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.

Keywords

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

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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 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 advertising, and by referrals from community mental health centers and from the UT Southwestern Medical Center out-patient psychiatric clinics. Individuals with a history of major neurological or decompensated medical illness, mental retardation, traumatic brain injury, substance abuse within the last month or substance dependence within the last 3 months were excluded. The study was approved by the institutional review board of the UT Southwestern Medical Center and was consistent with standards for the ethical conduct of human research. All volunteers provided written informed consent after the study procedures had been fully explained.

Demographic and clinical characteristics of the study sample are presented in Table 1. All volunteers were English-speaking, had normal IQ estimates, and were matched for age and education. The groups did not differ in any of the socio-demographic or psychiatric history characteristics, except for the duration of lifetime psychosis where SAD reported longer history of psychosis compared to either SZ (P=0.01) or BD-P (P=0.006). The psychosis volunteers included in this study were clinically stable medicated out-patients with active psychosis and/or mood symptoms that varied in severity from remission/euthymic state to mild symptoms. In addition to the Structured Clinical Interview for DSM-IV Axis I Disorders (First et al., 1996) used to determine the psychosis diagnoses, the Brief Psychiatric Rating Scale (Overall and Gorham, 1962) as a measure of active symptomatic severity and the Global Assessment of Functioning (DSM-IV Axis V) ratings were collected for the psychosis groups. No between group differences were obtained either in active symptom severity or in general level of functioning. Most subjects in the psychosis groups reported a chronic medication use history, and were being treated with a variety of psychotropic agents while participating in this study; only two subjects were off psychotropic medications at the time of the imaging acquisition.

2.2. MRI acquisition, voxel-based morphometry and FreeSurfer procedures

Structural magnetic resonance imaging was performed on a 3 T Siemens Magnetom Trio scanner. T1-weighted MPRAGE sequences were acquired using the following parameters: TR 2300 ms/TE 2.95 ms/TI 900 ms/BW 240 Hz/9° flip/total time 9:23 min, yielding 160 sagittal slices with a slice thickness of 1.2 mm with $1 \times 1 \times 1.2$ mm^3 voxel resolution. All structural images were processed by a single individual (EII, VBM, or AF, FS) blind to the volunteers' diagnoses.

VBM analysis was conducted in Statistical Parametric Mapping (SPM8) software on MATLAB with the following processing steps: reorientation, high-dimensional DARTEL segmentation/normalization (Ashburner, 2007), and smoothing. T1-weighted images were set to match the standard T1 template [Montreal Neurological Institute (MNI) space] for Anterior Commissure–Posterior Commissure alignment and were segmented into GM, white matter, and cerebro-spinal fluid compartments using non-linear DARTEL normalization which utilizes a high-dimensional warping process and increases registration accuracy between the individual images, resulting in improved localization and increased sensitivity in analysis. Furthermore, DARTEL allows precise correction for individual brain size (Ashburner, 2007). Segmented images were modulated or scaled by the amount of warping to maintain the total amount of GM volume. Modulated GM images were then smoothed with a 12-mm isotropic Gaussian kernel and were selected for further statistical analyses. All images are displayed in neurological convention. Reported brain regions were identified using the Group ICA for fMRI Gift toolbox, version 1.3i (Calhoun et al., 2001) and checked against the standardized anatomical brain atlas (Duvernoy, 1999).

FS analysis was conducted using FreeSurfer 4.3.1, 64-bit version (Massachusetts General Hospital, http://surfer.nmr.mgh.harvard.edu/). FS processing included motion correction of volumetric T1-weighted images, removal of nonbrain tissue using a hybrid watershed/ surface deformation procedure (Segonne et al., 2004), automated transformation, segmentation of the subcortical white matter and deep GM volumetric structures (Fischl et al., 2002, 2004), intensity normalization, tessellation of the GM/white matter boundary, automated topology correction (Fischl et al., 2001; Segonne et al., 2007), and surface deformation following intensity gradients to optimally place the GM/white matter and GM/ cerebro-spinal fluid borders at the location where the greatest shift in intensity defines the transition to the other tissue class (Dale et al., 1999). Image outputs for each stage of FS analysis were visually inspected and edited by an experienced imaging analyst (AF).

2.3. Statistical analyses

A one-way analysis of variance (ANOVA) with a subsequent post hoc Tukey HSD test and Yates corrected chi-square test were used as appropriate for demographic and clinical variables. For the VBM analyses, the processed GM images were analyzed using SPM8 parametric mapping for group comparisons using 'full factorial' function: analysis of covariance (ANCOVA), adjusted for age (using F contrast), with subsequent pairwise comparisons (using t contrast). Absolute threshold masking was set at 0.1. To further reduce the occurrence of GM and white matter difference map, a standard GM template within VBM8 was first binarized at a suitable threshold (0.4) where the majority of GM voxel intensities were included within the cut-off, then registered to the t-map, and finally applied as a mask on the resulting t-map. The VBM outcomes for the psychosis groups vs. HC contrast are reported at $P<0.05$, false discovery rate (FDR) corrected threshold. In the resulting t-maps only clusters with 100 or more contiguous voxels are reported. Since no GM volume differences between the psychosis groups (SZ vs. SAD vs. BD-P) remained significant after FDR correction, uncorrected outcomes for this comparison are reported at $P<0.005$. This less stringent threshold balanced with rather high voxel cluster size of 100

provided the most informative illustration of between-group differences within the psychosis dimension. Corresponding peak coordinates for each region of volume change based on the Gift outputs (Calhoun et al., 2001) are presented in Talairach space.

Analysis of covariance (ANCOVA) was used for the FS outcomes (automatically derived cortical and subcortical volumes) with individual volumes as dependent variables, group as an independent variable, and age and intracranial volume as covariates, similar to (Bhojraj et al., 2009). Bonferroni correction for regional comparisons within each lobe/subcortical structure was applied, similar to the procedure of Bhojraj et al., (2009) (detailed list of the regions provided in Table 3); both corrected and uncorrected probability values are reported.

Given a well-known effect of age on brain structure (see Reuter-Lorenz and Park, 2010 for review), both VBM and FS analyses were adjusted for age. In addition, FS analysis was adjusted for total intracranial volume, which was derived from FS parcellation and subsequently included as a covariate in ANCOVA. VBM analysis was adjusted for individual brain volume. Since VBM/DARTEL normalization incorporates an automatic adjustment for individual brain volume, total intracranial volume was not added as a covariate at the level of VBM group analyses. Volumetric measures, age and intracranial volume were normally distributed [Shapiro–Wilk's test, $P>0.1$]. The groups did not differ either in age [group mean ± standard deviation, years: SZ, 39.89±10.66; SAD, 45.12±10.14; BD-P, 38.24±7.28; HC, 43.9±9.86] or intracranial volume [group mean ± standard deviation, mm^3: SZ, 1,470,876±161,799; SAD, 1,515,886±170380; BD-P, 1,449,657±229610; HC, 1,431,969±98,123].

