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Structural brain features of borderline personality and bipolar disorders

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ABSTRACT

A potential overlap between bipolar disorder (BD) and borderline personality disorder (BPD) has been recently proposed. We aimed to assess similarities and differences of brain structural features in BD and BPD. Twenty-six in-patients with BPD, 14 with BD and 40 age and sex-matched healthy controls (HC) underwent structural magnetic resonance (MR). Voxel-based morphometry analysis with Statistical Parametric Mapping (SPM) was used to localize and quantify gray (GM) and white matter (WM) abnormalities in BD and BPD compared to HC and to identify those specifically affected in each patient group ($p < 0.001$ uncorrected). ROI-based analyses were used as a confirmatory analysis. GM density changes in BD are significantly more diffuse and severe than in BPD as resulting both from SPM- and ROI-based analyses. The topography of GM alterations shows some regions of overlap but each disorder showed the involvement of specific regions (involving both cortical and subcortical structures in BD, confined to mainly fronto- limbic regions in BPD). WM density changes are milder in both conditions and involved completely different regions. Although BPD and BD show a considerable overlap of GM changes, the topography of alterations is more consistent with the separate conditions hypothesis and with the vulnerability of separate neural systems.

1. Introduction

Borderline personality disorder (BPD) is a chronic condition characterized by impulsivity, mood fluctuations, instability of social interactions, sense of emptiness, and aggressive and para-suicidal behaviours. BPD is highly prevalent in both general and clinical populations (Lenzenweger, 2010; Rossi and de Girolamo, 2010). Since its introduction in the Diagnostic and Statistical Manual of Mental Disorder (DSM-III) (American Psychiatric Association, 1980) the hypothesis of a possible overlap between BPD and mood disorders, in particular bipolar disorder (BD) (Gunderson and Phillips, 1991) has been highly controversial. BD is a major mental illness that affects approximately 1.5% of the population and represents a significant source of individual morbidity and societal costs (Goldberg et al., 2005). Similarities between the two disorders have prompted some to question whether they belong to the same spectrum, although evidence for this hypothesis remains mixed (Akiskal et al., 1985; Akiskal, 2002; Benazzi, 2008; Deltito et al., 2001; Gunderson et al., 2006; Koenigsberg et al., 2002; Mackinnon and Pies, 2006; Magill, 2004; Paris et al., 2007; Smith et al., 2004; Wilson et al., 2007; Ruggero et al., 2010). Affective instability is a core feature of both disorders, albeit its nature and course may differ (Henry et al., 2001; Koenigsberg et al., 2002). The difficulty of controlling anger of BPD has been postulated akin to the irritability of a manic episode (American Psychiatric Association, 2000). Impulsivity is a common feature of BPD, but is also present in patients with BD (Links et al., 1999; Swann et al., 2003; Zanarini et al., 2003) particularly when accompanied by substance abuse (Swann et al., 2004). However, impulsive actions in BD tend to be more episodic (Swann et al., 2004), whereas BPD tends to be characterized by a pattern in which recurrent suicidal gestures and self-injury are used to reduce distress (Brown et al., 2002). Both disorders are also characterized by recurrent suicide attempts (Fyer et al., 1988; Ruggero et al., 2007; Zanarini et al., 2008).

Whether these clinical similarities correspond to common pathogenetic processes is still a matter of debate (Paris et al., 2007). The failure of frontolimbic functions has been linked to the

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core elements of the psychopathology of BPD, such as impulsivity, emotional instability and aggressiveness (Tebartz van Elst et al., 2003) and it has been suggested that emotional dysregulation in patients with BPD is caused by prefrontal deficits, hyperactivity of the limbic system, or a combination of both (Herpertz et al., 2001). According to this hypothesis, prefrontal deficits could lead to increased difficulty in controlling negative emotions (control-down modulation) and heightened activity in the limbic system to emotional disorders (bottom-up modulation). The vast majority assessed changes in structures of interest, in particular hippocampus and amygdale (Driessen et al., 2000; Tebartz van Elst et al., 2003; Schmahl et al., 2003; Brambilla et al., 2004; Nunes et al., 2009) and reported volume loss.

In BD, the prefrontal-subcortical and anterior limbic networks are thought to play a critical role (Strakowski et al., 2005). It has been suggested that BD might result from structural abnormalities in this circuit and subsequent impairment of emotional regulation (Strakowski et al., 2005). Recently, two structural MRI studies have shown widespread decrease of the gray matter (GM) involving the frontal, parietal, and temporal regions, and the basal ganglia (Li et al., 2011; Ha et al., 2009). In a recent meta-analysis of voxel-based morphometry studies (VBM), BD has been consistently associated with reductions in the right prefrontal and temporal lobe GM (Selvaraj et al., 2012).

Taken together, these heterogeneous results do not enable to reach a clear picture and definite conclusions about the relationship between BD and BPD. Furthermore, previous studies were focussed on either BD or BPD. In line with the hypothesis of distinct clinical entities, in a recent study on the morphological and volumetric differences in the hippocampal subdivisions of BPD and BD, we found that the two groups exhibit a distinct pattern of volumetric and topographic MRI changes in hippocampus which might be related to the clinical phenomenology of each disorder (Rossi et al., in press). To further investigate the spatial patterns associated with BD and BPD, we extended our previous analysis to the whole brain and assessed the severity and topography of gray and white matter (WM) volumes of BD and BPD in patients with VBM technique. We used the volumetric analysis to have a quantitative and wide measure of lobar volume reduction that was complementary to the topographic VBM analysis. Based on previous studies, we hypothesized that BD and BPD involve different circuits although some brain regions could represent the field of overlap. In particular, we hypothesized that the "same continuum hypothesis" should results in milder and more localized GM and WM volume reduction in BPD than BD, while the "separate condition" hypothesis would result in different topographic involvement, with distinct regions being specifically involved in the two disorders.

