Gray matter bases of psychotic features in adult bipolar disorder: A systematic review and voxel-based meta-analysis of neuroimaging studies

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Abstract
Psychotic bipolar disorder (P-BD) is a specific subset that presents greater risk of relapse and worse outcomes than nonpsychotic bipolar disorder (NP-BD). To explore the neuroanatomical bases of psychotic dimension in bipolar disorder (BD), a systematic review was carried out based on the gray matter volume (GMV) among P-BD and NP-BD patients and healthy controls (HC). Further, we conducted a meta-analysis of GMV differences between P-BD patients and HC using a whole-brain imaging approach. Our review revealed that P-BD patients exhibited smaller GMVs mainly in the prefronto-temporal and cingulate cortices, the precentral gyrus, and insula relative to HC both qualitatively and quantitatively. Qualitatively the comparison between P-BD and NP-BD patients suggested inconsistent GMV alterations mainly involving the prefrontal cortex, while NP-BD patients showed GMV deficits in local regions compared with HC. The higher proportions of female patients and patients taking psychotropic medication in P-BD and NP-BD patients suggested inconsistent GMV alterations mainly involving the prefrontal cortex, while NP-BD patients showed GMV deficits in local regions compared with HC. The higher proportions of female patients and patients taking psychotropic medication in P-BD and NP-BD type I were associated with smaller GMV in the right precentral gyrus and the right insula, respectively. In conclusions, psychosis in BD might be associated with specific cortical GMV deficits. Gender and psychotropic medication might have effects on the regional GMVs in P-BD patients. It is necessary to distinguish psychotic dimension in neuroimaging studies of BD.

KEYWORDS
gray matter volume (GMV), magnetic resonance imaging (MRI), meta-analysis, nonpsychotic bipolar disorder (NP-BD), psychotic bipolar disorder (P-BD), voxel-based morphometry (VBM)

1 | INTRODUCTION

Bipolar disorder (BD) is a prevalent condition, affecting approximately 1% of the population, that is associated with high disability if not promptly treated (Altamura, Buoli, & Serati, 2011). More than half of BD patients experience psychotic symptoms at least once in their lifetime (Fernandes, Ramaswamy, Marcil, & Petty, 2011; Keck et al., 2003). Psychotic symptoms are variably present depending on the patient and the different disease phases. Due to these psychotic symptoms, patients exhibit reduced therapeutic compliance, which results in more difficult clinical management. Preliminary evidence has suggested that psychotic bipolar disorder (P-BD) may represent a
distinct phenotype (Bora, Yucel, Fornito, Berk, & Pantelis, 2008), with a greater risk of relapse (Kessing, 2003), higher numbers of hospitalizations (Dell’Osso et al., 2017; Mazzarini et al., 2010), poorer clinical outcomes (Buoli, Caldiroli, & Altamura, 2013; Vythilingam et al., 2003), and enduring cognitive impairment (Simonsen et al., 2011) relative to nonpsychotic bipolar disorder (NP-BD). Recently, a particular focus has been placed on the psychotic dimension of BD, which may be neurobiologically determined.

An increasing number of studies are paying attention to the association between biomarkers and the psychotic features in BD. A growing body of literature has indicated that biological markers are most likely associated with the psychotic dimension in BD. Recent studies were consistent in recognizing P-BD as a subset with specific biological abnormalities in terms of genetic, immunological, endocrine, neurophysiological, brain imaging, and neuropsychological alterations, compared with both NP-BD and schizophrenia (Buoli et al., 2016; Moser et al., 2018; Palaniyappan et al., 2018). In regard to neuroimaging, the non-consideration of this factor may contribute to the heterogeneous findings across studies of BD (Ellison-Wright & Bullmore, 2010). Edmiston et al. (2011) reported an increase in the lateral ventricle volume (LVV) in adolescents and adults with P-BD compared with healthy controls (HC), but no difference was found between the NP-BD group and either the P-BD or HC groups, suggesting that LVV might be a morphologic feature associated with psychosis in BD. Similarly, no gray/white matter differences were found between P-BD and NP-BD patients (Jorgensen et al., 2016). However, another recent review reported that patients with P-BD exhibited gray matter volume (GMV) deficits in the frontal region compared with both NP-BD patients and HC, while NP-BD patients exhibited gray matter (GM) deficits in the subregions of the basal ganglia in comparison with both P-BD patients and HC (Maggioni, Altamura, & Brambilla, 2017). It has also been demonstrated that smaller hippocampal volume exists in P-BD patients compared with HC in the age range of 15–65 years (Mathew et al., 2014). Furthermore, Keramatian et al. (2016) found GMV deficits in a set of cortical regions and in the cerebellum in mood-incongruent P-BD patients compared with both mood-congruent P-BD and NP-BD patients. Thus, the psychotic dimension in BD may have a specific neuroanatomical basis, despite the fact that no definitive data are available currently. Additionally, studies including a review found evidence to support different underlying neuropsychological substrates for BD type I (BDI) and BD type II (BDII), using neuroanatomical methods (Abe et al., 2016; Caseras et al., 2015; Caseras, Lawrence, Murphy, Wise, & Phillips, 2013; Fawcett & Agius, 2015).

Currently, a relatively new quantitative coordinate-based meta-analytic approach, that is, the anisotropic effect size version of seed-based d mapping (AES-SDM), allows the results of individual studies to be weighted and controlled for several moderating variables, including demographic, clinical, and imaging factors and medication effects at the time of scanning (Moser et al., 2018). AES-SDM has been successfully applied to neuropsychiatric populations (Hall et al., 2015; Kimmel et al., 2016; Norman et al., 2016), and has been described in detail elsewhere (Hatton et al., 2012; Palaniyappan et al., 2018).

In attempt to clarify the neuroanatomical alterations associated with the psychotic dimension of BD, we reviewed magnetic resonance imaging (MRI) studies that investigated GMVs among P-BD and NP-BD patients and HC. We carried out a systematic review based on seminal articles, with references to relevant meta-analyses and qualitative reviews. Then, using AES-SDM, we conducted a coordinate-based meta-analysis of voxel-based morphometry (VBM) studies to identify the regional GMV differences between P-BD patients and HC. In addition, we also explored the possible demographic and clinical variables that may affect GMV, paying special attention to the effects of psychotropic medications.

2 | MATERIALS AND METHODS

2.1 | Literature search

To explore the neuroanatomical basis of P-BD, we conducted a systematic search of the PubMed, Embase, and Web of Science databases for studies that investigated brain GMVs in P-BD and/or NP-BD patients, published in English through December 2017. The following key words were used: “psychotic bipolar disorder” OR “bipolar disorder” AND (“psychotic symptoms” OR “psychotic features” OR “psychosis” OR “delusion” OR “hallucination”) AND (“magnetic resonance imaging” OR “MRI”). Broad search terms were used to minimize the likelihood of missing any relevant studies. We cross-referenced all relevant original articles, reviews and meta-analyses, including the reference lists of eligible articles, in order to identify studies that might have been missed in the literature searches, and we selected original articles that compared GMV measurements among P-BD and NP-BD patients and HC.

2.2 | Inclusion and exclusion criteria

In the present review, P-BD was defined if hallucinations and/or delusions occurred during at least one mood episode in BD patients, while NP-BD was defined as the absence of hallucinations and delusions in all mood episodes. To be considered for review, the studies had to meet the following criteria: (1) patients were diagnosed with P-BD and/or NP-BD; (2) brain GMV (including GM density) differences among P-BD or NP-BD patients and HC were available; and (3) original articles. To be included in the meta-analysis, the studies had to meet the following criteria: (1) have used a whole-brain VBM imaging approach and (2) reported stereotactic coordinates (in the Talairach space or the Montreal Neurological Institute [MNI] space).

