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Hippocampal volume in first episode and recurrent depression

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ABSTRACT

Abnormalities in limbic–thalamic–cortical networks are hypothesized to modulate human mood states. In the present study differences in hippocampal volumes of patients with a first episode of depression, recurrent major depression and healthy control subjects were examined with high-resolution magnetic resonance imaging (MRI). Male patients with a first episode of major depression had a significantly smaller left hippocampal volume than male control subjects. Also, these patients had a significant left–right asymmetry in hippocampal volume. Female patients showed no significant alterations in hippocampal volumes. The results support the hypothesis that the hippocampus plays an important role in the pathophysiology of the early phase of major depression, especially for male patients. Implications for the neurodevelopmental and the neurodegenerative model of hippocampal change are discussed.

1. Introduction

Increasing evidence has shown structural cerebral abnormalities in limbic–thalamic–cortical networks in patients with unipolar depression (Soares and Mann, 1997; Campbell and MacQueen, 2003, 2006). A core area in these networks is the hippocampus, which is involved in memory and emotional regulation deficits that often accompany depression. Several structural imaging studies have found abnormalities in hippocampal volumes in patients with depression. Some of these studies found a smaller volume unilaterally, others found a bilaterally smaller one, and still others could not find any differences compared with healthy controls (Videbech and Ravnkilde, 2004; Campbell et al., 2004; Campbell and MacQueen, 2006). In recent studies a smaller hippocampal volume has been found only in subsamples of depressed patients. It has been presumed that the inconsistencies in results cannot solely be ascribed to the heterogeneity of MRI methods but also to the sampling, which was inconsistent concerning the proportion of first episode and recurrently depressed patients as well as the gender ratio (Videbech and Ravnkilde, 2004; Campbell et al., 2004). Frodl et al. (2002) compared depressive men and women with healthy controls and found a smaller left hippocampal volume only for men with a first episode of major depression. MacMaster and Kusumakar (2004) found an even more pronounced reduction in left hippocampal volume in male adolescent patients. In contrast, MacQueen et al. (2003) found that patients with multiple episodes in comparison to first episode patients were more likely to have smaller hippocampal volumes. To date, only one study exists, namely that of MacQueen et al. (2003), which systematically compares first episode and recurrently depressed patients, and also considers gender effects. The aim of the present study therefore was to compare the hippocampal formation of male and female patients with a first episode and recurrent depression to that of healthy control subjects. The hypotheses were that depressed patients have a smaller hippocampal volume in comparison to healthy control subjects and that patients with multiple episodes have a smaller hippocampal volume in comparison to patients with a first episode of major depression.

2. Methods

2.1. Subjects

Fifty-seven inpatients with major depression according to DSM-IV (American Psychiatric Association, 1994) treated in the Department of Psychiatry of the University in Heidelberg were recruited. The diagnoses were made using a structured clinical interview (SCID; Wittchen et al., 1997). The mean age of the 33 female and 24 male patients was 43.54 (S.D. = 12.82, 18–64) at initial assessment. Twenty-seven (47.37%) patients were married. Twenty-two (38.60%) had a high and 35 (61.40%) a low level of school education. Twenty-six (45.61%) patients had a first episode of major depression. The mean score in the 17-item Hamilton Depression Rating Scale (HDRS; Hamilton, 1960) was 22.74 (S.D. = 6.58) at admission to treatment.

