Corpus callosum in first-episode patients with schizophrenia – a magnetic resonance imaging study

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ABSTRACT

Background. Morphometric studies on the corpus callosum (CC) in schizophrenia have yielded contradictory results. The aim of the present study was to investigate magnetic resonance imaging (MRI) abnormalities of the CC in first-episode patients with schizophrenic psychoses.

Method. We assessed volumetric MRI in 31 patients with diagnoses of schizophrenia, schizophréniform or schizoaffective disorder (DSM-IV) and a maximum exposure to neuroleptics of 2 weeks. As a control group, 12 healthy age- and sex-matched individuals were included in the study. A whole body scanner at 1.5 Tesla was used to obtain 3D T1- and T2-weighted MR datasets. The data were evaluated semi-automatically (intracranial volume, total brain volume) and manually (CC) with the software NMRwin.

Results. Patients had smaller CC and CC subdivisions than controls. Schizophrenic and unaffected women exhibited larger total CC and rostral subdivisions than men in both groups. Handedness did not exert an influence.

Conclusions. Our findings are in line with other in vivo morphometric studies on the CC in schizophrenia. The larger CC area in women may reflect general gender-related differences in CC size as described in healthy individuals.

INTRODUCTION

A vast body of neuroimaging research has established evidence for the presence of morphological brain pathology in schizophrenia (see McCarley et al. 1999 for a review). The corpus callosum (CC), the major interhemispheric commissure, is one of the brain regions that is likely to be affected (see Woodruff et al. 1995 for a review). It is the largest white-matter fibre tract and provides the majority of axonal transmissions between the neocortical association regions of the hemispheres. Abnormal interhemispheric connectivity in schizophrenia is likely, given the evidence for an alteration of brain asymmetry (Crow et al. 1989; Crow, 1993, 1998; Bilder et al. 1994; Falkai et al. 1995; DeLisi et al. 1997). Focal disruption of commissural connectivity is suggested by a recent diffusion tensor imaging study (Foong et al. 2000).

In vivo MRI studies have addressed the CC in schizophrenia. However, the diversity of results has defied clear-cut interpretations – which is not surprising given the fact that even in healthy individuals there are differences in brain asymmetry, fibre composition and connectivity of the CC, largely related to gender and lateralization (Flor-Henry, 1978; McGlone, 1980; Aboitiz et al. 1992a, 1996). Individual and regional differences of the human CC encompass the degree of myelination and the size as well as the density and the number of CC fibres with fibre numbers varying up to more than twofold. MRI studies have also revealed a decrease of CC area with ageing in healthy individuals (Weis et al. 1993).
With respect to schizophrenia, most studies report a smaller CC or a smaller CC to brain ratio for schizophrenic patients than for control subjects (Rossi et al. 1989; Stratta et al. 1989; Woodruff et al. 1993; Chua et al. 2000; Rossell et al. 2001), or smaller parts of the CC (DeQuardo et al. 1996; Downhill et al. 2000). To our knowledge, only two groups have, so far, looked at first-episode patients. They described gender differences in patients and controls (Hoff et al. 1994) and shape deformations in patients (DeQuardo et al. 1999).

We designed a prospective study to assess CC size in individuals with first-episode schizophrenia. Our goal was to examine a relatively homogenous population, namely previously untreated schizophrenic patients or patients with a maximum exposure to neuroleptic medication of 2 weeks. From the literature review we hypothesized that: (i) schizophrenic patients had smaller CC sizes than healthy controls; and that (ii) women had larger CC than men.

METHOD

Patients and control subjects

Thirty-one patients (17 female, 14 male, age 26.4±6.5 years) in the acute phase of their first psychotic episode, necessitating hospital admission, and 12 healthy, age- and sex-matched controls (six female, six male, age 25.8±2.7 years) were consecutively admitted into the study. MRI scans were obtained at the German Cancer Research Centre. Apart from this, the study was performed on one of the acute wards of the Psychiatric Hospital of the University of Heidelberg. It was approved by the ethics committee of the Medical Faculty of the University of Heidelberg.

