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Paolo Brambilla, *Section Editor*

# Exploring the neuroanatomical bases of psychotic features in bipolar disorder

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Although bipolar disorder (BD) is traditionally conceptualised as one diagnostic entity, the heterogeneity of pathophysiological manifestations in BD suggests the need to classify the subtypes of the illness based on neural markers. Specifically, the presence of psychotic symptoms seems to be relevant for the clinical outcome and may have specific neuroanatomical bases. The main objective of the present review was to assess whether the distinction between psychotic BD (PBD) and non-psychotic BD (NPBD) can improve the identification of the neurobiological markers of this complex illness. To this end, we summarised the findings from the magnetic resonance imaging studies that explored the cerebral correlates of psychosis in BD in terms of grey matter volume (GMV). Overall, the results suggest the presence of peculiar GMV differences between PBD and NPBD. Specifically, psychosis in BD seems to be associated with cortical GMV deficits compared with both healthy controls and NPBD, mainly in the frontal region. Conversely, NPBD patients showed GMV deficits in selective regions of the basal ganglia when compared with the other groups. Taken together, this evidence confirms the importance to classify BD based on the psychotic dimension, which may have a specific neurobiological architecture that partially overlaps across multiple psychotic disorders.

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Although bipolar disorder (BD) is traditionally considered as a discrete diagnostic entity, its phenotypic variability suggests the need to redefine this illness based on pathophysiology in the framework of research domain criteria (RDoC) (Insel *et al.* 2010). A recent focus has been placed on the dimension of psychotic symptoms, which is relevant for the clinical outcome of BD and may be neurobiologically determined. Psychotic BD (PBD) and non-psychotic BD (NPBD) may indeed represent two distinct biological subtypes of the illness, with the former clinically and genetically closer to schizophrenia (Mamah *et al.* 2016). The non-consideration of this factor may have also contributed to the heterogeneous findings of neuroimaging studies on BD (Ellison-Wright & Bullmore, 2010).

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Here, in the attempt to clarify the neuroanatomical differences within BD, we summarise the results of the few magnetic resonance imaging (MRI) studies that investigated grey matter volume (GMV) in PBD and NPBD. We conducted a bibliographic research on PubMed using 'bipolar psychosis MRI' and 'psychotic non-psychotic bipolar' as keywords. From the resulting lists of works (321 and 147, respectively), we selected the original articles that compared PBD and NPBD patients between each other and possibly to healthy controls and/or schizophrenia patients in terms of GMV. Only studies on adult patients (mean age >18 years) were considered.

The methods and results of the eight papers that met the inclusion criteria are summarised in Table 1. In these studies, the neuroanatomy was investigated at the voxel-level and/or in regions of interest. Half of them used voxel-based morphometry to locally compare GMV in the whole brain (Chen *et al.* 2007; Keramatian *et al.* 2016; Neves Mde *et al.* 2016; Ekman *et al.* 2017), whereas the other half compared GMV in a set of pre-defined subcortical regions (Strasser *et al.* 2005; Womer *et al.* 2014; Mamah *et al.* 2016) or in the cerebellum (Laidi *et al.* 2015). Except from Neves *et al.* (2016), who merely compared PBD with NPBD, all the works included a group of healthy subjects, and three of them also patients with schizophrenia.

Concerning global brain measures, all the studies that investigated total GMV agreed on the absence of significant differences among PBD, NPBD and healthy subjects (Chen *et al.* 2007; Keramatian *et al.* 2016; Mamah *et al.* 2016). However, the latter study found higher total GMV in both PBD and NPBD compared with schizophrenia (Mamah *et al.* 2016). As per the total intracranial volume, the findings are less consistent. Keramatian *et al.* (2016), who distinguished BD patients with mood congruent and mood incongruent psychosis, found lower total intracranial volume in mood congruent PBD compared with NPBD and healthy controls, whereas Mamah *et al.* (2016) reported significant differences only between PBD and schizophrenia, with higher intracranial volume in the former group.

