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# Brain gray matter phenotypes across the psychosis dimension

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ABSTRACT

This study sought to examine whole brain and regional gray matter (GM) phenotypes across the schizophrenia (SZ)–bipolar disorder psychosis dimension using voxel-based morphometry (VBM 8.0 with DARTEL segmentation/normalization) and semi-automated regional parcellation, FreeSurfer (FS 4.3.1/64 bit). 3T T1 MPRAGE images were acquired from 19 volunteers with schizophrenia (SZ), 16 with schizoaffective disorder (SAD), 17 with psychotic bipolar I disorder (BD-P) and 10 healthy controls (HC). Contrasted with HC, SZ showed extensive cortical GM reductions, most pronounced in fronto-temporal regions; SAD had GM reductions overlapping with SZ, albeit less extensive; and BD-P demonstrated no GM differences from HC. Within the psychosis dimension, BD-P showed larger volumes in fronto-temporal and other cortical/subcortical regions compared with SZ, whereas SAD showed intermediate GM volumes. The two volumetric methodologies, VBM and FS, revealed highly overlapping results for cortical GM, but partially divergent results for subcortical volumes (basal ganglia, amygdala). Overall, these findings suggest that individuals across the psychosis dimension show both overlapping and unique GM phenotypes: decreased GM, predominantly in fronto-temporal regions, is characteristic of SZ but not of psychotic BD-P, whereas SAD display GM deficits overlapping with SZ, albeit less extensive.

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## 1. Introduction

More than a century after Emil Kraepelin subdivided insanity into *dementia praecox* and *manic depressive psychosis*, the categorization of psychotic illnesses remains controversial. Recent large-scale genetic studies, as well as studies of intermediate phenotypes of psychosis, challenge a dichotomous conceptualization of psychosis and suggest that the two major psychotic illnesses, schizophrenia (SZ) and bipolar I disorder, display both shared and unique symptom dimensions, neurophysiological markers, and genetic underpinnings (O'Donnell et al., 2004; Sanchez-Morla et al., 2008; Purcell et al., 2009; Smith et al., 2009). Traditional manual region-of-interest morphometry, automated whole brain voxel-based morphometry (VBM) (Ashburner and Friston, 2000; Ashburner and Friston, 2005), as well as semi-automated regional brain segmentation and parcellation via FreeSurfer (FS) (Fischl et al., 1999; Dale et al., 1999; Fischl et al., 2004; Desikan et al., 2006) have been applied to address neuroanatomical correlatives of categorical and dimensional psychopathology in these disorders.

In schizophrenia, enlarged lateral ventricles and robust gray matter (GM) reductions in numerous regions, including but not limited to fronto-temporal cortices, hippocampus, cingulate, insula, thalamus, and cerebellum, have been consistently reported (see Woodruff et al., 1995; Nelson et al., 1998; Wright et al., 2000; Konick and Friedman, 2001; Honea et al., 2005; Baiano et al., 2007; Meda et al., 2008; Arnone et al., 2008; Ellison-Wright et al., 2008; Keshavan et al., 2008; Ellison-Wright and Bullmore,2010; Yu et al., 2010 for reviews and meta-analyses). In bipolar disorder, findings have varied widely, ranging from normal to both increased and decreased GM volume/density in fronto-temporal and cingulate cortex, amygdala, hippocampus, and thalamus (Altshuler et al., 1995; Videbech,1997; McDonald et al., 2004; Kempton et al., 2008; Yu et al. 2010; Hallahan et al., 2011). A few studies that specifically focused on psychotic bipolar disorder have also produced inconsistent results: while Strasser et al. (2005) found similar alterations in ventricular and hippocampal volumes in bipolar and schizophrenia psychoses, others reported distinct GM phenotypes with characteristically intact cortical GM in bipolar psychosis (Hirayasu et al., 1999; McDonald et al., 2005).

The volumetric studies that directly compared GM in individuals across the schizophrenia–bipolar disorder boundary are few; nevertheless, they have provided evidence for both overlapping and

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unique structural characteristics. Larger hippocampal (Kempton et al., 2008) and amygdala (Arnone et al., 2009) volumes have been reported in bipolar individuals compared to those with schizophrenia. Several VBM analyses have suggested that GM reductions are selectively associated with schizophrenia not bipolar disorder (Harvey et al., 1994; Zipursky et al., 1997; Pearlson et al., 1997; Altshuler et al., 2000; Hirayasu et al., 2001; McDonald et al., 2005; Farrow et al., 2005), whereas others found partially overlapping GM reductions in the two disorders, nevertheless more pronounced in schizophrenia (Friedman et al., 1999; McIntosh et al., 2004; Janssen et al., 2008; Ellison-Wright and Bullmore, 2010; Yu et al., 2010). Recent FS analyses have confirmed observations of shared (enlarged lateral ventricles, decreased bilateral hippocampi and left thalamus in both schizophrenia and bipolar disorder) and unique (widespread cortical thinning and enlarged right putamen in schizophrenia, and variable observations in cortical thickness in bipolar disorder) regional phenotypes (Lyoo et al., 2006; Rimol et al., 2010; Hartberg et al., 2011).

