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ORIGINAL PAPER

Differences in hippocampal volume between major depression and schizophrenia: a comparative neuroimaging study

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Abstract Several studies have demonstrated that structural brain change is detectable in the hippocampus in both patients, with schizophrenia and major depression. Only few studies, however, compared both clinical disease entities directly and no larger study has tried to take different disease stages into account. The objectives of this study are to investigate whether hippocampal volumes are reduced in patients with schizophrenia and those with major depression with the same duration of illness compared to healthy controls and to assess further changes at different disease stages. A total of 319 inpatients and healthy controls were enrolled and investigated with magnetic resonance imaging (MRI). Hippocampal volumes were measured using the segmentation software BRAINS. Bilateral hippocampal volume reductions were detected in both schizophrenic and depressed patients compared to healthy control (HC) subjects. Although younger, schizophrenic (SZ) patients showed in their MRI scans significant bilaterally reduced hippocampal volumes compared to patients with major depression. Although the hippocampal reductions were similar at the onset of symptomatic manifestation of both diseases, there was a further significant reduction of the left hippocampus in the recurrently ill SZ subgroup. The data suggest rather dynamic structural brain alterations in schizophrenia compared to major depression. Here, the presented application of the comparative neuroscience approach, by the use of large neuroimaging MRI databases, seems highly valuable. In the field of psychiatry, with its still controversial operationalized descriptive diagnostic entities, the cross-nosological approach provides a helpful tool to better elucidate the still unknown brain pathologies and their underlying molecular mechanisms beyond a single nosological entity.

Keywords Hippocampus · MRI · Schizophrenia · Depression

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Introduction

The hippocampus, which is a core region of the limbic system, is discussed to be a vulnerability marker in different CNS diseases. It is a part of the forebrain, located in the medial temporal lobe and plays a major role in executive functioning. Moreover, an intact hippocampus is necessary for episodic and declarative memory. It is required for the storage and processing of spatial information and the discovery of place cells led to the idea that the hippocampus might act as a cognitive map, which is a neural representation of the layout of the environment [42].

To reach these complex tasks the hippocampus is embedded in limbic-cortical and limbic-subcortical neurocircuits [56].

The results of a growing number of neuroimaging studies have already pointed in cross-sectional studies to a considerable overlap of structural brain alterations in different neuropsychiatric disorders. In many different psychiatric diseases such as Alzheimer's disease (AD), schizophrenia, affective disorders, epilepsy and personality disorders hippocampal volume reductions have been described with a notable range of percentage volume reductions in all clinical categories. The exact underlying cellular mechanisms are unclear.

During the last years, preparatory work for the DSM V/ICD-11 started and it is under discussion to probably change the traditional classification of psychiatric disorders. Moveover, the Kraepelinian dichotomy between schizophrenic disorders and affective disorders will potentially be omitted [36]. In fact, the current criticism of the categorical diagnostic system has originated predominantly from genetic findings [36]. Evidence from genetic epidemiology pointed to a notable overlap in the genetic susceptibility across the Kraepelinian border of clinical entities [36]. In this context, an effort to construct a psychiatric classification system, which is not only based on clinical aspects but also on neurobiological findings, is clearly needed. As the relevant genetic approach, neuroimaging research should clearly contribute, with findings from cross- and longitudinally investigated CNS alterations, comparatively detected for different psychiatric entities.

In this regard, especially the comparative CNS mapping of neurobiological alterations for different psychiatric diseases is a still underestimated tool. To date, there are only few imaging studies that compared the nature and extent of structural and functional brain alterations beyond one existing clinical entity, on the basis of large databases. In the search for underlying etiologies, the delineation of common and distinct structural and functional alterations of brain modules and supramodular systems may inform us about valuable "endophenotypes" or, in a more extended way, about the specific underlying dynamic pathophysiology in one neuropsychiatric disease compared to another.

Already in the past, common clinical overlaps in diseases such as schizophrenia and affective disorders raised the question if they share a common pathophysiological pattern or even have a common pathogenetic origin, as most radically conceptualized by the repeatedly discussed unitary psychosis ("*Einheitspsychose*"), which unifies also the schizophrenic and affective psychosis on the basis of a single etiopathological background [36].

Within the still valid framework of functional psychosis, as it was conceptualized by Emil Kraepelin, our study performed a structural investigation of the hippocampus as a core region of the limbic system. The aim of the study was to compare the total, gray and white matter hippocampal volumes between the two main diagnostic entities, schizophrenia and major depression (MD) in a large naturalistic sample of 319 MRI datasets including patients and matched healthy controls (HC). Furthermore, intra-nosological and inter-nosological hippocampal volume differences were investigated at different stages of both diseases (first episode vs. recurrently ill patients). The hippocampal volume reductions were compared for both patients groups with that of HC subjects. When looking at the different stages of the diseases, we hypothesized, furthermore, a salient decrease of hippocampal volumes in the schizophrenic groups compared to the depressed patients' group.

