Hippocampal and Amygdala Changes in Patients With Major Depressive Disorder and Healthy Controls During a 1-Year Follow-Up

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Background: Although the hippocampus has been found to be smaller in patients with depression, prospective longitudinal in vivo studies are necessary to investigate whether depression can result in a further diminution of hippocampal volumes or whether a smaller hippocampal volume predisposes an individual to the development of depression.

Method: Thirty patients with DSM-IV major depressive disorder as well as 30 healthy control subjects matched for age, gender, and handedness were examined at admission to the hospital and 1 year later using a documentation of the medical history and high-resolution magnetic resonance imaging (MRI) for the presence of depression and to determine changes in hippocampal as well as amygdala volumes. Patients were enrolled from March 2000 to August 2002.

Results: No significant hippocampal and amygdala volume changes were observed in patients or controls between baseline and 1-year follow-up investigations. However, the subgroup of patients who were nonremitted at the time of the follow-up investigation showed significantly reduced left and right hippocampal volumes at both baseline and the 1-year follow-up compared with remitted patients. Moreover, the right hippocampal volumes of nonremitted patients were significantly smaller compared with matched healthy controls.

Conclusion: These results do not support the hypothesis that hippocampal volumes diminish during the 1-year follow-up period. However, smaller hippocampal volumes may be related to a poor clinical outcome after 1 year.

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Experimental studies support the hypotheses that stress toxicity[1] and a lack of neurotrophic factors[2] result in the well-known structural abnormalities of the hippocampus. In the past few years, reduced hippocampal volumes have consistently been reported in elderly[3,4] and also in younger patients with depression.[5–7] The stress toxicity hypothesis states that hypercortisolism in patients with acute depression can affect the hippocampal neurons via glutamate excitation.[1] In animal studies, prolonged stress decreases the number of apical dendritic branch points and the length of apical dendrites, particularly in laminar CA3 of the hippocampus. This effect is glucocorticoid dependent and can emerge after 3 weeks of experimental corticosterone treatment.[8,9] Moreover, the neurotrophic hypothesis states that a failure of protective effects via a lack of neurotrophic factors such as brain-derived neurotrophic factor (BDNF) may also contribute to hippocampal changes during the development of depression, and the reversal of this deficiency by antidepressant treatments may contribute to the remission of depressive symptoms.[2,10,11]

However, recently, some studies have begun to address the issue that structural changes might predispose to depression, because hippocampal size has been found to be highly genetically determined.[12] Furthermore, in patients with major depressive disorder, the homozygosity for the L-allele of the serotonin transporter polymorphism

(5-HTTLPR) was associated with decreased hippocampal volumes.[13] It is unclear whether these changes occur before the beginning of the disease or whether they are triggered by a variety of factors such as stress or emotional trauma during the depressive episode. The finding of reduced left hippocampal volumes in first-episode patients with major depressive disorder raises the question of whether volumetric hippocampal changes might predispose an individual to depression.[7] An altered structure that might predispose an individual to the development of depression might also show a relationship to the severity of cognitive deficits or to other depressive symptoms.

The amygdala subserves affective processes such as fear learning, experience of negative affect, and perception of emotional stimuli.[14] It has many interconnections with the hippocampus and was found to be enlarged in first-episode depressive patients[15] and in patients with recurrent depression compared with that found in age-matched healthy controls.[6] However, 2 studies failed to find altered amygdala volumes in recurrent depression,[5,16] and 1 study detected reductions of a subregion of the amygdala, the amygdala core nuclei.[17]

Smaller hippocampal volumes, which might enhance the vulnerability to depression, might also predispose a patient to a poor clinical outcome. Prospective longitudinal studies are needed to determine the clinical relevance of changes in the hippocampal formation or the amygdala. Thus, the aim of the present study was to investigate in a prospective, longitudinal design the hypotheses that a smaller hippocampal volume and a larger amygdala volume predispose an individual to the development of depression and that depression can result in a progressive diminution of hippocampal and amygdala volumes.