In order to examine effect of medication on GM phenotypes, individuals across the psychosis groups independent of their diagnoses who were on (n=39) and off (n=11) AP, and on (n=16) and off (n=36) mood stabilizers while active in this study were contrasted with respect to whole brain (derived from VBM) and regional (derived from FS) GM volumes. Multiple regression analysis in SPM8 was used to examine correlations between GM volumes and lifetime duration of psychosis.

3. Results

3.1. Gray matter phenotypes in psychosis vs. healthy controls

3.1.1. Whole brain gray matter volume differences in psychosis vs. healthy controls (voxel-based morphometry)—Whole brain GM differences between the psychosis groups and HC ($P<0.05$, FDR corrected) are shown in Table 2 and Fig. 1(A). An overall ANCOVA showed a main effect of group [$F(3, 57)$=7,75, $P<0.05$, FDR corrected]. Subsequent pairwise comparisons between the psychosis groups and HC revealed overlapping GM reductions in SZ and SAD in frontal, temporal and insular cortices. SZ showed many additional regions of decreased GM throughout neocortex, most prominent in fronto-temporal, cingulate, and parietal cortices, as well as in basal ganglia, thalamus, and cerebellum. In contrast, BD-P showed no differences in cortical and subcortical GM volumes compared to HC. No increases in GM volume were found in any of the psychosis groups, compared to HC.

3.1.2. Regional gray matter volume differences in psychosis vs. healthy controls (FreeSurfer)—Regional cortical and subcortical volume differences between the psychosis groups and HC are shown in Table 3. Individual volumes distribution in the selected regions of interest (right superior frontal gyrus, left globus pallidus, right hippocampus, and right amygdala) are shown in Fig. 2. Consistent with the VBM results, FS analyses showed decreased volumes in several frontal and temporal regions bilaterally, the left parietal cortex and the right thalamus in SZ compared to HC. The differences in frontal

regions remained significant after Bonferroni correction, although the changes in temporal and parietal cortex and thalamus did not survive multiple comparisons correction. In addition, SZ showed a larger volume of the left globus pallidus compared to HC. SAD had smaller volumes in bilateral hippocampi (significant in the right hippocampus after Bonferroni correction), the right caudate and thalamus (non-significant after Bonferroni correction), compared to HC. No differences in cortical or subcortical volumes emerged between BD-P and HC.

3.2. Gray matter phenotypes across diagnoses in the psychosis dimension

3.2.1. Whole brain gray matter volume differences within the psychosis dimension (voxel-based morphometry)—Whole brain GM volume differences between the psychosis groups are shown in Table 2 and Fig. 1(B). An overall ANCOVA showed a main effect of group [$F(2, 48)=5,93$, $P<0.005$, uncorrected], although it was not significant after FDR correction. Similarly, no GM differences survived FDR correction when the individual psychosis groups were compared. The less stringent threshold ($P<0.005$, uncorrected) revealed a gradual pattern of GM changes (BD-P>SAD>SZ) where BD-P had larger volumes than SZ, and SAD showed intermediate volumes with less robust differences as compared to either SZ or BD-P. Specifically, SZ showed smaller GM volumes in bilateral fronto-temporal, insular, posterior cingulate, and parietal cortical regions, as well as in basal ganglia, and the right cerebellum, compared to BD-P. SAD had larger GM volumes in bilateral fronto-temporal, cingulate, parietal, and occipital cortices compared to SZ, and smaller volumes in bilateral parahippocampal gyri and basal ganglia compared to BD-P. In addition, SAD showed a few isolated clusters of larger GM in the right middle frontal, middle occipital and cerebellar regions compared to BD-P.

3.2.2. Regional gray matter volume differences within the psychosis dimension (FreeSurfer)—Regional cortical and subcortical volume differences between the psychosis groups are shown in Table 3. Consistent with the VBM results, FS analyses detected smaller volumes in fronto-temporal, cingulate, parietal, occipital, and cerebellar regions in SZ compared to BD-P. However, only differences in the left precuneus and lingual gyrus remained significant after Bonferroni correction. SAD showed larger GM volumes in the left inferior temporal and the right anterior cingulate gyri, compared to SZ; smaller hippocampal volumes bilaterally (significant after Bonferroni correction) compared to BD-P; and smaller volumes of thalamus compared to both BD-P and SZ. In addition, FS depicted enlarged volumes of amygdala in BD-P compared to both SZ and SAD, as well as an increased volume of the globus pallidus (the left-side difference significant after Bonferroni correction) in SZ compared to BD-P.

3.3. Associations between gray matter volume and medication, and lifetime psychosis duration

No differences in whole brain GM or regional cortical/subcortical volumes were obtained between SZ, SAD, and BD-P who were on- and off-AP or on-and off-mood stabilizer medications while active in this study. No correlations between GM cortical/ subcortical volumes and lifetime duration of psychosis were found in any of the psychosis groups.

4. Discussion

In this study we examined whole brain and regional GM phenotypes in individuals within the schizophrenia–bipolar disorder psychosis dimension. The analytic strategy employed two volumetric methodologies: VBM for the examination of global GM differences, and FS for precise characterization of regional cortical and subcortical GM phenotypes. Our findings suggest that individuals across the psychosis dimension show both unique (e.g., SZ

as compared to BD-P) and overlapping (e.g., SZ as compared to SAD) GM characteristics. Compared to HC, SZ showed extensive and diffuse cortical GM volume reductions, most prominent in fronto-temporal cortices, as well as in several subcortical structures including thalamus and cerebellum; SAD showed GM reductions overlapping with SZ, albeit less extensive reductions, whereas BD-P had cortical and subcortical GM volumes not different from HC. Direct contrast of GM phenotypes within the psychosis dimension revealed a step-wise pattern of differences where BD-P had larger GM volumes in fronto-temporal, insular, cingulate, and parietal cortices, as well as basal ganglia and cerebellum, compared with SZ, whereas SAD showed intermediate volumes in these regions as compared with either SZ or BD-P.

