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Longitudinal volumetric MRI study in first- and multiple-episode male schizophrenia patients

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Abstract

In this longitudinal study we compared brain volume changes in first- and multiple-episode patients with schizophrenia to normal aging changes observed in healthy control subjects scanned at comparable times. Two to four years after an initial examination including MRI volumetry, we followed up 21 first episode patients, 17 patients after multiple episodes of schizophrenia, and 20 healthy controls. Volumetric measurements of left and right hemispheres, total brain volume, lateral ventricles, hippocampus and amygdala as well as a clinical evaluation were performed. Patients with schizophrenia showed significant ventricular enlargement and volume reduction of the hippocampus–amygdala complex compared with healthy control subjects both at baseline and follow-up. While there were no differences between patients and controls with respect to mean annual volume changes in the measured regions, patients with schizophrenia showed higher between-subject variability in ventricular volume change. These data are consistent with cross-sectional studies demonstrating ventricular enlargement and hippocampal volume deficits in schizophrenia. However, we were not able to demonstrate a difference in the rate of volume changes over time that distinguished patients with schizophrenia from healthy controls for any of the brain structures measured. Drawbacks of the study are that the follow-up was done after a relatively short interval and that there was a difference in time to follow-up and age between patients and controls. Our results do not support the hypothesis that schizophrenia leads to progressive volume reduction in these areas, although there may be a subset of patients with morphologically visible disease progression.
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Keywords: Schizophrenia; Magnetic resonance imaging; Brain imaging; Hippocampus; Longitudinal study; First episode schizophrenia; Lateral ventricles; Brain morphology

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1. Introduction

Structural brain abnormalities in patients with schizophrenia have been studied extensively, and numerous cross-sectional studies have reported morphological brain abnormalities such as enlargement of the third and lateral ventricles, decreases in grey matter volumes and reduction of medial temporal lobe structures, including the hippocampus/amygdala complex (for reviews, or meta-analyses see Lawrie and Abukmeil, 1998; Nelson et al., 1998; McCarley et al., 1999; Wright et al., 2000; Velakoulis et al., 2000; Shenton et al., 2001). When considering the pathophysiology of schizophrenia, the discussion often revolves around the issue of whether schizophrenia is a degenerative-progressive or a neurodevelopmental disorder. The neurodevelopmental hypothesis postulates that etiopathogenetic factors impair brain development long before the onset of the disease and that structural brain changes that are apparent at the first presentation of the illness do not progress over time (Bogerts et al., 1990; Lim et al., 1996; Nopoulos et al., 1995). On the other hand, schizophrenia has long been thought to be a degenerative brain disease with neuropathological changes present early in the course of the illness progressing years after the first appearance of clinical symptoms (Lieberman, 1999; DeLisi et al., 1995, 1997). The question of whether morphological brain alterations in patients with schizophrenia are of neurodevelopmental origin or the result of an active disease process with continuing deterioration can only be addressed by long-term follow-up studies. Longitudinal studies have produced equivocal findings; some computed tomographic studies (Jaskiw et al., 1994; Vita et al., 1994) and very early magnetic resonance imaging (MRI) studies (DeLisi et al., 1992; Degreef et al., 1991) found no progressive structural changes, while others revealed a trend toward or a significant progression of ventricular enlargement (Nair et al., 1997; Lieberman et al., 2001; Saijo et al., 2001; Mathalon et al., 2001; Cahn et al., 2002; DeLisi et al., 2004), volume loss for the whole brain (DeLisi et al., 1995, 1997; Cahn et al., 2002; Wood et al., 2001) or specific brain regions, including the temporal (DeLisi et al., 1995; Gur et al., 1998; Davidson and Heinrichs, 2003) and frontal lobes (Gur et al., 1998; Ho et al., 2003; Davidson and Heinrichs, 2003; Bachmann et al., 2004), the hippocampus/amygdala complex and the basal ganglia (for review, see Velakoulis et al., 2000; see also Szeszko et al., 2002; Joyal et al., 2003). Special subgroups of patients were studied longitudinally and patients with childhood-onset of schizophrenia also showed progressive changes in brain morphology (Rapoport et al., 1997, 1999; Jacobsen et al., 1998; Giedd et al., 1999), whereas another study found non-progressive changes in adolescent-onset schizophrenia (James et al., 2004).