METHOD

Subjects

Thirty inpatients being treated in the Department of Psychiatry of the Ludwig-Maximilians-University in Munich, Germany, for an episode of major depressive disorder were recruited (age = 18–65 years; mean ± SD age = 48.4 ± 13.4 years) (Table 1). Psychiatric diagnoses based on DSM-IV criteria were determined by a consensus of at least 2 psychiatrists. Eleven patients had a first episode of major depressive disorder and 19 patients had recurrent depressive episodes. Mean ± SD illness duration was 9.1 ± 10.2 years. All subjects were examined by an experienced psychiatrist using a documentation of the medical history and with magnetic resonance imaging (MRI) within 2 weeks of admission to the hospital. Patients were enrolled from March 2000 to August 2002.

A second psychiatric examination and MRI investigation were performed 1 year after patients were discharged from the hospital. Clinical variables were documented using the Clinical Global Impressions scale[18] and the 21-item Hamilton Rating Scale for Depression (HAM-D).[19] Full remission was defined according to the criteria of Frank et al.[20] as a 17-item HAM-D (HAM-D-17) score of 7 or less. Patients were divided into those who were remitted (HAM-D-17 score ≤ 7) and those who were not remitted from depression (HAM-D-17 score > 7) at the time of the follow-up investigation. In this way, 18 patients were found to have a full remission (remitted) and 12 were depressed (nonremitted). Of the 12 nonremitted patients, 9 had responded to treatment in the hospital, 5 of whom had a full remission but relapsed during the first year after discharge. Four patients had only a partial remission, and 3 patients were fully symptomatic and treatment resistant.

At the time of admission to the hospital, 8 patients were taking tricyclic antidepressants (2 trimipramine, 3 amitriptyline, 3 doxepin), 9 patients were taking selective serotonin reuptake inhibitors (SSRIs: 3 citalopram, 4 paroxetine, 1 sertraline, 1 fluvoxamine), 11 patients were taking other new antidepressants (4 mirtazapine, 4 venlafaxine, 3 reboxetine), and 2 patients were not medicated. Seven patients were on lithium treatment at baseline. At the 1-year follow-up, 5 patients were taking no antidepressants, 6 patients were taking tricyclic antidepressants (2 trimipramine, 3 amitriptyline, 1 doxepin), 7 patients were taking SSRIs (2 sertraline, 4 citalopram, 1 paroxetine), and 12 patients were taking other antidepressants (2 mirtazapine, 9 venlafaxine, 1 reboxetine). Eleven patients were on lithium treatment at follow-up.

Table 1. Demographic and Clinical Data for Patients With a Major Depressive Episode and Healthy Controls[a]

	Patients With Major Depressive Episode			
Variable	Total (N = 30)	Remitted (N = 18)	Nonremitted (N = 12)	Controls (N = 30)
Age, mean ± SD, y	48.4 ± 13.4	46.4 ± 15.4	51.3 ± 9.6	45.7 ± 12.9
Gender, N				
Female	18	11	7	18
Male	12	7	5	12
Handedness, N				
Right	28	17	11	28
Left	2	1	1	2
Height, mean ± SD, cm	168.8 ± 7.6	170.3 ± 8.5	166.7 ± 5.6	173.1 ± 9.7
Weight, mean ± SD, kg	68.8 ± 14.1	67.7 ± 12.3	70.6 ± 16.7	69.5 ± 10.3
Age at onset, mean ± SD, y	39.3 ± 13.4	36.5 ± 15.5	43.5 ± 8.3	NA
Duration of illness, mean ± SD, y	9.1 ± 10.2	9.9 ± 11.5	7.8 ± 8.2	NA
Episode[b]				
First	11	9	2	NA
Recurrent	19	9	10	NA
HAM-D score, mean ± SD	23.7 ± 6.9	24.7 ± 7.0	22.2 ± 6.7	NA

[a]No significant differences were found between patients and controls or between remitted and nonremitted patients as measured with ANCOVA or chi-square test.
[b]Chi-square test: p = .063 between remitted and nonremitted.
Abbreviations: ANCOVA = analysis of covariance, HAM-D = Hamilton Rating Scale for Depression, NA = not applicable.