All patients and controls were Caucasians and had no lifetime history of exposure to neuroleptic medication of more than 2 weeks. Patients with a past history of or a concomitant neurological or severe medical disorder, persistent or severe substance abuse were excluded. Patients met diagnostic criteria for schizophrenia, schizoaffective or schizotypal disorder according to DSM-IV (American Psychiatric Association, 1994). Initial treatment consisted of butyrophenones such as benperidol in combination with biperiden; low-potency neuroleptics or benzodiazepines were administered as needed.

In clinical non-responders or patients who developed extrapyramidal side effects treatment was continued with the atypical neuroleptics clozapine, olanzapine, or risperidone, respectively.

Clinical assessment

Diagnoses were made with the Structured Clinical Interview for DSM-IV (SCID) (Wittchen et al. 1997). Psychopathological symptoms were rated on the Positive and Negative Syndrome Scale (PANSS) (Kay et al. 1987) on three occasions, namely admission to the hospital, seventh day of treatment, and after remission of the acute illness. Following previous studies of our group (Schröder et al. 1992, 1993) the latter was defined as the day of discharge or transfer to the rehabilitation ward. Side-effects were documented on the scales by Simpson & Angus (1979), Barnes (1989) and on the Abnormal Involuntary Movement Scale (AIMS) (National Institute of Mental Health, 1976). The Strauss–Carpenter–Scale (SCS) (Strauss & Carpenter, 1974) was used to assess predictors of outcome. Handedness of patients and controls were assessed with the Edinburgh Inventory (Oldfield, 1971). All ratings were performed by two raters who had undergone formal training.

Radiological assessment

Magnetic resonance imaging was performed as part of the diagnostic work-up required for a first onset of a psychiatric disease. With a 1.5-T whole body scanner (Magnetom Vision, Siemens Med. Systems, Germany) equipped with a standard head coil two 3D image sets of the brain were acquired for all subjects: first a set of T1-weighted images providing a good differentiation between the CC and the adjacent brain tissue as well as between the grey and white matter; and secondly a set of T2-weighted images providing differentiation between tissue and cerebrospinal fluid. A three-dimensional MPRAGE sequence (TE/TR/T1/α = 10 ms/4 ms/300 ms/12°) (Mugler & Brookeman, 1990) was used for the T1 and a three-dimensional DESS sequence (TE/TR/α = 9 ms/25 ms/35°) (Hardy et al. 1996) for the T2-weighted image data cubes. Both 3D image sets had an inplane resolution of 1.1 x 1.1 mm² and 128 3D-partitions of 1.8 mm thickness, resulting in a volume resolution of 2.178 mm³. Sagittal image sets were obtained.
in 30 cases (22 patients and eight controls) and coronal image in 13 cases (nine patients and four controls). Acquisition direction was changed during the study to allow for better analysis of other structures such as temporal lobe, amygdala and hippocampus. Head position was standardized. The total scan time was approximately 20 min per patient.

**Corpus callosum measurement**

Coronal image cubes were transformed into sagittal images prior to analysis. CC measurements were performed on a Pentium personal computer using the manual segmentation function of the software NMRWin. This requires the operator to define an exact region of interest (ROI) along the border lines of the structure to be analysed, where each ROI has a colour assigned to a specific structure. Detailed functions of the software NMRWin have been described elsewhere (Friedlinger et al. 1995). The size of the CC was sampled on the mid-sagittal slice and the four adjacent para-sagittal slices, each with a slice thickness of 1·8 mm. The mid-sagittal slice was chosen on the basis of the following criteria: (1) clearest visualization of the CC; (2) smallest dimension of the ventriculoseptal region; (3) minimal inclusion of white matter adjacent to the interhemispheric sulcus. Following selection of the mid-sagittal slice, the two adjacent left and right para-sagittal slices were also selected for analysis. Thus, we used those five slices of the CC that allowed the clearest demarcation from adjacent brain tissue. For the previously coronal image cubes the slice thickness amounted to 1·0 mm instead of 1·8 mm. Therefore, in addition to the mid-sagittal slice, two out of four adjacent left and right para-sagittal slices were measured choosing every second slice. The total width of the analysed region amounted to 9 mm (9 × 1·0 mm) as was the case for the 1·8 mm slices (5 × 1·8 mm). The area of the CC and its subsections were traced manually on each of the five slices separately by the same rater who was blind to diagnoses. Measurements were carried out using a modified version of the protocol described by Weis et al. (1991). Briefly, a horizontal line was drawn from the most anterior to the most posterior point of the CC. Subsequently, six vertical lines of equal distance were constructed perpendicular to the horizontal line (see Fig. 1). These lines dissected the CC into five subsections called CC1–CC5, where CC1 represents the most rostral part and CC5 the most caudal part of the structure. The resulting subsections correspond approximately to five anatomical subdivisions (CC1, rostrum and genu; CC2, rostral body; CC3, midbody; CC4, isthmus; CC5, splenium). The total callosal size was calculated by adding up the values for the five subsections for each slice separately. In order to address the potential impact of head-position-related variance, the corresponding areas of the five chosen slices were averaged before entering into the analysis following a suggestion by Coffman et al. (1989). To achieve a measure of test–retest reliability, 20 randomly selected scans were measured twice by the same rater, yielding an intra-class correlation of $r > 0·99$, $P < 0·0001$.

