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Original article

Structural and metabolic differentiation between bipolar disorder with psychosis and substance-induced psychosis: An integrated MRI/PET study

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ABSTRACT

Background: Bipolar disorder (BD) may be characterized by the presence of psychotic symptoms and comorbid substance abuse. In this context, structural and metabolic dysfunctions have been reported in both BD with psychosis and addiction, separately. In this study, we aimed at identifying neural substrates differentiating psychotic BD, with or without substance abuse, versus substance-induced psychosis (SIP) by coupling, for the first time, magnetic resonance imaging (MRI) and positron emission tomography (PET).
Methods: Twenty-seven BD type I psychotic patients with (n = 10) or without (n = 17) substance abuse, 16 SIP patients and 54 healthy controls were enrolled in this study. 3T MRI and 18-FDG-PET scanning were acquired.
Results: Gray matter (GM) volume and cerebral metabolism reductions in temporal cortices were observed in all patients compared to healthy controls. Moreover, a distinct pattern of fronto-limbic alterations were found in patients with substance abuse. Specifically, BD patients with substance abuse showed volume reductions in ventrolateral prefrontal cortex, anterior cingulate, insula and thalamus, whereas SIP patients in dorsolateral prefrontal cortex and posterior cingulate. Common alterations in cerebellum and parahippocampus were found in both BD with substance abuse and SIP. Finally, a unique pattern of GM volumes reduction, with concomitant increased of striatal metabolism, were observed in SIP patients.
Conclusions: These findings contribute to shed light on the identification of common and distinct neural markers associated with bipolar psychosis and substance abuse. Future longitudinal studies should explore the effect of single substances of abuse in patients at the first-episode of BD and substance-induced psychosis.

1. Introduction

Bipolar disorder (BD) is a chronic psychiatric disorder, characterized by severe disability and high economic burden [1]. The disease encompasses recurring mood swings between episodes of mania, hypomania and depression [2]. About 75% of patients with an acute manic episode displays psychotic symptoms and comorbid substance abuse [3–5] acting to exacerbate its clinical manifestation [6]. Therefore, several behavioral and genetic studies consistently suggested the clinical relevance of differentiating psychotic and nonpsychotic BD [7,8]. Indeed, psychotic symptoms seem to explain the phenotypic variability of BD in terms of severity and response to treatment, which in turn,

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Table 1
Q6 Socio-demographic and clinical variables.

	BDns patients	BDws patients	SIP patients	HC MRI study	HC PET study	Post-hoc results
n	17	10	16	27	27	
Age, years (SD)	38.7 (8.2)	35.7 (13.2)	25.7 (7.3)	34 (10)	49.4 (11.5)	SIP < all other groups All $P < 0.05$
Gender male/female (SD)	4/13	9/1	14/2	16/11	14/13	$X2 = 19.3$; $P < 0.001$
BPRS total (SD)	44.7 (5.4)	41.7 (8.6)	43.5 (4.7)	N/A	N/A	$P > 0.05$
BPRS-Dep (SD)	8.5 (2.9)	9.1 (5.3)	7.2 (3.0)	N/A	N/A	$P > 0.05$
BPRS-With (SD)	4.1 (1.6)	7.4 (4.6)	7.7 (2.6)	N/A	N/A	BDns < SIP $P < 0.05$
BPRS-Tho (SD)	7.1 (3.5)	9.8 (5.5)	11 (4.8)	N/A	N/A	BDns < SIP $P < 0.05$
BPRS-Act (SD)	5.4 (2.5)	7 (3.6)	6.3 (3.2)	N/A	N/A	$P > 0.05$
BPRS-host (SD)	6.3 (3.3)	8.4 (4.1)	9.5 (2.5)	N/A	N/A	BDns < SIP $P < 0.05$
Age of onset, years (SD)	25.7 (7.0)	25.6 (6.5)	21.8 (5.1)	N/A	N/A	All $P > 0.05$
Duration of illness, years (SD)	11.4 (7.0)	12.1 (8.5)	5.8 (7.2)	N/A	N/A	SIP < BDws $P < 0.05$
Substance use, months (SD)	N/A	93.6 (71.4)	68.4 (50.8)	N/A	N/A	
Drug use by substance (% of patients)		Cannabis: 6 (60%); cocaine: 1 (10%); polyabuser: 3 (30%)	Cannabis: 7 (44%); cocaine: 1 (6%); polyabuser: 8 (50%)	N/A	N/A	
Medications	AC (13); atypical AP (12); typical AP (2); AD (3)	AC (7); atypical AP (6); typical AP (6); AD (0)	AC (14); atypical AP (13); typical AP (13); AD (0)	N/A	N/A	

AC: anticonvulsive; AD: antidepressants; AP: antipsychotics; BDns: bipolar disorder without substance abuse; BDws: bipolar disorder with substance abuse; BPRS: Brief Psychiatric Rating Scale; BPRS-Dep: BPRS-depression/anxiety; BPRS-with: BPRS-withdrawal; BPRS-Tho: BPRS-thought disorders; BPRS-Act: BPRS-activity; BPRS-host: BPRS-hostility/suspiciousness; HC: healthy controls; SD: standard deviation; SIP: substance-induced psychosis.

