A study of bipolar disorder using magnetization transfer imaging and voxel-based morphometry

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Summary

Bipolar disorder (BP) traditionally has been considered as a recurrent illness with full recovery between episodes, and the absence of neuropathological abnormalities has usually been taken for granted. In recent times, the realization that, for many BP carries a poor prognosis, that cognitive deficits are often persistent and that structural brain abnormalities are detectable with modern imaging techniques has spurred the search for its neuropathological substrate. The shortcomings of post-mortem studies make the use of imaging techniques sensitive to neuropathological changes compelling. We report here the first study of BP patients using two such techniques in conjunction: magnetization transfer imaging (MTI) and voxel-based morphometry (VBM). Thirty-nine patients with BP (13 males and 26 females; 28 with BPI and 11 with BPII) and 35 healthy controls were investigated. Both high-resolution volumetric T1-weighted images and MT images were acquired from all subjects. Images were processed using a voxel-by-voxel analysis in statistical parametric mapping 2 (SPM2). The magnetization transfer ratio MTR, an index indicative of loss of macromolecular density, was reduced in the right subgenual anterior cingulate and adjacent white matter in bipolar patients compared with controls. VBM did not reveal significant volumetric differences between BP patients and controls in grey and white matter, but white matter density was significantly reduced bilaterally in prefrontal areas encompassing fronto-striatal connections. Our findings suggest that subtle abnormalities are present in the anterior cingulate and subgyral white matter in patients with BP in the absence of significant volumetric changes. These findings are in keeping with those of previously reported neuropathological studies and illustrate important similarities (involvement of the anterior cingulate) and differences (lack of widespread cortical abnormalities in BP) with our previous studies in schizophrenic patients using the same methodology.

Keywords: magnetization transfer imaging; voxel-based morphometry; bipolar disorder; neuroimaging

Abbreviations: BP = bipolar disorder; ECT = electroconvulsive therapy; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders—4th edition; FWHM = full width half maximum; MNI = Montreal Neurological Institute; MTI = magnetization transfer imaging; MTR = magnetization transfer ratio; PDw = proton density weighted; SPGR = spoiled gradient recalled echo; SPM = statistical parametric mapping; SVC = small volume correction; VBM = voxel-based morphometry

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Introduction

Bipolar disorder (BP) has been considered, since its original description (Kraepelin, 1921), as a benign condition where recovery between episodes was the norm. This concept, embedded in the modern classificatory systems, carries the implied assumption that brain pathology is absent. More recently, the increasing recognition of cognitive deficits (Martinez-Aran et al., 2000), poor functional outcome (Zarate et al., 2000) and, particularly, brain imaging abnormalities in these patients has spurred the search for the specific neural substrate of the disorder.

A meta-analysis of structural MRI studies (Elkis et al., 1995) confirmed the presence of generalized, non-specific abnormalities such as ventricular enlargement, sulcal prominence and T2 signal hyperintensities (Altshuler et al., 1995). Converging evidence from structural and functional neuroimaging (for a review see Drevets, 2000) and from neuropathological studies (for a review see Harrison, 2002) suggests a more specific role for the anterior cingulate and the prefrontal cortex. Reduced grey matter volume in the left subgenual anterior cingulate has been described in familial BP
patients (Drevets et al., 1997) and in first-episode affective psychosis (Hirayasu et al., 1999). Cerebral blood flow and metabolism are decreased in the subgenual prefrontal cortex in familial BP patients (Drevets et al., 1997). Euthymic normal subjects with induced sadness and depressed BP both show blood flow changes in the cingulate and in orbito-frontal regions (Krüger et al., 2003), and some of these changes seem to be reversed by antidepressant treatment (Mayberg et al., 2000).

Reduction in the number and density of glial cells, reduced neuronal size, neuronal density, decreased clustering of neurons (Benes et al., 1991; Öngür et al., 1998; Bouras et al., 2001; Cotter et al., 2001a; Chana et al., 2003) and reduction in synaptic markers such as synaptophysin, growth-associated protein-43 (GAP-43) and complexin II (Eastwood and Harrison, 2001) have been described in the anterior cingulate. The decreased cerebral blood flow and metabolic activity described by functional imaging studies (Drevets, 2000) are in keeping with these findings. Similar abnormalities have been found in orbital and dorso-lateral prefrontal cortex (Rajkowska et al., 2001). Less clear-cut abnormalities have also been described in the temporal lobes (Beyer and Krishnan, 2002).