For comparison, 30 healthy control subjects were matched in a 1-to-1 fashion with respect to age (age = 20–65 years; mean ± SD age = 45.7 ± 12.9 years), gender, and handedness. Patients and controls also did not differ with regard to educational level, height, and weight. Individual age pairings were such that the widest age-pairing difference was 4 years (2 pairs). Controls were also examined at baseline and 1 year later. Neither the healthy controls nor their first-degree relatives had a history of neurologic or mental illness.

Exclusion criteria for patients and controls were previous head injury, neurologic diseases, and comorbidity with other mental illnesses. Handedness was determined by the Edinburgh inventory.[21]

After a complete description of the study to the first-episode patients with major depressive disorder and the healthy controls, written informed consent was obtained. The study design was approved by the local ethics committee and was prepared in accordance with the ethical standards laid down in the Declaration of Helsinki.

MRI Procedures

MRI images were obtained (1.5 Tesla Magnetom Vision, Siemens, Germany) using a coronal T2-weighted and proton density-weighted Dual-Echo-Sequence (repetition time [TR] = 3710 ms/echo time [TE] = 22/90 ms; total acquisition time = 9 minutes, number of acquisitions = 1; field of view [FOV] = 230 mm; matrix = 240 × 256, slice thickness = 3 mm) and a 3D-MPRAGE sequence (TR = 11.6 ms/TE = 4.9 ms; total acquisition time = 9 minutes, number of acquisitions = 1; FOV = 230 mm; matrix = 512 × 512, slice thickness = 1.5 mm). The commercial software package ANALYZE (version 7c; Biomedical Imaging Resource, Mayo Foundation, Rochester, Minn.) was used to further process the images with size reduction from 16 to 8 bit and transformation to a uniform matrix of 256 × 256 on 192 slices of 1.0-mm slice thickness. All data sets were realigned and resampled 3-dimensionally in the anterior commissure-posterior commissure (AC-PC) line according to the coordinates of Tailairach with the software program BRAINS (Brain Research: Analysis of Images, Networks and Systems; developed by Andreasen et al.).[22] Regions of interest (ROIs) were marked with the aid of an interactive cursor-guided system on a computer display of coronal MRI images. The program BRAINS allowed the ROIs to be controlled on sagittal and transverse sections simultaneously and allowed the segmentation for calculation of the intracranial content (ICC) and gray and white matter volume (cm^3) within the defined ROI.

Definition of the Hippocampal Formation and the Amygdala

We used the definition of the hippocampus according to Niemann et al.[23] and the detection of the hippocampal-amygdala border from the description of Convit et al.[24] One rater with MRI and neuroanatomical experience measured the ROIs while blinded to the diagnosis and the date (baseline, follow-up) of the data sets. A short description is given below (see also Figure 1), whereas procedures are described in detail elsewhere.[7,15]

