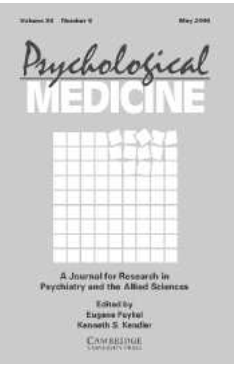

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Structural brain correlates of IQ changes in bipolar disorder

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ABSTRACT

Background. There is increasing evidence that cognitive deficits are present in bipolar disorder (BP), but their neural correlates have not been fully explored. The aim of this study is to correlate structural brain abnormalities with cognitive performance in BP and to explore differences between clinical subtypes.

Method. Thirty-six BP patients (13 men, 23 women) with a mean age of 39 years (range 21–63 years) underwent neuropsychological testing and imaging. Twenty-five patients had bipolar disorder I (BP I) and 11 had bipolar disorder II (BP II). Patients with co-morbid psychiatric diagnosis, drug and alcohol abuse or systemic illness were excluded. Correlations between cognitive performance and structural brain changes were explored using high-resolution anatomical imaging and magnetization transfer imaging (MTI).

Results. In the whole BP group the difference between estimated pre-morbid IQ and current IQ was significantly correlated with left-sided reduction of the magnetization transfer ratio (MTR) in the superior temporal gyrus, uncus and para-hippocampal gyrus. In BP II patients the areas where these correlations were significant extended to the right superior and middle temporal gyri, cingulate gyrus, pre-cuneus and adjacent frontal and parietal white matter. The volume of superior temporal white matter was also correlated with IQ difference in this subgroup.

Conclusions. The study highlights the association between fronto-temporal abnormalities and decline in IQ in BP. The more extensive abnormalities present in BP II patients suggest that persistent depression, rather than mania, may be a key pathophysiological factor or that BP II represents a clinical phenotype with a higher risk of developing cognitive abnormalities.

INTRODUCTION

Cognitive abnormalities are commonly observed in patients with bipolar disorder (BP) while euthymic, and during depressive and manic episodes (Quraishi & Frangou, 2002), but much less is known about the neural substrate of these abnormalities and whether they are specific to BP or overlap with those in unipolar depression and schizophrenia.

A number of recent reviews (Martínez-Arán *et al*. 2000; Bearden *et al*. 2001; Quraishi & Frangou, 2002; Taylor Tavares *et al*. 2003; Savitz *et al*. 2005) go some way to clarify the pattern of the abnormalities and their relationship to the clinical status of the patient. These studies suggest that deficits in attention, verbal memory, executive functions and, to a lesser extent, non-verbal memory are common in acutely depressed and manic patients, especially when psychotic symptoms are present, and that in many cases their severity is comparable to that seen in schizophrenia. In euthymic patients verbal memory is the function most often impaired. Some studies (Gourovitch *et al*. 1999; Kéri *et al*. 2001) have also found impaired verbal memory in unaffected monozygotic twins and

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siblings of BP patients, suggesting that it may be a genetically determined trait abnormality. Impairment of non-verbal memory and executive function in euthymic patients has also been reported (Rubinsztein *et al*. 2000; Thompson *et al*. 2005). A number of studies have consistently indicated that impaired neuropsychological performance is related to poor functional outcome (Atre-Vaidya *et al*. 1998; Zarate *et al*. 2000) and employment status (Dickerson *et al*. 2004).

The neural substrate of cognitive deficits remains to be established. Diffuse loss of cerebral volume, albeit less severe than that present in schizophrenia, has often been described in BP (Elkis *et al*. 1995). In common with other affective disorders, cortical and peri-ventricular white- matter hyperintensities in T_2-weighted magnetic resonance imaging (MRI) are present in BP (Figiel *et al*. 1991). Although such hyperintensities have been described at first hospitalization (Strakowski *et al*. 1993), they are more common in patients with chronic or late-onset BP (McDonald *et al*. 1991). White-matter hyperintensities are associated with vascular risk factors, poor clinical and functional outcome (Moore *et al*. 2001) and cognitive impairment (see Bearden *et al*. 2001, for review).