2. Methods

2.1. Participants

Twenty-six patients meeting the DSM-IV criteria for BPD and 14 for BD were enrolled in the study over a period of about 24 months. We included inpatiens admitted to the Psychiatric Rehabilitation Unit of the IRCCS San Giovanni di Dio-Fatebenefratelli, a residential facility of the national mental health for non-acute patients (de Girolamo et al., 2002). The study and recruitment procedures were approved by the Ethic Committee of the IRCCS Centro San Giovanni di Dio-Fatebenefratelli, Brescia, Italy. All the participants provided written informed consent. Patients underwent a multidimensional assessment, including a clinical, psychiatric and neuropsychological assessment. MRI was acquired for patients and a group of healthy controls (HCs). Exclusion criteria for patients were: acute or lifetime schizophrenia, schizoaffective disorder, major depressive disorder with psychotic features, anorexia, and drug or alcohol abuse in the last 3 months, cognitive impairment. The clinical diagnosis was confirmed by the structured clinical interview for DSM-IV (First et al., 1994; First et al., 1995) made by a clinically experienced interviewer. Clinical information was collected: demographics (age, sex, education, marital status), history of psychiatric disease (years), family psychiatric history, history of alcohol and drugs abuse, presence of suicidal attempts, self-injurious behaviours or aggression towards others, medications. Lifetime psychiatric comorbidities of the BPD patients were as follows: in the BPD group, 5 patients reported a lifetime history of depression, 3 eating disorder, 1 eating disorder and obsessive compulsive disorder (OCD), and 2 OCD; 3 BDP subjects satisfied criteria for antisocial personality disorder, 2 for dependent personality disorder. BD group included 13 (87%) subtype I and 2 subtype II (13%). At the time of MRI scan, patients were euthymic. Furthermore, alcohol and substance abuse were common in both groups (Table 1). All patients received psychotropic medication.

HC were 1:1 age- and sex-matched persons enrolled in a study on the normal features of cerebral morphology ("*The Cerebral Morphometric MRI Archive*") described in detail elsewhere (Galluzzi et al., 2009). Briefly, the study recruited volunteers or outpatients attending the Neuroradiology Unit of the Poliambulanza hospital, in Brescia, undergoing brain MR scan for reasons other than cognitive impairment (usually headache and vertigo) whose scan was negative for major stroke, tumor, aneurysm, or other focal lesions (Riello et al., 2005; Galluzzi et al., 2009). In our sample 3 persons underwent MR for headache, 5 for balance or acoustic problems, 1 for visual disturbances (diplopia, scotoma), 1 for paresthesias, 1 to exclude cerebrovascular diseases, for investigation on possible adenoma in pituitary gland ($N=2$) and in pineal gland ($N=1$), and 26 were volunteers. In this study HC underwent a clinical protocol investigating: sociodemographics and physiological habits (physical activity, alcohol use, handedness, climacteric information, if applicable); subjective memory complaints; risk factors for vascular diseases and dementia; depressive symptoms; somatic complaints; addictive drugs abuse; current pharmacological therapy; current and past medical diseases (Galluzzi et al., 2009).

BD and BPD patients underwent a multidimensional clinical and neuropsychological assessment. The following scales were administered: Brief Psychiatric Rating Scale (BPRS) (Roncone et al., 1999) to assess general psychopathology, Hamilton Depression Rating Scale (HAM-D) (Hamilton, 1960) to assess depressive symptoms, Personal and Social Performance scale assessing global functioning (Gigantesco et al., 2006), Toronto Alexithymia Scale (TAS) (Bagby et al., 1994; Bressi et al., 1996) to assess alexithymia (inability to express feelings with words), Barratt Impulsiveness Scale (BIS-11) (Patton et al., 1995; Fossati et al., 2001) to assess impulsivity and State and Trait Anxiety Inventory (STAI) (Spielberger et al., 1983) for the assessment of anxiety.

Global cognitive performance was assessed with the Mini Mental State Examination (Folstein et al., 1975).

2.2. MRI scans.

All the patients and HC underwent MRI scan on a 1.5 Tesla GE system in a single session. T1-weighted MR images were acquired with an inversion-recovery prepared fast spoiled gradient recalled (IRP-FSPGR) technique and the following parameters: TR=7.95 ms, TE=1.9 ms, IT=350 ms, flip angle=10°, acquisition matrix 192 × 192, voxel resolution=1 × 1.2 × 1.2 mm.

2.3. Voxel based morphometry (VBM) processing

MR images were cropped and reoriented following the AC-PC line with MRIcro (http://www.cabiatl.com/mricro/mricro/mricro.html). The resulting images (including brain, cerebellum, and brainstem) were then processed using the Statistical Parametric Mapping software (SPM5, www.fil.ion.ucl.ac.uk/spm) (Ashburner et al., 2003). First, the anterior commissure was manually set with SPM5 in each image as the origin of the spatial coordinates.

Images were registered to a group specific common space following the DARTEL procedure (Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra) implemented in SMP5 (Ashburner, 2007). The procedure involves the following steps: (1) segmentation of GM and WM tissue maps for each subject using the standard unified segmentation model of SPM5; (2) alignment of GM and WM tissue maps to a standard space through rigid-body transformations; (3) generation of GM and WM DARTEL templates through a six steps iterative procedure which involves (i) the creation and refining of the templates and (ii) the associated image warping fields. Briefly, a first template is created by normalising the initial images to a standard template and by averaging; subsequent templates are then iteratively defined by normalising images to the template obtained at the previous iteration. The final deformation is then parameterised as a warping field. (4) non-linear warping of the individual GM and WM images to the corresponding DARTEL template using the warping fields computed at the previous step; (5) modulation of GM and WM warped images in order to preserve the original amount of GM and WM volumes; (6) smoothing of the modulated images with a Gaussian kernel of 8x8x8 FWHM in order to improve the normality of data and therefore to increase the power of subsequent statistical analysis.

