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ORIGINAL PAPER

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White matter alterations in schizophrenic patients with pronounced negative symptomatology and with positive family history for schizophrenia

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Abstract *Background* In recent years, in vivo and post-mortem studies detected structural brain changes in schizophrenia. The aim of our analysis was to investigate potential changes of white matter in schizophrenic patients compared to controls, and the relationship to clinical characteristics. *Methods* Fifty male, right-handed schizophrenic patients who met DSM-IV criteria for schizophrenia were recruited. Fifty right-handed, age- and sex-matched subjects without a psychiatric disorder were enrolled as controls. Volumes of white matter in several brain regions were measured by 1.5 T MRI using a volumetry and segmentation software (BRAINS). Regions of interest including frontal, temporal, parietal, occipital and subcortical areas were determined using Talairach spaces. *Results* No significant differences in white matter volumes of total brain tissue and regions of interest were detected between patients and controls. A significant reduction of white matter in parietal cortex of right hemisphere was found in a subgroup of patients with pronounced negative symptoms. Furthermore, patients with first-grade relatives suffering from schizophrenia showed a reduction of subcortical white matter in the right hemisphere. *Conclusions* Our results indicate that subgroups of schizophrenic patients show alterations of white matter in distinct brain regions, including the right parietal lobe.

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Introduction

In the last decades numerous studies detected structural brain changes in schizophrenia [23]. With regard to the developmental hypothesis of schizophrenia [41], changes of cerebral gray matter were first in the focus of interest [23, 30, 37, 46, 50, 58, 59].

However there were also reports on changes of white matter in schizophrenia. Cerebral white matter was examined in volumetric studies by use of whole brain and region of interest (ROI) analyses [26, 32, 35, 58, 60, 61], or by voxel-based morphometry (VBM) (for review see [32]), by magnetic resonance spectroscopy [6, 53], and by diffusion tensor imaging (DTI) [1, 12, 17, 33, 53].

The hypothesis of alterations of brain connectivity in schizophrenia and its possible relationship to white matter disturbances attracted considerable interest [12, 19, 38]. Nevertheless reports on this topic remained controversial: Some authors found an increase [35], some a decrease [11, 26, 44, 58], others a region dependent increase or decrease [55], and some detected no changes of white matter volumes in schizophrenia [36, 60, 61].

There are indications that clinical parameters may have influenced the results. For example, white matter changes were reported in schizophrenic patients with pronounced negative symptomatology [44, 58]. In addition, changes of the largest white matter tract in humans, the corpus callosum were reported for patients with familial members affected with psychosis [39].

Structural white matter changes may be not diffuse but restricted to distinct brain regions such as the

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Table 1 Sociodemographic data of 50 right-handed male schizophrenic patients and matched healthy controls

	Patients ($n = 50$)	Healthy controls ($n = 50$)	*P* values
Age (years)	30.0 ± 8.4	30.2 ± 8.8	0.92
Height (m)	1.79 ± 0.07	1.81 ± 0.06	0.24
Weight (kg)	81.7 ± 15.2	75.3 ± 9.2	*0.013**
BPRS	42.2 ± 11.3	–	
PANSS	38.4 ± 10.1	–	
Thought disorder index (BPRS)	8.8 ± 3.79	–	
Age of onset (years)	23.1 ± 6.1	–	
Illness duration (years)	6.8 ± 6.9	–	

BPRS sum score of the Brief Psychiatric Rating Scale, *PANSS* sum scores of the Positive and Negative Syndrome Scale

prefrontal regions [58] or temporo-parietal structures [55]. In addition there may be a disturbance of normal asymmetry: Takahashi et al. [56] reported a reduction of normal white matter right > left asymmetry in the anterior cingulate gyrus in female schizophrenic patients and Kubicki et al. [33] reported a loss of normal left > right asymmetry in the uncinate fasciculus in schizophrenic patients.

