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Internal capsule size associated with outcome in first-episode schizophrenia

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Abstract Subtle structural brain abnormalities are an established finding in first-episode psychosis. Nevertheless their relationship to the clinical course of schizophrenia is controversially discussed. In a multicentre study 45 first-episode schizophrenia patients (FE-SZ) underwent standardized MRI scanning and were followed up to 1 year. In 32 FE-SZ volumetric measurement of three regions of interests (ROIs) potentially associated with disease course, hippocampus, lateral ventricle and the anterior limb of the internal capsule (ALIC) could be performed. The subgroups of FE-SZ with good (12 patients) and

poor outcome (11 patients), defined by a clinically relevant change of the PANSS score, were compared with regard to these volumetric measures. Multivariate analysis of covariance revealed a significant reduced maximal cross sectional area of the left ALIC in FE-SZ with clinically relevant deterioration compared to those with stable psychopathology. There were no differences in the other selected ROIs between the two subgroups. In conclusion, reduced maximal area of ALIC, which can be interpreted as a disturbance of fronto-thalamic connectivity, is associated with poor outcome during the 1 year course of first-episode schizophrenia.

Key words first-episode schizophrenia · magnetic resonance imaging · disease course · outcome

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Introduction

Structural brain abnormalities have been consistently described in schizophrenic patients compared to healthy controls [19, 27]. In a recent meta-analysis, volumetric deficits at diagnosis were seen in total brain volume, in the hippocampus, in cortical grey matter, in Heschl's gyrus, in the planum temporal and in temporal grey matter, and in longitudinal studies continued volumetric loss over time could be demonstrated in these structures [22]. In addition, the lateral ventricles were significantly larger than normal at onset of the illness and the ventricular volume tended to increase significantly in the disease course [22].

Only few studies focused on the predictive value of brain morphology for the course of schizophrenia in first-episode patients and reported inconsistent results [4, 5, 13, 16–18, 23]. It was observed that hippocampal volume was associated with a higher risk of relapse [16], greater ventricular expansion was related to an unremitting course and poor outcome [4, 5, 11], smaller temporal gray matter volume was associated with persistence of hallucinations, and more normal cerebral asymmetry was associated with adequate social/vocational functioning and full recovery [18]. Two other investigations could not demonstrate a correlation between volumetric measurement and treatment response [17] or 2-year outcome [23].

The aim of the presented study was to investigate if there is a difference in brain morphology focusing on structures suggested in previous studies to be relevant for the clinical course (hippocampus, lateral ventricles) in a sample consisting of first-episode patients well characterized for the outcome over 1 year. Based on previous findings of reduced internal capsule volume and cross sectional area in families affected with schizophrenia [25] and in first-episode patients [10], we decided to include volumetric measurement of the anterior limb of the internal capsule (ALIC).

Method

Subjects

The first-episode study program [6] of the German Research Network on Schizophrenia (GRNS) [26] consisted of an 8-week acute treatment phase and a consecutive 2-year long-term treatment phase (registered in ClinicalTrials.gov: NCT00159081). Between 2000 and 2004, 158 first-episode patients, aged 18–55 years and treated in inpatients departments of the participating centres, were randomly assigned to double-blind, low-dose haloperidol or risperidone. Drugs could be increased (up to 8 mg/day) or lowered (minimum 1 mg/day) depending on symptoms or side effects as indicated by the respective clinical global impressions (CGI) scales. Concomitant medications were permitted throughout the trial, except for additional antipsychotics or mood stabilizers. The results of the clinical study have been published recently [7]. Patients were diagnosed with schizophrenia according to DSM-IV by experienced clinical psychiatrists using a standardized clinical interview (SCID;

German Version) [24]. Before entering the long-term treatment study the diagnosis of schizophrenia was confirmed by independent experienced clinical psychiatrists.

