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ORIGINAL PAPER

Different gray matter patterns in chronic schizophrenia and chronic bipolar disorder patients identified using voxel-based morphometry

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Abstract Gray matter (GM) volume deficits have been described in patients with schizophrenia (Sz) and bipolar disorder (BD), but to date, few studies have directly compared GM volumes between these syndromes with methods allowing for whole-brain comparisons. We have used structural magnetic resonance imaging (MRI) and voxel-based morphometry (VBM) to compare GM volumes between 38 Sz and 19 BD chronic patients. We also included 24 healthy controls. The results revealed a widespread cortical (dorsolateral and medial prefrontal and precentral) and cerebellar deficit as well as GM deficits in putamen and thalamus in Sz when compared to BD patients. Besides, a subcortical GM deficit was shown by Sz and BD groups when compared to the healthy controls, although a putaminal reduction was only evident in the Sz patients. In this comparison, the BD patients showed a limited cortical and subcortical GM deficit. These results support a partly different pattern of GM deficits associated to chronic Sz and chronic BD, with some degree of overlapping.

Keywords Schizophrenia · Bipolar disorder · Gray matter · Voxel-based morphometry

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Introduction

Gray matter (GM) deficits in comparison with healthy controls have been described in patients with schizophrenia (Sz) [34, 65, 72] and bipolar disorder (BD) [4, 9, 36]. However, it is not completely clear how these deficits differ between both syndromes since although these deficits have been shown to be greater in Sz [43], some may be shared by BD patients [48]. Further investigation of the differences in structural alterations between Sz and BD seems thus advisable, taking into account their genetic, clinical and therapeutic commonalities [10, 15, 17, 38, 52, 58, 61].

Some direct comparisons of brain structure between Sz and BD have been reported, with different methods and discrepant findings. With methods based on the definition of regions of interest (ROIs), first-episode (FE) schizophrenia patients showed decreased planum temporale and Heschl gyrus volumes in comparison with bipolar patients [28], although a decrease in the same structure was later reported for BD [59]. Similarly, an insular GM reduction was found in Sz but not in BD patients [33]. In a study aimed to compare the volume of the fusiform gyrus between FE schizophrenia patients, FE affective psychotic patients (mostly bipolar disorder) and healthy controls, FE patients with schizophrenia showed a significant reduction in that structure [41]. Two recent reports have included

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meta-analyses of brain volume differences between Sz and BD, out of data from ROIs-based studies [4, 36]. Those meta-analyses showed smaller lateral and third ventricles [4, 36] and enlarged amygdalar volume [4] in BD patients when compared to their Sz counterparts, although ventricles were enlarged in BD patients in comparison with healthy controls, too. Both studies also detected widespread heterogeneity of MRI data within the BD diagnosis.

Voxel-based morphometry (VBM) and similar methods allow comparing the entire brain between groups, a promising approach to elucidate the structural differences between those syndromes given the complex pattern of abnormalities expected in Sz and BD. Such technique may contribute to identify GM deficits related to the ventricular enlargements found in BD [4, 36]. VBM also allows comparing cerebellar volumes between these syndromes, although this comparison can also be made using ROIs-based techniques, which is of interest given its possible alteration in schizophrenia [3] and the few previous comparisons of cerebellum between Sz and BD patients.

The results of comparing brain structure between BD and healthy controls with VBM and similar methods have revealed considerable heterogeneity [1, 51, 59, 64, 68]. Using VBM, a widespread GM deficit was found in Sz but not in BD patients [47], and BD and Sz groups have been separately compared to a common set of controls [40], with similar results. Finally, VBM was also used to compare Sz and BD patients and their relatives with healthy controls [51], describing decreased prefrontal and dorsomedial thalamic GM in Sz but not in BD subjects, as well as a reduction in anterior thalamus common to both syndromes.