The exclusion criteria were as follows: (1) subjects under 18 years of age, (2) mixed or not accurately described groups of patients (e.g., a group of P-BD patients including post-partum psychosis or a “psychosis group” including unipolar depression, NP-BD, schizoaffective disorder and schizophrenia patients), (3) the BD group was secondary to a somatic condition, such as temporal lobe epilepsy or multiple sclerosis, and was investigated solely as a comorbid psychiatric condition, and (4) the data were insufficient (e.g., missing neuroanatomical coordinates), even after the author(s) were contacted via e-mail. Each study was assessed by two reviewers (Xiuli Wang and Fangfang Tian). Coordinates were independently extracted by two authors (Xiuli Wang and Fangfang Tian) according to the AES-SDM method to minimize data extraction errors. Inconsistencies were resolved by a third assessor (Zhiyun Jia).
2.3 | Data analyses

2.3.1 | Descriptive analysis

We described the information regarding the sample size, gender, age, age at onset, duration of illness, severity of symptoms, medication, MRI method, data analysis method, and main findings of the included studies. In the systematic review, data summaries were categorized into results examining GMVs between P-BD and NP-BD patients and with HC. For the meta-analysis, we combined studies on the GMVs between P-BD patients and HC and calculated the mean ages, the percentages of female patients, and the percentages of P-BD patients taking medication in the included studies.

2.3.2 | Voxel-based meta-analysis of regional GMV

Using the latest version of AES-SDM (http://www.sdmproject.com/), version 5.141 (Moser et al., 2018), we analyzed GMV alterations in P-BD patients compared with HC using a whole-brain VBM imaging approach. The latest version includes some new features, such as possibility to combine repeated measures (e.g., from several contrasts of the same sample) and easy automatic creation of funnel plots and Egger tests (http://www.sdmproject.com/). This method has been thoroughly described elsewhere (Moser et al., 2018; Palaniyappan et al., 2018) and is briefly summarized here. First, the reported peak coordinates and effect sizes (derived, e.g., from t values of the GMV differences) were used to recreate a map of the effect size of the GMV differences between individuals with P-BD and HC for each study. Second, a standard MNI map of the differences in the GMVs was recreated for each study separately by means of an anisotropic Gaussian kernel, which assigned higher effect sizes to the voxels that were more strongly correlated with the peaks. Third, the mean map was generated via voxel-wise calculation of the random-effects mean of the study maps, weighted by sample size, within-study variance, and between-study heterogeneity. Division of the meta-analytic effect sizes by their standard errors yielded z-values, but these were not normally distributed, and thus, statistical significance was assessed using a permutation test. For all main analyses, it has been shown that $p < .005$ (uncorrected) with a cluster-level extent threshold of $k > 10$ optimally balances false positives and negatives (Palaniyappan et al., 2018). For each cluster that was significantly different between patients and controls, Egger's test was used to assess the potential publication bias (Egger, Davey Smith, Schneider, & Minder, 1997).

Additionally, a jackknife sensitivity analysis was conducted to assess the robustness of the results by iteratively repeating the mean analysis, excluding one dataset at a time to establish whether the results remained significant (Hatton et al., 2012). In addition, meta-regression analyses were conducted to identify potential demographic and clinical confounders of GMV abnormalities relative to HC, such as the mean age, percentage of female patients, Young Mania Rating Scale (YMRS) scores, psychotropic medications, lithium usage, antipsychotics, magnetic field strength, and the image smoothing level within patient groups using a more conservative voxel-level threshold of $p < .0005$ (uncorrected) in accordance with previous meta-analyses (Bora, Fornito, Yucel, & Pantelis, 2010; Nery et al., 2009), with only regions found in the main analyses being included (Hatton et al., 2012; Moser et al., 2018). The following variables could not be studied because the data were available in fewer than nine studies: handedness, age at onset, duration of illness, scores on the Hamilton depression scale (HAMDI), and scores on the positive and negative symptoms scale (PANSS). Finally, subgroup analyses were performed for the studies including only patients with P-BD type I (P-BDI), followed by jackknife and meta-regression analyses, as described above.

3 | RESULTS

3.1 | Included studies and sample characteristics

The searches of the databases provided a total of 2,699 citations with 787 duplicates. After reviewing the titles and abstracts, 1,779 citations were discarded since they did not meet our inclusion criteria. The full texts of the remaining 133 studies were examined in more detail by two reviewers. Then, an additional 99 studies were excluded according to the inclusion and exclusion criteria (e.g., reporting cortical surface area and thickness, only reporting white matter structures, or including other psychiatric disorder such as depressive disorder and schizoaffective disorder). An additional 3 studies that met the inclusion criteria were identified by checking the references of the selected relevant articles. Finally, a total of 37 studies were included in this systematic review (Figure 1), most of which enrolled a HC group, except for 6 studies (Foland-Ross et al., 2011; Haukvik et al., 2015; Hlibar et al., 2018; Neves Mde et al., 2016; Radaelli et al., 2014; Stanfield et al., 2009) that merely compared P-BD with NP-BD patients. Nearly half of the studies (18 studies) included only BDI patients, while the other studies did not specifically describe the subtypes of BD or included different subtypes of BDI, BDII, or not otherwise specified (NOS) in their research. We extracted the following data from each included study: author, year of publication, sample size, gender, mean age, illness duration, data acquisition parameters, magnetic field strength, data processing methods, and main study outcomes (Table 1).

Of the 37 studies, 14 VBM studies (Altmara, Delvecchio, et al., 2017; Altamura, Maggioni, et al., 2018; Chen, Wen, Malhi, Ivanovskii, & Sachdev, 2007; Chen et al., 2012; Cui et al., 2011; De Azevedo-Marques Perico et al., 2011; Ivleva et al., 2012, 2013, 2017; McDonald et al., 2005; Nenadic et al., 2015; Song et al., 2015; Tost et al., 2010; Yuksel et al., 2012) with 16 subsets met the inclusion criteria for the AES-SDM meta-analysis and were included in the meta-analysis to explore regional GMV alterations in P-BD patients relative to HC, comprising a total of 616 P-BD patients and 902 healthy subjects (Figure 1 and Table 2). The mean age of the P-BD patients was 35.8 years ($SD = 4.25$), 60.00% (351/585) of whom were female. The mean age of the HC was 34.7 years ($SD = 4.84$), of whom 51.76% (440/850) were female. Nine studies (64.29%) did not provide ages at onset, and 8 studies (57.14%) did not provide illness duration. Regarding the subtypes, 11 studies (78.57%) only included patients with bipolar disorder type I. Regarding the symptoms, 9 studies (64.29%) reported YMRS scores, and 11 studies (78.57%) and 10 studies (71.43%) did not provide information on depressive symptoms or psychotic symptoms, respectively. Regarding medication administration, 12 studies (85.71%) reported the number of medication administration users, 9 studies (64.29%) reported the number of lithium users,
and 12 studies (85.71%) provided the number of patients taking antipsychotic medication.

3.2 | Qualitative GMV findings

In the included GMV studies, 4 studies reported the total GMVs, and 37 studies reported regional GMV volumes (Table 1).

3.2.1 | Total GMV findings

Concerning the global GMV measures, the studies agreed on the absence of significant differences between P-BD patients and HC (Chen et al., 2007, 2012; Mamah, Alpert, Barch, Csernansky, & Wang, 2016), between P-BD and NP-BD patients (Chen et al., 2007; Mamah et al., 2016), and between NP-BD patients and HC (Chen et al., 2007; Mamah et al., 2016); however, one study (Tost et al., 2010) reported a total GMV reduction in P-BD patients in comparison to HC.

3.2.2 | Regional GMV findings

Focusing on the regional GMV alterations, the findings showed the presence of different features in P-BD and NP-BD patients as follows.