Since the templates generated by DARTEL represent the average shape of the subjects included in the analysis and therefore their reference space generally differs from MNI space, the normalized and modulated GM/WM images were converted into MNI space prior to smoothing (McLaren et al., 2010; Canu et al., 2010)

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The anatomical locations of the GM peak clusters were identified with MRIcron (http://www.sph.sc.edu/comd/rorden/mricron/). The anatomical locations of significant WM clusters were detected using two atlases implemented within FSL (http://fsl.fmrib.ox.ac.uk/fsl/data/atlas-descriptions.html): the Johns Hopkins University (JHU) WM tractography atlas and the ICBM-DTI white-matter labels atlas.

2.4. Regional volumes analysis

GM and WM volumes were calculated in different regions with the WFU PickAtlas toolbox, implemented within SPM (http://www.fil.ion.ucl.ac.uk/spm/ext/#WFU_PickAtlas). The following lobar volumes were investigated: the frontal, temporal, parietal, and occipital lobes, the cerebellum, the limbic system. The modulated images were masked with these lobar volumes and the regional volumes were computed. Volumes were normalised by total intracranial volume (TIV) to correct for differences in head size among subjects. The average percentage tissue loss in BPD and BD was computed as the ratio between regional volume of each patient and the mean volume of the reference control group.

2.5. Statistical analysis

VBM. GM and WM images of BPD and BD groups were compared to those of the age-, sex- and education-matched HC using an analysis of covariance (ANCOVA) model, by modelling the effect of group (BPD, BD, HC) and a set of parametric nuisance covariates (education, TIV, abuse of alcohol and substances as nuisance variables).The patterns of atrophy specific to each disorder were assessed with an exclusively masking procedure. This procedure enables to extract the cerebral pattern of abnormalities specifically associated with BPD and with BD through the appropriate comparison versus their matched controls, and then by subtracting all common features in these maps, thus isolating the specificities of the two patient groups. This procedure allows to obtain a direct comparison between patient groups that is methodological appropriate and that, at the same time, maximizes the power of the experiment. This design allows maximizing the power of the experiment, overcoming the problem of different patient numbers, by comparing directly not just the patients, but the statistical maps resulting by the appropriate comparisons of each patient group with the control group. Given the exploratory nature of the study, statistical significance was set at $p < 0.001$ uncorrected, with a minimum cluster size of 50 voxels. The threshold for the exclusive masking was set to $p > 0.001$. The percent GM and WM deficits in the resulting clusters were computed from the statistical maps resulting from VBM analysis.

The correlation between GM atrophy and psychological scores (TAS, STAI, FPS, HAM-D, BPRS) was assessed using a multiple regression model performed with SPM, adjusted for subject's TIV.

Sociodemographical, neuropsychological and volumetric differences between groups were assessed with parametric and non parametric tests (t-test or chi-square or Kruskal–Wallis and Mann–Whitney tests when the distribution of the data was not normal). Post-hoc pairwise comparisons between groups were done with Bonferroni test.

3. Results

Table 1 shows that patients with BPD, BD and HC did not differ for age and sex. BPD and BD differ from HC in years of education ($p < 0.0001$). BPD and BD were similar in years of illness. BD and BPD patients had similar disease severity, showing a moderate degree of psychopathology as assessed with BPRS (Tables 1 and 2). These two groups did not score differently on the HAM-D scale showing values compatible with moderate degree of depression. The BPD group showed higher level of anxiety as assessed with the STAI scale which approached significance. BPD and BD did not differ in the level of alexithymia (inability to express feelings with words) although BPD but not BD patients showed higher levels of alexithymia compared to their matched HC (53 ± 11, 45 ± 16, 44 ± 13, respectively; $p < 0.05$). Furthermore, BPD group showed significantly higher level of impulsiveness. The global functioning was similar in the two groups. Looking at the clinical criteria, we observed the expected distinction between BPD and BD in the majority of the clinically distinctive features of the two disorders (impulsivity, abandonment fear, chronic emptiness for BPD and manic and depressive episodes for BD) albeit some overlap was present (affective instability and identity disturbance).

Table 1
Demographic and clinical features of 26 patients with Borderline Personality Disorder and 14 with Bipolar Disorder.

	Groups						
	BPD ($N=26$)	**BD** ($N=14$)	**HC** ($N=40$)	**BPD versus HC**		**BD versus HC**	
				Test value	***p***	**Test value**	***p***
Sex (% females)	16 (61%)	5 (36%)	21 (53%)	0.523[a]	0.470	1.170 [a]	0.279
Age, years	36 ± 11	43 ± 8	40 ± 11	-1.340[b]	0.186	0.935 [b]	0.354
Education, years	10 ± 2	10 ± 3	14 ± 4	197.00[c]	0.000	98.50 [c]	0.000
				BPD versus BD			
Years of Illness	14 ± 11	17 ± 5		**Test value**	***p***		
Alcohol abuse	20 (77%)	8 (57%)	–	1.695[a]	193		
Substance abuse	21 (81%)	7 (50%)	–	4.103[a]	0.43		
Clinical criteria							
Cognitive:							
Identity disturbance: markedly and persistently unstable self-image or sense of self.	14 (54%)	2 (14%)	–	4.656[a]	0.31		
transient, stress-related paranoid ideation or severe dissociative symptoms.	14 (54%)	0	–	10.231[a]	0.01		
abandonment fear	15 (58%)	1 (7%)	–	8.206[a]	0.004		
Energy/behaviour:							
Impulsivity (sex, substances, self-harming)	22 (85%)	5 (36%)	–	7.363[a]	0.007		
Suicide attempt	20 (77%)	6 (43%)	–	2.754[a]	0.09		
Mood:							
affective instability due to a marked reactivity of mood (e.g., intense episodic dysphoria, irritability, or anxiety usually lasting a few hours and only rarely more than a few days)	18 (70%)	6 (43%)		1.305[a]	0.253		
chronic emptiness	19 (73%)	1 (8%)		13.805[a]	< 0.001		
Manic episode	1 (4%)	14 (100%)		35.897[a]	< 0.001		
Depressive episode	16 (61%)	14 (100%)		7.179[a]	0.007		

[a] Chi square.
[b] Of Mann–Whitney.
[c] Student's t test.

