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Corpus callosum areas in first-episode patients with bipolar disorder

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ABSTRACT

Background. Morphological changes in the corpus callosum (CC) have been described in bipolar disorder, but with inconsistencies among the reports. We investigated the CC areas by magnetic resonance imaging (MRI) in 12 first-episode patients with bipolar disorder and 12 controls.

Method. Twelve medication-naive patients with bipolar I disorder (six males, six females; aged $28{\cdot}2 \pm 6{\cdot}5$ years) with manic or mixed episodes and 12 age- and gender-matched healthy controls (six males, six females; aged $26{\cdot}8 \pm 7{\cdot}6$ years) were recruited to the study. MRI scans was obtained using a 1.5-T GE Signa Excite high-speed scanner. Anatomical measurements were conducted on a computer workstation with the software Scion Image Beta-3b for Windows. Statistical analysis was performed using an analysis of covariance (ANCOVA), the *t* test, χ^2 and partial correlation analyses.

Results. Bipolar patients had significantly smaller areas of total CC, anterior body posterior body and isthmus compared with healthy control subjects by ANCOVA, with age, gender and intracranial volume (ICV) as covariates. There was a negative correlation between total CC, posterior body and isthmus areas and Young Mania Rating Scale (YMRS) scores.

Conclusion. The findings suggest that CC morphology may be associated with the pathophysiology of bipolar disorder.

INTRODUCTION

An increasing number of imaging studies have been conducted recently in patients with various psychiatric disorders to identify morphometric changes in specific brain regions. In patients with bipolar disorder, investigations have reported a decrease in subgenual prefrontal cortex volume (Drevets *et al.* 1997; Hirayasu *et al.* 1999) in prefrontal grey matter (Lopez-Larson *et al.* 2002), and an increase in amygdala volume (Strakowski *et al.* 1999; Altshuler *et al.* 2000; Brambilla *et al.* 2003). However, increased white matter hyperintensities and decreased cerebellar areas have also been reported (Stoll *et al.* 2000; Lyoo *et al.* 2002). The majority of functional neuroimaging studies in bipolar disorder reveal hypermetabolism in striatal (Drevets *et al.* 1997; Blumberg *et al.* 2000) and pallidal (Mayberg, 2001) areas. The corpus callosum (CC) is a white matter midline structure that connects the two cerebral hemispheres, allowing inter-hemispheric communication. An abnormally decreased size of the CC has been found in patients with bipolar disorder in two controlled magnetic resonance imaging (MRI) studies (Coffman *et al.* 1990; Brambilla *et al.* 2003), although other studies showed no significant differences (Hauser *et al.* 1989; Yasar *et al.* 2006). Abnormalities in CC morphology, particularly in callosal subregions (i.e. genu, body and isthmus) that interconnect important association areas, such as prefrontal and temporal cortices, may result in altered inter-hemispheric

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connections, which could be relevant to the pathophysiology, and in particular the cognitive disturbances, found in bipolar disorder (Wilder-Willis *et al*. 2001). In human brain development, the size of the CC increases in the middle of the third decade of life because of the increase in myelination, affecting the speed of interhemispheric information processing, with increasing age (Pujol *et al*. 1993; Brizzolara *et al*. 1994; Jancke & Steinmetz, 1994; Keshavan *et al*. 2002*b*). CC also plays an important role in higher cognitive functions such as attention, arousal, language and memory (Phelps *et al*. 1991; Rueckert & Levy, 1996). Altered interhemispheric connectivity due to reduced callosal myelination may therefore be associated with the cognitive disturbances and pathophysiology of bipolar disorder, as suggested by Brambilla *et al*. (2004) and others (Soares & Mann, 1997; Strakowski *et al*. 2000; El-Badri *et al*. 2001). However, to the best of our knowledge, no prior study has measured abnormalities in CC volumes in first-episode medication-naive bipolar disordered patients. It has been well established that psychopharmacological interventions and psychotherapeutic approaches can affect areas of the brain. Thus, it is important to evaluate the brain areas of interest and their activity levels in first-episode medication-naive psychiatric patients. We therefore performed a morphometric MRI study in patients with bipolar disorder who were first-episode medication-naive, focusing on the *in vivo* neuroanatomy of the CC to further evaluate the hypothesis of abnormalities in CC areas in bipolar patients and their possible involvement in the pathophysiology of the disease.