A total of 75 patients of this long-term treatment phase first-episode sample participated in the MR-imaging study and were recruited from the Psychiatry Departments of the Universities of Bonn, Cologne, Düsseldorf, Duisburg-Essen, Jena, Mainz, Munich, and Tübingen, as well as from the Central Institute of Mental Health in Mannheim. Out of this sample only 45 patients received standardized rating of psychopathology with the positive and negative syndrome scale (PANSS) [9] at baseline and during follow-up, and underwent magnetic resonance imaging (MRI) at baseline due to a defined protocol fulfilling the quality-criteria. Exclusion criteria for the first-episode long-term study and the MRI study part were any psychiatric comorbidity (DSM-IV), neurological diseases, contraindication for antipsychotic treatment, suicidal behavior in previous history, mental retardation, pregnancy, substance dependence, disorders which affect cerebral metabolism, in addition to the usual exclusion criteria for MRI (e.g. metal implants, cardiac pace makers). After a complete description of the study, written informed consent was obtained from each patient. The local ethics committees approved the protocol, which is in accordance with the Declaration of Helsinki.

From the MRI study sample we extracted 39 first-episode patients, who received follow-up visits covering a period of at least 3 months up to 1 year (mean 46.6 ± 10.7 weeks). In this MR sample volumetric measurement of all regions of interest could be performed in 32 patients. We divided this patient sample in three subgroups according to PANSS rating during the 1-year follow-up: 12 patients with stable psychopathology (good outcome; increase of PANSS total score below 10% of baseline score, approximately 5 points), 9 patients with intermediate outcome (moderate worsening), and 11 patients with clinically relevant deterioration (bad outcome; increase of PANSS total score above 40% of baseline score, approximately 20 points).

The subgroup with good outcome did not show any clinically relevant worsening of symptoms, presenting a stable course (change of mean PANSS total score less than 4 points), while the subgroup with bad outcome demonstrated a clinically relevant increase of symptoms at least in one visit during the 1-year course, predominantly in negative symptoms and general psychopathology, (change of mean PANSS total score more than 40 points) (see Table 1).

We compared the subgroups of good and bad outcome with regard to volumetric measurement of three distinct brain regions: hippocampus, lateral ventricles and the ALIC.

Magnetic resonance imaging and measurements

Magnetic resonance imaging (MRI) was performed on Siemens and Phillips 1.5 Tesla MR scanners with T1-weighted 3D data (MPRAGE) sequences providing a spatial resolution of $1 \times 1 \times 1 \text{ mm}^3$ (repetition time = 11.4 ms, echo time = 4.4 ms, flip angle = 15°).

Manual area measurements for lateral ventricles, hippocampus and ALIC were obtained using the “region of interest” tool implemented in the software Analyze (version 3.0). Volumes of ROIs were calculated by multiplying the outlined areas with slice thickness, and relative volumes were calculated to adjust for differences in total brain volumes. Intra- and interrater reliability was measured in a subset of ten subjects. Intraclass correlation was sufficiently high (ICC >0.7) [20]. The total brain volume, gray and white matter volumes were determined using an automatic algorithm programmed in MATLAB and SPM99 (Statistical Parametric Mapping) [2].

The areas of the lateral ventricles were traced for each side separately in coronal slices, and hippocampal contours were drawn in the sagittal view following the borders described in the literature [19]. The correctness of the outlines was controlled in the two other views.

Table 1 Clinical and sociodemographic data in the first-episode subgroups

	FE-SZ stable (<i>n</i> = 12)		FE-SZ bad outcome (<i>n</i> = 11)		ANOVA	
	<i>m</i>	SD	<i>m</i>	SD	<i>F</i>	<i>P</i>
Age (years)	30.40	9.42	33.18	12.87	0.31	0.58
Education (years)	11.60	3.03	12.11	2.62	0.15	0.70
Education of parents (years)	12.67	3.46	13.29	4.50	0.10	0.76
Baseline PANSS positive score	10.83	3.93	8.82	2.52	2.10	0.16
Baseline PANSS negative score	15.33	6.11	11.09	3.18	4.24	0.052
Baseline PANSS gen. score	27.92	7.38	23.09	5.72	3.03	0.096
Maximal PANSS positive score	11.33	3.87	13.73	5.10	1.63	0.22
Maximal PANSS negative score	16.58	6.32	21.64	3.93	5.19	0.033
Maximal PANSS gen. sum score	28.42	6.91	48.91	12.84	23.28	<0.0005
Diff. PANSS positive score	0.50	1.24	4.91	4.97	8.88	0.007
Diff. PANSS negative score	1.25	1.60	10.55	3.08	84.68	<0.0005
Diff. PANSS gen. score	0.50	1.00	25.82	11.11	62.07	<0.0005
	FE-SZ stable		FE-SZ bad outcome		χ^2	<i>P</i>
Gender (male/female), <i>n</i>	6/6		6/5		0.05	0.83