The cause and specificity of these neuropathological changes have yet to be established, but the absence of gliosis and the presence of abnormalities early in the disease argue against a neurodegenerative aetiology.

The shortcomings of post-mortem studies (i.e. small samples, insufficient clinical documentation, difficulty in separating disease-related from co-morbid findings) make the use of neuroimaging to study brain abnormalities in psychiatric populations compelling. This applies especially to techniques with increased neuropathological sensitivity capable of detecting abnormalities before they lead to brain atrophy. Two techniques that are particularly interesting in this context are magnetization transfer imaging (MTI) and voxel-based morphometry (VBM). MTI (Wolff and Balaban, 1989) is based on the interaction of protons bound to macromolecular structures and free protons in tissue water. In brain, the major macromolecules in the bound proton pool are the cell membrane proteins and phospholipids in grey matter and myelin in white matter. Bound protons (undetected by conventional MRI because of their very short relaxation times) can be preferentially saturated using an off-resonance radio frequency pulse. Chemical exchange or direct dipolar coupling transfers macromolecular saturation from bound to free protons, causing decreased longitudinal magnetization. This leads to a reduction in signal intensity, which is dependent on macromolecular density. The nature of the interaction sites has yet to be fully determined (Henkelman et al., 2001); however, creatine-containing compounds appear to be involved in through-space dipolar interactions to a greater extent than glutamine/glutamate, N-acetyl-aspartate and lactate, whilst chemical interaction may be more important for the latter (Meyerhoff, 1999). The degree of signal loss, measured in percentage units, is the magnetization transfer ratio (MTR). MTR correlates with in vivo measurements of N-acetyl-aspartate, a marker of neuronal integrity (Pendlebury et al., 1999), and MTR reduction correlates with myelin and axonal loss in the white matter in post-mortem tissue and in vivo in a range of neurological diseases (van Buchem and Tofts, 2000). Grey matter abnormalities have been studied less extensively, but Wallerian degeneration triggered by distant axonal damage and microscopic lesions are thought to explain cortical MTR reductions in multiple sclerosis (Cercignani et al., 2001). The first study from our group to use MTR in schizophrenia (Foong et al., 2001) reported widespread cortical MTR reductions in chronic patients and, more recently, MTR reductions have also been reported in the insula and medial prefrontal cortex in first-episode schizophrenic patients (Bagary et al., 2003). These abnormalities, detected in the absence of volumetric changes, are thought to reflect changes in the neuropil density (Selemon and Goldman-Rakic, 1999).

VBM is a fully automated whole brain image analysis technique that involves the voxel-wise comparison of concentrations and volumes of segmented grey and white matter between two groups of subjects (Ashburner and Friston, 1999, 2000; Good et al., 2001). It has the advantage that macroscopic differences are discounted using normalization, and differences in local tissue composition can be explored without resorting to the use of manually placed regions of interest. We have used this technique previously to study schizophrenia (Bagary et al., 2003).

To the best of our knowledge, this study is the first application of these techniques to the investigation of BP patients. Our hypothesis was that subtle abnormalities would be detected in prefrontal structures of BP patients even in the absence of volumetric changes.

Methods

Subjects

Thirty-nine patients (13 males, 26 females) with BP and a mean age of 38.8 years (range 21–63) were included in the study. Twenty-eight patients met a Diagnostic and Statistical Manual of Mental Disorders—4th edition (DSM-IV) diagnosis for BPI (10 males, 18 females) and 11 for BPII (three males, eight females). Patients were recruited from those attending out-patient clinics in inner London psychiatric hospitals (n = 27) and from responders to an advertisement placed in the journal of the Manic-Depressive Fellowship (n = 12). Subjects with co-morbid psychiatric conditions, history of neurological or systemic disease, head injury leading to unconsciousness and substance abuse were excluded. Five additional patients were excluded because they did not meet diagnostic criteria (two) or had a history of substance misuse and/or head injury (three).

Three patients were not receiving medication at the time of the study and information about medication was incomplete in five. The rest were receiving mood stabilizers (23 lithium, three sodium valproate, four carbamazepine and three lamotrigine) and/or antidepressants (11) and neuroleptics (nine). Five patients had received electroconvulsive therapy (ECT) in the past.