In this study the individuals with the categorical DSM-IV diagnoses within the psychosis dimension (schizophrenia–schizoaffective disorder–psychotic bipolar I disorder) were directly compared in the same analyses. Overall, both cortical and subcortical GM structural phenotypes distinguished SZ and BD-P, whereas SAD appeared to have GM deficits overlapping with SZ, albeit less extensive deficits. The observations of GM reductions in SZ/SAD, and normal GM in BD-P, are consistent with previous reports that contrasted SZ and BD-P samples (Harvey et al., 1994; McDonald et al., 2005; Farrow et al., 2005). The differences in GM structural phenotype in SZ/SAD and BD-P can be interpreted to say that the GM reductions in SZ/SAD may be related to a primary disease pathophysiology that is not characteristic for BD-P. Although the exact mechanisms underlying GM reductions in schizophrenia are not understood, it is known from post-mortem examination that general neuronal loss is not present to any substantial extent in schizophrenia, excluding this as an explanation for decreased cortical volume observed with imaging. The same studies showed reductions in interstitial volume with increased neuronal cell packing, offering reductions in the dendritic branching as a more likely putative explanation (Selemon et al., 1995; Selemon and Goldman-Rakic, 1999). In addition, the possibility exists that GM volume preservation (or volume increase) in bipolar disorder may be secondary to an action of mood stabilizers and that, even if disease-associated loss of neocortical volume is present in BD-P, it is obscured by a volume-enchancing effect of mood stabilizers (Bearden et al., 2007; Moore et al., 2009). It is unlikely that the differential GM findings in SZ/SAD and BD-P are related to higher severity of illness in SZ/SAD compared to BD-P, given a careful psychiatric history characterization of the study sample and the absence of between-group differences in overall illness severity estimated by the lifetime number of hospitalizations and BPRS scores, as well as the absence of correlation between the duration of lifetime psychosis and GM outcomes.

Measurable alterations in the brain structure are first observed in individuals near the onset of psychosis, with some studies finding most pronounced changes in subcortical structures (e.g., hippocampus, basal ganglia, and thalamus) (Watson et al., 2012), as well as in fronto-temporal and fronto-parietal white matter (Whitford et al., 2007; Watson et al., 2012). These alterations are thought to progress rather rapidly during the initial years of psychosis (Whitford et al., 2007; Andreasen et al., 2011), and, although they may plateau during subsequent years (Andreasen et al., 2011), ultimately lead to a characteristic pattern of diffuse structural changes found in chronic SZ samples (Meisenzahl et al., 2008). Since individuals with psychosis are chronically exposed to various psychotropic treatments, as well as other disease-associated factors (e.g., substance use and increased medical comorbidities), disentangling the 'primary' GM changes from the 'secondary' disease-associated effects presents considerable difficulty. The reports from unmedicated early psychosis samples advocate for a 'primary' intrinsic effect of illness on GM) (Borgwardt et al., 2011; Fusar-Poli et al., 2011). At the same time, convincing evidence has cumulated to support an effect of psychotropic medications on GM structure (Gaser et al., 1999; Wilke et al., 2001; Kubicki et al., 2002; Lieberman et al., 2005; Crespo-Facorro et al., 2008; Jones et

al., 2009; Ho et al., 2011). It is possible that GM volume deficits in SZ/SAD found in this study could be, at least partially, accounted for by an effect of a lifetime treatment with first- and second-generation AP (Lieberman et al., 2005; Molina et al., 2007; Crespo-Facorro et al., 2008), whereas a preservation of GM volumes in BD-P could be related to chronic treatment with mood stabilizers (Usher et al., 2009). Not surprisingly, we did not find significant differences in GM volume in the psychosis volunteers that were on and off AP or mood stabilizers while active in this study. Given that this sample comprises chronically ill individuals the vast majority of whom had years of treatment prior to entering this study, acute effects of AP and mood stabilizers on brain structure were likely obscured by the longitudinal effects of both disease and medication.

In this study, both volumetric methodologies, VBM and FS, produced highly overlapping results with regard to cortical GM volume, although VBM depicted GM changes in broader regions compared to FS. However, the two analyses showed somewhat divergent outcomes for subcortical volumes. The schematic summary of overlapping and divergent VBM and FS outputs are presented in Table 4. For example, FS depicted larger volume of amygdala in BD-P compared to either SZ or SAD, which was not found with VBM. In addition, FS showed an enlargement of globus pallidus in SZ compared to HC and BD-P, whereas VBM depicted decreased GM volumes in basal ganglia (in the lentiform nucleus, caudate and claustrum regions) in SZ as compared to either HC or BD-P. The finding of enlarged amygdala in BD-P is consistent with many previous reports (Altshuler et al., 1998; Velakoulis et al., 2006; Brambilla et al., 2008; Arnone et al., 2009; Kalmar et al., 2009; Usher et al., 2009), with some attributing it to primary disease pathophysiology, such as increased response to emotional stimuli (Brambilla et al., 2008; Kalmar et al., 2009), and others to lifetime treatment with mood stabilizers, particularly, lithium (Usher et al., 2009; Hallahan et al., 2011). The divergent findings in basal ganglia may reflect differential changes in various subregions within this large subcortical structure related to disease process and/or medications. Similar to our findings, a recent large meta-analysis in SZ/ bipolar disorder GM phenotypes (Yu et al., 2010) reported mixed results with both reduced (in the caudate head) and increased (in the left lentiform nucleus, putamen, and globus pallidus) GM volumes in SZ and bipolar disorder. Earlier literature also provided variable observations, with some studies showing basal ganglia enlargement, likely associated with AP use (Gaser et al., 1999; Wilke et al., 2001; Kubicki et al., 2002; Ellison-Wright and Bullmore, 2010), and others reporting no difference in SZ vs. HC (Crespo-Facorro et al., 2007), especially prior to drug treatment (Chua et al., 2007; Leung et al., 2011). Furthermore, some studies provided evidence for basal ganglia functional dissociation, with the caudate head being responsible for feedback processing and linked to the dorsolateral prefrontal cortex, whereas the caudate body and tail mediated stimulus-category learning and were linked to the extrastriate and visual inferotemporal cortex (Seger and Cincotta, 2006). Therefore, there is a possibility that this functional dissociation may translate into differential structural morphology within the basal ganglia, although further work on the role of the caudate in psychosis is needed to support this observation. Alternately, these divergent observations in subcortical volumes derived from VBM and FS may be attributed to differences in volume estimation algorithms used in the two methodologies. While VBM utilizes the three-dimensional tissue classification method where each voxel is assigned a probability of belonging to a particular tissue class (GM, white matter, cerebro-spinal fluid) based on its intensity and prior probability maps (Ashburner and Friston, 2000), FS uses a Markov Random Fields approach where the probability of cortical/ subcortical labels at a given voxel is computed based on the tissue intensity, prior probabilities at each voxel, and spatial positioning of neighboring labels (Fischl et al., 2002). The latter approach may increase accuracy of voxel labeling, specifically, in subcortical structures known to have significantly heterogeneous tissue intensity properties (Fischl et al., 2002). In addition, subcortical structures may present a challenge for precise intersubject registration in VBM

(Meisenzahl et al., 2008), making detection of differences in such structures problematic. Overall, both volumetric methodologies, VBM and FS, have proven to be successful in characterization of the psychosis GM phenotypes. However, they produced both overlapping (e.g., cortical GM) and divergent (e.g., subcortical structures) outcomes. VBM showed somewhat higher sensitivity to cortical GM alterations, whereas FS demonstrated more substantial sensitivity to subcortical volume changes. Therefore, both methodologies may be used in conjunction for precise characterization of brain structure phenotypes.

