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Out of control: An altered parieto-occipital-cerebellar network for impulsivity in bipolar disorder

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ABSTRACT

Bipolar disorder is an affective disorder characterized by rapid fluctuations in mood ranging from episodes of depression to mania, as well as by increased impulsivity. Previous studies investigated the neural substrates of bipolar disorder mainly using univariate methods, with a particular focus on the neural circuitry underlying emotion regulation difficulties. In the present study, capitalizing on an innovative whole-brain multivariate method to structural analysis known as Source-based Morphometry, we investigated the neural substrates of bipolar disorder and their relation with impulsivity, assessed with both self-report measures and performance-based tasks. Structural images from 46 patients with diagnosis of bipolar disorder and 60 healthy controls were analysed. Compared to healthy controls, patients showed decreased gray matter concentration in a parietal-occipital-cerebellar network. Notably, the lower the gray matter concentration in this circuit, the higher the self-reported impulsivity. In conclusion, we provided new evidence of an altered brain network in bipolar disorder patients related to their abnormal impulsivity. Taken together, these findings extend our understanding of the neural and symptomatic characterization of bipolar disorder.

1. Introduction

Bipolar disorder (BD) refers to a clinical syndrome characterized by affective instability. This instability typically manifests in rapid emotional fluctuations, ranging from episodes of depression characterized by low mood and reduced energy, to episodes of mania with elated mood, increased energy, and reduced need for sleep [1,2]. Due to the heterogeneity of clinical presentation, and the lack of a clear neurophysiological basis (e.g., biomarkers [3]), BD is often difficult to diagnose accurately [1]. Indeed, because of the phenomenological overlap between BD and other psychopathologies such as Schizophrenia [4,5], Borderline Personality Disorder [6], and Major Depressive Disorder [7], it is frequently misdiagnosed, leading to incorrect clinical decisions and treatment [8].

In recent years, various neuroimaging techniques have been employed to explore the neural substrates of BD to both elucidate its pathophysiology [9] and to develop new and personalized treatments (see [10] for a review). As a result, networks of structural brain abnormalities, and their correlations with psychological functions [11], have been proposed as markers of BD. Morphometric abnormalities have been repeatedly found in fronto-limbic structures involved in mood regulation (see [12,13], for a review), with increased amygdala volume and widespread gray matter (GM) reduction in the hippocampal and parahippocampal cortex [3,14,15]. Meta-analytic studies also revealed structural GM decrease in the medial prefrontal system, including the anterior cingulate cortex (ACC) [16], as well as in the orbitofrontal cortex, inferior frontal gyrus, and ventrolateral prefrontal cortex (VLPFC) [12]. In addition, reduced GM concentration in parieto-occipital areas and portions of the cerebellum could be involved in an altered information processing that influences the evaluation and interpretation of emotional situations, at different perceptual stages [5]. Indeed, parietal regions are involved in the pathophysiology of BD [17,

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18], particularly during manic episodes [19], interfering with the ability to process emotional contents (e.g. precuneus and supramarginal gyrus hypoactivation [18]). According to this, Doris and colleagues [20] found decreased GM density in the parietal lobe in poor outcome bipolar subjects. Also, cortical thickness of parietal regions (e.g. supramarginal gyrus, bilateral inferior, and superior parietal lobule) was found to be reduced in BD patients [21]. On the other hand, the cerebellum has always been associated with motor control, coordination, and intentional voluntary movement, but there is evidence of its involvement in emotional processing and mood modulation ([22]; see [23] for a review [24]). Indeed, alterations in cerebellum characterize the pathophysiology of different psychiatric conditions, among others BD (see [23,25] for a review; [24,26]).

Along with such brain alterations related to the affective symptomatology, BD patients often exhibit increased impulsive behavior [27,28], a diagnostic criterion for mania [29] reported as a stable trait characteristic in the disorder [30]. Impulsivity leads to serious consequences in patients' daily life, including response disinhibition, self-injury, aggression, and risky behaviors as unprotected sex and substance abuse [27,31–33]. Real-world risk-taking can be considered a behavioral expression of impulsivity [34], and these two propensities seem to be highly correlated [35–37].

However, impulsivity is a multidimensional concept that comprises cognitive, behavioral, motivational, and affective components [38–40], and its multifaceted nature is not well characterized yet (see [41] for a review; [40]). In general, impulsivity can be defined as the predisposition toward rapid, unplanned reactions to internal or external stimuli, without regard to the negative consequences of these reactions to the individual or others (see [39,42] for a review), and it is involved in a wide range of maladaptive behaviors [43].

