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Distinct pattern of brain structural deficits in subsyndromes of schizophrenia delineated by psychopathology

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ABSTRACT

Brain morphological changes are among the best-studied potential endophenotypes in schizophrenia and linked to genetic liability and expression of disease phenotype. Yet, there is considerable heterogeneity across individual subjects making its use as a disease-specific marker difficult. In this study we consider psychopathological variability of disease phenotype to delineate subsyndromes of schizophrenia, link them to distinct brain morphological patterns, and use a classification approach to test specificity of achieved discrimination. We first applied voxel-based morphometry (VBM) to compare 99 patients with DSM-IV schizophrenia (stable psychopathology and antipsychotic medication) with 113 matched healthy controls, then delineated three subgroups within the patient cohort based on psychopathology pattern and compared differential patterns of grey matter abnormalities. Finally, we tested accuracy of assigning any individual MRI scan to either the control group or any of the three patient subgroups. While VBM analysis showed overlap of brain structural deficits mostly in prefrontal areas, the disorganised subsyndrome showed stronger deficits in medial temporal and cerebellar regions, the paranoid/hallucinatory subsyndrome showed additional effects in the superior temporal cortex, and the negative subsyndrome showed stronger deficits in the thalamus. Using an automated algorithm, we achieved 95.8% accuracy classifying any given scan to one of the subgroups. Patterns of psychopathology are meaningful parameters in reducing heterogeneity of brain morphological endophenotypes in schizophrenia.

Introduction

The clinical heterogeneity of schizophrenia is a major obstacle in identifying both phenotypes suitable as potential disease markers as well as studying the complex genetics of this disorder. Among the most robust biological markers of pathology in schizophrenia are alterations in brain structure as detected with magnetic resonance imaging (MRI). Grey matter reductions are already observed at the onset (Steen et al., 2006) of the disorder and possibly at prodromal stages (Pantelis et al., 2003) while showing modest disease-related subsequent progression (Weinberger and McClure, 2002). Studies in siblings (Honea et al., 2008) and in twins (Hulshoff Pol et al., 2004; Hulshoff Pol et al., 2006) furthermore demonstrate genetic influence on grey matter reductions. The most consistently reported regional abnormalities beside the enlargement of the lateral ventricles are grey matter reductions in the medial temporal lobe (hippocampus and amygdala), thalamus, prefrontal cortex, superior temporal cortex (Honea et al., 2005; Wright et al., 2000), and more recently also the cerebellum (Andreasen and Pierson, 2008). While this underlines the potential usefulness as an endophenotype for this disorder (Goldman et al., 2008), there are also limits to its use as a biological marker for schizophrenia. Using conventional volumetric or morphometric approaches, none of the single regional alterations on its own is either sensitive or specific enough to distinguish patients from control subjects.

Strategies aimed at overcoming these difficulties have included studies within the schizophrenia spectrum disorders (Hazlett et al., 2008; Takahashi et al., 2006) as well as comparison to other disorders sharing symptoms or clinical features of schizophrenia, such as (psychotic) bipolar disorder (Kasai et al., 2003; McDonald et al., 2006; McIntosh et al., 2006). Hippocampal volume reductions, for example, have been hypothesised to be present in schizophrenia but less so in bipolar disorder (McDonald et al., 2006). These studies have demonstrated some overlap both in the regional distribution as well as extent of local grey matter changes. This limitation might, however, be overcome by investigating the pattern of regional changes. More recent studies have shown that pattern classification techniques might be useful to enhance specificity of morphometric findings, making use of the set of changes across the entire brain (Davatzikos et al., 2005; Kawasaki et al., 2007; Soriano-Mas et al., 2007; Yushkevich et al., 2005). The advantage of this approach would be the use of multi-regional information – not limited to one single area – in developing a more specific brain structural signature of schizophrenia.

While the mentioned studies in schizophrenia and related disorders have produced important data, they are limited through their use of categorical diagnostic approaches. Thus, inclusion of

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additional information related to phenotypic variation *within* a sample might be useful to form subgroups, which are more homogeneous and could then be subject to classification analysis to prove or disprove sufficient specificity for brain structure as a biological marker.