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Mean duration of current depressive episode was 34.79 weeks (S.D. = 47.92) with a median of 15 weeks. Average age of onset of depression was 38.54 years (S.D. = 13.27), mean duration of illness was 5.00 years (S.D.=8.31), and mean number of episodes including the current episode of depression was 3.09 (S.D. = 4.83). Of the consecutively treated patients fulfilling the inclusion criteria, eight (11.76%) declined participation in the study and three (4.4%) could not take part because of fulfilling exclusion criteria for the MRI examination. There were no indications of a systematic selection bias. All patients were receiving antidepressant medication at the time of the MRI examination: 21 patients (36.84%) were taking serotonin reuptake inhibitors, 12 (21.05%) patients were taking tricyclic antidepressants and 24 (42.11%) patients were taking other new antidepressants. Additionally, 34 patients (59.65%) received some kind of comedication with benzodiazepines, neuroleptics or mood stabilizers. On average, patients had been treated with antidepressants for 25.21 weeks (S.D. = 53.59) with a median of 6 weeks. All the participants were screened for comorbid medical and psychiatric conditions by means of clinical, physical, and neurological examinations. Exclusion criteria for all participants were a history of substantial head injury, seizures, neurological diseases, dementia, impaired thyroid function, corticoid use or alcohol or substance abuse or dependence. Seventeen of the patients (29.8%) had a DSM-IV axis I co-morbidity mainly with anxiety disorders. No patient was diagnosed with posttraumatic stress disorder. Twenty-six of the patients (45.6%) had a personality disorder. For comparison, 30 healthy subjects (19 female, 11 male) without a history of psychiatric disorder according to the SCID and aged between 18 and 62 years ($m = 42.38$, S.D. = 12.86) were recruited. The mean score in the 17-item HDRS for the control group was 1.27 (S.D. = 1.36).

Patients with a first episode of major depression and recurrent depression did not differ significantly from healthy comparison subjects with respect to age, gender, height, weight, handedness, social class, education and alcohol consumption (see Table 1). There was a trend for first episode patients to be younger than multiple episode patients ($F = 2.17$, $df = 5,81$, $P = 0.12$); this effect, however, was not statistically significant. Therefore, age was included as a covariate in the volumetric analyses. No statistically significant sex effect was found between the groups ($chi^2 = 1.48$, $df = 2,85$, $P = 0.48$). There was a significant main effect ($F = 170.0$, $df = 5,81$, $P = 0.001$) for severity of depression (HDRS) with control subjects having lower HDRS scores compared with depressed patients. No significant difference in severity of depression was found between first episode patients and patients with recurrent depression. Patients with a first episode of major depression and recurrent depression did not differ significantly regarding age at onset of depression ($z = 0.19$, $df = 1,56$, $P = 0.85$). Patients with recurrent depression, as would be expected, had a significantly longer duration of illness compared with first episode patients ($z = -4.74$, $df = 1,56$, $P = 0.001$), but no significant differences were found for the duration of the current episode ($z = -1.48$, $df = 1,56$, $P = 0.16$). Multiple episode patients had suffered 4.84 episodes (S.D. = 6.06) on average. There were neither significant differences between first episode and multiple episode patients nor between male and female patients, regarding kind and duration of antidepressant medication (see Table 1).

After a complete description of the study was given to the patients and normal control subjects, written informed consent was obtained. The study protocol was approved by the local ethics committee and was prepared in accordance with the ethical standards laid down in the Declaration of Helsinki.

2.2. Magnetic resonance imaging and image analysis

MRI scans of the whole brain were obtained by using a Siemens 1.5-Tesla MR scanner (Siemens Medical Systems, Inc., Erlangen, Germany). T1-weighted three-dimensional magnetization-prepared rapid gradient echo sequences (3D-MPRAGE) were acquired with the following parameters: 124 1.5-mm coronal slices, TR = 11.6 ms, TE = 4.9 ms, total acquisition time = 9 min, FOV = 260 mm, number of acquisitions = 1, matrix = 512 × 512. T_2-weighted images were acquired with the following parameters: 2-mm coronal slices, TR = 7840 ms, TE = 54 ms, total acquisition time = 4 min, number of acquisitions = 1, FOV = 260 mm, matrix = 256 × 192. Image processing was performed on a computer workstation (Silicon Graphics Inc., Mountain View, Calif) using the BRAINS (Brain Research: Analysis of Images, Networks, and Systems) software package (Andreasen et al., 1992). As part of the segmentation procedure of BRAINS, intracranial volume total brain volume was determined semi-automatically. In this study, hippocampal volume was measured by using a reliable and validated method which was previously described in detail by Pantel et al. (2000). The hippocampal formation was measured according to

Table 1
Sociodemographical and clinical characteristics of the sample ($n = 87$).

