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Structural and Functional Brain Correlates of Cognitive Impairment in Euthymic Patients with Bipolar Disorder

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recommendations of the Weatherall report, "The use of non-human primates in research." The relevant guidelines followed and the committee that approved the study should be identified in the ethics statement. If anesthesia, euthanasia or any kind of animal sacrifice is part of the study, please include briefly in your statement which substances and/or methods were applied. Please enter the name of your Institutional Animal Care and Use Committee (IACUC) or other relevant ethics board, and indicate whether they approved this research or granted a formal waiver of ethical approval. Also include an approval number if one was obtained. **Field Permit** Please indicate the name of the institution or the relevant body that granted permission.	
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Please describe where your data may be	All demographic, neuropsychological and imaging data reported in the paper is

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Structural and Functional Brain Correlates of Cognitive Impairment in Euthymic Patients with Bipolar Disorder

Brain Correlates of Cognitive impairment in Bipolar Disorder

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Abstract

Background: Cognitive impairment persisting into the euthymic phase is a well-established finding in bipolar disorder. However, its brain structural and/or functional correlates are uncertain.

Methods: Voxel-based morphometry (VBM) was carried out in 33 euthymic bipolar patients with preserved memory and executive function, 28 euthymic bipolar patients with significant memory and/or executive impairment and 28 healthy controls. Twenty-seven of the cognitively preserved patients, 23 of the cognitively impaired patients and 28 controls also underwent fMRI during performance of the n-back working memory task.

Results: VBM failed to detect clusters of structural difference between the two patient groups, even at a liberal threshold. During n-back task performance, the cognitively impaired patients showed hypoactivation compared to the cognitively preserved patients in a circumscribed region in the right dorsolateral prefrontal cortex.

Conclusions: Cognitive impairment in euthymic bipolar patients appears to be unrelated to structural brain abnormality, but may be associated with altered prefrontal function.

Keywords: bipolar disorder; cognition; euthymia; brain imaging; voxel-based morphometry; fMRI.

BACKGROUND

Studies over the last two decades have demonstrated that a proportion of patients with bipolar disorder show neuropsychological deficits that persist beyond episodes of illness into euthymia [1]. These deficits are wide ranging[2], although they appear to involve executive function and long-term memory particularly [3], and they are associated with impaired functioning in daily life [4, 5]; there is little to suggest that they are attributable to the effects of medication[6] or residual mood disturbance [7]. Since patients with bipolar disorder do not show any evidence of premorbid intellectual disadvantage [8-10], some form of brain dysfunction presumably underlies this form of cognitive impairment. However, the nature of this remains unknown.

One possibility is that cognitive impairment in euthymic bipolar patients is a consequence of structural brain pathology. Bipolar disorder is known to be associated with lateral ventricular enlargement [11-13], and there is evidence for a small reduction in overall brain volume, although this was significant in only one of two recent meta-analyses [11-13]. Beyond this, studies using whole-brain techniques such as voxel-based morphometry (VBM) – which examine for changes across the whole cerebral cortex and is capable of detecting changes that are small and/or do not conform to anatomical boundaries – have found evidence for volume reductions in the anterior cingulate cortex, insula and inferior frontal cortex, among other regions [14-17]. White matter changes are also recognized in bipolar disorder, both in the form of subcortical signal hyperintensities [18] and reduced fractional anisotropy on diffusion tensor imaging (DTI) (eg see[19]).

Relatively few studies have examined whether these structural changes are related to presence of cognitive impairment in bipolar patients, and they have had inconsistent findings [20]; see also [21-25]. Only two such studies have so far been carried out on euthymic patients:

one [26] correlated VBM findings and performance on the Stroop test in 44 euthymic patients and found a negative correlation in one area, the right inferior parietal lobule, in the patients. In the other [27] a significant correlation was found between scores on an executive task (the Tower of London test) and some but not all of a range of different DTI measures in the fornix and the right thalamic radiation: However, there were no correlations between a memory test, the California Verbal Learning Test, and any of the DTI measures.

Findings from many functional imaging studies have led to a consensus that bipolar disorder is broadly characterized by reduced resting and task-related activity in the prefrontal cortex and some other cortical regions, coupled with overactivity in the amygdala, hippocampus and parahippocampal gyrus and the basal ganglia [28]. Not all of these abnormalities are present in euthymia, however, which would seem to be a prerequisite for their being associated with persistent cognitive impairment. In a meta-analysis pooling effect size data from PET, SPECT and fMRI studies, Kupferschmidt et al [29] found support for cognitive task-related hypoactivations in the inferior and middle frontal cortex and the dorsolateral prefrontal cortex (DLPFC) in euthymic bipolar patients, as well as hyperactivity in the superior temporal gyrus and ventrolateral prefrontal cortex. In contrast, Chen et al [30] found evidence of reduced activation only in the lingual gyrus in euthymic patients in a meta-analysis of voxel-based studies using cognitive and emotional tasks. Very few studies have explicitly examined brain activations in bipolar patients with cognitive impairment (eg[31-33], and only one of these was carried out on euthymic patients: Oertel-Knöchel et al [33] found that 26 euthymic patients were impaired on a verbal learning and recognition task, and also showed a pattern of reduced activation compared to healthy controls when they performed the same task while being scanned. The areas affected included the left middle and superior frontal gyrus during encoding, and in the bilateral middle and inferior frontal gyrus, plus the parahippocampal and other posterior medial cortical areas, during retrieval.