Therefore, different distribution and/or magnitude of GM decrease have been reported for BD and Sz across studies, and their specificity remains unclear. This may be related in part to the few direct comparisons made to date between BD and Sz patients, in particular including whole-brain comparisons [47]. To further contribute to clarify the respective patterns of GM alterations between Sz and BD, in the present report, we have used VBM to compare the cerebral GM volumes directly between Sz and BD patients and their respective alterations in comparison with healthy controls.

Subjects and methods

Subjects

Sz patients

Thirty-eight patients with schizophrenia (26 men) were included, of which 36 were of the paranoid and 2 of the undifferentiated subtypes (DSM-IV criteria). The clinical data are shown in Table 1. All but one were right-handed. Of them, 16 cases had shown a poor response to classical antipsychotics and as a result were included in a protocol or treatment with clozapine after the acquisition of the MRI data used in the present study. They had not achieved an adequate clinical response to at least two traditional chemically different antipsychotics used for more than 6 weeks during the preceding year at doses higher than 800 mg/d in chlorpromazine equivalents, with significant residual positive or disorganization symptoms and a CGI score equal to or higher than 4.

Prior to inclusion, previous treatment consisted of classical neuroleptics in most cases, in 5 cases combining two drugs (haloperidol in 26 cases, pimocide in 4 cases, levomepromazine in 3 cases, thioridazine in 2 cases; mean dose 671 ± 208 mg/d in chlorpromazine equivalents) and risperidone in three cases (6 mg/d). All patients had been continuously treated for a period longer than 3 years, mostly with classical drugs, but six of these patients had discontinued their usual medication for more than 2 weeks prior to inclusion.

Sz symptoms were assessed using the PANSS by one of two raters (VM and JS), previously trained in the use of the scales.

BD patients

Nineteen type I bipolar (DSM-IV criteria) patients (12 men) of similar illness duration than the Sz ones were included (Table 1). All of these patients were clinically stable and euthymic (i.e., without clinically relevant depressive or manic signs or symptoms) at the time of the MRI examination, without any change in their treatment in the last 6 months. Ten of these patients had a history of at least one manic or depressive episode with psychotic symptoms. Sixteen BD patients were receiving lithium by

Table 1 Clinical and sociodemographic characteristics of the subjects

	SZ	BD	Controls
Intracranial volume	1,429.3 (137.1)	1,510.0 (184.5)	1,424.1(185.2)
M:F ratio	26:12	12:7	16:8
Age	34.4 (10.5)	38.3 (8.3)	34.6 (8.6)
Duration of illness	9.8 (7.9)	12.0 (6.52)	N/A
Positive	23.2 (6.4)	N/A	N/A
Negative	27.0 (7.9)	N/A	N/A
General	49.5 (13.9)	N/A	N/A
Parental SES	2.2 (1.3)	2.2 (0.8)	2.3 (1.8)
Education	10.4 (6.5)	11.1 (4.7)	12.9 (5.4)

the time of the examination (11 out of them as monotherapy). Besides, 4 were receiving valproate, 2 carbamazepine, 2 lamotrigine and 1 risperidone. None had been previously treated with electroconvulsive therapy.

We excluded a substance abuse disorder in the Sz and BD groups using clinical interviews and records and urinalysis (see below).

Healthy controls

Twenty-four controls were included (16 men; Table 1). They were recruited from among the hospital staff and through advertisements in public information boards and received a courtesy remuneration for their cooperation. To match the patient group, they had to have a lower than college education level and not have received any psychiatric or neurological diagnosis or treatments. In this group, psychiatric diagnoses were discarded in a semi-structured interview [23]. Neither were significant differences in age or in parental socioeconomic status [30] detected between any group pairs.

The exclusion criteria for patients and controls included a history of neurological illness or MRI findings judged clinically relevant by a radiologist blind to diagnosis; cranial trauma with loss of consciousness; past or present substance abuse, except nicotine or caffeine; the presence of any other psychiatric processes or treatments; and treatment with drugs known to act on the CNS. A urinalysis was used to rule out current substance abuse.

Written informed consent was obtained from the patients, and their families after full written information had been provided. The research board of the participating centers endorsed the study.