		Total sample major depression ($N = 57$)		First episode major depression ($N = 26$)		Recurrent major depression ($N = 31$)		Healthy comparison subjects ($N = 30$)	
		Mean N	S.D.	Mean N	S.D.	Mean N	S.D.	Mean N	S.D.
Sex[a]	Men	24 (42.1%)		13 (50.0%)		11 (35.5%)		11 (36.7%)	
	Women	33 (57.9%)		13 (50.0%)		20 (64.5%)		19 (63.3%)	
Age[a]	Men	42.75	11.57	38.08	11.88	48.27	8.73	42.00	11.28
	Women	44.12	13.82	41.46	16.64	45.85	11.78	42.68	13.98
Hamilton Depression Rating Scale (HDRS)[b]	Men	21.04	6.22	23.00	5.94	18.72	5.97	1.64	1.36
	Women	23.97	6.64	25.62	6.34	22.90	6.77	1.05	1.35
Number of episode		3.09	4.83	1.00	0.00	4.84	6.06	NA	
First		26 (45.6%)		26 (100%)		0 (0.0%)			
Second		11 (19.3%)		_		11 (35.5%)			
Third		11 (19.3%)		_		11 (35.5%)			
Fourth or more		9 (15.8%)		_		9 (29.0%)			
Age at onset[c]	in years	38.54	13.27	38.88	14.41	38.26	12.46	NA	
Duration of illness[d]	in years	5.00	8.31	0.88	1.14	8.45	10.04	NA	
Duration of current episode[c]	in weeks	34.79	47.92	33.54	54.30	35.84	42.75	NA	
Antidepressants[c] comedication		57 (100%)		26 (100%)		31 (100)		NA	
		34 (59.65%)		12 (46.15%)		22 (70.97%)			
Duration of AD medication[c]	in weeks	25.21	53.59	21.12	44.67	28.65	60.59	NA	

For detailed F and P values see text.
NA: not applicable.
[a] No significant differences were found between patients and controls or between first episode patients and patients with recurrent depression.
[b] Significant differences were found between patients and controls but not between first episode patients and patients with recurrent depression.
[c] No significant differences were found between first episode patients and patients with recurrent depression.
[d] Significant differences were found between first episode patients and patients with recurrent depression.

Table 2
Hippocampal volumes of patients with first episode depression and recurrent depression in comparison with healthy comparison subjects.

Hippocampal volume (cm^3)		First episode major depression ($n=26$)		Recurrent major depression ($n=31$)		Healthy comparison subjects ($n=30$)		ANCOVA intracranial volume and age as cofactors		
		Mean	S.D.	Mean	S.D.	Mean	S.D.	*df*	*F*	*P*
Total	Men	5.81	0.90	6.07	0.85	6.49	0.49	2,31	2.60	0.09
	Women	5.52	0.57	5.59	0.73	5.51	0.66	2,48	0.12	0.89
Left	Men	2.81[a]	0.36	3.10	0.39	3.19	0.25	2,31	5.12	0.01
	Women	2.71	0.26	2.75	0.41	2.72	0.30	2,48	0.09	0.92
Right	Men	3.00	0.57	2.97	0.47	3.30	0.29	2,31	1.77	0.19
	Women	2.82	0.36	2.83	0.35	2.79	0.41	2,48	0.16	0.85

[a] Patients with first episode major depression < healthy comparison subjects.

its true anatomical definition based on the concise and extensive morphological description given by H.M. Duvernoy in his Atlas of Applied Hippocampal Anatomy (Duvernoy, 1988). The hippocampal formation was traced manually on the continuous segmented image (stereo image) provided by BRAINS. This could be accomplished by relying on the capacity of the used software (BRAINS) of simultaneous visualization in multiple planes, by the capacity to "telegraph" tracings or cursor position from one plane to another, and by simultaneously relying on information from the two different image modalities (T1 and T2). Once BRAINS had been started, the stereo image and the realigned and fitted T1 and T2 images were loaded. In accordance with most previously published methods for the volumetric measurement of the hippocampus, the regions of interest were defined on the coronal plane. However, tracing began with the generation of the auxiliary guideline traces on the sagittal plane. The auxiliary traces were necessary to provide a neuroanatomically correct separation of rostral (head) and caudal (tail) parts of the hippocampus from adjacent non-hippocampal brain tissue. A detailed description of boundary definition is provided at: http://iowa-mhcrc.psychiatry.uiowa.edu/mhcrc/IPLpages/manual_tracing.htm. Interrater reliability for two independent raters was calculated using the intraclass correlation coefficient (ICC) for volumetric assessments of the hippocampus in a subgroup of 16 randomly selected subjects. Raters were blind to diagnosis and other sociodemographical and clinical characteristics of the patients and control subjects, and images were randomly distributed. The ICCs were 0.97 for the left hippocampus and 0.98 for the right hippocampus.