**Volumetric measurement**

Volumetric measurements of the total brain volume (TBV) and the intracranial volume (ICV) were also performed using the software NMRWin. Method and proceedings have been described elsewhere (Pantel et al. 1997, 1999).

**Data analyses**

Demographic and clinical data of patients and controls were compared by calculating chi-square tests and analyses of variance. Treatment response was defined as the percentage of reduction of PANSS scores between admission and remission. For all morphometric data, namely total CC, CC substructures and TBV, analyses of variance (ANCOVA) were performed with ICV serving as a covariate to correct for interindividual differences in head size. Sex served as an additional independent variable. Main effects were calculated for diagnosis and gender, respectively, as well as interactions between these variables. To assess possible relationships between symptomatology and the CC and its subdivisions, Pearson correlation coefficients were determined. All analyses were performed with SPSS for Windows (SPSS Inc., 1999).
RESULTS
Clinical variables
Patients with first-episode schizophrenia did not differ significantly from healthy controls regarding age, gender and handedness. All patients and all but one control were predominantly righthanders.

Within the patient group the following diagnoses were ascertained: schizophreniform disorder ($N=9$), schizophrenia ($N=18$), schizoaffective disorder ($N=3$), psychosis NOS ($N=1$). Table 1 gives the clinical measures of the patient group. Patients exhibited high scores on the SCS, which predicts favourable outcome. Their PANSS scores amounted to 111 (range 97, 73–170) on admission and to 49 (range 54, 33–87) on remission, thus treatment response was 53.2% ($\pm$ 12.9) within 42.5 days ($\pm$ 25.1) of hospital treatment. Side-effects of medication were negligible.

Morphometric data
Total brain volume
The ANCOVA for TBV revealed a significant effect for diagnosis ($F=11.45$, df = 1, $P < 0.005$), indicating that patients had smaller TBVs than controls after correction for interindividual differences in head size by introduction of ICV as a covariate.
Corpus callosum

Significant effects for diagnosis – with patients exhibiting smaller areas than controls – were detected with respect to the total CC ($F = 8.02$, df = 1, $P < 0.01$) as well as to the subdivisions CC1 ($F = 5.41$, df = 1, $P < 0.05$), CC2 ($F = 7.25$, df = 1, $P < 0.05$), CC3 ($F = 9.86$, df = 1, $P < 0.005$), CC4 ($F = 6.05$, df = 1, $P < 0.05$), CC5 ($F = 6.02$, df = 1, $P < 0.05$) (Table 2). Additionally, there were main effects for gender for the total CC ($F = 5.00$, df = 1, $P < 0.05$), as well as for CC1 ($F = 4.39$, df = 1, $P < 0.05$) and CC2 ($F = 5.08$, df = 1, $P < 0.05$) with women having larger areas. Similarly, tendencies towards a difference were detected for CC3 ($F = 3.66$, df = 1, $P = 0.063$) and CC5 ($F = 3.85$, df = 1, $P = 0.057$). No significances appeared with respect to the diagnosis-by-gender interactions. This indicates that both schizophrenic and healthy women had larger total CC and rostral subdivisions than men in the respective diagnostic group.