Interestingly, the results of the DeLisi group (DeLisi et al., 1992, 1995, 1997, 2004) studying the same population over an increasing number of years, describe greater rates of change in schizophrenia patients with increasing time of follow-up — after 10 years, they detected a significantly greater ventricular enlargement during the second 5 years. The same applies to the Lieberman group: no change in earlier studies (Degreef et al., 1991) but after up to 6 years they found ventricular enlargement and anterior hippocampal volume reductions in first episode schizophrenia patients (Lieberman et al., 2001).This lack of agreement across studies may reflect differences in methodology. As pointed out by Puri et al. (2001) and McCarley et al. (1999), ideally, a longitudinal study should utilize high resolution imaging techniques, thinner slices and no gaps between slices for more precise MR morphometric volume measures. Most groups have used a slice thickness between 1 and 10 mm (for a short overview, see Table 1) (see also Wright et al., 2000; Shenton et al., 2001). Another possible explanation for heterogeneity of study results is gender. There is a growing body of literature examining the effects of gender on brain aging in nonpatient samples (for review, see Coffey et al., 1998). While findings have been inconsistent, a few investigators have reported sex differences in the effects of age on some brain structures (e.g., temporo-limbic and frontal brain volumes). In most cases males showed greater age-dependent changes than females (Gur et al., 1991, 2002; Murphy et al., 1996; Raz et al., 1997). To exclude a possible confounding influence of gender on the volume changes, we only studied men.

We have previously reported both hippocampal volume deficits and ventricular enlargement in first-episode and chronic schizophrenia patients as compared with healthy controls (Whitworth et al., 1998). Here, we report rates of brain volume change in a

Table 1
Longitudinal, volumetric MRI studies in schizophrenia with focus on whole brain volume, lateral ventricles and hippocampus, female and male subjects, if not otherwise mentioned

Author	Subjects	Time to follow-up (years)	Methods (slice thickness in mm)	Results for patient groups
DeGreef, 1991	13 FE 8 controls	1–2	3.1	No difference in rate of change for cortical and ventricular volume
DeLisi, 1992	50 FE 33 controls	2	5+2 mm gap	No difference in temporal lobe or ventricular volume; change in ventricular volume inversely correlated with time in hospital
Lieberman, 1996	62 FE 42 controls	1.5	3.1	Ventricular enlargement and reduced cortical volumes in poor-response patients
Nair, 1997	18 chronic 5 controls	2–3	1.95	Ventricular enlargement
DeLisi, 1995, 1997	50 FE 20 controls	4–5	5+2 mm gap	No difference for hippocampus; significant difference for l+r hemispheres, cerebellum
Gur, 1998	20 FE 20 chronic 17 controls	2–3	5 — no gap	More frontal and temporal lobe reductions in FE
Lieberman, 2001	51 FE 13 controls	2–3	3.1	Ventricular enlargement; anterior hippocampal volume reduction; no change over time
Puri, 2001	24 FE 12 controls (sex?)	0.6	1.6	No difference in ventricular volume, but more variable in patients
Wood, 2001	30 FE 12 chronic 26 controls	2	1.5	WBV loss; no changes in hippocampal and temporal lobe volumes
Saijo, 2001	15 chronic 12 controls	10	9+1 mm gap	Ventricular enlargement
Mathalon, 2001	24 chronic 25 controls all male	4	5+2.5 mm gap	Ventricular enlargement
Cahn, 2002	34 FE 36 controls	1	1.2	WBV+gray matter decreased, lateral ventricle volume increased
Ho, 2003	73 FE 23 controls	3	1.5	Frontal CSF increase
Bachmann, 2004	14 FE 13 controls	1.16	1.8	CSF increase
DeLisi, 2004	26 FE 10 controls	10	5+2 mm gap	Ventricular enlargement

Abbreviations: FE: first episode schizophrenia; WBV: whole brain volume; l: left; r: right; CSF: cerebrospinal fluid.

subgroup of these patients rescanned after 2–4 years and compare them with the normal aging changes observed in controls scanned at comparable intervals. This study was designed to examine whether schizophrenia is associated with accelerated brain volume loss compared with a healthy control group, as would be expected for a progressive or neurodegenerative disease.

2. Methods

2.1. Subjects

All patients (first- and multi-episode) and healthy controls who had participated in our first volumetric MRI study – described in detail in our original report (Whitworth et al., 1998) – were asked to undergo a second MR scan and a clinical interview. All patients and controls were male, right-handed and Caucasian. The procedure was explained to both patients and controls, and all provided informed consent.

In the patient groups, the clinical assessment consisted of the Structured Clinical Interview for DSM-III-R (SCID) (Spitzer et al., 1990) to confirm the diagnosis made at the first examination, the Positive and Negative Syndrome Scale (PANSS) (Kay, 1991), and a semistructured interview covering current occupation, marital status, living circumstances and information about the course of the disorder between the two examinations [number of relapses, total days of hospitalization, Global Assessment of Functioning-Score (GAF)]. Information was supplemented by reviewing outpatient records and hospital charts.

At the time of the initial scan, patients in the first-episode group were examined and scanned

during the first week of hospitalisation; they had received neuroleptic treatment for a maximum of 1 week. The diagnosis of a first episode of schizophrenia was defined by DSM-III-R criteria and was re-evaluated at least 1.5 to 2 years after the first assessment.