We examined the white matter in schizophrenic patients to answer following questions:

1. Is there a change of white matter volume (increase or decrease) in schizophrenia?
2. Are possible changes of white matter restricted to distinct brain regions?
3. Is there a loss of normal left/right white matter asymmetry?
4. Are changes of white matter correlated with enlargement of the ventricles?
5. Are white matter changes restricted to certain clinical entities (familial schizophrenia, negative symptomatology)?

For these reasons we applied a well established MRI volumetry method and a segmentation program to measure white and gray matter as well as cerebrospinal fluid in fifty male patients suffering from schizophrenia and age-matched controls.

Subjects and methods

Subjects

Fifty male right-handed schizophrenic patients (age range 18–50 years) who fulfilled DSM-IV criteria for schizophrenia were recruited over a 2-year period from the psychiatric hospital of the Ludwig-Maximilians University in Munich.

Fifty right-handed healthy control subjects without a personal history of psychiatric disorder or family history of psychosis were recruited from the community. They were matched to the patients by age [widest age pairing disparity was 3 years (two pairs)] and educational achievement. Sample characteristics of patients and controls are given in Table 1.

Subjects were excluded if they had current neurological disorders, a history of head injury resulting in loss of consciousness, alcohol or substance abuse, metallic objects in their body and cortisone or benzodiazepine medication in the last 3 months. Patients were also excluded if they had any comorbid DSM-IV axis I disorder, or previous electroconvulsive therapy.

Assessment

Diagnosis was made on the basis of interviews by two trained psychiatrists. Age of onset of schizophrenia was based on the age when patients first clearly manifested either delusions or hallucinations. Psychopathology was assessed with the Brief Psychiatric Rating Scale (BPRS, [43]) and Positive and Negative Syndrome Scale (PANSS, [28]). To differentiate between patients with high and low scores of negative (/positive) symptoms the median split of the negative (/positive) symptom subscore of the PANSS was computed. Handedness was determined by the Edinburgh Handedness Inventory [42]. Thought disorder index of BPRS was used [43]. All patients received neuroleptic medication and the type of medication was recorded. After complete and written description of the study to the patients and control subjects, written informed consent was obtained. The study was approved by the local ethics committee and performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

MRI collection and processing

MRI images were obtained (1.5 Tesla Magnetom Vision, Siemens) using a coronar T2- and protondensity-weighted Dual-Echo-Sequence (TR 3710 ms/TE 22/90 ms; total aquisition time: 9 min, number of aquisitions:1; FOV 230 mm; matrix 256 × 256, slice thickness 3 mm) and a 3D-MPRAGE sequence (TR/TE 11.6/4.9 ms; total aquisition time: 8 min, number of acquisitions: 1; FOV 230 mm; matrix 512 × 512, slice thickness 1.5 mm).

For further image processing with size reduction from 16 to 8 bit and transformation to a uniform matrix of 256 × 256 on 126 slices of 1.5 mm slice thickness, the commercial software package Analyze was used (ANALYZE, Biomedical Imaging Resource, Mayo Foundation, Rochester, MN). All datasets were realigned and resampled three-dimensionally according to the coordinates of Talairach. Specific tissue volume measurements were obtained by using the software program BRAINS (Brain Research: Analysis of Images, Networks, and Systems; developed by Andreasen et al. [2, 3, 22]).

Regions of interest including frontal, temporal, parietal, occipital and subcortical areas were determined using Talairach spaces [57] (see Fig. 1). Within these areas ("Talairach boxes") the volume of the white matter was calculated using the segmentation program BRAINS that enabled automatically tissue segmentation into gray matter, white matter and cerebrospinal fluid (see above, [2, 3, 22]).

Statistical analysis

Statistics were performed using the SPSS 10.0 software (statistical package for social sciences, SPSS, Inc., Chicago, 1999). *T* tests were applied to test for differences concerning sociodemographic variables between healthy controls and patients. Morphometric data were analyzed for region and laterality effects by a mixed model analysis of covariance (ANCOVA) with one between-subject-factor (diagnosis) and two within-subject-factors (Talairach region and side). The covariate intracranial volume was added to the analysis. Group differences were calculated by independent *t* tests. Correlations between morphometric data were performed by Pearson product moment correlation. Correlations between the morphometric data with psychopathology were examined by Spearman correlation analysis. Bonferroni corrections for multiple comparisons were performed.