MRI acquisition

MR imaging was performed with a Philips Gyroscan 1.5T scanner. For each subject, a 3D T1 acquisition was obtained with the following parameters: TR = 7.5 ms, TE = 3.5 ms, Flip angle: 8°, 0.78 × 0.78, FOV = 240 mm × 240 mm, matrix size = 256 × 256, 150 slices (1.1 mm thickness, axial orientation).

Image processing

Segmented, normalized, modulated, and smoothed images were used to do the group comparison. We follow the unified scheme based on [5] using the SPM8 version (http://www.fil.ion.ucl.ac.uk/spm/).

The anatomical 3D data were analyzed with SPM8 (Wellcome Department of Cognitive Neurology, www.fil.ion.ucl.ac.uk) to normalize to the Talairach space and to segment the data in gray and white matter [5]. Statistical analysis was performed with the voxel-based morphometry (VBM) [53, 71]. Spatial smoothing was applied using a 8 mm × 8 mm × 8 mm full-width half-maximum (FWHM) Gaussian kernel for subsequent statistical analyses. Statistical maps of differences in gray matter between patients and controls were obtained using a general linear model [24]. Age, gender and intracranial volume were introduced as confounding covariates. Inhomogeneity was corrected with a bias correction algorithm implicit in VBM-SPM8. Each registration was checked individually a manually corrected when it was required.

The output for each comparison was a statistical parametric map that revealed the location of gray matter differences between groups. These areas were superimposed on a T1-weighted template. Spatial locations of the abnormal brain regions were detailed with Talairach coordinates after MNI to Talairach conversion with http://imaging.mrc-cbu.cam.ac.uk/imaging/MniTalairach. SPM procedure provides three brain volumes with gray matter, white matter and LCR. The intracranial volume is obtained adding the individual volume of each substance after segmentation.

GM differences between groups were assessed. Significance level was set at a voxel level $P \leq 0.001$ (uncorrected) and cluster level $k \geq 20$ voxels for the whole-brain analysis in order to decrease the possibility of artifactual false positives. We also tested the significance of the differences at $P < 0.05$ after false discovery rate (FDR) correction, with a minimum of 20 contiguous voxels.

Results

Differences in age (Student's *t*-tests) and sex distribution (χ^2 test) were not statistically significant between either pair of groups ($P > 0.1$ in all cases).

GM comparisons

Sz vs. BD patients

In this comparison, two cerebellar regions in the right side showed less GM in Sz when compared to BD patients (anterior culmen and posterior lobe). Moreover, left BA 4 (precentral frontal) right BA 6 (medial anterior frontal) and left medial BA10 (dorsolateral frontal) showed less GM in Sz, as well as the right pulvinar thalamus. Sz patients also had a GM deficit in the right putamen when compared to the BD ones (Fig. 1a; Table 2).

In addition, Sz patients showed more GM than their BD counterparts in bilateral anterior cerebellar lobe and left anterior cingulate (BA 24) regions (Fig. 1b; Table 2).

