The impact of psychosis on brain anatomy in bipolar disorder: A structural MRI study

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ABSTRACT

Background: Bipolar disorder (BD) is a major psychiatric illness characterized by heterogeneous symptoms including psychotic features. Up until now, neuroimaging studies investigating cerebral morphology in patients with BD have underestimated the potential impact of psychosis on brain anatomy in BD patients. In this regard, psychotic and non-psychotic BD may represent biologically different subtypes of the disorder, being possibly associated with specific cerebral features.

Methods: In the present study, magnetic resonance imaging (MRI) at 3T was used to identify the neuroanatomical correlates of psychosis in an International sample of BD patients. A large sample of structural MRI data from healthy subjects (HC) and BD patients was collected across two research centers. Voxel based morphometry was used to compare gray matter (GM) volume among psychotic and non-psychotic BD patients and HC.

Results: We found specific structural alterations in the two patient groups, more extended in the psychotic sample. Psychotic patients showed GM volume deficits in left frontal cortex compared to HC, and in right temporo-parietal cortex compared to both HC and non-psychotic patients (p < 0.001, > 100 voxels). Psychotic patients also exhibited enhanced age-related GM volume deficits in a set of subcortical and cortical regions.

Limitations: The integration of multiple datasets may have affected the results.

Conclusions: Overall, our results confirm the importance of classifying BD based on psychosis. The knowledge of the neuronal bases of psychotic symptomatology in BD can provide a more comprehensive picture of the determinants of BD, in the light of the continuum characteristic of major psychoses.

1. Introduction

Bipolar disorder (BD) is a severe and chronic neuropsychiatric condition that affects mood regulation, being characterized by recurring depressive, manic or hypomanic, mixed and euthymic phases. This complex illness is associated with heterogeneous clinical features (Phillips and Kuper, 2013) and variable patterns of cognitive deficits (Martino et al., 2008), ultimately influencing patients’ clinical and functional outcome.

In the search for objective neurobiological markers of BD, advanced neuroimaging techniques have been increasingly employed. Indeed, the neural correlates of BD have been extensively investigated using Magnetic Resonance Imaging (MRI), with results showing structural alterations in BD patients compared to healthy controls (HC) (Arnone et al., 2008; Ellison-Wright and Bullmore, 2010; Hallahan et al., 2011; Selvaraj et al., 2012). However, taken together, the region-based and voxel-based neuroanatomical studies on BD led to rather inconsistent results.

This inconsistency might be related to the heterogeneous clinical manifestations within the BD spectrum, which were not adequately considered by most of the studies. In this regard, a feature that is worth of consideration is the presence of psychotic symptoms, which seems to...
have clinical, cognitive and psychosocial implications (Coryell et al., 2001; Glahn et al., 2007). For instance, a recent work from our group has shown that lifetime psychosis in BD is related to a worse socio-demographic and clinical profile (Dell’Osso et al., 2017). Literature evidence shows that more than half of BD patients experience psychotic symptoms at least once in the lifetime, more frequently during manic episodes (Goodwin and Jamison, 2007). Among patients with BD type I, prevalence rates of psychosis of up to 68% have been reported (Keck et al., 2003); as expected, psychotic symptoms occur in a lower percentage of BD type II patients, which was estimated in a range up to 45% (Mazzarini et al., 2010).

Besides influencing the choice of the pharmacological therapy, the presence of psychotic features was found to be associated with an earlier age of onset (Schurhoff et al., 2000), greater cross-sectional symptom severity and long-term morbidity (Coryell et al., 2001), as well as increased D2 dopamine receptor density (Pearlson et al., 1995). Family studies provided consistent evidence that psychotic symptoms aggregate in BD pedigrees and further suggested that liability to psychosis can be transmitted across different diagnoses within the psychotic spectrum, supporting the hypothesis that psychotic BD is associated with “overlapping” genes between BD and schizophrenia (SCZ) (Goes et al., 2008). Indeed, over recent years, researchers investigating the genetic bases of BD overcame the traditional diagnostic category by posing attention to different phenotypes within BD, with special interest towards psychotic features (Cradock et al., 2005; Park et al., 2004; Potash et al., 2003). A gradient of polygenic risk score association across SCZ and BD indexed by the presence and nature of psychosis has been recently demonstrated, with BD patients with mood-incongruent psychotic features carrying the highest burden of SCZ risk alleles (Allardycy et al., 2017).

Psychotic and non-psychotic BD may indeed represent different subtypes of the illness, relying on specific neuroanatomical bases. Therefore, in neuroimaging studies, the integration of BD patients with and without psychosis in a single diagnostic group might cause misinterpretations and obscure subgroup characterization (Strasser et al., 2005). Taking into consideration psychotic features can ameliorate the identification of the structural markers of BD, in line with the dimensional framework of Research Domain Criteria (RDoC) (Insel et al., 2010).