The aim of this study was to determine whether and to what extent cognitive impairment in euthymic bipolar patients has brain structural and/or functional correlates. We did this by recruiting well-matched groups of patients who either showed or did not show executive and/or memory impairment, defined according to predetermined criteria, outside episodes of illness. Healthy controls were also employed.

METHOD

Participants

The patient sample consisted of two groups of right-handed adults with bipolar disorder, recruited on the basis of showing (N=28) or not showing (N=33) cognitive impairment (as defined below) during euthymia. Patients were from the out-patient departments of two psychiatric hospitals in Barcelona: Benito Menni CASM and the University of Barcelona Hospital Clínic. They all met DSM-IV criteria for bipolar I disorder and were required to have had at least two episodes of illness. Patients were excluded a) if they were younger than 18 or older than 55 (this relatively young upper age limit was chosen in order to exclude late-onset affective disorder which has an association with vascular and neurodegenerative disease and so might be independently associated with cognitive impairment [34]; b) if they had a history of brain trauma or neurological disease, c) if they had shown alcohol/substance abuse within 12 months prior to participation; d) if they had undergone electroconvulsive therapy in the previous 12 months; and e) if they showed evidence of general intellectual impairment/handicap, indexed by a current IQ outside the normal range (i.e. below 70) as measured using four subtests of the Wechsler Adult Intelligence Scale III (WAIS-III) (vocabulary, similarities, block design, and matrix reasoning).

The patients were considered to be euthymic if they had had no episodes of illness for at least three months and if they had a score on Hamilton Rating Scale for Depression (HDRS-21) of ≤ 8 and Young Mania Rating Scale (YMRS) of ≤ 8 at the time of testing. These quite strict requirements were used in order to avoid the potentially confounding effects of subthreshold depressive and manic symptoms on cognitive function [35].

Patients in the cognitively preserved group were on treatment with mood stabilizers (lithium alone n=13, other mood stabilizers alone n= 6; lithium in combination with other mood stabilizers n= 9), antidepressants (n= 8) and antipsychotics (n= 21; second generation n= 21, first generation n= 2; mean chlorpromazine equivalent dose 284.65 ±337.31 mg/day). The cognitively impaired patients were also on treatment with mood stabilizers (lithium alone n=13, other mood stabilizers alone n=4; lithium in combination with other stabilizers n=7), antidepressants (n=7); 17 were taking antipsychotics (second generation n=15, first generation n=1, both n=1; mean chlorpromazine equivalent dose 245.20± 209.77 mg/day).

A group of 28 healthy controls were recruited via poster and web-based advertisement in the hospital and local community, plus word-of-mouth requests from staff in the research unit. The controls met the same exclusion criteria as the patients. They were also excluded if they reported a history of mental illness or treatment with psychotropic medication, and/or had a first-degree relative with a psychiatric illness. They were recruited to be matched to the patient groups for age, sex and TAP-estimated IQ.

The three groups were selected to be matched for age, sex and estimated IQ (premorbid IQ in the patients). IQ was estimated using the Word Accentuation Test (Test de Acentuación de Palabras, TAP) [36] a pronunciation test that is conceptually similar to the National Adult Reading Test (NART) used in the United Kingdom [37] and the Wide Range of Achievement

Test (WRAT) in the USA [38]. Subjects have to pronounce low-frequency Spanish words whose accents have been removed. Scores can be converted into IQ estimates [39].

All subjects gave written informed consent prior to participation in accordance to the Declaration of Helsinki. Only individuals judged to have decision-making capacity were included. The subjects in the cognitively impaired group were included on the basis that they showed memory and/or executive function as detected during the course of the neuropsychological testing carried out for the purpose of the study, not because they had been found to show clinically significant cognitive impairment by their treating clinicians. The research protocol was approved by the Clinical Research Ethics Committee of the Sisters Hospitallers (Comité de Ética de Investigación Clínica de las Hermanas Hospitalarias), which also approved this method of obtaining informed consent for the study.