Multi episode patients were also diagnosed according to DSM-III-R. The medication status of the patient groups between scans varied widely, and compliance was not formally assessed. The control group was also re-interviewed (mainly concerning any potential newly developed diseases as well as the use of drugs and alcohol).

2.2. MRI acquisition and volume measurements

Imaging was performed on a 1.5-T whole body system (Magnetom VISION, Siemens, Germany) using a conventional circular polarized head coil. A standard three-dimensional MP-RAGE sequence (Mugler and Brookeman, 1991) (TR = 9.7 ms, TE = 4 ms, $\alpha = 12^{\circ}$) was used to obtain T1-weighted images of the brain. The sequence enables a good delineation between cerebrospinal fluid (CSF) and parenchymal structures as well as a differentiation of gray and white matter. Usually between 128 and 150 contiguous slices in a sagittal orientation were acquired with an in-plane resolution of 0.9 mm and a slice thickness between 0.9 and 1.4 mm. Thus, nearly isotropic three-dimensional MR data sets were obtained, making highly accurate volumetric MR measurements possible.

After acquisition, the MR images were transferred to an external workstation for image processing. Volume measurements were performed on a commercially available workstation (Allegro; ISG Technologies, Canada). As described in our previous report (Whitworth et al., 1998), volume measurements with this workstation are typically performed using a combination of thresholding, region growing and manual tracing (Brant-Zawadzki et al., 1993). Before segmentation, the original MR images in sagittal orientation were reformatted into contiguous coronal slices with 1-mm thickness.

Measurements were performed by a single, trained rater (M.H.), who was blind to group membership. To assess intra-rater reliability of the obtained volumes, volumetric measurements of the lateral ventricles and the hippocampus/amygdala complex (HAC) were carried out twice for 10 patients/volunteers. Each data set was individually processed twice; the time between two successive sessions was 3–4 months. With this method we obtained an intra-rater reliability (intra-class correlation) of >0.99 for the lateral ventricles, 0.98 for hemispheres and 0.95 for the hippocampus/amygdala complex.

The whole brain measurement included both hemispheres, the brainstem, and the cerebellum. The medulla was separated from the spinal cord by a line between the caudal ends of the bulb of the medulla. The lateral ventricles were measured on coronal slices without determining different subdivisions. Measurements of the hippocampus–amygdala complex were performed following a method developed by Bogerts et al. (1990) — starting posteriorly at the level where the fornix surrounding the pulvinar is interrupted by the coronal sections. As a definite separation between hippocampus and amygdala was not possible, we measured both in one structure, which was then divided into a posterior and an anterior portion. The posterior/hippocampal portion extends from the fornix/pulvinar slice to the slice just posterior to the level of the mammillary bodies, including the slice immediately posterior, and contains mainly hippocampal tissue. The anterior/amygdala portion reaches from the mammillary body slice to the slice where the amygdaloid complex loses its typical oval shape and consists mainly of amygdala tissue. Greater details on the methods of mensuration for these assessments have been provided elsewhere (Bilder et al., 1995; Bogerts et al., 1990; Chakos et al., 1994; Degreef et al., 1992; Whitworth et al., 1998; Lieberman et al., 2001).

2.3. Statistical methods

The three groups (first-episode patients, patients with multiple episodes and controls) were compared with respect to sample characteristics using one-way analysis of variance (ANOVA, post hoc comparisons by means of the Tukey test) and Kruskal–Wallis test (post hoc comparisons by Mann–Whitney *U* test), depending on the variable type. Similarly, differences between re-examined subjects and subjects unavailable for the follow-up scan were evaluated by ANOVA and Mann–Whitney *U* test. Differences between these two groups regarding baseline volumetric

brain measurements were assessed using analysis of covariance (ANCOVA) with adjustment for total brain volume. Additional adjustments for age and height were made if these variables showed a significant effect or a trend towards significance ($P \leq 0.1$) in the ANCOVA. Before analysing the changes of the brain structures over time, we compared the three groups (and also the pooled patient group with the control group) with regard to their baseline and follow-up MR measurements by means of ANCOVA in the same way as above, i.e. with adjustment for total brain volume and, conditional on their *P*-values, also for age and height.

Linear regression through the origin, using change in size of brain structure as the dependent variable and time elapsed between baseline and follow-up as the independent variable, was applied to test for statistical significance of changes over time (null hypothesis of no change: slope of regression line = 0) and for possible departures from linearity (null hypothesis: quadratic coefficient = 0). As changes in the sizes of brain structures were found to be approximately proportional to the time elapsed between baseline and follow-up, subsequent analyses were performed using mean annual change, i.e. change divided by time elapsed between the two measurement points, as the dependent variable.