2.3. Statistical analyses

Morphometric data were normally distributed. They were subjected to a repeated measurement analysis of covariance (ANCOVA) assessing the main and interaction effects of the within-subjects factor hemisphere and the between-subjects factors diagnosis and gender by using total cranial volume and age as cofactors. Significant interactions of this model were resolved by univariate ANCOVAs on the hippocampal volumes for each region, and diagnostic group, total cranial volume and age were used as covariates. Contrasts were performed using the Tukey test. Dependent Student's *t*-tests were used for post hoc analysis of (left–right) hemispheric differences. Results were considered statistically significant if at or below the 5% probability level (two-tailed). Analyses were performed with SAS Version 9.12 (SAS System for Windows, 2002–2003).

3. Results

The hippocampal volumetric data are shown in Table 2. No significant main effects on hippocampal volume were found for diagnosis ($F=1.45$, $df=2,79$, $P=0.24$). The main gender effect was significant ($F=8.12$, $df=1,79$, $P=0.006$), with male subjects having a larger hippocampal volume than female subjects. The interaction between diagnosis and gender, however, was not significant ($F=1.53$, $df=2,79$, $P=0.22$). Also, the hemisphere (left–right asymmetry) main effect ($F=0.83$, $df=1,80$, $P=0.36$) was not significant. The interactions of diagnosis, hemisphere, and gender ($F=3.33$, $df=2,79$, $P=0.04$) on the other hand were significant, whereas the cofactors age ($F=1.50$, $df=2,79$, $P=0.22$) and intracranial volume ($F=0.01$, $df=2,79$, $P=0.99$) were not. Post hoc univariate ANCOVA revealed that male patients with a first episode of depression had a significantly smaller left hippocampal volume than healthy male control subjects ($F=5.12$, $df=2,31$, $P=0.01$). The right hippocampal volume, however, was not significantly different ($F=1.77$, $df=2,31$, $P=0.19$). For female patients with a first or recurrent episode, no significant differences in left ($F=0.19$, $df=2,48$, $P=0.92$) and right ($F=0.16$, $df=2,48$, $P=0.85$) hippocampal volume in comparison with healthy female subjects were found. Post hoc analysis revealed a significant left–right asymmetry in male first episode patients ($t=2.34$, $df=12$, $P=0.04$), whereas male patients with recurrent depression and healthy male control subjects did not show significant hemispheric differences. No significant left–right asymmetry was found for female patients and control subjects. Additionally, there was no significant difference in total brain volume between the three groups.

An analysis of the association of hippocampal volumes, duration of illness and duration of the index episode neither revealed a significant correlation for the whole group of depressed patients nor for the subgroups of first episode patients and patients with recurrent depression. Moreover, no significant correlations between the number of depressive episodes and hippocampal volume could be found for the whole group of depressed patients or for the male and female subgroups.

4. Discussion

The present study shows that male patients with a first episode of major depression have a significantly smaller left hippocampal volume compared with male control subjects. The reduction in hippocampal volume of nearly 10% found in meta-analyses on depression (Videbech and Ravnkilde, 2004; Campbell et al., 2004) could only be found in first episode male patients. Depressed male patients with a first episode of depression also showed a significant hemispheric asymmetry of hippocampal volume. It can be assumed that this left-right asymmetry indicates the beginning of volume loss in the area of the left hippocampus. Thus, our results confirm those of Frodl et al. (2002) and MacMaster and Kusumakar (2004), who also observed a smaller hippocampal volume only for male first episode patients and only in the left hippocampus. In the meta-analyses on hippocampal volume in depression (Videbech and Ravnkilde, 2004; Campbell et al., 2004), it was shown that more studies found a reduction in left than in right hippocampal volume. However, in most studies no sex effects in comparison with control groups could be identified, and Videbech and Ravnkilde (2004) did not find a significant sex effect in their meta-analysis either. This could be due to the relatively small sizes of the samples, the differences in gender ratio, and the fact that first and multiple episode patients were not differentiated. Accordingly, despite the non-significant sex effects in their meta-analysis, Videbech and Ravnkilde (2004) assumed that the heterogeneous findings of structural imaging studies can perhaps be explained by the high variety of the female-to-male ratio in several studies. Thus, differences in hippocampal volume abnormalities not only exist between different disorders but these abnormalities also differ depending on sex and course of the disorder. These associations are complicated by the fact that physiological gender differences in hippocampal volume exist in healthy subjects (Coffey et al., 1998). For example, it is well known that the hippocampal volume of healthy males is larger than that of healthy women and that hippocampal volume decreases over the life span only