Cognitive assessment

This was based on Spanish versions of two well-validated memory and executive test batteries, the Rivermead Behavioural Memory Test (RBMT) [40] and the Behavioural Assessment of the Dysexecutive Syndrome (BADS) [41]. The RBMT consists of 12 subtests examining verbal recall, recognition, orientation, remembering a route and three measures of prospective memory, the ability to remember to do things. Pass/fail scores are summed to give a 'screening' score. The BADS consists of 6 subtests covering cognitive estimation, rule shifting, planning, problem solving and decision making under multiple task demands (the Modified Six Elements Test). Scores from 0 to 4 on each subtest are summed to give an overall 'profile' score.

The patients were classified as cognitively preserved or impaired using 5^{th} percentile cutoffs based on normative data for normal adults that are available for the two tests. Thresholding for impairment at the 5^{th} percentile for the normal population is a established method in

207 neuropsychology [42]. Specifically, patients were considered cognitively impaired group if they
208 scored below the 5th percentile on the RBMT and/or the BADS (screening score of ≤7 on the
209 RBMT and profile score of ≤11 on the BADS), and were considered cognitively preserved if they
210 scored at or above the 5th percentile on both tests (≥8 or more on the RBMT and ≥12 on the
211 BADS).
212
213 **Scanning procedure**
214 All subjects underwent structural and functional MRI scanning using a 1.5 Tesla GE Signa
215 scanner (General Electric Medical Systems, Milwaukee, Wis) located at the Sant Joan de Déu
216 Hospital in Barcelona (Spain).
217
218 *Structural neuroimaging:* High resolution structural T1-weighted MRI data were acquired with
219 the following acquisition parameters: Matrix size 512x512; 180 contiguous axial slices; slice
220 thickness of 1 mm, slice gap of 0 mm; voxel resolution 0.47x0.47x1 mm^3; echo time (TE) = 3.93
221 ms, repetition time (TR) = 2000 ms and inversion time (TI) = 710 ms; flip angle 15º.
222
223 Structural data were analyzed with FSL-VBM, an optimized VBM style analysis [43, 44] carried
224 out with FSL tools; this yields a measure of difference in local grey matter volume. First,
225 structural images were brain-extracted [45]. Next, tissue-type segmentation was carried out.
226 The resulting grey matter partial volume images were then linearly aligned to MNI 152
227 standard space [46, 47], followed by nonlinear registration. The resulting images were
228 averaged to create a study-specific template, to which the native grey matter images were
229 then non-linearly re-registered. The registered partial volume images were then modulated by
230 dividing by the Jacobian of the warp field. The modulated gray matter segments were then
231 smoothed with an isotropic Gaussian kernel using a sigma of 4mm (technical details are shown
232 in www.fmrib.ox.ac.uk/fsl/fslvbm/).

All comparisons were carried out with permutation-based non-parametric tests. The TFCE (Threshold-Free Cluster Enhancement) method, also implemented in FSL, was used for this purpose. TFCE finds clusters in the data without having to define the initial cluster-forming threshold [48]. Cluster-like structures are enhanced but the image remains fundamentally voxel-wise. In the resulting maps, obtained with 5000 permutations, family-wise error (FWE) rate was used to control for multiple comparisons and only FWE-corrected cluster p-values <0.05 were considered.

Functional neuroimaging: For this we chose the n-back task [49], which has been widely used as a probe for executive function, specifically working memory, in fMRI studies in healthy subjects [50] and psychiatric disorders including schizophrenia [51] and bipolar disorder [52]. Two levels of memory load (1-back and 2-back) were presented in a blocked design manner; in the 1-back task, participants had to respond with a key press when a letter was the same as the one that was presented immediately previously, whereas in the 2-back task they had to respond when the letter was the same as that presented two letters previously. Each block consisted of 24 letters which were shown every two seconds (1 second on, one second off) and all blocks contained five repetitions (1-back and 2-back depending on the block) located randomly within block. Individuals had to detect these repetitions and respond by pressing a button. In order to identify which task had to be performed, characters were shown in green in the 1-back blocks and in red in the 2-back blocks. Four 1-back and four 2-back blocks were presented in an interleaved way, and between them, a baseline stimulus (an asterisk flashing with the same frequency as the letters) was presented for 16 seconds. All individuals went through a training session before entering the scanner.

Performance was measured using the signal detection theory index of sensitivity (d') of ability to discriminate targets from non-targets[53]. Higher values of d' indicate better ability to discriminate between targets and distractors. Subjects who had negative d' values in either or both of the 1-back and 2-back versions of the task, which suggests that they were not performing it, were a priori excluded from the analysis.