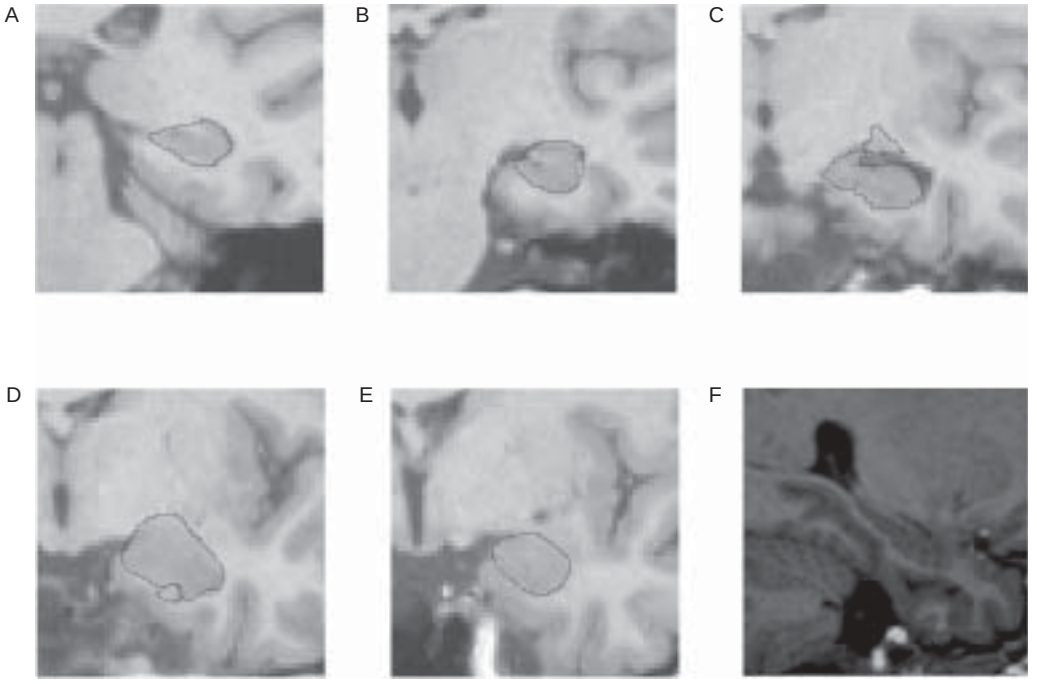
On each scan, we began with the most posterior coronal slice where the hippocampus was clearly detectable. Both the fimbria and the subiculum were included in the measurement. The uncal sulcus was of assistance in delineating the medial border. More anteriorly, the shape of the hippocampus may be compared with a rabbit whose head is directed vertically. There, the uncal sulcus separates the uncus from the underlying parahippocampal gyrus and forms the basal border of the hippocampus. The anterior part of the hippocampus ends where the cornu inferius of the lateral ventricle becomes vertically oriented. The amygdala-hippocampal boundaries were defined in the sagittal plane and then projected to the coronal plane. The superior-lateral borders of the amygdala are formed by a thin strip of white matter, which separates the amygdala from the claustrum and the tail of the caudate. A thin strip of parahippocampal white matter called the angular bundle was used to outline the medial border of the amygdala. Demarcation of the superior-medial border of the amygdala was performed using the semilunar gyrus. The inferior boundary is the hippocampus. The temporal lobe white matter and the extension of the temporal horn constitute the inferior-lateral border. The anterior pole of the amygdala was defined as the image in which its width was approximately 2.5 times the thickness of the adjacent temporal lobe.

In order to determine the interrater reliability of measuring hippocampal volumes, 10 brain scans were randomly chosen and ROIs determined independently by 2 raters (T.F., T.Z.). The intraclass correlations for the interrater reliability of measuring hippocampal gray matter ($r_{ICC} = 0.97$) and of measuring hippocampal white matter ($r_{ICC} = 0.82$) were high. To determine the intrarater reliability, hippocampal volumes from 10 subjects were determined 4 weeks apart by 1 rater (T.F.) (hippocampal gray matter: $r_{ICC} = 0.96$, hippocampal white matter: $r_{ICC} = 0.93$).

To investigate the interrater and intrarater reliability of measuring amygdala volumes, the ROIs of 12 randomly chosen brains were determined independently by 2 raters (T.F., T.Z.). The interrater reliability (total amygdala volume: $r_{ICC} = 0.93$) and the intrarater reliability (total amygdala volume: $r_{ICC} = 0.91$) were found to be high.

Test-retest reliability for the 30 healthy controls was measured twice, at the baseline and the 1-year follow-up, and was high for the total hippocampal volume ($r_{ICC} = 0.93$) and moderate for the total amygdala volume ($r_{ICC} = 0.75$).

Figure 1. Coronal MRI Slices That Run in Occipito-Rostral Direction[a]



[a](A) Most posterior coronal slice where the hippocampus was clearly detectable. (B) Hippocampal body. (C) The shape of the hippocampus may be compared with a rabbit whose head is directed vertically (lower and larger region of interest [ROI]); amygdala-hippocampal transition area (HATA) (upper and smaller ROI). (D) Posterior amygdala (upper and larger ROI) and its relationship to the hippocampus (lower and smaller ROI). (E) Slice through the medial part of the amygdala. (F) Sagittal slice through the temporal lobe and hippocampal formation.