Focusing on the cerebral cortex, the results of the voxel-based studies suggest the presence of specific features in PBD and NPBD. Except from Chen *et al.* (2007), who found two clusters of higher GMV in PBD than in controls, in right precentral and middle frontal gyri, the other studies did not report regions of increased GMV in the BD groups compared with the control group (Keramatian *et al.* 2016; Ekman *et al.* 2017). On the contrary, GMV deficits in PBD compared with HC were found in the middle temporal (Chen *et al.* 2007) and fusiform (Ekman *et al.* 2017) gyri of the left hemisphere, as well as bilaterally in regions of the prefrontal (Keramatian *et al.* 2016; Ekman *et al.* 2017) and anterior cingulate cortices (Keramatian *et al.* 2016). Only one study reported GMV deficits in NPBD compared with healthy subjects, in temporal and occipital clusters (Chen *et al.* 2007).

The direct comparisons between PBD and NPBD in terms of cortical GMV led to results that are only partially consistent. Only in the work from Chen *et al.* (2007) PBD showed increased GMV compared with NPBD in a set of clusters located in bilateral frontal cortex and right cuneus. Opposite findings emerged from Neves *et al.* (2016) and Ekman *et al.* (2017), reporting in PBD compared with NPBD GMV deficits in left fusiform and inferior frontal gyri and in right prefrontal, insular and parieto-occipital regions. Interestingly, Keramatian *et al.* (2016) found GMV deficits in mood incongruent PBD compared with both mood congruent PBD and NPBD in a set of cortical regions, as well as in the cerebellum. However, Laidi *et al.* (2015) did not find differences in cerebellar GMV between PBD and NPBD.

The studies that explored the subcortical structures reported no differences in hippocampal, amygdala and thalamic volumes among patients with PBD, NPBD and schizophrenia and healthy subjects (Strasser *et al.* 2005; Womer *et al.* 2014; Mamah *et al.* 2016). Interestingly, Womer *et al.* (2014) and Mamah *et al.* (2016) suggested GMV deficits in NPBD, specifically in the caudate when compared with controls, and in the globus pallidus when compared with PBD. Reduced GMV in the right caudate body of NPBD compared with PBD was also described (Chen *et al.* 2007). Moreover, GMV deficits in the caudate, globus pallidus and putamen emerged in BD compared with schizophrenia (Womer *et al.* 2014; Mamah *et al.* 2016), raising questions on the relationship among basal ganglia and psychotic symptomatology.

Taken together, these findings suggest the presence of GMV differences between PBD and NPBD, with the two groups showing specific abnormalities when compared with healthy controls. Indeed, the presence of psychosis in BD seems to be associated with reduced cortical GMV, spanning from prefrontal to temporo-occipital cortices, and increased subcortical GMV, mainly in the basal ganglia. Overall, this evidence confirms the importance to classify BD based on the psychotic dimension, which may have a specific neurobiological architecture that partially overlaps across PBD and schizophrenia. Future larger and longitudinal studies are needed to further explore fronto-striatal and fronto-limbic dysconnectivity in first episode psychotic patients and in subjects at risk to develop schizophrenia or BDs to have a better perspective on the neural basis of psychosis spectrum.

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**Table 1.** *Results of GMV comparisons among psychotic and non-psychotic bipolar patients as well as with healthy controls or schizophrenia patients. Only the results concerning bipolar patients and GMV or total intracranial volume are reported. Correlations among structural and clinical variables are listed only if relative to the bipolar subgroups*