In each individual scanning session 266 volumes were acquired. A gradient echo echo-planar sequence depicting the BOLD contrast was used. Each volume contained 16 axial planes acquired with the following parameters: TR = 2000 ms, TE = 20 ms, flip angle = 70 degrees, section thickness = 7 mm, section skip =0.7 mm, in-plane resolution = 3x3 mm. The first 10 volumes were discarded to avoid T1 saturation effects.

fMRI image analyses were performed with the FEAT module, included in FSL software [54]. Pre-processing with FSL-FEAT included: a) motion correction[47]; b) non-brain removal [45]; c) isotropic 5mm-FWHM Gaussian smoothing; d) high-pass temporal filtering; e) time-series statistical analysis with local autocorrelation correction [55]; and f) registration to the MNI 152 standard space [46, 47]. To minimize unwanted movement-related effects, participants with an estimated maximum absolute movement >3.0 mm or an average absolute movement >0.3 mm were excluded from the study.

General linear models (GLMs) were fitted to generate the individual activation maps for the 1-back vs baseline, 2-back vs baseline and 2-back vs 1-back comparisons. Differences in fMRI activation maps between patients and controls were generated within the FEAT module, using mixed effects GLM models [56]. FEAT uses Gaussian Random Field theory to properly account for the spatially distributed patterns when performing statistical tests. Specifically, the

analyses were performed with the FLAME stage 1 with default height threshold ($z > 2.3$) [55, 57] and a *p*-value < 0.05 corrected for multiple comparisons[58, 59].

Data analysis

In order to examine the relationship between presence of euthymic cognitive impairment and brain structure and function, we carried out two comparisons using a strategy we have employed previously for schizophrenia [60]. First, we contrasted the cognitively preserved group with the control group; this gives a measure of changes in brain structure and/or function that are attributable to bipolar disorder uncontaminated by presence of cognitive impairment. Secondly, to detect changes attributable to the presence of cognitive impairment, we contrasted the cognitively preserved and cognitively impaired patient groups.

RESULTS

Demographic characteristics of the patients and controls are shown in Table 1. The groups were matched for age, sex and TAP-estimated IQ. There were no differences in the psychopathological status (YMRS and HRSD scores), duration of the illness, functioning (GAF score) and antipsychotic dosage between the cognitively preserved and the cognitively impaired patients (see Table 1).

Table 1. Demographic, neurocognitive and psychopathological characteristics of the groups (SDs in brackets).

	Controls (n=28)	Cognitively preserved (n=33)	Cognitively impaired (n=28)	Statistics	Post hoc testing
Age	44.01 (6.03)	44.13 (6.63)	46.17 (7.40)	F=0.94 p=0.40	
Sex (male/female)	12/16	18/15	17/11	$\chi^2 = 1.85$ p=0.40	
Estimated premorbid IQ (TAP)	105.93 (7.25)	106.03 (6.32)	102.71 (8.81)	H=3.08 p=0.21	
BADS profile	19.18 (2.40)	17.12 (2.25)	13.89 (3.54)	F=26.09	CI < CP (p<0.001)

score				p<0.001	CI < CON (p<0.001) CP < CON (p=0.01)
RBMT screening score	10.61 (1.64)	9.76 (1.41)	6.11 (1.29)	H=55.43 p<0.001	CI < CP (p<0.001) CI < CON (p<0.001) CP < CON (p=0.02)
Duration of illness (years)	-	16.76 (7.44)	19.13 (8.16)	t=1.17 p=0.25	
YMRS score	-	1.18 (1.81)	1.77 (2.10)	U=360.50 p=025	
HRSD score	-	2.55 (2.02)	2.19 (2.35)	U=367.00 p=0.33	
GAF score	-	79.07 (11.35)	75.75 (12.72)	t=-0.99 p=0.33	

IQ, intelligence quotient; TAP, Word Accentuation Test; BADS, Behavioural Assessment of the Dysexecutive Syndrome; RBMT, Rivermead Behavioural Memory Test; YMRS, Young Mania Rating Scale; HRSD, Hamilton Rating Scale for Depression; GAF, Global Assessment of Functioning; CON, controls; CP, cognitively preserved; CI, cognitively impaired.

As expected, the two patient groups differed in their performance on the BADS and RBMT (see Table 1). The cognitively preserved group was also found to show significant differences from the healthy controls. A scatter plot of scores for all three subject groups is shown in Figure 1 and indicates that this latter finding was due to more cognitively preserved patients falling into low average ranges than the healthy controls.

[Figure 1 about here]

Figure 1: Scatter plots for the controls, cognitively preserved and cognitively impaired groups on the (a) the RBMT and (b) the BADS. The horizontal lines show the cutoffs for impairment used.

VBM findings

Controls vs cognitively preserved patients: At a corrected p value <0.05, the cognitively preserved patients showed significantly reduced grey matter volume in one small cluster located in right precentral gyrus [173 voxels, p=0.03; peak in BA6, MNI (38,-10,38)] (see Figure 2).

[Figure 2 about here]

Figure 2: Brain regions showing significant gray matter volume reduction in the cognitively preserved group with bipolar disorder compared with controls.

