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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Here, in the attempt to clarify the neuroanatomical differences within BD, we summarise the results of the few magnetic resonance imaging (fMRI) 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 gyr 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 BD, 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 temporoparietal 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.
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.

<table>
<thead>
<tr>
<th>Study</th>
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<td>Chen et al. (2007)</td>
<td>Subjects: 24 BD patients (38.21 ± 11.04 years) #PBD = 14, #NPBD = 10. 25 HC (38.44 ± 11.05 years). MR scanner: 1.5 T GE signa scanner</td>
<td>Analysis: optimised VBM with SPM2 software. Parameters: total GMV, local GMV (whole brain)</td>
<td>ANCOVA with age, sex and TIV covariates</td>
<td><strong>Significance: p &lt; 0.001, cluster &gt;200 voxels. PBD &gt; HC: right precentral gyrus, right middle frontal gyrus. PBD &lt; HC: left middle temporal gyrus. NPBD &lt; HC: left and right middle temporal gyrus, left middle occipital gyrus, left superior occipital gyrus. PBD &gt; NPBD: right caudate body, left superior frontal gyrus, right precentral gyrus, right middle frontal gyrus, right precuneus, left anterior cingulate</strong></td>
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<td>Ekman et al. (2017)</td>
<td>Subjects: 167 BD patients. #PBD = 85 (37 ± 13 years), #NPBD = 82 (40 ± 13 years). 102 HC (39 ± 15 years). MR scanner: 1.5 T GE Signa Excite scanner</td>
<td>Analysis: VBM with SPM12 software. Parameters: local GMV (whole brain)</td>
<td>PBD v. NPBD: two sample t-test with age, sex, scanner filter, ADHD diagnosis, months of AP treatment, current lithium treatment as covariates. Global normalisation using TIV. <strong>PBD/NPBD v. HC:</strong> Mask: only the significant clusters of PBD v. NPBD. Design: two sample t-test with age, sex and scanner filter covariates. Global normalisation using TIV <strong>PBD &lt; NPBD: left fusiform gyrus, right DLPFC, left inferior frontal gyrus (pars triangularis), right parieto-occipital area. PBD &lt; HC: left fusiform gyrus, right DLPFC, left inferior frontal gyrus (part triangularis) NPBD &lt; HC: /</strong></td>
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<td>Keramatian et al. (2016)</td>
<td>Subjects: 55 first episode manic patients. #MCPBD = 16 (23.38 ± 4.46 years), #MIPBD = 32 (22.69 ± 4.72 years), #NPBD = 7 (22.71 ± 3.4 years). 56 HC (22.28 ± 3.61 years). MR scanner: 3 T Philips Achieva scanner</td>
<td>Analysis: VBM with SPM8 software. Confirmatory ROI analysis. Parameters: total GMV, TIV, bilateral anterior cingulate volume, local GMV (whole brain)</td>
<td>Global/regional measures: ANCOVA with age, sex and TIV covariates. VBM design: age and sex covariates. Pairwise comparisons with independent two sample t-tests</td>
<td><strong>Significance: °: p &lt; 0.05, Bonferroni corrected (global/regional) <strong>: p &lt; 0.05, FWE and cluster corrected (VBM) #: p &lt; 0.001, &gt;100 voxels (VBM) PBD &lt; HC: bilateral anterior cingulate</strong>, medial PFC</strong>. MCPBD &lt; HC: TIV**. MCPBD &lt; NPBD: TIV**: MCPBD + NPBD &gt; MIPBD: left middle temporal gyrus*, right inferior parietal gyrus*, right fusiform gyrus*, left middle orbitofrontal gyrus* and cerebellum*</td>
</tr>
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| Laidi et al.     | **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) | **Analysis:** ROI analysis with Freesurfer software. **Parameters:** GMV of left and right cerebellum | **BD v. HC v. SCZ (French site)** ANCOVA with age, sex and TIV covariates. **PBD v. NPBD (multicentric sample)** ANCOVA with age, sex, TIV and site covariates | **Significance:** $p < 0.05$, Bonferroni correction  
SCZ < BD: left and right cerebellar GMV.  
SCZ < HC: left and right cerebellar GMV.  
PBD v. NPBD: no significant differences |
|                  | **MR scanner:** 3 T Siemens Tim Trio scanner                                           |                                                                                      |                                                           |                                                                        |
| Mamah et al.     | **Subjects:** 49 PBD patients, (25.2 ± 3.6 years), 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). | **Analysis:** ROI analysis with Freesurfer software and LDDMM. **Parameters:** TIV, total GMV, GMV of hippocampus, amygdala, caudate, putamen, globus pallidus, nucleus accumbens and thalamus | Repeated measures (hemisphere) **ANOVA** with age, sex and TIV covariates | **Significance:** Volume: $p < 0.05$  
NPBD < HC: bilateral caudate GMV, bilateral globus pallidus GMV  
PBD > SCZ: total GMV, TIV  
PBD < SCZ: total GMV. Bilateral caudate GMV, bilateral putamen GMV, bilateral globus pallidus GMV  
NPBD > SCZ: total GMV. PBD > NPBD: left globus pallidus.  
NPBD < SCZ: total GMV, bilateral caudate GMV, bilateral putamen GMV, bilateral globus pallidus GMV |
|                  | **MR scanner:** 3 T Siemens Tim Trio scanner                                           |                                                                                      |                                                           |                                                                        |
| Neves et al.     | **Subjects:** 9 PBD patients (37.66 ± 12.07 years), 12 NPBD patients (39.92 ± 14.99 years) | **Analysis:** VBM and ROI analysis with SPM8. **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.  
PBD < NPBD: right posterior insula (ROI analysis), significant also after controlling for age, sex and years of education |
|                  | **MR scanner:** 1.5 T Philips scanner                                                   |                                                                                      |                                                           |                                                                        |
| Strasser et al.  | **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). | **Analysis:** ROI analysis with MEASURE software. **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:** $p < 0.05$.  
No significant pairwise differences in any of the ROIs for PBD and NPBD |
|                  | **MR scanner:** 1.5 T GE Signa scanner                                                 |                                                                                      |                                                           |                                                                        |
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Conflict of Interest

None.

Ethical statement

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

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