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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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followed by an automated quality control using the VBM8 toolbox (http://dbm.neuro.uni-jena.de/vbm/check-sample-homogeneity).

For morphometric analysis, we used VBM8 (http://dbm.neuro.uni-jena.de/vbm8/), which is a freely available toolbox (developed by C.G.) integrated in the Statistical Parametric Mapping (SPM) software (Functional Imaging Laboratory, UCL, London; http://fil.ion.ucl.ac.uk/spm/). It makes use of the DARTEL algorithm for high-resolution spatial transformation processes, which includes a segmentation of the original T1-weighted images into grey matter, white matter and CSF/other maps. We used an internal threshold of 0.2 for grey matter (i.e. including only voxels as grey matter when they had a probability of 0.2 or higher for being grey matter), which is a more conservative measure than the commonly used 0.1 threshold, but reduces potential misclassification of voxels, esp. with respect to grey-matter borders. Images were smoothed with a 12 mm FWHM Gaussian kernel (Table 2).

2.3 . Statistical analysis

For statistical assessment, we considered a GLM (general linear model) implemented in SPM8, defining the three groups, as well as the variables age and gender (to exclude variance related to them, i.e. defining them as nuisance variables). We first tested the general effect of diagnosis (across the three groups) at a threshold of $p < 0.05$ with FDR correction for multiple comparisons. This was followed up by pair-wise direct comparisons between two groups on a post hoc basis, again applying a threshold of $p < 0.05$ (FDR corrected), i.e. analyses of a) comparison of HC vs. Sz, b) comparison of BP vs. Sz, and c) comparison of BP vs. Sz (and vice versa).

3. Results

The analysis of main effect of diagnosis, as shown in Fig. 1, Table 2 (A) revealed wide-spread effects in multiple frontal, temporal, and thalamic areas.

Contrasting Sz vs. healthy controls, the schizophrenia group showed several areas of cortical deficits, including right dorsolateral prefrontal, bilateral medial prefrontal, bilateral ventrolateral prefrontal and insular cortical areas, left medial temporal, as well as thalamus (bilateral), left superior temporal cortex, and minor right cerebellar and right temporal pole areas. There were no areas of higher grey matter values in schizophrenia patients compared to controls. Results are shown in Fig. 2, Table 2 (B).

Contrasting the schizophrenia with the psychotic bipolar I disorder group, there were similar effects, showing deficits of the schizophrenia group in bilateral medial prefrontal, bilateral dorsolateral prefrontal, thalamic, insular/ventrolateral prefrontal, and superior temporal cortical areas; in addition, there were significant effects in both medial temporal lobes, including the posterior hippocampus (bilaterally), right cerebellum, and also the infragenual cingulate cortex and adjacent orbitofrontal cortex. Results are shown in Fig. 3, Table 2 (D). There were no areas with the schizophrenia group showing higher grey matter values compared to the bipolar I disorder group.

Comparison of the BP group with healthy controls failed to show significant prefrontal or medial temporal areas at $p < 0.05$ FDR, but at $p < 0.001$ (uncorrected) only revealed a small right parietal cluster (supramarginal gyrus) and a left parieto-occipital cluster (shown in Fig. 4).

4 . Discussion

In this VBM study, we compared remitted schizophrenia patients with euthymic bipolar I disorder patients (with previous psychotic symptoms), and healthy controls using VBM. Our findings corroborate the assumption of widespread medial and lateral prefrontal grey matter losses in schizophrenia, but not in bipolar patients. In addition, we provide evidence for insular and thalamic reductions compared to controls, but only for schizophrenia and not bipolar patients.

As mentioned, there is considerable heterogeneity in the few studies that have directly compared schizophrenia and bipolar patients. Reasons for this might include minor differences in VBM methodology, medication effects, limited sample sizes, and more importantly also the choice of particular bipolar (sub)groups, as most but not all bipolar cohorts included psychotic bipolar disorder patients.