Several limitations to this study should be noted. The modest sample size, especially the limited number of HC, warrants cautious interpretation of these findings. The broad effects of race and gender on disease neuropathology were not considered in this analysis. In addition, within-group variability in volumetric characteristics could contribute to the lack of between-groups differences in SZ vs. SAD vs. BD-P contrast at corrected statistical threshold in VBM. Because the majority of subjects in this sample had a chronic treatment history with various psychotropic medications, here it was not possible to distinguish between primary disease effects and chronic medication effects on brain structure. Future longitudinal studies applying pre- and post-treatment imaging, studies in unmedicated psychosis individuals, as well as studies in biological relatives of probands with psychoses may provide better understanding of structural changes that reflect 'primary' markers of disease vs. an effect of confounding factors, such as medications.

In conclusion, this is the first study to directly compare GM phenotypes in individuals across the schizophrenia–bipolar disorder psychosis dimension using a combination of two volumetric approaches: global GM analysis (VBM) and regional analysis (FS). Our findings indicate that, parallel to clinical manifestations, where SZ, SAD, and BD-P demonstrate shared and unique symptom dimensions, they exhibit both overlapping and unique structural GM phenotypes: decreased GM, predominantly, in fronto-temporal regions, is characteristic of SZ, but not of psychotic, BD-P, whereas SAD display intermediate phenotype, with GM decreases partially overlapping but less robust than those seen in SZ. Future research examining brain structure and other phenotypes and their genetic underpinnings in larger family psychosis samples may shed further light on a dimensional definition of psychosis and aid in the development of a biologically based classification of psychosis which is treatment-relevant.

Acknowledgments

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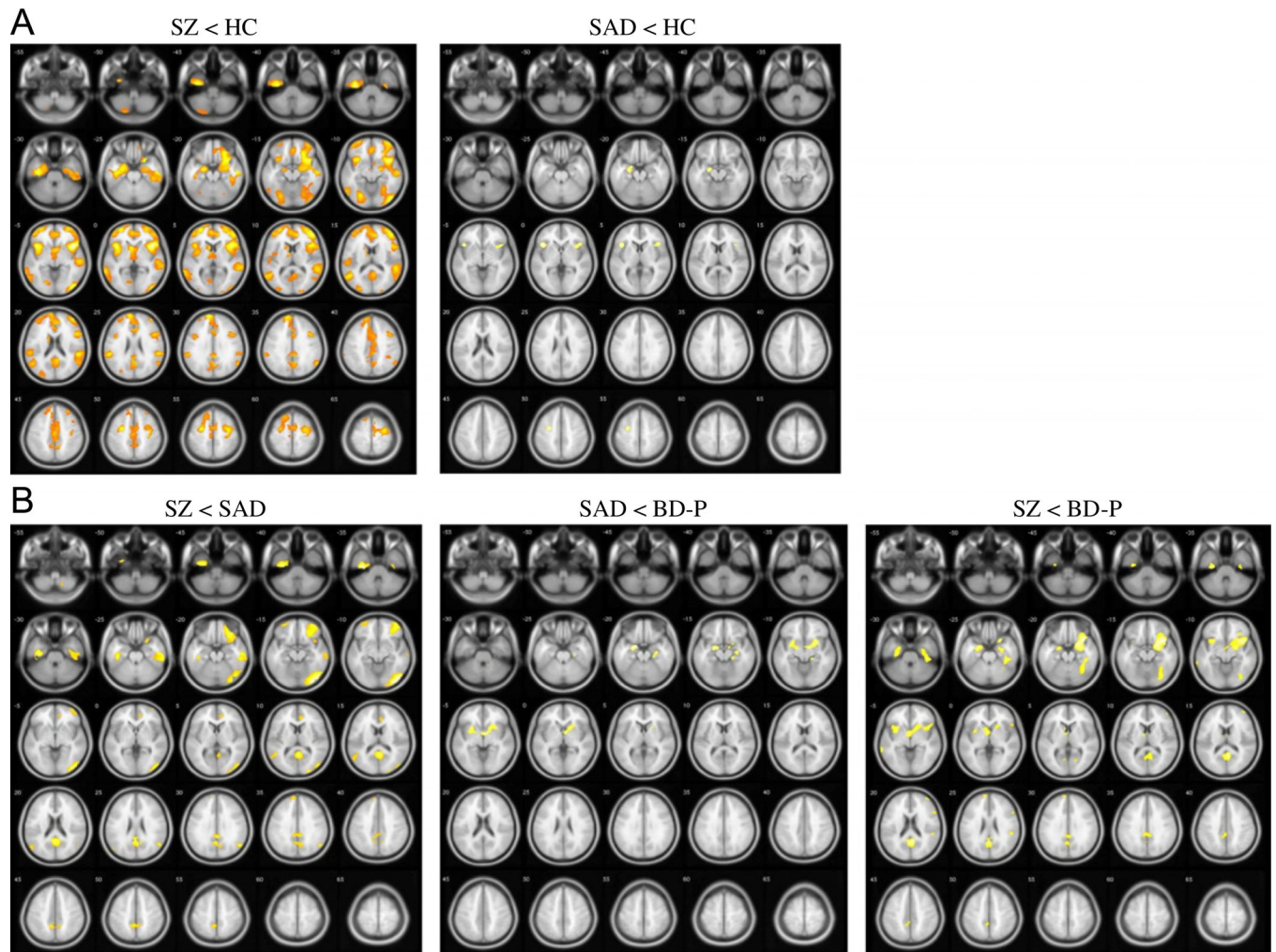
Fig. 1.
Whole brain gray matter phenotypes (A) between the psychosis groups and healthy controls and (B) across the psychosis dimension derived from the voxel-based morphometry analyses. SZ—individuals with schizophrenia, SAD—individuals with schizoaffective disorder, BD-P—individuals with psychotic bipolar I disorder, HC—healthy controls, FDR—false discovery rate correction for multiple comparisons. (A) Gray matter volume differences between the psychosis groups and healthy controls (P<0.05, FDR corrected, k=100). (B) Gray matter volume differences across the psychosis dimension (P<0.001, uncorrected, k=100).
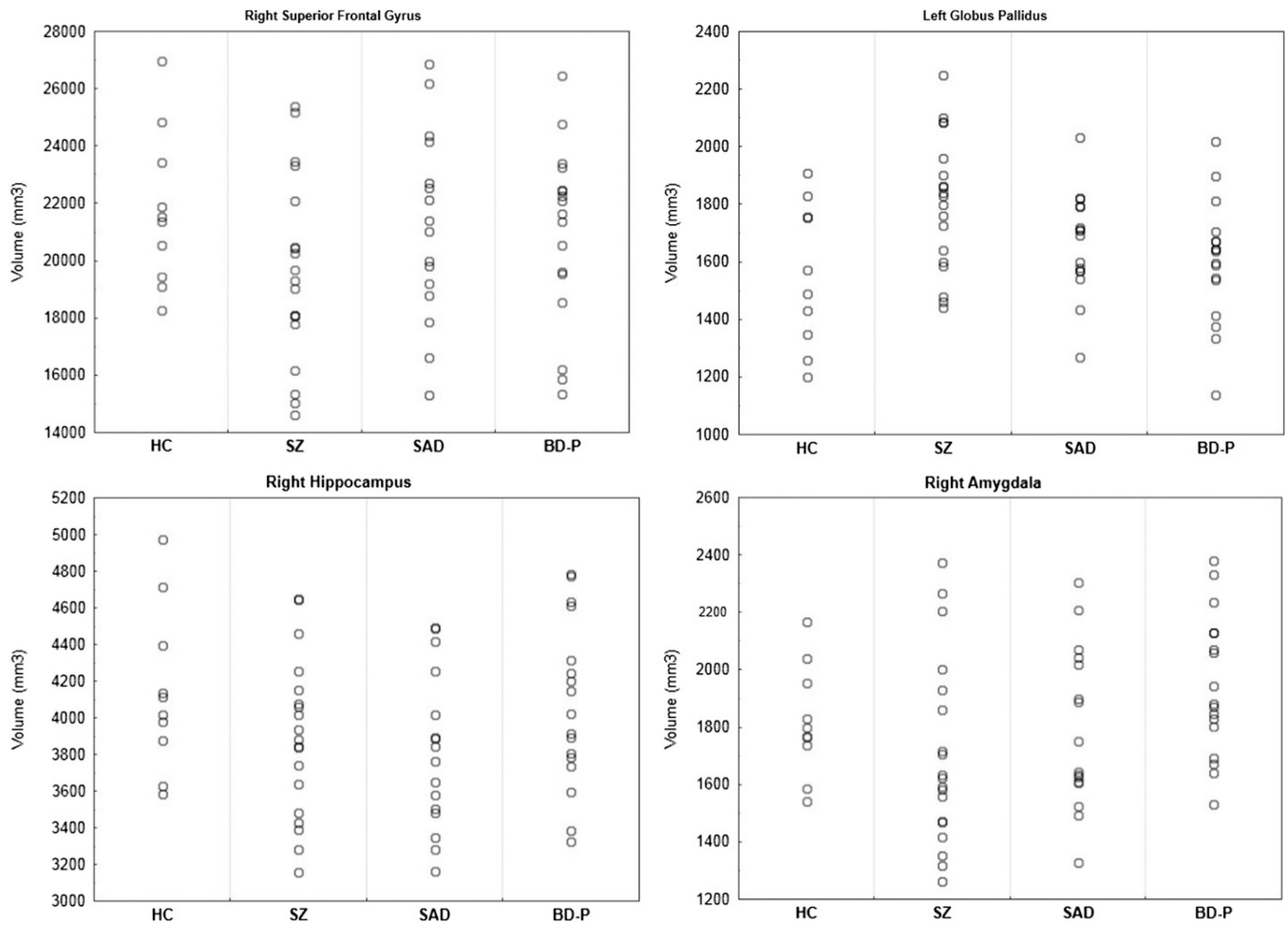
Fig. 2.
Individual volumes of selected regional outcomes derived from FreeSurfer analyses. SZ—
individuals with schizophrenia, SAD—individuals with schizoaffective disorder, BD-P—
individuals with psychotic bipolar I disorder, HC—healthy controls, FDR—false discovery
rate correction for multiple comparisons.