Goudriaan and collaborators [44] distinguished between phenotypic and endophenotypic measures, that take into account different components of impulsive behavior [45,46]. Self-report measures are indicators of the *phenotype* of the disorder (how the disorder appears) [46,47], and they allow to collect information on different types of acts and long-term patterns of behavior [39]. One of the most used self-report measures to assess the phenotypical level of impulsiveness is the Barratt Impulsiveness Scale (BIS-11, [48]), which integrates its behavioral and cognitive aspects [27]. On the other hand, performance-based tasks describe the *endophenotype* of the disorder (functions underlying the disorder) [44,46,47]. Some scholars consider the Balloon Analogue Risk Task (BART [49]) as a reliable behavioral impulsivity measure rather than only a decision-making task of escalating risk [45,50]. Nevertheless, a few studies related measures of decision-making with impulsivity, and the results are still contradictory [49,109].

In line with this conceptual separation, Swann [27] showed that trait impulsivity is high in BD, but its behavioral expression varies remarkably (e.g. patients do not consistently show deficits on behavioral tasks that require planning [37]). Thus, using both self-report measures and performance-based behavioral tasks, we aim to uncover multiple dimensions of impulsiveness in BD [37,47]. One intriguing question is whether extreme impulsivity in this disorder can be related to alterations of specific brain circuits. Several studies related impulsivity to dysfunctions in the interplay of cortical-limbic circuits (e.g. anterior cingulate cortex, basal ganglia, insula) [51–53], as well as to frontal GM and thickness alterations (e.g. orbitofrontal cortex, superior and inferior frontal gyrus) [54,55]. A functioning model has also been proposed by Frijda and colleagues [56], that considers impulsive behavior as based on the failure of the pragmatic anticipation of an action's effect and its sensory consequences, underlying the role of parietal associative regions, cerebellum, and subcortical structures [56]. Furthermore, damage to the cerebellum is related to the affective dimension of the cerebellar cognitive affective syndrome (CCAS) [108] characterized by depression and emotion dysregulation, as well as disinhibition, poor attentional and behavioral modulation, and impulsivity [57]. Specifically, altered cerebellar connections to structures that modulate attention and cognition (e.g. frontal, parietal) are involved in the symptomatology of disorders characterized by impulsive behavior, like ADHD [110].

1.1. Methodological considerations on previous morphometric studies

Morphometric research on BD has largely relied on univariate methods as region of interest (ROI) [58] and Voxel-based Morphometry (VBM) [59] analyses. However, they may be not the best methods to capture the neural heterogeneity that characterizes complex disorders as mood disorders, that suffer from large scale alterations [60–64]. Indeed, VBM does not provide information about how regions are related, comparing voxel by voxel and without taking into account the interrelationships among them. Moreover, VBM does not incorporate spatial filtering, and results appear generally noisy [60,64].

Multivariate approaches as Source-based morphometry (SBM) can overcome such problems by performing whole-brain, data-driven analyses. SBM combines information across different voxels, to identify patterns of covariation of GM concentration (GMC) in different areas using Independent Component Analysis (ICA) [60,65]. ICA is a form of unsupervised machine learning that allows isolating and reducing noisy artifacts. Thus, the SBM represents a more reliable approach to study psychiatric disorders, and brain-behavior studies can benefit from a whole-brain and network perspective [5,63,64,66].

1.2. The present study

The aim of the present study is twofold: on one hand, to find possible gray matter concentration (GMC) alterations in BD as compared to matched healthy controls; on the other hand, to explore the relationship between this circuit and impulsivity.

Based on the previous literature, impulsivity appears to be related to changes in large-scale networks [67]. Specifically, the main structures are fronto-limbic regions [53], as well as associative areas like the parietal ones [56], and the cerebellum with its connections to cortical structures [110]. However, impulsivity is a multifaceted construct that can be related to different cognitive mechanisms and brain networks, depending on the dimension considered (see [41] for a review; [53]).

To investigate the multidimensional characterization of impulsivity, we ran an exploratory analysis capitalizing on the data-driven, whole-brain approach of SBM, as compared to univariate approaches like VBM. Indeed, SBM allows for a broader exploration of brain alterations, assuming that structural variations in one region may affect multiple brain areas [65]. Data-driven methods (e.g. ICA) are free from prior assumptions on brain mechanisms, providing models that are determined by the statistical properties of data only [68].

Secondly, we hypothesized that the higher the impulsivity, the larger these GMC alterations. To the best of our knowledge, this is the first study that aims to identify neurostructural alterations of BD by capitalizing on Source-based Morphometry (SBM), and to explore its relationship with impulsivity. The study of BD can therefore be instrumental in giving a broader explanation of impulsiveness, considering its multifaceted nature and its exaggerated exhibition in this clinical population. Indeed, studying altered behaviors in psychiatric patients may be useful to unveil the inner mechanisms underlying those behaviors.