Volumetric changes in the temporal lobes have also been described in patients with BP (Beyer & Krishnan, 2002), but while some (Altshuler *et al*. 1991) have found smaller volumes in BP patients than in controls, others have found the opposite (Harvey *et al*. 1994; Roy *et al*. 1998), or no difference (Hauser *et al*. 2000).

Of greater interest are the more consistently reported imaging abnormalities in the prefrontal cortex that have been characterized in neuropathological studies (see Harrison, 2002 for a review of neuropathology of mood disorders). Reduced grey-matter volume in the left sub-genual anterior cingulate was first described in familial BP patients by Drevets *et al*. (1997) and later in first-episode affective psychosis by Hirayasu *et al*. (1999). Functional imaging studies have confirmed the involvement of these areas in mood regulation (Drevets, 2000).

The advantage of using multimodal imaging, with its potential for providing detailed information about tissue properties, is increasingly recognized (Kalus *et al*. 2005; Kubicki *et al*. 2005) and we have adopted this approach in previous studies (Foong *et al*. 2001; Bagary *et al*. 2003; Bruno *et al*. 2004). Using magnetization transfer imaging (MTI), an imaging technique capable of detecting myelin and axonal abnormalities before volume loss becomes detectable (Filippi *et al*. 1995; Silver *et al*. 1997), and high-resolution anatomical imaging, we have recently described (Bruno *et al*. 2004) abnormalities in the anterior cingulate and frontal white matter of BP patients compared with healthy controls. Here we present a study exploring the neural substrate of cognitive changes in the same group of patients using the same imaging techniques.

METHOD

Subjects

Thirty-six patients (13 males, 23 females) with BP, mean age 39 years (range 21–63 years), were included in the study. Twenty-five patients met a DSM-IV diagnosis for BP I (10 men, 15 women; mean age 37·4 years) and 11 for BP II (3 men, 8 women; mean age 42·8 years). Patients were recruited from out-patient clinics in inner London psychiatric hospitals ($n=25$) and from responders to an advertisement placed in the *Journal of the Manic-Depressive Fellowship* ($n=11$). Subjects with co-morbid psychiatric conditions or with a history of neurological or systemic disease, of head injury leading to unconsciousness, or of drug or alcohol abuse were excluded. Although some of the patients had a history of psychotic symptoms, no such symptoms were present at the time of the study.

Two patients were not receiving medication at the time of the study, and for four others information about medication was incomplete. The rest were receiving mood stabilizers (23 lithium, 3 sodium valproate, 4 carbamazepine, 3 lamotrigine) and/or antidepressants (11) and neuroleptics (9). The BP I and BP II groups did not differ as regards type of medication. Five patients (3 with BP I, 2 with BP II) had received ECT in the past.

The study was approved by the relevant ethical committees. Written informed consent was obtained from all participants.

Clinical assessment

All patients were interviewed by a trained psychiatrist (S.B.) using the Structured Clinical Interview for DSM-IV Axis I Disorders (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, medication, exposure to ECT and family history of psychiatric illness. All patients met DSM-IV diagnostic criteria for BP. The severity of depressive symptoms at the time of the study was assessed using Beck's Depression Inventory (BDI; Beck *et al*. 1961).

Neuropsychological assessment

An extensive neuropsychological battery was administered by a research assistant (K.P.) supervised by a trained neuropsychologist (L.C.). The assessment lasted 2–4 hours, including a short interval between tests. Available standardized normative data were used for comparison. The details of the neuropsychological assessment will be reported elsewhere. Only tests yielding parametric scores in which BP patients performed significantly worse than the standardization sample (Table 1) were included in this study.

Pre-morbid IQ was estimated using the National Adult Reading Test (NART; Nelson & Willison, 1991). General intellectual function was assessed with the Wechsler Adult Intelligence Scale – Revised (WAIS-R; Wechsler, 1981), and a Full Scale IQ was obtained from four verbal (vocabulary, digit span, arithmetic and similarities) and three non-verbal (picture completion, picture arrangement and block design) subtests. The difference between the estimated pre-morbid and the WAIS-R Full Scale IQ was used in the analysis. Verbal and visual memory were tested using the Recognition Memory Test (Warrington, 1984); the Paired Associate Learning Test (Warrington, 1996); the Rey–Osterreith Complex Figure Test (Osterreith, 1944; Rey, 1964) and the Shapes subtest from the Doors and People test (Baddeley *et al*. 1994). Executive functions were evaluated with Modified Card Sorting Test (MCST; Heaton, 1981). Spatial working memory and set-shifting were assessed using the Spatial Working Memory test (SWM) and the Intra-Dimensional/Extra-Dimensional Shift test from the Cambridge Neuropsychological Test Automated Battery (CANTAB, Cambridge Cognition Ltd, Cambridge, UK). In Table 1 we report the patients' performance on the tests used in the analysis.