Table 1

Socio-demographic and clinical characteristics of the study groups.

	SZ(n=19)	SAD(n=16)	BD-P(n=17)	HC(n=10)	Test statistic	P value
Socio-demographic characteristics						
Age, years; Mean (S.D.)	39.89(10.66)	45.12(10.14)	38.24(7.28)	43.9(9.86)	$F(3, 55) = 2.22$	0.1
Gender/male; n (%)	10(52.63)	9(56.25)	8(47.05)	4(40)	$\chi^2(3) = 0.76$	0.86
Left-handed; n (%)	4(21.05)	1(6.25)	2(11.76)	1(10)	$\chi^2(3) = 1.77$	0.62
Education, years; Mean (S.D.)	13.84(2.14)	15.43(2.63)	14.05(2.05)	13.3(0.95)	$F(3, 55) = 2.63$	0.12
Race; n (%)					$\chi^2(3) = 2.69$	0.44
Caucasian	13(68.42)	13(81.25)	14(82.35)	9(90.00)		
African-American	6(31.58)	2(12.5)	1(5.88)	1(10.00)		
Other	0(0.00)	1(6.25)	2(11.76)	0(0.00)		
Clinical characteristics, Mean (S.D.)						
Psychosis duration, years	15.74(8.99)	24.81(8.48)	14.76(9.07)	-	$F(2, 49) = 6.46$	0.003[a]
Age of the first hospitalization, years	27.53(7.37)	26.86(11.18)	27.73(6.25)	-	$F(2, 39) = 0.04$	0.96
Total number of hospitalizations	5.47(8.07)	9.13(11.14)	2.29(2.75)	-	$\chi^2(2) = 3.53$	0.17
BPRS, total score	46.63(11.88)	48.06(8.50)	44.82(8.89)	-	$F(2, 49) = 0.44$	0.64
GAF	56.44(14.19)	53.13(10.83)	57.07(11.30)	-	$F(2, 47) = 0.43$	0.65
WASI IQ	107.32 (11.70)	107.00(16.25)	108.76 (9.46)	114.70(6.88)	$F(3, 58) = 1.03$	0.39
Concomitant medications, n (%)						
Off medications	1(5.26)	0(0.00)	1(5.88)	10(100)		
Typical antipsychotics	5(26.31)	2(12.5)	0(0.00)	0(0.00)		
Atypical antipsychotics	12(63.16)	13(81.25)	9(52.94)	0(0.00)		
Antidepressants	12(63.16)	5(31.25)	9(52.94)	0(0.00)		
Mood stabilizers	1(5.26)	5(31.25)	13(76.47)	0(0.00)		
Other	5(26.31)	6(37.5)	7(41.18)	0(0.00)		
Combined medications	13(68.42)	12(75.0)	14(82.35)	0(0.00)		

SZ—individuals with schizophrenia, SAD—individuals with schizoaffective disorder, BD-P—individuals with psychotic bipolar I disorder, HC—healthy controls, BPRS—Brief Psychiatric Rating Scale, GAF—Global Assessment of Functioning scale, WASI IQ—Wechsler Abbreviated Scale of Intelligence IQ, S.D.—standard deviation.