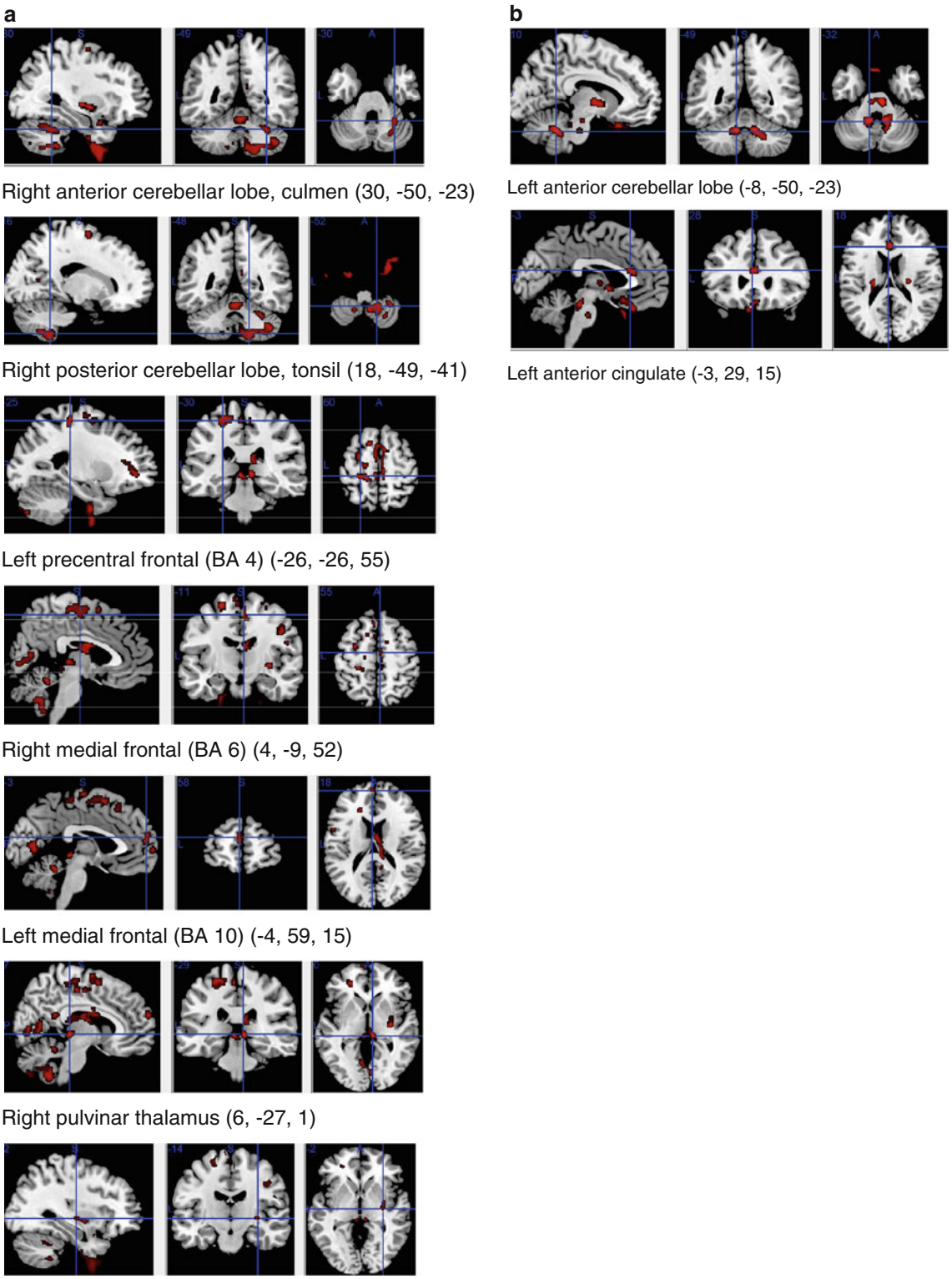


Fig. 1 Areas of GM decrease (**a**) and increase (**b**) in Sz when compared to BD patients ($P < 0.001$, uncorrected; $k > 30$ voxels)

These results were similar when only the 16 BD patients on lithium were included in the comparison.

None of those differences was significant at $P < 0.05$ FDR corrected level.

Sz vs. controls

In this comparison, Sz patients showed a significant GM decrease in left medial frontal regions (BA 6) as well in

Table 2 Location, peak coordinates and *t* value of the local maxima and voxel extent of the GM differences between each pair of groups ($P < 0.001$ uncorrected in all cases)