Statistical Analyses

The Kolmogorov-Smirnov test was applied to test for normal distribution of morphometric data. They were subjected to a repeated-measurement analysis of variance (ANOVA) assessing the main and interaction effects of the 2 within-subjects factors, time (baseline, 1-year follow-up) and hemisphere (left, right), and the between-subjects factor, diagnosis (depression, control). To investigate morphometric differences between remitted and nonremitted patients, a repeated-measurement analysis of covariance (ANCOVA) with the 2 within-subjects factors, time (baseline, 1-year follow-up) and hemisphere (left, right), as well as the between-subjects factor, remission (remitted/nonremitted), with age as the cofactor was assessed. To control for the total intracranial volume, ANOVA was applied to relative hippocampal and amygdala volumes (ROI/ICC). Student t tests were used for post hoc analysis. Pearson product moment correlations were used to explore the relationship between hippocampal volumes and age, age at onset, and illness duration. Spearman correlation coefficients were performed for the relationship between hippocampal volumes and HAM-D score at baseline and at the 1-year follow-up.

RESULTS

Morphometric data were normally distributed. An overview of the demographic variables is given in Table 1. Patients with an episode of major depressive disorder did not differ significantly from healthy controls in age, gender, handedness, educational level, height, and weight. Additionally, there was no significant difference in total brain volume between patients and controls. Moreover, the subgroup of patients who were fully remitted at follow-up (N = 18) did not differ in age ($t = 1.0$, $df = 1,28$; $p = .33$), gender ($\chi^2 = 0.023$, $df = 1,28$; $p = .88$), handedness ($\chi^2 = 0.09$, $df = 1,28$; $p = .77$), height ($t = 1.3$, $df = 1,28$; $p = .20$), weight ($t = 0.55$, $df = 1,28$; $p = .58$), illness duration ($t = 0.56$, $df = 1,28$; $p = .58$), age at onset ($t = 1.4$, $df = 1,28$; $p = .16$), severity of depression at baseline (HAM-D score: $t = 1.0$, $df = 1,28$; $p = .33$), or medication at follow-up ($\chi^2 = 1.1$, $df = 1,28$; $p = .77$) compared with the nonremitted patients (Table 1).

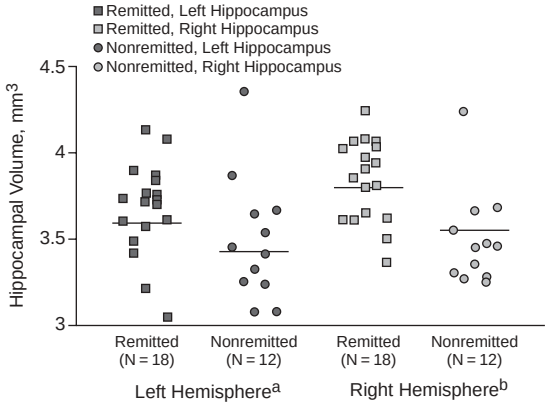
Interestingly, remitted patients more often had no antidepressant treatment (N = 4), because they had no symptoms and the medication was stopped, than did nonremitted patients (N = 1). Therefore, it does not seem that nonremitted patients were noncompliant in the present

Table 2. Hippocampal and Amygdala Volume Data for Patients With Major Depressive Disorder (N = 30) and Healthy Controls (N = 30) at Baseline and Follow-Up[a]

	Patients With MDD				Controls			
	Baseline		Follow-Up		Baseline		Follow-Up	
Variable	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Hippocampal volume, mm^3								
Left								
Total	3.70	0.33	3.72	0.28	3.82	0.34	3.82	0.40
Remitted	3.78	0.28	3.81	0.21	3.84	0.35	3.82	0.40
Nonremitted	3.58	0.37	3.59	0.34	3.80	0.35	3.81	0.43
Right								
Total	3.80	0.31	3.77	0.31	3.93	0.35	3.93	0.39
Remitted	3.94	0.25	3.88	0.30	3.92	0.39	3.89	0.41
Nonremitted	3.58	0.27	3.61	0.26	3.93	0.30	3.99	0.36
Amygdala volume, mm^3								
Left	1.69	0.20	1.67	0.19	1.66	0.24	1.70	0.25
Right	1.68	0.26	1.65	0.24	1.68	0.24	1.66	0.23

[a]Nonremitted patients (N = 12) had significantly smaller left and right hippocampal volumes than did remitted patients (N = 18) and had significantly smaller right hippocampal volumes than did their matched healthy controls.