2. Material and methods

2.1. Participants

We selected 187 participants from a shared neuroimaging dataset from the UCLA Consortium for Neuropsychiatric Phenomics (CNP) (https://openneuro.org/datasets/ds000030/versions/00001), a large study funded by the NIH Roadmap Initiative which includes a set of structural MRI and psychological tests. This dataset is shared through the OpenNeuro project, and formatted according to the Brain Imaging

Data Structure (BIDS) standard. We excluded 3 patients with BD and 78 healthy participants, based on age, sex, presence of artifacts in T1 MRI images, and/or missing behavioral measures. This selection left us with 106 participants: 46 patients diagnosed with bipolar disorder type I (BD, $M_{age} = 35.06$, $SD_{age} = 9.12$) and 60 healthy participants as controls (HC, $M_{age} = 34.78$, $SD_{age} = 8.78$). Demographic information about participants is shown in Table 1. Participants satisfied the following criteria: have completed at least 8 years of education, no history of head injury with loss of consciousness or cognitive sequelae, no use of psychoactive medications, substance dependence within past six months, no history of major mental illness, and currently free from mood or anxiety disorder. Self-reported history of psychopathology was verified through the administration of the SCID-IV [69]. BD patients' psychiatric symptoms were evaluated using the Brief Psychiatric Rating Scale (BPRS; [111]), the Hamilton Depression Rating Scale [112], and the Young Mania Rating Scale (YMRS; [113]). Participants who passed this first screening were admitted to the scanning phase if they successfully completed all previous testing sessions and did not meet the following additional exclusion criteria: history of significant medical illness, contraindications for MRI (including pregnancy), any mood-altering medication on scan day (based on self-report), vision that was insufficient to see task stimuli, and left-handedness. After receiving a thorough explanation of the study, all participants gave written informed consent according to the procedures approved by the University of California Los Angeles Institutional Review Board.

A high-resolution T1-weighted 3D magnetization prepared rapid gradient echo (MPRAGE) scan was acquired for each participant from UCLA Consortium for Neuropsychiatric Phenomics (CNP). Neuroimaging data were acquired on a 3T Siemens Trio scanner. T1-weighted high-resolution anatomical scans were collected with the following parameters: TR = 1.9 (s), TE = 2.26 (ms), flip angle = 90°. All remaining technical details are available on the database website (https://f1000research.com/articles/6-1262/v2).

2.2. Data analysis

2.2.1. Preprocessing neural data

After the quality check of the initial images to assess the homogeneity and the quality of the data, and before any analyses, data were preprocessed using the segmentation routines provided by the Computational Anatomy Toolbox (CAT12, http://www.neuro.uni-jena.de/cat/), included in SPM12 (http://www.fil.ion.ucl.ac.uk/spm/software) in the MATLAB environment. This toolbox was used for the segmentation of gray matter, white matter, and cerebrospinal fluid. Modulated normalized writing option was used. We capitalized on Diffeomorphic Anatomical Registration through Exponential Lie algebra (DARTEL) tools, a potential alternative to SPM's traditional registration approaches that operates using a whole-brain approach [70]. Normalization to MNI space with spatial smoothing (full-width at half maximum of Gaussian smoothing kernel [8,8,8]) was then applied on DARTEL images.

2.2.2. Source-based Morphometry analysis

Source-based morphometry (SBM) is a data-driven algorithm that provides a multivariate extension to VBM [71] using independent component analysis (ICA). SBM extracts spatially independent patterns of covariation (gray matter concentration, GMC) among participants [60,72]. We performed SBM by using Group ICA of fMRI Toolbox (GIFT) (http://mialab.mrn.org/software/gift/) on all datasets together. Initially, we asked for the estimation of 20 independent components (ICs) as set up by default in GIFT (see Pappaianni et al., 2020; [5] for a similar approach). A neural network algorithm (Infomax) that exploits the signal information coming from the images to maximize the recognition of independent components was used to perform ICA [73,74]. Then we selected the ICASSO method (http://research.ics.aalto.fi/ica/icasso/) to investigate the reliability of the ICs, as stability analysis. Both Random Initiation (RandInit) and bootstrapping modes were selected in the ICASSO analysis, to increase the stability of the estimated components [72]. We ran Independent Component Analysis 100 times, and for each IC we got a quality Index I_q [75,76]. An index of $I_q > 0.9$ usually indicates a highly stable ICA decomposition [75,76]. In the end, SBM converted GMC volumes of each component into loading coefficients (i.e. a numerical vector), creating a matrix composed of rows (the participants) and columns (the sources). Each numerical value of the matrix was representative of how a specific component was expressed in each participant. A multiple logistic regression was performed in R environment (http://www.R-project.org/) to examine whether suffering from BD was predicted by the independent components (i.e. networks of GM covariation) returned by the SBM analysis.