P-BD patients versus HCs

Most of the studies found extensively distributed GM volume/density deficits in P-BD patients compared with HC using whole-brain and/or region of interest (ROI) approaches. Using the whole-brain method, with the exception of one study (Cui et al., 2011) that revealed greater GMVs in the right putamen and cerebellum, an overwhelming number of studies showed smaller GMVs in the bilateral prefrontal cortex (PFC), involving the superior, middle and inferior frontal gyri (Altamura, Delvecchio, et al., 2017; Cui et al., 2011; Ivleva et al., 2013; Song et al., 2015; Tost et al., 2010); the medial frontal gyrus (Altamura, Delvecchio, et al., 2017; Ivleva et al., 2013); and the right precentral gyrus (Ivleva et al., 2013), as well as the bilateral cingulate cortices (Altamura, Delvecchio, et al., 2017; Ivleva et al., 2013; Tost et al., 2010). The studies also reported GMV deficits in the bilateral temporal cortices, including the superior, middle, and inferior temporal gyri (Altamura, Delvecchio, et al., 2017; Cui et al., 2011; Ivleva et al., 2013; Tost et al., 2010); bilateral insula (Altamura, Delvecchio, et al., 2017; Ivleva et al., 2013); parietal cortices (Cui et al., 2011; Ivleva et al., 2013; Song et al., 2015); right occipital gyrus (Cui et al., 2011); fusiform gyrus (Altamura, Delvecchio, et al., 2017; Song et al., 2015); and the left cerebellum (Altamura, Delvecchio, et al., 2017). Subcortical GMV deficits were also found in the bilateral parahippocampus (Altamura, Delvecchio, et al., 2017; Ivleva et al., 2013), left/right thalamus (Altamura, Delvecchio, et al., 2017; Chen et al., 2012) and bilateral basal ganglia, including the caudate nucleus and putamen and extending to the left claustrum (Chen et al., 2012; Cui et al., 2011). In contrast, other authors confirmed no significant differences in the GMVs between P-BD and NP-BD patients (De Azevedo-Marques Perico et al., 2011; Ivleva et al., 2012; McDonald et al., 2005; Nenadic et al., 2015; Yuksel et al., 2012). Using the ROI-based approach, the studies found greater GMVs in the right anterior cingulate cortex (ACC) (De Azevedo-Marques Perico et al., 2011) and the striatum (Getz et al., 2002), while smaller GMVs in the right dorsolateral prefrontal cortex (DLPFC), left inferior frontal gyrus, and left fusiform gyrus (Ekman et al., 2017) in P-BD patients compared with HC. In contrast, other studies did not identify significant differences in the GMVs of the ACC (Fornito et al., 2009; Javadapour et al., 2007), superior temporal regions (Hirayasu et al., 2000; Ratnanather et al., 2013; Salisbury et al., 2007), supramarginal and fusiform gyrus (Giakoumatos et al., 2013), amygdala (Haukvik et al., 2014; Mahon et al., 2012; Mamah et al., 2016), hippocampus (Arnold et al., 2015; Avery, Williams, Woolard, & Heckers, 2014; Haukvik et al., 2014; Javadapour et al., 2010; Mamah et al., 2016; Strasser et al., 2005), thalamus and basal ganglia (Liber, Ekman, Sellgren, Johansson, & Landen, 2015; Mamah et al., 2016; Womer et al., 2014) in P-BD patients relative to HC.

P-BD versus NP-BD patients

The research directly comparing GMVs between the patient groups identified inconsistent findings mainly regarding the PFC. Using the whole-brain analysis, the studies reported greater GMVs in the left superior frontal gyrus, right middle frontal gyrus, left ACC, right precentral gyrus, precuneus, and caudate body in P-BD patients compared with NP-BD patients (Chen et al., 2007). However, other studies found greater GMVs in the right DLPFC, left inferior frontal gyrus, right parieto-occipital area, and left fusiform gyrus (Ekman et al., 2017) or negative findings (Neves Mde et al., 2016) in P-BD patients relative to NP-BD patients. Using ROI-based analyses, the studies found greater GMVs in the globus pallidus and caudate (Mamah et al., 2016; Womer et al., 2014); smaller GM volumes/densities in the right inferior frontal gyrus, middle frontal gyrus (Radaelli et al., 2014), left/right insula (Neves Mde et al., 2016; Radaelli et al., 2014), and left middle temporal gyrus (Stanfield et al., 2009); or no GMV differences in the ventral PFC, encompassing the bilateral orbital and inferior frontal gyrus (Stanfield et al., 2009), in P-BD patients relative to NP-BD patients. Studies that explored subcortical structures also reported no GMV differences in the hippocampal regions (Haukvik et al., 2014, 2015; Javadapour et al., 2010; Strasser et al., 2010).
| Study                  | Subjects n (M:F)/mean ± SD, years | Age of onset/illness duration (years) | Field strength/smoothing | Software/methods (whole brain or ROI) | Areas of interest | Statistical analyses/correction for multiple comparisons | Main findings                                                                 |
|-----------------------|-----------------------------------|----------------------------------------|--------------------------|----------------------------------------|------------------|----------------------------------------------------------|------------------------------------------------------------------------------|
| Arnold et al. (2015)  | P-BD: 86 (25:71)/35.80 ± 13.0     | 19.8 ± 9.2/NA                          | 3 T/NA                   | FreeSurfer/semi-automated parcellation/ROI | Hippocampus      | One-way ANOVA/NA                                         | P-BD vs. HC: No difference in bilateral hippocampal volumes. NA              |
| Altamura et al.       | P-BD: 17 (4:13)/38.70 ± 8.2       | 25.7 ± 7.0/11.4 ± 7                    | 3 T/6 mm                 | SPM12/VBM/whole brain                  | NA               | ANCOVA/p < .05, FWE and FDR correction                   | P-BD < HC: Bilateral STG, R MFG, R medial frontal gyrus, L STG and MTG, bilateral ACC, R posterior cingulate, L insula, bilateral parahippocampus, R fusiform, R thalamus and L cerebellum. NA |
| Altamura et al.       | P-BD: 28 (9:19)/31.54 ± 5.54      | NA/NA                                  | 3 T/6 mm                 | SPM 12/VBM/whole brain                 | NA               | GLM/p < .001, FDR correction                            | P-BD < HC: R STG, L precentral gyrus, R STG, L middle cingulate cortex. P-BD > HC: R putamen, NP-BD > HC: R putamen. P-BD < NP-BD: R STG. |
| Avery et al. (2014)   | P-BD: 17 (7:10)/37.41 ± 10.37     | NA/15.90 ± 8.69                        | 3 T/5 mm                 | 3D slicer/segmentation protocol/ROI    | Hippocampus      | ANCOVA/p < .05, uncorrected                            | P-BD vs. HC: No difference in hippocampal volumes. NA                         |
| Chen et al. (2007)    | P-BD: 14 (NA)/NA                   | NA/NA                                  | 1.5 T/12 mm              | SPm2/optimized VBM/Whole brain         | NA               | ANCOVA/p < .001, uncorrected                            | P-BD < HC: L MTG, P-BD > HC: R precentral gyrus, R MFG. NP-BD < HC: Bilateral MTG, L superior and middle occipital gyrus, L SFG, R precentral gyrus, R putamen, R precuneus, L ACC. P-BD vs. NP-BD: No difference in total brain volumetric measures. P-BD vs. HC: No difference in total GM volume. |
| Chen et al. (2012)    | P-BD: 18 (NA)/32.0 ± 7.6          | 24.4 ± 6.8/4.2 ± 3.76                  | 3 T/8 mm                 | SPM5/VBM/whole brain                  | NA               | T-test/p < .001, uncorrected                            | P-BD > HC: L thalamus and bilateral basal ganglia, including putamen and extending to L claustrum. P-BD vs. HC: No difference in total GM volume. NA |

