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Corpus callosum size in schizophrenia – a magnetic resonance imaging analysis

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Abstract Previous MRI studies have shown differences in corpus callosum size between schizophrenic patients and controls. The corpus callosum (CC), as the main interhemispheric fiber tract, plays an important role in interhemispheric integration and communication. Though MRI studies suggest smaller CC in schizophrenia, there are still conflicting findings. Using in vivo magnetic resonance imaging, it was investigated whether the midsagittal area of CC differs between twenty-three right-handed male schizophrenic patients and twenty-three matched controls. Total CC area, five subregions of CC, total brain volume, gray and white matter were measured. No differences between schizophrenic patients and controls were found regarding all CC measurements, total brain volume, and gray matter tissue. However, a significant reduction of white matter tissue in the patient group emerged. There was no correlation between CC morphology and clinical variables such as age of onset, length of illness or symptom severity. Interestingly, five schizophrenic patients with a positive family history of schizophrenia showed significant reduction of the subregion C3, associated with a reduced total brain and gray and white matter volume. Significant reduction in the CC and its subregions was not confirmed in this group of patients with schizophrenia. In the subgroup of schizophrenic patients with a positive family history of schizophrenia, a significant reduction of the subregion corresponding to a part of the trunk of the CC was found.

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Introduction

In schizophrenia research, a growing body of evidence has provided support for the hypothesis that subtle neurodevelopmental disturbances, most likely of genetic origin, may play a pathogenetic role in schizophrenia. The most consistently replicated brain abnormality in schizophrenia is structural (Chua et al. 1995). A number of postmortem and structural in vivo imaging studies have clearly demonstrated structural brain changes in schizophrenia. The most consistent structural abnormality is lateral ventricle enlargement. There are still conflicting findings regarding other localized structural brain abnormalities which may be related to several factors, including clinical heterogenity within schizophrenia, measurement techniques, and methodological problems associated with the selection of controls (Chua et al. 1995, Lewis 1996).

Nevertheless, focal cortical brain reductions have pointed to the frontal lobes, prefrontal cortex, the temporal lobes, and limbic structures (Falkai et al. 1986, Dauphinais et al. 1990, Suddath et al. 1990, Barta et al. 1990, Shenton et al. 1992, Andreasen et al. 1994, Bilder et al. 1995). In this respect, one pathologic substrate of schizophrenia is discussed to be a cortical fronto-temporal disconnection syndrome with aberrant disorganization and connection of neocortical association regions responsible for higher cognitive functions.

A vivid interest in the corpus callosum (CC), the major interhemispheric commissure between neocortical association regions, has been incited by the observation that split-brain patients occasionally have quasi psychotic behavior (David 1993). Its fibers arise predominantly from larger pyramidal neurons in cortical layer III and callosal transfer plays an important role in interhemispheric communication and integration. The functional importance was highlighted by the split-brain research of Sperry (1982).

Early postmortem studies described an increase in the average width of the callosal trunk in ten chronic schizophrenics (Rosenthal and Bigelow 1972, Bigelow et al. 1983). In a seperate post mortem investigation, more severe gliosis in the callosi of late onset schizophrenic patients than in early onset schizophrenics or in the control group was described (Nashrallah et al. 1983 a). A recent postmortem investigation revealed a reduction in the total number of fibers in all regions of the corpus callosum except the rostrum in female schizophrenic patients (Highley et al. 1999).

To date, there have been 23 structural imaging studies with Magnetic Resonance Imaging (MRI) on the morphology of CC in patients with schizophrenia (Table 1).

Nashrallah replicated the post mortem results with a significantly increased size of total callosal area, callosal anterior/midline width, and callosal-brain ratio (CBR) in the schizophrenic groups. However, the data revealed important differences when gender was considered. Schizophrenic men were found not to differ from controls in callosal thickness whereas schizophrenic women were found to have a highly significant increase in callosal middle and anterior thickness compared to control women (Nashrallah et al. 1986).