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3.1. VBM results: BPD-specific and BD-specific patterns of atrophy

The regions of GM tissue loss specific to BD patients, resulting from the exclusive masking procedure, included wide regions in the frontal, temporal, and parietal regions, the cerebellum and the thalami bilaterally. The main cluster of less WM tissue in the BD group was localized in the posterior corpus callosum, in the left fronto-occipital fasciculus, in cortico-pontine tract and in the left anterior thalamic radiation (Fig. 1, top panel; Table 3).

Regions specific for the BPD group were located in the right hippocampus, temporal (inferior and middle gyri), frontal (rectus, precentral, inferior and middle gyri), and occipital lobes. The main clusters of WM tissue loss in BPD were localized in correspondence of the inferior longitudinal fasciculus, the main frontal-occipital WM connection and in temporal lobe in correspondence of the fornix, one of the major WM tracts of the limbic system. Both these tracts are association fibers that connect distal areas of the cortex. Furthermore, atrophy was also found in the corpus callosum (Fig. 1, bottom panel; Table 4).

Table 2
Clinical and psychological features of 26 patients with Borderline Personality Disorder (BPD) and 14 with Bipolar Disorder (BD).

	Groups			
	BD ($N=14$)	**BPD** ($N=26$)	**Test value**	***p***
BPRS	42 ± 7	45 ± 8	141.5[a]	0.25
HAM-D	18 ± 11	23 ± 9	107.0[a]	0.17
TAS	45 ± 16	53 ± 11	122.0[a]	0.12
BIS-11[b]	65 ± 8	71 ± 7	57.0[a]	0.05
STAI state	42 ± 9	49 ± 13	125.0[a]	0.07
STAI trait	48 ± 14	56 ± 12	112.5[a]	0.06
PSP scores	34 ± 6	34 ± 9	164.0[a]	0.624
Pharmacotherapy				
Typical antipsychotics	4 (29%)	7 (27%)	0.12[c]	0.911
Atypical antipsychotics	10 (71%)	14 (54%)	1.172[c]	0.279
SSRI	3 (21%)	8 (31%)	0.398[c]	0.528
Benzodiazepine	12 (83%)	24 (92%)	0.440[c]	0.507
Mood stabilizers	14 (100%)	17 (65%)	6.253[c]	0.012
Lithium	5 (36%)	2 (8%)		

BPRS: Brief Psychiatric Rating Scale; HAM-D: Hamilton Depression Scale; BIS-11: Barratt Impulsiveness Scale; STAI: State-Trait Anxiety Inventory; PSP: Personal and Social Performance scale; SSRI: Selective Serotonin Reuptake Inhibitor.

[a] Mann–Whitney U test.
[b] Barratt Impulsiveness Scale-11 was administered to 16 BPD and 11 BD.
[c] Chi-square.

3.2. VBM results: the topography of GM and WM atrophy in BD and BPD

VBM analyses showed that BD patients had less GM compared with HC (Fig. 2, top panel; Supplementary Table 1) widely in the temporal and frontal lobe, in the precuneus, cerebellum, and in the thalami bilaterally. The results concerning WM was similar to those obtained with the exclusive masking procedure. On average, the amount of tissue difference in the peak clusters was 12% in the GM (range 5–30) and 8% in WM (range 6–11%).

GM volume reductions in BPD (Fig. 2, bottom panel; Supplementary table 2) mapped to the hippocampus and amygdale bilaterally, and in several areas in frontal, parietal and occipital regions. Furthermore, BPD showed less GM tissue also