FE-SZ first-episode schizophrenic patients, Diff. difference, PANSS positive and negative syndrome scale, gen. general psychopathology, *n* sample size, *m* mean, *SD* standard deviation, ANOVA analysis of variance, *F* *F*-statistics, *P* probability, χ^2 Chi-Square-test

The measurement of ALIC was performed as described previously [25] dividing the internal capsule into an anterior and posterior part by a line bisecting the angle of internal capsule on horizontal slices. ALIC was defined medially by the caudate and laterally by the lentiform nucleus. The ventral boundary was determined by a line connecting the lateral edge of ventral part of the caudate and the medial edge of the ventral part of the lentiform nucleus. The first slice included was the most inferior one comprising a detectable amount of white matter belonging to the internal capsule. The last slice was the one inferior to the slice which comprised the merging of internal capsule and the lamina pallidi externa. The method of manual delineation required individual optimization of contrast and brightness in each slice. ALIC identification was controlled for each slice in coronal and sagittal orientation. Additionally, ALIC length and maximal cross sectional area were measured, length as the sum of slices containing ALIC, maximal cross section as maximal area of one particular slice among all slices (see Fig. 1). In all cases the slice with maximal

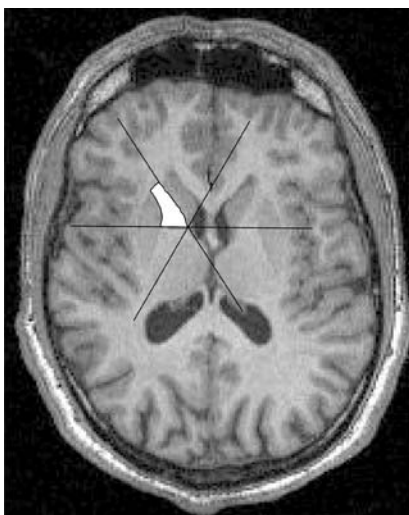


Fig. 1 Tracing of ALIC T1-weighted MR-image. The internal capsule is divided into an anterior (ALIC) and posterior part (PLIC) by a line bisecting the angle of internal capsule on horizontal slices. The right anterior limb of the internal capsule (ALIC) is marked

cross sectional area was identical to the most superior slice directly beneath the delta of merging internal capsule and lamina pallidi externa.

Statistics

Statistical analyses were performed with SPSS 10 for Windows. All tests were two-tailed. Dependent variables were bilateral volumes of the hippocampus and the ventricular system, and bilateral volumes, maximal cross sectional area and length of the ALIC. Independent variable was the outcome of the patients. Only the extreme groups with good or bad outcome were included into the analysis.

Boxplots were examined to identify extreme values. Kolmogorov-Smirnov tests were applied to test the assumption of normal distribution. Since there were no significant deviations from the normality assumption, the general linear model (GLM) was performed using a multivariate approach for left and right side measurements separately for the blocks of dependent variables. Independent factors outcome (good/bad) and gender and covariate age were included into the model. Thus, all analyses were adjusted for intervening influences of age and gender.

Results

The patient subgroups with good and poor outcome did not differ in sociodemographic data (see Table 1). First-episode patients who subsequently worsened during the first year of the illness revealed a significantly smaller maximal cross sectional area of the ALIC compared to those patients with stable psychopathology (GLM; multivariate: $F = 4.5$, $df = 2, 17$, $P = 0.028$). Subsequent univariate tests showed that this reduction was significant on the left side (-19% , $F = 8.2$, $df = 1, 18$, $P = 0.010$; see Fig. 2). Other measurements of ALIC, as well as hippocampal and lateral ventricular volumes were not significantly reduced in patients with poor outcome compared to the stable group (see Table 2).