Only a few structural MRI studies have addressed the issue of subgroups or subsyndromes within schizophrenia, even despite the availability of the subtyping according to DSM-IIIR or DSM-IV diagnostic criteria. For example, abnormalities in cortical folding have been shown to be more pronounced in the disorganised subtype of schizophrenia (Sallet et al., 2003a), although there was no indication of subgroups within patients in another study on cortical thickness (Lawyer et al., 2008), while yet another study dividing patients in paranoid vs. non-paranoid schizophrenia has given evidence for the negative symptom dimension to be related to increased rightward structural asymmetry (Sallet et al., 2003b).

In this study, we implemented such an approach by applying a classification analysis (based on voxel-based morphometric analysis of whole-brain MRI) on both a comparison of schizophrenia patients and healthy controls as well as subdividing the schizophrenia sample into subgroups based on symptoms. We tested whether the pattern of brain structural changes (i.e. combination of regionally distributed changes) would provide sufficiently accurate classification of a given brain scan from the cohort to be assigned to either schizophrenia or healthy control groups, and (for patients) to one of three schizophrenia subgroups. These three subgroups were formed on the basis of factor analysis applied to cross-sectional psychopathology. The rationale for this approach to forming subgroups was based on previous studies on robustness of three-factor models in schizophrenia (Cuesta and Peralta, 1995b; Peralta et al., 1997) as well as the fact that this grouping most closely matches the already established clinical subtypes within the DSM-IV and ICD-10 diagnostic systems. Secondly, we challenged the notion that there is a core pattern of changes independent of clinical or phenotypic variability, assuming that the most consistently reported structures in schizophrenia pathophysiology (hippocampus, thalamus, and dorsolateral prefrontal cortex) would be altered in all subgroups, while other structural changes (e.g. in the superior temporal cortex, cerebellum), which have been linked to particular psychopathological phenomena (Gaser et al., 2004), might be altered in only one of the subgroups expressing this particular disease phenotype.

Materials and methods

Subjects

We studied 99 patients with a DSM-IV diagnosis of schizophrenia and 113 healthy controls. The patients ($n = 99$; 57 male/42 female; mean age = 36.2 years, SD = 11.2) were recruited from the Department of Psychiatry in Jena and first screened with a semi-structured interview before being assessed by two psychiatrists establishing the DSM-IV diagnosis. None of the patients had a second psychiatric, a neurological or major medical condition. All patients were inpatients and none of them was in an acute episode of illness, all were in remitted clinical state, showed stable psychopathology, and were on stable antipsychotic medication. Current psychopathology in patients was assessed using the Scales for Assessment of Positive Symptoms (SAPS), and Scales for Assessment of Negative Symptoms (SANS), which was administered by an experienced and trained clinical psychiatrist. Healthy controls ($n = 113$; 70 male/43 female; mean age = 32.38 years, SD = 10.26) were recruited from the city of Jena and surrounding counties and matched to the patients with regards to gender, age, and overall school/academic achievement. They were screened to exclude a concurrent or past history of psychiatric, neurological, and major medical conditions using a semi-structured

Table 1
Demographics and psychopathology scores (mean global items and their standard deviation) of the schizophrenia subgroups.

	1— Negative	2— Disorganised	3—Hallucinatory/paranoid
Gender (M/F)	18/17	15/14	24/11
Age	35.07 (9.3)	35.95 (12.0)	37.64 (12.3)
Duration of illness	7.77 (7.5)	8.69 (8.5)	10.25 (8.7)
Age of onset	27.36 (7.9)	26.27 (8.8)	27.72 (8.6)
Hallucinations	1.66 (2.74)	1.79 (1.82)	6.63 (5.99)
Delusions	3.49 (4.57)	6.24 (6.21)	8.31 (7.33)
Bizarre behaviour	2.06 (2.39)	5.45 (3.67)	3.4 (3.54)
Positive formal thought disorder	3.57 (4.49)	11.55 (6.16)	4.17 (4.82)
Affective flattening	17.49 (5.03)	11.0 (6.73)	8.57 (7.42)
Alogia	7.2 (4.06)	5.97 (3.99)	3.23 (3.6)
Abulia	6.34 (3.11)	5.55 (2.38)	5.71 (4.0)
Avolition	3.31 (2.12)	3.59 (2.41)	1.77 (1.99)
Anhedonia	10.86 (3.58)	9.31 (3.61)	7.85 (4.55)

Table 2
Results of factor loadings and mean psychopathology ratings for subgroups: the three factors are delineated by colour (red for subgroup 1: negative; green for subgroup 2: disorganised; blue for subgroup 3: paranoid/hallucinatory).