Thirty-five controls from a large pool of healthy volunteers recruited for other imaging studies at the Institute of Neurology...
were matched to the BP patients for age, gender, handedness and estimated pre-morbid IQ (Table 1).

The study was approved by the National Hospital for Neurology and Neurosurgery and Institute of Neurology Joint Research Ethics Committee and other relevant ethical committees. Written informed consent was obtained for all participants.

Clinical assessment
All BP patients were interviewed by one of us (S.B.) using the SCID (First et al., 1997). Information was collected about developmental milestones, education and employment, substance misuse, medical history, duration of illness, number of hospital admissions, medications, exposure to ECT and family history. All patients met DSM-IV diagnostic criteria for BP.

Nineteen patients were classified as ‘familial’. Of these, nine had a first-degree relative with BP and the remainder had a first- or second-degree relative affected by other mood disorders.

Pre-morbid IQ was estimated using the National Adult Reading Test (NART) (Nelson and Willison, 1991). Handedness was established with the Annett Handedness Questionnaire (Annett, 1970). Presence and severity of depressive symptoms at the time of interview were assessed using the Beck’s Depression Inventory (Beck et al., 1961).

MRI
Image acquisition
All subjects were scanned on a GE Sigma 1.5 T scanner (General Electric, WI) using a standard quadrature head coil. A sagittal localizing scan was acquired. A three-dimensional T1-weighted spoiled gradient recalled echo (SPGR) sequence generating 124 contiguous, 1.5 mm coronal slices [echo time (TE) 4.2 ms, repetition time (TR) 15 ms, inversion time (TI) 450 ms, field of view (FOV) 24 cm², 256 × 192 matrix, flip angle 20°] was used to acquire high-resolution volumetric images. The 1 × 1.2 × 1.5 mm acquisition matrix was automatically interpolated to 1 × 1 × 1.5 mm voxel size, during image reconstruction.

Oblique axial MT images were acquired parallel to the anterior–posterior commissural axis, with a dual spin echo-based sequence (TE 30/80 ms, TR 1720 ms, 28 contiguous 5 mm axial slices, 256 × 128 pixel image matrix, 24 cm² FOV) with and without a saturation pulse (16 ms, 23.2 μT Hamming appodized three lobe sinc pulse applied 1 kHz from water resonance). The images were automatically reconstructed by the scanner to 1 × 1 × 5 mm voxel size. The MT sequence (Barker et al., 1996) generated proton density images, T2-weighted images and MT-weighted images that were inherently registered to each other and to the calculated MTR image. The total scanning time was 45 min.

Table 1 Demographic data

<table>
<thead>
<tr>
<th>Demographic data</th>
<th>BP patients (n = 39)</th>
<th>Control group (n = 35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (male/female)</td>
<td>13/26</td>
<td>10/25</td>
</tr>
<tr>
<td>Age (years)</td>
<td>Range 21–63</td>
<td>Range 26–54</td>
</tr>
<tr>
<td></td>
<td>mean 39.1</td>
<td>mean 34.8</td>
</tr>
<tr>
<td>Illness duration (years)</td>
<td>Range 1–32</td>
<td>mean 13.2</td>
</tr>
</tbody>
</table>

Table 1 shows the demographic data for the BP patients and control group.

Image processing
Following calculation of the MTR, images were processed on Sun Ultra workstations (Sun Microsystems, CA) using statistical parametric mapping 2 (SPM2; Wellcome Department of Cognitive Neurology, London, UK) in MATLAB (MathWorks, MA).

The SPGR images were re-oriented into oblique axial slices aligned parallel to the anterior–posterior commissural axis and the origin was set to the anterior commissure.

For each subject, the non-MT-weighted, first echo of the MTI scans (proton density weighted, PDw) was registered into the same space as the SPGR, using normalized mutual information as the cost function (Studholme et al., 1996). The registration parameters were then applied to the inherently co-registered MTR images. At this stage, for each subject, the SPGR, the PDw and the MTR were all in the same space.

Next, the SPGR images were processed according to a method that optimizes segmentation for VBM, as described by Good et al. (2001). In brief, this involves first the creation of a customized template and customized white matter, grey matter and CSF a priori probability density images, followed by an iterative procedure for segmentation and normalization of images.

