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Original articles

Anatomical characteristics of the corpus callosum and clinical correlates in schizophrenia

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Summary. Nineteen DSM-III-R schizophrenic patients and 15 normal subjects, matched for sex and age, were evaluated according to their clinical and corpus callosum structural characteristics. They were evaluated on their size of callosum by means of Magnetic Resonance Imaging. Neither diagnosis nor sex significantly affects corpus callosum indices. Statistical analysis evidentiates a relationship between DSM-III-R axis-V scores and corpus callosum length in schizophrenics, and between age at onset of the illness and corpus callosum length in schizophrenics.

Key words: Magnetic resonance imaging (MRI) – Schizophrenia – Corpus callosum (CC)

Introduction

Several magnetic resonance imaging (MRI) studies of corpus callosum (CC) size claim for CC structural abnormalities in schizophrenia (Raine et al. 1990; Rossi et al. 1988; Rossi et al. 1989; Uematsu and Kaiya 1988, Woodruff et al. 1993; David et al. 1993), while other studies fail to replicate these findings (Kelsoe et al. 1988; Smith et al. 1987; Smith and Tamminga 1985; Casanova et al. 1990). On the other hand, two CC post-mortem studies both show an increased CC thickness in schizophrenia (Rosenthal and Bigelow 1972; Bigelow et al. 1983) and the only one study available in literature which combines CC blood flow data and structural characteristics indicates that the increased CC size is paralleled by an increase of CC blood flow (Gunther et al., 1991).

Important differences in MRI technique (i.e., the choice of slice thickness) between the different studies and the widely recognized psychopathological and clinical heterogeneity of schizophrenic syndrome (Tsuang et al. 1990) might, in part, account for such a lack of consistency. Further, some recent MRI studies indicate a CC sexual dymorphisms (De Lacoste-Utamsing and Holloway 1982) and an influence of gender on the CC functioning (Potter and Graves 1988; Georgy et al. 1993). Furthermore, some studies in neurological (McGlone and Fox 1982) and psychiatric patients (Flor-Henry et al. 1983) show an important effect of sex in determining the strength and the direction of the hemispheric information processing impairment.

The first step of the study is the evaluation of MRI CC characteristics in a sample of 19 schizophrenic patients and 15 normal subjects homogeneous for sex and age and the influence of sex on those anatomical measures. The second is to relate DSM-III-R clinical features to the CC neuroanatomical measures. In fact, if the CC malfunctioning is critical in determining schizophrenic pathology, it seems reasonable to suppose its direct influence on clinical assessment of the patients.

Subjects and methods

Nineteen schizophrenic patients (13 M, 6 F, mean age 25.9 years ± 6.4) and 15 normal subjects (9 M, 6 F, mean age 29.6 ± 5.2 years) underwent MRI examination. All subjects were right-handed; assessment of the hand preference was made by means of a standardized questionnaire (Raczkowski et al. 1974). The following demographic variables were documented for all subjects: sex, age, education, height, weight, handedness. The following clinical variables were also documented for all patients: age at onset of illness, cumulative duration of hospitalization (in months), personal-social relations and global adjustment factor (GAF), diagnostic subtype, course of illness, drug treatment. The diagnosis of schizophrenia, the diagnostic subtype, the course of the illness (i.e. subchronic or chronic) and the GAF scores were assessed according to DSM-III-R criteria (APA 1987) using the standardized diagnostic interview (DIS-III-R) (Robins et al. 1989). Out of the 19 schizophrenics, 4 were paranoid, 7 were disorganized, 8 undifferentiated, 6 subchronic and 13 chronic. All schizophrenics were being treated with haloperidol at the time of their MRI (range 10–20 mg/day). All normal subjects were recruited among hospital workers and nursing staff; they were all submitted to a complete physical and neurological clinical examination in order to exclude the presence of any illness. The subjects with a personal history of neurological or psychiatric illness or taking medications affecting brain size or with a history of alcohol or drug abuse were excluded from the study as were all subjects with personal history of perinatal injuries or cranial trauma. Table 1 summarizes the demographic and clinical characteristics of the study sample. The two groups are homogeneous in terms of age (t-test with 32 $df = -1.81$, P = n.s.). Nor-

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Table 1. Background characteristics of normal subjects and schizophrenics[f]