Symptom	Factor 1	Factor 2	Factor 3
auditory hallucinations	0.04	-0.23	**0.87**
voices commenting	0.16	-0.17	**0.90**
voices conversing	-0.01	-0.10	**0.76**
somatic hallucinations	-0.09	0.18	0.26
olfactory hallucinations	-0.13	0.02	0.15
visual hallucinations	-0.05	0.27	0.04
persecutory delusions	-0.09	0.10	**0.69**
delusions of jealousy	0.05	0.25	-0.05
delusions of guilt/sin	-0.07	0.25	0.24
grandiose delusions	-0.13	**0.31**	-0.06
religious delusions	-0.14	0.20	0.09
somatic delusions	-0.07	**0.38**	-0.11
delusions of reference	0.02	0.14	**0.52**
delusions of being controlled	0.01	0.11	**0.53**
delusions of mind reading	0.01	0.03	**0.77**
thought broadcasting	0.11	0.03	**0.40**
thought withdrawal	-0.05	0.08	**0.34**
thought insertion	-0.02	0.20	**0.40**
clothing and appearance	0.17	**0.48**	0.17
social and sexual behavior	-0.07	**0.56**	0.13
aggressive behavior	-0.23	**0.40**	**0.35**
stereotyped behavior	-0.07	**0.74**	-0.22
derailment	-0.15	**0.71**	0.17
tangentiality	0.03	**0.83**	-0.16
incoherence	0.05	**0.69**	0.18
illogicality	-0.01	**0.74**	-0.05
circumstantiality	0.06	**0.58**	-0.29
pressure of speech	-0.35	**0.73**	-0.01
distractible speech	-0.01	**0.59**	0.14
clanging	0.14	**0.41**	-0.03
facial expression	**0.91**	-0.12	0.02
spontaneous movements	**0.88**	-0.20	0.11
expressive gestures	**0.96**	-0.19	0.08
poor eye contact	**0.64**	0.05	-0.03
affective nonresponsivity	**0.80**	-0.03	0.08
inappropriate affect	-0.09	**0.66**	-0.09
vocal inflections	**0.68**	0.19	-0.08
poverty of speech	**0.63**	0.26	-0.01
poverty of content	**0.67**	0.28	-0.32
blocking	**0.37**	0.23	-0.04
latency of responce	**0.56**	0.16	-0.10
grooming and hygiene	0.24	0.27	0.08
impersistence at work	0.09	0.05	0.15
physical anergia	**0.65**	-0.28	0.17
recreational interests	**0.57**	-0.23	0.19
sexual interests	**0.33**	-0.00	0.05
intimacy and closeness	**0.50**	0.08	0.17
relationships with friends	**0.53**	0.10	0.15
social inattentiveness	**0.39**	**0.41**	-0.16
inattentiveness during testing	0.28	**0.39**	-0.08

Symptoms of the SANS/SAPS list are colour coded for loading on each of the three factors.