The finding of prefrontal and superior temporal changes is in line with the notion of schizophrenia being associated with more extensive brain structural changes than bipolar disorder, especially in the prefrontal cortex. Reviewing the more recent VBM studies, both the location and extent of these prefrontal changes, however, vary considerably from smaller clusters in the medial and lateral PFC (Brown et al., 2011; Cui et al., 2011) to more extensive changes spanning most of the DLPFC (Molina et al., 2011; Ivleva et al., 2012; Yuksel et al., 2012). Interestingly, the location of changes seems to vary even more. In our study, the comparison between schizophrenia and healthy controls yielded strongest PFC findings in ventrolateral PFC and medial PFC regions, with minor deficits in the more superior part of the DLPFC. Changes in the middle and superior prefrontal cortex have, indeed, been featured only in a minority of studies (Ivleva et al., 2012), while medial PFC and ACC changes, although often smaller, have been reported in several studies (Brown et al., 2011; Molina et al., 2011; Ivleva et al., 2012). Hence, although PFC changes compared to either healthy controls or bipolar patients are one of the most consistent features of VBM studies, there is limited knowledge on the factors contributing to regional heterogeneity. Psychosis severity or duration has been assessed in one previous study, which did not provide clear evidence for this factor contributing to any noteworthy changes. It is unclear to which extent genetic factors may impact on the overlap of prefrontal findings (or lack thereof). A large twin study did not provide support for (shared) genetic liability of prefrontal cortices, but it did for parahippocampal and orbitofrontal cortices (Hulshoff Pol et al., 2012).

The common (and conceivable) interpretation of these changes reflecting the more severe and detrimental clinical course of schizophrenia compared to bipolar disorder, however, is only partly supported by the data. Even when selecting bipolar I disorder patients with (previous) psychotic features, a subgroup of bipolar disorder most similar to schizophrenia in clinical phenotype, there is a lack of valid instruments to assess and compare overall disease severity both cross-sectionally and longitudinally. There seems to be a tendency for some of the mentioned studies (Brown et al., 2011; Molina et al., 2011; Yuksel et al., 2012), as well as our own findings, to actually show little if any PFC grey matter loss in (psychotic) bipolar disorder. One potential reason for this might be lack of statistical power, given that the bipolar groups in those studies, including our own, were notably smaller than either schizophrenia or healthy control cohorts. In spite of the fact that our study adds to an increasing consistency for PFC findings with this type of morphometric analysis, there are still major obstacles in interpreting findings as either supportive or refusing the classical Kraepelinian dichotomy. The study by Ivleva et al. is so far the only to use a patient group with schizoaffective disorder, finding intermediate results in several grey matter parameters, which would indeed suggest an actual continuum possibly related to overall (typical) disease course (Ivleva et al., 2012). One smaller VBM study in bipolar disorder patients with mood-incongruent psychotic symptoms (persecutory delusions) did find left DLPFC reductions compared to healthy controls, but there was no comparison with schizophrenia patients (Tost et al., 2010).

Findings in other brain regions, however, appear to be more consistent. Our own data show strong effects of volume loss in the thalamus in schizophrenia patients compared to both healthy controls and bipolar subjects. This replicates and extends findings of several of the previous studies identifying such an effect comparing schizophrenia patients to either healthy controls or bipolar patients (Brown et al., 2011; Molina et al., 2011; Ivleva et al., 2012), thus lending support to relative

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Table 2
Significant clusters of grey matter differences in voxel-based morphometry (VBM) analysis ($p < 0.05$, FDR corrected; only clusters $k = 5$ or larger are mentioned).