An asymmetry coefficient (AC) was calculated as described previously for other brain regions [54]: AC = [right white matter (wm) volume − left wm volume]/[0.5 × (right wm volume + left

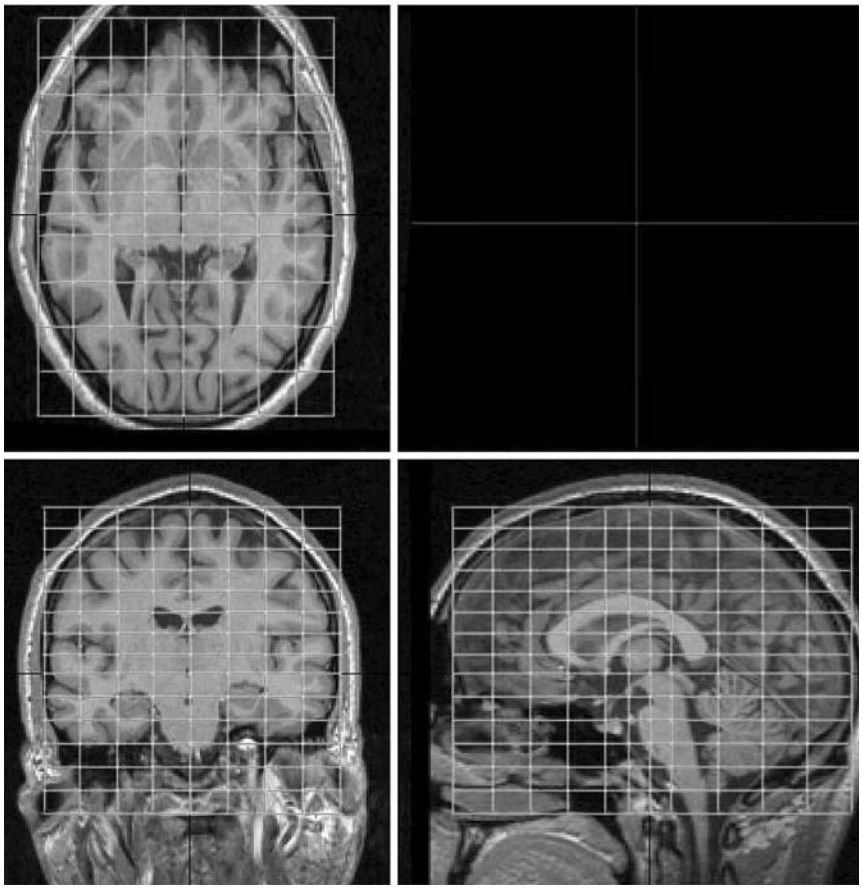

Fig. 1 Application of MRI frames for determination of Talairach spaces

wm volume)]. The calculations were made for the whole brain (left and right hemisphere), and for each of the Talairach boxes (frontal, parietal, temporal and occipital lobe, subcortical region) separately.

Results

Our sample of 50 patient and 50 controls was homogeneous with regard to gender and handedness as we examined only right-handed male patients and controls. The examined control group was matched for both variables in addition to age. The only significant difference was a higher weight in the patient group.

With regard to our first hypothesis we found no significant differences between the patient and the control group regarding total brain white matter volume, after controlling for total brain volume (see Table 2). Results of white matter volumes of specific separated Talairach boxes are also presented in Table 2. Again, after controlling for total brain volume, no significant differences between patients and controls were found in these areas, including frontal, temporal, parietal, occipital and total subcortical regions.

However, significant differences with regard to white matter volumes were detected between clinical subgroups of schizophrenic patients (see Tables 3, 4).

Patients with high negative symptomatology according to the PANSS scale showed a reduction of white matter in right parietal cortex (t test, $P = 0.01$, $df = 48$, $T = 2.668$). The difference remained significant after correction for total intracranial volumes ($P = 0.004$, $F = 9.352$) and after correction for multiple comparisons.