Comparisons between patients and controls with respect to mean annual change in size of brain structures (hypothesis testing and calculation of confidence intervals) were performed by weighted least squares ANCOVA, with adjustment made for age, interscan interval, total brain volume and baseline volume of the brain structure studied. A weight variable proportional to the squared elapsed time between baseline and follow-up measurement was used, since the main source of error is measurement error and therefore the variance of the mean annual change is approximately inversely proportional to the squared time between the two measurements. To account for a potential bias due to regression-to-the-mean effects, the dependent variable was adjusted accordingly (Hayes, 1988). Due to the non-normal distribution of the mean annual changes of the left and right ventricles, additional non-parametric analyses by Mann–Whitney *U* test were performed in these two instances, comparing the results with those of the parametric analyses.

Variance heterogeneity between the pooled patient group and the control group was tested by Levene's test for homogeneity of variance. Comparisons between the right and left sides were performed with paired *t*-tests, using the same weight variable as above.

The potential impact of clinical variables on the change in volume of brain structures was investigated by multiple linear regression with stepwise backward variable selection. In addition, a division of the complete group of patients into a group with a very large increase of right/left lateral ventricle size (annual increase exceeding the upper bound of the mean ± 2 S.D. range of the control group) and a group containing all other patients was made. The potential dependence of this grouping on the above-mentioned clinical variables was examined using logistic regression. The same procedure was used for a grouping according to decrease in hippocampus size.

Throughout, a two-tailed α-level of 0.05 was used for statistical testing. Adjustments for multiple testing were dispensed with because the increase of the type II error caused by such an adjustment has to be considered as more serious than the loss of control over the overall type I error (Rothman, 1990).

3. Results

3.1. Sample characteristics

From the original sample of 42 first-episode patients we were able to trace and re-examine 21; 17 of 30 patients with multiple episode schizophrenia and 20 of 32 healthy controls could be followed up. Demographic data and illness-related variables are summarized in Table 2.

There were no statistically significant differences between re-examined subjects and those lost to follow-up, with two exceptions: patients who were examined a second time showed a somewhat lower level of education than patients who dropped out (10.1 vs. 11.4 years on average, $P = 0.009$, Mann–Whitney *U* test) and they had smaller left lateral ventricles at the time of the first scan (4.5 vs. 5.6 ccm, $F = 4.77$; $df = 1,61$; $P = 0.033$, ANCOVA with adjustment for age, height and total brain volume). No

Table 2
Sample characteristics

	FE ($n=21$)	ME ($n=17$)	Controls ($n=20$)
	Mean (S.D.)	Mean (S.D.)	Mean (S.D.)
Age at follow-up, years	25.00 (4.75)	28.41 (4.03)	31.50 (4.94)
Height, cm	177.25 (4.79)	178.20 (5.43)	179.40 (6.85)
Education, years	10.57 (1.78)	9.82 (1.81)	10.57 (2.3)
Parental education, years	11.45 (3.27)	10.94 (3.33)	9.75 (1.74)
Time to follow-up, years	2.54 (0.80)	3.29 (1.22)	3.70 (1.63)
Duration of illness at baseline (first positive symptoms, in months)	8.3 (17.7)	93.7 (72.6)	
Total PANSS at baseline	122.90 (21.39)	115.06 (33.85)	
Total PANSS at follow-up	62.76 (24.17)	66.50 (17.19)	
GAF score at follow-up	61.07 (20.45)	63.58 (16.26)	
Days of hospitalizations between examinations	14.76 (34.70)	19.12 (31.17)	

PANSS: Positive and Negative Syndrome Scale, GAF: Global Assessment of Functioning, FE = first episode, ME = multiple episode schizophrenia patients.

statistically significant differences between dropouts and re-examined subjects were seen in the control group.

The three groups (first episode, multiple episode patients, healthy controls) differed significantly with regard to the interval between scans ($P=0.017$, one-way ANOVA); control subjects had significantly longer interscan intervals than first episode patients ($P=0.014$, Tukey test) while the differences between the other groups did not attain significance. The control subjects were older than the patients. The three groups differed significantly with respect to age ($F=10.14$; $df=2,55$; $P<0.001$). First-episode patients were younger than controls ($P<0.001$, Tukey test) and, at a trend level, also younger than multiple episode patients ($P=0.070$).

Severity ratings on the PANSS at first admission, respectively, were 122.90+21.39 (positive symptoms: 30.10+5.10, negative: 30.15+9.27, always mean+-standard deviation) for first episode and 115.06+33.85 (positive symptoms: 26.44+8.72, negative: 30.76+10.81) for multiple episode patients. The corresponding follow-up ratings were 62.76+24.17 (positive symptoms: 13.47+6.33, negative: 17.87+9.29) and 66.50+17.19 (positive symptoms: 12.83+4.02, negative: 19.67+7.87), respectively. Both patient groups showed significant improvements in PANSS positive, negative and total scores between baseline and follow-up assessment (always $t>2.39$, $df=15–20$, $P<0.035$). However, the two patient groups did not differ with regard to PANSS scores or subscores at baseline or at follow-up.