Creation of the templates
The SPGR images were spatially normalized to the standard Montreal Neurological Institute (MNI) T1 template in SPM2 and re-sliced to 2 × 2 × 2 isotropic voxels. Normalization involved two steps: estimation of the optimum 12 parameter affine transformation, followed by 16 non-linear iterations (Ashburner and Friston, 1999). The images were segmented into white matter, grey matter and CSF, using image intensity non-uniformity corrections (Ashburner and Friston, 2000). In SPM, the segmentation algorithm is based on cluster analysis combined with a priori knowledge of tissue distribution (Ashburner and Friston, 2000). During template creation, the standard SPM priors were used for this purpose. Normalized structural images were then averaged and the resulting image was smoothed with an 8 mm Gaussian kernel to create a customized template. Grey matter, white matter and CSF segments were also averaged and smoothed with an 8 mm Gaussian kernel to create template images for the three classes of tissues. These three templates are used as priors during image segmentation, and the grey matter template is also used as a target for image normalization, as described below.

Normalization and segmentation
The original axial structural images underwent automatic segmentation (using the customized grey matter, white matter and CSF priors) and brain extraction, producing extracted grey and white matter partitions in native space. The extracted segmented grey matter images were then normalized to the previously created grey matter template and the normalization parameters were reapplied to the original structural SPGR images, and to the co-registered PDw and MTR images. Finally, the optimally normalized whole brain structural SPGR images were segmented, producing grey, white matter and CSF maps in MNI space. Voxel values in segmented images were multiplied by the Jacobian determinants derived from spatial normalization to provide intensity correction for induced regional volumetric changes, thus preserving within-voxel volumes that may have been altered.
during non-linear normalization (Ashburner and Friston, 2000). The analysis of these ‘modulated’ data tests for regional differences in absolute tissue volume. Unmodulated data analysis is a complementary test for regional differences in tissue concentration per unit volume based on differences in image intensity. The images were smoothed to 12 mm using a FWHM (full width half-maximum) Gaussian filter. As a consequence of smoothing, each voxel in these ‘unmodulated’ images contains the average concentration of grey matter from around that voxel, while each voxel in the ‘modulated’ images contains an absolute measure of grey matter volume.

Normalized PDw images were skull-stripped using the brain extraction tool (BET) from the FSL library (www.fmrib.ox.ac.uk/fsl). The extracted brain images were then used to mask the normalized MTR maps, thus removing the scalp and the background noise.

The MTR images were smoothed to 15 mm using a FWHM Gaussian filter. A larger kernel was chosen for these images due to their lower original resolution (Friston et al., 1996; Stoeckael et al., 2001).

Statistical analysis

T-tests and Mann–Whitney U tests were used to compare continuous and categorical demographic variables.

A group comparison of BP patients and healthy controls was performed in SPM2 using the model ‘compare-populations: one scan/subject (two sample t test)’ with default threshold (0.8). The analysis is based on the general linear model and the theory of Gaussian random fields. For the SPGR data, this framework allows the testing, on a voxel-by-voxel basis, of the null hypothesis that the grey matter volume and concentration in the two populations (patients and controls) is the same. Similarly, for the MTR data, one can test the null hypothesis that the average MTR value in the two populations is the same. The resulting statistical parameters constitute a SPM of the t statistic (SPM (t)). Gaussian random fields theory provides a method for correcting P values for multiple comparisons as an alternative to the Bonferroni correction. Given the strong suggestions from previous studies that the main site of neuropathological abnormalities in BP is the anterior cingulate, we restricted the analysis to this region using a small volume correction (SVC). A sphere of 15 mm radius was placed bilaterally on the subgenual anterior cingulate, which was identified using MRICro (Rorden and Brett, 2000).

In this study, we have used both voxel and cluster analysis. When performing the voxel analysis, P values <0.05 were considered significant, after correction for the entire search volume. When performing a cluster analysis, the uncorrected P values were used, together with some spatial extent thresholds. In this kind of analysis, the P values are based on the probability of obtaining a cluster of a given number of adjacent voxels, all showing statistical significance.

We also compared ‘familial’ patients with matched healthy controls as previous literature (Drevets, 2000) suggested the presence of more severe abnormalities in this group. To investigate possible disease effects, BPI and BPII patients were compared with controls separately. Correlations with age and duration of illness were explored using the SPM02 model ‘single subject: covariates only’ where age and duration of illness were introduced as covariates of interest. This model allows identification of the regional pattern of these correlations.