Other studies confirmed the sex differences of callosal thickness in schizophrenic patients. While male healthy controls had thicker CC than female healthy controls, fe-

Table 1 Published MRI studies of the corpus callosum (CC) in schizophrenia (SZ)

Source, y	Patients with SZ		Control subjects		MRI scanning	Diag. criteria	Variables (*)
	Total no. SZ (m/f)	Mean Age, y	Total no. (m/f)	Mean Age, y			
Smith et al. 1984	9/–	27.4	4/1	38.2	0.3 Tesla	RDC	TCA ratio
Mathew et al. 1985	11/7	38.4	10/8	38.6	0.5 Tesla	DSM III	TCA, CCL
Smith et al. 1985	23	31.4	8/9	31.5	0.3 Tesla	RDC	CBR
Nahsrallah et al. 1986	28/10	33.2	21/20	28.0	0.5 Tesla	DSM III	TCA, 4 subregions CCL, CCW, CBR
Kelsoe et al. 1988	22/5	29.1	10/4	31.1	0.5 Tesla	DSM III	TCA, CCW 3 subregions
Rossi et al. 1988	15/–	33.2	15/–	32.6	0.5 Tesla	DSM III	TCA, CCL, CBR
Uematsu et al. 1988	40/–	32.2	17/–	31.5	0.5 Tesla	DSM III	TCA, 3 subregions CCL, CBR, $CCW_{max/min}$
Rossi et al. 1989	8/4	31.5	8/4	30.6	0.5 Tesla	DSM III	TCA, CCL, CBR
Stratta et al. 1989	15/5	33.2	15/5	32.3	0.5 Tesla	DSM III	TCA, CBR
Hauser et al. 1989	11/13	33.0	14/11	37.0	0.5 Tesla	DSM III	TCA, 4 subregions CCL, CCW, CBR
Casanova et al. 1990	12 (monozy. twins, discordant for SZ, affected twin)	32.6	12 unaffected twin		1.5 Tesla	DSM III-R	TCA, CCL, CCW 3 subregions
Raine et al. 1990	9/6	34.0	9/9	34.1	0.1 Tesla	DSM III-R	TCA, CCL, CCW
Günther et al. 1991	19/12	32.3	19/12	32.3	0.5 Tesla	DSM III	TCA, CBR
Woodruff et al. 1993	23/7	19.9	34/10	–	1.5 Tesla	DSM III	TCA, CCL 4 subregions, CCW, CBR
Keshavan et al. 1993	8 unmedicated	24.9	–	–	1.5 Tesla	DSM III	TCA, 4 subregions
Colombo et al. 1993	13/6	25.9	9/6	29.6	0.5 Tesla	DSM III	TCA, CCL 3 subregions
Hoff et al. 1994	39/23	24.9/29.1	20/15	27.9/27.3	1.5 Tesla	DSM III-R	TCA, CBR, 5 subregions
DeLisi et al. 1995	15/5 Follow-up of 2, 3 and 4 years	27.3	3/2	28.2	1.5 Tesla	DSM III-R	TCA, CBR
DeLisi et al. 1997	32/18 Follow-up of 4 years	27.4	12/8	26.5	1.5 Tesla	DSM III-R	TCA, 5 subregions
Woodruff et al. 1997	42/–	32.4	43/–	30.2	1.5 Tesla	DSM III-R	TCA, 4 subregions
Jacobsen et al. 1997	13/12	13.9	31/24	14.1	1.5 Tesla	DSM III-R	TCA, 7 subregions, CBR
Tibbo et al. 1998	79/–	28.9	65/–	26.9	1.5 Tesla	DSM III-R	TCA
DeQuardo et al. 1999	13/7	23.9	15/7	25.0	1.5 Tesla	DSM III-R	Landmark-based shape analysis

(*): TCA = Total Callosal Area; CCL = Corpus Callosum Length; CBR = Callosal-Brain Ratio; CCW = Corpus Callosum Width

male schizophrenics showed a thicker posterior callosum than male schizophrenics (Raine et al. 1990, Colombo et al. 1993). However, Hoff described a smaller total callosal area in first-episode schizophrenic females (Hoff et al. 1994).

There are still conflicting findings concerning increase (Nashrallah et al. 1986, Uematsu and Kaiya 1988) or decrease of total callosal area and its subregions (Woodruff et al. 1993, Rossi et al. 1988, 1989, Stratta et al. 1989, Tibbo et al. 1998), and the majority failed to demonstrate significant changes of CC size in schizophrenia (Smith et al. 1984, 1985, Mathew and Partain 1985, Kelsoe et al. 1988, Hauser et al. 1989, Raine et al. 1990, Casanova et al. 1990, Colombo et al. 1994, Woodruff et al. 1997). In addition, reports of regional patterns of callosal volume change have not been consistent due to the wide range of different measurement methods used (Tibbo et al. 1998).