Cognitively preserved vs cognitively impaired patients: There were no areas of significant grey matter volume difference between the matched subgroup of cognitively preserved patients and the cognitively impaired patients at P<0.05, corrected. Lowering the threshold to p<0.005, uncorrected did not result in the appearance of any clusters.

Functional imaging findings

Twenty-eight of the healthy controls, 27 of the cognitively preserved patients and 23 of the cognitively impaired patients participated in this part of the study (5 cognitively preserved patients and 5 cognitively impaired patients could not be included because of technical problems with the acquisition and processing of the images; 1 cognitively preserved patient was excluded because of excessive movement). As shown in Table 2 there continued to be no significant differences between the three groups in demographic characteristics, and between the two patient groups in clinical ratings.

There were no differences in n-back performance between the cognitively preserved patients and the cognitively impaired patients and controls on the 1-back version of the task and on the 2-back version. However, the cognitively impaired patients were impaired compared to the healthy controls.

Table 2. Demographic and psychopathological characteristics in the fMRI sample (SDs in brackets).

	Controls (n=28)	Cognitively preserved	Cognitively impaired	Statistics	Post hoc testing

		(n=27)	(n=23)		
Age	44.01 (6.03)	44.49 (6.99)	46.50 (7.82)	F=0.89 p=0.41	
Sex (M/F)	12/16	15/12	13/10	χ^2=1.25 p=0.54	
Estimated premorbid IQ (TAP)	105.93 (7.25)	106.70 (5.59)	103.52 (8.97)	H=1.75 p=0.42	
BADS profile score	19.18 (2.40)	17.33 (2.11)	13.91 (3.50)	F=24.57 p<0.001	CI < CP (p<0.001) CI < CON (p<0.001) CP < CON (p=0.04)
RBMT screening score	10.61 (1.64)	9.93 (1.47)	6.17 (1.30)	H=45.99 p<0.001	CI < CP (p<0.001) CI < CON (p<0.001)
Duration of illness (years)		16.60 (7.19)	18.98 (8.64)	t=1.06 p=0.29	
YMRS score		1.33 (1.90)	1.95 (2.17)	U=247.50 p=0.29	
HRSD score		2.44 (2.10)	2.41 (2.38)	U=281.5 p=0.75	
GAF score		79.76 (11.99)	75.52 (12.57)	t=-1.12 p=0.27	
D' 1-back	4.40 (0.57)	4.17 (0.63)	3.67 (1.09)	H=7.56 p=0.02	CI < HC (p=0. 01)
D' 2-back	3.33 (0.83)	3.00 (0.69)	2.52 (0.73)	F=7.32 p<0.001	CI < HC (p=0.001)

IQ, intelligence quotient; TAP, Word Accentuation Test; BADS, Behavioural Assessment of the Dysexecutive Syndrome; RBMT, Rivermead Behavioural Memory Test; YMRS, Young Mania Rating Scale; HRSD, Hamilton Rating Scale for Depression; GAF, Global Assessment of Functioning; CON, controls; CP, cognitively preserved; CI, cognitively impaired.

Controls vs cognitively preserved patients: There were no activation differences between the healthy controls and the cognitively preserved patients in any of the three contrasts (1-back vs baseline, 2-back vs baseline and 2-back vs 1-back).

The cognitively preserved patients did, however, show a cluster of failure of de-activation in comparison to the healthy controls in both the 2-back vs baseline and 2-back vs 1-back contrasts. In the 2-back vs baseline contrast this cluster was located in the medial prefrontal cortex affecting the gyrus rectus and extended to the medial orbitofrontal and anterior cingulate cortex [4743 voxels, $p=2.18 \times 10^{-9}$; peak activation in BA11, MNI (4, 34,-8), z score=4.5]. In the 2-back vs 1-back contrast the cluster occupied a similar but smaller area in

the medial prefrontal cortex [1718 voxels, $p=2.04x10^{-4}$; peak activation in BA25, MNI (2,36,6), z score=4.16]. The findings for the 2-back vs 1-back contrast are shown in Figure 3. Boxplots of the averaged values in the medial prefrontal region-of-interest (ROI) for the controls and the cognitively preserved patients for this contrast confirm that the differences represented failure of de-activation: the controls showed a clearly negative activation whereas the patients showed a mean value close to zero (see Figure 3).

[Figure 3 about here]

Figure 3 (a): Brain regions where the cognitively preserved group showed significant failure to de-activate compared with the controls in the 2-back v. 1-back contrast. **(b):** Boxplots of the averaged values in this ROI.