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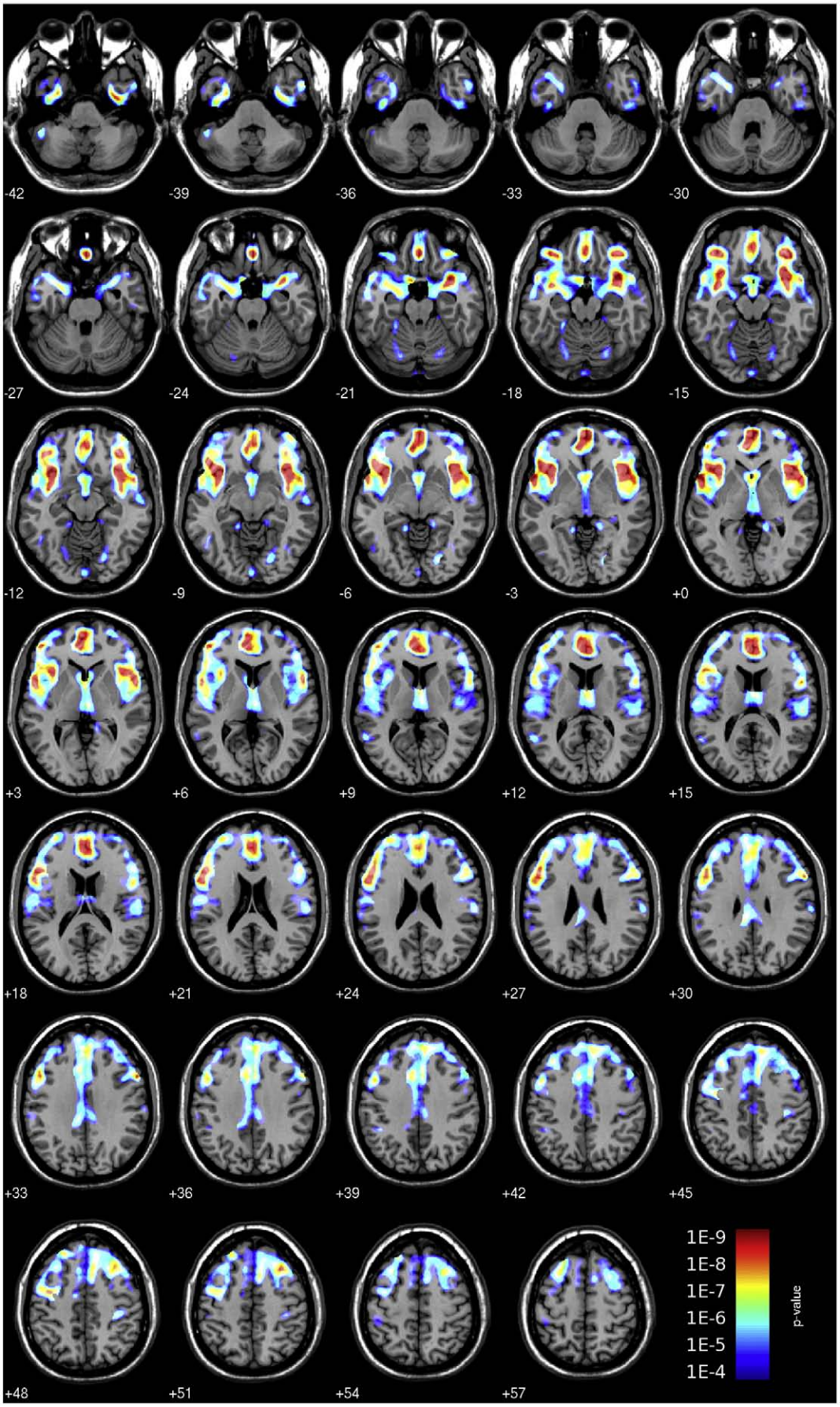

Fig. 1. Voxel-based morphometry (VBM) comparison of 99 patients with schizophrenia vs. 113 healthy controls ($p < 0.01$, FDR corrected for multiple comparisons; extent threshold $p = 0.05$): axial slices showing significant results superimposed on a single subject template T1 scan in MNI space, indicating z co-ordinates; p values are colour coded.