2.2.3. Voxel-based morphometry analysis

Voxel-based morphometry (VBM) is a univariate approach to structural images that consists in "a voxel-wise comparison of the local concentration of gray matter (GM) between two groups" [60,71]. To assess possible significant GM differences between groups, a set of voxel-wise parametric statistical tests was performed following by a group comparison using a two samples t-test, considering the total intracranial volume (TIV) as a covariate.

2.2.4. Self-reported impulsivity

Both patients and controls were tested with the Barratt Impulsiveness Scale (BIS-11) [48], to assess the phenotypical level of impulsiveness. BIS-11 is a self-report measure of impulsiveness considered a reliable indicator of impulsivity as a stable trait characteristic, which is part of the symptomatology of BD [27,28]. The current version of the BIS-11 is composed of 30 items describing common impulsive or non-impulsive behaviors and preferences. It is suggested to report at least the three second-order factors (Attentional, Motor, Non-planning Impulsiveness) as a measure of impulsivity traits [36]. Attentional impulsiveness is defined as a lack of focus on an ongoing task, and is made up of two first-order factors: attention and cognitive instability. Motor impulsiveness can be described as action without inhibition of strong responses, and it includes two first-order factors: motor and perseverance. Non-planning impulsiveness is considered as an orientation towards the present rather than to the future, and it includes two first-order factors: self-control and cognitive complexity [77]. Normality assumptions check was carried out by computing the Shapiro-Wilk test for normality [114] using JASP software (https://jasp-stats.org/).

Table 1
Demographic information about participants. The presented values for 'Age' and 'Education' are the relative arithmetic averages of years. Values in round brackets are the standard deviations.

	Bipolar Disorder	Healthy Controls	All	t-test
Participants	46	60	106	
Age	$Mage = 35.06$ (±9.12)	$Mage = 34.78$ (±8.78)	$Mage = 34.90$ (±8.88)	$t(104) = 0.161$, $p = 0.872$, $d = 0.032$
Gender	F = 20, M = 26	F = 26, M = 34	F = 46, M = 60	$t(104) = 0.015$, $p = 0.988$, $d = 0.003$
Education	$Mage = 14.58$ (±1.98)	$Mage = 15.08$ (±1.75)	≥ 8 years of formal education	$t(104) = -1.362$, $p = 0.176$, $d = -0.267$
Screening	Neurological disease, psychoactive substance, mental illness (SCID-IV)			
Exclusion Criteria	Diagnosis in at least 2 different patient groups, pregnancy			

2.2.5. Performance-based risk-taking

The Balloon Analogue Risk Task (BART) was administered to both patients and controls, to shed light on the endophenotype of the disorder. BART is a computerized experimental measure of risk-taking that models real-life situations in which excessive risk can lead to diminishing returns and poorer outcomes [49], and it correlates with several naturalistic risky behaviors as stealing, unprotected sex, smoking, and substance abuse [28,78]. In this task, participants are instructed to pump up a balloon to gain increasing amounts of money but, if the balloon explodes, they lose everything they had previously gained. Participants know that the balloon can explode at some point, but they do not know when this is going to happen. Thus, each pump represents a risky choice, where participants have to choose whether to keep pumping the balloon in order to gain more money or to "cash-out" (i.e., to stop pumping before the balloon explodes) to secure the money obtained during the trial [78]. Performance on the BART is assessed by the average of adjusted pumps (the average number of pumps on balloons that did not explode), with higher scores indicating greater risk-taking behavior, resulting in a plausible index of riskiness [49,79]. Even in this case, normality assumptions have been verified through the Shapiro-Wilk test for normality [114] in JASP environment.

2.2.6. Neuro-behavioral correlations

To better characterize the psychological influence of the morphometric abnormalities, we correlated GMC with measures of impulsiveness and risky behavior, using the participants' performance on the Barratt Impulsiveness Scale (BIS-11, [48]) and Balloon Analogue Risk Task (BART, [49]) respectively. We used Spearman's rho as rank-order correlation coefficient to test for possible associations between abnormal SBM networks and behavioral performance expressed by the self-report measure (BIS-11) and performance-measure (BART). Related to BIS-11, we took into account the three second-order factors (Attentional, Motor, Non-planning Impulsiveness) as a measure of impulsivity traits [36]. To assess the performance in the BART, we computed the average of adjusted pumps (the average number of pumps on balloons that did not explode), with higher scores indicating greater risk-taking behavior, resulting in an index of riskiness [49,79].