Patients with first grade relatives suffering from schizophrenia showed a significant reduction of subcortical white matter in right hemisphere (t test: $P = 0.01$, $df = 48$, $T = 2.678$). The difference remained significant after correction for total intracranial volume (ANOVA: $P = 0.024$, $F = 5.439$), but not after correction for multiple comparisons.

Correlation analysis showed a significant positive correlation between severity of negative symptoms as measured by PANSS and reduction of white matter volume in right parietal lobe ($\rho = -0.30$, $P = 0.03$). In addition, a significant positive correlation was detected between negative symptoms and reduction of white matter volumes of right frontal lobe ($\rho = -0.28$, $P = 0.048$) and occipital lobe ($\rho = -0.35$, $P = 0.01$).

No significant correlations were detected between positive symptoms according to PANSS and white matter volumes in all subregions under examination (see also Table 4). In addition, we did not detect any significant differences of asymmetry coefficients of

Table 2 Comparisons of white matter morphometric Talairach data between 50 schizophrenic patients and 50 healthy controls, controlled for total brain volume

ROI white matter (ccm, mean ± SD)	Patients (n = 50)	Healthy controls (n = 50)	ANCOVA	
			F value	Signif.
Total intracranial white matter	479.6 ± 46.2	495.4 ± 55.9	0.10	0.75
Left FL, white matter	90.7 ± 10.1	93.8 ± 12.9	0.01	0.92
Right FL, white matter	95.2 ± 9.5	98.8 ± 13.4	0.25	0.61
Left TL, white matter	39.0 ± 4.8	40.2 ± 4.9	0.07	0.78
Right TL, white matter	38.0 ± 4.4	39.9 ± 4.9	1.69	0.19
Left PL, white matter	60.4 ± 7.1	62.3 ± 7.5	0.01	0.95
Right PL, white matter	58.8 ± 6.5	59.8 ± 7.5	0.87	0.35
Left OL, white matter	28.7 ± 4.8	29.6 ± 5.0	0.01	0.94
Right OL, white matter	25.3 ± 4.4	25.7 ± 4.0	0.58	0.44
Subcortical white matter left	21.2 ± 2.2	22.0 ± 2.9	1.44	0.23
Subcortical white matter right	21.4 ± 2.3	22.2 ± 2.6	0.91	0.34

FL frontal lobe, *TL* temporal lobe, *PL* parietal lobe, *OL* occipital lobe, *ROI* region of interest, *Signif.* significance

global and regional values (frontal, temporal, parietal and occipital lobe, subcortical region) between schizophrenic patients and controls, which were also true for the subgroup of schizophrenic patients with pronounced negative symptomatology. Furthermore, we did not found correlations between regional white matter volumes and ventricular size.

Discussion

With regard to the whole group of schizophrenic patients we detected no significant differences between patients and controls concerning the volume of the white matter in the whole brain and in subregions according to Talairach coordinates. These results are in accordance with previous volumetric studies, which did not found alterations of white matter in schizophrenia [60, 61]. However, we detected changes in subgroups of schizophrenic patients: patients with a more pronounced negative symptomatology showed a significant reduction of white matter volume in the right parietal lobe. In addition, subjects with a positive family history of schizophrenia showed a reduction of right subcortical white matter.

As we included exclusively males and right-handed individuals we examined a homogeneous group with regard to gender and handedness. Both are known to have influence on brain morphology [8]. There is some indication that white matter changes are at least in part gender specific [56]. The fact that previous studies partly included females or left-handed subjects may explain some discrepancies in the results. It seems not probable that our results were due to technical reasons including different brain weight as the differences remained significant after correction the data for total brain volume.