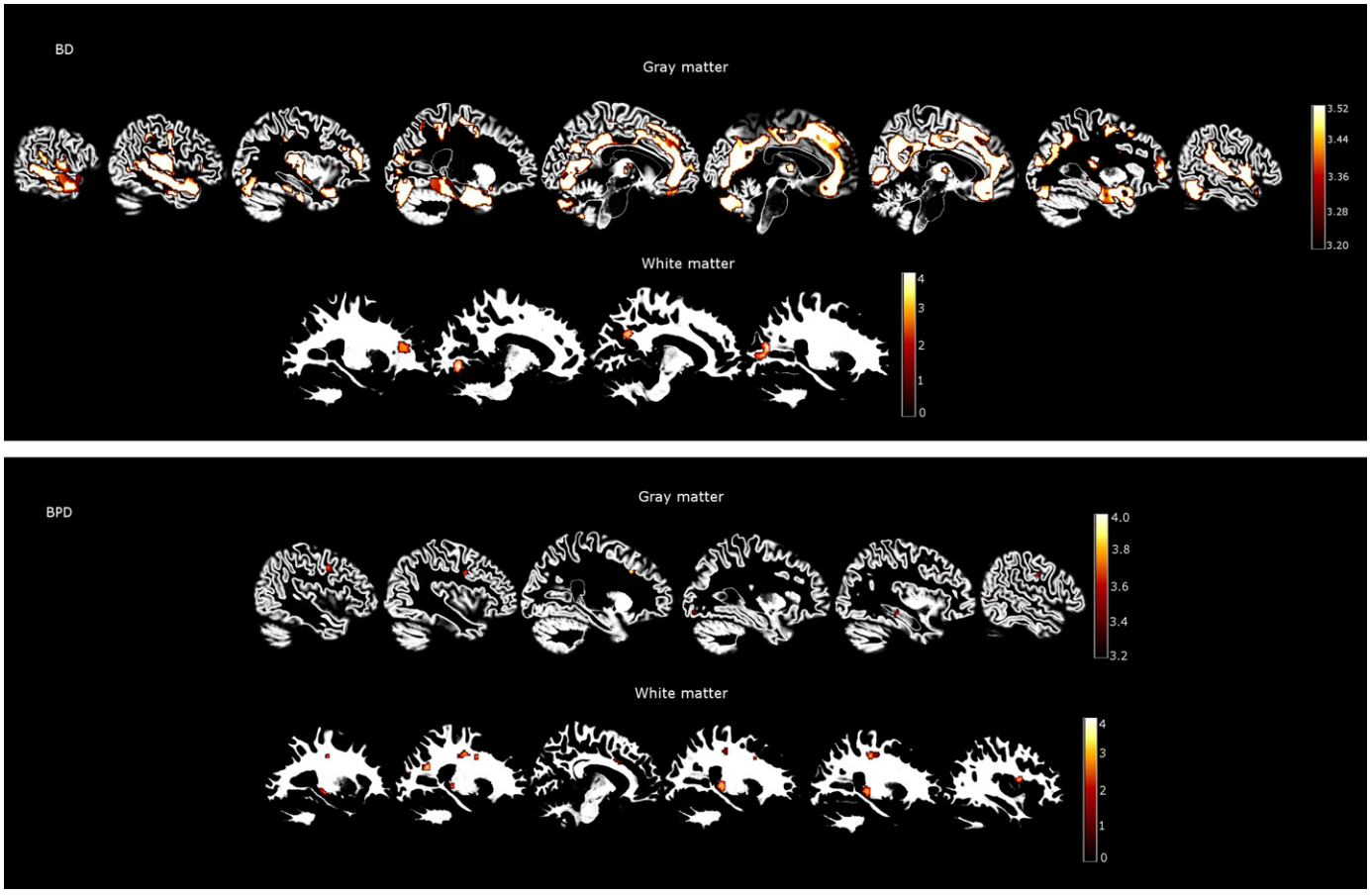

Fig. 1. Specific regions of gray and white matter alterations in Bipolar Disorder (top panel) and in Borderline Personality Disorder (bottom panel) ($P < 0.001$ uncorrected) resulting from the exclusive masking procedures.

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Table 3
Regions of specific tissue reduction in Bipolar Disorder (BD) group resulting from the comparison BD versus healthy controls (HC) exclusively masked with Borderline Personality Disorder versus HC for the gray and white matter experiments ($P < 0.001$ uncorrected).

Cluster size Voxel no.	Regions	Side	Stereotaxic coordinates (mm)			Z score
			x	y	z	
	GM					
40728	Middle cingulate	L	−1	−9	38	5.04
Including:	Anterior cingulate	R	5	45	21	
	Anterior cingulate	L	−5	44	5	
	Superior frontal gyrus	R	6	29	53	
	Superior frontal gyrus	L	−3	33	45	
	Hippocampus	R	23	−6	−26	
	Hippocampus	L	23	−6	−26	
	Orbitofrontal cortex	R	3	35	−13	
	Orbitofrontal cortex	L	−2	38	−13	
1066	Angular gyrus	R	31	−54	43	4.03
767	Middle frontal gyrus	L	−32	44	15	3.56
40	Inferior frontal gyrus	R	36	37	−0	3.76
70	Inferior frontal gyrus	L	−47	22	6	3.60
130	Middle temporal gyrus	R	−61	−33	−9	3.50
51	Middle frontal gyrus	L	−29	21	47	3.43
139	Thalamus	L	−5	−6	8	3.42
Including	Thalamus	R	5	−8	8	3.22
121	Inferior frontal gyrus	R	34	5	23	3.38
57	Cerebellum	L	−6	−63	−47	3.34
36	Supplem motor area	R	16	−25	52	3.33
	WM					
307	Posterior corpus callosum	R	25	−76	16	3.93
263	Inferior fronto-occipital fasciculs	L	−17	−73	−3	3.77
169	Posterior cingulum	R	7	−60	25	3.62
153	Anterior thalamic radiation	L	−26	35	16	3.58

Table 4
Regions of specific tissue reduction in Borderline Personality Disorder (BPD)group resulting from the comparison BDP versus healthy controls (HC) exclusively masked with Bipolar Disorder versus HC in gray and white matter experiments ($P < 0.001$ uncorrected).

Cluster size Voxel No.	Regions	Side	Stereotaxic coordinates (mm)			Z score
			x	y	z	
	GM					
66	Middle frontal gyrus	R	26	20	31	4.13
40	Rectus gyrus	L	−12	34	−15	3.65
140	Rolandic operculum/ precentral gyrus	R	46	−6	23	3.62
213	Precentral gyrus	L	−44	−1	40	3.57
59	Hippocampus	R	36	−25	−13	3.55
51	Superior occipital gyrus	L	−13	−83	22	3.55
67	Inferior occipital gyrus	R	30	−83	−10	3.54
162	Middle temporal gyrus	R	48	−73	10	3.53
59	Inferior frontal gyrus	R	32	18	33	3.46
48	Middle temporal gyrus	L	−57	−31	−15	3.37
72	Inferior temporal gyrus	R	54	−17	−20	3.35
	WM					
196	Inferior longitudinal fasciculus	L	−39	−64	6	4.05
338	Fornix	R	18	−30	6	3.72
152	Posterior corpus callosum	L	−24	−61	25	3.65
118	Superior longitudinal fasciculus	R	34	0	13	3.64
77	Corpus callosum	L	−20	−82	19	3.64
116	Cingulum	R	10	14	31	3.57
191	Superior longitudinal fasciculus	R	27	−24	46	3.47
205	Cortico-spinal tract	L	−20	0	40	3.39
103	Fornix	L	−15	−30	7	3.39
71	Fornix	L	−30	−27	−6	3.37

in the prefrontal cortex. WM results were very similar to those resulted in the exclusive masking (Supplemetary table 2). On average, the amount of tissue loss in the peak clusters was 9% in the GM (range 4–23) and 9% in WM (range 7–16%). The opposite comparisons (HC versus BPD or HC versus BD) were negative.