MRI techniques

We used MTI (Wolff & Balaban, 1989), an imaging technique that can detect subtle abnormalities in otherwise normal-appearing brain tissue in the absence of volume loss.

MTI exploits the preferential saturation of protons bound to macromolecular structures (which are undetected by conventional MRI because of their very short relaxation times) using an off-resonance radio frequency pulse. This induces a transfer of magnetization from bound protons to protons free in tissue water, which in turn produces a measurable loss of signal, quantified as the magnetization transfer ratio (MTR). In brain tissue the major macromolecules in the bound proton pool are the cell membrane constituents, proteins and phospholipids. In white matter the bound water is mainly trapped in myelin; therefore the reduction in the MTR reflects changes in myelin and/or reduced axonal density. In grey matter a reduced MTR is likely to reflect decreases in dendritic density and neuronal size and number. MTI has been successfully used by our group to detect subtle brain abnormalities in chronic and first-episode schizophrenia (Foong *et al*. 2001; Bagary *et al*. 2003).

We also used voxel-based morphometry (VBM), a fully automated technique for whole-brain analysis that involves the comparison of pre-determined volumes (voxels) of segmented grey and white matter between two groups of subjects without introducing operator bias. It allows regional comparisons of tissue volume by spatially normalizing the image to standard space. We have previously used this technique to study schizophrenia (Bagary *et al*. 2003) and BP (Bruno *et al*. 2004).

Image acquisition

All subjects were scanned on a GE Signa 1.5 T scanner using a standard quadrature head coil. A sagittal localizing scan was acquired. A 3-D T_1-weighted spoiled gradient recalled echo (SPGR) sequence generating 124 contiguous, 1·5-mm coronal slices (TE 4·2 ms, TR 15 ms, TI 450 ms, FOV 24 cm^2, 256×192 matrix, flip angle 20°) was used to acquire high-resolution volumetric images. The $1 \times 1{\cdot}2 \times 1{\cdot}5$ mm acquisition matrix was automatically interpolated to $1 \times 1 \times 1{\cdot}5$ mm voxel size during image reconstruction.

Table 1. *Standardized neuropsychological test scores for bipolar disorder I (BP I) and bipolar disorder II (BP II) subtypes, compared with published normative data*

Standardized neuropsychological test	Patients with BP I					Patients with BP II				
	Score		No. at or below specified centile of standard sample			Score		No. at or below specified centile of standard sample		
	Mean (S.D.)	Range	5th centile	10th centile	No. tested	Mean (S.D.)	Range	5th centile	10th centile	No. tested
IQ										
Pre-morbid IQ estimate (NART)	114·29 (9·88)				24	116·45 (5·34)				11
WAIS-R Full IQ	113·60 (18·01)	82–143	0	0	25	103·64 (12·09)	84–128	0	0	11
NART Full IQ – WAIS-R Full IQ	−0·50 (12·67)	−30 to 18	0	3	24	12·82 (8·93)	−7 to 24	2	5	11
Memory										
RMW	44·28 (6·29)	25–50	4*	6*	25	43·27 (4·67)	34–50	2*	4**	11
RMF	42·00 (5·02)	29–50	3	9***	24	37·82 (4·05)	31–43	4***	7***	11
Paired-Associate Learning										
Trial 1	18·68 (4·72)	6–24	3	5	25	15·36 (4·11)	9–20	3***	4**	11
Trial 2	22·72 (2·39)	13–24	1	2		22·36 (2·24)	17–24	1	4**	
Rey Recall	21·93 (5·99)	12·5–34		3	20	17·30 (9·04)	10·5–34		7***	10
DPVR: Shapes	31·92 (4·61)	21–36	3	5	25	27·91 (6·61)	19–36	5***	6***	11
Executive functions										
MCST[a]										
Total errors	9·17 (15·83)	0–77	4	6	23	11·09 (12·39)	1–35	5	6	11
Perseverative errors	4·13 (6·72)	0–31				3·90 (4·39)	0–12			
Intra-/Extra-Dimensional Set Shift										
Stages achieved	8·52 (0·846)	7–9	0	4	23	8·56 (0·882)	7–9	0	2	9
Total errors	19·74 (13·35)	7–57	2	7**		19·00 (11·11)	7–35	0	3*	
Adjusted error score	25·17 (21·46)	7–66	3	4		24·44 (20·43)	7–58	2*	3*	
Spatial Working Memory										
Between search errors	27·95 (22·73)	0–70	3	4	21	50·89 (25·10)	10–82	3***	4***	9
Strategy	34·71 (6·16)	20–45	4**	6**		38·78 (2·22)	34–41	5***	6***	