Materials and methods

Participants

A total of 319 MRI datasets was included in the study. The MRI database included 92 inpatients with MD, 89 SZ patients from the Department of Psychiatry and Psychotherapy, Ludwig-Maximilian University, Munich, Germany, and 138 HC subjects. Patients were recruited from a large catchment area.

Psychiatric diagnoses based on DSM-IV criteria and on the structured clinical interview were determined by at least two psychiatrists. Age, gender, handedness, height and medication were documented. The degree of psychopathology was rated using the 21-item Hamilton Depression Rating Scale in the MD group, and the Positive and Negative Symptom Scale (PANSS) in the SZ group. 46 patients had a first episode of MD (F-MD) and 46 patients had recurrent depressive episodes (R-MD). 45 patients had a first episode of schizophrenia (F-SZ) and 44 patients had the diagnosis of a recurrent schizophrenic disorder (R-SZ). Age of onset was defined according to the criteria of Lieberman et al. [30] and the modified F-SZ definition of the Hillside Hospital first-episode study.

Magnetic resonance imaging (MRI) was performed at the time of admission to the hospital. On the day of MRI imaging, MD patients were taking the following medications: 21 patients were taking serotonin reuptake inhibitors (paroxetine [$N = 6$ (20–40 mg/day)], citalopram [$N = 8$ (20–80 mg/day)], fluvoxamine [$N = 2$ (100 mg/day)], sertraline [$N = 5$ (100–200 mg/day)], 23 patients were taking tricyclic/tetracyclic antidepressants (amitryptiline [$N = 10$ (90–250 mg/day)], clomipramine [$N = 1$ (75 mg/day)], doxepine [$N = 7$ (25–250 mg/day)], trimipramine [$N = 2$ (50 mg/day)], maprotiline [$N = 3$ (75–150 mg/d)], 43 patients were taking other antidepressants (reboxetine

[$N = 8$ (4–12 mg/day)], venlafaxine [$N = 15$ (50–375 mg/day)], mirtazapine [$N = 14$ (30–60 mg/day)], lithium [$N = 9$ (450–900 mg/day)], valproate [$N = 3$ (900–2,000 mg/day], lamotrigine [$N = 1$ (25 mg/day)]. Six MD patients were medication free at the time of MRI imaging.

In the SZ group, three patients were medication free, 44 patients were treated with typical neuroleptics (haloperidole [$N = 21$ (5–15 mg/day)], perazine [$N = 8$ (75–300 mg/day)], flupenthixole [$N = 6$ (2.5–20 mg/day)], pimozide [$N = 5$ (2–8 mg/day)], fluspirilen [$N = 2$ (5 ml/weekly)], benperidole [$N = 1$ (16 mg/day)], levomepromazine [$N = 1$ (50 mg/day)]) and 63 patients were treated with atypical neuroleptics (clozapine [$N = 22$ (100–550 mg/day)], olanzapine [$N = 12$ (5–30 mg/day)], risperidone [$N = 17$ (2–6 mg/day)], quetiapine [$N = 1$ (500 mg/day)], amisulpride [$N = 11$ (200–800 mg/day)]). The mean ± SD chlorpromazine equivalents (CPZ) for the SZ group were 395.75 ± 356.8.

One hundred and thirty-eight HCs were recruited from the community of Munich, Germany. A standardized and structured interview for the assessment of the medical history and the inclusion and exclusion criteria of all participants was used. All subjects with a positive medical history for diseases that have an impact on brain function, previous head injuries with loss of consciousness, neurological diseases, and co-morbidity with other mental illnesses including any alcohol or drug abuse/dependency, personality disorders or previous ECT treatments were excluded prior to the study.

HC subjects with a personal or family history of psychiatric illness were excluded. Neither the HC nor their first-degree relatives had a history of neurologic or mental illness. Handedness was determined by the Edinburgh Inventory [43]. The study was approved by the local research and ethics committee, and was prepared in accordance with the ethical standards laid down in the Declaration of Helsinki. Written informed consent was obtained from all participants after a complete description of the study.