Co-ordinates of maximum voxel	k (number of voxels)	F	Anatomical region
A) Effect of group			
−40, −9, −3	19,035	19.98	Left hemisphere cluster, including: insula, left superior and middle temporal cortex and Heschl gyrus, left lateral prefrontal cortex, left amygdala and hippocampus, left inferior parietal
33, 17, −0	30,663	19.58	Right hemisphere cluster, including: insula, left superior and middle temporal cortex and Heschl gyrus, thalamus, left lateral prefrontal cortex, amygdala, hippocampus, parahippocampal cortex, left cerebellum
15, 53, 6	9935	14.72	Bilateral superior medial prefrontal and anterior cingulate cortex, bilateral orbitofrontal cortex, left SMA
−30, −91, 25	1256	10.61	Left middle and superior occipital cortex
10, −64, −59	2971	9.64	Right (and left) cerebellum, vermis
44, −40, 31	77	8.22	Right supramarginal gyrus
58, −7, 42	27	6.90	Right precentral and postcentral gyrus
−14, −21, −18	61	6.61	Left parahippocampal cortex
20, −42, −24	630	6.52	Right cerebellum
8, 21, −11	698	6.37	Right medial orbitofrontal and olfactory cortex, bilateral gyrus rectus
46, −60, −42	574	6.21	Right cerebellum
39, −42, 48	92	6.06	Right inferior and superior parietal cortex
69, −10, −12	38	5.94	Right middle and superior temporal gyrus
18, 12, 67	128	5.91	Right SMA and superior frontal cortex
21, −79, −15	97	5.84	Right cerebellum, right fusiform and lingual cortex
27, −85, −3	23	5.80	Right lingual and fusiform cortex
−15, −42, 57	36	5.74	Left precuneus
−45, 50, 8	60	5.70	Left middle orbitofrontal cortex
−14, −87, −5	21	5.69	Left lingual, middle occipital, calcarine cortex
39, 14, −48	41	5.54	Right middle temporal pole
36, −84, −39	85	5.50	Right cerebellum
32, −55, −30	45	5.27	Right cerebellum
Co-ordinates of maximum voxel	k (number of voxels)	T	Anatomical region
B) Healthy controls > schizophrenia patients			
32, 18, 1	38,193	5.29	Right hemisphere cluster, including: superior temporal, superior, middle, and inferior temporal pole, amygdala and hippocampus, inferior lateral prefrontal, middle and posterior cingulated, supramarginal, olfactory, and fusiform cortices, Left thalamus
−38, 17, −3	44,241	5.20	Left hemisphere cluster, including: superior and middle temporal, superior middle prefrontal, middle and inferior lateral prefrontal, anterior and middle cingulate, inferior parietal, fusiform, orbitofrontal cortices, temporal pole, SMA, insula, left amygdala and hippocampus
−30, −91, 25	4067	4.54	Left middle, superior, inferior occipital cortices, left calcarine, left lingual, left cuneus, left fusiform
10, −64, −59	22,887	3.66	Bilateral cerebellum
−16, −43, 55	415	3.11	Left precuneus, left postcentral, left superior parietal cortex
−28, 17, 37	141	3.02	Left middle frontal cortex (lateral)
27, −93, 21	276	2.56	Right superior and middle occipital cortex, right cuneus
−6, 21, 63	18	2.45	Left SMA and medial superior frontal
58, −66, −5	50	2.39	Right inferior and middle temporal cortex
27, 30, 52	5	2.31	Right superior frontal cortex
18, −94, 13	5	2.28	Right cuneus
C) Healthy controls > bipolar I disorder patients (with previous psychotic symptoms)			
No significant clusters at $p < 0.05$ FDR			
D) Bipolar I disorder patients (with previous psychotic symptoms) > schizophrenia patients			
−39, −10, −5	108,936	6.12	Bilateral hemisphere cluster, including: Bilateral insular cortices, inferior and middle lateral prefrontal cortices, medial prefrontal cortices, anterior and posterior cingulate cortices, superior temporal cortices (extending to Heschl's gyri), bilateral thalamus, bilateral temporal polar cortices, precuneus and cuneus, bilateral lingual and fusiform cortices, right and left amygdala, right and left parahippocampal cortex, vermis, lateral cerebellum (bilateral); right SMA; left caudate and putamen;
58, −7, 42	236	3.58	Right precentral and postcentral gyri
−36, −94, 10	543	3.32	Left middle occipital cortex
32, −10, −42	587	3.28	Richt fusiform and parahippocampal cortex
69, −12, −12	362	3.08	Right middle and superior temporal gyri
39, −66, 49	409	2.90	Right angular gyrus (and right superior parietal cortex)
−54, −66, 37	87	2.66	Left angular gyrus (and right superior parietal cortex)
21, −91, 31	42	2.50	Right superior occipital cortex
−32, −13, −44	69	2.50	Left fusiform and inferior temporal cortex

specificity of thalamic changes for schizophrenia. A recent study of thalamic shape in schizophrenia-spectrum disorders vs. bipolar disorder did, however, not report significant differences (Womer et al., 2014), which might be related to the type of morphometric changes assessed.

Notably, a more recent study has also suggested that planum temporale morphology might be a good parameter allowing discrimination between schizophrenia and bipolar disorder (Ratnanather et al., 2013). While our study found reduced superior temporal cortical grey matter in schizophrenia (compared to either of the other two groups), there was no difference between the bipolar patients and healthy controls.