Cognitively preserved vs cognitively impaired patients: There were no differences between the two patient groups in the 1-back vs baseline and the 2-back vs baseline contrasts. The 2-back vs 1-back contrast, however, revealed a cluster of reduced activation in the cognitively impaired group in the right lateral frontal cortex, extending from the inferior frontal operculum to lateral superior frontal regions and including parts of the DLPFC [905 voxels, *p*=0.008; peak activation in BA8, right superior frontal, MNI (24, 20, 46), z score=4.12]. The findings are shown in Figure 4. The two patient groups did not show differences in de-activation.

[Figure 4 about here]

Figure 4 (a): Brain regions where the cognitively impaired group with bipolar disorder showed significant failure to activate compared with the preserved group in the 2-back v. 1-back contrast. **(b):** Boxplots of the averaged values in this ROI.

DISCUSSION

Cognitive impairment in the euthymic phase – ie that is persistent and unrelated to mood disturbance – is now a well-established finding in bipolar disorder. Our study suggests that its basis does not lie in brain structural change. However, there was a positive signal in relation to brain function, with the cognitively impaired patients showing reduced activation in the right DLPFC compared to the cognitively preserved patients.

Given that structural brain damage in neurological disorders is commonly associated with neuropsychological deficits, our failure to find differences in grey matter volume between bipolar patients with and without cognitive impairment might be considered surprising. One possible reason is that, with sample sizes of 33 preserved and 28 impaired patients, the study might simply have lacked sufficient power to detect differences. Against this, however, is the fact that changes were not seen in the VBM analysis even at a liberal threshold of $p<0.005$ uncorrected, that would normally be considered to run a considerable risk of false positive findings. Given the lack of other studies addressing this issue, it is arguable that the default assumption has to be that euthymic cognitive impairment in bipolar disorder is not associated with grey matter changes until proved otherwise.

Our negative structural imaging findings seem at first sight incompatible with the current consensus view that euthymic cognitive impairment reflects a neurodegenerative process [61]. Here, though, it should be noted that the evidence for progressive brain structural change in bipolar disorder is currently weak. Thus, reviewing longitudinal studies carried out to date, Lim

et al[62] found no evidence for change in whole brain volume over time. Progressive volume reductions in the frontal lobe cortex were found in two small studies (Ns of 8 and 10) but not in a third, larger study (N=58) which also employed healthy controls. Findings were likewise conflicting for the anterior cingulate cortex, amygdala and hippocampus. Nevertheless, our study was cross sectional in design and so has to be considered as bearing only in a preliminary and indirect way on this broader question.

On the other hand, we did find evidence that cognitive impairment is associated with brain functional changes, specifically reduced activation in a single, circumscribed region that conformed reasonably closely to the right DLPFC. The DLPFC is implicated in cognitive aspects of frontal lobe function particularly (eg[63] and so is a plausible location for brain functional changes associated with cognitive impairment. Our findings here are also quite similar to those of Oertel-Knöchel et al [33] using a memory, rather than an executive task: they found that 26 euthymic patients showed reduced activations in the left middle superior frontal gyrus during encoding, and in the middle inferior frontal gryus bilaterally during retrieval, compared to 25 healthy controls, although the patients also showed reduced activations in other regions during retrieval.

A potential obstacle to this interpretation of our findings exists in that while functional imaging changes have commonly been found in the prefrontal cortex in bipolar disorder these have mostly been localized to regions such as the orbitofrontal cortex [64-66], the ventrolateral prefrontal cortex [67] or the frontal pole [68, 69] rather than the DLPFC. These latter localizations, however, could simply reflect that the above studies mostly used tasks that involved inhibition of responses, such as the go/no-go task and the Stroop test (and a gambling/decision-making task in one case[69]). In fact, all of a small number of studies that

443 have examined bipolar patients during performance of working memory tasks have found
444 reduced activation in or close to the DLPFC [52]; see also [70] [71].
445
446 A further finding in our study was failure of de-activation in the medial frontal cortex. This has
447 previously been found in several other studies of bipolar disorder [70, 72, 73], with one
448 additional study [74] finding failure of de-activation in the posterior cingulate
449 cortex/precuneus. Our findings here go further than these studies in documenting that failure
450 of de-activation is unrelated to presence of cognitive impairment: while it distinguished the
451 euthymic bipolar patients without cognitive impairment from the controls, the cognitively
452 impaired patients did not show differences from the cognitively preserved patients.
453
454 Both the medial frontal cortex and the posterior cingulate cortex/precuneus are important
455 components of the default mode network, a series of interconnected brain regions that are
456 active at rest but which de-activate during performance of attention-demanding tasks [75].
457 The function or functions of the default mode network remain largely unknown, but there are
458 many indications that it contributes to normal cognitive functioning. Thus, in addition to de-
459 activating when attention-demanding tasks have to be performed, lower default mode
460 network activity is associated with more successful task performance in healthy subjects,
461 whereas lapses of attention are associated with reduced de-activation (for a review see[76]).
462 Our finding that medial frontal failure of de-activation does not distinguish cognitively
463 preserved from cognitively impaired euthymic patients may thus have an important
464 consequence – it argues against default mode network dysfunction playing a role in the
465 cognitive impairment seen in bipolar disorder, at least during the euthymic phase.
466
467 **LIMITATIONS**