in men (Pruessner et al., 2001; Lupien et al., 2007). In summary, our first hypothesis that depressed patients have a smaller hippocampal volume in comparison to healthy control subjects could be confirmed only for male patients with a first depressive episode. The second hypothesis that patients with recurrent depression have a smaller hippocampal volume in comparison to first episode patients could not be supported. Since no significant differences in total brain volume could be found between the groups, the effect of hippocampal volume change can be regarded as being specific and cannot be attributed to general brain morphological changes or age effects which were controlled.

In the present study, no significant differences could be shown between recurrently depressed patients and healthy controls, a finding which contradicts that of MacQueen et al. (2003) and Neumeister et al. (2005) who found smaller hippocampal volumes in patients with multiple episodes. One explanation for the missing differences in the present study could be that the patients of the MacQueen et al. (2003) study were considerably younger than the patients we examined. Early onset, however, is more frequently associated with traumatization than later onset is. Vythilingam and Heim (2002) found a smaller hippocampal volume only in depressed women with prepubertal abuse whereas postpubertal abuse was not associated with a smaller volume. Also, a reduction in hippocampal volume could be found in subjects having traumatic experiences without suffering from posttraumatic stress disorder (Smith, 2005; Karl et al., 2006; Kitayama et al., 2005).

The effect of smaller hippocampal volumes in first episode patients in comparison to multiple episode patients is probably not specific for depression. Strakowski et al. (2002) found a larger hippocampus, corresponding to that of healthy controls, in multiple episode bipolar patients compared with first episode patients. These results could be explained within the context of the kindling hypothesis, which states that first depressive episodes are characterized more strongly by psychosocial triggering than later depressive episodes (Post, 1992; Monroe and Harkness, 2005). Possibly, this means that a stress and hypercortisolism related reduction in hippocampal volume is more typical for patients with first episodes than for patients with multiple past episodes for whom other biological mechanisms may be more relevant. Another explanation for this association is the influence pharmacological treatment has on hippocampal volume. The group of multiple episode patients included more patients receiving lithium. Yucel et al. (2007) showed that patients treated with lithium had a significantly larger hippocampus within a brief treatment period compared to untreated patients or patients treated with other medications.

These findings could also be relevant for the interpretation of inconsistent results concerning the association of the duration of depression and hippocampal volume. Several studies have found a negative correlation between lifetime duration of depression and hippocampal volume since Sheline et al. (1999) had first reported this in women. However, in some studies this result could not be replicated (Bremner et al., 2000; Posener and Wang, 2003; Frodl et al., 2002). In a study on early onset depression, duration of illness was significantly positively correlated with left hippocampal volume (MacMaster and Kusumakar, 2004). In the meta-analysis of Videbech and Ravnkilde (2004), the number of depressed episodes correlated with smaller volume of right but not left hippocampus. However, the number of depressed episodes was only loosely correlated with the accumulative duration of depression. Sheline et al. (2003) found a strong association between the number of days of untreated depression and hippocampal volume in depressed outpatient women but no significant association between duration of treated depression and hippocampal volume. In the present study, we did not find a significant correlation between cumulative duration of depression or duration of the index episode with hippocampal volumes. Also, no significant correlation could be found between number of depressive episodes and hippocampal volume. Furthermore, patients with recurrent depression often have shorter periods of untreated depression which could also account for larger hippocampal volume since treatment of depression may stop hippocampal atrophy and stimulate neurogenesis (Lucassen et al., 2006; Dranovsky and Henn, 2006). Possibly, differences in treatment utilization behavior of male and female patients are relevant to explain gender effects in hippocampus morphometry. Depressive men, especially in their first episode, seek medical treatment at a later point in time than depressive women do (Piccinelli and Wilkinson, 2000; Möller-Leimkühler, 2002).