3.2. Volumetric measurements at baseline and follow-up

The volumes of the individual brain structures in first- and multiple-episode patients as well as healthy controls, determined at baseline and at follow-up, are summarized in Table 3. Significant main effects for groups were found for lateral ventricular volume and hippocampus–amygdala complex (HAC). At both time points, the sizes of the left and right lateral ventricles were significantly increased in both groups of patients compared with controls (ANCOVA results in Table 3; post hoc comparisons with control group: left side $t>2.88$, $df=52$, $P<=0.006$; right side: $t>3.81$, $df=52$, $P<0.001$). Measurements of the HAC showed significantly smaller values in patients (schizophrenia patients merged) than in controls both for the left and the right side. The same pattern was generally observed for the sub-structures of the HAC, hippocampus and amygdala, but the differences between the merged patient groups and the control group attained statistical significance only in some instances, probably due to the moderate sample size (details in Table 3). No significant differences between patients and controls were found regarding the volumes of the left and right hemisphere.

3.3. Changes in volumetric measures within groups

Changes of brain structures between the two measurement points were approximately proportional

Table 3
Volume of brain structures in first-episode patients (FE), multiple-episode patients (ME) and controls at baseline and at follow-up

Brain region	Side	Time	Mean ± S.D.[†]			ANCOVA (all 3 groups)[§]			Patients (pooled) vs. controls
			FE (n=21)	ME (n=17)	Control (n=20)	F	df	P	P
Lateral ventricle	l	1	4.37 ± 2.90	6.36 ± 4.19	2.77 ± 1.47	8.59	2,53	0.001	0.000
		2	4.81 ± 2.78	6.55 ± 4.05	3.26 ± 1.44	7.96	2,53	0.001	0.000
	r	1	4.43 ± 2.76	4.76 ± 2.17	2.99 ± 1.85	5.85	2,53	0.005	0.001
		2	4.82 ± 2.56	5.08 ± 2.22	3.18 ± 1.69	6.39	2,53	0.003	0.001
HAC	l	1	4.44 ± 0.58	4.52 ± 0.57	4.90 ± 0.54	3.51	2,54	0.037	0.013
		2	4.28 ± 0.63	4.26 ± 0.42	4.67 ± 0.52	3.21	2,54	0.048	0.014
	r	1	4.43 ± 0.72	4.49 ± 0.54	4.89 ± 0.47	3.13	2,54	0.052	0.017
		2	4.34 ± 0.73	4.35 ± 0.26	4.80 ± 0.39	4.55	2,54	0.015	0.004
Hippocampus	l	1	2.38 ± 0.48	2.57 ± 0.44	2.66 ± 0.42	2.15	2,54	0.126	n.s. (0.182)
		2	2.23 ± 0.41	2.25 ± 0.35	2.44 ± 0.41	1.67	2,54	0.197	n.s. (0.107)
	r	1	2.37 ± 0.35	2.43 ± 0.37	2.62 ± 0.39	1.98	2,54	0.148	0.068
		2	2.28 ± 0.40	2.28 ± 0.25	2.52 ± 0.36	2.67	2,54	0.079	0.024
Amygdala	l	1	2.05 ± 0.40	1.95 ± 0.40	2.23 ± 0.45	1.85	2,54	0.166	0.076
		2	2.05 ± 0.43	2.01 ± 0.27	2.23 ± 0.33	2.93	2,54	0.141	0.050
	r	1	2.06 ± 0.62	2.05 ± 0.41	2.28 ± 0.46	0.99	2,54	0.376	n.s. (0.160)
		2	2.06 ± 0.62	2.07 ± 0.21	2.28 ± 0.34	1.99	2,54	0.146	0.049
Hemispheres	l	1	510.6 ± 57.7	499.0 ± 46.9	519.1 ± 38.6	0.68	2,54	0.509	n.s.
		2	507.9 ± 56.4	514.1 ± 48.4	525.4 ± 41.2	0.65	2,53	0.529	n.s.
	r	1	510.8 ± 53.0	505.0 ± 51.7	519.0 ± 40.8	0.29	2,54	0.750	n.s.
		2	516.9 ± 50.5	517.9 ± 49.6	523.9 ± 40.6	0.13	2,54	0.881	n.s.

[†] Raw (unadjusted) means and S.D.'s.
[§] Adjustment for total brain volume (additional adjustment for age and/or height if required).

to the time elapsed between measurements (no significant quadratic term in the regression model; see Section 2.3). Therefore, the mean annual change in the sizes of brain structures represents a meaningful measure of change, accounting for individual differences in the interscan interval. Values of this measure are displayed in Table 4.