Correlations between CC size and clinical features showed larger collosal areas for patients with poor outcome (Uematsu and Kaiya 1988) or increased CBR for patients with mainly positive symptoms (Günther et al. 1991). Other findings support the hypothesis that anterior CC area (Woodruff et al. 1997) or decrement of total CC size is related to negative symptoms (Tibbo et al. 1998). Recent investigations of childhood onset schizophrenic patients describe a larger total CC area in the patient group (Jacobsen et al. 1997). A landmark-based shape analysis with image averaging of first-episode schizophrenic patients demonstrated significant shape deformation differences involving primarily the posterior corpus callosum between patients and controls (DeQuardo et al. 1999).

Recently, remarkable follow-up studies over an observation period of 4 years showed a significant reduction of the isthmus of CC between schizophrenics and controls (DeLisi et al. 1995, DeLisi et al. 1997).

In this study, we measured callosal size in 23 male right-handed patients with schizophrenia compared with 23 age- and educational achievement-matched volunteers using a new method for defining collosal subregions that is accurate and reproducible (Hampel et al. 1998). We predicted that CC size would be reduced in schizophrenic right-handed male patients.

Subjects and methods

Subjects

The study comprised twenty-three male right-handed schizophrenic patients (SZ) (age 19–47 years, mean age 28.6, SD 7.7) from the psychiatric hospital of the Ludwig-Maximilians University in Munich. Psychiatric diagnoses were determined by the consensus of at least two psychiatrists who concurred on a diagnosis of ICD-10 and DSM IV. Demographic information and past and current symptom history as family history of all subjects were obtained using a semistructured interview that embedded a variety of measures which were relevant to the study. Handedness was determined by the Edinburgh inventory (Oldfield et al. 1971). All patients had received neuroleptic medications. The illness duration ranged from 6 months to 23 years (mean illness duration 72.0 months; SD 83.1) and the number of hospitalizations ranged from 2 to 14. Clinical variables were documented for all patients (Phillips-Scale, Brief Psychiatric Rating Scale, Positive and Negative Syndrome Scale, Scale for Assessment of Negative Symptoms, Extrapyramidal-Scale). Five of twenty-three patients had a positive family history with one first-degree relative with schizophrenia who had been treated in the hospital.

For comparison, twenty-three healthy right-handed unmedicated male volunteers (HC), recruited from the community (age 19–47 years, mean age 28.3; SD 7.8) and matched for age and educational achievement, underwent the same procedure. They did not differ from the schizophrenic group according to age, verbal IQ, height, and alcohol consumption. Individual age pairings were such that the widest age pairing disparity was 3 years (2 pairs). However, weight differed significantly between the groups (Table 2).

Neither the healthy controls nor their first or second relatives had a history of neurological or mental illness. Exclusion criteria for the patients and the controls were head injury in the past, cortisol or benzodiazepine medication in the last 3 months, neurological diseases, comorbidity with other mental illnesses or electroconvulsive therapy previously. After complete description of the study of the patients and control subjects, written informed consent was obtained. The study was approved by the local ethics committee and in accordance to the ethical standards laid down in the 1964 Declaration of Helsinki.

Table 2 Demographic and clinical variables of schizophrenic patients (SZ) and healthy controls (HC)

Variables	SZ	HC	p Value
Age (years)	28.6 (±7.7)	28.3 (±7.8)	0.91
Height (cm)	1.78 (±5.8)	1.80 (±7.1)	0.39
Weight (kg)	80.2 (+13.8)	72.3 (±8.9)	0.026*
Alcohol consumption (g/daily)	21.9 (±4.2)	19.9 (±5.4)	0.82
Age of Onset	23.13 (±5.7)		
Duration of illness (months)	72.09 (±83.07)		
Verbal IQ	109.7 (±15.1)	116.8 (±8.1)	0.054
BPRS score	42.3 (±10.9)	–	
PANSS	12.3 (±5.1)	–	
Positive score			
PANSS	25.8 (±6.9)	–	
Negative score			
PANSS total	38.3 (±9.6)	–	
SANS score	53.5 (±21.2)		
Phillips scale	5.9 (±3.5)		
EPS scale	0.26 (±0.45)	–	