This study recruited patients who were above and below cutoffs for memory and/or executive impairment. This strategy meant that the cognitively preserved patients could not be matched with the controls for cognitive function, and in fact they showed significantly poorer performance than the healthy controls. They should accordingly be considered to have been only relatively rather than fully cognitively preserved. Secondly, although structural differences between the cognitively impaired and cognitively preserved patients were not found even when a liberal threshold was employed, it remains a realistic concern that the sample sizes in the structural imaging comparison may have been too small to detect subtle volume differences between the two patient groups. Finally, we only examined grey matter and it remains possible that white matter changes, either volumetric or in terms of integrity as measured by DTI, are more pronounced in cognitively impaired than in cognitively preserved bipolar patients.

CONCLUSIONS

Our findings do not suggest that grey matter volume reductions seen in bipolar disorder are related to the persistent cognitive impairment that develops in a proportion of patients. However, euthymic cognitive impairment does seem to be related to – and may even be a direct consequence of – functional changes in the prefrontal cortex.

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Figure1

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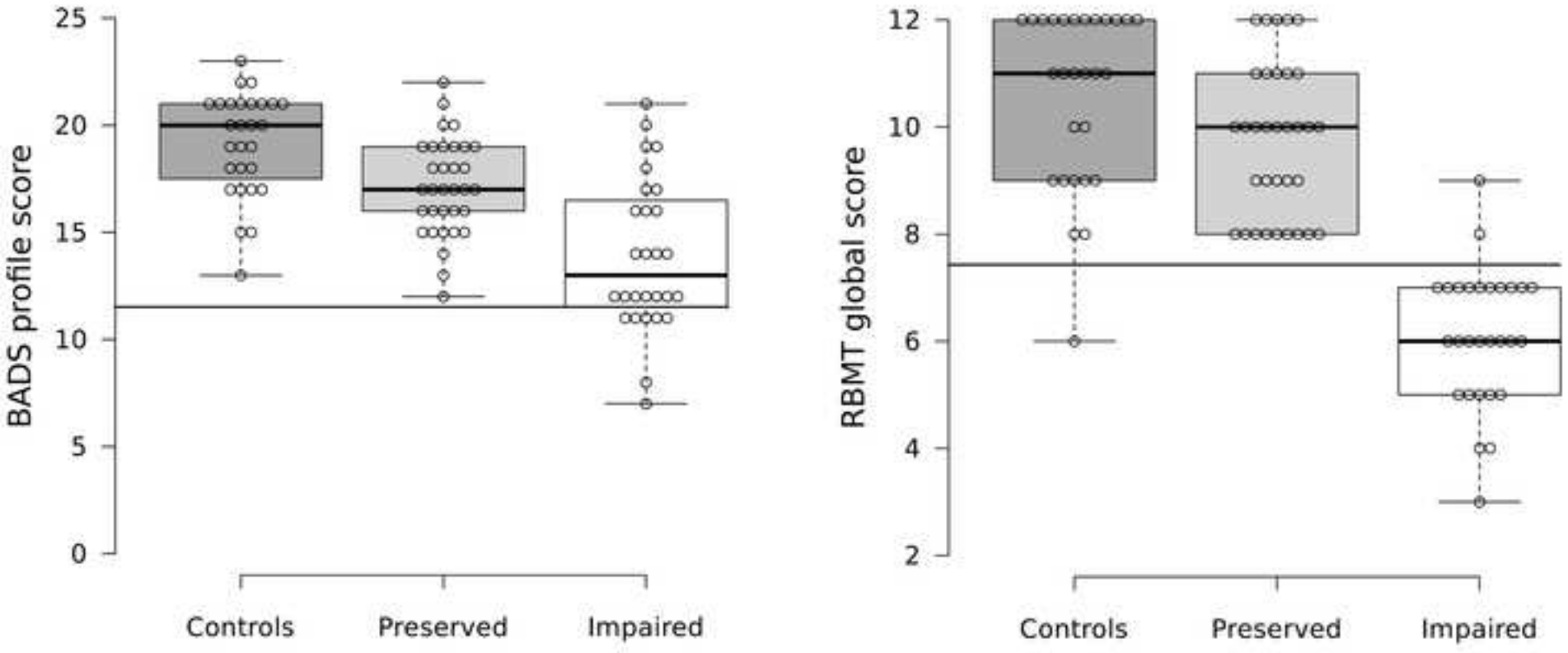

