Morphometry of the corpus callosum in monozygotic twins discordant for schizophrenia: a magnetic resonance imaging study

Manuel F Casanova, Richard D Sanders, Terry E Goldberg, Llewellyn B Bigelow, George Christison, E Fuller Torrey, Daniel R Weinberger

Abstract

The corpus callosum (CC) has been the focus of several morphometric studies of patients with schizophrenia, but the results of these studies have been contradictory. In an attempt to improve the reliability of morphometric measurements of the corpus callosum, a computerised image analysis system was used to measure the shape, area, thickness and length of the CC on magnetic resonance imaging (MRI) in 12 pairs of monozygotic twins discordant for schizophrenia (SC). No differences in CC area (anterior, middle, posterior thirds and total), length or vertical thickness of the CC body (at three levels) were demonstrated by *t* test comparisons of the affected SC and unaffected twins. Statistical analysis of a Fourier expansion series suggested differences in shape between normal and SC cotwins in the second harmonic of the anterior and middle segments and effects of gender on posterior CC shape. These results fail to replicate previous findings of altered length, thickness and area in the schizophrenic CC, but implicate disease-related shape differences in the anterior and middle segment of the corpus callosum and gender-related differences in splenium shape. The disease-related shape distortion suggest ventriculomegaly rather than an intrinsic abnormality of the corpus callosum.

The idea that mental illness might be the result of faulty interhemispheric communication¹ is ingrained within the term schizophrenia ("splitting of the psychic functions").² Although methodological handicaps have limited testing this hypothesis, a series of ingenious experiments by Sperry³ in patients who had partial or total sectioning of the interhemispheric commissures, defined a "disconnection syndrome" characterised by abnormal responses to lateralised stimuli. In

patients with schizophrenia, similar testing paradigms including abnormalities in tasks requiring matching of tachistoscopically presented verbal and nonverbal material,⁴ monaural asymmetries to complex speech comprehension,^{5,6} the transfer of learned information,^{7,8} the cross-localisation of tactile stimulation,⁹ and alterations in EEG¹⁰ and evoked potential studies¹¹ have suggested an impairment of interhemispheric communication. Since the corpus callosum (CC) provides the major conduit for association bundles connecting the hemispheres, there have been several morphometric studies searching for abnormalities of this structure in schizophrenic patients (tables 1 and 2). Results of these studies have been contradictory. This has also been true of attempts to relate CC morphology to handedness, gender, age and brain size.¹³⁻¹⁵

Because human CC morphology is highly variable,^{14,15} and the determinants of its size and shape are still unknown, optimally matched controls are of utmost importance in eliminating confounding variables. The present MRI study compared measures of CC size and shape in twelve schizophrenic patients and their unaffected monozygotic cotwins. Quantitative analyses of CC shape was employed for the first time in schizophrenia. Given that the experimental and control groups were matched completely for inherited genome and partially for pre- and postnatal environment, any differences in CC gross morphology might represent pathological features inherent to the schizophrenic syndrome.

Methods

Patients

The patients were pairs of identical twins discordant for schizophrenia recruited from all parts of the United States and Canada under the project Biological Markers in Discordant Monozygotic Twins. Measures taken to insure that recruited twins were in fact identical included examination of school

Clinical Brain Disorders Branch, Intramural Research Program, National Institute of Mental Health, Washington, DC, United States

M F Casanova
R D Sanders
T E Goldberg
L B Bigelow
G Christison
E F Torrey
D R Weinberger

Correspondence to:
Dr M F Casanova,
Neurosciences Center at St
Elizabeths, CBDB-NIMH,
2700 Martin Luther King Jr
Ave SE, Washington, DC
20032, United States

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Table 1 Necropsy studies of callosal gross morphology in schizophrenia.

Study	Patient	Control	Thickness	Area
Rosenthal and Bigelow ⁴³	10 Langfeldt "bad prognosis"	10 mixed psychiatric	> body	—
Bigelow <i>et al</i> ⁴⁴	21 RDC onset < 30 years	14 psychiatric, 13 neurologic	> body (anterior, and middle average)	—
Brown <i>et al</i> ⁴⁵	26 Feighner	29 affective	NS (one level)	—
Machiyama <i>et al</i> ⁴⁶	5 ?criterion	7 normal	> body (anterior only)	NS

— Not specified
NS Not significant
> Increased

Table 2 MRI studies of callosal morphology in schizophrenia.