Comparison	Region	MNI coordinates	*T* value	Cluster size (voxels)
GM reductions in BD when compared to Sz patients	Left anterior cerebellar lobe	(−8, −50, −23)	5.34	117
	Left anterior cingulate	(−3, 29, 15)	4.64	61
GM reductions in Sz when compared to BD patients	Right anterior cerebellar lobe, culmen	(30, −50, 23)	2.94	200
	Right posterior cerebellar lobe, tonsil	(18, −49, −41)	3.54	553
	Left precentral frontal (BA 4)	(−26, −26, 55)	3.49	97
	Right medial frontal (BA 6)	(4, −9, 52)	3.97	447
	Left medial frontal (BA 10)	(−4, 59, 15)	3.29	34
	Right pulvinar thalamus	(6, −27, 1)	3.85	86
	Right putamen	(32, −14, −1)	3.92	80
GM reductions in SZ when compared to healthy controls	Left, Medial Frontal, BA6	(−2, 46, 36)	4.89	864
	Right putamen	(24, 8, 3)	4.05	40
	Left putamen	(−22, 4, 3)	4.10	63
GM increase in Sz in comparison with healthy controls	Anterior cerebellar lobes	(−8, −46, −25)	6.82	2,781
	Right medial frontal (BA 11)	(6, 27, −11)	5.11	585
GM reductions in BD patients when compared to healthy controls	Right caudate head	(8, 4, 2)	5.06	49
	Left Medial Frontal BA 9	(−2, 54, 44)	4.87	446

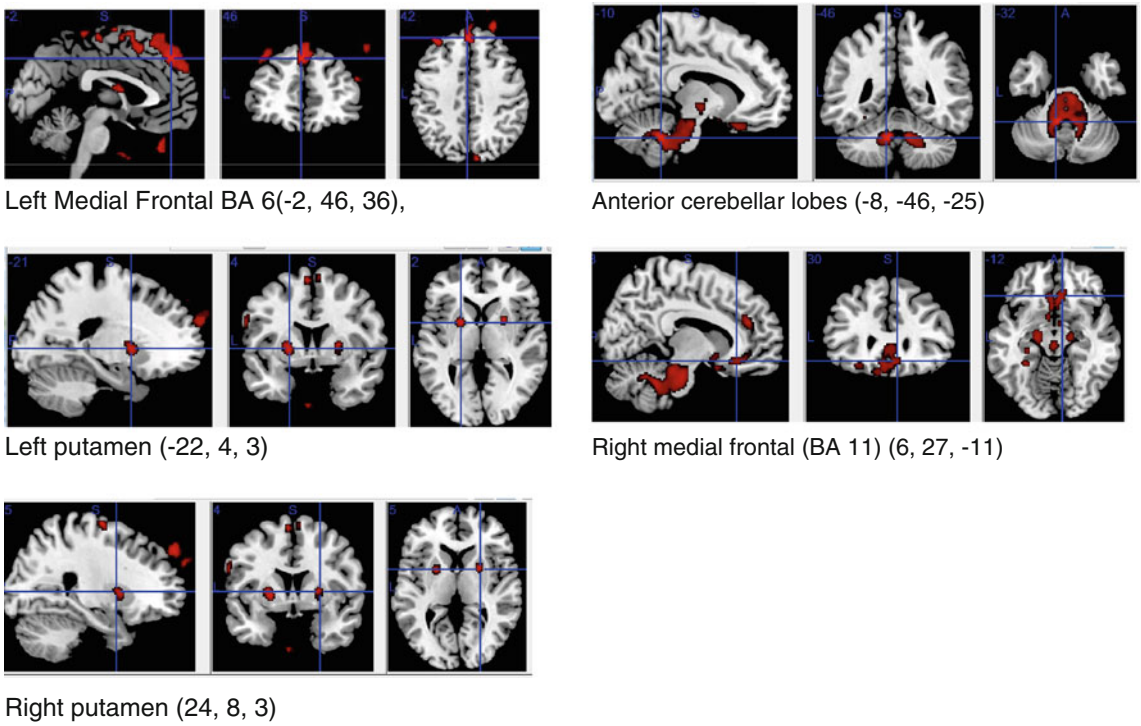
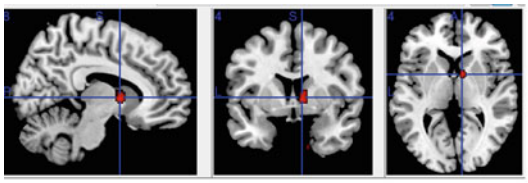


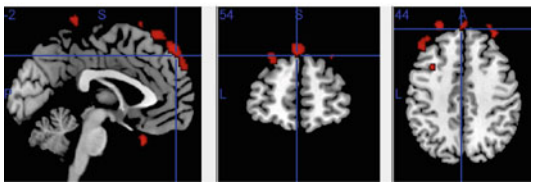
Fig. 2 Areas of GM volume decrease (**a**) and increase (**b**) in chronic Sz patients when compared to healthy controls ($P < 0.001$)

both basal ganglia regions, (Fig. 2a; Table 2). These differences were still significant at $P < 0.05$ FDR corrected level.