Our result of white matter changes in subgroups of schizophrenic patients is consistent with previous finding of Paillere-Martinot et al. [44] and Wible et al. [58] who detected white matter changes in schizophrenic patients with a pronounced negative symptomatology. In addition, changes of the largest white matter fiber tract in humans, the corpus callosum were reported for patients with familial members affected with psychosis [39]. In accordance with

Table 3 Comparisons of white matter morphometric Talairach data between schizophrenic patients with low and high scores of *negative symptoms* (PANSS) and with and without a family history of schizophrenia, controlled for total brain volume

ROI white matter (ccm, mean ± SD)	Low negative symptoms (n = 22)	High negative symptoms (n = 28)	ANCOVA		No family history (n = 40)	Positive family history (n = 10)	ANCOVA	
			F value	Signif.			F value	Signif.
Total intracranial white matter	492.2 ± 41.6	469.7 ± 48.0	2.83	0.09	485.1 ± 45.4	457.9 ± 45.1	0.61	0.44
Left FL, white matter	92.7 ± 10.2	89.2 ± 9.9	0.70	0.40	91.5 ± 10.2	87.5 ± 9.5	0.00	0.99
Right FL, white matter	97.9 ± 8.8	93.0 ± 9.5	2.93	0.09	96.1 ± 9.6	91.2 ± 8.2	0.37	0.54
Left TL, white matter	39.1 ± 4.7	38.8 ± 4.9	0.14	0.71	39.2 ± 5.0	38.0 ± 3.8	0.06	0.81
Right TL, white matter	38.1 ± 4.1	37.9 ± 4.7	0.11	0.74	38.2 ± 4.6	37.1 ± 3.6	0.01	0.91
Left PL, white matter	62.1 ± 6.0	59.0 ± 7.8	1.81	0.18	61.1 ± 7.0	57.8 ± 7.6	0.01	0.90
Right PL, white matter	61.4 ± 6.1	56.7 ± 6.2	*9.35*	*0.004*	59.5 ± 6.2	56.0 ± 7.4	0.36	0.55
Left OL, white matter	29.9 ± 3.7	27.7 ± 5.3	1.67	0.20	29.2 ± 4.4	26.4 ± 5.7	0.82	0.36
Right OL, white matter	26.8 ± 3.8	24.2 ± 4.5	3.78	0.05	26.0 ± 3.9	22.8 ± 5.6	2.07	0.15
Subcortical white matter left	21.5 ± 2.5	21.0 ± 2.0	0.31	0.58	21.5 ± 2.1	20.0 ± 2.4	2.62	0.11
Subcortical white matter right	21.5 ± 2.3	21.4 ± 2.2	0.02	0.89	21.8 ± 2.2	19.78 ± 1.6	*5.44*	*0.02*

FL frontal lobe, *TL* temporal lobe, *PL* parietal lobe, *OL* occipital lobe, *ROI* region of interest, *Signif.* significance

Table 4 Comparisons of white matter morphometric Talairach data between schizophrenic patients with low and high scores of *positive symptoms* (PANSS), controlled for total brain volume

ROI white matter (ccm, mean ± SD)	Low positive symptoms (n = 27)	High positive symptoms (n = 23)	ANCOVA	
			F value	Signif.
Total intracranial white matter	481.4 ± 48.8	477.5 ± 44.1	0.06	0.81
Left FL, white matter	91.2 ± 10.5	90.1 ± 9.8	0.01	0.97
Right FL, white matter	96.3 ± 9.4	93.8 ± 9.2	0.63	0.43
Left TL, white matter	38.9 ± 4.1	39.0 ± 5.2	0.22	0.64
Right TL, white matter	38.2 ± 4.3	37.7 ± 4.6	0.01	0.92
Left PL, white matter	60.8 ± 7.5	59.9 ± 6.5	0.00	0.98
Right PL, white matter	58.4 ± 7.1	59.2 ± 60	1.68	0.20
Left OL, white matter	29.5 ± 5.2	27.7 ± 4.3	1.49	0.22
Right OL, white matter	25.1 ± 5.2	25.7 ± 3.4	1.16	0.28
Subcortical white matter left	20.8 ± 2.2	21.6 ± 2.3	0.22	0.64
Subcortical white matter right	21.3 ± 2.3	21.6 ± 2.4	0.01	0.92

FL frontal lobe, *TL* temporal lobe, *PL* parietal lobe, *OL* occipital lobe, *ROI* region of interest, *Signif.* significance

previous studies [44, 58] we detected no correlation with positive symptomatology.