Recent work has shown that laterality and effects related to gender distribution might be a major aspect in the divergence of brain structural effects across the schizophrenia–bipolar spectrum (Crow

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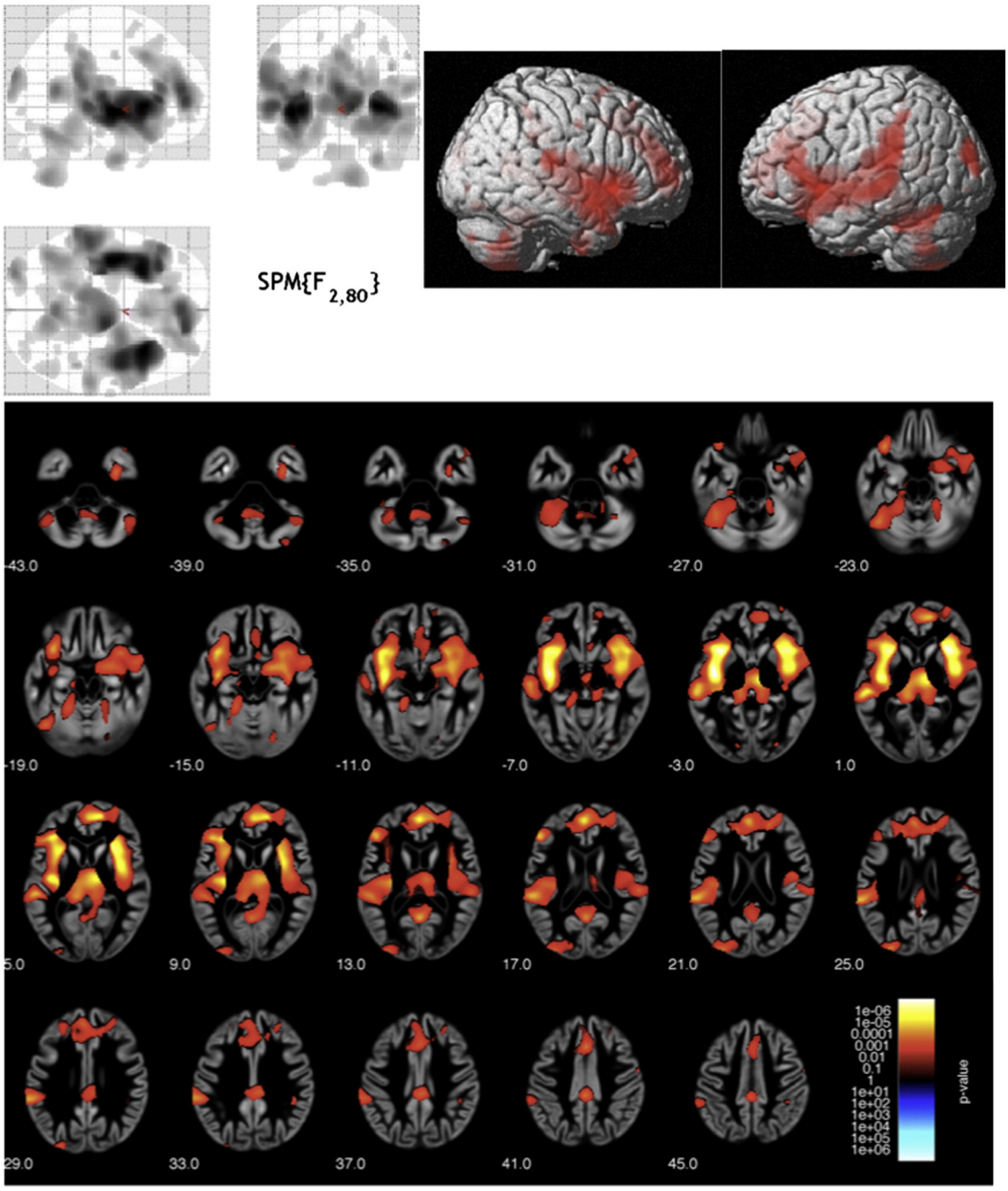

Fig. 1. VBM analysis of group effects (schizophrenia; bipolar; healthy controls) on regional brain grey matter ($p < 0.05$; FDR correction); top left: maximum intensity projection (MIP), top right: render views (significant voxels projected onto surface); bottom: selected sections.

et al., 2013). As noted in an earlier meta-analysis (Bora et al., 2012), the difference in gender balance across schizophrenia vs. bipolar samples (with the former often including more male patients, who might show a more severe course of illness) might substantially contribute to results. It is therefore worthwhile pointing out that our samples were gender-balanced, hence the much stronger and more widespread effects in schizophrenia patients (as opposed to bipolar patients) cannot be reduced to a mere gender effect. Yet, our findings have a distribution pattern of left vs. right hemisphere changes, which are consistent with the conclusion derived by Crow et al., whereby changes in schizophrenia are more prominent in the left hemisphere and those in bipolar more in the right hemisphere. As shown in Fig. 2, the spatial extent of mid-dorsolateral and superior temporal effects in schizophrenia appears to be stronger in the left hemisphere. However, it should be pointed out that VBM studies normally do not assess laterality in a strict sense, for example as expressed in a laterality index.