(Continues)
| Study                  | Subjects n (M:F)/mean ± SD (years) | Age of onset/illness duration (years) | Field strength/smoothing | Software/methods (whole brain or ROI) | Areas of interest | Statistical analyses/correction for multiple comparisons | Main findings                                                                 |
|-----------------------|------------------------------------|--------------------------------------|--------------------------|---------------------------------------|-------------------|----------------------------------------------------------|--------------------------------------------------------------------------------|
| Cui et al. (2011)     | P-BD: 24 (15:9)/28.42 ± 6.64       | 22 ± 9/16 ± 10/11/19 ± 14            | 3 T/8 mm                 | SPM 5/VBM/whole brain                 | NA                | ANCOVA/β < .001, uncorrected                            | P-BD < HC: R MFG, R STG, L MTG, L inferior parietal lobe, R occipital gyrus, L caudate nucleus, L caudate nucleus. P-BD > HC: Cerebellum and R putamen. |
| Ekman et al., 2017    | P-BD: 85 (30:55)/37 ± 13           | 22 ± 9/16 ± 10/11/19 ± 14            | 1.5 T/8 mm               | SPM 12/VBM/whole brain and ROI       | R DLPFC, L IFG, L fusiform gyrus | T-test/β < .05, FWE P-BD < HC: R DLPFC, L IFG, L fusiform gyrus by ROI. NP-BD vs. HC: No difference by ROI. P-BD < NP-BD: R DLPFC, L IFG, L fusiform gyrus by ROI. |
| Fornito et al. (2009) | P-BD: 26 (16:10)/31.64 ± 3.23      | NA/NA                                | 1.5 T/NA                 | Freesurfer/NA/ROI                    | ACC subregions    | ANOVA/β < .05, Bonferroni-adjusted correction           | P-BD vs. HC: No difference in ACC.                                                |
| Getz et al. (2002)    | P-BD: 12 (8:4)/29.2 ± 8.7          | 25.9 ± 7.2/NA                        | 1.5 T/NA                 | Brain image/Semi-automated segmentation/ROI | Prefrontal cortex, thalamus, striatum, amygdale, hippocampus, globus pallidus and cerebrum | Multivariate ANCOVA/NA/NA | P-BD > HC: Striatum.                                      |
| Giakoumatos et al. (2013) | P-BD: 51 (NA)/(NA)                 | 25.9 ± 7.2/NA                        | 1.5 T/NA                 | FreeSurfer/automated segmentation/whole brain | NA                | ANOVA/β < .05, Hochberg correction                      | P-BD < HC: L supramarginal and R fusiform gyri. P-BD vs. HC: No difference.     |
| Haukvik et al. (2014) | P-BD: 48 (23:25)/25.7 ± 6.7        | 25.9 ± 7.2/NA                        | 1.5 T/NA                 | FreeSurfer/automated segmentation/ROI | Hippocampus and amygdala | GLM/NA | P-BD/NA-BD vs. HC: No difference in hippocampus and amygdale. |
| Haukvik et al. (2015) | P-BD: NA/NA                        | 25.9 ± 7.2/NA                        | 1.5 T/NA                 | FreeSurfer/automated segmentation/ROI | Hippocampus        | ANCOVA/NA. Bonferroni-adjusted correction                | P-BD vs. NP-BD: No difference in total or subfields of hippocampus.            |
| Study                  | Subjects n (M:F)/(mean ± SD, years) | Age of onset/illness duration (years) | Field strength/smoothing | Software/methods (whole brain or ROI) | Areas of interest | Statistical analyses/correction for multiple comparisons | Main findings                                      |
|------------------------|-------------------------------------|---------------------------------------|--------------------------|---------------------------------------|-------------------|----------------------------------------------------------|--------------------------------------------------|
| Hirayasu et al. (2000) | P-BD: 24 (18:6)/23.6 ± 5.0 HC: 22 (20:2)/24.5 ± 4.7 | NA/NA | 1.5 T/NA | FreeSurfer/semi-automated segmentation/ROI | Planum temporal and Heschl gyrus | ANOVA/p < .05, FDR correction | P-BD vs. HC: No difference. NA |
| Ivleva et al. (2012)   | P-BD: 17 (8:9)/38.24 ± 7.28 HC: 10 (4:6)/43.9 ± 9.86 | NA/14.76 ± 9.07 | 3 T/12 mm | SPM8 and FreeSurfer/VBM/whole brain | NA | ANOVA/p < .05, FDR correction | P-BD vs. HC: No difference. NA |
| Ivleva et al. (2013)   | P-BD: 115 (36:79)/35.4 ± 12.5 HC: 200 (92:108)/39.8 ± 12.1 | 20.2 ± 8.70/NA | 3 T/12 mm | SPM8/VBM/whole brain | NA | Factorial models/p < .05, FWE correction | P-BD < HC: ACC, frontal, posterior cingulate, insular, temporal, and parietal cortices. NA |
| Ivleva et al. (2017)   | P-BD: 177 (60:191)/19.8 ± 8.8/NA HC: 251 (109:68)/38.04 ± 11.1 | 19.8 ± 8.8/NA | 3 T/8 mm | SPM8/VBM/whole brain | NA | Factorial models/p < .05, FWE correction | P-BD < HC: The frontal, cingulate, insular, temporal, parietal and occipital regions. NA |
| Javadapour et al. (2007)| P-BD: 14 (NA)/NA NP-BD: 10 (NA)/NA HC: 24 (6:18)/3804 ± 11.1 | NA/NA | 1.5 T/NA | Analyze software/Manually outlined ACC/ROI | ACC | Pair-wise t test/p < .01, Bonferroni-adjusted correction | P-BD/NP-BD vs. HC: No difference in ACC. NA |
| Javadapour et al. (2010)| P-BD: 14 (NA)/NA NP-BD: 10 (NA)/NA HC: 24 (NA)/3804 ± 11.1 | NA/NA | 1.5 T/NA | Analyze software/Manually outlined hippocampus/ROI | Hippocampus | Pair-wise t test/NA | P-BD/NP-BD vs. HC: No difference in hippocampus. P-BD vs. NP-BD: No difference in hippocampus. NA |
| Laidi et al. (2015)    | P-BD: 53 (25:28)/35 ± 4.7 NP-BD: 62 (26:36)/37.3 ± 10.6 HC: 52 (21:31)/37.2 ± 11.8 | 20 ± 8/NA | 3 T/NA | FreeSurfer/semi-automated segmentation/ROI | Cerebellum | ANOVA/p < .05, Bonferroni-adjusted correction | NA |
| Liberg et al. (2015)   | P-BD: 20 (9:11)/42.3 ± 12.9 HC: 20 (9:11)/43.2 ± 13.4 | 21.6 ± 7.5/19.6 ± 10.3 | 1.5 T/NA | FreeSurfer/automatic segmentation/ROI | Audate nucleus, putamen, pallidum, and thalamus | Student’s t test/p < .05, NA | P-BD vs. HC: No difference in basal ganglia or thalamus. NA |
| Mahon et al. (2012)    | P-BD: 36 (19:17)/39.9 ± 11.1 HC: 27 (12:15)/44.0 ± 15.6 | NA/17.6 ± 12.7 | 1.5 T/NA | FreeSurfer/semi-automated segmentation/ROI | Amygdale | T test/p < .05, Bonferroni-adjusted correction | P-BD vs. HC: No difference in amygdale. NA |
| Mahon et al. (2015)    | P-BD: 36 (19:17)/39.9 ± 11.1 HC: 27 (12:15)/44.0 ± 15.6 | NA/17.6 ± 12.7 | 1.5 T/NA | FreeSurfer/semi-automated segmentation by MRISoftware/ROI | Amygdale subregions | GLM/p < .05, FWE correction | P-BD vs. HC: No difference in amygdale subregions. NA |

