabins *et al.* (42), who found widespread cortical and subcortical atrophy in geriatric patients with major depression, and Rothschild *et al.* (43), who found larger ventricle-to-brain ratios indicative of cortical atrophy in depressed patients with abnormal dexamethasone suppression tests. To our knowledge, however, the present study is the first to study only subjects without medical or neurological comorbidities capable of affecting brain volume. It is critical to know whether patients with changes in brain structure volumes had concurrent physical illnesses, especially with age-related increases in incidence of medical conditions potentially affecting the brain (44, 45). Before concluding that specific regional volume decrements are associated with depression, this possibility must be excluded. While previous studies have included a physical exam to exclude significant neurological illness, common medical conditions, such as hypertension, diabetes, and history of myocardial infarct, have not been specifically excluded. In the present study, we selected only subjects with no current medical or neurological condition and made special effort to exclude subjects with cerebrovascular disease risk factors that could increase the incidence of subclinical infarcts. An increased incidence of microinfarction has been linked to both chronic hypertension (46) and diabetes (47, 48). We also excluded patients with any history of substance abuse or dependence, since alcohol dependence can cause cerebral atrophy (49).

Further study will be needed to determine the exact nature of the observed association between recurrent depression and the hippocampal volume reduction. We cannot exclude the possibility that the loss of hippocampal volume preceded the development of depression, or that this volume reduction is a signature of some brain abnormality that predisposes to depression. However, we favor the alternative possibility that the recurrent episodes of depression actually caused hippocampal neuronal loss, perhaps through the mechanism of glucocorticoid-induced neurotoxicity (7). Favoring this possibility, the extent of left hippocampal volume loss in depressed subjects correlated with total lifetime cumulative duration of depression. Furthermore, large (diameter $\geq$ 4.5 mm) hippocampal LSF were found, and their number also correlated with the total number of days depressed. To our knowledge, this is the first report of such lesions in the hippocampus and we attribute them to atrophy.

One confound in this and other studies to date is ECT therapy. While direct evidence to date demonstrating ECT-induced structural brain changes has been lacking (50), animal studies suggest that sustained seizures can produce neuronal loss and gliosis in the hippocampus (51), and more recent study (52) has suggested that even brief kindled seizures may also induce some selective hippocampal neuronal loss. It was impractical to exclude patients who had received any ECT, since to do so would exclude the patients with the most severe histories of depression. However, we did exclude from the study any patient with more than three courses of ECT treatment or anyone with a history of ECT within the past year. Even if the three subjects who received ECT were excluded in a post hoc analysis, however, there were still significant differences in left ($P = 0.007$) and right ($P = 0.05$) hippocampal gray matter volumes between depressed subjects and normal controls. In addition, there was still a significant correlation between total days depressed and left hippocampal gray matter volume ($P = 0.03$). Another confound was medication treatment. While there is no known evidence for reductions in brain structure volumes associated with neuroleptics or antidepressants, this possibility cannot be excluded. The relationship between hippocampal gray matter volume with duration of depression appears to be fairly specific because no relationship was found between hippocampal volumes and other clinical variables in post hoc analyses. The variables examined were average number of depressive symptoms, duration of depression weighted by severity, and time

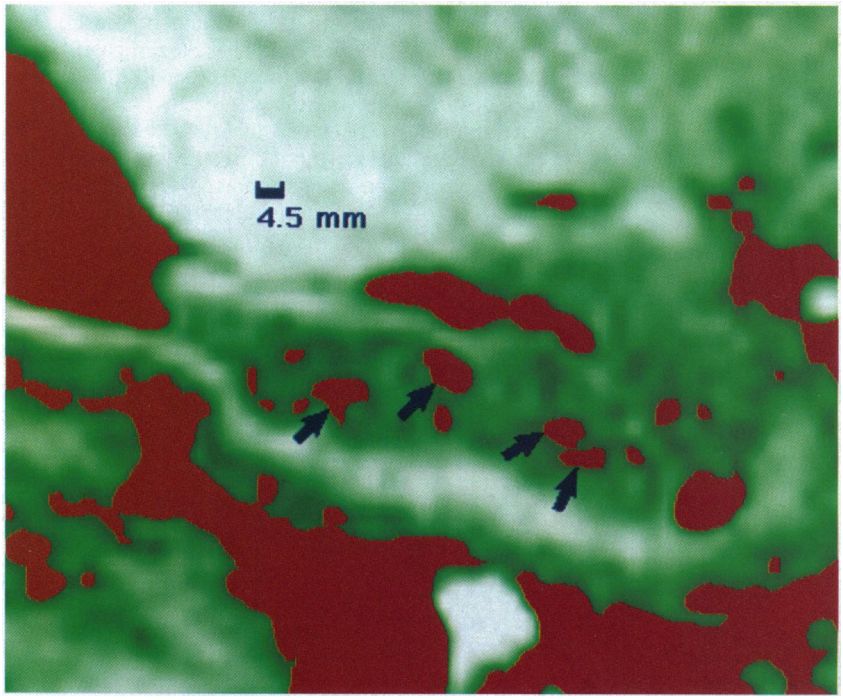

FIG. 4. Sagittal view of the hippocampus displaying small (<4.5 mm) LSF and four large (≥4.5 mm) LSF marked by arrows. (Scale bar, 4.5 mm.)

since most recent episode of depression. There was no correlation between average severity of depression and hippocampal volumes ($P = 0.46, 0.20, 0.29$ for the correlations with left, right, and total hippocampal volumes, respectively). When the duration of depression was weighted for severity (this was done by multiplying the duration of each episode of depression by its severity and summing over all episodes), there was also no correlation with hippocampal volumes ($P = 0.21, 0.38, 0.23$ for the correlations with left, right, and total hippocampal volumes, respectively). This may suggest that above the threshold of symptoms sufficient to meet criteria for major depression, additional symptoms do not further increase the degree of hippocampal atrophy. There was no correlation between time since most recent episode of depression and hippocampal volumes ($P = 0.10, 0.52, 0.26$ for the correlations with left, right, and total hippocampal volumes, respectively). The lack of correlation was not surprising since the potential acute effects of hypercortisolemia could be expected to be resolved by 6 months, the smallest elapsed time since depression in our study, although resolution of brain effects of hypercortisolemia have not been systematically studied.

In conclusion, the present study provides evidence supporting the possibility that depression per se is associated with structural changes in the hippocampus, perhaps reflecting neuronal loss. Such hippocampal damage might be responsible for an increase in corticotropin-releasing factor secretory drive that contributes to the hypothalamic–pituitary–adrenal axis abnormalities seen in depression (53). In combination with the loss of negative feedback inhibition described above (2), this could lead to enhanced vulnerability to subsequent depression through a feed-forward cycle of depression–hippocampal damage–depression, occurring with each episode of major depression. Neuroprotective approaches directed at preventing depression and reducing this hippocampal damage might ameliorate the severe morbidity associated with this disorder in later life.

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