Corpus callosum signal intensity in patients with bipolar and unipolar disorder

P Brambilla, M Nicoletti, R B Sassi, A G Mallinger, E Frank, M S Keshavan, J C Soares

Background: Anatomical abnormalities in the corpus callosum have been reported in magnetic resonance imaging (MRI) studies in patients with bipolar but not unipolar disorder. MRI signal intensity can be used as a putative index of corpus callosum myelination. 

Objectives: To measure MRI signal intensity in patients with bipolar and unipolar disorder to investigate abnormalities of corpus callosum myelination.

Methods: The study involved 29 DSM-IV bipolar patients (mean (SD) age, 35 (11) years; 16 male, 13 female), 23 DSM-IV unipolar patients (41 (10) years; 4 male, 19 female), and 36 healthy controls (37 (10) years; 23 male, 13 female). A 1.5T GE Signa magnet was employed, with a fast spin echo sequence. Corpus callosum signal intensity was obtained blindly using the semiautomated software NIH Image 1.62.

Results: Bipolar patients had lower corpus callosum signal intensity for all callosal subregions (genu, anterior and posterior body, isthmus, splenium) than healthy controls (ANCOVA, age and sex as covariates, p<0.05). No significant differences were found between unipolar and healthy subjects (ANCOVA, age and sex as covariates, p>0.05).

Conclusions: The findings suggest abnormalities in corpus callosum white matter in bipolar but not unipolar patients, possibly because of altered myelination. Such abnormalities could lead to impaired interhemispheric communication in bipolar disorder. Longitudinal MRI studies involving first episode and early onset bipolar patients will be necessary for a better understanding of the potential role of abnormalities of corpus callosum myelination in the pathophysiology of bipolar disorder.
for at least two weeks, and 18 bipolar subjects were on lithium monotherapy (age 33 (11) years; 10 male, 8 female; 14 euthymic, 4 depressed).

The study was approved by the University of Pittsburgh biomedical institutional review board. All subjects provided signed informed consent after having understood all the issues involved in participation.

The patients met the DSM-IV diagnostic criteria for unipolar or bipolar disorder, as determined by the structured clinical interview for DSM-IV (SCID), and had had no comorbid psychiatric disorder, current medical problems, or alcohol or substance abuse within the six months preceding the study. Patients’ clinical information was retrieved from psychiatric interviews and medical case notes. Healthy controls had no DSM-IV axis I disorders, as determined by the SCID-IV non-patient version (SCID-NP), no current medical problems, and no history of psychiatric disorders among first degree relatives. Patients and healthy controls did not differ significantly in educational level (16 bipolar patients, 15 unipolar patients, and 15 controls had completed high school; 13 bipolar patients, 8 unipolar patients, and 22 controls completed college or a professional school; $\chi^2 = 3.67$, $df = 2$, $p = 0.16$).

**MRI procedure**

MRI scans were acquired with a 1.5T GE Signa imaging system running Signa version 5.4.3 software (General Electric Medical Systems, Milwaukee, Wisconsin, USA). Between 16 and 28 sagittal slices covering the entire brain were obtained, using a fast spin echo (FSE) sequence (time of repetition, 25 ms; time of echo, 17 ms; flip angle 40°; field of view, 24 cm; slice thickness, 3 mm; NEX = 1; matrix size, 256×192). Additionally, a double echo–spin echo sequence was used to obtain T2 and proton density images in the axial plane to screen for neuroradiological abnormalities.

**Corpus callosum measurements**

Using landmarks adapted from Witelson, a computer macro automatically divided the corpus callosum into five subregions: genu, anterior body, posterior body, isthmus, and splenium (fig 1). MRI signal intensity is the average pixel intensity in a selected region. Mean measures of MRI signal intensity were separately computed for circular regions of interest within each of the five subregions (fig 2A), and a homogeneous region of the vitreous humour was chosen as a control region in order to normalise the corpus callosum signal intensity measures (fig 2B). A trained rater, blind to group assignment and to subjects’ identity, conducted all signal intensity measurements (PB). The intra-class correlation coefficients for the MRI signal intensity measures were established on 10 training scans and were $r = 0.99$ for callosal subregions, and $r = 0.98$ for vitreous humour. The measures were conducted on an Apple Macintosh Power PC (Mac OS 7.5.5), using the semiautomated software NIH Image, version 1.62 (National Institutes of Health).