Considerable debate surrounds the conceptualization of schizoaffective disorder (SAD) as a distinct diagnostic entity. Some suggest that a dimensional approach to schizoaffective disorder that emphasizes the psychosis and mood symptoms phenotypes within this categorical diagnosis offers a more useful framework for the studies of underlying disease neurobiology (see Abrams et al., 2008, for review). In the field of imaging, individuals with schizoaffective disorder are routinely clustered with the schizophrenia samples (Cannon et al., 2002; Prasad et al., 2004; Buchanan et al., 2004). The few studies that have focused on schizoaffective disorder alone (all based on small samples) have found diminished cerebral volume (Getz et al., 2002), increased sulcal cerebro-spinal fluid volume (Cannon et al., 1998), reduced cortical GM with most deficits found in fronto-temporal regions (Cannon et al. 1998), smaller hippocampal volumes (van Erp et al., 2004; Radonic et al., 2011) and larger volumes of striatum and globus pallidus (Getz et al., 2002). Overall, these findings point at a considerable overlap in cortical and subcortical alterations in schizoaffective disorder and schizophrenia, although similar neuroanatomical characteristics in schizoaffective and bipolar patients have also been reported (Getz et al., 2002). In addition, Smith et al. (2011) have recently reported thalamic surface deformities in medial and lateral regions unique to schizoaffective disorder as compared to schizophrenia, although the overall volume of the thalamus in schizoaffective patients did not differ from that in controls.

Taken together, this literature suggests that individuals within the schizophrenia–bipolar disorder dimension may have both unique (e.g., GM volume reductions throughout fronto-temporal regions in schizophrenia and schizoaffective disorder in contrast to largely normal GM in bipolar disorder) and overlapping (e.g., decreased volume of hippocampi in all three psychoses) volumetric phenotypes, with less known specifically about schizoaffective disorder and the psychotic variant of bipolar disorder.

The question of whether the structural brain alterations that are consistently observed in psychotic individuals are related to primary disease pathophysiology or reflect disease-associated factors (e.g., effect of psychotropic agents, co-morbid substance use) remains debatable. Typical structural alterations have been observed in individuals at high risk for psychosis and the psychosis prodrom (Keshavan et al., 2005; Steen et al., 2006; Kuroki et al., 2006; Vita et al., 2006; Sun et al., 2009) in first break schizophrenia (Kasai et al., 2003; Ho et al., 2003; DeLisi et al., 2004; Whitworth et al., 2005; Steen et al., 2006; Vita et al., 2006; Schultz et al., 2010; Gutierrez-Galve et al., 2010), and in medication-naïve individuals with schizophrenia (Keshavan et al., 2005; Steen et al., 2006; Kuroki et al., 2006), suggesting that neither psychosis duration nor chronic treatment is entirely responsible for the typical GM changes.

However, evidence suggests that treatment with psychotropic medications undoubtedly has an effect on brain structure. Use of typical antipsychotics (AP) has been associated with increased GM density/volume of basal ganglia and decreased GM in fronto-temporal cortex (Keshavan et al., 1994; Gaser et al., 1999; Wilke et al., 2001; Kubicki et al., 2002; Lieberman et al., 2005; Molina et al., 2007; Crespo-Facorro et al., 2008; Smieskova et al., 2009; Ho et al., 2011). The data on atypical AP are less consistent, with some studies reporting frontal GM reductions, and caudate/putamen volume increases, although less severe, compared to those found with typical AP (Molina et al., 2007; Ho et al., 2011); whereas others find minimal to no effect of atypicals on cortical GM and basal ganglia (Lieberman et al., 2005; Scherk and Falkai,2006; Smieskova et al., 2009), or even a reversal of the basal ganglia enlargement after switching from typical to atypical AP (Scherk and Falkai, 2006; Smieskova et al., 2009) or discontinuation of AP (Boonstra et al., 2011). Decreased white matter, but not GM, volumes have been associated with AP use in bipolar disorder (Jones et al., 2009). Longer duration of AP treatment has been associated with more pronounced cortical and subcortical alterations (Ho et al., 2011), although some suggest that the volume changes accompanying typical AP use can be detected as early as after 12 weeks (Scherk and Falkai, 2006).

Furthermore, there is accumulating evidence that lithium and other mood stabilizers may increase amygdala volume (Usher et al., 2009) and GM density in diffuse cortical regions (Kempton et al., 2008; Langan and McDonald, 2009) with greatest effect seen in prefrontal, cingulate, and paralimbic cortices (Bearden et al., 2007; Moore et al., 2009). Since the majority of individuals with schizophrenia and bipolar psychoses are chronically treated with a mixture of psychotropic agents, disentangling 'primary' disease phenotypes from medication effects poses a significant difficulty and has been acknowledged in the recent reports (Navari and Dazzan, 2009; Ho et al., 2011).

This study sought to examine GM phenotypes across the psychosis dimension in individuals with schizophrenia (SZ), schizoaffective disorder (SAD), and psychotic bipolar I disorder (BD-P) to test for a common psychosis phenotype. We hypothesized that (1) contrasted with HC, SZ will show GM reductions in numerous cortical and subcortical regions with most pronounced changes in fronto-temporal cortices, whereas BD-P will have largely normal GM volumes; and SAD will show cortical and subcortical GM changes intermediate between those in SZ and BD-P; and (2) within the psychosis dimension, SZ, SAD, and BD-P will show step-wise changes in GM from overall smaller volumes in SZ to larger volumes in BD-P. To test these hypotheses, we concomitantly used two volumetric methodologies: VBM and FS. VBM is an automated, highly repeatable approach to morphometry, and is often used to provide whole brain GM characterization (Kennedy et al., 2009), while automated parcellation and measurement of anatomically defined regions, such as those available with FS, provide high anatomical validity. For this reason, in order to explicitly characterize GM phenotypes across the SZ/BD-P boundary, we applied two analytic approaches: VBM, in order to define whole brain GM alterations, and FS, in order to verify regional cortical and subcortical GM phenotypes.

## 2. Methods

### 2.1. Subjects

The study included individuals who met the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) (American Psychiatric Association, 1994) criteria for schizophrenia (SZ, $n=19$), schizoaffective disorder (SAD, $n=16$) or bipolar disorder, type I, with lifetime history of psychotic symptoms (BD-P, $n=17$), and 10 HC. All volunteers were recruited concurrently through