Moreover, Sz patients showed more GM in the anterior part of both cerebellar hemispheres and the right medial orbitofrontal lobe (BA 11) (Fig. 2b;



Right caudate head (8, 4,2)



Left, Medial Frontal, BA 9 (-2,54,44)

Fig. 3 Areas of GM decrease in BD patients in comparison with healthy controls (uncorrected $P < 0.001$)

Table 2). This difference did not persist after FDR correction.

BD vs. controls

Bipolar patients showed a significant decrease in the right caudate head and in the left medial frontal cortex (BA9) (Fig. 3; Table 2). No GM increases were found in BD patients with respect to healthy controls.

These results were also similar when only the 16 BD patients on lithium were included in the comparison, but did not persist after FDR correction.

Discussion

According to the present data, chronic Sz and BD patients of similar age and illness duration shared to some extent certain GM regional volume deficits (basal ganglia and, in part, frontal), which were more extensive in the former, also including in this case frontal, thalamic, putaminal and cerebellar regions.

These results seem compatible with the meta-analyses of ROI-based studies comparing brain volumes between Sz and BD patients that showed more dilated ventricles in the former [4, 36]. For instance, the thalamic deficit in our Sz group might contribute to the greater enlargement of the third ventricle in Sz in comparison with BD patients [36], and the widespread cortical and subcortical GM deficit in our Sz group may contribute to the widening of the ventricular system in that syndrome [4]. Those studies [4, 36] also revealed significant enlargements of the ventricular system in the BD patients when compared to the normal population that seem compatible with the GM deficit in our BD patients when compared to the healthy controls.

Our results and others suggest that GM deficit is wider among the Sz than the BD patients. Among these, McDonald et al. [47] reported using computational morphometry that Sz out-patients (17 year of duration, two thirds on atypicals) showed a distributed GM deficit involving neocortex, medial temporal lobe, insula, basal ganglia, thalamus and cerebellum, whereas psychotic BD patients with the same illness duration had no significant regions of gray matter abnormality. Later, the same group using a ROIs approach reported a significant volume reduction in hippocampus and a significant increase in lateral and third ventricles in chronic schizophrenia, not present in chronic BD patients [49]. Other groups have reported deficits in Sz but not in BD in hippocampus [2] and in total and prefrontal GM volume [29]. GM deficits were reported for the thalamus in BD, while cortical deficits were evident also in Sz patients [51]. In the same direction, FE patients, respectively, diagnosed as Sz and affective psychoses were compared to the same set of healthy controls [40]. While FE Sz patients showed in that study deficits in superior temporal gyri, bilateral anterior cingulate gyri and insula, and unilateral parietal lobe and hippocampus, no alterations were detected in the affective patients. In one report that compared 9 BD and 9 Sz patients, significant GM reductions were described in the former less marked than in the Sz group[43]. There are other reports showing no significant structural decreases in FE [1] or chronic [64] BD patients.

The proposed greater severity of GM deficit in Sz when compared to BD also receives support by previous assessments of the structural correlate of the genetic risk in Sz and BD. Using optimized VBM to assess the structural correlates of the genetic risk for Sz and BD, the risk for Sz was specifically associated with distributed GM volume deficits in the bilateral fronto-striato-thalamic and left lateral temporal regions, whereas genetic risk for BD was specifically associated with GM deficits only in the right anterior cingulate gyrus and ventral striatum [48]. This is similar to the results of our comparison between BD and healthy controls (smaller right caudate head in BD) and between Sz and BD groups (less anterior cingulate GM in BD). Later on, the same group showed that genetic liability to Sz was associated with decreased GM volume in dorsolateral and ventrolateral prefrontal cortices [52], while no relationship was demonstrated between a genetic liability to BD and GM volume. In an already cited report, first-degree relatives of the Sz patients showed a significant enlargement of ventricles, not present in the relatives of BD patients [49].

