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Hippocampal volume in first episode and recurrent depression

Klaus-Thomas Kronmüller[a,*], Johannes Schröder[b], Sebastian Köhler[a], Bianca Götz[a], Daniela Victor[a], Jörg Unger[a], Frederic Giesel[c], Vincent Magnotta[d], Christoph Mundt[a], Marco Essig[c], Johannes Pantel[e]

[a]Department of Psychiatry, University of Heidelberg, Germany
[b]Section of Geriatric Psychiatry, University of Heidelberg, Germany
[c]Department of Radiology, German Cancer Research Center, Heidelberg, Germany
[d]Mental Health Clinical Research Center, Department of Psychiatry, University of Iowa, Iowa City, IA, USA
[e]Department of Psychiatry and Psychotherapy, University of Frankfurt/Main, Germany

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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.

* Corresponding author. Department of Psychiatry, University of Heidelberg, Voßstraße 4, D-69115 Heidelberg, Germany. Tel.: +49 6221 5632747; fax: +49 6221 565477.
E-mail address: klaus_kronmueller@med.uni-heidelberg.de (K.-T. Kronmüller).

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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.