METHOD

Subjects and clinical evaluation

We studied 12 (six males and six females, with a mean age of $28{\cdot}2 \pm 6{\cdot}5$ years) first-episode medication-naive patients meeting DSM-IV criteria for bipolar disorder without psychotic features, as determined by the Structured Clinical Interview for DSM-IV (SCID; First *et al*. 1997), who consecutively applied to the Firat University School of Medicine Emergency Unit or directly to the Department of Psychiatry and who were experiencing manic (10 patients) or mixed episodes (two patients). Twelve healthy subjects (six males and six females, with a mean age of $26{\cdot}8 \pm 7{\cdot}6$ years) served as controls. All participants were right-handed. The local ethics committee approved the study. Written informed consent for voluntary participation in this research was obtained from all subjects.

Exclusion criteria were the presence of any co-morbid psychiatric disorder, current medical problems and/or alcohol/substance abuse within the 6 months preceding the study. Of the 12 patients, two had obsessive-compulsive personality disorder and one had histrionic personality traits. The healthy control subjects had no DSM-IV Axis I disorders in self or in a first-degree relative, as determined by the SCID non-patient version, no current medical problems, neurological or psychiatric histories, and no use of psychoactive medication within 2 weeks of the study. Healthy controls were selected from hospital staff.

Symptom severity was rated by using the Young Mania Rating Scale (YMRS) for manic symptoms (Young *et al*. 1978) and the Hamilton Depression Rating Scale (HDRS; Hamilton, 1960) for depressive symptoms. Scores of 20 or more on the YMRS were necessary for the patients with manic episodes. All patients already had scores of 20 or higher ($28{\cdot}9 \pm 3{\cdot}8$) on the YMRS and all were in the manic state. Participants also completed the HDRS. If necessary, benzodiazepine medication (lorazepam or diazepam) was allowed before scanning took place.

MRI procedure

MRI scans were conducted using a 1.5-T GE Signa Excite high-speed scanner (Milwakuee, USA). Spiral pulse sequences were used because of its insensitivity to subject motion. A high-resolution structural image of the entire brain was obtained using sagittally acquired three-dimensional spiral fast spin–echo high-resolution images [repetition time (TR) = 2000 ms, echo time (TE) = 15·6 ms, field of view (FOV) = 240 mm, flip angle = 20°, bandwidth = 20·8, slice thickness = 2·4 mm, echo spacing = 15·6 ms, eight echoes, resolution = $0{\cdot}9375 \times 0{\cdot}9375 \times 1{\cdot}328$ mm].

Anatomical measurements were conducted on a computer workstation with the software Scion Image Beta-3b for Windows (Scion Corporation, Frederick, MD, USA). A trained evaluator blind to group assignment and to the

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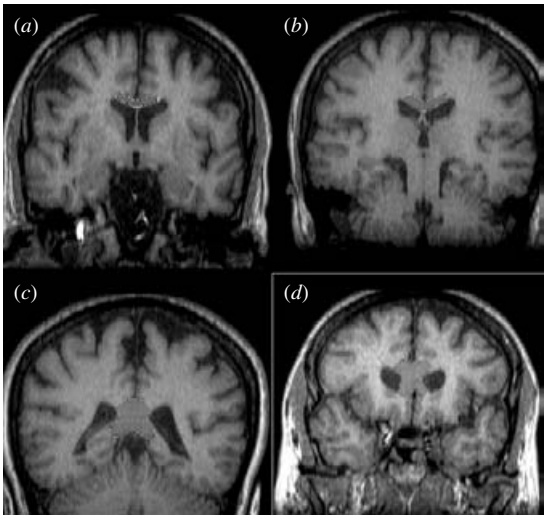

FIG. 1(*a–d*). Anatomical landmarks for tracing the structures evaluated.

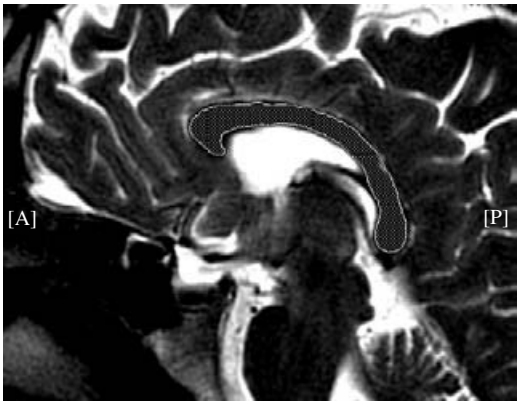

FIG. 2. Sagittal tracing of corpus callosum.