The cortical deficit in our Sz group was more intense on the anterior part of the brain when compared to BD group, as it was in previous reports [47, 51, 52]. In relation to this, we have published elsewhere that NAA levels in the

prefrontal region in a subsample of the here presented showed intermediate levels in the BD cases between controls and SZ patients [57]. This may indicate a greater neuronal affectation at that level in Sz when compared to BD patients, which seems coherent with data showing that FE patients evolving into Sz or BD shared a left prefrontal GM deficit, being that deficit broader in the former [31]. This possibility is also supported by a longitudinal study including 8 BD and 25 Sz patients. After 2-year follow-up, Sz patients showed additional extensive losses in lateral fronto-temporal regions and left anterior cingulate gyrus. By contrast, in the BD group, GM additional loss over time was observed only in the anterior cingulate cortex [22]. The greater cortical deficit in Sz is also compatible with the greater cognitive deficits reported in that process in comparison with BD, in particular for working memory [7].

A reduction in putamen in comparison with controls was found in our Sz but not in our BD patients, and putamen was also reduced in the Sz group in the direct comparison with the BD one. Such reduction may not be a medication artifact, since treatment with typical antipsychotics (to which most of them had been chronically exposed) indeed increases basal ganglia (BG) volume [18, 69]. The specificity of putaminal reduction is in agreement with a previous report comparing MRI scans between Sz and BD patients [47] and with the absence of BG reduction in BD according to several meta-analyses [4, 36, 50]. Nevertheless, the genetic risk to BD was found to be related to a reduction in ventral striatum [48]. This, together with the absence of significant differences at this level in the direct comparison between Sz and BD patients, may indicate that the striatum size in the latter may also occupy an intermediate position between that of Sz and controls. A striatal size decrease in schizophrenia receives support from previous MRI studies, in particular those performed in neuroleptic-free and neuroleptic-naïve patients [8, 16, 25, 37, 39, 42, 54, 66, 67].

The decrease in BG volume in our Sz patients is consistent with the proportion of treatment-resistant patients in this group, since in this kind of patients, this reduction may be more marked: smaller caudate and putamen volumes found in chronic patients with severe and unremitting courses [12] and reductions in caudate and putamen volumes were only found in recurrently ill chronic Sz patients in a longitudinal report [55]. In relation to this, we have recently reported (using a sample partially overlapping with the used in the present study) marked structural differences at subcortical level between treatment-resistant Sz patients with bad outcome in the long-term ("kraepelinian" group) and Sz patients without these characteristics [56]. The differences between these groups were much smaller at cortical level, suggesting that the differences between BD and Sz patients in the present report are not simply due to the 16 treatment-resistant patients' subgroup.

Our Sz patients showed a pulvinar thalamic reduction when compared to BD patients. A pulvinar reduction in Sz is in agreement with previous MRI [35] and postmortem [13, 19] results.

This is not to say, however, that GM deficits are absent from BD patients. Indeed, our BD patients showed a medial frontal GM decrease with respect to the healthy controls that seems coherent with the results of a recent meta-analysis of GM deficits in BD in comparison with healthy controls using 21 voxel-based morphometry studies [11]. Moreover, unmedicated BD patients have been reported to show decreases at posterior cingulate and superior temporal regions with respect to medicated ones in a sample mostly including type II bipolar patients [59]. Type I BD patients were reported to show extended GM decreases [27], while other groups found GM deficits in BD to be limited to orbital and right inferior frontal regions [68] or to the posterior middle temporal lobe. An increase in left thalamic volumes along with increases in cerebellum and left fusiform gyrus has also been reported for type I BD patients [1].