further supports the presence of a clinical overlap with schizophrenia [9]. Furthermore, it has been shown that BD patients with a history of psychotic symptoms show a deteriorating course of the disease, poorer outcomes, and enduring cognitive impairment [10]. However, although behavioral and genetic studies consistently support the clinical relevance of differentiating psychotic and nonpsychotic BD [7,8], biological markers associated with these aspects remain poorly investigated. Nonetheless, it is worth remarking that the magnetic resonance imaging (MRI) research reported that psychotic symptoms in BD are associated with reduced gray matter (GM) density and connectivity in several prefrontal, temporal and limbic regions in both adult [11,12] and pediatric [13] BD patients. Similarly, it is still not fully elucidated how the co-occurrence of substance abuse may interact with psychosis in affecting the bipolar brain [14,15]. In this context, it is worth noting that the disruptive metabolic and morphological effects of substance abuse have been reported in heavy drug abusers, independently of the drug used, in several brain regions, including prefrontal [16–19], temporal [16] and cerebellar [20] cortices as well as subcortical areas [21]. Nonetheless, the specific neural underpinnings of drug abuse in BD have been explored only by two MRI studies [22,23]. Jarvis et al. [22] showed decreased GM volumes in the fusiform gyrus and increased GM volumes in the caudate and precentral gyrus in BD with co-occurring abuse disorder, compared to BD without substance abuse. Further, Hassel et al. [23] reported that substance use severity correlated with decreased activation in the prefrontal cortex and in the caudate during an emotional processing task in patients with BD. Finally, the interplay between psychosis and substance abuse in BD has almost been neglected. Interestingly, in the framework of psychosis spectrum, a review of 15 structural MRI studies found that psychotic patients with co-occurrence cannabis use showed decreased GM volumes in the cingulum, the dorsolateral prefrontal cortex (DLPFC) and the cerebellum [24].

In this context, to the best of our knowledge, this study aims for the first time at characterizing the effects of psychosis and substance abuse on morphology and metabolism in BD with full-blown psychotic patients, coupling MRI and positron emission tomography (PET). We hypothesized that substance abuse would determine a specific and more extensive pattern of structural and metabolic dysfunctions in BD and SIP in comparison to BD without substance abuse.

2. Methods

2.1. Participants

Patients were recruited at the Psychiatric inward of the University Policlinico Hospital of Milan, Italy. It comprised 10 BD type I psychotic patients with substance abuse, 17 BD type I psychotic patients without substance abuse, 16 patients with substance-induced psychosis (SIP); all of them were on stable pharmacological treatment with different psychotropic compounds (Table 1). BD or SIP patients fulfilled the diagnostic criteria of the Diagnostic and Statistical Manual of Mental Disorders, 4th edition, text revision (DSM-IV-TR) [25], based on the Structured Clinical Interview for Diagnosis (SCID-I) [26,27]. All patients were experiencing mild to acute symptomatology at the time of the scanning (mean Brief Psychiatric Rating Scale [BPRS] scores below 45 for all patients). Regardless of the diagnosis, 8 abusers out of 26 were taking only cannabis and 2 out of 26 only cocaine whereas all the others were polyabusers with reported past use of cannabis in combination with cocaine, meta-amphetamine and LSD (16 out of 26). Substance abuse was assessed with the SCID-I, which was a comorbid diagnosis in BD. Moreover, the type of drug, the intensity and the duration of abuse were confirmed with the SCICA [28]. The BPRS was administered to all the patients [29] and the mean scores and standard deviations of the sub-domains of the BPRS are shown in Table 1. We also included a group of healthy controls based on the absence of a personal or family lifetime history of any psychiatric disorder. Two independent samples of 27 healthy controls for the MRI and PET were included for the analyses. Exclusion criteria for all participants were a diagnosis of mental retardation, any current major medical or neurological illness, a history of traumatic head injury with loss of consciousness, and any other Axis I disorders, including alcohol abuse. The study was approved by the local Ethical Committee. Informed consent was obtained for all participants.

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2.2. Magnetic resonance imaging

Acquisition parameters: MR images were acquired using a 3-Tesla Philips Achieva MRI scanner. All the participants reclined in a supine position on the bed of the scanner and a radio frequency (RF) coil (Bruker NMR Instruments Inc., Fremont, California) was placed over their head. Earplugs and headphones were provided to block background noise. Following a 3-plane gradient echo scan for alignment and localization, a shim procedure was performed to generate a homogeneous, constant magnetic field. A total of 165 contiguous 1-mm sagittal slices extending superiorly from the inferior aspect of the cerebellum to encompass most of the brain were selected from a sagittal localizer scan. A high-resolution T1-weighted three-dimensional brain scan was then obtained using a modified driven equilibrium Fourier transform (MDEFT) protocol (repetition time [TR] = 6.9, echo time [TE] = 3.4 msec, field of view [FOV] = 25 × 25 × 18.2, 228 × 227, flip angle = 8°). Precautions were taken to minimize subject motion during the MRI study by instructing subjects to remain still and packing around their heads with foam padding.