Table 1. *Clinical and demographic characteristics of first-episode patients with bipolar disorder and normal control subjects*

	First-episode ($n=12$)	Controls ($n=12$)
Age (years)	28·2 ± 6·5	26·8 ± 7·6
Gender (female/male)	6/6	6/6
Age at onset (years)	27·4 ± 6·1	—
Education		
First	2	1
Elementary	2	2
High	8	9
Socio-economic status		
High	3	2
Moderate	5	6
Poor	4	4
Height (cm)	165·3	167·9
Right-handedness	12	12
Duration of illness (years)*	0·3 ± 0·4	—
Treatment duration (years)	—	—
Number of manic patients	10	—
Number of mixed episode patients	2	—
Number of euthymic patients	—	12
YMRS score*	28·9 ± 3·8	4·9 ± 2·1
HDRS score*	7·4 ± 2·9	5·6 ± 2·4

YMRS, Young Mania Rating Scale; HDRS, Hamilton Depression Rating Scale.

No significant differences exist between groups with regard to age, handedness, height, education, socio-economic status and gender composition.

* $p<0·01$.

subjects' identities obtained volumetric measurements of the regions studied. The CC was traced manually. Morphometric measurements of the CC were performed on the basis of the methods of Keshavan *et al.* (2002*a*, *b*), adapted from Brambilla *et al.* (2003, 2004). The CC was traced following its edge in the midsagittal slice, defined as the slice in which the CC, the septum pellucidum, the cerebellum and the patency of the aqueduct were the most apparent. A line was then drawn to connect the most anterior CC pixel with the most posterior CC pixel, providing the overall callosal length. A computer-automated division of the CC into genu, body, isthmus and splenium was then performed, using landmarks adapted from Witelson (1989). Intracranial volume (ICV), total grey and white matter volumes are given in cm^3 and CC regions in cm^2. The coronal slices that had been corrected for head tilt were reformatted into consecutive 5-mm-thick sagittal slices. Based on the method of Eritaia *et al.* (2000), the intra-cranial cavity (ICC) was traced manually in each slice using the anatomical landmarks. The ICV was calculated by summing the measured volumes of all slices. All inter- and intra-rater reliability scores were equal to or greater than 0·82, demonstrating adequate inter- and intra-reliability.

Statistical analysis

Analysis of covariance (ANCOVA), the *t* test, χ^2 and partial correlation analyses were conducted using SPSS version 10.0 (SPSS Inc.,

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Table 2. *Callosal measurements in patients with bipolar I disorder and healthy control subjects*

Callosal measurements	Patients with bipolar disorder ($n=12$)	Healthy control subjects ($n=12$)	p
Whole brain volume (cm^3)	1125·4±127·5	1134·7±140·6	>0·05
Grey matter volume (cm^3)	778·2±80·3	802·3±84·1	>0·05
White matter volume (cm^3)	347·2±23·2	332·4±30·8	>0·05
Anterior body (cm^2)	0·63±0·10	0·72±0·13	<0·036
Posterior body (cm^2)	0·57±0·14	0·66±0·19	<0·017
Callosal length (cm)	7·23±0·41	7·33±0·44	>0·05
Genu (cm^2)	2·21±0·27	2·28±0·40	>0·05
Isthmus (cm^2)	0·46±0·17	0·58±0·15	<0·0023
Splenium (cm^2)	1·79±0·50	1·81±0·59	>0·05
Splenium circularity (cm)	0·78±0·09	0·71±0·15	>0·05
Total callosal (cm^2)	6·01±0·88	6·76±1·12	<0·014

The significance of differences was determined by two-way and one-way analyses of variance (ANOVAs), followed by Bonferroni's test for multi-group comparisons.

Chicago, IL, USA). The significance of differences was determined by two-way and one-way analyses of variance (ANOVAs), followed by Bonferroni's test for multi-group comparisons. For correlation purposes, partial correlation analyses were conducted.

RESULTS

Demographic variables

There were no significant differences in the demographic variables of age and gender between the patients with bipolar disorder and healthy controls ($p>0·05$), as shown in Table 1.

ICV measurements

The ICV volumes in patients with bipolar disorder and control subjects were not statistically significantly different ($1412·4\pm135·3\ cm^3$ *v.* $1446·1\pm144·5\ cm^3$). ANCOVA showed that gender had no significant main effect ($F=1·12$, $p=0·84$), and there was no significant main effect for group ($F=0·71$, $p=0·75$) or group × gender interaction ($F=0·08$, $p=0·84$). In addition, no differences were found for total grey and white matter volumes between groups.

CC measurements

Table 2 shows the CC measurements in first-episode patients with bipolar disorder and control subjects. The bipolar patients had significantly smaller areas of total CC, anterior body, posterior body and isthmus compared with healthy control subjects [ANCOVA with age, gender, ICV and white matter as covariates: $F=4·52$, $p=0·041$; $F=6·49$, $p=0·019$; $F=4·04$, $p=0·045$; $F=5·41$, $p=0·036$; and $F=5·82$, $p=0·027$ respectively]. There was no main effect for gender ($F=1·06$; $p=0·82$).