[a] Psychosis duration, post hoc Tukey HSD: SAD vs. SZ, P=0.01; SAD vs. BD-P, P=0.006.

Table 2

Regions of gray matter volume difference between the psychosis groups and healthy controls, and across the psychosis dimension based on voxel-based morphometry analyses.

Group comparison	Brain region	*k* (voxels), right/left	Pseudo-t *(x, y, z)*, S right/left
Psychosis groups vs. healthy controls contrast [*P*=0.05, FDR corrected, *k*=100]			
SZ < HCM	***Frontal***		
	Inferior frontal gyrus	5422/1600	5.7 (43, 16, −5)/4.9 (−40, 16, −3)
	Middle frontal gyrus	4978/2637	4.5 (45, 44, 7)/4.4.(−27, −2, 46)
	Superior frontal gyrus	1689/3348	3.6 (30, 57, −5)/4.1 (−28, 54, 0)
	Medial frontal gyrus	2193/2548	3.4(4,43, 14)/3.5(−6, 59, 19)
	Precental gyrus	2015/237	4.4 (43, 19, 7)/3.6 (−30, −8, 52)
	Paracentral lobule	296/207	3.3 (0, −15, 44)/3.1 (−3, −18, 45)
	Temporal		
	Superior temporal gyrus	3644/1067	4.3 (40, 10, −12)/3.8 (−49, −56, 17)
	Middle temporal gyrus	1689/1926	3.9 (53, −12, −16)/3.6 (−64, −45, 4)
	Parahippocampal gyrus	1452/1363	3.8(27,5, −17)/4.3(−36, −17, −24)
	Fusiform gyrus	1067/415	3.5 (46, −33, −19)/4.1 (−39, −14, −23)
	Inferior temporal gyrus	504/770	4.2(56, −15, −18)/4.4(−37, −20, −28)
	Uncus	237/593	4.1 (25,8, −19)/4.7(−36, −16, −28)
	Insula	1926/1511	5.3 (40, 16, *−2)143*(−37, 16, −1)
	Cingulate gyrus		
	Cingulate gyrus (BA 23, 24, 31, 32)	2281/1244	3.3 (10, −33, 35)/3.1 (−3, −42, 28)
	Anterior cingulate (BA 10, 24, 25, 32, 33)	1126/919	3.6(13, 44, 5)/3.3(−1,48, 4)
	Posterior cingulate (BA 23, 29, 30, 31)	711/385	3.4 (6, −51, 21)/3.0 (−3, −53, 22)
	Parietal		
	Precuneus	1067/444	3.3 (12, −50, 40)/2.9 (−4, −52, 33)
	Inferior parietal lobule	919/900	3.9 (56, −34, 22)/3.9 (−55, −34, 25)
	Supramarginal gyrus	444/89	3.3 (56, −58, 32)/2.6 (−55, −39, 31)
	Postcentral gyrus	119/148	3.6 (34, −20, 45)/3.1 (−55, −28, 19)
	Occipital		
	Middle occipital gyrus	1304/770	4.4 (48, −77, −4)/3.3 (−53, −60, −5)
	Inferior occipital gyrus	622/207	4.7 (45, −80, −4)/2.8 (−30, −82, −6)
	Lingual gyrus	356/1067	3.0 (27, −60, −6)/3.9 (−25, −72, −5)
	Cuneus	119/385	2.9 (3, −64, 31)/2.8 (−27, −86, 22)
	Basal ganglia		
	Caudate	148/533	3.5 (4, 7, −4)/3.9 (−4, 12, −1)
	Claustrum	148/144	3.1 (28, 16, 3)/3.8 (−34, 7, −2)
	Lentiform nucleus	−/119	−/2.7 (−30, −1, 1)
	Thalamus	119/296	2.5 (3, −12, 1)/3.4 (−9, −4, 7)
	Cerebellum		
	Declive	119/−	2.6(24, −66, −11)/−
	Pyramis	−/178	−/2.6(−31, −83, −34)

Group comparison	Brain region	*k* (voxels), right/left	Pseudo-t *(x, y, z)*, S right/left
	Inferior semi-lunar lobule	–/296	–/2.8 (−19, −83, −37)
SAD < HC			
	Frontal		
	Inferior frontal gyrus	296/385	4.5 (42, 22, 6)/5.2 (−42, 19, −1)
	Middle frontal gyrus	–/296	–/4.9(−27, −3,49)
	Temporal		
	Parahippocampal gyrus	–/267	–/4.6(−21, −9, −13)
	Insula	207/200	4.2 (39, 17, −l)/4.8 (−39, 19, 2)
Psychosis dimension contrast [*P*=0.005, uncorrected, k=100]			
SZ < BD-P			
	Frontal		
	Inferior frontal gyrus	1570/119	4.2 (37, 14, −13)/3.1 (−40, 16, −6)
	Superior frontal gyrus	–/119	–/3.0(−9, 62, 22)
	Middle frontal gyrus	119/–	3.0 (39, 55, 12)/–
	Temporal		
	Parahippocampal gyrus	919/444	3.8 (24, 5, −15)/3.4 (− 22, − 7, −17)
	Fusiform gyrus	563/–	3.4(39, −34, −17)/–
	Superior temporal gyrus	326/–	3.9(40, 11, −13)/–
	Uncus	148/296	3.8 (24, 6, −19)/3.6 (−24, −4, −20)
	Middle temporal gyrus	–/207	–/3.3 (−67, −39, −3)
	Insula	119/148	3.1 (40, 11, −4)/3.1 (−33, 13, −4)
	Cingulate gyrus		
	Posterior cingulate (BA 23, 29, 30, 31)	830/267	3.8 (6, −53, 19)/3.4 (−3, −53, 25)
	Posterior cingulate (BA 31)	356/385	3.3 (1, −51, 27)/3.2 (−1, −55,28)
	Parietal		
	Precuneus	237/237	3.2 (3, −60, 18)/3.1 (−4, −59, 21)
	Inferior parietla lobule	119/–	3.1 (50, −34, 22)/–
	Basal ganglia		
	Lentiform nucleus	267/	3.3 (15, 13, −6)/–
	Caudate	–/119	–/3.3(−6,4, −1)
	Cerebellum		
	Declive	237/	3.0(31, −53, −11)/–
	Culmen	119/	2.9(39, −39, −21)/–
SZ < SAD			
	Frontal		
	Middle frontal gyrus	1244/119	3.8(42,53, −13)/3.2 (−34, 53, −14)
	Inferior frontal gyrus	919/–	3.7 (27,31, −19)/–
	Superior frontal gyrus	474/503	3.5 (34, 49, −15)/3.3 (9, 57, 32)
	Paracentral lobule	–/119	–/3.2(−4, −44,53)
	Temporal		
	Fusiform gyrus	800/237	3.6(56, −32, −19)/4.1 (−37, −17, −26)
	Inferior temporal gyrus	593/207	3.7 (53, −30, −16)/3.7 (−40, −17, −28)