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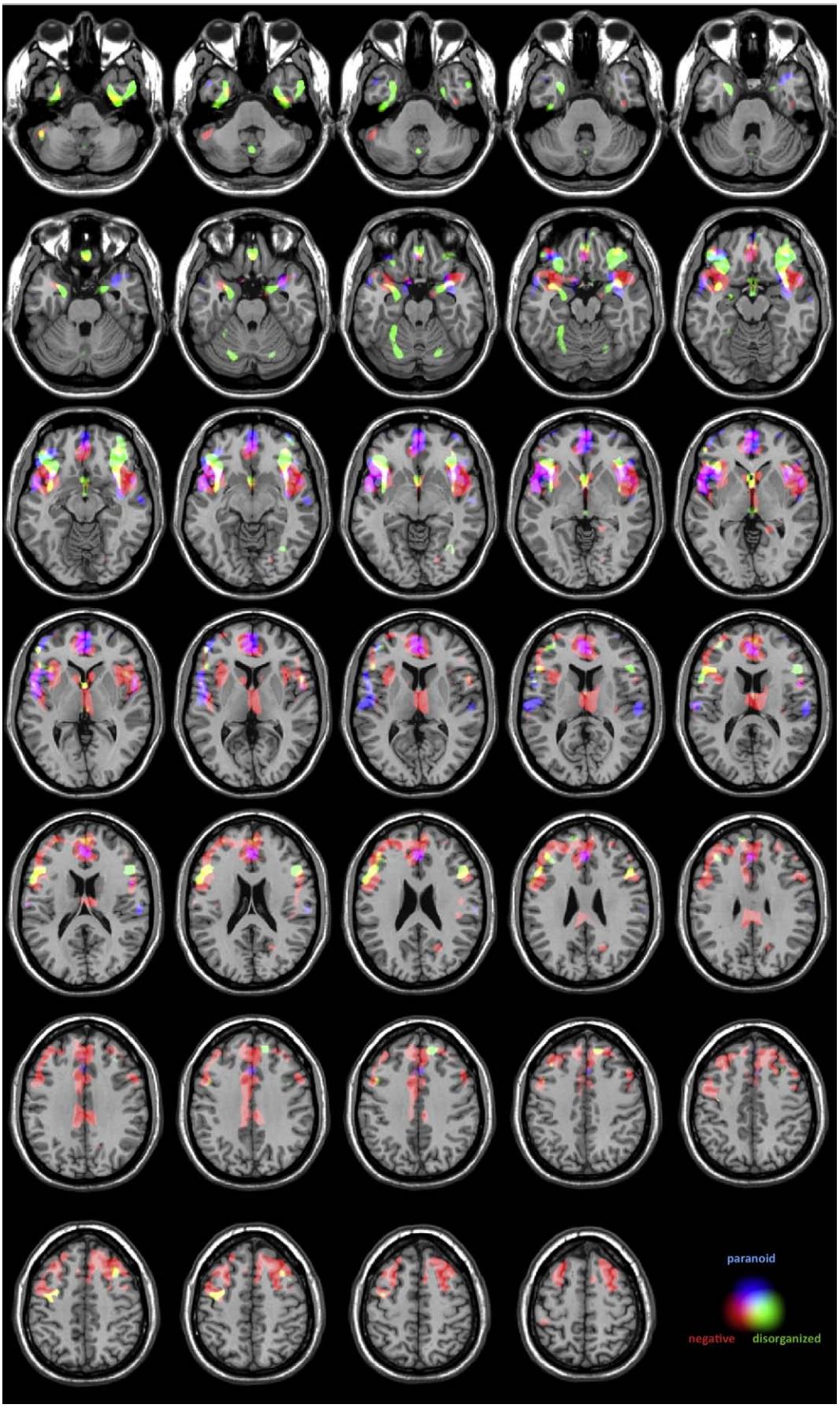

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interview. Further exclusion criteria for both samples were a history of head trauma, concurrent or previous substance dependence or alcoholism, and learning disability (mental retardation). All subjects were right-handed as scored from the short version of the Edinburgh Handedness Scale (Oldfield, 1971). All participants gave written informed consent to a study protocol approved by the Ethics Committee of the Friedrich-Schiller-University of Jena.

Subgroup formation

The delineation of subgroups of schizophrenia patients was based on cross-sectional psychopathology and factor analysis, dividing the patients into three groups with a similar profile of symptoms. Many previous studies on the factor structure of schizophrenic symptoms have derived a three-factor solution (Andreasen et al., 1995), and this three-factor solution appears to be most stable, although alternative four-factor or even five-factor models have been proposed. The three-factor solutions have normally produced groups dominated by negative symptoms/psychomotor poverty, by psychotic/paranoid/reality distortion symptoms, and by disorganisation. In order to avoid confounds of longitudinal symptom change (Marengo et al., 2000), all patients included were chronic schizophrenia patients.