WAIS-R, Wechsler Adult Intelligence Scale – Revised; NART, National Adult Reading Test; RMW, Recognition Memory for Words; RMF, Recognition Memory for Faces; DPVR, Doors & People Visual Recall; MCST, Modified Card Sorting Test.

[a] Impairment on the MCST was based not on standardization data, but on a combination of number of categories achieved and total perseverative errors (Kapur *et al.* 2003).

* $p < 0{\cdot}05$, ** $p < 0{\cdot}01$, *** $p < 0{\cdot}001$ significance of the difference between the expected and actual numbers of BP patients scoring at or below the 5th or 10th centile of the standard sample.

Oblique axial magnetization transfer 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, FOV 24 cm^2) with and without a saturation pulse (16 ms, $23{\cdot}2 \times 10^{-3}$ mT Hamming appodized 3-lobe sinc pulse applied 1 kHz from water resonance). The images were automatically reconstructed by the scanner to $1 \times 1 \times 5$ mm voxel size. The MT sequence (Barker *et al*. 1996) generated proton-density images, T_2-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.

Image processing

Following calculation of the MTR, images were processed on Sun Ultra workstations (Sun Microsystems, Santa Clara, CA, USA) using SPM2 (Wellcome Department of Cognitive Neurology, London, UK) in MATLAB (MathWorks, Natick, MA, USA). The processing of the images is fully automated and, therefore, not subject to observer bias.

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, PDw and 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 cerebrospinal fluid (CSF) *a priori* probability density images, followed by an iterative procedure for segmentation and normalization of images. The use of customized templates improves the quality of the segmentation process (Good *et al*. 2001) and increases the sensitivity to small changes.

Normalization and segmentation

The original axial SPGR images underwent automatic segmentation (using the customized grey matter, white matter and CSF priors) and brain extraction, producing grey-matter 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-matter, white-matter and CSF maps in Montreal Neurological Institute (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 nonlinear normalization (Ashburner & Friston, 1999, 2000). The analysis of these 'modulated' data tests for regional differences in absolute tissue volume. The images were smoothed to 12 mm using a FWHM (full-width half-maximum) Gaussian filter. Smoothing has three fundamental advantages: it improves the signal-to-noise ratio in the images; it corrects for small anatomical variability and it makes the data more normally distributed, which is a prerequisite for the statistical analysis.

Normalized PDw images were skull-stripped using the brain extraction tool (BET) from the FMRIB Software 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, because of their lower original resolution (Friston *et al*. 1996; Stoeckael *et al*. 2001). The use of a large smoothing kernel also reduces the proportion of voxels in the brain with non-normally distributed residuals (Ashburner & Friston, 2000).

Statistical analysis

Demographic and clinical variables (age, age of onset, duration of illness and depressive symptomatology) for the BP I and BP II patients

were compared using the *t* test. The significance of the difference between the expected and actual numbers of BP patients scoring at or below the 5th or 10th centile of the standardized sample on various neuropsychological tests was explored using χ^2 tests (Table 1).