3. Results

3.1. Source-based morphometry results

All 20 ICs survived the threshold of goodness of $I_q > 0.9$. A matrix of 106 rows (the participants) per 20 columns (the sources) was obtained. Afterwards, a multiple logistic regression was performed to examine whether suffering from BD was predicted by the independent components (i.e. networks of GM concertation) returned by the SBM analysis. One component (IC14) emerged as a statistically significant predictor of BD (OR = 1.87, 95% CI [0.04 1.28], $SE = 0.314$, z = 1.99, $p = .045$). This component (IC14) showed that patients group had smaller loading coefficients than healthy controls (HC), meaning less GMC in this network. IC14 is a parietal-occipital and cerebellar network that includes parts of the inferior parietal lobule, and precuneus, as well as several portions of the cerebellum, and occipital cortex like cuneus (Table 2, Fig. 1). All the other ICs did not significantly predict BD [IC1 ($p = .77$), IC2 ($p = .18$), IC3 ($p = .83$), IC4 ($p = .61$), IC5 ($p = .58$), IC6 ($p = .10$), IC7 ($p = .25$), IC8 ($p = .09$), IC9 ($p = .34$), IC10($p = .14$), IC11 ($p = .18$), IC 12 ($p = .17$), IC13 ($p = .76$), IC15 ($p = .66$), IC16 ($p = .08$), IC17 ($p = .88$), IC18 ($p = .51$), IC19 ($p = .96$), IC20 ($p = .14$)].

3.2. Voxel-based morphometry results

Voxel-based morphometry analysis returned one cluster of voxels in the left hemisphere (middle temporal gyrus $k = 2$), and three clusters in the right hemisphere (precuneus $k = 7$, inferior temporal gyrus $k = 9$, angular gyrus $k = 4$), but none of them was significantly different between the two groups ($p > .001$ unc.).

Table 2
Independent Component 14. Talairach labels of regions of interest, Brodmann area, volume (expressed in cc), and spatial MNI coordinates are shown.

Area	volume (cc) L/R	MNI (x, y, z) L/R
IntraParietal Sulcus	1.0/1.2	(-31, -49, 39)/(43, -54, -10)
Inferior Parietal Lobule	0.2/0.0	(-34, -52, 39)/ -
Supramarginal Gyrus	0.1/0.0	(-37, -46, 36)/ -
Precuneus	0.0/0.1	- /(28, -61, 34)
Angular Gyrus	0.0/0.1	-/(36, -70, 28)
Culmen	0.1/0.0	(-1, -52, -7)/ -
Cerebellar Tonsil	0.0/0.5	- /(15, -49, -52)
Declive	0.0/0.3	- /(13, -73, -27)
Pyramis	0.0/0.1	- /(24, -73, -36)
Tuber	0.0/0.1	- /(28, -73, -37)
Uvula	0.0/0.1	- /(21, -73, -33)
Primary Visual Cortex	0.1/0.0	(-24, -64, 6)/ -
Primary Visual Cortex	0.1/0.0	(-21, -69, 6)/ -
Cuneus	0.1/0.0	(-18, -72, 7)/ -
Extrastriate Cortex	0.0/0.1	- /36, -73, 25)
Parahippocampal Gyrus	0.1/0.1	(-33, -31, -16)/(33, -36, -13)
Caudate	0.0/0.3	- /(13, 18, 3)

3.3. Self-reported impulsivity

The Shapiro-Wilk test [114] suggested a deviation from normality in the Attentional and Motor Impulsiveness subscales ($p < .05$). For this reason, the non-parametric Mann-Whitney test was performed to assess behavioral differences between groups.

The two groups differed in all the three second-order factors of the BIS-11, with BD patients having higher scores than HC: Attentional Impulsiveness ($U = 2227$, $p < .001$), Motor Impulsiveness ($U = 2014$, $p < .001$), Non-planning Impulsiveness ($U = 2265$, $p < .001$). These results confirm that patients with BD show higher impulsiveness than controls when tested with self-report measures [28,30,80] (Fig. 2A–C).

3.4. Performance-based risk-taking

The non-parametric Mann-Whitney test was performed to assess behavioral differences between groups.

The two groups did not differ in the risk-taking behavior assessed with the BART (average of adjusted pumps: $U = 1391$, $p = .947$) (Fig. 2D).

3.5. Neuro-behavioral correlations

Negative correlations emerged between loading coefficients in IC14, that is the parietal-occipital and cerebellar network that significantly predicted BD, and the three self-report measures of impulsiveness assessed with BIS-11: Attentional Impulsiveness ($rho = -0.278$, $p = .004$), Motor Impulsiveness ($rho = -0.202$, $p = .037$), Non-planning Impulsiveness ($rho = -0.281$, $p = .004$) (Fig. 3A–C). This means that the less the GMC in the parietal-occipital-cerebellar network, the greater the impulsiveness. No statistically significant correlations came out between GM covariation in IC14 and participants' risky behavior assessed with BART ($rho = -0.115$, $p = .241$) (Fig. 3D). About the demographic variables, neither age (Attentional impulsivity $rho = 0.01$, $p = .871$; Motor impulsivity $rho = 0.14$, $p = .153$; Non-planning impulsivity $rho = 0.02$, $p = .830$) nor education (Attentional impulsivity $rho = -0.09$, $p = .348$; Motor impulsivity $rho = -0.08$, $p = .400$; Non-planning impulsivity $rho = -0.17$, $p = .077$) appeared correlated with the three dimensions of impulsiveness.

