

Brief Reports

Hippocampal Volume Reduction in Major Depression

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Objective: Elevated levels of glucocorticoids in depression have been hypothesized to be associated with damage to the hippocampus, a brain area involved in learning and memory. The purpose of this study was to measure hippocampal volume in patients with depression. **Method:** Magnetic resonance imaging was used to measure the volume of the hippocampus in 16 patients with major depression in remission and 16 case-matched non-depressed comparison subjects. **Results:** Patients with depression had a statistically significant 19% smaller left hippocampal volume than comparison subjects, without smaller volumes of comparison regions (amygdala, caudate, frontal lobe, and temporal lobe) or whole brain volume. The findings were significant after brain size, alcohol exposure, age, and education were controlled for. **Conclusions:** These findings are consistent with smaller left hippocampal volume in depression.

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Major depression is a common psychiatric disorder that is associated with considerable morbidity. Depressive episodes are associated with high levels of cortisol in about 40%–50% of patients (1). Elevated levels of glucocorticoids seen in stress have been associated with damage to hippocampal neurons, and the diagnosis of posttraumatic stress disorder (PTSD) has been associated with hippocampal volume reduction and deficits in declarative memory function (2, 3). Hippocampal dysfunction may contribute to verbal declarative memory deficits in depression (4, 5). Few studies, however, have examined hippocampal volume in patients with depression. Neuroimaging findings in affective disorders include ventricular enlargement, widening of the cortical sulci (6), and smaller volumes

in the right hippocampus (7), left amygdala (8), and temporal lobe (9) in bipolar disorder and increased subcortical white matter areas of increased signal intensity (10), smaller caudate and putamen volumes (11), alterations in hippocampal T₁ relaxation time (12), and reductions in gray matter in the left temporal lobe (13) in unipolar depression. Studies of hippocampal volume in unipolar depression have had conflicting findings; some studies of amygdala/hippocampal volume (combined) found no difference in comparison with control subjects (14), and others found a reduction (15). The purpose of the current study was to compare hippocampal volume of patients with treated unipolar depression and nondepressed subjects.

METHOD

The study group consisted of 16 patients with a history of depression based on the Structured Interview for DSM-IV currently treated on an outpatient basis with antidepressant medication (paroxetine, fluoxetine, or desipramine). Ten of the patients were men, and six were women. Patients were excluded according to criteria described elsewhere (3); in addition, patients with a history of PTSD or current medication use other than antidepressant were excluded. Depressed patients had a mean of three inpatient hospitalizations (SD=4, range=0–10), they had been in remission from depression for a mean of 31 weeks (SD=33, range=6–120), and they had experienced an average of two previous episodes of depression (SD=3, range=0–10).

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TABLE 1. Volume of the Hippocampus and Other Brain Regions in 16 Patients With Major Depression and 16 Nondepressed Comparison Subjects

Area	Volume (mm ³)				Analysis	
	Patients With Major Depression		Comparison Subjects			
	Mean	SD	Mean	SD	F (df=1, 30)	p
Hippocampus						
Left	940	208	1,166	248	7.78	0.009 ^a
Right	982	269	1,113	194	2.29	0.13
Mean	961	239	1,140	221	5.23	0.03
Caudate						
Left	2,668	710	2,767	571	0.19	0.67
Right	2,712	765	2,802	613	0.13	0.72
Mean	2,690	738	2,785	592	0.16	0.70
Amygdala						
Left	1,652	455	1,347	448	3.64	0.07
Right	1,699	493	1,335	450	4.75	0.04 ^b
Mean	1,676	474	1,341	449	4.33	0.05 ^b
Frontal lobe						
Left	140,856	41,597	154,267	24,141	1.24	0.27
Right	143,101	45,265	164,471	27,150	2.62	0.12
Mean	141,979	43,431	159,369	25,646	1.95	0.17
Temporal lobe						
Left	17,931	4,170	18,227	1,791	0.07	0.80
Right	18,207	4,260	19,475	2,707	1.01	0.32
Mean	18,069	4,215	18,851	2,249	0.45	0.51
Whole brain	1,404,586	179,994	1,390,789	153,948	0.05	0.82

^a Significant difference after correction for multiple comparisons ($p < 0.03$) and covarying for whole brain size.