	Normal Subjects	Schizophrenics
Age, y	29.66 (± 5.27)	25.94 (± 6.40)[a]
Sex, M/F	9/6	13/6[b]
Education	16.46 (± 4.06)	10.36 (± 3.04)[c]
Height, cm	1.73 (± 0.11)	1.70 (± 0.07)[d]
Weight, kg	68.14 (± 13.78)	69.15 (± 12.66)[e]
Age at onset	–	21.57 (± 4.16)
Dur. illness (years)	–	4.42 (± 3.76)
Hospitalization (months)	–	5.89 (± 6.60)
GAF	–	49.10 (± 14.88)

[a] *t*-test $t = -1.81$ with 32 d.f., P = n.s.
[b] chi-square with 1 d.f. = < 1, P = n.s.
[c] *t*-test $t = -5.01$ with 32 d.f., $P = < 0.01$
[d] *t*-test $t = < 1$ with 32 d.f., P = n.s.
[e] *t*-test $t = < 1$ with 31 d.f., P = n.s.
[f] Values are mean (± SD)

mal subjects had more years of education (*t*-test with 36 $df = 5.01$, $P < 0.01$). Both the patients and the normal subjects had to certify their voluntary consent to take part in the study.

MRI procedures and scoring

All subjects were scanned on a Toshiba MRI unit operating at 0.5 T. The midsagittal cut was scanned with T1-weighted spin-echo sequences (TR 500, TE 30). The interslice-gap was 0.5 mm, the slice thickness was 5 mm. MRI images of midsagittal cut were analyzed with an image analysis system produced by Kontron Electronics (Munich, Germany). This system consists of a video camera, a light box and an image processor (digitizer) within the computer. MRI images were placed over the light box and stored on the computer. Measurements for each patient were calibrated by a scale fixed according to each MRI slice. The background room illumination conditions where measures were performed was standarized, the spatial distortion was corrected. The semiautomatic measures were obtained by using a mouse-controlled cursor to outline structures of interest. The system gave a semiautomatic definition of the boundaries of the corpus callosum to be obtained by setting the threshold between light and dark areas in such a way that the corpus callosum appeared as a bright area that could be coloured and automatically measured by the computer. Maximal anterior-posterior length of corpus callosum (CC LENGTH) can be obtained by a two-point level definition that permits the system to derive the measure automatically.

Because of the lack of accurate anatomical MRI limits, the total length of the corpus callosum was divided in three equal parts identifying the anterior, middle and posterior areas of the corpus callosum; these three measures were then taken as an index of prevalence of anterior (CC ANT), middle (CC MID) or posterior (CC POST) callosal area. These areas were obtained by opening a window that includes only the region of interest: the same procedure used for calculation of the total callosal area (CC TOT) was then applied here (threshold between dark and light). Maximal anterior-posterior length on the midsagittal cut was taken as an index of Total Cerebral Size (TCS) and measured with the two-point level definition. The structural measurements were performed by two independent raters who did not know the identity of the subjects. The reliability of the raters was satisfactory ($r = 0.90$, $P = 0.01$).

Statistical analysis

The raw data obtained from the anatomical measurements were z-transformed in order to normalize their distribution before statistical analysis. Analysis of covariance (ANCOVA) (SPSS 1986) was used to test the differences between schizophrenics and normal subjects in CC LENGTH, CC ANT, CC MID and CC POST measures. Four ANCOVAs were performed with sex and diagnosis as independent variables, CC ANT, CC MID, CC POST and CC LENGTH as dependent ones, education and TCS as covariates.

Multiple linear regression analysis (MLR) (SPSS 1986), stepwise type, was used in the schizophrenic group to build the model that relates clinical characteristics (i.e. age at onset, GAF) to CC morphological measures (i.e. CC LENGTH, CC ANT, CC MID, CC POST, CC TOT) and demographic features (i.e. education, height and weight). In the first analysis GAF, education, height, weight, CC LENGTH , CC ANT, CC MID, CC POST, CC TOT were the variables used, GAF being the dependent variable. In the second one age at onset, education, height, weight, CC LENGTH, CC ANT, CC MID, CC POST, CC TOT were the variables used, age at onset being the dependent variable.