2.3. Positron emission tomography (PET)

Acquisition parameters: PET scans were obtained with a Biograph Truepoint 64 PET/computed tomography (CT) scanner (Siemens, Erlangen, Germany) at the Nuclear Medicine Department of Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico in Milan. All patients underwent 18-FDG-PET scanning at rest after intravenous injection of 170 MBq. Patients were positioned comfortably in a quiet, dimly lit room several minutes before FDG administration and for at least 30 min during the uptake phase of FDG. They were instructed not to speak, read or be otherwise active. Each acquisition included a CT transmission scan of the head (50 mAs lasting 16 s) followed by a 3D static emission of 15 min using a Biograph Truepoint 64 PET/CT scanner (v). PET sections were reconstructed in the form of transaxial images of 128 × 128 pixels of 2 mm, using an iterative algorithm, ordered subset expectation maximization, corrected for scatter and for attenuation using density coefficients derived from the low-dose CT scan of the head obtained with the same scanner, with the proprietary software. The resolution of the PET system was 4–5 mm FWHM.

2.4. Neuroimaging data analysis

Pre-processing: two different and complementary analyses were performed: a voxel-based morphometry (VBM) analysis and a PET analysis using Statistical Parametric Mapping (SPM12) (http://www.fil.ion.ucl.ac.uk/spm/software/spm12/) implemented in MATLAB R2012b (MathWorks Inc. USA). All the images were co-registered to the Montreal Neurological Institute template, which was then segmented according to GM, white matter and cerebrospinal fluid tissue probability maps. The resulting images were spatially normalized into the MNI space using an affine spatial normalization. For the PET images, the standardized uptake value (SUV) maps have been derived from the original [^{18}F]FDG images. Subsequently, the SUV images have been spatially normalized into the T1-weighted MR images. Finally, MRI and PET images were smoothed with an isotropic Gaussian kernel of 6 mm full width at half maximum (FWHM) to increase the signal-to-noise ratio and to account for subtle variations in anatomic structures. Before the VBM and PET analyses, we extracted the total intracranial volume using SPM12.

2.5. Statistical analyses

For demographic and clinical variables, we performed Chi^2 tests for categorical variables and analysis of variance (ANOVA) for quantitative variables (Table 1). For the MRI and PET investigations, we performed a full-factorial analysis of covariance (ANCOVA) with nuisance covariates of age, gender and intracranial volumes. Then, we performed post-hoc analyses using two-sample t tests between the groups (please refer to Tables 2 and 3 with the details of all the contrasts employed in this study for both the VBM and PET analysis). For the VBM analyses, suprathreshold clusters were identified using peak Family Wise Error (pFWE) correction of $P < 0.05$ for the ANCOVA together with cluster False Discovery Rate (cFDR) corrected for all post-hoc analyses. For PET analyses, $P < 0.005$ uncorrected was considered significant and a minimum cluster size of 440 mm^3 was employed. Stereotactic coordinates of the peak maxima of the suprathreshold clusters were converted (http://www.mrc-cbu.cam.ac.uk/Imaging/mnispace.html/) from the Montreal Neurological Institute spatial array (http://www.mni.mcgill.ca/) to that of Talairach and Tournoux [30].

3. Results

A total of 10 BD type I psychotic patients with substance abuse, 17 BD type I psychotic patients without substance abuse, 16 SIP patients and 54 healthy controls (27 for PET and 27 for MRI analyses) were enrolled in this study. Due to movement artifacts during the MRI acquisition, two BD type I psychotic patients with substance abuse and one SIP patient were excluded from the study.

3.1. Analysis of socio-demographic and clinical variables

For socio-demographic measures, we observed a significant age difference between SIP patients compared to all the other groups ($P < 0.05$). Moreover, regardless of diagnosis, a significant gender difference was detected within all patients' samples ($P < 0.05$). Finally, for clinical variables, no difference was observed in the total scores of the BPRS across all patients' groups. However, BD patients without substance abuse showed lower mean scores compared to SIP patients in three sub-domains of the BPRS, including BPRS-Though Disorders, BPRS-Withdrawal and BPRS-Hostility/Suspiciousness (all $P < 0.05$). Further, SIP patients showed a significantly shorter duration of illness compared to BD with substance abuse ($P < 0.05$). Details of socio-demographic and clinical variables are shown in Table 1.

3.2. Analysis of MRI data

3.2.1. Group comparisons

3.2.1.1. BD patients without substance abuse vs. healthy controls. - Compared to healthy controls, BD patients without substance abuse showed abnormally reduced GM volumes in superior temporal gyrus bilaterally (Brodmann area [BA] 38, $P < 0.05$ pFWE corrected and cFDR corrected) (Table 2; Figs. 1 and 2). Q3

3.2.1.2. BD patients with substance abuse vs. healthy controls. Compared to healthy controls, BD patients with substance abuse showed abnormally reduced GM volumes in right middle (BA11) and medial (BA25) frontal gyrus, inferior frontal gyrus bilaterally (BA45 and BA47), left superior (BA38) and middle (BA21) temporal gyrus, right fusiform gyrus (BA37), anterior cingulate cortex (ACC) bilaterally (BA32), right posterior cingulate cortex (PCC, BA23), left insula (BA13), parahippocampus bilaterally (BA35 and BA28), right thalamus and left cerebellum ($P < 0.05$ pFWE corrected and cFDR corrected).

3.2.1.3. Substance-induced psychosis (SIP) patients vs. healthy controls. Compared to healthy controls, SIP patients showed

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Table 2
VBM results. Brain regions showing significant reduced GM volumes between the four groups of subjects (all $P < 0.05$ pFWE corrected and cFDR corrected).