In respect to our results it is of interest that also Wible et al. [58] reported volume reductions of white matter in the right hemisphere. The right hemisphere and the parietal cortex are part of the neural network for attention which is frequently disturbed in schizophrenia [7, 14, 15, 40]. Although a majority of studies point to alterations of the left hemisphere in schizophrenia [23, 37] disturbances of the right hemisphere were repeatedly detected by functional brain studies [5, 20, 52]. In a PET study, Potkin et al. [48] reported recently a decreased metabolism in the right hemisphere for schizophrenic subjects with negative symptomatology.

Our findings of white matter alterations in the parietal lobe of schizophrenic patients are supported by post-mortem studies: of special interest is the finding of Kirkpatrick et al. [29] who found an abnormal increased density of white matter cells (interstitial cells of the white matter, ICWMs) in the inferior parietal region in schizophrenic patients with deficit syndromes. Other post-mortem studies of schizophrenic brains detected alterations of synaptic proteins in the gray matter of the parietal cortex [10].

The application of magnetization transfer imaging (MTI) provided evidence for alterations in the parieto-occipital region in schizophrenia [18]. This novel MRI technique is supposed to be more sensitive to subtle or early neuropathological changes than conventional MRI. In addition, functional brain imaging studies showed alterations in the parietal lobe of schizophrenic patients. In a PET study by Lahti et al. [34] patients with primary negative symptoms showed a reduced parietal activation during a decision task. Reduction of cerebral blood flow in the parietal lobe of schizophrenic patients was detected by Andreasen et al. [4] and by Schultz et al. [49]. By application of fMRI methods abnormal parietal activations were reported for schizophrenic patients [13, 45].

Alterations of normal brain asymmetries of gray matter were frequently reported in schizophrenia (for example [9, 51], for review see [16, 21, 47]). In addition, studies using MRI volumetry and DTI detected asymmetries of the white matter [33, 56]. With respect to white matter volumes we detected no alterations of asymmetry coefficients in our sample of schizophrenic patients. Reasons for these apparent discrepancies could be that brain asymmetries may be more pronounced in the gray than in the white matter of schizophrenic patients, or that alterations of white matter asymmetry are restricted to female patients [56], which were not examined in our study.

A disarray of white matter fiber tracts but no volume reduction may exist in schizophrenia which could predispose for psychotic symptomatology. To examine this question the application of alternative techniques such as postmortem examinations, tensor imaging studies or voxel-based MRI analysis would be necessary which allow an examination of white matter fiber tracts with higher resolution than it is possible for conventional MRI techniques (see [1, 12, 55]). In addition, white matter disturbances could be caused by changes in neurotransmitter or lipid metabolism [6]. All these changes could produce alterations which would be beyond the detectability and threshold of macroscopic volumetric MRI examinations. It is of interest that in a study with DTI the authors reported that they did not found volume differences in white matter regions where they detected reduced fractional anisotropy [1]. Therefore, we could not exclude that more widespread changes of the white matter exist in schizophrenia. However, even by application of DTI not all studies detected alterations of white matter in schizophrenia [17].

In order to validate the hypothesis of a relationship between clinical symptomatology and white matter alterations future research should focus on clinical subgroups of schizophrenic patients. These could include patients with pronounced negative symptomatology or with positive family history for schizophrenia. Another clinical feature of interest could be aggressive behavior which was correlated with white matter changes [24]. In addition the combination

of different techniques could give new insights in pathology [32]. In this respect it would be of interest to examine brain regions which show white matter volume reduction with the recently established technique of DTI [25, 27, 31] in order to find out if there exists a disarray of white matter tracts in these regions.

In summary the results of our volumetric analyses are in accordance with the assumption that regional brain abnormalities in schizophrenia are restricted to clinical subgroups of schizophrenic patients. Therefore, differences in clinical symptomatology in the examined populations may be one reason for the inconsistencies of studies which previously examined white matter changes in schizophrenia.

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