Results

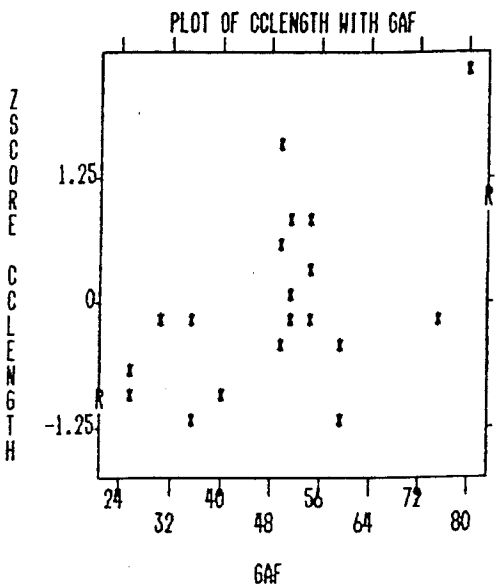
Table 2 shows the mean values of anatomical CC measures and the summary of the four ANCOVAs.

Table 2. The mean values of anatomical corpus callosum measures and the summary of the four ANCOVAs

	CC ANT	CC MID	CC POST	CC LENGTH	TCS
Schizophrenics	2.65	1.46	2.36	7.21	16.42
Normal subjects	2.56	1.37	2.39	7.26	16.02
Covariates					
Education	$F(1.28) < 1$, P = ns	$F(1.28) < 1$, P = ns	$F(1.28) < 1$, P = ns	$F(1.28) = 2.64$, P = ns	
Brain Length	$F(1.28) = 1.73$, P = ns	$F(1.28) < 1$, P = ns	$F(1.28) < 1$, P = ns	$F(1.28) = 5.35$, P = ns	
Main effects					
Diagnosis	$F(1.28) < 1$, P = ns	$F(1.28) < 1$, P = ns	$F(1.28) < 1$, P = ns	$F(1.28) < 1$, P = ns	
Sex	$F(1.28) < 1$, P = ns	$F(1.28) = 2.44$, P = ns	$F(1.28) = 1.60$, P = ns	$F(1.28) < 1$, P = ns	
Interactions					
Diagnosis by Sex	$F(1.28) = 3.55$, P = ns	$F(1.28) = 2.15$, P = ns	$F(1.28) = 3.69$, P = ns	$F(1.28) < 1$, P = ns	

CC ANT = corpus callosum anterior area in squared cm, CC MID = corpus callosum middle area in squared cm, CC POST = corpus callosum posterior area in squared cm, CC LENGTH = corpus callosum length in cm, TCS = brain length in cm

Table 3. Stepwise multiple regression analysis of the relationships between anatomical measures (z-transformed) and clinical variables in schizophrenics



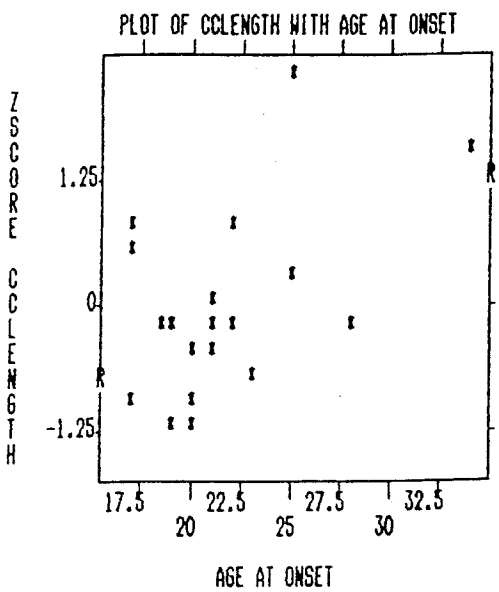
Dependent variable	Independent variable entered	Multiple Reg 0.55	R2 0.30	*F* (1.17) 7.48	*P* 0.01
GAF	CC LENGTH				

Variables not in the equation

	Beta Coeff.	Partial	Min Toler	*F*	Sig F
CC TOT	0.01444	0.01397	0.64936	0.003	0.9561
CC ANT	0.16440	0.16133	0.66869	0.428	0.5225
CC MID	0.13552	0.14295	0.77265	0.334	0.5715
CC POST	–0.23903	–0.26440	0.84961	1.203	0.2890
Education	–0.08205	–0.09477	0.92640	0.145	0.7084
Weight	0.25768	0.30263	0.95770	1.613	0.2222
Height	0.34977	0.39693	0.89425	2.992	0.1029