MRI procedures

For all patients and HC subjects, the same scanner with the same MRI sequences was used. MRI images were obtained on a 1.5 T Magnetom Vision system (Siemens, Germany) using a coronal T2- and proton density-weighted Dual-Echo-Sequence (TR 3710 ms/TE 22/90 ms; total acquisition time: 9 min, number of acquisitions: 1; FOV 230 mm; matrix 240 × 256, slice thickness: 3 mm) as well as a 3D-MPRAGE sequence (TR/TE 11.6 ms/4.9 ms; total acquisition time: 9 min, number of acquisitions: 1; FOV 230 mm; matrix 512 × 512, slice thickness: 1.5 mm). The commercial software package Analyze was used (ANALYZE, Biomedical Imaging Resource, Mayo Foundation, Rochester, Minnesota) to further process the images. Signal encoding was reduced from 12 to 8 bit and scans were interpolated to a uniform matrix of 256 × 256 × 192 with a 1.0 mm isotropic voxel resolution. All scans were realigned and resampled three-dimensionally in the AC-PC line according to the Tailairach coordinate system using BRAINS (Brain Research: Analysis of Images, Networks and Systems; developed by NC [2]. Regions of interest (ROI) were marked with the aid of an interactive cursor-guided system on a computer display. The program BRAINS allows simultaneous drawing of ROIs in all three orthogonal sections. BRAINS allows the segmentation for calculation of the intracranial content (ICC) and gray and white matter volume (ml) within the defined ROIs [1, 3, 18, 34].

Definition of the hippocampal formation

We used the definition of the hippocampus according to Niemann [41] and the detection of the hippocampal-amygdala border from the description of Convit et al. [12]. This method has previously been described in detail [17]. The hippocampal boundaries were defined in the sagittal plane and then projected to the coronal plane. In order to determine the inter-rater reliability of the hippocampus, ten brains were randomly chosen and ROIs determined independently by two raters. The intraclass correlation for the inter-rater reliability of hippocampal gray matter ($r_{ICC} = 0.97$) and of hippocampal white matter ($r_{ICC} = 0.82$) was high. To determine the intra-rater reliability, hippocampal volumes from ten subjects were determined 4 weeks apart by one rater (hippocampal gray matter: $r_{ICC} = 0.96$, hippocampal white matter: $r_{ICC} = 0.93$) [17].

Statistical analyses

The software package SPSS 15 was used for the statistical analysis. Morphometric measurements in all three groups were tested for normal distribution and for homogeneity of variance by means of Kolmogorov–Smirnov tests. Hippocampal volumes were subjected to an analysis of covariance (ANCOVA) assessing the main and interaction effects of the within-subject factor of hemisphere (left, right) and the between-subject factors of diagnosis (patients, controls), controlled for intracranial content (ICC), age and gender. In order to control for total brain volume, also the relative hippocampal/ICC volumes were subjected to ANCOVAs. This did not change the results so that absolute values will be described in detail. *T* tests and analyses of variance were used to test for between-group differences of sociodemographic variables. Chi-square tests were used to evaluate the gender and handedness distributions between patients and controls. Post hoc

analyses were carried out in order to test for hippocampal volume differences between diagnostic groups.

Results

Sociodemographic variables

An overview of the sociodemographic variables is given in Table 1.

ANOVA analysis revealed a significant group effect for age ($F = 39.1$, $df = 2$, $P < 0.0001$) and gender ($X^2 = 23.42$, $df = 2$, $P = 0.0001$), while no effect emerged for handedness ($P = 0.80$). Post hoc comparison showed a significant difference of age between the group of MD and the two other groups (MD > HC: $t = -6.83$, $df = 228$, $P < 0.0001$; MD > SZ: $t = -8.61$, $df = 179$, $P < 0.0001$), but no significant difference between the HC and SZ groups (HC-SZ: $t = 1.75$, $df = 225$, $P = 0.08$). No differences emerged regarding illness duration between the patient groups (MD-SZ: $t = -0.949$, $df = 179$, $P = 0.34$). For the MD group, the Hamilton Depression Scale (HAMD) had a mean ± SD of 23.5 ± 6.7. In the SZ group, the mean ± SD PANSS score was 75.1 ± 22.1. Mean ± SD CPZ equivalents were 403.57 ± 366.54.

Within the MD group, 46 patients had a first depressive episode (F-MD) and 46 had a recurrent episode of MD (R-MD). The subgroups were significantly different regarding age ($t = 0.44$, $df = 90$, $P = 0.03$) and HAMD scores ($t = -2.48$, $df = 85$, $P = 0.045$), while no differences emerged for gender ($X^2 = 0.39$, $df = 1$, $P = 0.53$) and handedness ($X^2 = 0.21$, $df = 1$, $P = 0.65$).

Within the SZ group, 45 patients had a first manifestation (F-SZ) and 44 patients had a recurrent schizophrenic disease (R-SZ). The subgroups differed significantly regarding age ($t = 2.06$, $df = 87$, $P = 0.04$) gender ($X^2 = 4.66$, $df = 1$, $P = 0.03$) and PANSS scores ($t = -2.104$, $df = 85$, $P = 0.03$), but not in handedness ($X^2 = 3.53$, $df = 1$, $P = 0.11$) or CPZ equivalents ($t = 0.43$, $df = 81$, $P = 0.67$).