| Study | Sample and acquisition | Structural measures | Statistical analyses | Results |
|---|---|---|---|---|
| Chen *et al.* (2007) | *Subjects:* 24 BD patients (38.21 ± 11.04 years) #PBD = 14, #NPBD = 10.<br>25 HC (38.44 ± 11.05 years).<br>*MR scanner:* 1.5 T GE signa scanner | *Analysis:* optimised VBM with SPM2 software.<br>*Parameters:* total GMV, local GMV (whole brain) | ANCOVA with age, sex and TIV covariates | *Significance:* $p < 0.001$, cluster >200 voxels.<br>PBD > HC: right precentral gyrus, right middle frontal gyrus.<br>PBD < HC: left middle temporal gyrus.<br>NPBD < HC: left and right middle temporal gyrus, left middle occipital gyrus, left superior occipital gyrus.<br>PBD > NPBD: right caudate body, left superior frontal gyrus, right precentral gyrus, right middle frontal gyrus, right precuneus, left anterior cingulate |
| Ekman *et al.* (2017) | *Subjects:* 167 BD patients. #PBD = 85 (37 ± 13 years), #NPBD = 82 (40 ± 13 years).<br>102 HC (39 ± 15 years).<br>*MR scanner:* 1.5 T GE Signa Excite scanner | *Analysis:* VBM with SPM12 software.<br>*Parameters:* local GMV (whole brain) | *PBD v. NPBD:* two sample *t*-test with age, sex, scanner filter, ADHD diagnosis, months of AP treatment, current lithium treatment as covariates.<br>Global normalisation using TIV.<br>*PBD/NPBD v. HC:*<br>Mask: only the significant clusters of PBD *v.* NPBD.<br>Design: two sample *t*-test with age, sex and scanner filter covariates. Global normalisation using TIV | *Significance:* $p < 0.05$, FWE corrected.<br>PBD < NPBD: left fusiform gyrus, right DLPFC, left inferior frontal gyrus (pars triangularis), right parieto-occipital area.<br>PBD < HC: left fusiform gyrus, right DLPFC, left inferior frontal gyrus (part triangularis)<br>NPBD < HC: / |
| Keramatian *et al.* (2016) | *Subjects:* 55 first episode manic patients. #MCPBD = 16 (23.38 ± 4.46 years), #MIPBD = 32 (22.69 ± 4.72 years),<br>#NPBD = 7 (22.71 ± 3.4 years).<br>56 HC (22.28 ± 3.61 years).<br>*MR scanner:*<br>3 T Philips Achieva scanner | *Analysis:* VBM with SPM8 software. Confirmatory ROI analysis.<br>*Parameters:* total GMV, TIV, bilateral anterior cingulate volume, local GMV (whole brain) | *Global/regional measures:*<br>ANCOVA with age, sex and TIV covariates.<br>*VBM design:* age and sex covariates.<br>Pairwise comparisons with independent two sample *t*-tests | *Significance:*<br>°: $p < 0.05$, Bonferroni corrected (global/regional)<br>**: $p < 0.05$, FWE and cluster corrected (VBM)<br>*: $p < 0.001$, >100 voxels (VBM)<br>PBD < HC: bilateral anterior cingulate**, medial PFC**.<br>MCPBD < HC: TIV°.<br>MCPBD < NPBD: TIV°.<br>MCPBD + NPBD > MIPBD: left middle temporal gyrus*, right inferior parietal gyrus*, right fusiform gyrus*, left middle orbitofrontal gyrus* and cerebellum* |