Gyrus	BA	Laterality	x	y	z	Cluster size	z-values
BD without substance abuse < healthy controls							
Superior temporal	38	Right	33	12	-28	23	5.9
Superior temporal	38	Left	−36	7	−14	26	5.2
BD with substance abuse < healthy controls							
Middle frontal	11	Right	0	33	−13	194	5.9
Inferior frontal	45	Left	−59	18	7	32	5.9
Inferior frontal	47	Right	33	19	−5	84	5.6
Medial frontal	25	Right	4	3	−18	116	5.7
Superior temporal	38	Left	−34	14	−31	53	5.9
Middle temporal	21	Left	−55	−21	−5	62	5.6
Fusiform	37	Right	27	−40	−13	189	5.5
Anterior cingulate	32	Left	−6	33	23	106	6.1
Anterior cingulate	32	Right	9	34	18	46	5.5
Posterior cingulate	23	Right	0	−23	33	102	5.4
Insula	13	Left	−42	−15	16	48	5.1
Parahippocampus	35	Left	−30	−21	−13	1183	6.6
Parahippocampus	28	Right	31	5	−19	69	5.6
Thalamus	–	Right	19	−28	−2	1509	6.8
Cerebellum	–	Left	−40	−50	−38	315	6.9
Substance-induced psychosis < healthy controls							
Middle frontal	10	Right	43	40	10	92	6.8
Middle frontal	10	Left	−28	42	21	106	6.0
Middle frontal	46	Right	43	40	20	50	6.0
Middle frontal	46	Left	−46	29	22	74	5.5
Superior frontal	6	Left	−6	9	59	174	6.5
Middle frontal	6	Right	40	−3	54	81	5.5
Middle frontal	11	Right	4	27	−14	538	6.4
Middle frontal	9	Right	30	34	37	28	5.5
Middle frontal	9	Left	−40	22	36	26	5.4
Medial frontal	8	Left	−4	30	41	27	5.2
Middle temporal	21	Left	−56	−19	−8	509	6.9
Middle temporal	21	Right	62	−9	−13	232	6.0
Superior temporal	38	Right	−22	13	−30	60	5.2
Inferior temporal	20	Right	53	−10	−30	62	5.2
Posterior cingulate	23	Left	−1	−23	33	3589	6.9
Parahippocampus	28	Left	−22	−19	−8	16,138	7.5
Parahippocampus	36	Right	30	−41	−3	55	5.4
Cerebellum	–	Left	−40	−48	−37	644	7.7
Cerebellum	–	Right	22	−47	−42	234	6.8
Putamen	–	Right	34	−15	13	83	5.9
Caudate	–	Left	−2	18	1	40	5.7
Substance-induced psychosis < BD with substance abuse							
No sopratreshold clusters							
Substance-induced psychosis < BD without substance abuse							
No sopratreshold clusters							
BD with substance abuse < BD without substance abuse							
Parahippocampus	35	Left	−28	−18	−14	33	5.1
Thalamus	–	Right	10	−20	9	75	5.4
Cerebellum	–	Left	−27	−39	−22	58	5.5
BD without substance abuse < BD with substance abuse							
No suprathreshold clusters							
BD without substance abuse < substance-induced psychosis							
No suprathreshold clusters							
BD with substance abuse < substance-induced psychosis							
No suprathreshold clusters							

VBM: voxel-based morphometry; GM: Gray matter; pFWE: peak Family Wise Error; cFDR: cluster False Discovery Rate; BD: bipolar disorder; BA: Brodmann area.

abnormally reduced GM volumes in left superior frontal gyrus (BA6), middle frontal gyrus bilaterally (BA10, BA11, BA9, BA46 and BA6), medial frontal gyrus (BA8), middle temporal gyrus bilaterally (BA21), right superior (BA38) and inferior (BA20) temporal gyrus, left PCC (BA23), parahippocampus bilaterally (BA28 and BA36), cerebellum bilaterally and right putamen and caudate ($P < 0.05$, pFWE corrected and cFDR corrected).

3.2.1.4. BD patients with substance abuse vs. BD patients without substance abuse. BD patients with substance abuse showed reduced GM volumes in left parahippocampus (BA35), right thalamus and left cerebellum compared to BD patients without substance abuse ($P < 0.05$ pFWE corrected and cFDR corrected).

3.3. Analysis of PET data

3.3.1. Group comparisons

3.3.1.1. BD patients without substance abuse vs. healthy controls. BD patients without substance abuse had abnormally decreased GM metabolism in the left middle temporal gyrus (BA21) and inferior occipital gyrus (BA19) (Table 3; Figs. 3 and 4). Additionally, BD patients without substance abuse showed increased metabolism in right postcentral gyrus (BA3), right ACC (BA32) and left thalamus compared to healthy controls (all $P < 0.005$ uncorrected).

3.3.1.2. BD patients with substance abuse vs. healthy controls. Compared to healthy controls, BD patients with substance abuse had

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Table 3
PET results. Brain regions showing significant GM metabolic dysfunctions between the four groups of subjects (all $P < 0.005$ uncorrected).