(Continues)
| Study                  | Subjects n (M:F)/mean ± SD (years) | Age of onset/illness duration (years) | Field strength/smoothing | Software/methods (whole brain or ROI) | Areas of interest | Statistical analyses/correction for multiple comparisons | Main findings                                      |
|------------------------|-------------------------------------|---------------------------------------|--------------------------|---------------------------------------|-------------------|----------------------------------------------------------|---------------------------------------------------|
| Mamah et al. (2016)    | P-BD: 49 (20:29)/25.2 ± 3.6         | NA/N/A                                | 3 T/NA                   | Freesurfer/automated segmentation/ROI | Hippocampus, amygdale, caudate, putamen, globus pallidus, nucleus accumbens, and thalamus | ANCOVA/NA                                               | NP-BD < HC: Bilateral caudate and globus pallidus. P-BD/NP-BD vs. HC: No difference in total GM volume. |
|                        | NP-BD: 24 (8:16)/26.2 ± 3.7         |                                       |                          |                                       |                   | ANCOVA/NA                                               | P-BD > NP-BD: L globus pallidus. P-BD < NP-BD: No difference in total GM volume. |
|                        | HC: 40 (20:20)/24.9 ± 5             |                                       |                          |                                       |                   | ANCOVA/NA                                               | P-BD > NP-BD: R posterior insula in ROI.             |
| McDonald et al. (2005) | P-BD: 37 (15:22)/4.07 ± 11.6        | 22.9 ± 5.5/178 ± 11.3                 | 1.5 T/8 mm               | SPM99/VBM/whole brain                | NA                | ANCOVA/NA                                               | P-BD < NP-BD vs. HC: No difference in major regions. |
|                        | HC: 52 (24:28)/39.3 ± 11.3          |                                       |                          |                                       |                   | NA                                                       | NA                                                |
| Nenadic et al. (2015)  | P-BD: 17 (9:8)/37.69 ± 11.13        | NA/9.9 ± 8.7                          | 3 T/NA                   | SPM/VBM/whole brain                 | NA                | GLM/p < .05, FDR correction                               | P-BD vs. HC: No differences.                         |
|                        | NC: 34 (18:16)/34.33 ± 10.62        |                                       |                          |                                       |                   | ANOVA/p < .05, FWE correction                             | NA                                                |
| Neves et al. (2016)    | P-BD: 9 (3:6)/37.66 ± 12.07         | NA/12.22 ± 8.7                        | 1.5 T/8 mm               | SPM8/VBM/whole brain and ROI        | Ventral prefrontal cortex, orbitofrontal cortex, insula, cingulated gyrus, fusiform gyrus, superior temporal sulcus, amygdale and thalamus | GLM/p < .05, FWE correction                         | P-BD vs. NP-BD: No difference in whole brain analysis. P-BD < NP-BD: R posterior insula in ROI. |
|                        | NP-BD: 12 (6:6)/39.92 ± 14.99       | NA/11.91 ± 9.59                       |                           |                                       |                   | ANOVA/p < .05, FWE correction                             | NA                                                |
| Perico et al. (2011)   | P-BD: 26 (10:16)/27.1 ± 8.5         | NA/N/A                                | 1.5 T/12 mm              | SM2/optimized VBM/Whole brain and ROI | The prefrontal cortex, insula, temporolimbic region, and ACC | ANOVA/p < .05, FWE correction                         | P-BD vs. HC: No differences in whole brain analysis. P-BD > HC: R ACC by ROI. |
|                        | HC: 94 (53:41)/30.2 ± 8.4           |                                       |                          |                                       |                   | ANOVA/p < .05, FWE correction                             | NA                                                |
| Radaelli et al. (2014) | P-BD: 34 (23:11)/43.67 ± 10.28      | 15.73 ± 8.65/28.16 ± 9.80/16.56 ± 8.67/28.82 ± 9.22 | 3 T/8 mm                 | SPM8/VBM/ROI                        | The prefrontal cortex, ACC, insula, and amygdala           | T test/p < .000, uncorrected                        | NA                                                |
|                        | NP-BD: 39 (27:12)/44.05 ± 9.52      |                                       |                          |                                       |                   | ANOVA/p < .05, FWE correction                             | P-BD < NP-BD: DLPFC and insula.                     |
| Ratnanather et al. (2013)| P-BD: 36 (19:17)/39.9 ± 11.1      | NA/17.6 ± 12.7                        | 1.5 T/NA                 | FreeSurfer/Bayesian segmentation/ROI | STG and planum temporale                                 | Multivariate ANOVA/NA                               | P-BD vs. HC: No differences.                         |
|                        | HC: 27 (12:15)/44.0 ± 15.6          |                                       |                          |                                       |                   | ANOVA/NA                                                | NA                                                |
| Salisbury et al. (2007)| P-BD: 21 (7:14)/21.8 ± 5.0         | NA/N/A                                | 1.5 T/NA                 | NA/NA/ROI                            | Heschl gyrus and planum temporale                          | ANOVA/NA                                                | P-BD vs. HC: No difference.                         |
|                        | HC: 32 (22:10)/24.1 ± 3.7           |                                       |                          |                                       |                   | ANOVA/NA                                                | NA                                                |
| Study                  | Subjects n (M:F)/mean ± SD, years | Age of onset/illness duration (years) | Field strength/smoothing | Software/methods (whole brain or ROI) | Areas of interest | Statistical analyses/correction for multiple comparisons | Main findings                                                                 |
|-----------------------|-----------------------------------|--------------------------------------|--------------------------|---------------------------------------|-------------------|----------------------------------------------------------|-------------------------------------------------------------------------------|
| Song et al. (2015)    | P-BD: 44 (19:25)/34.8 ± 14.1       | NA/NA                                | 3 T/8 mm                 | SPM8/VBM/whole brain                  | NA                | ANCOVA/p < .0001, uncorrected                           | P-BD < HC: L MFG, R parietal postcentral gyrus and L fusiform gyrus.          |
|                       | HC: 35 (11:24)/33.9 ± 14.5         |                                      |                          |                                       |                   |                                                          |                                                                                |
| Stanfield et al. (2009)| eP-BD: 17 (NA)/NA                  | NA/NA                                | 1.5 T/12 mm              | SPM8/VBM/SVC                          | The ventral prefrontal and temporal cortex. | NA/p < .05, Bonferroni-adjusted correction | NA                                                                 |
|                       | NP-BD: 49 (NA)/NA                  |                                      |                          |                                       |                   |                                                          |                                                                                |
|                       | fP-BD: 57 (NA)/NA                  |                                      |                          |                                       |                   |                                                          |                                                                                |
|                       | NA/NA                              |                                      |                          |                                       |                   |                                                          |                                                                                |
|                       | fP-BD: 9 (NA)/NA                   |                                      |                          |                                       |                   |                                                          |                                                                                |
|                       | NA/NA                              |                                      |                          |                                       |                   |                                                          |                                                                                |
| Tost et al. (2010)    | P-BD: 30 (13:17)/42.7 ± 13.0        | 28.1 ± 12.1/15.4 ± 9.2, 27.9 ± 7.5/19.8 ± 9.1 | 1.5 T/12 mm              | SPM2/VBM/whole brain                  | NA                | Mancova                                                  | P-BD < HC: Bilateral middle temporal lobe, STG, cingulate, lateral prefrontal cortex and total GM volume. |
|                       | F-P-BD: 15 (7:8)/46.6 ± 11.9        |                                      |                          |                                       |                   |                                                          |                                                                                |
|                       | HC: 44/42/22/39.61 ± 11.7          |                                      |                          |                                       |                   |                                                          |                                                                                |
| Womer et al. (2014)   | P-BD: 21 (13:8)/24.6 ± 3.7          | NA/NA                                | 3 T/NA                   | Freesurfer/automated segmentation/ROI | Caudate, putamen, globus pallidus, nucleus accumbens and thalamus | MANCOVA/p < .05, FDR correction | P-BD vs. HC: No difference. NP-BD < HC: Bilateral caudate and globus pallidus. |
|                       | NP-BD: 12 (4:8)/27 ± 3.8           |                                      |                          |                                       |                   |                                                          |                                                                                |
|                       | HC: 27/13/14/25.5 ± 0.3            |                                      |                          |                                       |                   |                                                          |                                                                                |
| Yuksel et al., 2012   | P-BD: 28 (17:10)/36.4 ± 10.5       | NA/NA                                | 3 T/12 mm                | FSL-VBM/whole brain                   | NA                | GLM/p < .05, FWE correction                              | P-BD vs. HC: No difference.                                                   |
|                       | HC: 43 (28:15)/32.9 ± 11.9         |                                      |                          |                                       |                   |                                                          |                                                                                |

Only the results concerning bipolar patients and GMV are reported (mean ± SD).