MRI procedures

MRI images were obtained (1.5 Tesla Magnetom Vision, Siemens) using 3 coronal T2- and protondensity-weighted Dual-Echo-Sequences (TR 3710 ms/TE 22/90 ms; total aquisition time: 9 minutes, number of aquisitions: 1; FOV 230 mm; matrix 240 × 256, slice thickness 3 mm) and a 3D-MPRAGE sequence (TR/TE 11.6 ms/4.9 ms; total aquisition time: 8 minutes, number of acquisitions: 1; FOV 230 mm, matrix 240 × 256, slice thickness 1.5 mm).

Further image processing was performed with the software program BRAINS (Brain Research: Analysis of Images, Networks, and Systems; developed by Nancy Andreasen et al.) (Andreasen et al. 1992, 1993) with size reduction from 16 to 8 bit and transformation to a uniform matrix of 256 × 256 on 192 slices of 1.5 mm slice thickness using the commercial software package Analyze (ANALYZE, Biomedical Imaging Resource, Mayo Foundation, Rochester, Minn). To obtain scans on which no callosal structure deviated from midline, all datasets were realigned and resampled three-dimensionally according to the coordinates of Talairach with the software program BRAINS. The same software package (BRAINS) was used for volumetric measurements of total brain volume, total gray and white matter volume in cm^3.

Callosal area measurements

Areas of the total CC and 5 callosal subregions were measured by 1 rater, who was unaware of the subject's diagnosis, on a Silicon Graphics (SGI) workstation on the sagittal T1-weighted MRI slices that best represented the midsagittal section (Hampel et al. 1998). This slice was chosen using anatomical landmarks in a hierarchial order (Talairach et al. 1993). First, slices were selected which showed no or only minimal white matter in the cortical mantle surrounding the CC. If more than 1 slice fulfilled this criterion, the medial thalamic nuclei served as an anatomical landmark of a second order. The selected slice then showed the interthalamic adhesion connecting the left and the right medial thalamic nuclei, or only the smallest size of the thalamus of either one or the other side. The transparent septum and the cerebral aqueduct were used in the third step to confirm the selection when 2 slices remained which showed a similar amount of thalamic substance.

After determining the midsagittal slice, the total callosal area was measured on a SGI workstation by manually tracing the outer edge of the CC on this slice using the software package Analyze.

The areas of 5 callosal subregions were outlined in 2 subsequent steps (Fig. 1). First, a rectangle was placed over the CC. The lower side of the rectangle cut the 2 lowest points of the anterior and the posterior parts of the CC tangentially. The rectangle's length was determined by 2 lines perpendicular to this lower side which cut the most anterior and the most posterior points of the CC. In the second step, a radial divider with 10 rays equidistant from each other was placed at the midpoint on the lower side of the rectangle. Its 4 upper rays divided the CC into 5 subregions. The number of pixels within each region was summed automatically and multiplied by the pixel size to obtain absolute values in millimeters squared for the areas of total CC and the 5 subregions (labeled C1–C5 in a rostral-occipital direction).