Study	Patients	Controls	Area	Thickness	Length
Smith <i>et al</i> ⁷	9 RDC	5 normal	NS	—	—
Smith and Tamminga ⁴⁸	23 RDC	17 normal	NS	NS	—
Mathew <i>et al</i> ⁴⁹	18 DSMIII	18 normal	NS	—	>*
Nasrallah <i>et al</i> ⁵⁰	28 DSMIII	41 normal	>	> **	NS
Smith <i>et al</i> ⁵¹	29 DSMIII @	21 normal	NS	NS	—
Kelsoe <i>et al</i> ⁵²	24 DSMIII	14 normal	NS	NS	—
Rossi <i>et al</i> ⁵³	12 ##	12 normal	<	—	—
Uematsu <i>et al</i> ⁵⁴	24 DSMIII	7 normal	> @@@	—	NS
Uematsu and Kaiya ⁵⁵	40 DSMIII	17 normal	> @@@	NS	NS
Rossi <i>et al</i> ⁵⁶	15 DSMIII	15 normal	<	—	—
Stratta <i>et al</i> ⁵⁷	20 DSMIII	20 normal	< #	—	—
Swayze <i>et al</i> ⁵⁸	54 ##	48 manic	NS	NS	>

χ Included two cases of acute schizophrenia and one schizoaffective psychosis.

* Using the data given in the article, the difference is not statistically significant.

** Increased thickness in anterior and middle (but not posterior) sections.

@ Includes schizoaffective and schizophreniform patients.

@@ Increased only in the ratio of the anterior third to the midsagittal brain area.

Only the ratio of CC to midsagittal brain area is reported.

Diagnostic criteria not specified.

> Increased.

< Decreased.

pictures, use of a questionnaire¹⁶ and profiles of human lymphocyte antigen and 19 red blood cells groupings. In all, there were twelve discordant pairs, consisting of five males and seven female pairs.

All twins had a standardised structured diagnostic interview (SCID)¹⁷ to establish DSM III-R diagnoses. The members diagnosed with schizophrenia were subtyped as follows: eight undifferentiated, two paranoid, and two residual. Nine of the cotwins without schizophrenia were not given psychiatric diagnosis. Three met criteria for drug abuse (sedative/hypnotic, cannabis, and sympathomimetic dependence), which had ceased several years before the study. The ages of the twins ranged from 25 to 44 years with a mean of 32.6 years. The twins with schizophrenia had a duration of illness (time since initial psychiatric referral) ranging from two to 24 years with a mean of 10.3 years. The affected member had had three to 28 admissions to hospital, with a mean of 8.7 admissions. All pairs had been discordant for at least five years (range 5–24 years) with a mean of 10.4 years; this makes it unlikely that these twins will become concordant in the future. All affected individuals were taking neuroleptic medication at the time of testing, and three had received electroconvulsive therapy in the past. Three of the twelve pairs had a first or second degree relative with a definite or probable diagnosis of schizophrenia.

The perinatal and postnatal histories of the twins were closely examined for evidence of organic factors which might result in cerebral abnormalities. One affected twin had what was probably a postnatal encephalitis and one control twin had pulmonary stenosis that was corrected with surgery. No other differences between the twins could be explained by known potential causes of cerebral abnormalities.

Magnetic resonance imaging

All twins were scanned in the same General Electric 1.5 tesla scanner. Contiguous sagittal slices 5 mm thick were T1 weighted with a recovery time (TR) of 800 ms. Four excitations were used in most cases, however, two were used to shorten scanning time for

patients who had difficulties tolerating the procedure. This was necessary for both members of three pairs and one member of another pair. Selection of the midsagittal level in our study was based on the visualisation of the crest of the gyri in the mesial aspect of the hemispheres.