We found no significant correlations between the cumulative doses of risperidone or haloperidol and

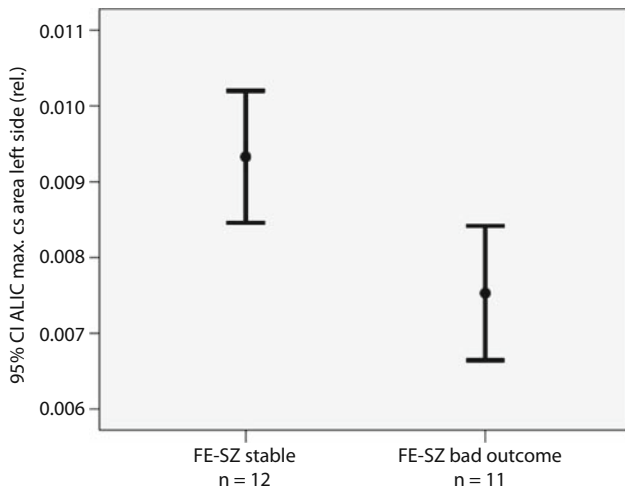


Fig. 2 Relative left ALIC maximal cross sectional area in first-episode schizophrenia patients. ALIC, anterior limb of the internal capsule; FE-SZ, first-episode schizophrenia patients; CI, confidence interval; max. cs, maximal cross sectional; rel., relative

the ALIC maximal cross sectional area in the total group of patients and in the subgroups of schizophrenic patients with stable psychopathology or clinically relevant deterioration in the 1-year course. The cumulative doses of risperidone and haloperidol were not significantly different in both subgroups ($df = 1$, $F = 0.001$; $P = 0.98$, oneway-ANOVA), and the daily doses of risperidone and haloperidol in the subgroups were comparable (FE-SZ stable psychopathology: risperidone 4.3 ± 2.0 mg/day, haloperidol 3.0 ± 1.5 mg/day; FE-SZ poor outcome: risperidone 3.8 ± 1.3 mg/day, haloperidol 3.1 ± 1.6 mg/day).

While the educational level may have influenced out results we repeated the analysis with education as covariate. The results were similar, first-episode patients with deterioration during the first year of the illness still presented with a significantly smaller maximal cross sectional area of the ALIC compared to

those patients with stable psychopathology (MANCOVA; $P = 0.020$).

Discussion

The main result of our study assessing the relationship of brain morphology and clinical outcome in first-episode schizophrenia is the significant reduced maximal cross sectional area of the anterior limb of the internal capsule (ALIC) in the subgroup of patients with clinical deterioration during the 1-year course compared to patients with stable psychopathology. There was no volumetric difference between the two subgroups with regard to the other selected regions of interest, hippocampus and lateral ventricles.

While most prominent replicable brain abnormalities in schizophrenia are volume changes of the grey matter (e.g. 19, 22, 27), some studies using voxel-based morphometry revealed evidence for white matter abnormalities, e.g. bilaterally in the frontal lobe [14] or in the left temporal and frontal lobe of schizophrenic patients with predominant negative symptoms [21]. In addition, significant decreases in white matter density were detected in connecting structures like the genu and truncus of the corpus callosum, the right ALIC and the right anterior commissure compared to healthy subjects [8].

Only a few studies assessed white matter changes in schizophrenia that were hypothesis-driven using the region of interest (ROI) approach. In the present study we morphometrically assessed the hippocampus and the lateral ventricles, whose volumetric alterations are most consistently associated with the course of the illness, as well as the anterior limb of the internal capsule, a connecting white matter structure, which has been found to exhibit decreased volumes both in schizophrenia [28] and in unaffected first-degree relatives of schizophrenic patients [25].