Results

There were no significant age or gender differences between patients and controls (see Table 1). There were no significant differences between BPI and BPII in age, gender, number of admissions, age of onset and duration of illness. The same applies to familial and non-familial patients.

MTI

In the SVC area corresponding to the right subgenual anterior cingulate and adjacent white matter, MTR was significantly reduced (P = 0.025 family-wise error correction and P = 0.017 false discovery rate correction with peak voxel at MNI coordinates [16, 24, −10]) in BP patients compared with controls (Fig. 1). When the whole brain was compared, no significant differences in MTR between the two groups were found using both cluster and voxel level statistics.

There were no MTR differences between familial and non-familial BP patients and between BPI and BPII patients.

MTR reduction correlated with age in BP patients and in healthy controls in both temporal lobes. No such correlation was detected in the SVC area that included the cingulate. There was no correlation between MTR reduction and duration of illness.

Voxel-based morphometry

There were no differences in grey matter concentration and volume between patients and controls using the whole brain analysis or SVC. There were no differences between the groups in white matter volume, but white matter concentration was reduced bilaterally in pre-frontal areas in clusters with peak voxel at MNI coordinates [24, 36, 10] (corrected P = 0.001) on the right and [−22, 38, 0] (corrected P = 0.02) on the left (Fig. 2).

There was no significant correlation between changes in white matter concentration and age or illness duration.

Discussion

In this first MTI and VBM study of bipolar disorder, we have demonstrated the presence of structural abnormalities in the anterior cingulate in the absence of volumetric loss. In addition, prefrontal white matter abnormalities encompassing fronto-striatal connections were also detected using VBM.

Some limitations to this study need to be considered. First, there are potential problems in the use of voxel-by-voxel analysis (Bagary et al., 2003). In essence, this analysis, originally intended for use in large samples, requires smoothing of the images, with loss of resolution for small structures, and the large number of comparisons requires corrections that greatly reduce the power of the study. This could explain why we did not find significant MTR differences between BP patients and controls on a whole brain analysis. Secondly, the small size of our subgroups (BPI and BPII, familial and
non-familial) makes the results vulnerable to type I or type II
errors and precludes generalization of our findings, although
we felt justified in tentatively exploring differences
between these subgroups. Thirdly, the location of the MTI
and VBM abnormalities overlapped but was not identical.
This apparent inconsistency could be due to the use of a region
of interest (SVC) that, while increasing the power of the

Fig. 1 (A) A statistical parametric map showing significantly
lower MTR in the right prefrontal subgenual cingulate cortex and
subgyral white matter in bipolar patients compared with healthy
controls in a ‘glass brain’ projection. (B) The same statistical
parametric map (thresholded at $T = 3.21$) projected on orthogonal
sections through a T1-weighted averaged image. The orthogonal
lines cross at MNI coordinates $[16, 24, -10]$ corresponding to
the greatest MTR reduction.

Fig. 2 (A) A statistical parametric map showing significantly
lower white matter density in bilateral frontal white matter in
bipolar patients compared with healthy controls in a ‘glass brain’
projection. (B) The same statistical parametric map (thresholded
at $T = 3.21$) projected on contiguous 2 mm thick axial
T1-weighted averaged images, throughout the area of significantly
lower white matter density. The numbers at the left bottom
corner of each section represent the $z$ MNI coordinate.
analysis by reducing the number of comparisons, may exclude potentially abnormal areas. Furthermore, the segmented VBM images, with a slice thickness of 1.5 mm, have higher resolution and ability to differentiate white and grey matter abnormalities than the unsegmented MTI images with a slice thickness of 5 mm. Additionally, segmented grey matter and white matter have a smaller search volume, which affects sensitivity.

Studies comparing global grey matter volumes, with the exception of that of Lim et al. (1999), have not reported significant changes, but those using the region of interest approach, more suitable to investigate small structures such as the subgenual anterior cingulate, have reported significant results (Drevets et al., 1997; Hirayasu et al., 1999; Sharma et al., 2003). The same applies to a small study looking at grey matter density in BP patients with poor outcome (Doris et al., 2004). The evidence from neuropathological studies (Harrison, 2002) suggests that the abnormalities in the anterior cingulate are bilateral, while imaging studies have localized them to the right (our findings and those of Sharma et al., 2003) or to the left (Drevets et al., 1997; Hirayasu et al., 1999). There is no clear explanation for these discrepancies, although methodological differences in the imaging studies and the greater sensitivity of the microscopic findings are likely to be relevant.