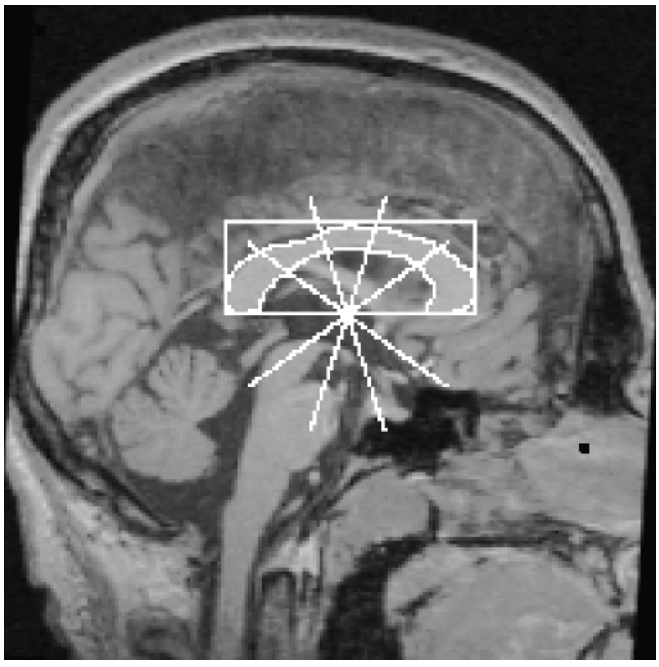

Fig. 1 Corpus callosum measurement: The outer edge of the Corpus callosum was traced in the midsaggital area. After that, the areas of five callosal subregions were outlined in two steps. First, a rectangle was placed over the CC. The lower side of the rectangle cut the two lowest points of the anterior and the posterior parts of the CC tangentially. In the second step, a radial divider with ten rays equidistant from each other was placed at the midpoint on the lower side of the rectangle. Its four upper rays divided the CC into five subregions

Interrater and intrarater reliability of the CC measurement

To assess interrater reliability, 2 independent researchers, who were unaware of the diagnosis, measured the total callosal area in 10 randomly chosen subjects. To evaluate intrarater reliability, 1 researcher, who was also unaware of the diagnosis, twice measured the total callosal area and areas of the callosal subregions in 10 randomly chosen subjects.

The intraclass correlation coefficient for the total callosal area was 0.98 for the interrater and 0.97 for the intrarater reliability; for regional CC measurements, intrarater reliability ranged from 0.94 for the subregion C1 to 0.91 for the subregion C5.

Statistics

Exploratory data analysis revealed normally distributed morphometric measurements in both groups, without any outliers, and the variance did not differ between the groups. Differences of total brain volume, gray and white matter tissue, and total CC area between the groups were tested with Student's t-test. ANOVA for repeated measurements was used to assess group differences in the distribution of callosal subregions, with the groups as the between-subjects factor and the five callosal subregions as the within-subject factor. Differences between family history positive patients and family history negative patients as well as to their matched controls were calculated using the Wilcoxon rank-sum test. Correlations regarding morphometric measurements and psychopathological scales were determined by using the Spearman rank-order correlation. Correlations with age, age of onset, illness duration, height, weight and alcohol consumption were tested with the Pearson product-moment correlation.

Results

Corpus callosum measurements and brain volumetry

Total cranial volume was smaller for schizophrenic patients than for healthy controls, but did not reach statistical significance. Total volume of gray matter did not reveal differences between the group of schizophrenic patients and the controls. The total volume of white matter was significantly smaller in schizophrenics than in healthy controls ($p = 0.012$).

The absolute mean total callosal area in millimeters squared did not differ in the group with SZ than in the control group ($p = 0.75$). A repeated-measures ANOVA did not reveal any significant difference in the distribution of callosal area between patients with SZ and the control group ($p = 0.53$). Areas of the 5 callosal subregions were compared separately between the group with schizophrenia and the control group. None of the subregions differed significantly between the two groups (Table 3). Corpus callosum and the subregions in relation to the total brain volume were not significantly different between schizophrenic patients and healthy controls.

Table 3 Measurements of total cranial volume (cm^3), total gray and white matter (cm^3), and cross-sectional areas of corpus callosum (CC) and its subregions (mm^2) in patients with schizophrenia (SZ) and control subjects (HC)

Region	SZ (N = 23)	HC (N = 23)	p Value
Total cran. volume	1286.1 (±103.9)	1337.7 (±104.7)	0.19
Total gray matter	805.6 (±65.9)	818.1 (+67.1)	0.53
Total white matter	480.5 (±45.6)	519.6 (±55.4)	0.012*
Total CC area	605.3 (±94.2)	596.4 (±93.5)	0.75
C1	164.3 (±20.9)	166.5 (±30.8)	0.78
C2	90.6 (±21.9)	92.5 (±20.2)	0.75
C3	75.7 (±19.9)	76.5 (±13.3)	0.87
C4	76.4 (±20.9)	73.0 (±22.5)	0.59
C5	164.1 (±24.9)	157.6 (±21.6)	0.35

Corpus callosum and age

The total callosal area did not correlate with age either in the patients with schizophrenia ($r = –0.088$; $p = 0.69$) or in the control group ($r = 0.024$; $p = 0.91$). No other significant correlations were found for the subregions in both groups.