Figure 2. Left and Right Hippocampal Volumes for Remitted and Nonremitted Patients With Depression at Baseline



[a]Left hemisphere (t = 1.6, df = 1,28; p = .11).
[b]Right hemisphere (t = 3.7, df = 1,28; p = .001).

study. There were tendencies for higher numbers of patients with recurrent depression in the nonremitted group (χ^2 = 3.4, df = 1,28; p = .063).

In order to control for total brain volume, the relative hippocampal/ICC volumes were subjected to ANCOVAs. This did not change the results, so that the absolute values will be described in detail.

Hippocampal Volume

Hippocampal volumes for baseline and follow-up are shown in Table 2. No significant diagnosis effect (F = 2.4, df = 1,58; p = .13) or time effect (F = 0.01, df = 1,58; p = .91) occurred. Furthermore, there was no significant interaction of time and diagnosis (F = 0.001, df = 1,58; p = .99), indicating that the hippocampal volumes in both patients with major depressive disorder and healthy controls did not change during the 1-year follow-up investigation.

A significant hemisphere effect, indicating larger right than left hippocampal volumes (F = 12.9, df = 1,58; p = .001) without significant interactions of hemisphere and diagnosis (F = 0.45, df = 1,58; p = .50), was detected.

Amygdala Volume

Amygdala volumes for baseline and follow-up are shown in Table 2. No significant main diagnosis effect (F = 0.001, df = 1,58; p = .98) occurred. Furthermore, there was no significant time effect (F = 0.32, df = 1,58; p = .57) or hemisphere effect (F = 0.45, df = 1,58; p = .50) and no significant interactions between these factors and diagnosis.

Hippocampal Volume and Clinical Remission

ANOVA, with remission at the 1-year follow-up (remitted, unremitted) as the between-subjects factor, performed on the hippocampal volumes of the patients revealed a significant remission effect (F = 6.7, df = 1,27; p = .015, Figure 2). Patients who were not remitted at the 1-year follow-up investigation had significantly smaller right and left hippocampal volumes at baseline and at the 1-year follow-up timepoint compared with those of remitted patients. There was no significant time effect (F = 0.070, df = 1,27; p = .79), hemisphere effect (F = 0.017, df = 1,27; p = .90), interaction of time and remission (F = 0.43 df = 1,27; p = .52), or interaction between hemisphere and remission (F = 1.5, df = 1,27; p = .24).

Moreover, as compared with matched healthy controls, nonremitted patients had significantly smaller right hippocampal volumes at baseline (t = 2.9, df = 22, p = .009) and at follow-up (t = 2.6, df = 22, p = .016). Left hippocampal volumes did not differ significantly between nonremitted patients and their matched controls (baseline: t = 1.4, df = 22, p = .16; follow-up: t = 1.4, df = 22, p = .18). Remitted patients did not differ from their matched healthy controls in left (baseline: t = 0.58, df = 34, p = .57; follow-up: t = 0.18, df = 34, p = .86) and right (baseline: t = 0.11, df = 34, p = .91; follow-up: t = 0.09, df = 34, p = .93) hippocampal volumes.

No significant differences were observed in hippocampal volumes between first-episode or recurrent-episode patients in either nonremitted or remitted patients.

Amygdala Volume and Remission

Regarding the amygdala, no significant remission effect was observed (F = 1.8, df = 1,27; p = .19) and no significant interaction of time and remission occurred (F = 2.3, df = 1,27; p = .14). No significant differences were found between remitted patients and their matched healthy controls or between nonremitted patients and their matched healthy controls.