Note: Abbreviations: ACC, anterior cingulate cortex; ANCOVA, analysis of covariance; ANOVA, analysis of variance; BD-I, bipolar disorder type I; DLPFC, dorsolateral prefrontal cortex; FDR, false discovery rate correction; FWE, family wise error correction; GLM, general linear model; GRF, Gaussian random field; HC, healthy control; IFG, inferior frontal gyrus; L, left; MCC, multiple comparison correction; MFG, middle frontal gyrus; MTG, middle temporal gyrus; NA, not applicable/available; NP-BD, nonpsychotic bipolar disorder; P-BD, psychotic bipolar disorder; R, right; ROI, region of interest; SFG, superior frontal gyrus; SPM, statistical parametric mapping; STG, superior temporal gyrus; SVC, small volume correction; T, Tesla; VBM, voxel-based morphometry.

a With substance abuse.
b Without substance abuse.
c With suicide attempts.
d With nonattempts.
e With hallucination.
f With delusion.
| Study                  | Bipolar disorder patients | Healthy controls |
|------------------------|---------------------------|------------------|
|                        | N  | Age | Females, % | R handedness, % | Age onset | Illness duration | Subtype I | HAMD-17 | YMRS | PANSS | Medication, % | Lithium, % | Antipsychotic medication, % | N  | Age | Females, % | R handedness, % |
| Altamura et al. (2017) | 17 | 38.7 ± 8.20 | 7.647 | NA | 25.7 ± 7.0 | 11.4 ± 7.0 | 17 | NA | NA | NA | 100.00 | NA | 70.59 | 27 | 34 ± 10.00 | 40.74 | NA |
| Altamura et al. (2017) | 10 | 35.7 ± 13.20 | 10.00 | NA | 25.6 ± 6.5 | 12.1 ± 8.5 | 10 | NA | NA | NA | 100.00 | NA | 60.00 | 27 | 34 ± 10.00 | 40.74 | NA |
| Altamura et al. (2017) | 28 | 31.54 ± 5.54 | 67.9 | NA | NA | NA | 26 | NA | NA | NA | NA | NA | NA | 26 | 27.69 ± 2.94 | 42.3 | NA |
| Chen et al. (2007)     | 14 | NA | NA | 100.00 | NA | NA | 14 | NA | NA | NA | NA | NA | NA | 25 | 38.44 ± 11.05 | NA | 100.00 |
| Chen et al. (2012)     | 18 | NA | NA | 100.00 | NA | NA | NA | 3.2 ± 1.1 | 24.8 ± 6.8 | NA | 100.00 | 83.33 | 16.67 | 27 | 31.3 ± 6.80 | NA | 100.00 |
| Cui et al. (2011)      | 24 | NA | 37.5 | 100.00 | NA | NA | 24 | NA | 25.9 ± 6.86 | NA | 41.67 | 70.83 | 41.67 | 36 | 26.56 ± 6.70 | 41.67 | 100.00 |
| Mleva et al. (2012)    | 17 | 38.24 ± 7.28 | 52.94 | NA | NA | 14.76 ± 9.07 | 17 | NA | NA | NA | 94.12 | NA | 52.94 | 10 | 43.9 ± 9.86 | 60.00 | NA |
| Mleva et al. (2013)    | 115 | 35.4 ± 12.50 | 68.70 | 82.61 | 20.2 ± 8.7 | NA | 115 | 5.7 ± 6.3 | 56.0 ± 13.7 | 93.91 | 22.61 | 71.30 | 200 | 39.8 ± 12.10 | 54.00 | 89.5 |
| Mleva et al. (2017)    | 177 | 36.1 ± 13.1 | 66.10 | 84.70 | 19.8 ± 8.8 | NA | 177 | 5.9 ± 6.7 | 54.2 ± 13.9 | 92.7 | 25.4 | 72.9 | 251 | 36.9 ± 12.1 | 56.6 | 86.5 |
| McDonald et al. (2005) | 37 | 40.7 ± 11.60 | 59.46 | NA | 22.9 ± 5.5 | 17.8 ± 11.3 | 37 | NA | NA | NA | 86.49 | 59.46 | 24.32 | 52 | 39.3 ± 14.80 | 53.85 | NA |
| Nenadic et al. (2015)  | 17 | 37.69 ± 11.13 | 47.06 | NA | 9.9 ± 8.7 | 17 | 2.7 ± 2.3 | 2.7 ± 2.2 | NA | 100.00 | 47.06 | 64.71 | 34 | 34.33 ± 10.62 | 47.06 | NA |
| Perico et al. (2011)   | 26 | 27.1 ± 8.50 | 61.54 | 100.00 | NA | 0.48 ± 0.34 | 26 | 7.6 ± 10.1 | 7.4 ± 10.4 | NA | 73.08 | 23.08 | 42.31 | 94 | 30.2 ± 8.40 | 43.62 | 96.81 |
| Song et al. (2015)     | 44 | 34.8 ± 14.10 | 52.27 | 95.45 | NA | NA | NA | NA | 23.9 ± 12.2 | 70.3 ± 9.1 | 0.00 | 20.45 | 100.00 | 35 | 33.9 ± 14.5 | 68.57 | 94.29 |
| Tost et al. (2010)     | 30 | 42.7 ± 13.00 | 56.7 | NA | 28.1 ± 12.1 | 15.4 ± 9.2 | 30 | NA | 13.1 ± 1.6 | NA | 90.00 | NA | 50.00 | 42 | 42.2 ± 13.60 | 54.76 | NA |
| Tost et al. (2010)     | 15 | 46.6 ± 11.90 | 53.3 | NA | 27.9 ± 7.5 | 19.8 ± 9.1 | 15 | NA | 15.5 ± 17.8 | NA | 86.67 | NA | 66.67 | 42 | 42.2 ± 13.60 | 54.76 | NA |
| Yuksel et al. (2012)   | 27 | 32.9 ± 11.90 | 35.71 | NA | NA | NA | 27 | NA | 22.8 ± 10.3 | 56.1 ± 13.9 | 100.00 | 48.15 | 0.00 | 43 | 36.4 ± 10.50 | 34.88 | NA |

Note: BD-I, bipolar disorder type I; HAMD-17, Hamilton Depression Rating Scale 17-item; NA, not available; PANSS, positive and negative syndrome scale; P-BD, psychotic bipolar disorder; YMRS, Young Mania Rating Scale.
2005), amygdala (Haukvik et al., 2014), or cerebellum (Laidi et al., 2015) between patients with P-BD and patients with NP-BD. Additionally, one study showed more GMV decreases in the left DLPFC in P-BD patients with mood-incongruent persecutory delusions than in P-BD patients with mood-congruent psychosis (Tost et al., 2010).

NP-BD patients versus HC

Only a few studies that compared GMVs between nonpsychotic patients and HC identified GMV deficits in local regions. The studies showed smaller GMVs in the bilateral temporal and left occipital clusters using a whole-brain analysis (Chen et al., 2007), as well as in the bilateral caudate and globus pallidus (Mamah et al., 2016; Womer et al., 2014), and no GMV differences in the right middle frontal gyrus, left inferior frontal gyrus (Ekman et al., 2017), ACC (Javadapour et al., 2007), fusiform gyrus (Ekman et al., 2017), amygdala (Haukvik et al., 2014), or hippocampus (Haukvik et al., 2014; Javadapour et al., 2010) using an ROI-based method in NP-BD patients compared with HC.