The correlations between performance on the cognitive tasks and structural abnormalities expressed as MTR change and change in grey-matter and white-matter volumes (VBM), were explored with SPM2 using multiple regression analysis, with the test scores being entered as covariates of interest and with age and gender being entered as nuisance variables. This was done first in the whole group of patients and subsequently in the two BP subgroups. We felt it was justified to examine cognitive/structural brain correlations separately in the two subgroups, as we have already demonstrated a different pattern of structural brain abnormalities (Bruno *et al*. 2004) and cognitive deficits (Summers *et al*. unpublished observations) in the same subgroups of BP I and BP II patients.

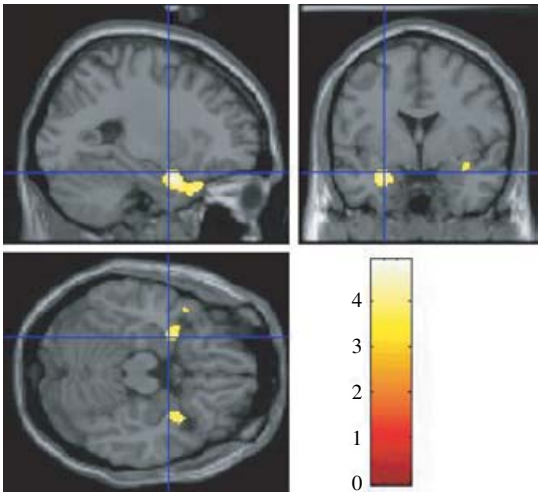

FIG. 1. Statistical parametric maps representing the areas of significant correlation between IQ reduction (measured as difference between NART IQ and WAIS-R IQ) and MTR reduction in the left superior temporal gyrus, the uncus and and the para-hippocampus in patients with BP, corrected for age and gender and overlaid on a T_1 image. The colour scale visually represents the degree of statistical significance (*t* value), with lighter colour indicating higher significance.

RESULTS

Demographic and clinical variables

The BP I and BP II groups did not differ significantly in mean age, age at onset of illness, duration of illness or number of admissions.

Eight patients (seven with BP I and one with BP II) scored in the mild, and five (two BD I and three BD II) in the moderate depression range of the BDI. For eight patients it was not possible to obtain BDI scores; of those, three met SCID criteria for current depressive episode, two did not and three did not complete the assessment.

The means and S.D.s of the neuropsychological test scores are shown in Table 1. Patients showed impairment in verbal and visual memory, attention, set-shifting and spatial working memory. BP II patients performed significantly worse than BP I patients when the two groups were compared with the standardization sample across the various cognitive domains.

Imaging

No gross structural abnormalities were present in any subject when the scans were reviewed by an experienced neuroradiologist.

MTI

The difference between pre-morbid IQ and current IQ correlated with lower MTR in the left and right temporal lobes of the BP patients analysed as a whole group. After correction for multiple comparisons only the cluster in the left temporal lobe remained significant ($p = 0{\cdot}034$, voxel analysis $p = 0{\cdot}08$). This cluster of MTR reduction, which corresponds to the left superior temporal gyrus, the uncus and the para-hippocampal gyrus has peak coordinates (-30, 6, -24) (Fig. 1). In order to ensure that the difference between pre-morbid IQ and current IQ, rather than these individual measures, accounted for the MTR reduction, we explored separately the correlations between MTR and pre-morbid IQ and between MTR and current IQ, but found no significant correlations between them.

When the subgroups were analysed separately, in BP I patients there were no significant correlations between IQ change and MTR reduction. In BP II patients there were areas of correlation between IQ decline and MTR reduction in both hemispheres, but only those involving the right superior and middle temporal gyri and sub-gyral white matter [after