Corpus callosum and clinical variables

Total CC size and its subregions did not correlate significantly with age of onset, duration of illness, or clinical psychopathological scales in the patient group. No significant correlations between negative symptoms from the SANS (Scale of Assessment of Negative Symptoms) and from the PANSS (Positive and Negative Symptom Scale) and total CC size or CC subregions were found.

Corpus callosum, brain volumetry, and family history

Family history positive (Fam Pos) schizophrenic patients ($N = 5$) had a significantly smaller sized callosal subregion C3 than family history negative (Fam Neg) schizophrenic patients. There was a trend for smaller areas of C2, C4, and total CC (Table 4). Total CC size and its subregions were not significantly correlated with age of onset, duration of illness or clinical psychopathological scales in the patient group with positive family history.

Furthermore, total brain volume (Fam Pos = 1208.0 cm^3 ± 64.5 cm^3 vs. Fam Neg = 1307.9 cm^3 ± 103.5 cm^3) ($p = 0.024$), total gray (Fam Pos = 766.5 cm^3 ± 35.3 cm^3 vs. Fam Neg = 816.5 cm^3 ± 69.0 cm^3) ($p = 0.045$) and white matter (Fam Pos = 441.6 cm^3 ± 35.0 cm^3 vs Fam Neg = 491.4 cm^3 ± 42.9 cm^3) ($p = 0.029$) were significantly smaller for family history positive patients than for family history negative patients.

Total CC size and all subregions did not differ between the family negative patients and their matched controls. Significant differences in subregion C3 were confirmed between the family positive patients and their matched controls. There were no significant influences from demographic and clinical variables in the family negative and family positive patients.

Table 4 Measurements of cross-sectional areas of corpus callosum (CC) (mm^2) and its five subregions (mm^2) in schizophrenic patients (SZ) with positive family history (Fam Pos) and patients with negative family history (Fam Neg)

Region	Fam Pos (SZ) (N = 5)	Fam Neg (SZ) (N = 18)	P Value*
Total CC area	547.1 (±84.6)	621.5 (±92.4)	0.16
C1	159.4 (±9.9)	165.8 (±23.2)	0.65
C2	77.8 (±16.9)	94.2 (±94.2)	0.13
C3	60.3 (±10.9)	80.0 (±20.0)	0.015*
C4	64.8 (±16.0)	79.7 (±21.4)	0.19
C5	154.8 (±33.2)	166.7 (±22.7)	0.310

* Tested with Wilcoxon rank-sum test

Discussion

This study compared the total CC area and its subregions in male schizophrenics to healthy male controls using a new accurate and reproducible method for defining five callosal subregions (Hampel et al. 1998). As any variation in head position in the scanner may lead to a great variability in subsequent measurements of the CC, standard realignment of the brains was performed for all subjects to a standard position. Differences among previous studies of CC measurement may be related to various factors, including differences in age (Aboitz et al. 1996), gender (Steinmetz et al. 1995), handedness (Witelson 1989), and the employment of medical staff as a control group. Therefore, our study design tried to avoid these confounders. Our current findings support previous studies which did not show callosal area reduction in patients with schizophrenia compared to controls (Raine et al. 1990, Smith et al. 1984, 1985, Mathew and Partain 1985, Colombo et al. 1994, Kelsoe et al. 1988, Hauser et al. 1989, Casanova et al. 1990, Woodruff et al. 1997) but are in contrast to others (Nashrallah et al. 1986, Uematsu and Kaiya 1988; Rossi et al. 1988, 1989, Stratta et al. 1989, Woodruff et al. 1993, Tibbo et al. 1998).

However, our measurements of total brain, gray and white matter volume demonstrated a significant decrease in overall brain white matter tissue volume in schizophrenics compared to controls. Nevertheless, this decrease did not lead to an overall brain volume reduction. Structural schizophrenia research has focused on gray matter volume measurements and segmentation studies suggest that gray matter is reduced in schizophrenic patients. However, some but not all studies have demonstrated grey matter volume reductions in schizophrenic patients. In addition, there are other questions left unanswered, such as whether there may be alterations of white matter tissue. Axonal loss in the white matter surrounding the inferior horns of the lateral ventricles might account for the consistently reported increase in ventricular volume in schizophrenia. Additionally, studies of white matter reduction may be of special interest because alterations of neurons may influence white matter to a higher extent than gray matter volume. In this respect, white matter atrophy could be an indirect indicator of nerve cell loss since the volume of nerve cell is much smaller than its myelinated fiber (Meier-Ruge et al. 1992). This assumption is supported by a post mortem study on brain atrophy during normal aging. In this morphometric investigation, a mean difference of 16–20% was found between the oldest and the youngest age groups of brains studied, representing white matter atrophy in the former group. In contrast, the cortex of the corresponding gyri showed a difference of less than 6% between the groups (Meier-Ruge et al. 1992).