The main limitations of our study are the limited sample size, lack of a non-psychotic patient group, and potential medication effects. Although our samples were larger than in several other studies, the bipolar group was substantially smaller than the other two (mostly owing to the restrictive inclusion criteria, which also asked for euthymic state at the time of scanning). All of our patients were medicated, and

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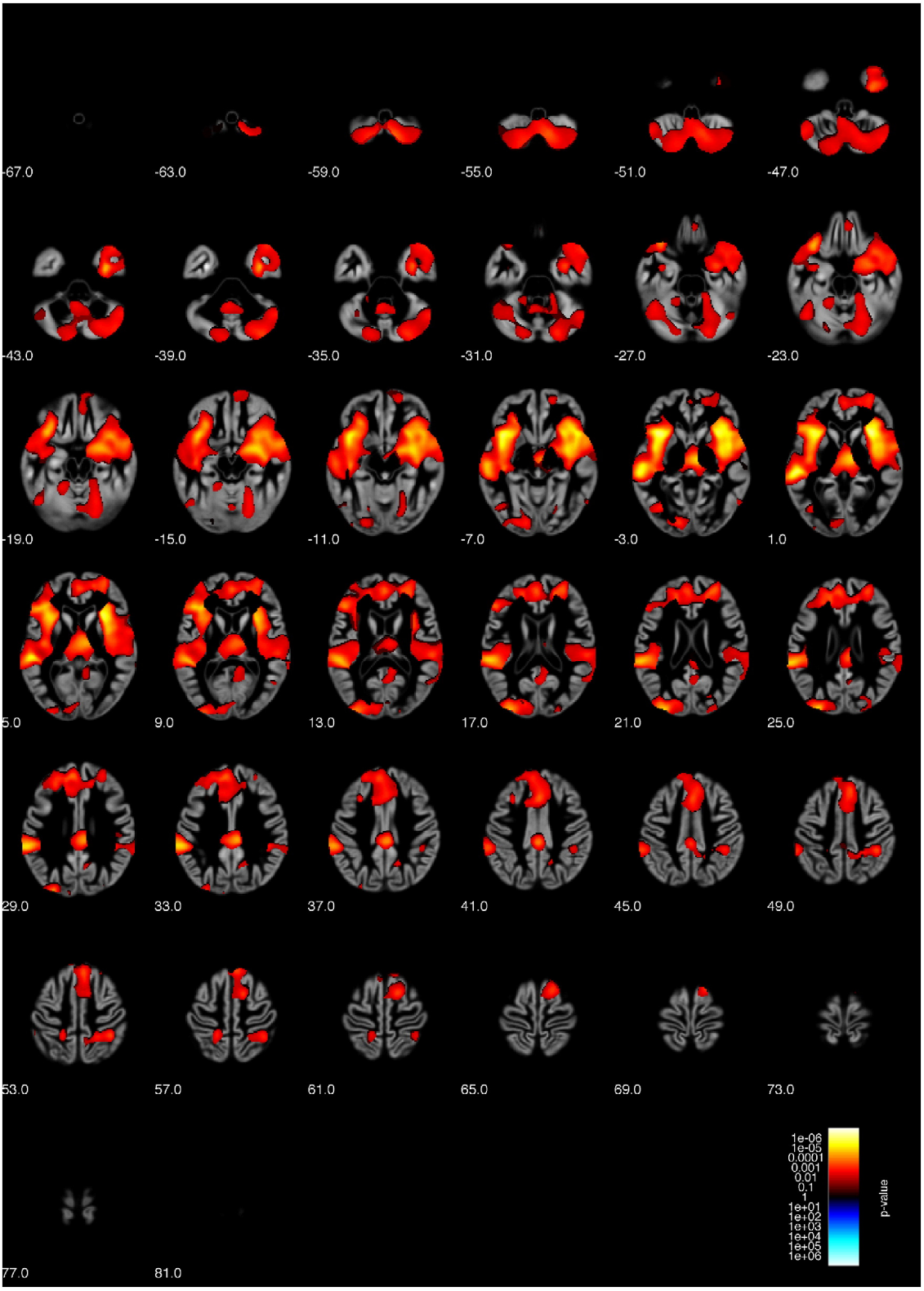