4. Discussion

Bipolar disorder (BD) is a complex affective disorder whose neurobiological mechanisms are still unclear [3]. Given its complexity,

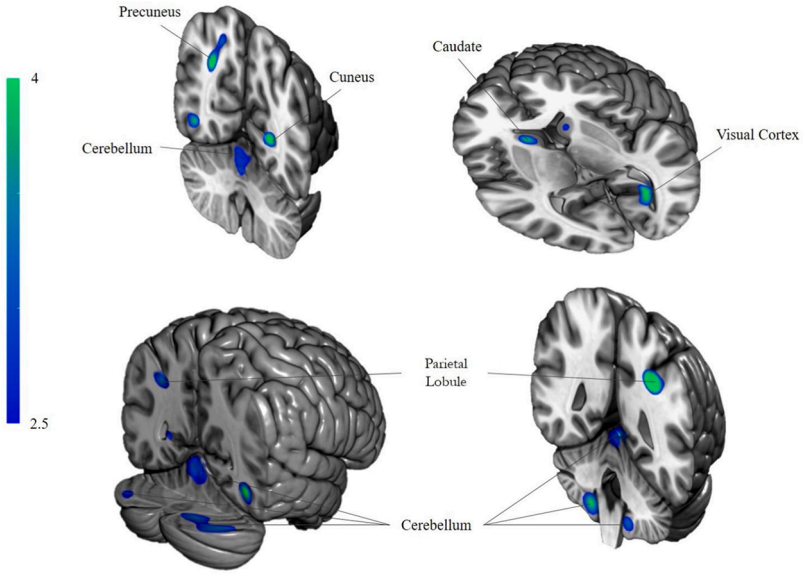

Fig. 1. SBM analysis. IC14 emerged as a statistically significant predictor of BD (SE = 0.314, z = 1.99, $p = .045$), showing less GMC in patients compared to healthy controls. IC14 is a parietal-occipital and cerebellar network that includes parts of the inferior parietal lobule, and precuneus, as well as several portions of the cerebellum, and occipital cortex like the cuneus.

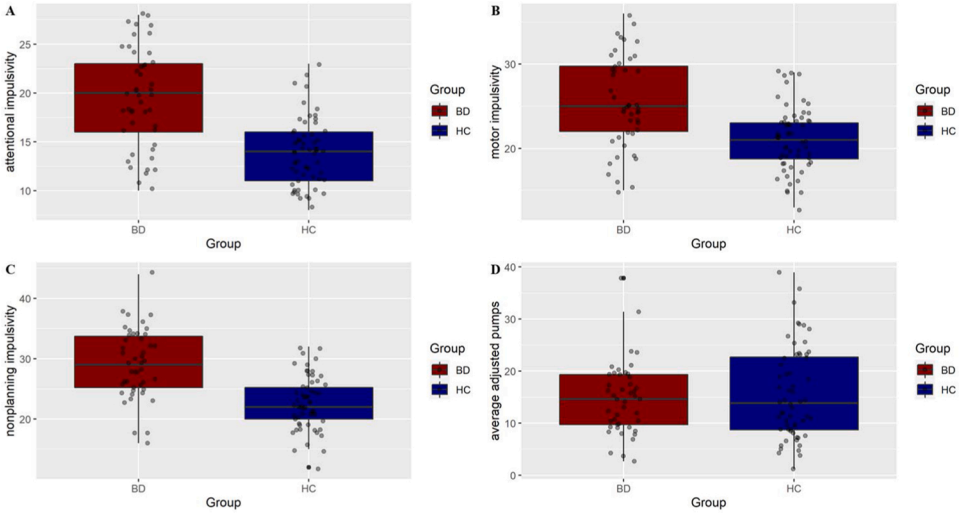

Fig. 2. Participants' performance in both BIS-11 (**A, B, C**) and BART (**D**). The two groups differed in all the three second-order factors of the BIS-11, with patients having higher scores than controls ($p < .001$). No significant differences emerged between participants' behavior in BART.

univariate approaches may fail to capture the neural heterogeneity that characterizes complex syndromes such as mood disorders [61,62]. Conversely, multivariate approaches using data-driven methods that combine information across different voxels [65] may be of great help in clarifying whole-brain abnormalities. Indeed, there is evidence about multivariate analyses showing different components of impulsivity associated with distinct changes in structural connectivity [81].