In line with previous studies, neither total CC size nor its five subregions were significantly correlated with age in either group. Moreover, our study failed to demonstrate any correlation between clinical variables and size of CC in male schizophrenic patients. Very few studies have addressed the association between morphological changes in the CC and correlation to clinical variables (Tibbo et al. 1998), and previous reports on this topic have not been consistent. While Uematsu and Kaiya (1988) described significantly larger callosal areas for male patients with poor outcome, Günther et al. (1991) demonstrated smaller size of CC for patients with mainly negative symptoms. A recent study in male subjects, the largest sample to date, suggests in line with Günther the inverse correlation between size of CC and negative symptoms (Tibbo et al. 1998).

Interestingly, the present results suggest a significant reduction in the callosal subregion C3 in a subgroup of five schizophrenic male patients with a family history of schizophrenia. Moreover, adjacent callosal subareas C2 and C4 tended to be smaller. This was associated with a significant decrease in overall brain volume and gray and white matter tissue in the patient group. Family history was obtained using a semistructured interview that embedded a variety of measures relevant to the study. Patients were classified as family history positive if a first or second degree relative had been hospitalized for schizophrenia. Patients not meeting this criterion were classified as family history negative. In our study, all five patients had a first degree relative hospitalized for schizophrenia. Possible limitations, due to the lack of information obtained from a face-to-face interview with the patient's mother or another close family member have to be considered. On the other hand, all family history information of the patient group was controlled from all clinical documents available.

Although the conclusions can only be tentative due to the limited number of subjects involved, the pathological implication of decreased subregion C3 in a subgroup of schizophrenic patients with a family positive history deserves discussion.

First, classification of patients on the basis of family history of psychiatric illness has been proposed as a strategy to examine characteristics of patients. The existence of an important genetic influence on the etiology of schizophrenia has been established from family, twin, and adoption studies (Corrigal and Murray 1994). However,

studies of brain morphology in familial and nonfamilial patients have been inconsistent. Imaging studies most commonly assessed cerebral lateral ventricular size. A higher incidence of ventricular enlargement size has been described in schizophrenic patients without a family history of schizophrenia (Turner et al. 1986, Silverman et al. 1998) but others have noted larger ventricular size in patients with family positive history (Nashrallah et al. 1983b, Kaiya et al. 1989) or no differences between the groups (Farmer et al. 1987, Schwarzkopf et al. 1991). Uematsu et al. (1988) found that length of corpus callosum was correlated with positive family history in male schizophrenic patients.

Second, the area C3 represents, together with the subareas C2 and C4, the trunk of the CC. Interestingly, during normal aging the anterior part of the trunk of the corpus callosum is significantly decreased (Weis et al. 1993). Intraoperative electrophysiologic stimulation of the CC in patients with epilepsy has shown that the rostrum, the genu, and the rostral part of the truncus project mainly into the frontal and posterotemporal lobe (Yu-ling et al. 1991). Therefore, local size decreased in this area may suggest alterations of frontal and temporal interhemispheric fiber systems in the subgroup of male schizophrenic patients with a family history of schizophrenia.

In conclusion, the present study has shown that there is a decrease of the subregion C3, corresponding to the trunk, in a subgroup of male schizophrenics with a family history of schizophrenia. Additionally, a reduction of overall brain volume and the tissues of gray and white matter was seen in this subgroup. Clinical correlations between the morphometric data and the family positive schizophrenic subgroup could not be demonstrated. Nevertheless, these results have to be viewed with caution due to the limited sample size of this subgroup, and further evaluations are needed. Still, few studies have addressed the association between local morphological changes and genetically determined familial schizophrenic subgroups. Though this study failed to demonstrate CC differences for the whole schizophrenic group compared to controls, there was a significant reduction of overall white matter size in brain measurements in schizophrenic patients.

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