In order to form the subgroups, we entered all SANS and SAPS single items into a factor analysis defining a three-factor solution and applying a Promax rotation. The analysis yielded three approximately equally sized groups with 35 patients in the negative subgroup (18 male/17 female; mean age = 35.1, SD = 9.3), 29 in the disorganised subgroup (15 male, 14 female; mean age = 36.0, SD = 12.0), and 35 in the paranoid subgroup (24 male/11 female; mean age = 37.6, SD = 12.3). Demographics and raw psychopathology scores (SAPS and SANS mean global items) of these subgroups are given in Table 1. Results of the factor loadings and mean psychopathology ratings for the subgroups are given in Table 2. This analysis was compared to previous studies to confirm that the subsamples match the negative, paranoid, and disorganised subgroups described in previous studies.

Imaging protocol

We obtained a high-resolution structural MRI for each subject on a 1.5-T Phillips Gyroscan ASCII system using a T1-weighted sequence obtaining 256 sagittal slices covering the entire brain (TR = 13 ms, TE = 5 ms, a 25°, field of view [FOV] = 256 mm, voxel dimensions = $1 \times 1 \times 1$ mm^3) for all subjects. Foam pads were used where appropriate to further restrict head movement of subjects. Prior to image processing, each image was checked manually for artefacts. In addition, we used an automated tool for detection of outliers implemented in the VBM2 package (see below). All scans passed both the manual and automated quality checks.

Image analysis and classification analysis

We first applied voxel-based morphometry (VBM) using VBM2 software. VBM2 is a toolbox (available on http://dbm.neuro.uni-jena.de/vbm) implemented in SPM2 (Statistical Parametric Mapping, Institute of Neurology, London, UK) and uses an optimised VBM protocol (Ashburner and Friston, 2000; Good et al., 2001) as well as a model based on hidden Markov random fields (HMRF) developed to increase signal-to-noise ratio (Cuadra et al., 2005).

First, we created a customised template image using a two-step segmentation approach. Segmentation in this process assigns each voxel to a tissue class (i.e. grey matter, white matter or CSF) and is optimised using a modified Gaussian mixture model (Ashburner and Friston, 2000) incorporating prior knowledge into the assignment of each voxel. The two-step segmentation first applies segmentation to the grey matter image derived from each individual scan, then normalising the segmented image to a standard template (MNI template) and averaging these normalised images to obtain a customised template for this study population. Using a customised template has advantages of accounting for differences between the study populations and the population used for standard templates as well as taking into account scanner-specific non-uniformities in image intensity and inhomogeneities of the B0 field. Secondly, we then used this customised template for normalisation of each study subject's scan. These grey matter images are then compared across the group applying a general linear model within each voxel to test for differences in grey matter "concentration" or density. The VBM2 algorithm also includes an automated quality control for images based on their homogeneity, calculating the standard deviation as the squared distance of each image (sum of intensity values) from the sample mean image.

Statistical analyses of VBM included first a comparison of the group of schizophrenia patients with healthy controls, and secondly a comparison of each subgroup with the healthy controls. Age and gender were entered as confound variables to remove effects related to minor differences between groups. For all comparisons, we applied a threshold of $p < 0.01$ corrected for multiple comparisons (FDR) as well as an extent threshold of $p < 0.05$ to exclude smaller clusters failing to reach the statistical extent criterion.

For classification analysis, we applied a method based on an orthonormalised partial least square (OPLS) approach based on a multivariate statistical model, which we have described in detail in a previous paper (Soriano-Mas et al., 2007). The OPLS is based on a singular value decomposition (SVD) of the orthonormalised predictor values (equals the design matrix) X and the data Y and results in Eigenimages V, Eigenvalues Λ, and Eigenvectors U'. The Eigenimages and the grey matter images for each subject can be used to calculate a so-called expression value for each subject. This single value expresses the extent to which this subject represents the pattern of the Eigenimage. Using the expression values for each subject, we can compute the probability for belonging to a particular group

To further test the findings, we used a jackknife ("leave-one-out") approach, in which the whole computation was performed leaving out one subject, resulting in a new ordering of group differences and a new individual expression values and probabilities for a total of 212 computations.