Table 2 Results of volumetric measurements

Region of interest	FE-SZ stable (n = 12)		FE-SZ bad outcome (n = 11)		Diff (%)	MANCOVA		
	m	SD	m	SD		F	df	P
Hippocampus volume left side (rel.)	0.00328	0.00044	0.00313	0.00034	-4.4	0.4	1, 17	0.23
Hippocampus volume right side (rel.)	0.00315	0.00055	0.00307	0.00037	-2.5	0.4	1, 17	0.45
Lateral ventricle volume left side (rel.)	0.01139	0.00467	0.00977	0.00528	-14.2	0.8	1, 18	0.38
Lateral ventricle volume right side (rel.)	0.01038	0.00466	0.00946	0.00507	-8.8	0.2	1, 18	0.64
ALIC volume left side (rel.)	0.00056	0.00011	0.00055	0.00010	-1.7	0.0	1, 18	1.00
ALIC volume right side (rel.)	0.00059	0.00010	0.00051	0.00010	-12.3	2.2	1, 18	0.15
ALIC max. cs. area left side (rel.)	0.0093	0.0014	0.0075	0.0013	-19.3	8.2	1, 18	0.010
ALIC max. cs. area right side (rel.)	0.0085	0.0015	0.0079	0.0013	-6.9	0.8	1, 18	0.38
ALIC length left side (rel.)	0.0923	0.0128	0.0945	0.0116	2.5	0.6	1, 18	0.44
ALIC length right side (rel.)	0.0930	0.0108	0.0955	0.0120	2.7	0.8	1, 18	0.39
Total brain volume (absolute, cm ³)	1136.5	116.6	1133.1	103.2	1.4	0.1	1, 18	0.73

FE-SZ first-episode schizophrenic patients, Diff. difference, n sample size, m mean, SD standard deviation, F F-statistics, df degrees of freedom, P probability, rel. relative, max. cs. maximal cross sectional, MANCOVA multivariate analysis of covariance, F, P for factor subgroup

Out of the three mentioned structures, in our study only the left maximal cross sectional area of the anterior limb of the internal capsule was associated with the clinical course in first-episode schizophrenia. In this sample of first-episode patients those with poor outcome (high increase of positive symptoms) showed a reduced maximal cross sectional area of the ALIC on the left side compared to those with good outcome. However, when left and right ALIC maximal cross sectional areas of both subgroups are compared, there is an inverse relationship. In the good outcome group the mean left ALIC maximal cross sectional area is larger than the right one, and in the bad outcome group it is the other way round. This inverse relationship may be at least in part responsible for the significant difference between the subgroups. This may point towards a different asymmetry or shape of this structure in the subgroups. Nevertheless we can not rule out the possibility that the left ALIC maximal cross sectional area in the patients with good outcome group may be disproportionately large in our sample.

The ALIC is a very important connecting structure linking the frontal cortex to subcortical structures through the medial [15] and the basolateral limbic circuit [12]. Abnormalities in the ALIC can thus be taken as measure for disturbances in the frontothalamic connectivity that is discussed to be relevant for the pathophysiology of schizophrenia [1].

Interestingly, a recent study shows that a reduced area of the ALIC in dorsal MRI slices was associated with poor outcome based on longitudinal analysis of self-care deficits in chronic schizophrenia [3]. The authors suggest disruption of internal capsule fibers in poor-outcome patients with schizophrenia, which is supported by the results of our study. The reduced maximal cross sectional area measured in our investigation corresponds to the reduced ALIC area in dorsal MRI slices of the cited study. Additionally, our results indicate that reduced white fiber structures in this area might increase the risk not only for a poor outcome in chronic schizophrenic patients, but also increase the vulnerability for the onset of schizophrenic psychosis and an unfavourable course in first-episode schizophrenia. To our knowledge this study is the first one investigating the relevance of white matter structures, especially the ALIC, for the course of first-episode schizophrenia.

There are several limitations of our study. We were not able to control for the influence of possible confounding factors determining poor outcome, e.g. psychosocial circumstances or neurocognitive function. Secondly, the follow-up observational period without any intermediate anchor point may be too long to document the disease course adequately. Medication could serve as a confounding factor in structural neuroimaging. While the cumulative and daily doses of risperidone and haloperidol were low

and similar distributed in both subgroups we do not assume a relevant influence of antipsychotic medication on our volumetric results or on clinical outcome, for instance by the induction of secondary negative symptoms.

In conclusion our finding of reduced internal capsule size in patients with bad outcome supports the dysconnectivity concept of schizophrenia [28] and points towards disturbances in the striato-thalamo-cortical neuronal circuit and abnormalities in related structures.

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