The results of the multiple regression models showed that a significant negative correlations were present only between TAS scores and GM in right (21 −90 17; *Z* score=4.68; cluster size: 1032 voxels) and left (−23 −67 24; *Z* score=3.47; cluster size: 61 voxels) occipital gyrus, right (13 −64 −20; *Z* score=3.85; cluster size: 1385 voxels) and left cerebellum (−14 −54 −26; Z score 3,47; cluster size 483 voxels), right inferior frontal gyrus (35 10 31; *Z* score=3.81; cluster: size 66 voxels), left angular gyrus (45 −46 28; *Z* score=4.53; cluster size: 77 voxels) in BPD and in a small cluster (92 voxels) in the left middle temporal gyrus (−68 −5 −10; *Z* score=4.08) in BD. Furthermore, in BPD there was a negative correlations between STAI trait scores and GM in the left occipital gyrus (−43 −81 −15, *Z* score=3.76; cluster size: 64 voxels) and in the right (0 −76 −26; *Z* score=3.67; cluster size: 76 voxels) and left (10 −53 −6; *Z* score=55; cluster size: 55 voxels) cerebellum.

3.3. Regional volumes analyses

Table 5 shows the results of the global volumes analyses. BPD and BD showed smaller global GM and WM regional volumes compared with HC. Furthermore, BD showed significantly less GM volume compared with BPD in the frontal, limbic, parietal and cerebellar regions. We observed differences also in temporal, occipital regions although they did not reach statistical significance. Conversely, BPD and BD showed similar WM volumes. The statistical significance did not survive using the Bonferroni's correction for multiple comparisons.

4. Discussion

In this study we used structural neuroimaging to test the "continuum" and the "separate conditions" hypotheses of BD and BPD. We observed a difference in the severity of GM involvement (volumetric differences in BD are about twice than BPD compared with HC) and in its distribution (diffuse in BD involving both cortical and subcortical structures, confined to mainly fronto-limbic regions in BPD). As resulting in the exclusive masking procedure, our data are in line with the "separate conditions" hypothesis since BD and BPD showed several regions of specificity both in GM than in WM tissues although the presence of GM regions of overlaps existed. The regions of overlaps were more pronounced in GM tissue. Conversely, regions of lower WM volume seem to be more distinctive for the two disorders as we observed specific sets of clusters with minimal overlaps.

The result of the exclusive masking procedure showed that BD involves a network comprising extensively cortical and cerebellar and subcortical regions. WM tracts involved in BD are associative fibers but also projection fibers connecting the cortex to subcortical structures (Wakana et al., 2004). Regarding BPD, most regions with reduced volumes in BPD were involved also in BD. Interestingly, the regions that we observed selectively involved in BPD are strongly correlated with the BPD clinical phenomenology: deficits in emotional processing (hippocampus, middle and inferior temporal gyrus) (Guitart-Masip et al., 2009), capacity of empathy and mentalizing (inferior and superior frontal gyrus,

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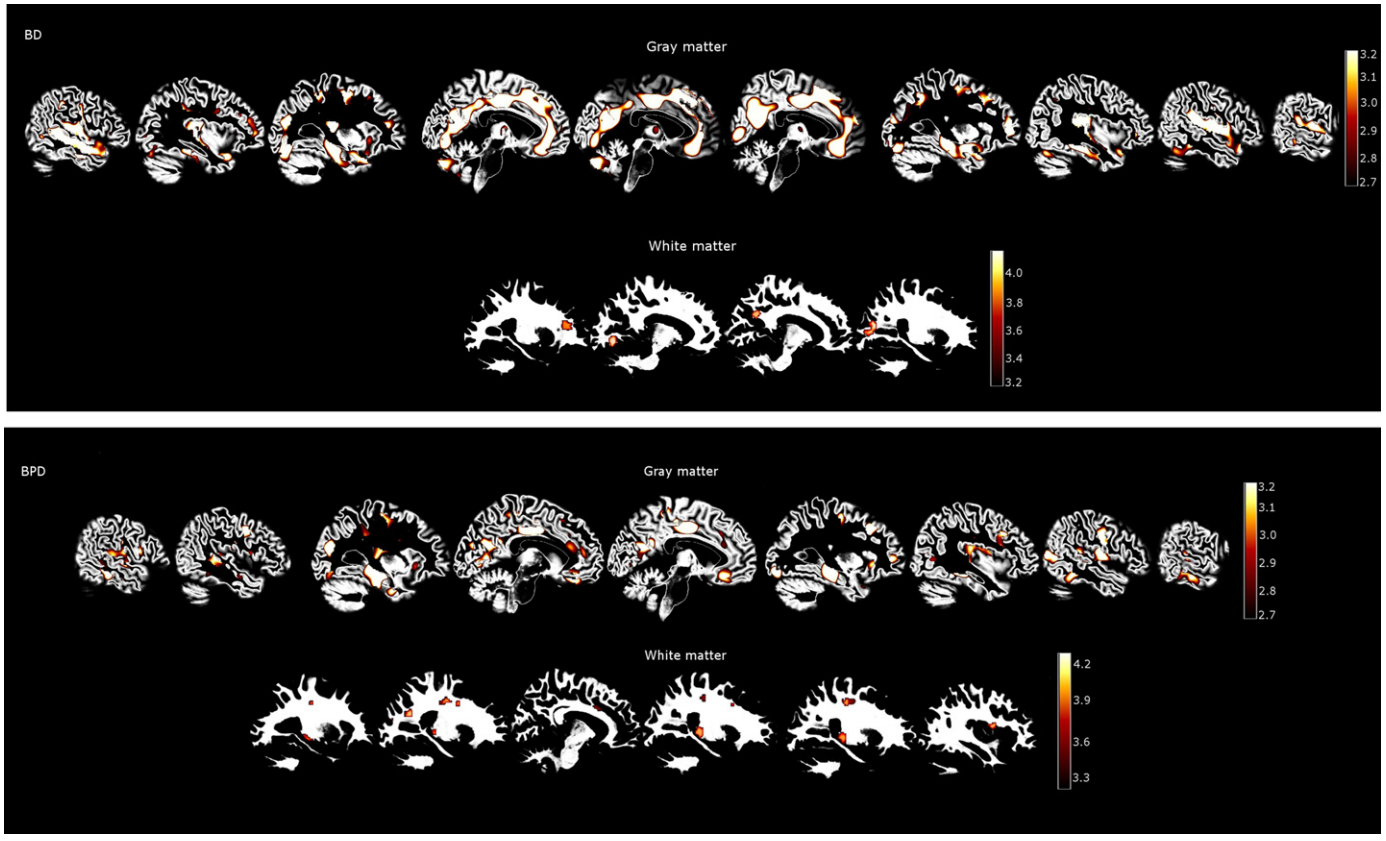