Results

Group-wise voxel-based morphometry

The first comparison, contrasting the schizophrenia patient sample and healthy controls showed significant reductions of grey matter in patients in several cortical and subcortical areas, as shown in Fig. 1. This included the prefrontal cortices (dorsolateral, medial, and orbitofrontal areas), temporal lobe (including amygdala, hippocampus, lateral temporal pole, and superior temporal cortex), and thalamus. Within the prefrontal cortex, the dorsolateral and medial areas were most widely affected, whereas the orbitofrontal cortex showed reductions in its lateral parts with relative sparing of medial (posterior) areas. Within the temporal lobe, the medial temporal structures (including amygdala and hippocampus) were reduced in grey matter as well as the temporal pole (both lateral and medial aspects) and superior temporal gyrus, with sparing of the mid and posterior middle and inferior temporal gyri.

Fig. 2. Voxel-based morphometry (VBM) comparison of schizophrenia subgroups healthy controls ($p < 0.01$, FDR corrected for multiple comparisons; extent threshold $p = 0.05$): Composite image of group-wise comparisons with negative subgroup (red), disorganised subgroups (green), and hallucinatory subgroup (blue); intermediate colours reflect overlap (axial slices superimposed on single subject T1 scan).

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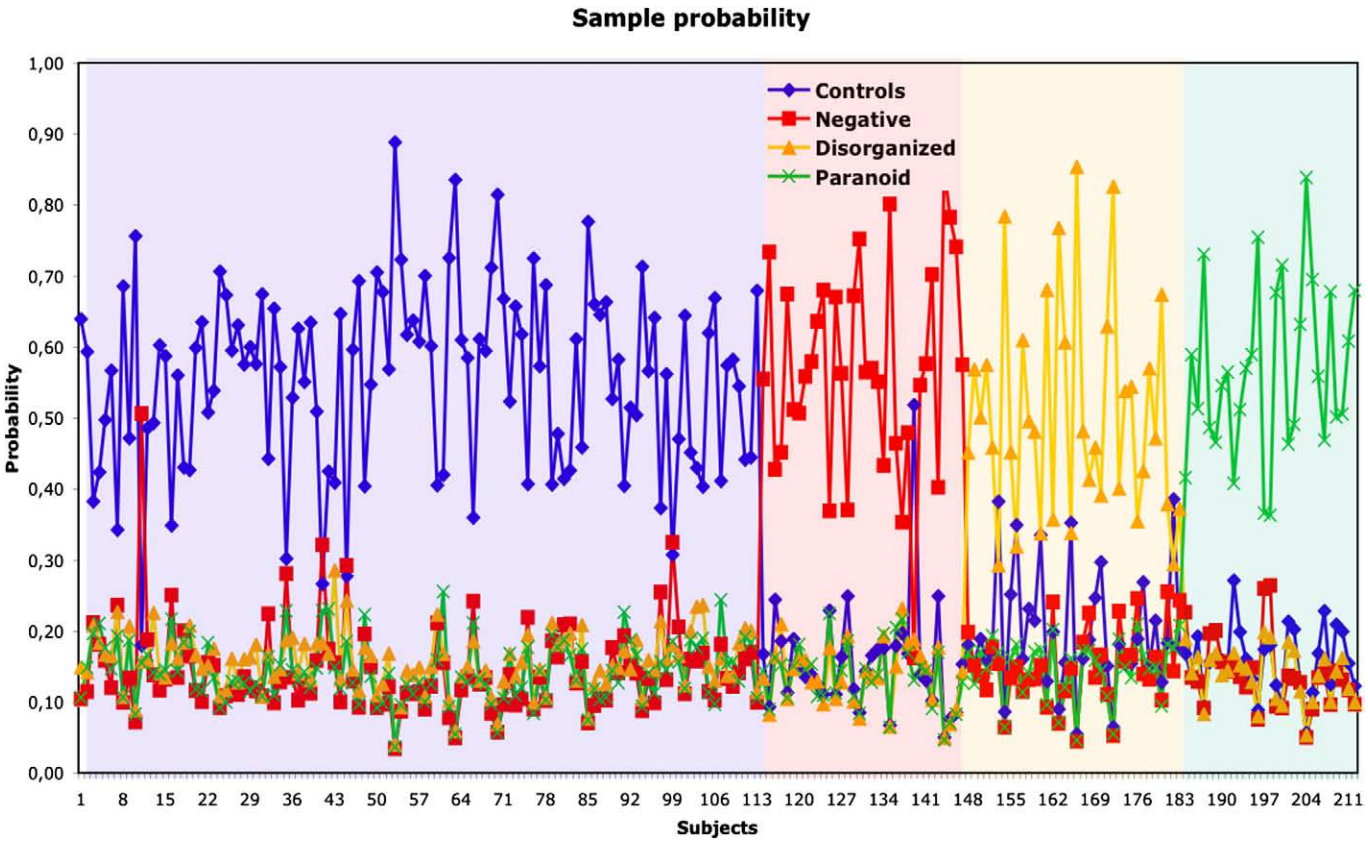