In contrast to the findings of Drevets et al. (1997) and Hirayasu et al. (1999), we found no differences in MTR or VBM between familial patients and controls or between familial and non-familial patients, although the small numbers of these subgroups raise concerns about the validity of such comparisons. The same applies to our failure to detect differences between BPI and BPII patients.

The MT signal is largely dependent on the macromolecular density of cell membranes and phospholipids, and grey matter MTR reductions in our patients are likely to reflect decreases in the size and number of neurons and dendritic density, while those in the white matter are likely to reflect myelin changes and/or reduced axonal density. The neuropathological counterparts of our VBM findings are less clear. The reduced density of frontal white matter, resulting from altered MR signal, suggests a pathological process that alters tissue composition and decreases its probability to be recognized as white matter. This is in keeping with the presence of white matter abnormalities, such as focal areas of signal hyperintensity described in a variety of affective disorders (Altshuler et al., 1995).

The mechanisms responsible for the abnormalities reported here are still unclear. One possibility is that stress-induced hyperactivity of the hypothalamic–pituitary–adrenal axis may lead to cell damage through glucocorticoid-mediated glutamatergic neurotoxicity and reduced astrocytic activation, with decreased uptake of glucose and altered neuronal metabolism resulting in reduced neuronal volume and dendritic arborization (Cotter et al., 2001b). This process is unlikely to be specific to BP, and may operate in major depression, schizophrenia and post-traumatic stress disorder.

A genetic and/or developmental process could explain the structural abnormalities present in the early stages of the illness (Hirayasu et al., 1999), and plasticity-related changes in neural circuitry (i.e. synaptic alterations) may also be relevant. Some support for the latter accrues from the work of Benes et al. (2000) who described reduction in GABAergic terminals in the anterior cingulate and prefrontal cortex.

The functional significance of these abnormalities is, on the other hand, easier to understand. The medial prefrontal cortex is part of a cortico-striatal-pallido-thalamic circuit implicated in regulation of mood and behaviour (Price, 1999), and bilateral damage to the anterior cingulate cortex in neurological patients is known to produce abnormal emotional responses to complex stimuli (Damasio, 1997) and impairment of decision making in relation to risk and reward (Bechara et al., 1997). The abnormalities in the anterior cingulate gyrus and prefrontal white matter could also account for some of the cognitive deficits encountered in BP patients and in particular difficulties with selective attention, task monitoring and working memory (Clark et al., 2002). The possibility that our results could be due to medication needs to be considered. However, we were not able to examine this possibility directly as only three of our patients were unmedicated at the time of the study and the others were receiving mood stabilizers and some also had neuroleptics and antidepressants. There is little support in the literature for medication-related neuropathological changes of the type described here. On the contrary, increases in grey matter volume and in the neuronal marker N-acetyl-aspartate in BP patients re-scanned after 4 weeks of lithium treatment (Moore et al., 2000a,b) suggest a neuroprotective and neurotrophic role. There is experimental evidence that antidepressants may promote axonal regeneration and neurogenesis and prevent loss of dendritic spines (Harrison, 2002). Animal studies mainly using haloperidol (Harrison, 1999) suggest that, apart from alterations of synaptic populations in the basal ganglia, neuroleptics do not cause persistent neuropathological abnormalities. Our strict inclusion criteria make it unlikely that drug or alcohol abuse could account for the imaging abnormalities.

The findings of this study have some similarities to, but also important differences from the results of our previous studies in schizophrenia using the same methodology. MTR reduction was detected bilaterally in the anterior cingulate in patients with first episode schizophrenia (Bagary et al., 2003), but even at this early stage of the illness, in contrast to BP patients, MTR abnormalities extended to the insula and fronto-temporal white matter in schizophrenic patients. Similarly, the widespread cortical MTR reductions present in chronic schizophrenics (Foong et al., 2001) were absent in BP patients. The more circumscribed brain abnormalities in BP patients exclusively involving areas related to mood regulation might explain the better outcome in BP disorder compared with schizophrenia.
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References