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|---|---|---|---|---|
| Laidi *et al.* (2015) | *Subjects:* 53 PBD patients (35.4 ± 10.7 years), 62 NPBD patients (37.3 ± 10.6 years), 32 SCZ patients (31.4 ± 10.2 years), 52 HC (37.2 ± 11.8 years)<br>*MR scanner:* 3 T Siemens Tim Trio scanner | *Analysis:* ROI analysis with Freesurfer software.<br>*Parameters:* GMV of left and right cerebellum | *BD v. HC v. SCZ* (*French site*)<br>ANCOVA with age, sex and TIV covariates.<br>*PBD v. NPBD* (*multicentric sample*)<br>ANCOVA with age, sex, TIV and site covariates | *Significance:* $p < 0.05$, Bonferroni correction<br>SCZ < BD: left and right cerebellar GMV.<br>SCZ < HC: left and right cerebellar GMV.<br>PBD *v.* NPBD: no significant differences |
| Mamah *et al.* (2016) | *Subjects:* 49 PBD patients, (25.2 ± 3.6 years),<br>24 NPBD patients (26.2 ± 3.7 years), 52 SCZ patients (26.1 ± 4.1 years), 12 ST patients (22.4 ± 3.5 years), 40 HC (24.9 ± 5 years).<br>*MR scanner:* 3 T Siemens Tim Trio scanner | *Analysis:* ROI analysis with Freesurfer software and LDDMM.<br>*Parameters:* TIV, total GMV, GMV of hippocampus, amygdala, caudate, putamen, globus pallidus, nucleus accumbens and thalamus | Repeated measures (hemisphere) ANCOVA with age, sex and TIV covariates | *Significance:*<br>Volume: $p < 0.05$<br>NPBD < HC: bilateral caudate GMV, bilateral globus pallidus GMV<br>PBD > SCZ: total GMV, TIV.<br>PBD < SCZ: total GMV. Bilateral caudate GMV, bilateral putamen GMV, bilateral globus pallidus GMV.<br>NPBD > SCZ: total GMV.<br>PBD > NPBD: left globus pallidus.<br>NPBD < SCZ: total GMV, bilateral caudate GMV, bilateral putamen GMV, bilateral globus pallidus GMV |
| Neves *et al.* (2016) | *Subjects:* 9 PBD patients (37.66 ± 12.07 years), 12 NPBD patients (39.92 ± 14.99 years).<br>*MR scanner:* 1.5 T Philips scanner | *Analysis:* VBM and ROI analysis with SPM8.<br>*Parameters:* GMV in whole brain + regional GMV in orbitofrontal cortex, ventral prefrontal cortex, cingulate gyrus, fusiform gyrus, superior temporal sulcus, amygdala, insula and thalamus | GLM design with psychosis factor and total GMV covariate | *Significance:* $p < 0.05$. FWE correction in whole brain analyses. SVC correction for ROI analysis.<br>PBD < NPBD: right posterior insula (ROI analysis), significant also after controlling for age, sex and years of education |
| Strasser *et al.* (2005) | *Subjects:* 23 PBD patients (36.39 ± 11.7 years), 15 NPBD patients (40.8 ± 14.1 years), 33 SCZ patients (41.67 ± 14 years), 44 HC (39.61 ± 11.7 years).<br>*MR scanner:* 1.5 T GE Signa scanner | *Analysis:* ROI analysis with MEASURE software.<br>*Parameters:* volume of hippocampus and lateral and third ventricles | MANCOVA with hippocampal and ventricle volumes and TBV covariate. *Post hoc* analysis with Bonferroni LSD | *Significance:* $p < 0.05$.<br>No significant pairwise differences in any of the ROIs for PBD and NPBD |

*Continued*

**Table 1.** *Continued*

| Study | Sample and acquisition | Structural measures | Statistical analyses | Results |
|---|---|---|---|---|
| Womer *et al.* (2014) | *Subjects:* 21 PBD patients (24.6 ± 3.7 years), 12 NPBD patients (27 ± 3.8 years), 32 SCZ-S patients (25.8 ± 4.1 years), 27 HC (25.5 ± 0.3 years).<br>*MR scanner:* 3 T Siemens Tim Trio scanner | *Analysis:* ROI analysis with Freesurfer software and LDDMM.<br>*Parameters:* GMV of caudate, putamen, globus pallidus, nucleus accumbens and thalamus | MANOVA with basal ganglia and thalamus volumes with group factor and age, sex and cortical GMV covariates.<br>Repeated measures (hemisphere) ANOVA with group effect and age, gender and cortical GMV covariates | Volume: $p < 0.05$<br>No significant pairwise differences in any of the ROIs for PBD and NPBD.<br>BD < SCZ-S: left caudate GMV, bilateral globus pallidi GMV.<br>BD < HC: left caudate GMV, bilateral globus pallidi GMV.<br>NPBD < SCZ-S: bilateral caudate GMV, bilateral globus pallidi GMV.<br>PBD < SCZ-S: left globus pallidus GMV.<br>NPBD < PBD: right globus pallidus GMV.<br>NPBD < HC: bilateral caudate volumes |