Gyrus	BA	Laterality	x	y	z	Cluster size	z-values
BD without substance abuse < healthy controls							
Middle temporal	21	Left	−58	−48	−3	1048	4.7
Inferior occipital	19	Left	−36	−79	−4	640	4.7
BD without substance abuse > healthy controls							
Postcentral	3	Right	9	−32	68	2144	5.3
Anterior cingulate	32	Right	17	34	13	4405	5.6
Thalamus	–	Left	−25	−23	10	2965	6.5
Substance-induced psychosis < healthy controls							
Superior temporal	42	Left	−62	−23	10	1895	6.2
Superior temporal	41	Right	48	−30	11	972	4.7
Inferior temporal	20	Right	53	−57	−13	1456	4.6
Inferior temporal	37	Left	−41	−68	−3	839	5.3
Substance-induced psychosis > healthy controls							
Putamen	–	Right	25	−4	22	2032	5.3
Putamen	–	Left	−19	−8	−4	2303	5.4
Caudate	–	Right	39	−29	−3	639	4.5
Cerebellum	–	Right	10	−51	−27	2214	5.0
BD with substance abuse < healthy controls							
Medial frontal	10	Left	−1	46	12	440	4.4
Superior temporal	42	Left	−62	−23	10	1895	6.2
Superior temporal	41	Right	43	−30	11	972	4.7
Inferior temporal	20	Right	53	−57	−13	1456	4.6
Inferior temporal	37	Left	−41	−68	−3	839	4.8
BD with substance abuse > healthy controls							
Thalamus	–	Right	15	−9	5	634	4.7
Cerebellum	–	Right	10	−53	−27	4691	5.8
Substance-induced psychosis < BD without substance abuse							
Posterior cingulate	29	Left	−4	−41	11	446	3.4
BD with substance abuse < BD without substance abuse							
Posterior cingulate	29	Right	1	−41	11	487	3.3
Substance-induced psychosis > BD with substance abuse							
No sopratreshold clusters							
Substance-induced psychosis < BD with substance abuse							
No sopratreshold clusters							
Substance-induced psychosis > BD without substance abuse							
No sopratreshold clusters							
BD with substance abuse > BD without substance abuse							
No sopratreshold clusters							

PET: positron emission tomography; VBM: voxel-based morphometry; GM: Gray matter; BD: bipolar disorder; BA: Brodmann area.

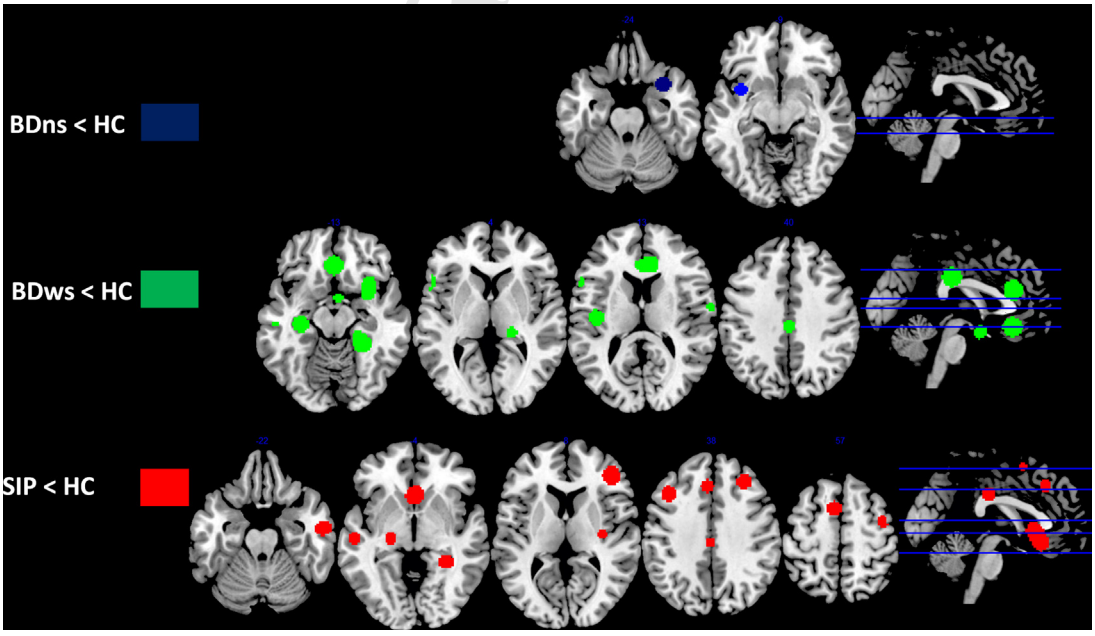

Fig. 1. Regions showing significant gray matter (GM) volume reductions in bipolar disorder (BD) with substance abuse (BDws) or without substance abuse (BDns) substance abuse and substance-induced psychosis (SIP) patients compared to healthy controls (HC) (all $P < 0.05$, peak Family Wise Error [pfWE] corrected and cluster False Discovery Rate [cFDR] corrected).

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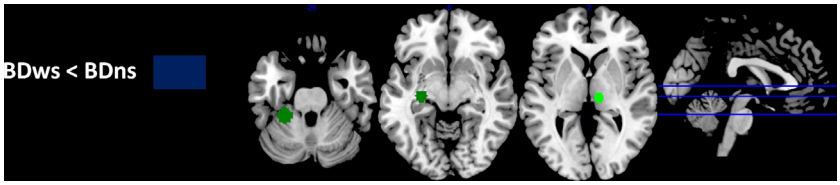

Fig. 2. Regions showing significant gray matter (GM) volume reductions in bipolar disorder (BD) with substance abuse (BDws) compared to BD without substance abuse (BDns) ($P < 0.05$, peak Family Wise Error [pfWE] corrected and cluster False Discovery Rate [cFDR] corrected).