Finally, post hoc analysis between the F-MD and F-SZ groups showed significant differences regarding age ($t = -6.70$, $df = 89$, $P < 0.001$) and gender ($X^2 = 7.22$, $df = 1$, $P < 0.007$) but no significant differences in duration of illness ($t = 0.934$, $df = 89$, $P = 0.35$) and handedness ($X^2 = 0.762$, $df = 1$, $P = 0.38$).

Between the R-MD and R-SZ groups significant differences emerged with respect to age ($t = -5.49$, $df = 88$, $P = 0.001$) and gender ($X^2 = 16.43$, $df = 1$, $P = 0.001$), again no differences were found regarding duration of illness ($t = -1.46$, $df = 88$, $P = 0.14$) and handedness ($X^2 = 2.97$, $df = 1$, $P = 0.08$).

Structural measurements of the hippocampus

All measurements and effect sizes are shown in Tables 2 and 3 (measurements in ml). In Figs. 1 and 2 the hippocampal volumes of all subgroups are shown. There was no significant effect for diagnosis on total brain volume ($F = 3.31$, $df = 2$, $P = 0.38$). All subsequent statistical analyses of hippocampal measurements were performed after controlling ICC, age and gender.

Comparison between the main groups MD and SZ, compared to HC (Fig. 1; Table 2)

The ANCOVA showed a significant effect of diagnosis on bilateral hippocampal volumes ($F = 15.1$, $df = 2$, $P < 0.001$), hippocampal gray matter ($F = 13.59$, $df = 2$, $P < 0.001$) and white matter volumes ($F = 9.8$, $df = 2$, $P < 0.0001$) (Fig. 1).

Post hoc multivariate analysis revealed that bilateral hippocampal volumes were significantly different between the HC and MD group with bilaterally smaller hippocampal volumes in MD patients (total left HK: $F = 6.5$, $df = 1$, $P = 0.01$; total right HK: $F = 4.3$, $df = 1$,

Table 1 Demographic data for the 319 study participants

	MD	F-MD	R-MD	SZ	F-SZ	R-SZ	HC
Patients total (*n*)	92	47	45	89	45	44	138
Age	44.6 (12.3)	41.8 (13.50)	45.5 (11.1)	30.6 (9.1)	28.7 (7.4)	32.6 (10.3)	33.3 (12.2)
Illness duration	5.7 (7.55)	1.6 (3.1)	10.0 (8.3)	4.7 (5.9)	1.4 (2.7)	8.09 (6.5)	
CPZ eq.				403.5 (366.5)	387.2 (359.1)	422.0 (378.5)	
Gender (f/m)	47/45	26/21	21/24	16/73	12/33	4/40	60/78
Handedness (r./l.)	86/5	45/2	42/3	85/4	41/4	44/0	129/9
PANSS				75.1 (22.1)	70.3 (24.1)	80.1 (18.7)	
Hamilton	23.5 (6.7)	25.0 (6.1)	22.1 (7.1)				

All data are given as mean (SD) except of gender, handedness, PANSS and Hamilton scores

f female, *m* male

Table 2 Structural data for the 92 patients with major depression, the 89 schizophrenic participants and the 138 healthy control subjects

Hippocampal measurements	MD (vol/mm^3)	MD (%)	F-MD (vol/mm^3)	F-MD (%)	R-MD (vol/mm^3)	R-MD (%)	SZ [vol/mm^3 (SD)]	SZ (%)	F-SZ [vol/mm^3 (SD)]	F-SZ (%)	R-SZ [vol/mm^3 (SD)]	R-SZ (%)	HC [vol/mm^3 (SD)]
Gray matter (l)	3.54 (0.39)	−3.70	3.60 (0.39)	−2.14	3.49 (0.38)	−5.26	3.45 (0.40)	−6.31	3.52 (0.42)	−4.47	3.38 (0.36)	−8.19	3.68 (0.40)
Gray matter (r)	3.67 (0.40)	−3.94	3.70 (0.43)	−2.17	3.60 (0.37)	−5.72	3.62 (0.41)	−5.28	3.62 (0.47)	−5.30	3.62 (0.34)	−5.27	3.82 (0.39)
White matter (l)	0.12 (0.04)	−17.37	0.13 (0.04)	−11.15	0.11 (0.04)	−23.52	0.11 (0.05)	−19.13	0.12 (0.06)	−12.64	0.10 (0.05)	−25.76	0.14 (0.05)
White matter (r)	0.10 (0.04)	−14.27	0.10 (0.04)	−9.85	0.09 (0.04)	−18.69	0.10 (0.05)	−9.26	0.11 (0.05)	−4.92	0.10 (0.04)	−13.67	0.11 (0.04)
Hippo (l)	3.67 (0.41)	−4.23	3.73 (0.41)	−2.49	3.60 (0.40)	−5.97	3.57 (0.43)	−6.81	3.65 (0.45)	−4.79	3.49 (0.39)	−8.87	3.83 (0.41)
Hippo (r)	3.77 (0.42)	−4.25	3.84 (0.44)	−2.40	3.70 (0.39)	−6.10	3.72 (0.44)	−5.40	3.73 (0.50)	−5.29	3.72 (0.36)	−5.52	3.94 (0.41)
ICC (t)	1,251.2 (105.88)	−3.40	1,267.1 (104.60)	−2.17	1,235.29 (105.88)	−4.64	1,212.64 (121.92)	1.33	1,292.26 (120.00)	−0.24	1,333.48 (121.68)	2.93	1,295.40 (141.98)

