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Brain structure in schizophrenia vs. psychotic bipolar I disorder: A VBM study

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ABSTRACT

While schizophrenia and bipolar disorder have been assumed to share phenotypic and genotypic features, there is also evidence for overlapping brain structural correlates, although it is unclear whether these relate to shared psychotic features. In this study, we used voxel-based morphometry (VBM8) in 34 schizophrenia patients, 17 euthymic bipolar I disorder patients (with a history of psychotic symptoms), and 34 healthy controls. Our results indicate that compared to healthy controls schizophrenia patients show grey matter deficits ($p < 0.05$, FDR corrected) in medial and right dorsolateral prefrontal, as well as bilaterally in ventrolateral prefrontal and insular cortical areas, thalamus (bilaterally), left superior temporal cortex, and minor medial parietal and parietooccipital areas. Comparing schizophrenia vs. bipolar I patients ($p < 0.05$, FDR corrected) yielded a similar pattern, however, there was an additional significant reduction in schizophrenia patients in the (posterior) hippocampus bilaterally, left dorsolateral prefrontal cortex, and left cerebellum. Compared to healthy controls, the deficits in bipolar I patients only reached significance at $p < 0.001$ (uncorr.) for a minor parietal cluster, but not for prefrontal areas. Our results suggest that the more extensive prefrontal, thalamic, and hippocampal deficits that might set apart schizophrenia and bipolar disorder might not be related to mere appearance of psychotic symptoms at some stage of the disorders.

1. Introduction

Brain structural changes have been demonstrated in schizophrenia and bipolar disorder and interest has grown regarding areas of spatial overlap, in particular as both disorders share some clinical features and risk genes (Thaker, 2008). Given that brain structural changes are a putative endophenotype of schizophrenia and possibly bipolar disorder as well, the comparison of changes occurring in both disorders is of particular interest in understanding putative biomarker characteristics, for example with respect to specificity to a particular disorder or symptom characteristics.

Initial comparative studies have suggested that patients with schizophrenia might show volume loss in middle prefrontal and thalamic regions (McIntosh et al., 2004), and in total hippocampal volume (McDonald et al., 2006). Another study suggested more widespread prefrontal and temporal grey matter loss in schizophrenia, but not in bipolar disorder, for which sparing of cortical changes was observed (McDonald et al., 2005).

Subsequently, studies applying voxel-based morphometry (VBM) have been conducted to compare patients with schizophrenia and bipolar disorder. There has been some support from the notion of these initial studies that fronto-temporal grey matter deficits are more extensive in schizophrenia than in (psychotic) bipolar disorder (Brown et al., 2011; Molina et al., 2011; Ivleva et al., 2012; Yuksel et al., 2012), but results have been rather inconclusive for the thalamus and hippocampus, which had been as further focus of earlier studies.

Another approach to compare brain structural changes has been to conduct meta-analyses of VBM studies in these disorders (Bora et al., 2012): the results indicate that the observed changes within the prefrontal areas may differ in location, with schizophrenia showing reductions in dorsolateral prefrontal cortex (DLPFC) and anterior cingulate cortex (ACC) vs. fronto-insular reductions in bipolar disorder. Another aspect of this meta-analysis, which has been highlighted by a subsequent review of meta-analyses by Crow et al., is the issue of laterality (Crow et al., 2013): these authors identified a pattern of diverging laterality, which might be explained by the gender ratio across studies. Indeed, the meta-analysis by Bora et al. shows that the changes in bipolar disorder mostly manifest in the right hemisphere (e.g. right

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fronto-insular cortex, right subgenual/medial prefrontal, and right ACC/medial prefrontal cortex), while changes in schizophrenia studies more frequently show changes in right hemisphere structures (Bora et al., 2012). Differences in gender composition, esp. higher rates of male patients with schizophrenia, who might show more severe illness, might be a contributing factor.

However, such meta-analyses are limited as they normally do not include direct comparison between schizophrenia and bipolar disorder groups, and because it is also difficult to control for the numerous smaller systematic differences across studies, such as gender imbalance, details of VBM pre-processing and analyses. In fact, the current meta-analyses (Ellison-Wright and Bullmore, 2010; Yu et al., 2010; Bora et al., 2012) do not take into account those original studies (mostly published after these meta-analyses), which directly compare schizophrenia vs. bipolar disorder cohorts, and they do not take into account the heterogeneity within the patient samples (esp. the bipolar cohorts), which often include both bipolar I and II patients, as well as those with and without psychotic symptoms.

In this study, we aimed to add new insight to the ongoing study of brain structural differences between schizophrenia and bipolar disorder. We focused on comparing schizophrenia patients with a subgroup of bipolar disorder patients with (previous) psychotic symptoms, using an updated version of VBM, as implemented in the VBM8 toolbox, and restricting recruitment of patient to those in remission. Based on the cited previous studies, we hypothesised that schizophrenia patients would show volume reductions in DLPFC, thalamus, and hippocampus, exceeding those seen in (euthymic) bipolar disorder patients.