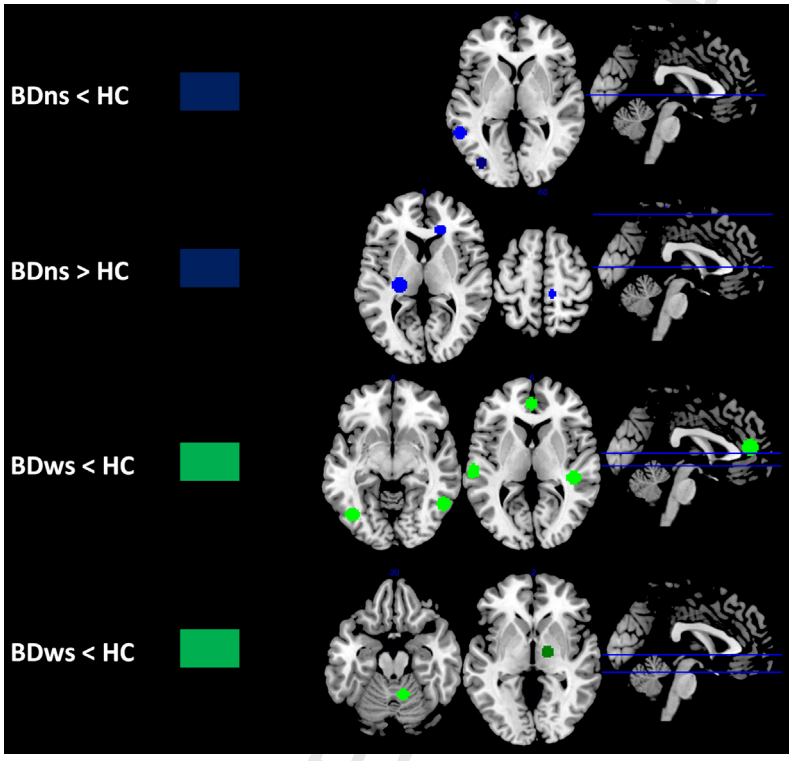

Fig. 3. Regions showing significant cerebral metabolism alterations in bipolar disorder (BD) with substance abuse (BDws) or without substance abuse (BDns) substance abuse patients compared to healthy controls (HC) (all $P < 0.005$, uncorrected).

abnormally decreased GM metabolism in superior temporal gyrus (BA41 and BA42) and inferior temporal gyrus (BA20 and BA37) bilaterally. In addition, BD patients with substance abuse showed increased metabolism in right thalamus and right cerebellum (all $P < 0.005$ uncorrected).

3.3.1.3. SIP patients vs. healthy controls. Compared to healthy controls, SIP patients had abnormally decreased GM metabolism in superior (BA41 and BA42) and inferior (BA20 and BA37) temporal gyrus bilaterally. Moreover, they showed increased GM metabolism in putamen bilaterally, right caudate, right hippocampus and right cerebellum (all $P < 0.005$ uncorrected).

3.3.1.4. SIP patients vs. BD patients without substance abuse. Compared to BD patients without substance abuse, SIP patients showed decreased metabolism in left posterior cingulate (BA29) ($P < 0.005$ uncorrected).

3.3.1.5. BD patients with substance abuse vs. BD patients without substance abuse. Compared to BD patients without substance abuse, BD patients with substance abuse showed decreased metabolism in right posterior cingulate (BA29) ($P < 0.005$ uncorrected).

4. Discussion

Our group analysis, for both MRI and PET analyses, showed significant abnormalities in GM volumes and cerebral metabolism in the three groups of patients compared to healthy controls in an extended network, encompassing frontal, temporal, limbic, cerebellar and striatal areas. Interestingly, the multiple pairwise comparisons showed four key findings. First, a common pattern of structural and metabolic brain alterations between BD patients with and without substance abuse and SIP patients within temporal regions. Second, a diagnosis specific pattern of brain alterations in the substance abusers within a fronto-limbic network. Particularly, BD patients with substance abuse showed GM volumes reduction in the ventrolateral prefrontal cortex (VLPFC), anterior cingulate cortex (ACC), thalamus and insula, whereas SIP patients had significant GM volumes reduction in dorsolateral prefrontal cortex (DLPFC), and posterior cingulate cortex (PCC). Additionally, SIP patients reported abnormal cerebral metabolism in PCC compared to the other two group of patients. Third, subjects with substance abuse, either BD or SIP, had a unique pattern of GM volume reduction in parahippocampal and cerebellar regions. Finally, SIP patients showed GM volumes reduction coupled with cerebral metabolism alterations in