Clinical Variables

Age was significantly correlated with hippocampal volumes in healthy controls (left baseline: r = –0.50, p = .004, slope = –0.0134 mL/year; right baseline: r = –0.46, p = .010, slope = –0.0127 mL/year; left follow-up: r = –0.49, p = .006, slope = –0.0153 mL/year; right follow-up: r = –0.45, p = .013, slope = –0.0134 mL/year). However, no significant age correlation was detected in the group of patients with major depressive disorder. Furthermore, age at onset and illness duration were not significantly correlated with hippocampal volumes.

HAM-D scores were significantly negatively correlated with the right gray matter density of the hippocampus (baseline: r = –0.58, p = .001; follow-up: r = –0.38, p = .04). Neither the left hippocampal gray matter density nor the amygdala volumes were significantly correlated with HAM-D scores. No significant differences were found between medication groups and hippocampal or amygdala volumes.

DISCUSSION

In this prospective, longitudinal in vivo study, we investigated whether depression can result in a further diminution of hippocampal volumes or whether a smaller hippocampal volume predisposes an individual to depression or to a certain course of the illness.

The new and interesting finding of this longitudinal study was that nonremitted, depressed patients showed reduced hippocampal volumes at baseline and at follow-up. Therefore, our findings support the hypothesis that subtle brain lesions such as reduced hippocampal volumes may predispose patients to a poor clinical outcome without full remission from depression. A relationship between structural alterations and the course of the illness was first pointed out by cross-sectional studies. One study found significant associations between chronic depression and reduced left hippocampal gray matter density measured by voxel-based analysis.[25] A recent study found with statistical parametric mapping that the right hippocampus is reduced in elder patients with depression, particularly in patients with a longer course of illness.[26] Moreover, a relationship between hippocampal volume decline and longer cumulative illness duration was described.[3] Chronicity was also related to more severe white matter and subcortical hyperintensities in cross-sectional structural MRI investigations.[27,28]

These results underline that differences in sample characteristics like chronicity or treatment resistance might account for different results between studies. One limitation of the present study might be that patients were taking different medications. However, interestingly, there were no significant differences in the type of antidepressant medication for remitted compared with nonremitted patients. Remitted patients more often had no antidepressant treatment (N = 4) than did nonremitted patients (N = 1) at the follow-up, because they had no symptoms and the medication was stopped. Therefore, it seems unlikely that nonremitted patients were noncompliant in the present study. They had been continuously treated, but were simply unable to attain a response.

Interestingly, nonremitted patients were mainly those patients with recurrent depression. Thus, it might be that previous episodes resulted in a hippocampal change, which, in turn, resulted in a poor clinical outcome. However, since hippocampal volumes of first-episode patients did not differ from those of patients with recurrent episodes in the remitted or nonremitted group, the hippocampal volume difference between remitted and nonremitted patients might not result from differences in the number of first-episode versus recurrent-episode patients. Otherwise, it is also possible that patients with a smaller hippocampus more often have recurrence of depressive episodes.

Investigations of the influence of serotonin transporter polymorphisms (5-HTTLPR) on hippocampal volumes found reduced hippocampal volumes particularly in patients with the L/L genotype compared with healthy controls.[13] Patients with L/L genotype may have a higher vulnerability to hippocampal changes. It remains unclear whether these changes occur before the beginning of the disease or whether they are triggered by a variety of factors such as stress or emotional trauma during the depressive episode.

Some studies support the idea that the changes occur before the beginning of the disease. Stressful life events or other biological factors that influence neuronal development (like prenatal, perinatal, or postnatal infections and genetic vulnerability) may change hippocampal structures in a way that would render subjects more vulnerable to the development of major depressive disorder. Schatzberg[12] reported that paternal genetics, but not early stress, appeared to account for much of the variance in hippocampal size in squirrel monkeys. They used a model involving paternal half-siblings among squirrel monkeys to explore the relative contributions of early life stress and genetics to hippocampal size in young adulthood. Specific fathers appeared to sire offspring who had smaller hippocampi. These animals also demonstrated greater cortisol responses at weaning, suggesting a risk factor for depression.