In light of this, in the present study we aimed to identify neuro-structural markers for impulsivity in BD by capitalizing on a multivariate method as Source-based Morphometry (SBM). To the best of our knowledge, this is the first time that SBM has been applied to investigate brain structural features of patients with BD, looking for a relationship with impulsive behavior. SBM is a multivariate data-driven approach based on independent component analysis (ICA), that takes into account cross-voxel information to find different naturally grouped patterns of gray matter (GM) covariation [60]. Furthermore, two types of measures were considered to assess the multifaceted nature of impulsiveness of patients and healthy controls: phenotypical self-report measure (BIS-11), and endophenotypical performance-based measure (BART). Their performance on these tasks was then correlated with GM concentration changes.

Using the ICA, the SBM yielded twenty independent sources of GM covariation extracted from the groups of participants. Of these, one structural network (IC14) emerged as a significant predictor of BD. This network included portions of the inferior parietal lobule, precuneus, the occipital cortex, and parts of the cerebellum, as well as subcortical structures caudate nucleus. At the phenotypical level, BD patients showed greater impulsiveness than healthy controls (HC). On the contrary, at the endophenotypical level, patients did not differ from controls. This is in line with previous findings by [28] who showed that BD patients scored higher than HC on self-reported impulsivity, but performed similarly to them on behavioral risk-taking (BART). Thus, our findings suggest that impulsivity and risky behavior, as operationalized by self-report and behavioral measures, are separable constructs that

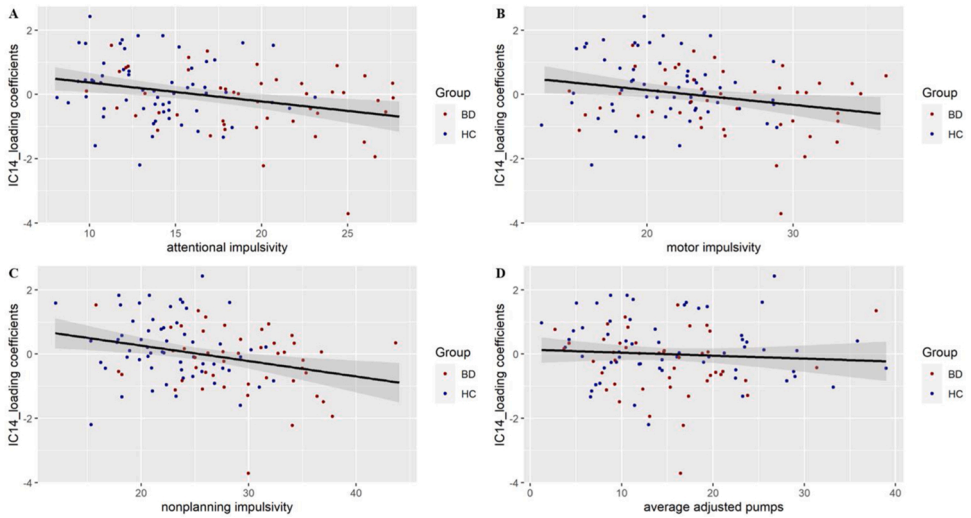

Fig. 3. Correlation analysis between IC14 and participants' performance in both BIS-11 (**A, B, C**) and BART (**D**). Participants' impulsive behavior is negatively related to variations in GMC of IC14 network: the less the GMC in the network, the greater the impulsiveness. No significant correlation emerged between participants' risky behavior and the variations in GMC of IC14.

point out distinct, dimensional factors of the BD [28,37,43–45,82]. Interestingly, participants' self-reported measures of impulsiveness (BIS-11) negatively correlated with abnormalities in this parietal-occipital and cerebellar network (IC14), that means the less the GM concentration in this network, the more impulsivity exhibited. On the contrary, no correlations emerged with their performance in the risk-taking task (BART). Thus, the ability of SBM to return a set of different areas considered as a structural circuit allowed us to reveal the possible neural basis of impulsive symptomatology in BD.

4.1. *Brain structural basis of impulsivity in BD*

We here discuss our findings with respect to both the neurobiological bases of impulsivity in relation to psychopathological conditions, and the evidence regarding brain structural and functional features of BD.

As said, we found an abnormal structural network in BD including parietal, occipital, cerebellar and subcortical areas. Involvement of posterior areas is not new in BD, and those regions may contribute together to the impulsive symptomatology. In addition to previous studies focused on the interaction between prefrontal and subcortical structures [12,53], our evidence suggests the importance of considering perceptual and attentional processes in psychopathological conditions that can refer to impulsivity [83]. Structural abnormalities in sensory and sensory association cortices are related to impairments in neuropsychological functions of BD patients [84], as visual and motor processing impairments due to structural abnormalities in ventro-temporal and occipital areas [85–87]. Indeed, inappropriate recruitment of posterior cortical regions (e.g. occipital) may underlie visual processing abnormalities that characterize BD patients [88] that, in addition to motor impairment, may contribute to impulsivity as final result. Furthermore, the supramarginal and angular gyri, that together are part of the inferior parietal lobule [89], are involved in higher-order cortical circuits associated with altered attention, perception, and affect recognition, due to their interconnections with frontal regions and the limbic system [90,91]. Frontal and parietal regions are important for immediate reward consumption [92] and executive control, and reduced GM volume in such areas has been reported in patients with high impulsivity [93]. It is worth noting that both attention and executive control deficits are part of the symptomatology of BD patients, that is corroborated by the fact that patients with BD show less GM volume in the inferior parietal lobule compared to HC [20,91]. In addition, it positively correlates with inhibitory control [115], suggesting a key role of parietal regions in the inhibition-impulsivity dyad. In addition, the inferior parietal regions may be also involved in directing attention to reappraisal-relevant stimulus features, keeping in mind reappraisal contents and goals [94], and parietal impairments might lead to a flawed perception of reality and altered representation of self-related concepts [5].