The size of the lateral ventricles, both right and left, generally showed an increase between baseline and follow-up, not only in the two patient groups but also in the control group. Except for the right lateral ventricle in the first-episode group and the left lateral ventricle in the multiple-episode group, this increase was significant (linear regression through the origin; always $F>4.5$; $df=1,16$ to $1,20$; $P\leq 0.050$). The two non-significant changes may be due to sample size; when the two patient groups were merged, the increase in both right and left lateral ventricle size became significant (right: $F=6.92$; $df=1,37$; $P=0.012$; left: $F=6.93$; $df=1,36$; $P=0.012$). The sizes of right and left hippocampal volumes decreased in both patients and controls. However, these changes were significant only for the left hippocampus ($F>4.9$; $df=1,16$ to $1,20$; $P\leq 0.038$). Regarding the volumes of the left and right hemispheres, there was a small but significant mean increase between scans in the multiple-episode group ($F>5.5$; $df=1,16$; $P\leq 0.034$); in the two other groups these changes did not reach statistical significance.

3.4. Laterality differences

Within the individual groups, neither baseline values nor change measures showed a significant difference between right and left brain measures. However, in the total patient group, i.e. first-episode and multiple-episode patients pooled, the annual decrease of the left hippocampal volume was found to be larger than that of the right hippocampus (mean values of −0.072 vs. −0.038 ccm/year, $t=2.10$, $df=37$, $P=0.042$, t-test with weighted least squares).

3.5. Changes in brain volumes—comparison between groups

A comparison of schizophrenia patients and controls with respect to mean annual changes in the volumes of brain structures is presented in Table 4.

Table 4
Mean annual change (± S.D.) of volume of brain structures in first-episode patients (FE), multipl-episode patients (ME) and controls

Structure	Side	Mean annual change[†]				Group difference (patients minus controls)	
		FE	ME	All patients	Control	Adjusted mean difference[$]	95% confidence interval[$]
Lateral ventricle	l	+0.142 ± 0.236*	+0.063 ± 0.210	+0.095 ± 0.221*	+0.092 ± 0.089**	+0.022	(−0.089, 0.134)
	r	+0.146 ± 0.371 (*)	+0.096 ± 0.188*	+0.117 ± 0.274*	+0.046 ± 0.080*	+0.070	(−0.075, 0.216)
Hippocampus	l	−0.058 ± 0.122*	−0.081 ± 0.083**	−0.072 ± 0.100**	−0.052 ± 0.083*	−0.033	(−0.088, 0.015)
	r	−0.033 ± 0.124	−0.041 ± 0.091 (*)	−0.038 ± 0.104*	−0.014 ± 0.084	−0.034	(−0.086, 0.017)
Amygdala	l	+0.005 ± 0.177	+0.006 ± 0.095	+0.006 ± 0.132	−0.002 ± 0.049	−0.012	(−0.068, 0.044)
	r	+0.001 ± 0.126	+0.011 ± 0.095	+0.007 ± 0.105	+0.003 ± 0.062	−0.027	(−0.070, 0.016)
HAC	l	−0.052 ± 0.211	−0.075 ± 0.102**	−0.066 ± 0.154*	−0.054 ± 0.097*	−0.043	(−0.123, 0.037)
	r	−0.032 ± 0.185	−0.030 ± 0.122	−0.031 ± 0.149	−0.011 ± 0.099	−0.057	(−0.131, 0.018)
Hemispheres	l	−0.14 ± 13.37	+4.64 ± 7.90*	+2.58 ± 10.74	+1.44 ± 4.71	+0.37	(−4.33, 5.07)
	r	+2.40 ± 10.80	+4.01 ± 6.74*	+3.34 ± 8.59*	+1.27 ± 4.39	+1.45	(−2.30, 5.19)

[†] Weighted means were used to adjust for time elapsed between baseline and follow-up measurement (weight = time^2).
* $P<0.05$, ** $P<0.01$, (*)$P<0.10$: test for changes *within groups* using linear regression through the origin (dependent variable: absolute change in size of brain structure measured; independent variable: time elapsed between baseline and follow-up; null hypothesis: slope of regression line = 0).
[$] Adjusted for baseline value of the respective brain measure, interscan interval, age, and total brain volume. All confidence intervals cover the value 0, indicating no significant difference in mean between patients and controls (always $P>0.1$).

There were no significant differences between patients and controls for any of the brain structures with regard to the mean of the change measure (non-parametric testing confirmed this finding for the case of the non-normally distributed changes of the left and right ventricles). This result is substantiated by observing that all of the 95% confidence intervals cover the value zero. The same applied when comparing the two subgroups of schizophrenia patients, first and multiple episode patients (data not shown).