Such a diversity of findings may be in part explained by methodological reasons (for example, the variation in the methods used to control for errors arising from multiple comparisons). However, that diversity of findings may also relate in part to a possible heterogeneity biological within the label of BD, which may be reflected in diverse patters of GM alterations dimensionally distributed across the bipolar spectrum. This contention is coherent with the differences in GM deficits found between type I and II BD patients [27] and by a meta-analysis of morphometry in BD that described an enlargement of the right ventricle as the only consistent deviation in that syndrome along with a strong heterogeneity of GM volumes for several regions [50].

We cannot discard that the treatment received by the Sz group had contributed to decrease their cortical GM volume, as supported by preclinical data [21]. Longitudinal MRI studies in patients treated with typical antipsychotics have shown a measurable GM reduction in these patients [26], although such a reduction also occurs in the transition from high-risk to psychotic states [60] and thus cannot be solely attributed to the effect of those drugs. Moreover, these GM cortical changes seem quantitatively weak [46], which also argues against a simply pharmacological origin for the GM deficit observed in our Sz patients. In relation to this, a GM decrease with typical antipsychotics would imply that the confounding effects due to the 6 Sz patients who had abandoned their treatment before inclusion would be small, since that abandon could have a positive effect, if any, on cortical GM volume.

It is also theoretically possible that the lesser GM deficit in BD was due to the positive trophic effects described for the lithium on total GM [44, 63], although the more severe GM deficits reported in FE Sz than in FE BD patients [28, 31, 33, 40, 41], would indicate that the lesser GM deficits in the latter are not simply a medication effect. Also supporting this, some GM deficits were shared by medicated and unmedicated BD (mixed Type I and II) patients [59].

Unexpected GM increases were found in our Sz patients in comparison with the healthy control in a small region within the OF lobe and in part of the cerebellar hemispheres. Although we cannot discard a type I error in this case, a recent follow-up study in neuroleptic-naïve patients suggests that the antipsychotic treatment may induce a bilateral volume increase in the cerebellum after 8 weeks of treatment [20]. Since our Sz patients had been receiving antipsychotics for a much longer time, it could be speculated with a role of such treatment in the detected cerebellar volume increase. Cerebellar volume has been reported to be both reduced [32] and normal [14] in neuroleptic-naïve Sz patients.

Our study has limitations, notably the absence of an untreated group. However, relevant information can be gathered in this population about the long-term outcome of the cerebral abnormalities associated with those syndromes, and such work would have been unfeasible if treated chronic Sz or BD patients had to be excluded. The fact that nearly half of our Sz patients were resistant to conventional antipsychotics might partly explain the higher severity of the GM deficits in the Sz group. However, the proportion of resistance to conventional antipsychotics in our sample is quite similar to the corresponding estimations in the schizophrenia population [45, 62], the GM deficits in our Sz patients being similar to those found by other groups [47]. We have not discriminated between BD patients with and without a history of psychosis, but our results were similar to those of a comparison between Sz and psychotic bipolar patients [47].

The statistical significance of the differences between BD patients and controls and BD and Sz patients disappeared when we applied FDR correction, and the significance of the GM decrease in Sz vs. healthy controls differences survived that correction. Although this may suggest of the possibility of type I errors in the uncorrected results of the comparisons between Sz and BD patients, this is also compatible with an intermediate degree of structural deviation in BD patients between that of healthy controls and that of Sz patients that would require higher numbers of bipolar patients to be detected. The widespread heterogeneity of MRI data within BD patients revealed by recent meta-analyses of brain volume differences between Sz and BD [4, 36] might also contribute to that lower statistical significance. On the other hand, *P* values for clusters have been considered inexact [6] and voxel-wise corrections may be overly conservative [70]. In this context, the validity of the present results is additionally supported by their similarities with those of other groups.

In conclusion, our data support that chronic Sz patients may show a GM deficit that is not found in BD patients with similar illness duration. The pattern of GM reduction in the latter may have some commonalities with the Sz group, although it tended to be less intense.

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Conflicts of interest None.

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