3.3.2 | Meta-regression analyses

Using a stringent threshold of \( p < .0005 \) to minimize spurious findings, the meta-regression analyses indicated that greater proportions of female patients were associated with lower GMVs in the right precentral gyrus in P-BD patients (BA = 6, peak MNI = 42, −8, 48, \( Z = −3.364, p < .001, 14 \) voxels; Figure 3(a)) and in P-BDI patients (BA = 6, peak MNI = 46, −8, 44, \( Z = −3.307, p < .001, 18 \) voxels; Figure 3(c)) relative to controls. In addition, greater proportions of patients taking psychotropic medications were associated with lower GMVs in the right insula in P-BD patients (BA = 48, peak MNI = 42, −8, −12, \( Z = −2.887, p < .001, 18 \) voxels; Figure 3(b)) and in P-BDI patients (BA = 48, peak MNI = 40, −6, 6, \( Z = −3.663, p < .0001, 599 \) voxels; Figure 3(d)) relative to controls.

We found no significant associations with age, YMRS scores, lithium usage, antipsychotic administration, or methodological variables, including MRI field strength and image smoothing levels in P-BD patients relative to controls. We found no significant associations with age, antipsychotic medication use, magnetic field strength, or image smoothing levels in P-BDI patients relative to controls.

4 | DISCUSSION

The current review revealed GMV deficits that were mainly involved in the prefronto-temporal and cingulate cortices, precentral gyrus, and insula in P-BD patients relative to HC both qualitatively and quantitatively. Qualitatively, this review identified inconsistent GMV alterations that were mainly in the prefrontal cortex between P-BD patients and NP-BD patients and GMV deficits in the posterior (temporo-occipital) sensory regions and basal ganglia in NP-BD patients relative to HC in a few studies. Meanwhile, no GMV abnormalities were found in the amygdala or hippocampus among P-BD patients, NP-BD patients, and HC. Moreover, this study observed negative effects of the proportion of female patients and psychotropic medication on the GMVs of psychotic patients compared with HC. These findings suggested that P-BD and NP-BD patients presented distinct patterns of brain GM structural abnormalities, indicating the importance of distinguishing the psychotic dimension in neuroimaging studies of BD.

4.1 | Common GMV abnormalities

In this review, GMV deficits in the temporal cortex existed in both P-BD patients and NP-BD patients compared with HC that may be possible neuroanatomical markers of BD. This finding was in line with those of several recent reviews (Maggioni et al., 2017; Wise et al., 2017). The role of the temporal cortex in psychosis has been suggested by a recent large study of BD (Hibar et al., 2018). However,
FIGURE 2  Brain regions differed significantly between groups in the meta-analyses. Images are presented in radiological orientation. (a) Areas of smaller (blue) brain GMVs in patients with psychotic bipolar disorder compared with healthy controls; (b) Areas of smaller (blue) brain GMVs in patients with psychotic bipolar disorder type I compared with healthy controls. ACPG, anterior cingulate/paracingulate cortex; B, bilateral; GMV, gray matter volume; L, left; mCPG, medial cingulate paracingulate gyri; preCG, precentral gyrus; R, right; ROL, rolandic operculum; SFG, superior frontal gyrus. Statistical inferences were made with a voxel-level statistical threshold (p < .005) and a minimum cluster size of more than 10 voxels [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 3  Clusters showing gray matter differences between P-BD and controls and in subgroup analyses that met our criteria for robustness

| Brain regions                    | Maximum cluster | MNI coordinates  | SDM-Z   | p value | Voxels | Breakdown                                      |
|----------------------------------|------------------|------------------|---------|---------|--------|------------------------------------------------|
| P-BD > HC                        | None             |                  |         |         |        |                                                |
| P-BD < HC                        | Right insula, BA 48 | 42, 8, −12 | −2.608  | <.001   | 218    | Right insula, BA 48 (undefined), BA 47         |
|                                  | Left insula, BA 48 | −46, 4, 2  | −2.425  | <.001   | 22     | Right temporal pole, superior temporal gyrus   |
|                                  | Right superior frontal gyrus, medial, BA 10 | 4, 52, 26 | −2.44   | <.001   | 131    | Left superior frontal gyrus, medial, BA 10    |
|                                  | Right precentral gyrus, BA 4 | 46, −10, 42 | −2.467  | <.001   | 85     | Left anterior cingulate/paracingulate gyri, BA 10 |
|                                  | Left median cingulate/paracingulate gyri | −10, −30, 46 | −2.633  | <.001   | 97     | Left median cingulate/paracingulate gyri       |
| P-BDI > controls                 | None             |                  |         |         |        |                                                |
| P-BDI < controls                 | Right insula     | 44, 6, −12     | −2.682  | <.001   | 250    | Right insula, BA 48                            |
|                                  | Left insula, BA 48 | −42, 0, 4     | −2.798  | <.001   | 172    | Left insula, BA 48                             |
|                                  | Left superior frontal gyrus, medial, BA 10 | −4, 54, 8  | −2.484  | <.001   | 120    | Left superior frontal gyrus, medial, BA 10    |
|                                  | Left median cingulate/paracingulate gyri | −12, −34, 40 | −2.74   | <.001   | 86     | Left median cingulate/paracingulate gyri       |
|                                  | Right precentral gyrus, BA 6 | 48, −6, 42  | −2.53   | <.001   | 65     | Right precentral gyrus, BA 6                   |
|                                  | Right rolandic operculum, BA 48 | 50, 2, 6   | −2.581  | <.001   | 51     | Right rolandic operculum, BA 48                |
|                                  | Right median network, cingulum | 10, −10, 38 | −2.703  | <.001   | 20     | Right median cingulate/paracingulate gyri       |

Note: P-BD, psychotic bipolar disorder; P-BDI, psychotic bipolar disorder type I.
one morphologic study did not find any abnormality in the surface area of the superior temporal gyrus (Ratnanather et al., 2013) in P-BD patients relative to HC. This discrepancy may have been partially due to differences in the study designs: Ratnanather et al. employed a surface-based approach at the regional level, which was in contrast to the voxel-based approach of our study, and it inspected different morphological parameters. In this respect, future parallel voxel-based and region-based investigations are encouraged to obtain a more complete understanding of the GM correlates of psychosis in BD.

Notably, our review consistently showed negative findings in the subcortical amygdalar and hippocampal regions in P-BD and NP-BD patients. Similarly, no abnormalities in the shape of the hippocampus or the amygdala (Mahon et al., 2015; Mamah et al., 2016) have been demonstrated in P-BD patients relative to HC using ROIs. However, VBM analyses may have insufficient sensitivities in detecting between-group differences in small limbic structures (e.g., the amygdala and hippocampus) that are implicated in the pathologies of psychiatric disorders (Bergouignan et al., 2009). Therefore, further research is needed to confirm these considerations.

4.2 | Specific GMV abnormalities

Our study consistently recognized P-BD as a subset of BD with specific regional GMV alterations. Partly consistent with previous structural MRI studies on psychosis in BD (Maggioni et al., 2017), we found more extensive GMV deficits in the prefrontal-temporal and cingulate cortices, as well as in the precentral gyrus and the insula in psychotic than in nonpsychotic patients compared with HC. The brain abnormalities associated with genetic risks of developing BD were limited to GM loss in the frontal lobe and the insula (Van der Schot et al., 2010). The studies suggested varying findings in BD, with the psychotic phenotype showing GMV alterations mainly in fronto-temporal regions, similar to those observed in schizophrenia (Gong, Lui, & Sweeney, 2016; Zhang et al., 2015). Lower cortical complexity in the frontal cortex emerged as a common characteristic in BD and schizophrenia patients (Squarcina et al., 2015). Additionally, within the P-BD spectrum, mood-incongruent features have been associated with GMV deficits in regions that seem to be involved in schizophrenia (Keramatian et al., 2016), supporting the hypothesis of a dimensional continuity among psychotic BD and schizophrenia. The GMV deficits in the cingulate cortex were demonstrated in this review, despite the fact that no abnormalities were found in the surface area of the ACC subregions in P-BD patients relative to HC (Fornito et al., 2009).