Predicted GAF = –1.73 + 0.03 (CC LENGTH)

Table 4. Stepwise multiple regression analysis of the relationships between anatomical measures (z-transformed) and clinical variables in schizophrenics



Dependent variable	Independent variable entered	Multiple Reg 0.49	R2 0.24	*F* (1.17) 5.49	*P* 0.03
Age at onset	CC LENGTH				

Variables not in the equation

	Beta Coeff.	Partial	Min Toler	*F*	Sig F
CC TOT	–0.21440	–0.19875	0.64936	0.658	0.4292
CC ANT	–0.08070	–0.07591	0.66869	0.093	0.7646
CC MID	–0.23862	–0.24130	0.77265	0.989	0.3347
CC POST	–0.17194	–0.18232	0.84961	0.550	0.4690
Education	0.28090	0.31103	0.92640	1.714	0.2090
Weight	–6.729E–03	–0.00758	0.95770	0.001	0.9762
Height	–0.14102	–0.15341	0.89425	0.386	0.5434

Predicted Age at onset = –2.41 + 0.10 (CC LENGTH)

Neither diagnosis nor sex significantly affects CC indices. The interaction diagnosis × sex is also not significant. Multiple Linear Regression analysis built a significant model which relates GAF, neuroanatomical measures, education, height and weight in schizophrenics (R-squared = 0.30, F with 1.17 *df* = 7.48, *P* = 0.01). Among the four CC anatomical incides CC LENGTH is the only one which enters in the regression equation. Education, height and weight do not enter in the regression equation. For this equation the beta coefficient is 0.55, thus indicating a positive correlation between CC LENGTH and GAF.

Multiple Linear Regression analysis built a significant model which relates age at onset, neuroanatomical measures, education, height and weight in schizophrenics (R-squared = 0.24, F with 1.17 *df* = 5.49, *P* = 0.03). Among the four-CC anatomical indices CC LENGTH is the only one which enters in the regression equation. Education,

height and weight do not enter in the regression equation. For this equation the beta coefficient is 0.49 thus indicating a positive correlation between CC LENGTH and age at onset.

Discussion

The MRI CC measures investigated in the present study are not affected by the diagnosis, thus supporting the literature which failed to find any significant difference in CC structural characteristics of schizophrenic patients (Kelsoe et al. 1988; Smith et al. 1987; Smith and Tamminga 1985).

Otherwise the low level of inter-study consistency in different independent lines of research (Kishimoto et al. 1987; Gur et al. 1987; Flor-Henry 1979; Stevens et al. 1979) could be explained by the hypothesis of not only clinical but also biological different phenotypes within the schizophrenia syndrome (Tsuang et al.1990). Sex does not influence the CC size and the interaction diagnosis by sex is also not significant. These data appear to be inconsistent with data from a similar recent experiment (Raine et al. 1990). In fact, even if some recent MRI studies indicates a CC sexual dimorphism (De Lacoste-Utamsing and Holloway 1982) and an influence of gender has been suggested on the CC functioning (Potter and Graves 1989), however, several studies examining possible sex differences in the CC size in normal subjects, lead to discordant results (for a review see Witelson 1989) and additional data will be needed. The CC length was related to GAF and age at onset. These data suggest a positive relationship between a structural measure and two clinical characteristics (GAF and age at onset) which are considered good prognosis markers in schizophrenia (Kendel 1983; Lehmann and Cancro 1990): despite the variability of outcome, there is good agreement on the characteristics of the illness predicting a good outcome. An acute onset, a high score at GAF and a later age at onset of illness indicate a better course of disease (Kendell 1983; Lehmann and Cancro 1990). Therefore, it seems reasonable to assume a parallelism between the presence of some good prognosis features and a "normalization" of the structural measure.

Finally, a number of studies have hypothesized a relationship between brain morphology and education (Andreasen 1989). It should be noted that, in this study, education is a variable which never contributed to the building of the regression equation suggesting a scarce influence on central nervous system functional assessment.

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