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Voxel-based morphometry of patients with schizophrenia or bipolar I disorder: A matched control study

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ABSTRACT

Controlled trials provide critical tests of hypotheses generated by meta-analyses. Two recent meta-analyses have reported that gray matter volumes of schizophrenia and bipolar I patients differ in the amygdala, hippocampus, or perigenual anterior cingulate. The present magnetic resonance imaging study tested these hypotheses in a cross-sectional voxel-based morphometry (VBM) design of 17 chronic schizophrenia and 15 chronic bipolar patients and 21 healthy subjects matched for age, gender and duration of illness. Whole brain gray matter volume of both the schizophrenia and bipolar groups was smaller than among healthy control subjects. Regional voxel-wise comparisons showed that gray matter volume was smallest within frontal and temporal regions of both patient groups. Region of interest analyses found moderately large to large differences between schizophrenia and healthy subjects in the amygdala and hippocampus. There were no group differences in the perigenual anterior cingulate. When schizophrenia and bipolar groups were directly compared, the schizophrenia group showed smaller gray matter volumes in right subcortical regions involving the right hippocampus, putamen, and amygdala. The hippocampal and amygdala findings confirm predictions derived from recent meta-analyses. These structural abnormalities may be important factors in the differential manifestations of these two functional psychotic disorders.

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1. Introduction

The issue of differences and similarities in the neuroanatomical structure between schizophrenia and bipolar disorder, and how each group differs from healthy individuals, is a long-standing question in psychiatry (Baumann and Bogerts, 1999). Over the past two decades, magnetic resonance imaging (MRI) has been useful in revealing neuroanatomical substrates in patients with bipolar disorder and schizophrenia. More recently, voxel-based morphometry (VBM) (Ashburner and Friston, 2000) has been increasingly applied to further elucidate structural brain changes associated with these functional mental disorders. VBM is a fully automated whole brain image analysis technique that involves the voxel-wise comparison of segmented gray and white matter between at least two groups of subjects (Ridgway et al., 2008). It allows for comprehensive exploration of whole brain structures that can be integrated with a priori hypotheses about regions of interest.

Two meta-analyses completed to date have sought to clarify the neuroanatomical differences between bipolar and schizophrenia patients and to identify differences between each patient group and healthy controls. In a meta-analysis of VBM studies that encompassed 2058 schizophrenia patients and 366 with bipolar disorder, Ellison-Wright and Bullmore (2010) found widespread gray matter reductions in the schizophrenia group compared with healthy controls that included the insula bilaterally, dorsolateral prefrontal cortex, superior temporal cortex, bilateral hippocampal–amygdala region, thalamus, anterior cingulate, medial frontal gyrus and posterior cingulate. Increases were found in the right globus pallidus extending to the head of the left caudate nucleus. In the same meta-analysis, smaller gray matter volumes were found in the right and left insula, perigenual anterior cingulate, and subgenual anterior cingulate in the bipolar studies, though not in the bilateral hippocampal–amygdala regions. The areas of reduced gray matter observed in studies of biplolar patients overlapped substantially with areas of reduced gray matter in schizophrenia patients, though the reductions seen bilaterally in the hippocampal–amygdala area among schizophrenia patients were not observed in bipolar patients. An area of the perigenual anterior cingulate cortex was selectively smaller among bipolar patients than healthy controls, a region where no differences between schizophrenia patients and healthy controls have been found. Arnone et al. (2009) carried out a meta-analysis of volumetric studies, using a variety of methods to segment magnetic resonance images, and found smaller volumes in the right amygdala among

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schizophrenia patients when they were directly compared with bipolar patients (Arnone et al., 2009). Moreover, Arnone found that age, illness duration, and gender were significant sources of heterogeneity in study findings (Arnone et al., 2009).

Although meta-analyses generally increase both statistical power and generalizability of results compared with individual studies, the results of meta-analysis are constrained by the quality of the studies comprising the analysis. A limitation of the literature available for the Ellison-Wright and Bullmore (2010) study was that few published VBM studies have directly compared schizophrenia with bipolar I patients. In our own PubMed search of the literature (December, 2010), we found only three papers when searching with the terms "VBM and schizophrenia and bipolar" or "voxel based morphometry and schizophrenia and bipolar" that reported using voxel based morphometry to study anatomical differences between schizophrenia and bipolar patients (McIntosh et al., 2004, 2006; Cui et al., 2010). Two of the papers reported on the same samples of patients and did not directly compare the two groups (McIntosh et al., 2004, 2006). The sparsity of VBM studies where schizophrenia and bipolar patients were matched on variables, such as chronicity, age, gender, and symptom severity, which are known to influence volumetric data, means that important sources of variation might not have been optimally controlled in current meta-analyses of the two patient groups (see also Yoshihara et al., 2008; Bose et al., 2009; Nesvåg et al., 2009; Sarnicola et al., 2009). Volumetric studies of schizophrenia patients and controls using methods besides VBM have directly compared schizophrenia patients and controls (Arnone et al., 2009). Among these studies, however, the wide variety of tissue segmentation, coregistration, normalization, and anatomical labeling methods used are an important uncontrolled source of variation.