Research has also suggested that certain morphological alterations in the ACC may be related to a high risk of psychosis (Bersani et al., 2014; Park et al., 2013). The lateral prefrontal dysfunction might be specifically associated with vulnerability to psychosis, particularly to delusions and hallucinations (Redpath, Cooper, & Lawrie, 2013). A resting-state functional MRI study of P-BD and schizophrenia suggested a role of hypoactivity of the prefrontal and cingulate cortices in the pathogenesis of major psychoses, possibly leading to abnormalities in cognition, behavior, and emotion (Lui et al., 2015). The precentral gyrus is involved in cognitive processing and emotion regulation (Seo et al., 2014), and damage to this area can cause emotion-recognition deficits (Adolphs, 2010). Overall, our study showed a possible role of the fronto-temporal and cingulate cortices and of the insula in P-BD patients, and further investigations are needed to confirm these findings and to determine how the deficits in these regions are associated with the severity of psychotic symptomatology.

The direct comparison of the two subtypes of BD highlighted inconsistent prefrontal GMV alterations that was also specifically
associated with psychosis in BD. Studies demonstrated that P-BD patients presented thinner cortices in the PFC (Foland-Ross et al., 2011), while no differences were found in the cortical thickness or surface area in cortical ROIs relative to NP-BD patients (Hibar et al., 2018). Interestingly, relative to the mood-congruent psychotic features in BD, mood-incongruent psychotic features were found to be associated with GMV reductions in the left middle orbitofrontal gyrus, middle temporal gyrus, right inferior parietal gyrus, and fusiform gyrus in subjects 16–34 years of age (Keramatian et al., 2016), suggesting the PFC as one of the regions with GMV deficits that may be proportional to the severity of psychotic symptomatology. Meanwhile, our review preliminarily suggested GM deficits in the local regions of the temporoooccipital regions and the basal ganglia in nonpsychotic patients compared with HC only in a few studies. Similar to our findings, studies have also found shape abnormalities in the caudate in NP-BD patients relative to HC (Womer et al., 2014) and GM deficits in the caudate and globus pallidus in NP-BD patients compared with schizophrenia patients (Mamah et al., 2016; Womer et al., 2014). In light of the limited research on NP-BD, these preliminary findings need to be further investigated in future research.

The abovementioned findings indicated that P-BD and NP-BD patients showed specific GM deficits, which were further extended in the psychotic group, compared with controls. These findings were in favor of the hypothesis of the presence of specific GM abnormalities in P-BD, suggesting the importance of classifying BD based on the psychotic dimension. From a clinical point of view, these important GM alterations might be related to the lower treatment response rate during the acute phase and to the more difficult stabilization in the long-term course, and they may compose a neuroanatomical basis for the clinical and psycho-social detrimental effects of psychosis in BD.

In addition, the P-BD group and P-BDI subgroup quantitatively indicated similar alterations at the neuroanatomical level. Our findings supported the viewpoint of a review to a certain extent (Parker & Fletcher, 2014). In their review, Parker and Fletcher pointed out that DSM-V decision rules were similar to those used by DSM-IV to differentiate BDI and BDII. They argued that, as for DSM-IV, psychotic features were among the only features that provided any "cleavage" between DSM-V definitions of manic and hypomanic episodes (thus assignment of BDI and BDII diagnoses).

### 4.3 Effects of demographic and clinical variables

Our meta-regression analysis revealed that a greater percentage of female patients and a higher proportion of patients taking psychotropic medication among P-BD and P-BDI patients were associated with smaller GMVs in the right precentral gyrus and the right insula, respectively. Among first-episode P-BD patients, increased thickness in the right ACC was found to exist in male but not female patients compared with HC (Fornito et al., 2009). A meta-analysis also reported gender differences in the GM volumes and densities of the planum temporale, insula, amygdala, and hippocampus, with larger global brain volumes in males than in females on average (Ruigrok et al., 2014), suggesting that the precentral gyrus might be one of the candidate regions for understanding sex-biased psychiatric disorders.

Considering the medication effects, a negative effect of medication administration on the GMV of the right insula was found in patients with P-BD and P-BDI. Medication has been proposed as a partial explanation for the inconsistencies in brain structural findings in BD (Bora et al., 2010). Our study indicated that psychotropic medication usage might be one of the important contributors to the heterogeneity across studies in BD. One review suggested that mood stabilizers, antipsychotics and antidepressants could be neuroprotective in patients and animal models of psychiatric disorders (Hunsberger, Austin, Henter, & Chen, 2009), whereas other reviews reported little or no effect of psychopharmacological treatment on structural and functional brain findings in BD patients (Hafeman, Chang, Garrett, Sanders, & Phillips, 2012; Ivleva et al., 2013). No evidence suggested relationships between antidepressants, antipsychotics or mood stabilizers and alterations in cortical thickness or brain GMV (Bora et al., 2010; Fornito et al., 2009; Hatton et al., 2012; Nenadic et al., 2015; Nery et al., 2009). Thus, the influence of psychotropic medication on alterations in GMV in P-BD remains contentious.

Based on the above findings, these data further raised the possibility that demographics and psychotropic drugs could be major confounding factors in both cross-sectional and longitudinal volume comparisons and might account for at least some of the inconsistencies and wide volumetric variability in affective psychosis, especially regarding BD (Hunsberger et al., 2009).

This review had some limitations. First, we could not determine whether these structural alterations were part of the pathogenesis or a consequence of the disorder because of the nature of cross-sectional studies. Second, the patients in the included studies may have been recruited in different phases, and they were on various psychotropic medications, each of which could be a potential confounder. Third, from a clinical perspective there are no universally acclaimed criteria for defining a psychotic bipolar subtype. In the included studies, the authors defined P-BD using different criteria (e.g., current vs. lifetime psychotic symptoms, including vs. excluding psychotic symptoms in manic episodes). It may impact the results of the current meta-analysis. Furthermore, the current study did not perform a quantitative meta-analysis between P-BD and NP-BD patients or between NP-BD patients and HC due to only few studies exploring the between-group GMV differences. In addition, only articles written in English were considered.

### 5 Conclusions

The present review suggested the presence of specific cortical GMV abnormalities in P-BD and NP-BD patients compared with controls. The presence of psychosis in BD was associated with smaller cortical GMVs, involving the prefronto-temporal and cingulate cortices, as well as the precentral gyrus and the insula. Gender and psychotropic medication may have effects on GMV in psychotic patients. Our findings supported the hypothesis that BD with psychotic features may represent a neurobiologically homogeneous subphenotype of the disorder, suggesting the importance of distinguishing the psychotic dimension in neuroimaging studies of BD. Uniform multimodal imaging techniques, coupled with genetic and molecular testing, and
prospective and longitudinal studies are needed to elucidate the neurobiological mechanisms underlying psychotic features in BD and to further clarify the trajectories of neurobiological changes and their associations with clinical features and specific medication exposure (e.g., lithium) over time.

CONFLICT OF INTERESTS

The authors declare that they have no conflict of interests.

AUTHOR CONTRIBUTIONS

Zhiyun Jia contributed to the conception of the study. Xiuli Wang, Fangfang Tian and Zhiyun Jia contributed significantly to analysis and manuscript preparation; Xiuli Wang and Fangfang Tian performed the data analyses and the drafting of the article. Song Wang, Bochao Cheng, Lihua Qiu, Manxi He, Hongming Wang, Jing Dai and Mingjun Duan contributed to interpretation and completion of the figures and tables. All authors read and approved the final manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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