Group comparison	Brain region	k (voxels), right/left	Pseudo-t (x, y, z), S right/left
	Middle temporal gyrus	474/356	3.3 (48, −78, 14)/3.0 (−52, −67, 23)
	Parahippocampal gyrus	−/296	−/4.2 (−34, −20, −25)
	Uncus	119/267	3.3 (36, −14, −27)/4.7 (34, −17, −28)
	Superiore temporal gyrus	237/237	3.4 (50, −57, 28)/3.2 (−46, −50, 12)
	Cingulate gyrus		
	Posterior cingulate (BA 23, 29, 30, 31)	859/385	3.9 (3, −52, 15)/3.7 (−4, −51, 25)
	Posterior cingulate (BA 31, 32)	474/593	3.5 (4, −56, 26)/3.5 (−1, −51, 27)
	Anterior cingulate	385/−	3.0 (9, 35, 9)/−
	Parietal		
	Precuneus	770/415	3.3 (6, −59, 18)/3.4 (−7, −44, 51)
	Occipital		
	Middle occipital gyrus	1541/−	4.5(43, −78, −9)/−
	Inferior occipital gyrus	800/−	4.8(36, −88, −7)1−
	Lingual gyrus	356/−	3.4(30, −76, −10)/−
SAD < BD-P			
	Temporal		
	Parahippocampal gyrus	267/356	3.0(30, −15, −13)/3.8 (−19, −4, −15)
	Basal ganglia		
	Lentiform nucleus	356/207	3.9(15, 10, −2)/3.0(−25, 1, −6)
SAD > BD-P			
	Frontal		
	Middle frontal gyrus	119/−	3.0 (27, 39, 44)/−
	Middle occipital gyrus	237/−	3.2 (50, −68, −10)/−
	Cerebellum (Tonsil)	148/−	3.0(27, −53, −40)/−

SZ—individuals with schizophrenia, SAD—individuals with schizoaffective disorder, BD-P—individuals with psychotic bipolar I disorder, HC—healthy controls, BA—Brodmann area, FDR—false discovery rate correction for multiple comparisons.

Table 3

Regional cortical and subcortical volume differences between the psychosis groups and healthy controls, and across the psychosis dimension based on FreeSurfer analyses.

Region of interest	Volume (mm³), Mean ± S.D.				ANCOVA
	SZ	SAD	BD-P	HC	
Psychosis groups vs. healthy controls contrast					
Frontal					**SZ<HC**
Left inferior frontal gyrus (pars triangularis)	3058 ± 649	3576 ± 710	3489 ± 864	3830 ± 779	$F_{(1,25)}=9.74$, $P=0.005$ *
Left precentral gyrus	12755 ± 1587	13439 ± 1799	13013 ± 1658	13598 ± 1779	$F_{(1,25)} = 10.02$, $P=0.004$n
Right precentral gyrus	12730 ± 1697	13760 ± 1874	1334 ± 2099	13849 ± 1572	$F_{(1,25)}=10.23$, $P=0.004$ *
Right superior frontal gyrus	20304 ± 3226	21449 ± 3024	20846 ± 3259	21731 ± 2705	$F_{(1,25)} = 9.42$, $P=0.005$ *
Right paracentral lobule	3727 ± 599	4151 ± 853	3993 ± 603	4110 ± 455	$F_{(1,25)} = 10.02$, $P=0.004$n
Temporal					
Left middle temporal gyrus	10783 ± 1902	11694 ± 1774	10751 ± 2248	11368 ± 846	$F_{(1,25)}=5.85$, $P=0.023$
Left inferior temporal gyrus	10088 ± 1697	11217 ± 1981	10713 ± 2549	10734 ± 1621	$F_{(1,25)}=7.79$, $P=0.01$
Right middle temporal gyrus	11384 ± 1666	12160 ± 1919	11952 ± 2545	12393 ± 1119	$F_{(1,25)} = 7.83$, $P=0.01$
Parietal					
Left precuneus	9112 ± 1556	10039 ± 1332	10181 ± 2100	9700 ± 1087	$F_{(1,25)} = 6.23$, $P=0.02$
Left inferior parietal gyrus	12895 ± 2356	13793 ± 1780	12911 ± 2311	14187 ± 2636	$F_{(1,25)}=5.64$, $P=0.026$
Limbic (right hippocampus)	3916 ± 489	3815 ± 428	3975 ± 644	4091 ± 439	$F_{(1,25)}=4.63$, $P=0.041$
Right thalamus	6765 ± 793	6672 ± 852	6854 ± 1208	6799 ± 714	$F_{(1,25)}=6.36$, $P=0.02$
Right thalamus	6765 ± 793	6672 ± 852	6854 ± 1208	6799 ± 714	**SZ > HC**
Basal ganglia (left globus pallidus)	1808 ± 244	1634 ± 271	1691 ± 249	1569 ± 245	$F_{(1,25)} = 5.58$, $P=0.03$
Limbic					**SAD < HC**
Left hippocampus	4049 ± 496	3885 ± 439	4096 ± 610	4073 ± 324	$F_{(1,22)}=4.91$, $P=0.037$
Right hippocampus	3916 ± 489	3815 ± 428	3975 ± 644	4091 ± 439	$F_{(1,22)}=6.63$, $P=0.017$ *
Basal ganglia (right caudate)	3651 ± 618	3538 ± 399	3666 ± 532	3694 ± 410	$F_{(1,22)} = 5.24$, $P=0.032$
Right thalamus	6765 ± 793	6672 ± 852	6854 ± 1208	6799 ± 714	$F_{(1,22)} = 5.33$, $P=0.031$
Psychosis dimension contrast					