All data are given as mean (SD) except where indicated otherwise

l left, *r* right, *t* total

$P = 0.03$) For gray matter volume the left side was reduced ($F = 4.4$, $df = 1$, $P = 0.03$) and the right side showed a trend toward reduction compared to HC ($F = 3.3$, $df = 1$, $P = 0.06$). White matter volumes were reduced bilaterally in patients with MD (left: $F = 16.1$, $df = 1$, $P = 0.001$; right: $F = 5.1$, $df = 1$, $P = 0.02$).

Post hoc multivariate analysis with the main groups HC and SZ showed bilaterally smaller hippocampi (left: $F = 29.4$, $df = 1$, $P < 0.0001$; right: $F = 23.7$, $df = 1$, $P < 0.0001$), bilaterally smaller gray matter volumes (left: $F = 25.2$, $df = 1$, $P < 0.0001$; right: $F = 22.9$, $df = 1$, $P < 0.0001$) and reduced left white matter volumes ($F = 18.7$, $df = 1$, $P < 0.0001$) in the SZ group.

Finally, the direct comparison between the MD and SZ groups revealed bilaterally significantly smaller hippocampal volumes (left: $F = 7.5$, $df = 1$, $P = 0.006$; right: $F = 4.4$, $df = 1$, $P = 0.03$) and gray matter hippocampal volumes (left: $F = 7.6$, $df = 1$, $P = 0.006$; right: $F = 5.2$, $df = 1$, $P = 0.02$) in the SZ group. No differences emerged between MD and SZ regarding white matter volumes.

Comparison between the subgroups of first episode patients (F-MD vs. F-SZ) and the recurrently ill patients (R-MD vs. R-SZ) (Fig. 2; Table 2)

No significant difference emerged between the patients with a first episode of depression (F-MD) and the recurrently ill patients (R-MD) regarding all total hippocampal volume measurements (left: $F = 1.3$, $df = 1$, $P = 0.24$; right: $F = 1.5$, $df = 1$, $P = 0.21$; gray matter left**:** $F = 1.096$, $df = 1$, $P = 0.29$; gray matter right: $F = 1.397$, $df = 1$, $P = 0.24$; white matter left: $F = 2.86$, $df = 1$, $P = 0.09$; white matter right: $F = 0.78$, $df = 1$, $P = 0.38$).

Between the patients with a first episode of schizophrenia (F-SZ) and the recurrently ill patients (R-SZ) a smaller left hippocampal volume was detectable in the R-SZ group ($F = 10.8$, $df = 1$, $P = 0.001$) while the right hippocampus did not differ between the groups ($F = 2.4$, $df = 1$, $P = 0.12$). Again, in the left gray matter ($F = 9.58$, $df = 1$, $P = 0.003$), but not the right gray matter ($F = 1.79$, $df = 1$, $P = 0.185$) and bilaterally in the white matter volumes (left: $F = 7.34$, $df = 1$, $P = 0.008$; right: $F = 5.99$, $df = 1$, $P = 0.016$) volumes were significantly smaller for the patients with R-SZ.

In the comparison among the depressive and schizophrenic first episode groups (F-MD and F-SZ), no differences emerged in any of the measurements performed including total, gray and white matter hippocampal volumes.

When comparing the recurrently ill subgroups (R-MD and R-SZ), significant differences emerged regarding the left hippocampal volume ($F = 12.3$, $df = 1$, $P = 0.001$),

Table 3 Effect sizes of all structural data for the 92 participants with major depression and for the 89 schizophrenic participants