Fig. 2. Regions of gray and white matter alterations in 14 Bipolar disorder (top panel) and 26 Borderline Personality Disorder (bottom panel) matter compared with 40 healthy age- sex-matched controls. ($P < 0.001$ uncorrected).

precentral gyrus) (Hooker et al., 2010). These results are consistent with the hypothesis that BPD seems to be characterized by a GM prefrontal/frontal/limbic pattern and by a marked involvement of the fornix, a complex of fibers belonging to the limbic system that connects the hippocampus to the hypothalamus (Wakana et al., 2004). Regional lobar volumes confirmed that BPD and BD differed in the degree of GM involvement, while WM volumes were similar. Using the Bonferroni's correction for multiple comparisons ($p=0.0083$ for $n=6$ comparisons) these results did not achieve statistical significance. In order to carry out a slightly less restrictive correction for multiple comparisons, we computed the proportion of false positive results that we can expect from this kind of experiment. Specifically, since we set a significant threshold of $p=0.05$, we know that the probability of a false positive for the whole experiment ($n=6$ tests) is 30%. Our findings are partially in line with the literature. A systematic review of voxel-based morphometry studies in BD showed less gray matter in the anterior cingulate and bilateral insula (Ellison-Wright and Bullmore, 2010). The involvement of the anterior limbic regions was reported also in two recent meta-analyses of GM abnormalities in BD using VBM (Bora et al., 2010; Selvaraj et al., 2012). However, MRI findings in BD are inconsistent with lateral ventricular enlargement being the most consistently reported finding (Kempton et al., 2008), while extensive heterogeneity existed for several other brain regions, including the amygdala, subgenual prefrontal cortex, thalamus, and the third ventricle (McDonald et al., 2005). One possible reason for the discrepancies observed in the literature could be the heterogeneity of the patients included in different studies, such as differences in sample size, age, and duration of illness. Furthermore, it should be noted that some abnormalities, such as those in prefrontal cortical areas, striatum and amydgala, occur early in the course of the disease while other regions, such as the cerebellum, lateral ventricles and other prefrontal regions (left inferior), generally appear to develop with repeated affective episodes. BD is characterized by a progression and some abnormalities may be more evident depending on the stage and severity of the disease. A model for BD has been widely proposed (Strakowski et al., 2005) suggesting that dysfunction within the subcortical-prefrontal networks and the associated limbic regions (amygdale, midline cerebellum) might underlie the expression of BD (Strakowski et al., 2000). Our findings are consistent with this view, and we could hypothesize that BD might present a relatively diminished prefrontal modulation of subcortical and medial temporal structures within the limbic system (amygdale and thalamus), resulting in dysregulation of mood. Furthermore, in BD we found specific differences in volumes also in the cerebellum resulting both in the VBM and in the regional volumetric analyses. Previous MRI studies similarly reported smaller cerebellum and vermis in bipolar individuals as compared with controls (Brambilla et al., 2005). These differences seem to increase with the number of affective episodes (DelBello et al., 1999; Brambilla et al., 2001).

Regarding BPD, only few previous VBM studies were reported. Rüsch et al. (2003) compared 20 female BPD patients with 21 controls and found a significant volume reduction in the left amygdala. In a more recent study, Soloff and colleagues (Soloff et al., 2008) used VBM in 34 subjects with BPD and 30 healthy control subjects. BPD subjects had significant bilateral reductions in GM concentrations in the ventral cingulate gyrus and several regions of the medial temporal lobe, including the hippocampus, amygdala, parahippocampal gyrus, and uncus. The abnormalities of hippocampus and amygdala in BPD are well documented (Nunes et al., 2009). Furthermore, a preliminary study on 7 male patients (Völlm et al., 2009) with BPD and 6 control men reported

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Table 5
Global volumes and percentage of difference in BPD, BD and HC. All comparisons among the three groups except the cerebellar WM are significant at $p < 0.05$ on ANOVA.