However, a significant difference between the patients and the controls was observed with respect to the variance (or standard deviation) of the change measure for the right lateral ventricle ($F=8.98$; $df=1,56$; $P=0.004$); to a lesser extent this was also seen for the left lateral ventricle ($F=2.71$; $df=1,55$; $P=0.106$, NS). In both instances the patient group showed a larger variability of the change measure than the control group. For the right lateral ventricle, this finding was not due to outliers; after deletion of the four cases with the most extreme annual changes in left and/or right ventricular volume (three first-episode patients and one multiple-episode patient), the variance heterogeneity between the two groups remained significant. A certain amount of variance heterogeneity between patients and controls was also found for the left amygdala ($F=3.08$; $df=1,56$; $P=0.085$). In all three instances, first-episode patients had the largest standard deviations, whereas controls had the smallest.

A graphical illustration of these results for the lateral ventricle is given in Fig. 1. The pattern for the other brain structures is similar.

3.6. Relationship with clinical characteristics

In a multiple regression analysis, no association between annual change of brain structure size in

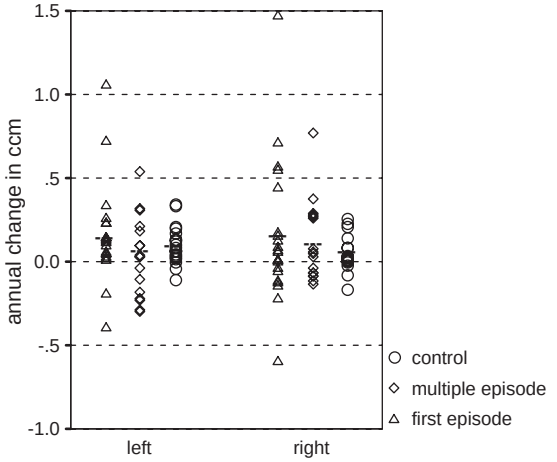

Fig. 1. Mean annual change in left and right lateral ventricle volume.

patients and duration of illness (time since first hospitalization), PANSS subscores (positive, negative), PANSS total score, GAF score, residual symptoms, work situation (all at follow-up) and cumulative days of inpatient treatment per year could be established. Moreover, when splitting the pooled patient group into patients with and without an extreme annual increase in left and/or right ventricle size (annual increase exceeding the upper boundary of the mean ± 2 S.D. range of the control group), no differences between these two groups (11 patients = 29% with extreme increase vs. 27 patients = 71% without extreme increase in ventricle size) with respect to the above-mentioned clinical variables were found in a logistic regression analysis. The same held true when the total group of patients was subdivided according to the decrease in hippocampal size.

4. Discussion

This longitudinal study compared volume changes for the total brain, the lateral ventricles and the hippocampus/amygdala complex in first- and multiple-episode schizophrenia patients with healthy control subjects. Our study confirms previously reported cross-sectional findings of ventricular enlargement and hippocampal volume deficits in chronic and first-episode patients with schizophrenia (for review, see: McCarley et al., 1999; Wright et al., 2000; Shenton et al., 2001).

However, we were not able to demonstrate any significant differences regarding annual volume changes that distinguish patients with schizophrenia from healthy controls for any of the brain structures measured. More specifically, there were no reductions in cortical and hippocampal volumes of patients over time. In fact, cortical volumes of multiple-episode schizophrenia patients increased over time compared with those of first-episode patients and controls, which remained essentially unchanged. This expansion of cortical volumes could be related to a treatment effect. There is some evidence that treatment with antipsychotic drugs contributes to morphological changes in specific brain regions, such as in the caudate and lenticular nuclei (Chakos et al., 1994, 1995, 1998; Roberts et al., 1996) and in prefrontal nuclei (Selemon et al., 1999).

Longitudinal neuroanatomical findings regarding volume-changes of the hippocampus in schizophrenia are still sparse and controversial. DeLisi et al. (1997) and Wood et al. (2001) failed to find volume differences in the hippocampus between schizophrenia patients and healthy control subjects over time. Lieberman et al. (2001) showed an increase of hippocampal volume only in a subgroup of patients with poor outcome, but there were no significant reductions in cortical and hippocampal volumes over time in the other groups. Jacobsen et al. (1998) reported that treatment-refractory patients with childhood-onset schizophrenia showed significantly greater decreases than healthy subjects in left hippocampal volumes.

In the present study, hippocampal volume decreased both in patients and controls. In the total patient group, the annual decrease of left hippocampal volume was found to be significantly larger than that of the right hippocampus. Our finding underscores the three-hit model of Velakoulis et al. (2000), which postulates that an early neurodevelopmental lesion renders the left hippocampus particularly vulnerable to further insult later in life. As a result, the left hippocampus shows a faster volume reduction than the right hippocampus with continued psychotic illness. With progression to chronic persistent illness, further insults involving the hippocampus are suggested to occur bilaterally.