GMV, grey matter volume; TIV, total intracranial volume; TBV, total brain volume; BD, bipolar disorder; PBD, psychotic bipolar disorder; NPBD, non-psychotic bipolar disorder; MCPBD, mood congruent psychotic bipolar disorder; MIPBD, mood incongruent psychotic bipolar disorder; HC, healthy controls; SCZ, schizophrenia; SCZ-S, schizophrenia spectrum; ST, schizotypal personality disorder; ADHD, attention deficit hyperactivity disorder; AP, antipsychotic; VBM, voxel-based morphometry; ROI, region of interest; LDDMM, Large Deformation Diffeomorphic Metric Mapping; ANOVA, analysis of variance; ANCOVA, analysis of covariance; MANOVA, multivariate analysis of variance; MANCOVA, multivariate analysis of covariance; FWE, family wise error; SVC, small volume correction; LSD, least significant difference; FDR, false discovery rate; DLPFC, dorsolateral prefrontal cortex.


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## Conflict of Interest

None.

## Ethical statement

The authors declare that no human or animal experimentation was conducted for this work.

## References


**Chen X, Wen W, Malhi GS, Ivanovski B, Sachdev PS** (2007). Regional gray matter changes in bipolar disorder: a voxel-based morphometric study. *Australian and New Zealand Journal of Psychiatry* **41**, 327–336.

**Ekman CJ, Petrovic P, Johansson AG, Sellgren C, Ingvar M, Landen M** (2017). A history of psychosis in bipolar disorder is associated with gray matter volume reduction. *Schizophrenia Bulletin* **43**, 99–107.

**Ellison-Wright I, Bullmore E** (2010). Anatomy of bipolar disorder and schizophrenia: a meta-analysis. *Schizophrenia Research* **117**, 1–12.

**Insel T, Cuthbert B, Garvey M, Heinssen R, Pine DS, Quinn K, Sanislow C, Wang P** (2010). Research domain criteria (RDoC): toward a new classification framework for research on mental disorders. *American Journal of Psychiatry* **167**, 748–751.

**Keramatian K, Dhanoa T, McGirr A, Lang DJ, Honer WG, Lam RW, Yatham LN** (2016). Structural brain changes in first episode mania with and without psychosis: data from the systematic treatment optimization program for early mania (STOP-EM). *The World Journal of Biological Psychiatry*, 1–11.

**Laidi C, d'Albis MA, Wessa M, Linke J, Phillips ML, Delavest M, Bellivier F, Versace A, Almeida J, Sarrazin S, Poupon C, Le Dudal K, Daban C, Hamdani N, Leboyer M, Houenou J** (2015). Cerebellar volume in schizophrenia and bipolar I disorder with and without psychotic features. *Acta Psychiatrica Scandinavica* **131**, 223–233.

**Mamah D, Alpert KI, Barch DM, Csernansky JG, Wang L** (2016). Subcortical neuromorphometry in schizophrenia spectrum and bipolar disorders. *Neuroimage: Clinical* **11**, 276–286.

**Neves Mde C, Duarte DG, Albuquerque MR, Nicolato R, Neves FS, Souza-Duran FL, Busatto G, Correa H** (2016).

Neural correlates of hallucinations in bipolar disorder. *Revista Brasileira de Psiquiatria* **38**, 1–5.

**Strasser HC, Lilyestrom J, Ashby ER, Honeycutt NA, Schretlen DJ, Pulver AE, Hopkins RO, Depaulo JR, Potash JB, Schweizer B, Yates KO, Kurian E, Barta PE, Pearlson GD** (2005). Hippocampal and ventricular volumes in psychotic and nonpsychotic bipolar patients compared with schizophrenia patients and community control subjects: a pilot study. *Biological Psychiatry* **57**, 633–639.

**Womer FY, Wang L, Alpert KI, Smith MJ, Csernansky JG, Barch DM, Mamah D** (2014). Basal ganglia and thalamic morphology in schizophrenia and bipolar disorder. *Psychiatry Research: Neuroimaging* **223**, 75–83.

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