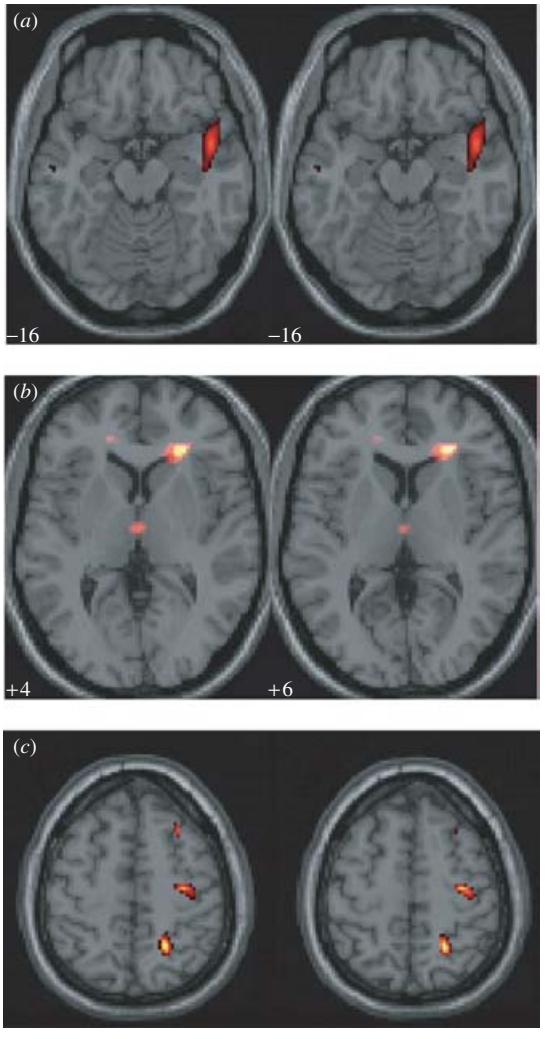

FIG. 2. Correlation between IQ reduction and lower MTR in the right superior and middle temporal gyri and sub-gyral white matter, the right anterior cingulate and surrounding white matter, the pre-cuneus and right parietal white matter in patients with BP II, corrected for age and gender and overlaid on an averaged T_1 image.

correction: cluster analysis $p=0{\cdot}001$; peak co-ordinates (48, −2, −16)], right cingulate gyrus, adjacent white matter and pre-cuneus [after correction: cluster analysis $p=0{\cdot}01$; peak co-ordinates (34, −16, 58)], frontal white matter [after correction: cluster analysis $p=0{\cdot}002$; peak coordinates (28, 34, 6)] and parietal white matter [after correction: cluster analysis $p=0{\cdot}001$; peak coordinates (22, −54, 56)] (Fig. 2*a*, *b*) remained significant after correction for multiple comparisons.

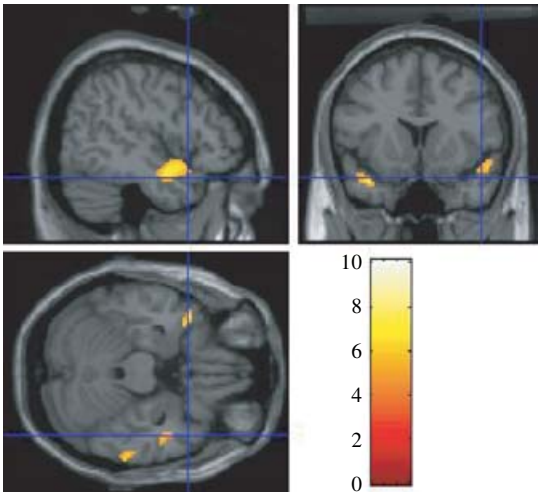

FIG. 3. Correlation between IQ reduction and loss of white-matter volume in left and right superior temporal sub-gyral white matter in patients with BP II, corrected for age and gender and overlaid on an averaged T_1 image.

VBM

There were no significant correlations between IQ decline and volumetric changes in the group as a whole or in BP I patients. In BP II patients IQ reduction was correlated with reduction in volume in the left and right superior temporal sub-gyral white matter. After correction for multiple comparisons these correlations reached statistical significance only on the left side [$p=0{\cdot}003$; peak coordinates (−46, −18, −12)] (Fig. 3).

No significant correlations were present between MTR or volumetric changes and the performance on memory and executive tests when the individual test scores were entered as covariates of interest.

DISCUSSION

This study proposes that the IQ changes observed in BP are associated with structural abnormalities detectable with highly sensitive MRI techniques. The reduction in IQ in patients with BP, although not severe, represents a global measure of cognitive deterioration that was linked to structural abnormalities in areas known to subserve important cognitive functions. Thus, the medial temporal structures, superior temporal gyrus, hippocampus and parahippocampal cortex are important for learning

and memory storage. The frontal cortex and the parietal cortex are important association areas, the former involved in judgement, planning and working memory, the latter subserving sensory integration and visuo-spatial functions (Kandel *et al*. 2000).