Computerised image analysis

Digitisation of MRI scans was performed with a LOATS computerised image analysis system. Illumination was maximised and referenced for correction of individual scans. Films were placed over a light box and digitised with a DAGE 68 camera interfaced to an IBM PC AT via an expansion chassis. A single digitisation mode was selected. The image was enlarged 2.8 ×, contrast enhanced, and plotted on a monitor for visual inspection. The resulting resolution (that is, the actual length of the image across the monitor screen divided by the number of pixels across the same axis) was 0.31 mm. All measurements were calibrated against the horizontal metric scale of the MRI scans. The corpus callosum was divided into thirds with a Gerber variable scale and each individual segment, as well as the whole corpus callosum, was manually outlined with an electronic mouse and magnetic tablet using a "polygon function". Thickness, defined as the longest vertical height, was measured in pixel units. The corpus callosum length, defined as the distance from the splenium to the genu, was also measured in pixel units.

Shape analysis^{18–20} was performed by outlining the periphery of the desired structure with a "polygon function". The centroid was then determined in a Cartesian coordinate system by projecting vectors from candidate points to the boundary of the figure. The vectors tracked the boundary in a clockwise fashion. Moments of the vectors with respect to the x and y axis were obtained, those belonging to each axis added and then divided by the area of the structure. Since the clockwise movement of the vector returned to the original starting point, it represents a repeating function that can be described by a Fourier expansion series. This was achieved by transforming the points defining the periphery of the object into polar coordinates and expressing the resulting contour in terms of an addition series of either sine or cosine functions. In this series, each one of the harmonic amplitudes defines a weighting factor which characterises the contributions of different and successively more complex geometrical figures to the shape of the object. All the harmonic amplitudes were normalised against the 0 harmonic. The phase angles for the different harmonics served as a measure of rotational orientation for each of the geometrical shapes defined by the particular harmonics.

Statistics

Area analyses were made by match-pair *t* tests. For nonparametric tests of harmonics,

Table 3 *T* test analysis of corpus callosum length, thickness, and area.

	C	SC	<i>t</i>	<i>p</i>
Length	71.5 (4.30)	71.91 (3.65)	0.75	0.46
Anterior thickness	4.38 (0.94)	4.63 (0.67)	0.25	0.81
Middle thickness	4.99 (0.76)	4.63 (0.94)	0.19	0.85
Posterior thickness	4.47 (1.11)	4.55 (1.51)	0.15	0.88
Posterior area	1.54 (0.41)	1.59 (0.43)	0.29	0.77
Middle area	0.96 (0.25)	0.97 (0.30)	0.61	0.94
Anterior area	1.52 (0.47)	1.54 (0.49)	0.13	0.90
Whole area	4.08 (1.08)	4.13 (1.15)	0.09	0.92
Hemisphere area	71.43 (1.79)	69.87 (6.57)	0.57	0.57

analysis of the groups utilised rank order tests. For parametric tests, scores were square root transformed because the distribution of shape scores was skewed.

Results

Areas of the anterior, middle, and posterior parts of the corpus callosum were compared between groups by matched pair *t* test. No differences emerged (table 3). The hemispheric areas in the sagittal plane also did not differ between the groups. The length of the corpus callosum was not significantly different between the groups. No area comparison attained significance by matched pair *t* test analysis.

Shape analysis utilising harmonics was applied. The overall shape of the corpus callosum did not differ significantly (non-

parametric Kruskal Wallis rank order analysis) between the groups by harmonics 1, 2, 3, or 4 (table 4). On further analysis, the second harmonic (the predominant determinant of shape in this study) displayed variations with diagnosis that approached statistical significance in the anterior and middle segments by Kruskal Wallis tests ($p = 0.057$ and $p = 0.061$ respectively) (table 4). Matched pair *t* test analysis supported these results. In the middle segments a trend for between pair differences was found for harmonic 2 ($p = 0.09$). A similar trend was found in the anterior segment for harmonic 2 ($p = 0.09$).

Significant sex difference in the shape of the corpus callosum were also found in harmonics 1 and 3 in the posterior segment, but not in the dominant second harmonic by Kruskal Wallis tests (table 4). Sex differences were not discerned in the anterior or middle segments.