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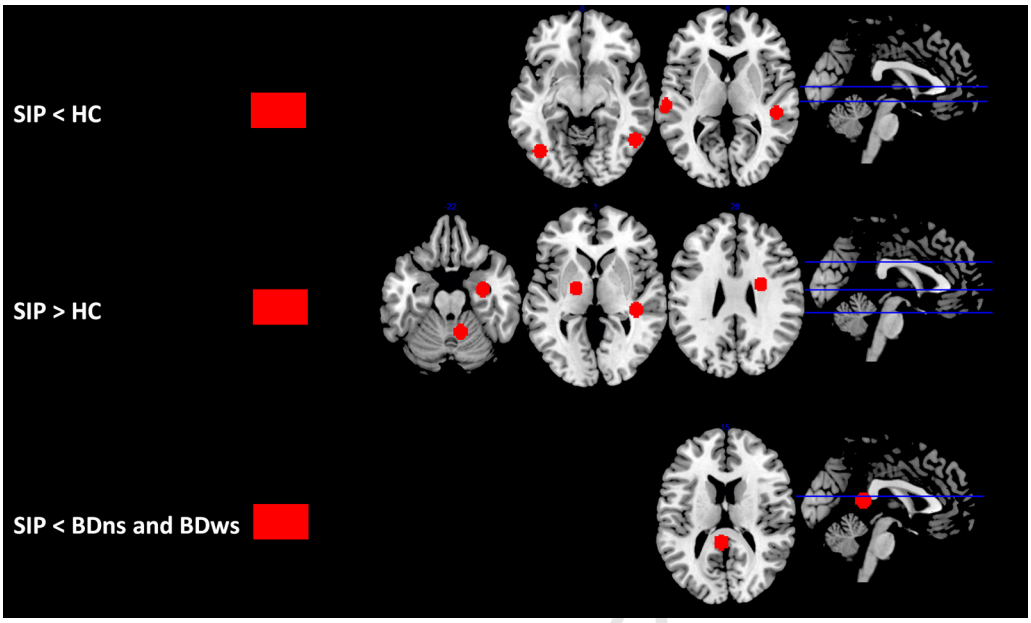

Fig. 4. Regions showing significant gray matter (GM) volume reductions in substance-induced psychosis (SIP) patients compared to healthy controls (HC) and bipolar disorder (BD) with substance abuse (BDws) or without substance abuse (BDns) substance abuse (all $P < 0.05$, peak Family Wise Error [pfWE] corrected and cluster False Discovery Rate [cFDR] corrected).

putamen and caudate compared to healthy controls (for VBM results see Table 2, Figs. 1 and 2; for PET results see Table 3, Figs. 3 and 4).

4.1. Temporal abnormalities: a neurobiological marker of psychosis?

Regardless of the diagnosis, patients revealed GM volume and cerebral metabolism alterations in temporal regions compared to healthy controls. However, the extent of these abnormalities differed across diagnosis. Indeed, while BD patients without substance abuse showed GM volume reductions only in the superior temporal gyrus (BA38), BD patients with substance abuse and SIP patients showed a wider temporal alterations encompassing the superior, middle and inferior temporal gyri. In this regard, it should be mentioned that the superior temporal gyrus is involved in auditory and language processing [31] and theory of mind [32], abilities that are notably abnormal in individuals with psychosis [31,33–36]. Therefore, it is plausible that this common brain dysfunction in the superior temporal gyrus, transversally present in all the three groups of patients with psychosis, could be considered a biological marker of psychosis [37]. Specifically, for BD patients without substance abuse, the superior temporal gyrus reductions are in line with previous studies, but not all [38–40], showing thinning [41,42] as well as altered metabolism [43] in BD. Indeed, the superior temporal gyrus has been reported to be part of a neural network implicated in emotional processing [44], a core function that has been consistently found to be impaired in BD [45].

Furthermore, our results suggest that substance abuse exacerbates structural and metabolic impairments in the temporal cortex. Indeed, both BD patients with substance of abuse and SIP patients showed a similar and a more extensive pattern of brain dysfunction in this area in comparison with BD patients without substance of abuse. Although there is no evidence of GM and metabolic abnormalities in temporal cortices in BD patients with substance abuse, several studies reported an association with GM volume reductions in this area in substance dependent individuals compared to healthy controls [46,47]. Similarly, the reduction in temporal regions in SIP patients might be in line with brain dysfunctions observed in recent years by MRI studies in schizophrenia [48]. Indeed, the theoretical model of schizophrenia proposed that psychotic and cognitive symptoms result from alterations in fronto-temporal and subcortical networks [49–56]. Therefore, these common patterns of brain dysfunctions further support the hypothesis that substance-induced psychosis might lie within a "grey" overlapping zone between schizophrenia and BD within a psychosis continuum [9,57]. In conclusion, although the presence of a significant overlapping of temporal alterations in the three groups when compared to healthy controls, our results demonstrated that substance abuse has negative effects on brain structures and functions by determining wider temporal GM and metabolic dysfunctions.

4.2. Differential fronto-limbic involvement in BD patients with substance abuse and SIP patients: a possible biomarker of substance abuse?

Compared to healthy controls, patients with substance abuse had diagnosis specific bilateral abnormalities in fronto-limbic regions. In particular, BD patients with substance abuse showed GM volumes reduction in VLPFC (BA45 and BA47), ACC (BA32), insula (BA13) and thalamus. These regions have been consistently reported to be altered in BD patients [45,58–61] but the lack of GM abnormalities found in our sample of BD patients without substance abuse suggests that drug abuse might have accelerated and deepen the appearance of morphological abnormalities usually reported in BD. As a matter of fact, VLPFC and ACC-cognitive impairments were found in chronic stimulants abusers [62] and they seem to be associated with reward-based cognitive inflexibility and risky decision making in Internet addictions [63].