Structural abnormalities in frontal and temporal areas in patients with BP have been shown in previous studies, using voxel-based morphometry (Lochhead *et al*. 2004; Lyoo *et al*. 2004) and other studies (Coffman *et al*. 1990; Sax *et al*. 1999; Ali *et al*. 2000) have attempted to correlate cognitive deficits and structural brain changes using 'region of interest' approaches, which may yield inconsistent results and be subject to observer bias. Our study is the first to directly explore cognition and brain structure using VBM. Our findings indicate that the structural/cognitive correlates are more extensive in BP II, the subgroup in which depression is the predominant and more persistent mood abnormality. There are a number of potential mechanisms that may lead to structural brain changes in depression. One such mechanism is glutamatergic neurotoxicity related to hypothalamic–pituitary–adrenal axis dysregulation. The hippocampus and the prefrontal cortex are rich in glucocorticoid receptors and, therefore, particularly vulnerable to glucocorticoid-mediated neurotoxicity (Sherwood Brown *et al*. 1999). Other putative mechanisms also linked to depression are stress-induced inhibition of neurogenesis and reduction of neurotrophic factors, implying that chronicity and repeated episodes of depression may result in cognitive and structural brain changes. However, this may not be the only explanation (see Sheline, 2003 for a review). Indeed, recent studies have reported the presence of structural brain changes in first-episode psychosis (Hirayasu *et al*. 1999; Kasai *et al*. 2003) and in adolescents with BP (Wilke *et al*. 2004). A recent study (Dickstein *et al*. 2004) has shown that BP patients aged 6–17 years already show deficits in attentional set-shifting and visuo-spatial memory. The presence of cognitive deficits in the non-BP twin (Gourovitch *et al*. 1999) and in siblings of BP patients (Kéri *et al*. 2001) also suggests that cognitive deficits may occur very early or be trait markers of the disease. The idea that cognitive and structural abnormalities may represent genetic trait markers (endophenotypes) is gaining support (Savitz *et al*. 2005). The presence of residual depressive symptomatology as a contributor to cognitive impairment needs to be considered. However, this is unlikely to have played a part in our results, as in a detailed study of cognitive performance in the same group of patients we did not find significant differences in test performance between patients with normal BDI scores and those who had residual depressive symptoms (Summers *et al*. unpublished observations). This finding is also in keeping with the findings of other recent studies (Thompson *et al*. 2005). It is, therefore, possible that in a given patient a combination of genetic, disease-related and co-morbid factors (e.g. vascular disease) could contribute to the cognitive and structural brain changes.

The main limitation to this study is the lack of a healthy control group. This makes it impossible to know whether the neuroanatomical substrate of cognitive function in patients with BP deviates from that of normal subjects, although the lack of such a control group does not invalidate the finding of differences between the two subgroups of patients with BP in our study. In our earlier report (Bruno *et al*. 2004) we detected in the same patients significant volumetric and MTR changes in more circumscribed areas (i.e. the sub-genual anterior cingulate and pre-frontal white matter) thought to be primarily involved in mood regulation. The partially overlapping but more extensive areas correlated with cognitive dysfunction described in this study may represent more subtle neuropathological changes, which, although of functional relevance, were undetectable in our earlier study (Bruno *et al*. 2004).

Another major limitation of the study is the small sample size, in particular for BP II patients. This may have obscured differences between the subgroups and could account for the lack of significant correlations between tests tapping specific cognitive domains and structural abnormalities. It remains possible that the effects of medication, in particular lithium (Honig *et al*. 1999), could have affected our results, although it is unlikely that the cognitive differences between the two subgroups could have been distorted by these effects, as similar proportions of patients in each group were receiving lithium or other mood stabilizers. The effects of ECT are also unlikely to have contributed significantly to

our results, because very few of these patients received ECT, and the numbers were similar in the two groups. Moreover, there is no evidence that ECT causes structural brain changes detectable with conventional imaging (Nobler *et al.* 2000), although MTI may detect subtler changes.

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DECLARATION OF INTEREST

None.

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