Different models for the explanation of changes in hippocampal volume have been discussed. For schizophrenic patients, it was assumed that the reduction in volume increases exponentially with the course of the disorder (DeLisi et al., 2004), whereas MacQueen et al. (2003) suggested that, in depressive patients, volume reduction takes place logarithmically, that is in the early phase of the disorder. Besides this degenerative-progressive model of volume reduction, a neurodevelopmental hypothesis was formulated. This postulates that etiopathogenetic factors impair brain development long before the onset of depression and that structural brain changes observable at the first appearance of the illness do not progress over time. Some studies have recently begun to address the hypothesis that structural changes might predispose to depression, because hippocampal size has been found to be highly genetically determined (Schatzberg, 2002a,b; Gilbertson et al., 2002; Frodl et al., 2007). A fact not considered in both models is that hippocampal volume may increase again (Lucassen et al., 2006; Dranovsky and Henn, 2006; Yucel et al., 2007). Also, findings of recent studies challenge the implicit assumption that a smaller hippocampus is associated with several dysfunctions. For example, Petten van (2004) found that a smaller hippocampus correlated with a better cognitive performance in adolescents. Also, in a study with subjects at high risk for schizophrenia, it was found that persons with a larger hippocampus are more likely to develop schizophrenia (Phillips et al., 2002). Velakoulis et al., (2006) found no significant differences in hippocampal volume between depressed patients and ultra high risk persons without depression. Studies on the amygdala also show that brain structures change over the course of depression. Here, convergent results exist showing that the amygdala volume increases in the first depressive episodes whereas in patients with recurrent depression smaller volumes are found (Lange and Irle, 2004). Frodl et al. (2003) and Velakoulis et al. (2006) found abnormalities in the amygdala volume only in first episode patients but not in multiple episode patients compared to healthy controls. However, no follow-up studies exist.

The results of the present study do not support the hypothesis of depression as a neurodegenerative disease and also do not support a neurodevelopmental model positing that structural brain changes do not progress over the course of depression. It seems that both models are not elaborated enough to explain the dynamics of changes in hippocampal volume. It can rather be assumed that a dynamic process of central nervous system changes may occur during the onset and long-term course of depression in which gender effects, stress and the kindling effect, but also neuroprotection and antidepressant medication, play an important role. This hypothesis of a gender- and illness-phase-specific dynamic model of hippocampal volume change, however, should be interpreted with caution since sample selection biases cannot be ruled out, particularly in pseudo-longitudinal studies.

The comparison of first episode and recurrently depressed patients can provide some information on aspects of the course of the disorder, but it cannot substitute for longitudinal studies. Recurrently depressed patients were all first episode patients in the past but, not all first episode patients will suffer a relapse or seek in-patient treatment in case of relapse. Selection bias is a problem of studies that compare patients in different illness stages. To date, no study exists that could show a decrease or increase of hippocampal volumes in depression. The only longitudinal structural imaging study in depression revealed no significant changes in hippocampal volumes in the 1-year course (Frodl et al., 2004). However, this study did not differentiate between

first episode and recurrent depression or between sexes. However, what can only be differentiated by longitudinal data is the question whether the hippocampus volume decreases or increases over the course of depression or whether there are different subgroups of first episode patients that premorbidly differ in hippocampal volume.

The study has several limitations which need to be mentioned. First of all, the study sample is relatively small and includes only inpatients. We also did not differentiate between grey and white matter and did not examine any substructures of the hippocampus. The study did not include patients not receiving medication. Nevertheless, the results do support the hypothesis that the hippocampus plays an important role in the pathophysiology of major depression, especially in the early phase of the disorder and especially in male patients. The findings also revealed that it is of great importance to consider sex effects and to differentiate between different phases of the disorder when studying hippocampal volume in depressive patients. Thus, the results can contribute to the reformulation of neuroanatomic models of the pathophysiology of depression in a more gender-specific conceptualization. In future studies the mechanisms behind decreased hippocampal volume and its relevance for clinical outcome of depression should be addressed.

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