^b Difference was not statistically significant after difference in whole brain size was controlled for ($p > 0.05$).

Comparison subjects ($N=16$) were case-matched to patients for sex and handedness. There were no differences between patients and comparison subjects in age (mean=43 years, $SD=8$, versus mean=45 years, $SD=10$), years of alcohol abuse (mean=4, $SD=7$, versus mean=3, $SD=5$), or years of education (mean=14, $SD=2$, versus mean=15, $SD=2$). One of the patients had a past history of alcohol dependence, three had a past history of alcohol abuse, and two had a past history of polysubstance abuse. One of the patients had current panic disorder without agoraphobia. All patients and comparison subjects gave written informed consent before participating in the study.

Magnetic resonance images were obtained and analyzed by using methods described in detail elsewhere (3), including measurements of a mid-hippocampal segment performed by two blind raters. Volumetric assessments were also made of other regions (table 1) for purposes of comparison and to determine if volume changes were specific to the hippocampus as previously reported (3). Frontal lobe measurements were performed by measuring the frontal lobe on all coronal slices anterior to the anterior commissure. There was a high level of interrater reliability for hippocampal volume measurements between the two independent raters for the left hippocampus ($r=0.93$, $df=31$, $p<0.05$) and the right hippocampus ($r=0.94$, $df=31$, $p<0.05$).

Repeated measures analysis of variance (ANOVA) with side (left versus right hemisphere) as the repeated factor was performed to compare left and right hippocampal volume (as well as comparison regions) between patients and nondepressed subjects. Univariate statistics were used to compare left and right hippocampal volume; a level of significance of $p<0.03$ was applied to correct for multiple comparisons. Multiple linear regression was used to examine the relationship between hippocampal volume and diagnosis while controlling for potential confounders.

RESULTS

Repeated measures ANOVA with side (left versus right hemisphere) as the repeated factor showed a significant main effect for diagnosis (table 1) and no significant main effect for side or side-by-diagnosis inter-

action. Univariate analyses showed a statistically significant 19% smaller volume of the left hippocampus in the depressed patients than the comparison subjects; the difference remained significant after differences in whole brain volume were controlled for, but a 12% difference in right hippocampal volume between the groups was not significant (table 1). There were no differences in volume in the comparison regions with the exception of the right amygdala, which was related to a larger volume of the right amygdala in depression (table 1). This effect was not significant, however, after differences in whole brain volume were controlled for.

There was no correlation between left hippocampal volume and clinical variables, including number of weeks in remission, number of previous episodes of depression, or number of hospitalizations for depression. Multiple linear regression to control for possible confounders that may affect hippocampal volume, including age, years of education, and years of alcohol abuse, continued to show differences in left hippocampal volume between patients and comparison subjects when these potential confounders were entered in the model.

DISCUSSION

Patients with remitted major depression in this study had a 19% smaller volume of the left hippocampus than matched comparison subjects. There were no differences in volumes of comparison regions between the groups in the temporal lobe, caudate, frontal lobe, or whole brain.

There are several possible explanations for our findings of hippocampal volume reduction in depression.

Elevated levels of glucocorticoids during depressive episodes could cause hippocampal damage, leading to a reduction in volume. In this model, chronic repeated episodes of depression may lead to progressive hippocampal atrophy over time, possibly increasing the risk for subsequent depressive relapse. Other factors, such as reductions in neurotrophins, could also be responsible for hippocampal volume reduction. However, the current study did not include measures of cortisol during depressive episodes, and future studies are needed to evaluate the relationship between cortisol and hippocampal volume in depression. It is also possible that smaller hippocampal volume from birth, or secondary to some premorbid environmental factor, is a risk factor for depression.

Amygdala volume was larger in depression but not significantly larger after we controlled for brain size. The meaning of these findings is unclear and should be replicated. It may account for the finding of Axelson et al. (14) of no difference in combined amygdala/hippocampal volume in patients with unipolar depression.

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