**Statistical analyses**

All analyses were conducted using the SPSS for Windows software, version 10.0 (SPSS Inc, Chicago, Illinois, USA), and the two tailed statistical significance level was set at $p < 0.05$. All measures were normally distributed, as determined by the Shapiro–Wilks test. The MRI signal intensity measures for corpus callosum were corrected for the signal intensity of the vitreous humour by dividing the individual signal intensity within each corpus callosum subregion by the respective vitreous humour signal intensity, and multiplying the result by the mean vitreous humour signal intensity of the corresponding group. Analysis of covariance (ANCOVA) with age and sex as covariates was done to compare the values of corpus callosum MRI signal intensity among bipolar patients, unipolar patients, and healthy controls. The non-parametric Mann–Whitney U test was used to perform comparisons between bipolar patient subgroups. Analysis of variance (ANOVA) with the Scheffé test as a post-hoc test was used to evaluate the effects of sex on corpus callosum MRI signal intensity.
Corpus callosum signal intensity in mood disorders

**RESULTS**

Bipolar patients had significantly reduced MRI signal intensity in all measured callosal regions compared with healthy controls (table 1; fig 3) (ANCOVA, age and sex as covariates; genu: F = 6.95, df = 1/61, p = 0.01; anterior body: F = 7.38, df = 1/61, p = 0.001; posterior body: F = 6.96, df = 1/61, p = 0.01; isthmus: F = 7.07, df = 1/61, p < 0.01; splenium: F = 7.43, df = 1/61, p < 0.01). Furthermore, there were trends to reduced MRI signal intensity values (ANCOVA, age and sex as covariates; genu: F = 4.10, df = 1/48, p = 0.05; anterior body: F = 4.09, df = 1/48, p = 0.05; posterior body: F = 3.89, df = 1/48, p = 0.05; splenium: F = 3.86, df = 1/48, p = 0.05), and significantly reduced values in the isthmus (F = 5.20, df = 1/48, p = 0.02) in bipolar compared with unipolar patients. Unipolar individuals did not differ significantly from healthy controls in any measures of callosal MRI signal intensity (genu: F = 0.11, df = 1/55, p = 0.74; anterior body: F = 0.00, df = 1/55, p = 0.99; posterior body: F = 0.01, df = 1/55, p = 0.92; isthmus: F = 0.24, df = 1/55, p = 0.62; splenium: F = 0.00, df = 1/55, p = 0.94).

After considering educational level as a covariate, bipolar patients had significantly reduced corpus callosum signal intensity measures compared with unipolar patients and healthy controls (ANCOVA, age, sex, and educational level as covariates; p < 0.02). Moreover, no effects of length of illness were found on any callosal MRI signal intensity measures, as these did not differ significantly between the bipolar and unipolar groups after they were subdivided according to the respective medians for length of illness (bipolar patients: 14 subjects with <15 years of illness, 15 subjects with ≥15 years of illness; unipolar patients: 11 subjects with <9 years of illness, 12 subjects with ≥9 years of illness; ANCOVA, age and sex as covariates, p > 0.05). No significant differences were found between lithium treated and drug-free bipolar patients for callosal signal intensity measures (Mann–Whitney test, p > 0.05).

No significant relation was found between age and MRI signal intensity measures in any callosal subregion in bipolar patients, unipolar patients, or healthy controls (Pearson correlation coefficients, p > 0.05). There was no significant correlation between any callosal signal intensity measures and specific clinical variables in either bipolar patients (mean (SD) length of illness, 15 (10) years, median 15; mean number of previous affective episodes, 16 (16), median 6.5; mean HDRS, 8 (10), median 4; mean lithium dose in lithium treated patients, 1104 (358) mg/day, median 975; mean weeks on lithium in lithium treated patients, 134 (250) weeks, median 28), or unipolar patients (mean length of illness, 11 (9) years, median 9; mean number of previous affective episodes, 4 (3), median 3; mean Hamilton depression rating scale score, 11 (9), median 12) (Spearman correlation coefficients, p > 0.05).

**DISCUSSION**

In this study we found abnormally reduced MRI signal intensity in bipolar but not unipolar subjects across various subregions of the corpus callosum. Such a reduction in MRI signal intensity may be caused by increased free water detectable by MRI in these brain regions, and may reflect decreased corpus callosum myelination. Previous controlled MRI studies reported decreased size of the corpus callosum in bipolar patients, indicating a possible role for callosal abnormalities in the pathophysiology of bipolar disorder. On the other hand, our findings suggest integrity of the corpus callosum in unipolar patients, which has also been suggested in two previous controlled anatomical MRI studies. Thus abnormally reduced myelination could underlie the findings of reduced corpus callosum size and MRI signal intensity in bipolar patients. Interestingly, such findings may be specific to bipolar disorder, and not present in unipolar disorder.

In normal development, the size of the corpus callosum increases up to the middle of the third decade of life, and such increases mainly reflect the ongoing myelination of higher association areas. The speed of interhemispheric information processing increases with age, and is thought to be associated with increased myelination and size of the corpus callosum. Furthermore, the corpus callosum plays a crucial role in higher cognitive functions, such as sensory-motor stimulations, attention, arousal, language, and memory, and increased myelination of the corpus callosum is thought to relate to increased cognitive capacity during adolescence. Thus a reduction in myelination in the corpus callosum of bipolar patients could lead to decreased speed or quantity of interhemispheric communication, and result in cognitive abnormalities. It is possible, therefore, that altered interhemispheric connectivity from reduced callosal myelination is relevant to the cognitive disturbances and pathophysiology of bipolar disorder.