Clinical correlations

There were negative correlations between total CC, posterior body and isthmus areas and the YMRS scores ($r=-0·52$, $p=0·0038$ for total CC; $r=-0·59$, $p=0·0024$ for posterior body; and $r=-0·60$, $p=0·0019$ for isthmus; partial correlation coefficient, controlled for age).

DISCUSSION

To the best of our knowledge, no prior study has measured CC areas in first-episode bipolar patients. However, it has been well established that psychopharmacological interventions and psychotherapeutic approaches can affect both the activity and measurements of brain areas. Thus, we considered it important to evaluate the brain areas of interest and activity levels in first-episode psychiatric patients. We therefore performed an MRI study in first-episode patients with bipolar disorder, focusing on the *in vivo* neuroanatomy of CC areas to further evaluate the hypothesis of abnormalities in CC volumes in bipolar patients and their possible involvement in the pathophysiology of the disease. The major findings we found in the present study were as follows: (i) bipolar patients had significantly smaller areas of total CC, total

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body and isthmus compared with healthy control subjects; (ii) there was a negative correlation between total CC, posterior body and isthmus areas and the YMRS scores. There are a limited number of studies evaluating CC abnormalities in patients with bipolar disorder. In the first controlled MRI study performed by Coffman *et al.* (1990), CC areas were found to be smaller in bipolar patients compared with normal control subjects. Brambilla *et al.* (2003) found that bipolar I patients had significantly smaller total CC, genu, anterior body, posterior body and isthmus areas compared with right-handed healthy control subjects. However, Hauser *et al.* (1989) reported no callosal abnormalities despite an abnormally short callosal length. A smaller CC has been described in various psychiatric conditions. De Bellis *et al.* (1999) reported smaller total midsagittal areas of the CC and middle and posterior regions in patients with post-traumatic stress disorder while Keshavan *et al.* (2002*b*) found that patients with schizophrenia had a smaller CC, anterior genu, anterior body, isthmus and anterior splenium than normal controls, suggesting that impaired inter-hemispheric communication may be a common feature of several neuropsychiatric disorders, as noted by Brambilla *et al.* (2003). Brambilla *et al.* (2004) measured MRI signal intensities in the CC in patients with bipolar disorder. They found abnormally reduced myelination of the CC and concluded that this indicated a possible role for the CC in cognitive abnormalities and in the pathophysiology of bipolar disorder. Consequently, they proposed new MRI studies involving first-episode patients. Their study therefore increases the importance of our study, which comprises first-episode (manic episodes in 10 patients and mixed episodes in two patients) bipolar patients. Moreover, we can argue that abnormalities of CC subregions might have preceded the onset of the disease itself. We did not find any effects of gender on CC volumes in the patients with bipolar disorder and in the control subjects, in accordance with the study of Brambilla *et al.* (2003). It can therefore be assumed that male and female patients with bipolar disorder have similar patterns of structural brain abnormalities.

In the present study, there was a negative correlation between total CC, posterior body and isthmus areas and the YMRS scores. As far as we know, no investigation has evaluated the interaction between the severity of the disorder and CC areas apart from Brambilla *et al.* (2003), who reported that there was no correlation between HDRS scores and CC measures. The findings of our study emphasize an inverse association between the severity of bipolar illness and morphometric reductions of the CC. Given the small sample size, our findings of a relationship between the severity of bipolar illness and this reduction in CC size must be considered preliminary and require replication.

A few caveats on the limitations of this study should be considered before any conclusions can be drawn. First, the study design was not longitudinal. Further studies with a prospective longitudinal design should be performed to clarify the timing and course of the morphometric changes in the CC observed in bipolar disorder. Second, the small sample size is a limitation. Third, we did not evaluate the IQ levels of the patients and controls. However, as shown in Table 1, no difference was found with regard to education levels of the groups. Fourth, we only examined a limited section of the brain structures. An additional comprehensive assessment of multiple brain regions in the same group of subjects is essential for understanding the brain morphological characteristics underlying bipolar disorder.

In conclusion, we found a reduction in the CC areas in both male and female patients with bipolar disorder. The findings of the present study also suggest that there may be a degenerative process concerning the CC morphology in bipolar disorder patients. Combined imaging studies using technologies such as magnetic resonance spectroscopy and diffusion tensor imaging should be used to further investigate the integrity of the CC in bipolar disorder.

DECLARATION OF INTEREST

None.

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