Figure2

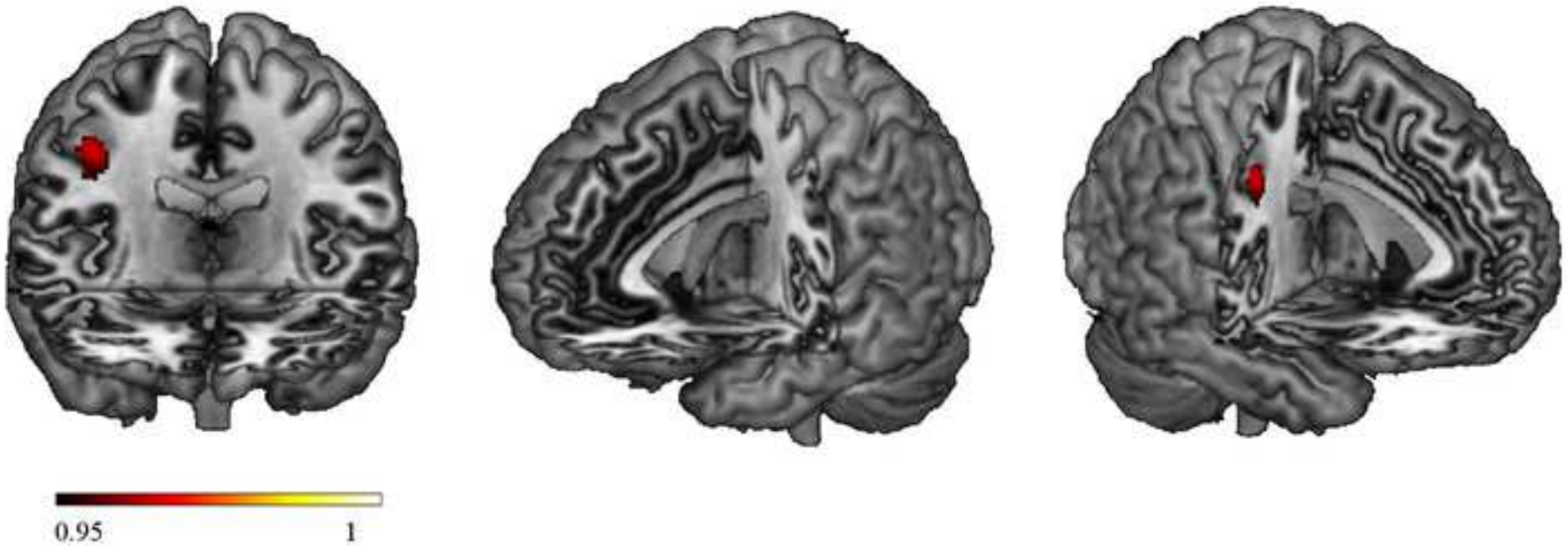

Figure3

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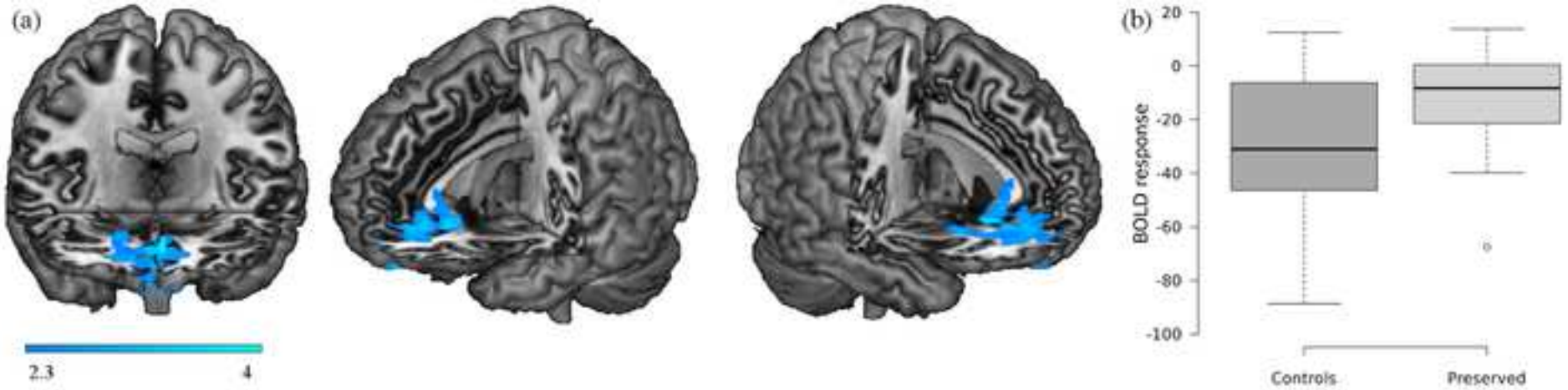

Figure4

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