Although ventricular enlargement is the most consistently replicated brain abnormality found in schizophrenia (recently reviewed by Buckley, 1998; McCarley et al., 1999; DeLisi et al., 2004), it is still a controversial issue, whether this represents a static or a progressive neuropathological process. A number of longitudinal studies of chronic and first episode patients with schizophrenia have reported no change of ventricular size (Degreef et al., 1991; DeLisi et al., 1992; Gur et al., 1998; Puri et al., 2001) while others have found ventricular expansion over time (Woods et al., 1990; DeLisi et al., 1995, 1997) and a study of chronic patients found continuing changes in ventricular size only in poor prognosis patients (Nair et al., 1997).

We found a significant increase in the volumes of the lateral ventricles in schizophrenia patients over time, but this was not different from healthy control subjects. There were no differences between patients and controls with respect to the mean annual change

in ventricular volume. Interestingly, patients with schizophrenia showed a greater inter-subject variability in ventricular volume changes over time. This finding is essentially in line with findings of Puri et al. (2001) and DeLisi et al. (1992), who also reported greater heterogeneity in the change of ventricular volume in schizophrenia patients than in healthy controls, although there were no differences in the mean change between the two groups over time. This heterogeneity might explain controversial findings, reporting either stability or expansion of ventricular size over time. Taken together, the available evidence suggests that there might be a subset of patients with a morphologically visible disease progression and that this may be indicative of poor outcome (DeLisi et al., 1992; Davis et al., 1998; Lieberman et al., 2001; Nair et al., 1997).

Finally, in the current study, we were not able to show a relationship between progressive brain volume changes and outcome measures like duration of illness, positive and negative symptoms as rated with the PANSS, GAF score, residual symptoms, work situation and cumulative days of inpatient treatment. Moreover, the complete patient group was divided into patients with and without an extreme annual increase in ventricle size or decrease in the size of the hippocampus, no statistically significant differences between these two groups were found in a logistic regression analysis. Clinically, the patients' presentation was comparable to that observed in larger samples, and both groups of patients showed the expected clinical improvement associated with treatment, as in other samples.

Prospective studies that have addressed the correlation between progressive brain volume changes and outcome in schizophrenia have produced equivocal findings. On the one hand, a relationship between poor outcome, increases in ventricle volume (Nair et al., 1997; Lieberman et al., 2001) and decreases in gray matter volume (Mathalon et al., 2001) has been reported. On the other, several studies have failed to find a relationship between brain changes and outcome (DeLisi et al., 1992, 1995, 1997) or have even reported an inverse relationship (Gur et al., 1998). These inconsistencies could be the result of sampling differences or the use of varying rating/assessment scales for clinical variables. Furthermore, symptom severity and hospitalization may not adequately reflect outcome (Carpenter and Strauss, 1991).

When interpreting the results of this study, one has to keep in mind that we, as others before us (Gur et al., 1998; Puri et al., 2001; Wood et al., 2001; Saijo et al., 2001; Mathalon et al., 2001; Cahn et al., 2002; DeLisi et al., 2004; Bachmann et al., 2004), have analyzed a fairly small sample. While the sample size has adequate power for testing hypotheses on global measures of anatomical and clinical changes, larger samples are needed to probe for more detailed and specific low-magnitude correlations with confidence. In addition, the age difference between patients and control subjects, despite being fairly small, may have reduced the power to detect differences between patients and control subjects. We also acknowledge the limitation of our measuring the hippocampus–amygdala complex as one structure and then dividing it into an anterior and a posterior portion, using the mammillary bodies as landmarks. A number of other investigators (Lieberman et al., 2001; Bilder et al., 1995; Bogerts et al., 1990; Chakos et al., 1994; Degreef et al., 1992) have used the same method; therefore, our results can be compared to these reports.

Although drug and alcohol abuse were excluded through in depth psychiatric interviews at both examination points, we cannot completely rule out the influence of this potentially confounding variable. It is certainly a drawback that we did not include a specific laboratory screen for drugs and alcohol. The question whether drug treatment has an influence on the volumes of different brain regions also cannot be answered by our study, as we found the data concerning the use of medication incomplete and heterogeneous and we did not include any control for compliance.

Given the fact that schizophrenia generally extends over the course of a patient's entire life, a follow-up period of 2–4 years may be too short to demonstrate subtle changes. Alternatively, the follow-up period may not have covered the period of the illness in which maximal changes occurred.

It must also be considered that the actual variance in brain morphology measured in longitudinal imaging studies is not necessarily a primary disease consequence. It may derive from multiple additional sources such as external factors like treatment,

hydration, nutritional factors, weight gain or substance abuse comorbidity.

In summary, this study has demonstrated ventricular enlargement and hippocampal volume deficits in patients with schizophrenia. However, we were not able to distinguish patients with schizophrenia from healthy controls with regard to the rate of volume changes for any of the brain structures measured. Although we were unable to detect morphological evidence of disease progression, the higher variance of morphometric changes in patients may suggest that there is a subset of patients with progressive changes in distinct brain structures.

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