	MD vs. HC	F-MD vs. HC	R-MD vs. HC	SZ vs. HC	F-SZ vs. HC	R-SZ vs. HC	F-SZ vs. R-SZ	F-MD vs. R-MD	R-MD vs. R-SZ	F-MD vs. F-SZ
Gray matter (l)	0.34	0.20	0.50	0.58	0.40	0.79	0.35	0.30	−0.29	−0.21
Gray matter (r)	0.37	0.20	0.57	0.50	0.46	0.54	0.00	0.33	0.05	−0.26
White matter (l)	0.54	0.35	0.73	0.52	0.33	0.75	0.34	0.42	−0.07	−0.04
White matter (r)	0.36	0.25	0.47	0.22	0.11	0.34	0.20	0.23	0.13	0.12
Hippo (l)	0.39	0.23	0.56	0.62	0.42	0.84	0.37	0.33	−0.28	−0.20
Hippo (r)	0.40	0.22	0.60	0.50	0.45	0.56	0.02	0.35	0.06	−0.24
ICC (t)	0.35	0.23	0.48	−0.13	0.02	−0.29	−0.34	0.30	0.86	0.22

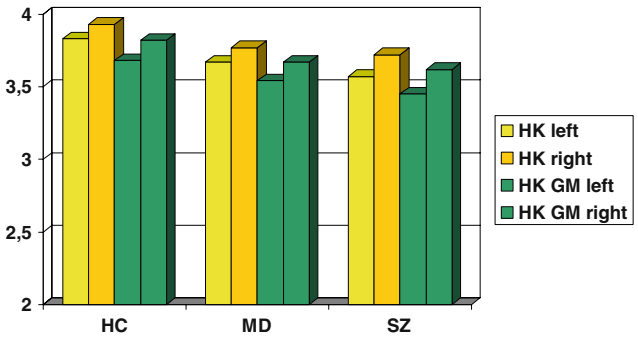

Fig. 1 Hippocampal measurements of total hippocampus (*HK*) volume and gray matter volumes of the hippocampus, *left* and *right* (*HK GM*)

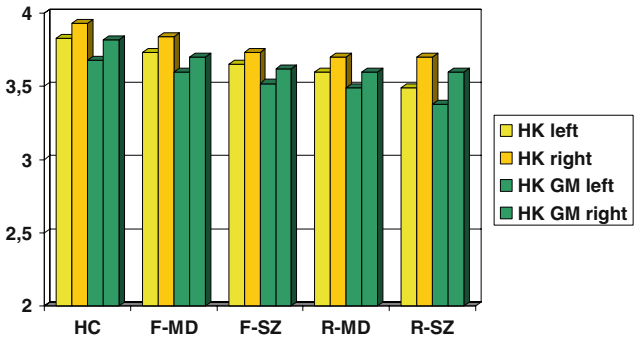

Fig. 2 Hippocampal measurements of total hippocampus (*HK*) volume and gray matter volumes of the hippocampus, *left* and *right* (*HK GM*) in the subgroups of first (*F-MD*; *F-SZ*) and recurrently ill patients (*R-MD*; *R-SZ*) and healthy controls (*HC*)

which was significantly smaller in R-SZ. No differences emerged for the right hemisphere. Regarding gray matter, the R-SZ group showed smaller volumes for the left hemisphere (left: $F = 12.24$, $df = 1$, $P = 0.001$) while no differences emerged for the right hemisphere. Bilateral white matter volumes of the hippocampus did not differ between the R-MD and R-SZ group.

Discussion

The first aim of the study was to compare bilateral hippocampal volumes across the major psychiatric clinical entities including MD and schizophrenia versus HC subjects. The total hippocampal and gray/white matter volumes were analyzed in a large-scale naturalistic sample of 319 MRI datasets from patients as well as from HCs.

The study revealed a significant bilateral reduction of all hippocampal volume measurements for both psychiatric disorders. Regarding MD, this finding is in line with results of brain imaging studies showing bilateral hippocampal volume decline compared to HC subjects [7, 23, 29, 31, 33, 40, 46, 47] (for a recent review, see [19]). Hippocampal volume reductions of depressed patients in previous studies ranged between −1.4 and −19% relative to HC subjects [54], our own data revealed a mean reduction of −4.2% bilaterally. In a well-conducted meta-analysis of hippocampal volume abnormalities in MD, Videbech and Ravnkilde [54] found strong evidence for hippocampal volume reduction in depressed patients, especially in those with repeated depressive episodes. The authors included 12 studies of unipolar depression that met their data criteria for meta-analysis. They found an average hippocampal volume reduction of −8% in the left and −10% in the right hemisphere.

Furthermore, "region of interest" (ROI) evaluations of the hippocampus in schizophrenia showed in the majority of the studies a bilateral hippocampal volume loss [39, 48, 57]. In the meta-analysis of [57], which included 54 ROI studies, the left and right hippocampus showed a reduction of −6% in the left and −7% in the right hippocampus of patients with schizophrenia. A further recent meta-analysis of first-episode patients including 52 cross-sectional and 16 longitudinal investigations [48] suggests bilateral hippocampal volume reductions of about −8%. This is consistent with our results that revealed a left-hemispheric hippocampal volume reduction of −6.8% and a right-hemispheric reduction of −5.4% in the schizophrenic sample compared to the HC group. Additionally, the observed

reductions of gray and white matter volumes support the results of the total hippocampal volume measurements reported for each group. Therefore, our results confirm the well-known findings of hippocampal volume reductions in each diagnostic entity compared to healthy control subjects, respectively.