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	SZ	SAD	BD-P	SZ < **BD-P**
Frontal				
Left inferior frontal gyrus (pars triangularis)	3058 ± 649	3576 ± 710	3489 ± 864	$F(1,32)=4.59$, $P=0.039$
Left inferior frontal gyrus (pars opercularis)	4494 ± 869	4992 ± 722	5063 ± 1040	$F(1,32)=6.07$, $P=0.019$
Right superior frontal gyrus (paracentral lobule)	3727 ± 599	4151 ± 853	3993 ± 603	$F(1,32)=4.02$, $P=0.05$
Temporal				
Left parahippocampal gyrus	2381 ± 356	2604 ± 447	2635 ± 575	$F(1,32)=7.07$, $P=0.012$
Cingulate gyrus				
Left isthmus/central cingulate	2271 ± 391	2513 ± 460	2580 ± 636	$F(1,32)=5.72$, $P=0.023$
Parietal				
Left superior parietal gyrus	12878 ± 1805	13123 ± 1577	13766 ± 2503	$F(1,32)=4.63$, $P=0.039$
Left precuneus	9112 ± 1556	10038 ± 1332	10180 ± 2100	$F(1,32)=11.72$, $P=0.002$ *
Right precuneus	9165 ± 1267	9566 ± 1195	9820 ± 1859	$F(1,32)=6.04$, $P=0.02$
Occipital				
Left lingual gyrus	7478 ± 1175	7791 ± 1517	8330 ± 1928	$F(1,32)=7.93$, $P=0.008$ *
Right lingual gyrus	6794 ± 1222	6993 ± 1251	7434 ± 1549	$F(1,32)=5.66$, $P=0.023$
Right pericalcarine gyrus	2249 ± 554	2401 ± 491	2647 ± 561	$F(1,32)=6.11$, $P=0.019$
Limbic (Right amygdala)	1728 ± 379	1790 ± 279	1850 ± 220	$F(1,32)=4.25$, $P=0.047$
Left cerebellar cortex	52590 ± 6119	51376 ± 5193	49602 ± 6947	$F(1,32)=5.28$, $P=0.028$
				SAD > SZ
Temporal				
Left inferior temporal gyrus	10088 ± 1697	11217 ± 1981	10713 ± 2549	$F(1,31)=9.93$, $P=0.004$n
Cingulate gyrus				
Right rostral anterior cingulate	1784 ± 427	2073 ± 319	1839 ± 509	$F(1,31)=5.35$, $P=0.028$
				SAD < BD-P
Limbic				
Left hippocampus	4049 ± 496	3885 ± 439	4096 ± 610	$F(1,29)=9.64$, $P=0.004$n
Right hippocampus	3916 ± 489	3814 ± 428	3975 ± 644	$F(1,29)=6.76$, $P=0.014$ *
Left amygdala	1572 ± 265	1565 ± 155	1646 ± 322	$F(1,29)=5.49$, $P=0.026$
Right thalamus	6519 ± 669	6389 ± 745	6751 ± 1190	$F(1,29)=6.2$, $P=0.002$
Left thalamus	6765 ± 793	6672 ± 852	6854 ± 1208	$F(1,29)=11.5$, $P=0.019$
				SZ > BD-P
Basal ganglia				
Left globus pallidus	1808 ± 244	1634 ± 271	691 ± 249	$F(1,32)=5.81$, $P=0.02$ *
Right globus pallidu	1760 ± 261	1592 ± 317	1631 ± 241	$F(1,32)=5.07$, $P=0.031$
				SZ > SAD

	SZ	SAD	BD-P	
Left thalamus	6765 ± 793	6389 ± 745	6854 ± 1208	$F(1,29) = 6.20$, $P=0.019$
Cingulate gyrus				SAD > BD-P
Left caudal anterior cingulate	1957 ± 417	2139 ± 538	1811 ± 428	$F(1,29) = 5.89$, $P=0.022$

SZ—individuals with schizophrenia, SAD—individuals with schizoaffective disorder, BD-P—individuals with psychotic bipolar I disorder, HC—healthy controls, S.D.—standard deviation.

ANCOVA (analyses of covariance) were adjusted for age and intracranial volume. Only statistically significant between group differences are reported. Regions that remained significant after Bonferroni correction marked with asterisk. Bonferroni correction within each lobe/subcortical regions were applied: (1) frontal lobe included 11 regions (superior frontal gyrus, rostral and caudal middle frontal gyrus, pars triangularis, pars opercularis, pars orbitalis, medial and lateral orbito-frontal gyrus, frontal pole, precentral gyrus, and paracentral lobule), corrected $P=0.005$; (2) temporal lobe included 8 regions (superior, medial, inferior, transverse, fusiform, parahippocampal gyri, entorhinal cortex, and temporal pole), corrected $P = 0.006$; (3) cingulate gyrus included 4 regions (rostral and caudal anterior cingulate, isthmus and posterior cingulate), corrected $P=0.01$; parietal lobe included 5 regions (superior, inferior, precentral and supramarginal gyri, and precuneus), corrected $P=0.01$; occipital lobe included 4 regions (cuneus, lingual, pericalcarine, and lateral occipital gyri), corrected $P=0.01$; limbic system included 3 regions (hippocampus, amygdala, and thalamus), corrected $P=0.02$; basal ganglia included 3 regions (caudate, putamen, globus pallidus), corrected $P=0.02$.

Table 4

The schematic summary of neocortical and subcortical gray matter differences detected with the two volumetric methodologies: voxel-based morphometry and FreeSurfer.

	VBM			FS		
	Psychosis groups vs. healthy controls					
	SZ < HC	**SAD < HC**	**BD-P < HC**	**SZ < HC**	**SAD < HC**	**BD-P < HC**
Cortical regions						
Frontal	↓↓↓	↓	-	↓↓↓	-	-
Temporal	↓↓↓	↓	-	↓↓	-	-
Insular	↓↓↓	↓	-	-	-	-
Cingulate	↓↓↓	-	-	-	-	-
Parietal	↓↓	-	-	↓	-	-
Occipital	↓↓	-	-	-	-	-
Subcortical regions						
Hippocampus	-	-	-	↓	↓↓	-
Amygdala	-	-	-	-	-	-
Basal ganglia*	↓↓↑*	-	-	↑*↓	↓	-
Thalamus	↓	-	-	↓	↓	-
Cerebellum	↓	-	-	-	-	-
	Psychosis dimension					
	SZ < BD-P	**SZ < SAD**	**SAD < BD-P**	**SZ < BD-P**	**SZ < SAD**	**SAD < BD-P**
Cortical regions						
Frontal	↓↓	↓↓	←	↓↓	↓↓	-
Temporal	↓↓↓	↓↓↓	↓	↓	↓	-
Insular	↓	-	-	-	-	-
Cingulate	↓↓	↓↓↓	-	↓	↓	←
Parietal	↓	↓	-	↓↓	-	←
Occipital	-	↓↓	←	↓↓	-	←
Subcortical regions						
Hippocampus	-	-	-	-	-	↓↓
Amygdala*	-	-	-	↓*↓	-	↓*↓

	VBM			FS		
	Psychosis groups vs. healthy controls					
	SZ < HC	**SAD < HC**	**BD-P < HC**	**SZ < HC**	**SAD < HC**	**BD-P < HC**
Basal ganglia*	↓*	-	↓↓	↑↑*	-	-
Thalamus	-	-	-	-	↑	↓↓
Cerebellum	↓	-	↑	↓	-	-

VBM - Voxel-Based Morphometry, FS - FreeSurfer, SZ - individuals with schizophrenia, SAD - individuals with schizoaffective disorder, BD-P - individuals with psychotic bipolar I disorder, HC - healthy controls.

The regions with divergent VBM and FS findings are marked with an asterisk.