In contrast, SIP patients had more prominent GM volumes reduction in DLPFC (BA9, BA10 and BA46) and in PCC (BA23 and BA29) as well as decreased cerebral metabolism in PCC compared to BD patients with and without substance abuse. Our results are in line with previous literature showing DLPFC volume reduction in patients abusing cocaine [64,65], methamphetamine [66], and heroin [67]. Interestingly, a large body of evidence reported the role of DLPFC in working memory and attention [47,62] as well as

in self-control and motivated behaviors [62], abilities that have been reported to characterize individuals with drug addiction or dependence [46]. Similarly, PCC is a core region of the default mode network (DMN) in humans [68] and alterations have been described in chronic abusers [24,69,70]. Finally, deficits in the DLPFC and in the PCC have been largely described in schizophrenia [71,72], supporting the hypothesis that SIP lies between schizophrenia and BD, as mentioned previously. Hence, a deeper insight in SIP might help to understand the notion of psychosis continuum.

4.3. Cerebellar and parahippocampal alterations: a unique pattern of brain dysfunction characterizing only psychotic patients with substance abuse?

Volume and metabolic reductions of cerebellar regions were detected in both BD patients with substance abuse and SIP patients compared to healthy controls. Additionally, BD patients with substance abuse showed significant GM volume reduction in cerebellar volumes compared to BD patients without substance abuse. In recent years, the role of the cerebellum has been widely studied in psychiatric illnesses, including BD [73], and is thought to be involved in the regulation of emotion and cognition [74,75]. However, with regards to BD, the available literature reported contradictory findings, with decreased GM volumes [76,77] as well as no differences [78,79] in cerebellar regions in BD patients compared to healthy controls. In contrast, the effect of drug addiction, mainly cannabis and cocaine, on cerebellar integrity has been consistently suggested [80,81]. Indeed, several strands of evidence have reported that the systematic exposure to these drugs causes molecular and structural/functional alterations in the cerebellum [82–85].

Furthermore, BD patients with substance abuse and SIP patients also share a common GM volume decrease in parahippocampus compared to healthy controls. For BD patients specifically, structural [86] and functional [87] alterations in the parahippocampus have been consistently suggested due to its involvement in emotional processing [87]. Additionally, a single-photon emission computed tomography study also reported a significant inverse association between resting regional blood flow in parahippocampal gyrus and severity of depressive mood, further sustaining its involvement in mood disorders [88]. Finally, independent MRI studies suggested the involvement of this structure in both addiction [89] and psychosis [90–92].

In conclusion, taken together these findings suggest that the exposure to drugs, regardless of the diagnosis, increases the susceptibility to cerebellar and parahippocampal pathology, which might be related to the direct neurotoxic effect of drugs on GM density.

4.4. Striatal alterations: a unique feature of Substance-Induced Psychosis patients?

The direct comparison between SIP patients and healthy controls also showed a significant GM volumes reduction with concomitant increased metabolic activity in both the putamen and caudate. These regions are part of the striatum which has been reported to be connected with both cortical and midbrain dopamine cell body regions [93]. Moreover, cannabis and cocaine affect the mesolimbic dopamine system, including putamen and caudate [94–97], which is crucial to the reward-processing and drug addiction [98,99]. Indeed, previous studies underlined that a dysfunction in the reward system relate to increased risk of substance abuse [100–102]. Specifically, it has been found altered mesocorticolimbic connectivity in abusers of methamphetamine [103], cannabis [104] and in offspring of abusers [105].

Therefore, our results suggest that striatal alterations are closely linked to the consumption of drugs, which act to disrupt the reward system that is evident in SIP patients.

4.5. Limitations

Some limitations to our study should be taken into account when interpreting the results. First, the relatively small sample size might have limited the statistical power of our analyses, although it is in line with PET and MRI studies investigating substance abuse [22,23,69]. Second, patients were not fully matched for age and gender. However, we included these variables as covariates in the statistical analyses. Third, we cannot exclude the impact of psychotropic drugs on our results since all patients were taking mood stabilizers and/or antipsychotics. Fourth, it was not possible to explore the effects of only one substance of abuse, since the majority of the abusers were taking cannabis and cocaine. Fifth, the inclusion of two independent samples of healthy controls for the MRI and PET analyses might have affected the comparison of the results across these two techniques. Finally, the cross-sectional design employed in this study did not allow for the investigation of GM volumes and metabolic changes over time.

5. Conclusions

To the best of our knowledge, this is the first study trying to integrate metabolic and morphological data to study the interplay between psychosis and substance abuse in BD. We provide evidence of common and diagnosis specific abnormalities between the three groups of patients compared to healthy controls. Specifically, we found volume and metabolic reductions in temporal regions in all patients in comparison to healthy controls. However, more extensive patterns of abnormalities were found in patients with substance abuse, independently of the diagnosis. Furthermore, distinct GM volume and metabolic dysfunctions were observed in fronto-limbic regions in BD with substance abuse and in SIP, with common alterations in cerebellum and parahippocampus. Finally, structural and metabolic striatal abnormalities were found only in SIP patients, supporting the disruption of the dopamine reward system in psychosis, induced by the abuse of recreational substances.

Taken as a whole, our findings help in leading towards the identification of specific neural markers associated with bipolar psychosis and substance abuse. Future longitudinal studies are needed to corroborate our results by identifying the direct effect of a single substance of abuse in patients at the first-episode of BD and substance-induced psychosis.

Disclosure of interest

The authors declare that they have no competing interest.

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