To further examine the influence of diagnosis and sex, as well as their combined influence (for example, diagnosis $\times$ sex interaction), MANOVAs were performed on the square root transformed harmonics (table 5). In the anterior segment a trend for a main effect of diagnosis was present as well as a significant interaction of diagnosis and sex (notably in harmonics 2 and 4). In the middle segment a trend for a significant interaction of

Table 4 Rank order harmonic amplitude analysis by diagnosis and gender

		Sc		N		M		Gender					
		$\bar{x}$	sd	$\bar{x}$	sd	H	p	$\bar{x}$	sd	$\bar{x}$	sd	H	p
Anterior	h1	0.16	0.6	0.17	0.07	0.03	0.86	0.18	0.07	0.16	0.05	0.14	0.20
	h2	0.45	0.05	0.39	0.07	3.63	0.06	0.42	0.05	0.42	0.09	0.00	1.0
	h3	0.17	0.05	0.19	0.05	1.40	0.24	0.19	0.06	0.17	0.05	1.89	0.17
	h4	0.13	0.04	0.11	0.02	2.09	0.15	0.12	0.02	0.13	0.04	0.07	0.79
Middle	h1	0.14	0.06	0.14	0.09	0.33	0.56	0.13	0.07	0.15	0.08	0.67	0.41
	h2	0.64	0.03	0.66	0.03	3.52	0.06	0.66	0.03	0.65	0.03	0.58	0.45
	h3	0.4	0.04	0.03	0.02	0.0	0.98	0.03	0.02	0.04	0.03	0.15	0.20
	h4	0.35	0.04	0.37	0.05	0.40	0.52	0.36	0.05	0.36	0.05	0.09	0.77
Posterior	h1	0.35	0.10	0.33	0.10	0.21	0.64	0.40	0.04	0.30	0.11	7.26	0.01
	h2	0.46	0.10	0.42	0.09	2.71	0.10	0.45	0.09	0.43	0.10	0.12	0.72
	h3	0.17	0.06	0.19	0.05	0.61	0.44	0.14	0.05	0.20	0.05	7.91	0.005
	h4	0.15	0.05	0.14	0.03	1.08	0.30	0.14	0.05	0.15	0.04	0.22	0.64
Whole	h1	0.24	0.04	0.24	0.03	0.08	0.77	0.25	0.03	0.24	0.04	0.99	0.32
	h2	0.27	0.04	0.30	0.08	1.2	0.27	0.29	0.07	0.28	0.06	0.10	0.25
	h3	0.07	0.05	0.08	0.06	0.48	0.49	0.10	0.07	0.06	0.03	1.37	0.24
	h4	0.18	0.04	0.19	0.06	0.33	0.56	0.18	0.06	0.19	0.04	0.0	1.0

h1-4; harmonic amplitudes 1-4.

Table 5 Multivariate analysis of variance (MANOVA) of diagnosis and sex on the harmonic amplitudes

Manova Main Effect			Univariate Contrasts P			
			h1	h2	h3	h4
Anterior	Dx	L = 0.66, $p = 0.11$	—	—	—	—
	Sex	L = 0.91, $p = 0.77$	—	—	—	—
	Dx & Sex	L = 0.41, $p = 0.003$	—	yes	—	yes
Middle	Dx	L = 1.04, $p = 0.42$	—	—	—	—
	Sex	L = 0.93, $p = 0.86$	—	—	—	—
	Dx & Sex	L = 2.38, $p = 0.09$	—	—	yes	—
Posterior	Dx	L = 0.89, $p = 0.72$	—	—	—	—
	Sex	L = 0.59, $p = 0.05$	yes	—	yes	—
	Dx & Sex	L = 0.98, $p = 0.98$	—	—	—	—

h1-4; harmonic amplitudes 1-4.

Wilks; Wilks Lambda test for significance.

diagnosis and sex was present while in the posterior segment a significant main effect for sex was present (notably in harmonics 1 and 3).

Discussion

This study compared the morphology of the CC of normal and schizophrenic cotwins and found no difference in any of the indices of CC area, length and thickness. Shape analysis revealed alterations in the secondary harmonics of the posterior CC of the affected twin, but the minor contributions of these harmonics to the overall shape of the segment renders them difficult to interpret.^{18,21} Our study also disclosed differences in the dominant second harmonic of the anterior and middle segments.