Interestingly, controlled MRI studies have also shown abnormalities in the corpus callosum in other neuropsychiatric disorders of childhood and adolescence, such as schizophrenia, obsessive-compulsive disorder, Tourette syndrome, autism, attention deficit hyperactivity disorder, and dyslexia. These findings suggest that a callosal misconnection may be a feature of several neuropsychiatric disorders.

Some limitations of our study should be taken in account. We investigated bipolar patients at different illness stages, and did not enrol patients in their first episode. Our sample was mainly composed of young adults with several previous episodes of illness. For this reason, we were not able to examine whether the abnormalities in corpus callosum signal intensity preceded the onset of the illness or appeared subsequently as a result of the illness course. Age is an important factor when considering corpus callosum size or MRI signal intensity, as increases in size of the corpus callosum have been reported to occur during childhood and adolescence, and continue in young adulthood. Future longitudinal follow up MRI studies involving high risk and first episode juvenile bipolar individuals will be necessary to investigate corpus callosum development in bipolar disorder, and to investigate whether abnormalities of corpus callosum myelination may precede the appearance of symptoms. Furthermore, our unipolar group had a skewed sex distribution compared with the bipolar and healthy control groups, which is a potential limitation of our study design for

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Corpus callosum signal intensity</th>
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<tbody>
<tr>
<td>Subregion</td>
<td>Healthy controls (n = 34)</td>
</tr>
<tr>
<td>Genu</td>
<td>1.49 (0.37)</td>
</tr>
<tr>
<td>Anterior body</td>
<td>1.46 (0.35)</td>
</tr>
<tr>
<td>Posterior body</td>
<td>1.44 (0.33)</td>
</tr>
<tr>
<td>Isthmus</td>
<td>1.45 (0.34)</td>
</tr>
<tr>
<td>Splenium</td>
<td>1.47 (0.36)</td>
</tr>
</tbody>
</table>

Values are mean (SD). Units are arbitrary. All MRI signal intensity measures for corpus callosum subregions were corrected for the MRI signal intensity of the vitreous humour.

*MRI signal intensity was significantly reduced in bipolar patients compared with healthy controls (analysis of covariance (ANCOVA), age and sex as covariates; p < 0.01). No significant differences were found between unipolar patients and healthy controls (ANCOVA, age and sex as covariates; p > 0.05).
findings relating to unipolar disorder. However, sex composition was taken into account in our analyses by including sex as a covariate. Finally, the finding of reduced corpus callosum signal intensity in bipolar patients could be explained by factors other than myelinisation—for example, changes in sizes of axons or changes in intra-axonal microtubular density.10 15 25 26 27 Thus neuropathological studies of the corpus callosum will be needed to clarify the basis of the reduced MRI signal intensity in patients suffering from bipolar disorder.

Conclusions

To our knowledge, this is the first study reporting abnormally reduced MRI signal intensity in the corpus callosum in patients with bipolar disorder. These findings suggest abnormally reduced myelination of the corpus callosum in this disease. Our findings also provide further evidence for a possible role of the corpus callosum in cognitive abnormalities and in the pathophysiology of bipolar disorder.12 13 15 17–19 55 56 but not of unipolar disorder.14 15 Longitudinal MRI studies involving larger patient samples should try to replicate these findings. Studies involving early onset cases, first episode patients, and high risk populations will be needed for further characterisation of the relevance of these abnormalities to the development of the illness. Furthermore, studies using novel magnetic resonance techniques that provide more information on white matter composition (for example, diffusion tensor MRI or magnetisation transfer imaging)28 and necropsy histology will be extremely helpful in clarifying whether decreased corpus callosum signal intensity in bipolar patients reflects decreased myelination.

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Oral atypical antipsychotics for agitated patients in emergency situations

Support for the use of atypical antipsychotics for treating agitated patients in emergency situations comes from a recent review of published studies.

Five trials were identified with a total of 711 subjects. Atypical antipsychotics were found to be at least as effective as the classic antipsychotics and/or benzodiazepines and with fewer extrapyramidal side effects. A lack of consistency among the studies meant that it was not possible to perform meta-analysis. Instead improvement rates were reported. Risperidone, ziprasidone and olanzapine were all identified as potential atypical antipsychotics which could be used.

A further review in the same report looked at 11 trials only comparing classic antipsychotics with benzodiazepines and/or a combination of both. This review, with 701 subjects, was less conclusive but found that combination treatment might be superior to either agent alone, and suggested combining haloperidol with lorazepam as an effective approach.

Overall the review recommended oral treatment over intramuscular treatment as being more appropriate for the treatment of agitated patients in emergency settings. The onset of action of intramuscular drugs was not significantly faster to warrant their use as a first intervention, and it recommended that they should be reserved for patients for whom it is the only feasible alternative.

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