Our analysis reported a cluster of abnormal GM concentration in BD within the caudate. In addition to its crucial role in reward processing [95], a link between this region and impulsivity has already been reported in the literature. Tschernegg and colleagues [96] highlighted a relationship between GM volume in the caudate and impulsivity traits. Moreover, cocaine-dependent individuals who are characterized by strong impulsivity due to their addiction, show reduced GM volume in bilateral caudate [97], while caudate asymmetry seems to contribute to attentional impulsivity in ADHD [98]. Referring to BD, evidence reports that caudate structural anomalies may appear at early stage of the disease [10], and that its shape is different in drug-naïve BD patients [99].

Lastly, cerebellar clusters emerged in our structural network. This finding is in line with growing evidence suggesting an important role of the cerebellum with respect to impulsive symptomatology in several neuropsychiatric disorders [100]. Moreover, the cerebellum is important for operations of timing, prediction, and learning, integrating them into processes of novelty/error detection, working memory, and mental manipulation [101]. This allows the cerebellum to take part not only in motor control, but also in attentional switching, language processing, imagery, and decision making [101]. Considering the cerebellar cognitive affective syndrome (CCAS) [108], along with motor impairments, damage to the cerebellum can cause a wide range of non-motor symptoms. These include lethargy, depression, lack of empathy and dysregulation, as well as irritability, disinhibition, poor attentional and behavioral modulation, and, not lastly, impulsivity [57], which are all parts of the symptomatology of BD. Lee and colleagues (2011) reported a positive correlation between impulsivity and the right cerebellum volume, and argued that impulse control and response inhibition were mediated by networks involving the prefrontal cortex, anterior cingulate cortex, as well as posterior cingulate, basal ganglia (bilateral caudate), right thalamus, supramarginal and angular gyri and visual cortex [102,103]. A recent functional resting-state investigation reported decreased functional connectivity within visual, temporal, motor and cerebellar networks in BD [104]. It is worth noting that these circuits include regions associated with our abnormal structural network in BD, emphasizing how structural abnormalities can be linked to functional abnormalities. Therefore, it is possible to speculate that cerebellar

structural abnormalities, along with those reported in cortical and subcortical regions, may contribute to the impulsive symptomatology typical of BD at the functional level.

5. Conclusions

This is the first time that a multivariate approach to morphometric analyses as the Source-based Morphometry [60] has been applied to study BD, assuming that changes in patients' gray matter concentration (GMC) may reflect neuropathological effects of the symptomatology [105]. We isolated one component (IC14) representing a parieto-occipital and cerebellar network. This network is involved in attentional processes and cognitive control, and its alteration might be responsible for impulsiveness [106,110]. The comorbidity of impulsivity in several psychiatric disorders (e.g. bipolar disorder, personality disorders, substance abuse) may be associated with the neurobiological substrates of the disorders [39], assuming the existence of a neural model of impulsivity. However, impulsivity is a multifaceted construct [39,107], and different dimensions can be investigated depending on the disorder considered [39] and on the instrument used to measure it [83].

These findings can give a broader explanation of BD that has typically been associated with emotional alterations only, suggesting a crucial role of attentional dysfunction in impulsivity and in the etiology of the disorder. Nevertheless, to be useful in clinical practice, any biomarker needs to be specific for the disorder. Further studies comparing different mental disorders (e.g. bipolar, schizophrenia, major depression) are therefore needed to improve the comprehension of both unique and shared factors across the continuum of mental disorders [5].

Disclosures

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

CRediT authorship contribution statement

Gaia Lapomarda: Conceptualization, Methodology, Formal analysis, Investigation, Resources, Data curation, Writing - original draft, Visualization. **Edoardo Pappaianni:** Resources, Writing - review & editing. **Roma Siugzdaite:** Software, Formal analysis, Writing - review & editing. **Alan G. Sanfey:** Writing - review & editing. **Raffaella I. Rumiati:** Writing - review & editing. **Alessandro Grecucci:** Conceptualization, Supervision, Project administration, Writing - review & editing.

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