Fig. 2. VBM comparison of healthy control group vs. schizophrenia group: significant clusters ($p < 0.05$, FDR correction) are colour coded with significance levels given in colour scheme (bottom right), superimposed on standard grey matter axial images; numbers indicate axial levels. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

although previous continuum analyses have suggested that at least mood-stabilisers do not interfere significantly, it is a noteworthy and potential confound (Ivleva et al., 2012). Given that retrospective assessment of several years of (antipsychotic) medication is difficult, our study cannot rule out differential medication effects between the two patient groups. While our design was chosen to focus on a psychotic

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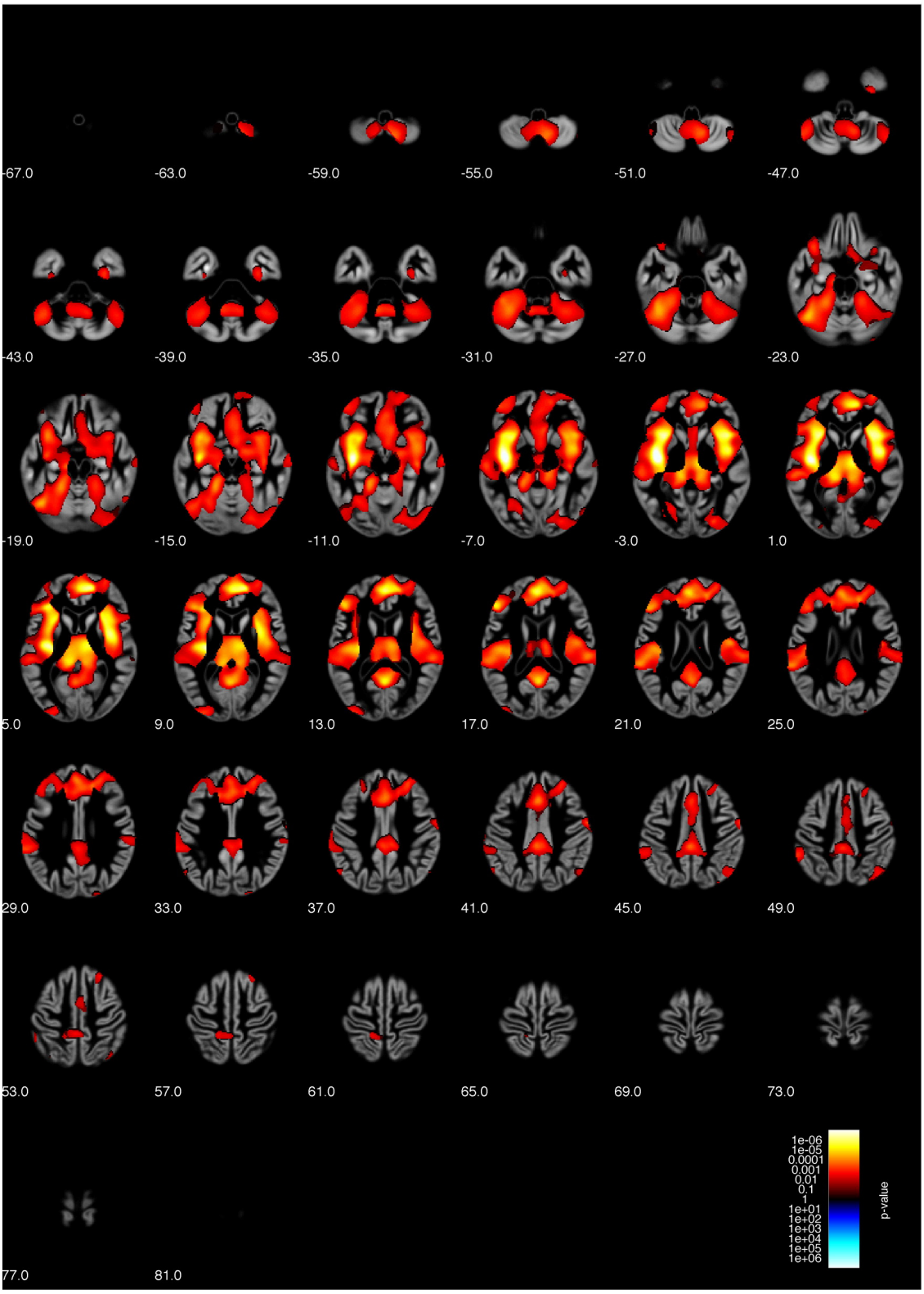