Some clinical trials experts recommend performing a direct comparison of study medications whenever a meta-analysis indicates improved outcome for a particular drug (Chalmers, 1988). The aim of the direct comparison is to test hypotheses derived from meta-analysis in a controlled study. This recommendation appears useful when evaluating the results from any meta-analysis, especially from imaging meta-analyses that draw conclusions about morphometric differences among patient groups by comparing each group with healthy controls. Such conclusions not only rest on the assumption that patient groups do not differ on variables that might influence brain structure other than diagnosis, they also involve the assumption that the control groups used to study one patient group are comparable to controls used to study other patient groups. The meta-analyses reported by Ellison-Wright and Bullmore (2010) and by Arnone et al. (2009) identified several anatomical regions where morphometric measurements might differentiate schizophrenia and bipolar patients in a study of well matched patient groups. These include the perigenual anterior cingulate and hippocampal region reported by Ellison-Wright and Bullmore (2010) and the amygdala identified by both meta-analyses. The one VBM analysis that directly compared schizophrenia and bipolar patients did not confirm any of these findings, though the authors did not use regions of interest to directly confirm the findings of the previous meta-analyses (Cui et al., 2010).

The aim of the present study was to use whole brain and region of interest data to directly compare gray matter (GM) volumes in a cross-sectional design involving subjects with chronic schizophrenia, chronic bipolar I disorder, and healthy controls matched for age, gender and duration of illness. Based on previous meta-analytic studies, we tested the following hypotheses: 1) patients with schizophrenia as compared to matched patients with bipolar I disorder would show smaller GM volumes in the hippocampus and amygdala; 2) bipolar I disorder patients would show smaller GM volumes in the perigenual anterior cingulate cortex compared with matched schizophrenia patients. To aid in the interpretation of the results of the hypothesis testing, we also examined whether broad tissue compartments (gray matter, white matter, and ventricular volume) differed among the three groups studied and examined correlations of indices of psychopathology with GM volume.

2. Methods

2.1. Subjects

Seventeen subjects with schizophrenia (SZ) (eight males and nine females), 15 subjects with bipolar I disorder (BP) (seven males and eight females), and 21 healthy control (HC) subjects (10 males and 11 females) without psychiatric illness were studied (Table 1). BP and SZ subjects were recruited from outpatient mental health clinics at the University of California at San Diego and Veterans Affairs San Diego Healthcare System. Healthy controls were recruited from a community sample.

Study inclusion criteria were 1) age: 25–70; 2) duration of illness: over 3 years; and 3) DSM-IV criteria for schizophrenia or bipolar I disorder, as determined by the structured clinical interview (SCID) (First et al., 1995). Exclusion criteria were 1) lifetime history of neurologic illness; 2) head trauma leading to loss of consciousness; 3) history of electroconvulsive therapy; 4) DSM-IV substance abuse or substance dependence disorder; 5) Mini-Mental State Examination (MMSE)<25; and 6) contraindication to magnetic resonance (MR) scanning. The SCID was also administered to all HC subjects to exclude subjects with axis I or axis II psychiatric disorder.

Clinical evaluations (Table 1) included the Mini-Mental State Examination (MMSE) to exclude cognitive impairment (Folstein et al., 1975), the 28-item version of the Hamilton Depression Rating Scale (HDRS) to rate severity of depressive symptoms (Hamilton, 1960) and the Positive and Negative Syndrome Scale (PANSS) to rate severity of psychotic symptoms (Kay et al., 1987). HC subjects with neurologic or psychiatric histories, or with histories or current use of psychotropic medications were excluded. All subjects signed University of California, San Diego Institutional Review Board approved informed consent prior to undergoing study procedures.

2.2. MRI image acquisition

Scans were performed with a 1.5-Tesla Siemens Magnetom Vision scanner. Earplugs and headphones were provided to block the scanner noise. Structural images were obtained using a magnetization prepared rapid gradient-echo (MPRAGE) protocol (TR = 24 ms, TE = 5 ms, flip angle = 10°, 180 contiguous axial slices of 1.0 mm thickness, voxel size = 1.0 × 1.0 × 1.0 mm). Precautions were taken to minimize subjects' motion during the MRI study by instructing subjects to remain as still as possible and tightly packing the area around their heads with foam padding. Every scan was checked for image artifacts and gross anatomical abnormalities.

2.3. MRI image processing

Data analysis was performed using the SPM5 software package (Wellcome Department of Cognitive Neurology, London, UK) running under MATLAB 2006a (The MathWorks, Natick, MA, USA), as well as the VBM5 toolbox (http://dbm.neuro.uni-jena.de/vbm/vbm5-for-spm5/), which utilizes and extends the new unified segmentation approach implemented in SPM5 (Ashburner and Friston, 2005). The unified segmentation provides a generative model of VBM preprocessing that integrates tissue classification, image registration and MRI inhomogeneity bias correction. In addition, the VBM5 toolbox uses Hidden Markov Field (HMRF) model on the segmented tissue maps in order to increase the quality of segmentation (Cuadra et al., 2005). The HMRF algorithm provides spatial constraints based on neighboring voxel intensities within a 3 × 3 × 3 voxel cube. It removes isolated voxels which are unlikely to be a member of a certain tissue class and