2. Methods

2.1. Subjects

We included a total of 85 subjects, who had provided written informed consent to study protocols approved by the Ethics Committee of the Friedrich-Schiller-University Medical School and in accordance with the current version of the Declaration of Helsinki. We only included subjects able to provide consent to participate in compliance with the Declaration of Helsinki, as well as local and national regulations. Our study included three groups recruited from in-patient, day clinic, and out-patient services of Jena University Hospital (in the case of patients) or the local community (healthy controls). General exclusion criteria for all subjects were: history of traumatic brain injury, concurrent substance dependence, learning disability or estimated IQ smaller than 80 (estimated from the German MWT-B, a test to estimate pre-morbid IQ, similar to the NART), as well as general exclusion criteria preventing MRI studies. Psychopathology ratings in patients were obtained by a board-certified psychiatrist (I.N.). Demographic group details are given in Table 1.

Group 1 (Sz) included 34 subjects with a DSM-IV diagnosis of schizophrenia as diagnosed by a board certified psychiatrist; all (except n = 3) of these patients had been ill for more than 2 years (thus meeting DSM-IIIR criteria for chronic schizophrenia) and were enrolled and scanned while being in remission, i.e., not during an active psychotic episode. Patients had previously met the criteria for paranoid subtype, but at the time of scanning (i.e. after remission) they were classified as residual type. Current psychopathology was rated using the Scales for Assessment of Positive Symptoms (SAPS), and Negative Symptoms (SANS), as well as the Brief Psychiatric Rating Scale (BPRS). Psychopathology ratings, along with clinical information are given in Table 1. Most schizophrenia patients were on stable antipsychotic medication with either one second-generation antipsychotic (n = 18) or a combination of two second-generation antipsychotics (n = 12), and n = 4 were currently off antipsychotic medication; antipsychotics used included (note multiple use in some patients): amisulpride (n = 7; 200–800 mg/d), aripiprazole (n = 11; <5–20 mg/d), quetiapine (n = 19; 50–800 mg/d), olanzapine (n = 2; 10–20 mg/d), risperidone (n = 4; 1–4 mg/d plus long-acting in n = 3 patients), and clozapine (n = 8; 100–400 mg/d); one patient received lithium (n = 1) and n = 4 were additionally on an antidepressant (either citalopram or venlafaxine).

Group 2 (BP) included 17 subjects with a DSM-IV diagnosis of bipolar I disorder, as established by a board-certified psychiatrist (I.N.); in addition to meeting this diagnosis, all patients were euthymic at the time of the scan, which was defined by: a) lack of a current depressive, (hypo)manic, or mixed affective episode (as defined by DSM-IV criteria), and b) maximum scores of 7 on the Young Mania Rating Scale (YMRS), and Hamilton Depression Scale (HAMD). These BP patients had experienced psychotic symptoms during previous mood episodes in the past (either grandiose delusions, delusions of reference, or persecutory delusions). Two of the patients had a history of alcohol abuse (but not dependence), but no concurrent abuse/dependence. All of the BP patients were on stable mood stabilising and/or antipsychotic medication (n = 3 were on lithium only, n = 5 on lithium plus an atypical antipsychotic; one patient each was on valproic acid or pregabalin monotherapy, resp.; one was on valproic acid plus an atypical antipsychotic; n = 3 were on monotherapy with an atypical antipsychotic, and n = 2 were on monotherapy with an atypical mood-stabilising antipsychotic, and in one case information was not available).

Group 3 (HC) consisted of 34 healthy controls recruited from the community, none of whom had a concurrent or previous psychiatric or neurological disorder, psychotherapeutic treatment, psychotropic medication, or a first-degree relative with a psychotic or affective disorder.

The three groups did not differ in age (ANOVA; p = 0.294), gender (Chi^2-Test; p = 0.724), handedness (comparing laterality scores derived from the Edinburgh Handedness Inventory EHI (Oldfield, 1971): ANOVA; p = 0.174), or estimated pre-morbid IQ based on MWT-B scores (ANOVA; p = 0.500).

Demographic details as well as an overview of the clinical characteristics of the samples are given in Table 1.

2.2. MRI acquisition and VBM analysis

We acquired high-resolution T1-weighted MRI scans on a 3 Tesla scanner (Siemens Tim Trio, Siemens, Erlangen, Germany) using a MPRAGE sequence (TR 2300 ms, TE 3.03 ms, TI 900 ms, alpha 9°) with an isotropic voxel resolution of $1 \times 1 \times 1$ mm^3 (192 sagittal slices, in-plane resolution 256×256). All scans successfully passed a quality assessment protocol, which included first a visual inspection for gross artefacts

Table 1
Demographic details of the three study groups.

	HC (healthy controls)	SZ (schizophrenia)	BP-I (bipolar I disorder w/ psychotic symptoms)
n	34	34	17
Gender distribution (female/male)	16/18	13/21	8/9
Age (mean and SD)	34.33 (10.62)	32.97 (8.91)	37.69 (11.13)
Age range	20.77–55.49a	21.39–51.43a	23.84–57.77a
Duration of illness: mean (SD)	n/a	8.9 (5.9)	9.9 (8.7)
SAPS score: mean (SD) and range	n/a	20.9 (11.3) 5–42	n/a
SANS score: mean (SD) and range	n/a	44.1 (15.3) 11–74	n/a
BPRS score: mean (SD) and range	n/a	39.1 (7.1) 23–54	n/a
YMRS score: mean (SD) and range	n/a	n/a	2.7 (2.2) 0–7
HAMD score: mean (SD) and range	n/a	n/a	2.7 (2.3) 0–7

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