Correlation analyses between the level of symptoms and the CC including its substructures did not reveal any significant result.

DISCUSSION

In our study previously untreated schizophrenic patients were compared to age- and sex-matched healthy subjects. The following results were detected: (i) patients had smaller total corpora callosa and CC subdivisions than controls; (ii) women were found to have larger CC than men in patients as well as in controls.

Schizophrenic patients and healthy controls

Although most previous studies were not performed with first-episode patients, our results of smaller total CC and CC subdivision areas in the schizophrenia group are in line with the majority of studies that compared schizophrenic patients to healthy controls (Rossi et al. 1989; Stratta et al. 1989; Woodruff et al. 1993; DeQuardo et al. 1996; Tibbo et al. 1998; Chua et al. 2000; Downhill et al. 2000). Meisenzahl et al. (1999) differentiated grey and white matter and found a significant reduction of white matter tissue in the patient group. In the study of Rossell et al. (2001), a significant association between CC area and overall grey and white matter volumes was found in schizophrenic patients with auditory–verbal hallucinations only. However, the presented data are not in keeping with those of Nasrallah et al. (1986) and Jacobsen et al. (1997) who reported on an enlargement of the CC. Our findings also differ from those of several groups who found cases and controls to be similar (Rossi et al. 1990; Blackwood et al. 1991; Günther et al. 1991; Woodruff et al. 1997; Sachdev & Brodaty, 1999; Meisenzahl et al. 1999).

Methodological fallacies in studies on the CC of schizophrenic patients – which might account for differing results – are brought about by two aspects. First, patient samples differ. Especially the factors gender (see below), handedness, age, and chronicity of illness may confound results. Handedness exerted an influence in the post-mortem study on healthy individuals by Witelson (1989). Age in the first two decades of life has been shown to be positively correlated with CC mid-sagittal area (Rauch & Jinkins, 1994; Giedd et al. 1996) due to continuation of myelination; an inverse relation of CC size to age was detected in controls by Woodruff et al. (1997), and in the same study length of illness was negatively correlated with the posterior CC area. Secondly, measurement techniques of the CC vary widely. Researchers have measured overall size or shape (DeQuardo et al. 1996; Downhill et al. 2000), width and area only (Kelsoe et al. 1988), length in combination with area or callosum-to-brain-ratio (Mathew & Partain, 1985; Rossi et al. 1988, 1989; Colombo et al. 1994), area and/or callosum-to-brain-ratio (Smith et al. 1984; Smith & Tamminga, 1985; Stratta et al. 1989; Günther et al. 1991; DeLisi et al. 1995; Tibbo et al. 1998), a combination of area, length and width (Nasrallah et al. 1986; Uematsu & Kaiya 1988; Hauser et al. 1989;
Casanova et al. 1990; Raine et al. 1990; Woodruff et al. 1993), or area divided into three to five subregions (Hauser et al. 1989; Woodruff et al. 1993, 1997; Hoff et al. 1994; DeLisi et al. 1997; Jacobsen et al. 1997). Moreover, as opposed to our study most researchers have measured the CC on one slice only with slice thickness ranging from 10 mm (Raine et al. 1990) to 1.5 mm (Chua et al. 2000). It is conceivable that these varying approaches only partially correspond, so that – given the fact that the CC is a small structure – they are likely to exert a great effect.