The largest study on cortical thickness and cortical surface area in BD, recently published from the ENIGMA group, showed an association between lifetime psychosis and deficits of cortical surface area in selective frontal and temporal regions (Hibar et al., 2017). Specifically, adolescents with psychotic BD showed deficits in right caudal anterior cingulate cortex and left inferior temporal gyrus compared to adolescents with non-psychotic BD, whereas adults with psychotic BD were characterized by deficits in right frontal pole compared to non-psychotic BD patients in the same age range.

Mixed results came from the investigation of gray matter (GM) volume in these patients. Indeed, there is just a handful of MRI studies that compared psychotic and non-psychotic BD patients in terms of GM volume (Chen et al., 2007; Ekman et al., 2017; Keramatian et al., 2016; Laidi et al., 2015; Mamah et al., 2016; Neves et al., 2016; Strasser et al., 2005; Womer et al., 2014). As recently summarized by our group (Maggioni et al., 2017), the findings of these studies suggest that psychotic and non-psychotic BD patients show specific volume alterations, enhanced in the psychotic group, when compared to controls. The results from the direct comparisons between the two BD subtypes suggest that psychosis is associated with smaller cortical volume, especially in the frontal area, and larger volume in selective regions of the basal ganglia. Additionally, within the psychotic BD spectrum, mood-incongruent features have been recently associated with enhanced GM volume alterations, in regions that seem to be involved in SCZ (Keramatian et al., 2016).

The above-mentioned results support the hypothesis that BD with psychotic features may represent a neurobiologically homogeneous subphenotype of the disorder; however, firm conclusions cannot be drawn given the limited number of studies, smaller sample sizes and inconsistencies in the results. The present work was undertaken to gain more robust understanding of the neuroanatomical underpinnings of psychosis. By adopting an unbiased exploratory perspective, we investigated whole-brain GM volume in a large structural MRI dataset of HC and patients with psychotic and non-psychotic BD, which was collected across different Research Centers, the IRCCS Fondazione Ca’ Granda Ospedale Maggiore Policlinico in Milan, Italy, and the University of British Columbia affiliated Hospitals in Vancouver, Canada. The Canadian dataset was obtained from the Systematic Treatment Optimization Program for Early Mania (STOP-EM), whose protocol is described elsewhere (Yatham et al., 2009). Structural and functional MRI studies on subsets of the multicenter dataset have been recently published (Dell’Osso et al., 2015; Keramatian et al., 2016).

2. Materials and methods

2.1. Subjects

One-hundred seventy-one subjects (114 BD patients and 57 HC) were recruited across the two research centers. Preliminarily to the MRI acquisition, all the subjects signed a written informed consent to the protocol, in accordance with the Declaration of Helsinki and the local ethical committee guidelines. After a quality check procedure, 164 subjects were selected for the analysis. The analysis of the entire dataset (Dataset1, n = 164) was accompanied by the analysis of a reduced dataset of adults in the 25–45 years age range (Dataset2, n = 81).

2.2. Recruitment

In the two research centers, the recruited patients met the DSM-IV-TR criteria for BD (American Psychiatric Association, 2000). In Milan, the diagnosis of BD was assessed through the Structured Clinical Interview for Axis-I DSM disorders (SCID-I) (First and Gibbon, 2004) and confirmed by the clinical consensus of an expert psychiatrist. In Vancouver, the diagnosis of BD type I was based on a clinical interview and the Mini International Neuropsychiatric Interview (Sheehan et al., 1998). Lifetime psychosis was defined as the occurrence of hallucination and/or delusions during one or more mood episodes. In both Milan and Vancouver, the presence of lifetime psychosis was assessed based on the SCID-I and through the review of medical charts. In all centers, patients with comorbidities were not excluded, provided that BD was their primary disorder. In most of the patients, hypomanic/manic and depressive symptoms were investigated using either the Hamilton Rating Scale for Depression (HRSD) (Hamilton, 1960) or the Montgomery-Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979) and the Young Mania Rating Scale (YMRS) (Young et al., 1978). The healthy subjects used for reference were recruited from the local communities of Milan and Vancouver and had no current or past DSM-IV Axis I disorder, alcohol or substance abuse, head trauma or neurological or major medical illnesses.

2.3. Demographic and clinical data processing

The demographic and clinical variables, including psychopathological scores, BD type, age of onset and pharmacological therapy, were compared between psychotic and non-psychotic BD patients using either the Chi-Squared test or the analysis of variance (ANOVA), as appropriate. The level of significance was placed at 0.05. If significant differences in terms of clinical variables emerged, clinical-neuroanatomical correlation analyses (described in Section 2.5.2) were performed to assess any effects of the selected variables on GM volume.
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