The direct comparison between the MD and SZ samples revealed significant bilateral total hippocampal volume reductions as well as reductions of hippocampal gray matter volume in patients with schizophrenia compared to the patients with MD. These differences in hippocampal volume were not accounted for by differences in whole-brain volume. It is of main significance that both diagnostic groups had the same duration of illness and therefore, an effect of unspecific chronicity in terms of longer disease duration can be for the most part excluded. Additionally, both groups had an equal number of first-episode and recurrently ill patients. The factor of age, which differed significantly between groups, was added as a confounding variable in the statistical design. However, although depressed patients were significantly older than schizophrenic patients, the latter showed clearly and bilaterally stronger hippocampal reductions regarding total and gray matter hippocampal volumes.

To date, comparisons of structural brain differences between these major diagnostic groups are scarce in the existing literature. Hirayasu et al. [24] compared first-episode schizophrenic patients to a mixed sample of patients with first-episode affective disorders. The affectively ill sample comprised mostly bipolar patients and to a lesser extent patients with unipolar depression. Their ROI analysis revealed significantly reduced gray matter volume of the left posterior superior temporal gyrus compared to the affectively ill patients and concluded that this brain region is specifically altered in schizophrenia. Further structural imaging studies by the same group [28, 38] underlined again already significant structural differences between the schizophrenic patients and the predominantly bipolar patients in the affective spectrum.

The underlying mechanisms that cause the hippocampal reductions in both clinical groups are unknown. In this regard, basically three major assumptions can be formulated. First, it can be speculated whether these significant differences are basically caused by the same underlying mechanism, differing between schizophrenia and MD only with respect to its pathophysiological intensity. In this view, our results could support that these pathophysiological mechanisms may then be more severe in patients with schizophrenia. However, the finding of a left pronounced laterality of hippocampal volume declines in the SZ and the significantly stronger decline of the hippocampal volumes in the SZ group may argue against this.

Secondly, another interpretation may be that there are basically two different pathophysiological mechanisms, e.g., different neurotransmitter dysbalances that distinguish both diseases but nonetheless share overlapping pathophysiological features. In this conceptualization, the hippocampal alterations may represent a common sequelae of the two mechanisms underlying both diseases. Thirdly, distinct pathophysiological mechanisms subserve the different clinical profiles of both diseases. The hippocampal alterations that show further significant decline were detected in the SZ group while the MD group remained stable.

At first, in schizophrenia research the neurodevelopmental model proposed that structural brain changes in early life predispose to the development of schizophrenia [26, 55]. In this context, some neuropathological studies [4, 5, 25] support the concept of specific and early non-progressive lesions of the hippocampus present prior to the clinical onset of the disease. In MD, stressful life events with elevated levels of glucocorticoids, indicating that the HPA axis is overactive, have been put forward as a major causative factor underlying hippocampal volume reductions [13]. Nevertheless, during the last years human post-mortem studies of depressed patients could not detect any cell pathology such as major cell loss [32, 37, 49].

It should be noted that beside schizophrenia and MD hippocampal shrinkage is observed in a large range of other neuropsychiatric diseases such as AD and personality disorders [21, 22, 50, 59]. Furthermore, hippocampal volume reductions have been identified in neurological conditions affecting the CNS such as HSV encephalitis [9, 11, 58] with volume reductions of around −46% [11]. This fairly high value might be due to the vigorous inflammation in the whole temporal area, as it correlates with the observed volume reduction of about −44% of the temporal lobe. The impact of normal pressure hydrocephalus on the hippocampus has been investigated with a size reduction between −9 and −11% [45]. One study compared the hippocampal volume between patients with Parkinson's disease with or without dementia with a HC group and observed a mean reduction of 9 and 16%, respectively [8]. Finally, the volume of the hippocampus in patients with vascular dementia has been reported to be reduced about 18% [15]. Taken together, apart from HSV encephalitis, a hippocampal size reduction ranging between 9 and 19% can be observed in different, predominantly neurodegenerative diseases.

Interestingly, the comparison of hippocampal volume between our first-episode subgroups, the first-episode depressed and schizophrenic patients, revealed no significant volume differences. This is inline with a prior study of Velakoulis and colleagues [51] that showed no hippocampal volume differences between first-episode schizophrenic patients and first-episode patients with affective disorders. Although their affective group consisted mainly

of bipolar patients and not MD patients as in our study, the authors stated that smaller hippocampal volumes are a rather unspecific finding.