**Sexual dimorphism**

In our study, women had larger CC and rostral subdivisions than men in both healthy subjects and schizophrenic patients, tendencies towards similar differences were present in the caudal subdivisions. This finding is consistent with the majority of post-mortem studies on healthy individuals that report either a larger relative posterior portion of the CC, a larger relative CC (Witelson, 1989; De Lacoste et al. 1990; Holloway et al. 1993) or an absolute larger size of the CC (Holloway & De Lacoste, 1986) in women as compared to men. In vivo MRI studies on healthy subjects support the aforementioned evidence (Clarke & Zaidel, 1994; Steinmetz et al. 1993; Jäncke et al. 1997). Our results are also in keeping with those conveyed by several groups with respect to schizophrenia (Nasrallah et al. 1986; Raine et al. 1990; Colombo et al. 1994). The studies of Raine et al. (1990) and Colombo et al. (1994) provide evidence for a thicker posterior callosum in female patients. Lewine et al. (1990) found a significantly higher proportion of qualitatively abnormal MRI readings in males than in females. In their childhood onset study, Jacobsen et al. (1997) did not detect a gender difference. However, methods differ to some extent since they adjusted for cerebral volume whereas we corrected for ICV. Interestingly, the study on CC in first episode patients presented by Hoff et al. (1994) does not support our findings. Although corpora callosa were defined via area and were divided in five regions, the measurement technique thus being very similar to ours, CC were found to be smaller in women than in men. The contradiction can only be explained by other factors such as handedness. It has been suggested that discrepancies in CC size are a reflection of factors such as gender and handedness in healthy subjects (De Lacoste-Utamsing & Holloway, 1982; Witelson, 1989) as well as in schizophrenics (Nasrallah et al. 1986; Raine et al. 1990). Age was controlled for in both studies. No information on the level of psychopathology is available from the study by Hoff et al. This has to be cautioned since the extent of symptomatology on admission has been shown to explain differences in CC area by Günther et al. (1991) and Woodruff et al. (1993). The authors found larger callosal areas in type I patients compared to type II patients, which is consistent with Andreasen’s hypothesis of a ‘hyperconnection syndrome’ (Andreasen, 1987) in positive schizophrenia (type I). The Andreasen-group themselves (Tibbo et al. 1998) reported an inverse correlation between CC size and negative symptoms (type II). Other methodological differences are the use of T1 sequences only, a slice thickness of 5 mm with an interslice gap of 2 mm, and total brain volume as a co- variate in the study by Hoff et al. It has been argued (Bergin et al. 1994) that the use of thick slices may increase errors and partial volume artefacts, whereas technical improvements over time may have accounted for an increased measurement sensitivity in our study. On the other hand, the number of patients in the study by Hoff et al. is twice as high and their control group three times larger compared to ours, meaning that our study may have yielded less reliable results.

Overall, results in schizophrenia research with respect to sexual dimorphism conflict to some extent. After inclusion of the literature on healthy individuals, the gender differences of the CC area in our study can be conceived of as an aspect of the sex differences of the normal human brain (McGlone, 1980; Holloway & De Lacoste, 1986; Witelson, 1989; De Lacoste et al. 1990; Holloway et al. 1993; Clarke & Zaidel, 1994; Steinmetz et al. 1995), which have been revealed in schizophrenia as well (Flor-Henry, 1978). They are perceived to represent a sex-dependent, pathway-specific decrease in interhemispheric connectivity with increased lateralization yielding an inverse correlation between connectivity and number of callosal fibres on the one hand, and asymmetry and lateralization on the other hand (Aboitiz et al. 1992b, 1996).
Limitations
Some authors have pointed at a relationship between brain size and CC size (Jäncke et al. 1997; Highley et al. 1999). Since we corrected for ICV which includes brain size, the reduction of the CC in our study is not merely a reflection of a change in brain size. Also, handedness might have confounded our results. The population we studied consisted of right-handers – which holds true for patients and controls (with one exception). Thus, a pre-existing laterality effect becomes unlikely. Regarding the methodology it has to be critically mentioned that MR images were obtained in two different orientations and coronal image cubes had to be transformed into sagittal image cubes prior to further analysis. Data, however, revealed comparable values for both orientations. Although corpus callosum measurements by two independent raters would have been preferable, intra-rater-reliability in this study was high.

In summary, previously untreated schizophrenic patients had smaller corpora callosa compared to healthy controls. CC in women were larger than in men which is consistent with disease related changes in fibre composition of the human corpus callosum. To shed more light onto the question as to when schizophrenia related changes of the CC start in schizophrenia and to whether they progress, researchers should try to achieve comparability of studies by using similar imaging and measurement techniques as well as comparable patient samples with preference for first-episode patients including follow-up examinations.

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