Regions	BPD	BD	HC	Test value Student's t-test	p
Frontal GM	166.9 ± 18.7	153.2 ± 19.5	180.9 ± 15.3		
% difference	7.7 ± 10.3	15.3 ± 10.8	Reference	2.180	0.04
Limbic GM	58.9 ± 6.3	54.2 ± 5.8	64.2 ± 5.0		
% difference	8.3 ± 9.7	15.6 ± 9.1	Reference	2.315	0.03
Temporal GM	97.6 ± 11.2	92.2 ± 10.7	106.2 ± 9.2		
% difference	8.1 ± 10.6	13.1 ± 10.0	Reference	1.453	0.15
Parietal GM	73.4 ± 9.4	67.1 ± 7.1	79.3 ± 7.9		
% difference	7.4 ± 11.9	13.1 ± 10.0	Reference	2.206	0.03
Occipital GM	59.7 ± 6.2	54.2 ± 4.4	64.7 ± 5.4		
% difference	7.7 ± 10.9	13.6 ± 6.8	Reference	1.831	0.07
Cerebellum GM	88.9 ± 8.6	81.4 ± 8.3	93.4 ± 9.2		
% difference	4.8 ± 9.2	15.4 ± 8.8	Reference	2.693	0.01
Total GM	545.4 ± 57.0	503.9 ± 51.9	588.6 ± 45.9		
% difference	7.3 ± 9.7	14.4 ± 8.8	Reference	2.262	0.03
Frontal WM	147.1 ± 9.1	148.7 ± 9.6	156.8 ± 9.6		
% difference	6.2 ± 5.8	5.2 ± 6.1	Reference	−0.509	0.61
Limbic WM	58.9 ± 6.2	54.2 ± 5.8	64.2 ± 5.0		
% difference	5.5 ± 5.5	4.8 ± 7.8	Reference	−0.365	0.72
Temporal WM	64.3 ± 4.8	66.1 ± 7.2	68.6 ± 5.3		
% difference	6.1 ± 7.0	3.6 ± 10.6	Reference	−0.801	0.43
Parietal WM	55.1 ± 4.3	55.0 ± 4.4	59.5 ± 4.8		
% difference	7.3 ± 7.2	7.5 ± 7.5	Reference	0.114	0.91
Occipital WM	33.2 ± 4.0	32.4 ± 5.1	35.7 ± 3.6		
% difference	6.9 ± 11.3	9.1 ± 14.4	Reference	0.535	0.59
Cerebellum WM	22.5 ± 2.7	22.5 ± 2.6	23.5 ± 2.9		
% difference	4.5 ± 9.6	4.5 ± 10.9	Reference	−0.008	0.99
Total WM	354.4 ± 57.0	357.2 ± 25.2	378.3 ± 22.2		
% difference	6.3 ± 5.2	5.6 ± 6.7	Reference	0.364	0.72

a reduction of GM tissue in the superior, middle frontal gyrus, lateral orbitofrontal and inferior frontal cortex, precentral and postcentral gyrus, anterior cingulate, middle temporal gyrus and temporal pole, superior parietal cortex and inferior parietal lobule. Most of the regions reported to be involved in the previous studies were also specifically involved in our report. However, the extension of atrophic changes is more diffuse in our study than in previous reports, the reasons for this discrepancy possibly being the older age of our patients and the longer duration of the disease. It has been reported that some alterations in BPD are present early in the course of the disease, such as those in the anterior cingulate cortex and in the orbitofrontal cortex (Chanen et al., 2008; Whittle et al., 2009), while other features might develop later (Chanen et al., 2008).

The results of the multiple regression models showed a different involvement of GM volumes associated with anxiety and alexithymia in the two disorders that need further analysis.

To the best of our knowledge, this is the first voxel-based study including both BPD and BD patients and assessing the pattern of GM and WM tissue reductions associated with the two disorders. Due to the preliminary nature of our results, further replications on independent samples are needed.

Strengths of the present study include the concomitant analysis of BPD and BD cases and the analysis of both GM and WM volumes using a fully automated technique. Some caveats should be taken into account when interpreting our data. One limitation is that the sample study is unselected and the hospital-based cohort cannot be considered as fully representative of BD and BPD and a replication is needed. The inclusion of rating scales to assess the specific severity of BPD and or BD should be useful to better characterize patients. Furthermore, patients were on psychotropic medications. The impact of drugs on brain structures is a matter of debate, some psychotropic agents affecting neurons, such as fluoxetine (Santarelli et al., 2003) and atypical antipsychotics (Braus et al., 2001), and others, conversely, showing a positive effect of brain structure, such as lithium treatment (Germanà et al., 2010). However, it is not clear whether the potential effect of drugs on brain morphology is stable over time or reversible after switching. In neuroimaging studies, the potential confounding effect of medications is a major issue, and this is especially problematic for studies of complex pathology such as BPD or BD, in which the majority of individuals may be receiving psychotropic medication (Phillips et al., 2008). One possible strategy to avoid the potential confound of medication on neuroimaging measures is to restrict the studies to medication-naive individuals. This strategy, however, would largely limit recruitment to small group of participants who might not be representative of the populations typically managed in most clinical settings. In our sample, at the time of MRI scans, BD and BPD differed for the use of mood stabilizers, while there were no differences in the use of other pharmacological treatments. Since we found different patterns of alteration in BD and BPD, we believe that this difference cannot be attributed to pharmacotherapy, as this would have similar impact on both groups.

Furthermore, BPD and BD are heterogeneous diagnostic categories whose clinical picture is often complicated by the presence of other comorbidities (e.g. other personality disorders, alcohol and/or substance abuse, anxiety disorders) (Oldham et al., 1995; Skodol et al., 2005). Although this could be a bias in BPD and BD studies, it should be stressed that this sample is representative of the clinical population admitted to the rehabilitation units, needing a pharmaco-, psycho-, and rehabilitative- therapy. The exclusion of such patients means to refuse to tackle a relevant clinical issue. In the future, the inclusion of a greater number of patients will enable to study more homogeneous subgroups of patients in terms of clinical features and medications. In our study, we controlled for the variability associate with the possible confounders (alcohol and substance abuse) by including these factors as covariates in our analyses.

Furthermore, given the small scale and exploratory nature of our study, we used a lenient threshold for the VBM analysis ($p < 0.001$ uncorrected). On the one hand, this might increase the

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possibility of Type I error and the results should therefore be interpreted with caution. On the other hand, however, this is the first study comparing the patterns of GM and WM changes in patients with BD and BPD. These results can therefore provide researchers data on which to generate hypotheses for future studies in this area.

Lastly, due to the relevance of WM results further studies including DTI techniques are needed.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.pscychresns.2012.07.002.

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