In this context, our results may point to a vulnerability of the hippocampus with volume reductions that may occur before the first clinical manifestation. It is not clear whether these volume reductions represent a long-standing, genetically mediated structural brain abnormality or develop progressively during the prodromal phase of both diseases. However, our data could suggest that during the first clinical manifestation of both diseases, the detected hippocampal alterations do not seem to be specific for either schizophrenia or MD. However, in contrast, the comparison between the recurrently ill patients of both diagnostic groups demonstrated that patients with schizophrenia show a significantly stronger reduction in the left hippocampus compared to the recurrently ill depressed patients. Additionally, there was also a significant reduction of the left total/gray matter hippocampal volume in the recurrently ill schizophrenic patients compared to the first-episode schizophrenic patients.

Interestingly, Velakoulis and colleagues showed an association between hippocampal volume and illness duration in their group of schizophrenic patients. Recent cross-sectional VBM studies on structural brain alterations at different stages of schizophrenia [52, 53] and, furthermore, our previous cross-sectional VBM study on structural brain alterations at different stages of schizophrenia [35] point to an expansion of gray matter density abnormalities within the medial temporal regions when comparing 72 recurrently ill patients to 93 first-episode patients. Our findings show that hippocampal abnormalities are already present at the onset of the disease. If we assume that our patients with first-episode and recurrent schizophrenia constitute a continuum of a common underlying disease, our data would agree additionally with the assumption of a longitudinal decrement of hippocampal volume at least in the left hemisphere after the onset of the disease.

Regarding the patients with MD, our study showed no significant hippocampal differences between the first-episode and the recurrently ill patients. Our cross-sectional findings are supported by our own longitudinal MRI results. In a recently published prospective 3-year follow up investigation of the hippocampus in patients with MD, no further decrease in hippocampal volume was detected after 3 years of follow-up [20]. Furthermore, in the subgroup of patients who took antidepressants over the full 3 years, the left hippocampal volumes increased significantly. Therefore, hippocampal volume reductions in MD patients seem to be stable over time. Alternatively, antidepressants may have an active effect on the hippocampus through neuroplastic processes which have been suggested based on the results of experimental studies [16, 44].

Taken together, these findings support that bilateral hippocampal reductions are present in both diagnostic entities with significantly stronger reductions being associated with a longer lasting schizophrenic illness as compared to depression with the same illness duration.

Limitations

Regions of interest analyses of hippocampal volumes have to consider that the hippocampus is embedded in complex and distributed CNS networks. Therefore, these analyses may provide only limited information regarding alterations within these cortical networks. It can only be speculated whether the significant difference between hippocampal reductions in both disease groups relates to different etiopathologies between these diseases.

The cross-nosological comparison of the hippocampal volumes conducted in our study might have been biased by significantly different ages of onsets and gender distribution of both disease groups. These factors can only be partially controlled by entering them as covariates in our general linear models. Nevertheless, in our study the highly relevant effect of different stages of chronicity due to different duration of illness was excluded.

Furthermore, the influence of medication on brain structure is still a matter of debate and it cannot be excluded that medication effects may have had an influence on the results of our study. It was shown that especially the volume of the basal ganglia changed after long-term exposure to antipsychotic treatment [10, 14, 27]. Typical and atypical antipsychotics may differentially affect the basal ganglia and other brain structures. In our schizophrenic subgroups, no differences emerged regarding chlorpromazine equivalents. However, most of the recurrently ill patients in our study changed medication several times during the course of disease. Therefore, the evaluation of lifetime cumulative medication dose does not provide enough reliable information in order to study its effects on brain morphology within a cross-sectional design. Finally, antidepressants may also have active effects through neuroplastic processes. In our own longitudinal MRI study left hippocampal volume increases were detected in patients who took antidepressants over the whole 3-year period [20].

Implications

Bilateral hippocampal volume reductions were detected in both schizophrenic and patients with MD compared to HC subjects. Schizophrenic patients showed in their MRI

scans significantly bilaterally reduced hippocampal volumes compared to patients with MD. Although the hippocampal reductions were similar at the first clinical manifestation of both diseases, the further significant reduction of the left hippocampus in the recurrently ill SZ subgroup may suggest a rather dynamic and progressive CNS structural change indicating an enhanced disease acuity compared to patients with MD. This seems supported by findings from longitudinal MRI studies in schizophrenia [6].

Here, the presented application of the approach of comparative neuroscience, accompanied by the use of reliably large neuroimaging MRI databases is highly valuable in the search of valid endophenotypes or real pathophysiological mechanisms.

For the field of psychiatry, with its still controversial clinical and diagnostic entities, the cross-nosological approach provides a helpful tool to better elucidate the still unknown neurobiological underpinnings beyond a single nosological disease entity.

Conflict of interest statement None.

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