Moreover, a stable nature of hippocampal volume may be suggested from the finding that no significant changes in hippocampal volumes occurred during the 1-year follow-up. Only a small decline in the hippocampal volume with increasing age was found in our sample. This is in line with in vivo[29–32] and post mortem studies,[33,34] which found little or no hippocampal volume changes with increasing age. Therefore, the failure to find significant differences during a 1-year period in healthy controls or in a

group of depressive patients, in which most of the patients were remitted from depression, is not astonishing.

Furthermore, the finding that the hippocampus is already reduced in first-episode patients with major depressive disorder also supports the idea that reduced hippocampal volume might predispose an individual to depression.[7] However, a recent study found no hippocampal volume reduction in first-episode patients with major depressive disorder, whereas, in the same study, patients with recurrent episodes had significant volume reductions,[35] and significant relationships were found between hippocampal volumes and the cumulative illness duration, indicating changes that occurred during depressive episodes.[3]

Thus, prospective studies following up patients and controls for a few years must shed more light on whether hippocampal changes are present before the beginning of depression, whether the reductions are the result of depression, or whether both aspects play a role.

In the present study, hippocampal volumes showed no significant reductions in the overall patient group compared with healthy controls. However, nonremitted patients with a poor clinical outcome at the 1-year follow-up had significantly smaller left and right hippocampal volumes compared with those of remitted patients and had significantly smaller right hippocampal volumes compared with those of their matched controls. Since only 12 patients were nonremitted after 1 year, the statistical analysis comparing these patients with their matched controls has little power, so it is not surprising that although left hippocampal volumes were smaller in the patient group, these results did not reach significance. Therefore, the results from the present study are partly in line with earlier studies on hippocampal volumes. Steffens et al.[4] showed tendencies for reduced hippocampal volumes, whereas others found reduced hippocampal volumes in elderly[3] and also in younger patients with depression.[5–7]

The reason for the failure to identify a hippocampal reduction in the overall patient group needs to be discussed. Because patients who do not remit within the first year after a depressive episode seem to have smaller hippocampal volumes, as reported in the present study, and patients with a longer cumulative illness duration also show smaller hippocampal volumes than do patients with shorter illness durations,[3] the course of a depressive episode may be an important factor related to hippocampal volumes, and vice versa. Speculatively, it may be that mainly patients with a good clinical outcome participated in the follow-up investigation, whereas nonremitted patients with a poor clinical outcome did not. This study bias might explain the failure to find significantly reduced hippocampal volumes in the overall patient group, because, in the present study, particularly the smaller number of nonremitted patients showed pronounced hippocampal volume reductions, whereas remitted patients were unchanged.

Amygdala volumes were not significantly altered in our mixed sample of recurrent and first-episode patients with major depressive disorder. This is in line with earlier studies, including our own investigations, which failed to find altered amygdala volumes in patients with recurrent depression.[5,16] One study in elderly patients with recurrent depression detected reductions of a subregion of the amygdala, the amygdala core nuclei, which were related to illness duration.[17] Because we recently found increased amygdala volumes in patients with a first episode of major depressive disorder,[15] one might postulate that amygdala volume declines during the course of the disease. However, the results from the present study do not yet support this hypothesis because no significant differences between amygdala volumes in remitted and nonremitted patients were found. However, a 1-year interval seems to be too short to obtain significant differences.

In summary, the present data indicate that a smaller hippocampal volume might predispose subjects to develop depression and, additionally, might prevent them from achieving remission from depression, which supports the idea that reduced hippocampal volumes may render subjects sensitive to developing depression. However, it is not possible to conclude from the present study whether hippocampal changes were present before the disease became apparent or whether they occurred during the acute depressive episodes. To investigate this question, studies in high-risk family members of patients with depression may be necessary.

Drug names: amitriptyline (Elavil and others), citalopram (Celexa), doxepin (Sinequan and others), mirtazapine (Remeron and others), paroxetine (Paxil and others), sertraline (Zoloft), trimipramine (Surmontil), venlafaxine (Effexor).

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