Fig. 3. VBM comparison of psychotic (currently euthymic) bipolar I disorder group vs. schizophrenia group: significant clusters ($p < 0.001$) are colour coded with significance levels given in colour scheme (bottom right), superimposed on standard grey matter slices; numbers indicate axial levels. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

subgroup of bipolar patients, future studies might include non-psychotic controls to enhance the detection of specificity for either disease entity or major clinical phenotypes, such as psychotic symptoms/episodes. It might be stressed that the bipolar group included in the present study probably has most similarities to schizophrenia, when considering the bipolar spectrum.

Taken together, our findings extend previous VBM studies, providing evidence for more extensive prefrontal and thalamic grey matter loss

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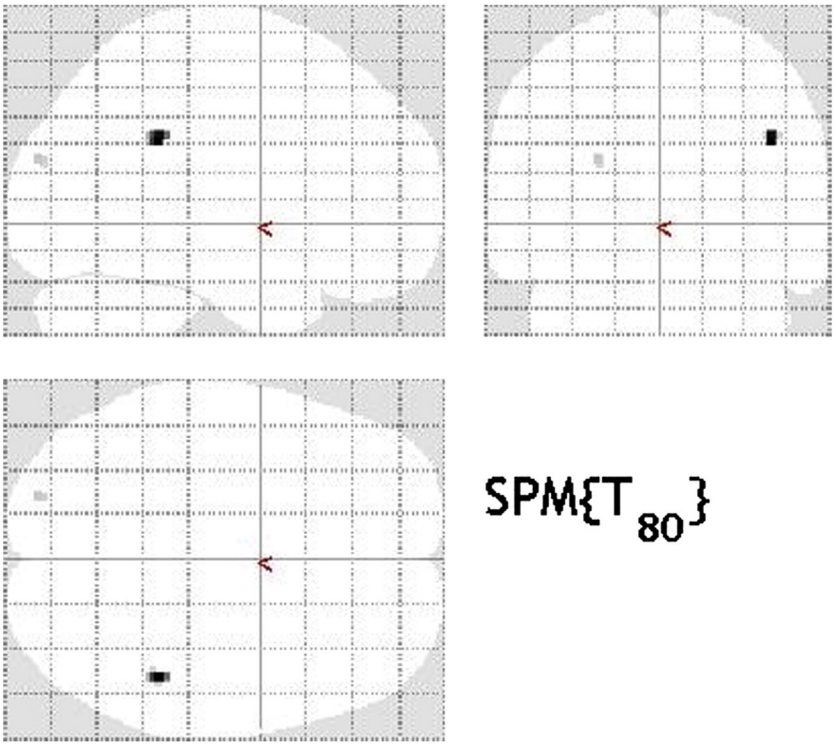

Fig. 4. Maximum intensity projection (MIP) of comparison healthy controls vs. psychotic (currently euthymic) bipolar I disorder group for grey matter VBM analysis ($p < 0.001$, uncorrected) showing two significant clusters in the right supramarginal gyrus (maximum voxel co-ordinates: 44; −40; 31) and left superior occipital cortex (−24; −87; 24).

in schizophrenia compared to bipolar disorder. Defining clinical phenotypes for selection of appropriate study designs remains a crucial issue.

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The authors declare that the funding institutions had no influence on the analyses carried out and presented here.

Contributors

I.N. and C.G. designed the study.

I.N., K.L., M.D., St.S., and H.S., contributed to patient recruitment and scanning.

I.N., R.M., K.L., M.D., C.L., J.R.R., St.S., and C.G. contributed to data collection, processing, and pre-processing.

I.N., R.M., C.L., and C.G. contributed to implementation of the image processing pipeline and imaging data analysis.

I.N. wrote the first drafts of the manuscript and all authors commented on/approved the final version.

Conflicts of interest statement

The authors declare that they have no conflicts of interest, in particular no relevant financial interests. The funding institutions had no influence on the analyses carried out and presented here.

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