Figure 1 Anatomical sketches of the genu (g) and splenium (s) of the corpus callosum in our patient population. The spatial relation between these anatomical structures have been preserved and drawn to proportion. Shape analysis based on a Fourier expansion series suggested no major differences between these subdivisions of the corpus callosum in schizophrenic patients and the controls.

The necessary inclusion of two artificial linear borders in the middle segment, (that is, two cuts were made through the corpus callosum to divide it into equal thirds) would, if anything, tend to reduce the shape variability in this segment. These differences suggest that a relationship may exist between CC gross morphology for this segment and schizophrenia in identical twins discordant for the syndrome (fig 1). Analysis of the harmonic amplitude pattern reveals that the distortion of the CC represents an upward bowing which is magnified in its middle-most segment (fig 2). This pattern is characteristic of hydrocephalus,²² and may be related to the finding of ventricular enlargement in schizophrenia.²³ Thus our findings suggest that the observed distortion is secondary to ventricular enlargement rather than an intrinsic abnormality of the CC itself.

In a study of the morphology of the CC in 450 midline sagittal MRI scans, McLeod *et al*²⁴ differentiated congenital from acquired abnormalities based on clinical information. Acquired changes resulting in hydrocephalus manifested significant differences in the length and thickness of the corpus callosum. The absence of similar changes in our series suggests that the hydrocephalic process observed in schizophrenic patients is more typical of congenital origin. Another possibility is that the majority of acquired cases reported by McLeod *et al*²⁴ were caused by obstruction of

the cerebrospinal flow leading to pressure atrophy of the corpus callosum. Unfortunately, McLeod *et al*²⁴ did not differentiate cases according to their underlying pathophysiology.

Although this study was not designed to study sex differences, it allowed the opportunity to investigate claims²⁵⁻²⁷ that the shape of the splenium varies with gender. Two of the harmonics of the posterior third of the CC (including but not limited to the splenium) showed highly significant differences attributable to gender, but the MANOVA comparison (incorporating all four harmonics) was not significant. Thus, these data partially support the existence of some minor sex differences in the shape of the caudal CC. Harmonic shape analysis should be applied to larger groups of normal subjects to study this phenomenon further.

Males had longer CC than females. This did not appear to be attributable to brain size differences, as length and hemisphere area were not correlated. None of the four previous studies that examined this variable in terms of gender^{14 25 28 29} found a difference. Consistent with other studies of CC and gender, area measurements did not differ; this held even when these were "corrected" for brain size (that is, divided by mid-sagittal area of the right hemisphere), which was predictably larger in the males.^{30 31}

The corpus callosum connects in an orderly fashion homologous cortical regions of the two hemispheres. Fibres joining parts of the frontal lobes project through the so-called forceps minor which funnels into the callosal genu, while occipital radiations pass through the splenium.³² In our study, we found no significant area differences in the anterior part of the corpus callosum. Conformational changes in this segment were attributed to ventriculomegaly. Given the large number of studies reporting a dysfunction of the frontal lobes in schizophrenia,³³⁻³⁶ our results do not support the notion that abnormalities in this region, if present, are the result of aberrant projections joining both frontal cortices. Rather, frontal lobe dysfunction in schizophrenia is more likely to manifest abnormalities in other areas.³⁴

As the preponderant corticocortical tract, the CC is a reasonable first site of investigation for those seeking an anatomic counterpart to the lack of connections between expressed thoughts of schizophrenic patients emphasised by Bleuler² and prominent in Schneider's³⁷ first-rank symptoms. Recent studies have suggested that schizophrenic symptomatology may be, in part, the manifestation of a disconnection syndrome. It should be noted, however, that surgically sectioned CC patients or children with lesions of the CC do not develop schizophreniform symptoms.³⁸⁻⁴⁰ Similarly, there has been only one case report of schizophrenia associated with complete agenesis of the corpus callosum.^{41 42} Our study suggests that if a defect of interhemispheric integration exists in schizophrenia, its structural counterpart is not detectable at the macroscopic level.

Figure 2 Midsagittal sections of the brain reveal an upward bowing of the corpus callosum of a patient with schizophrenia (A) compared with his asymptomatic cotwin (A'). Coronal sections of the same subjects (B-schizophrenic, B'-normal cotwin) suggest that the bowing is related to ventriculomegaly.

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