Fig. 3. Discrimination analysis diagram illustrating probability of every 212 subject from the total population being assigned to either healthy controls or one of the schizophrenia subgroups: subjects are listed on the *x* axis and for each individual there are four scalar values indicating the probability to be assigned to one of the four groups (e.g. red squares indicate the probability of being assigned to the negative subgroup of schizophrenia patients, yellow triangles for the disorganised subgroup, etc.).

Comparing each subgroup separately against the healthy controls, we identified diverging as well as overlapping areas of alteration. A composite image illustrating the areas of overlap and difference is shown in Fig. 2.

All groups showed grey matter reductions in the prefrontal cortices, although to a different magnitude and extent and also in differing locations. Most extensive prefrontal cortical deficits were seen in the negative patient group, whereas the medial temporal changes where mostly present in the disorganised subgroup. Reductions in the thalamus were most prominent in the negative subgroup.

Classification analysis

The jacknife validation achieved an accuracy of 95.8% of correctly differentiating between the three schizophrenia subgroups and the control group. Only 9 subjects out of the total sample of 212 subjects were misclassified (4 control subjects and 5 patients, see Fig. 3).

Discussion

Subgrouping patients with schizophrenia has become a major target for deriving more homogeneous patient groups that might be associated with a less complex genotype (Jablensky, 2006). The most commonly applied strategy recently has been the study of the impact of risk haplotypes (or even single nucleotide polymorphisms) on brain structure and function. Although these have been successful in elucidating many single-gene/single-phenotype correlations (Bearden et al., 2007; Meyer-Lindenberg and Weinberger, 2006; Tan et al., 2008), there is no pattern emerging to allow a more detailed subtyping other than dichotomous stratification in carriers vs. non-carriers of a risk haplotype. In particular, we are still lacking easily accessible methods that could be tested across several cohorts (Cannon, 2005). The results of the present study offer some new perspectives on this problem combining a classification approach using VBM data and a classification based on psychopathology.

Firstly, our results demonstrate that subtyping based on psychopathology gives not only a sufficiently robust separation within the schizophrenia spectrum but also demonstrates a biological underpinning. In particular, our classification analysis shows a set of brain abnormalities, which is sufficiently precise in this sample to define a signature of brain structural changes. This is not only in line with previous similar studies on schizophrenia (Davatzikos et al., 2005; Yushkevich et al., 2005) but extends these by showing that the assumption also holds true for psychopathologically delineated subgroups. Therefore, these findings support the assumption that this subgrouping holds biological plausibility and is not a mere epiphenomenon of multiple correlations (as might be the case with studies of single symptoms). There are several advantages and disadvantages to using psychopathological information for this subtyping as well as limitations. Our choice of the three-factor model was supported by the large literature on factor analyses in schizophrenia. Although alternative models have also been proposed, the three-factor solution has received most wide-spread support based on clinical grounds (Cuesta and Peralta, 1995b; Peralta et al., 1997). There is also a growing body of evidence that the three subsyndromes are differentially related to biological markers of the disease, such as cognitive impairment (Cuesta and Peralta, 1995a; Liddle and Morris, 1991) or local brain structure (Chua et al., 1997; Koutsouleris et al., 2008), blood flow (Liddle et al., 1992), regional glucose metabolism (Schroder et al., 1996), and task-related brain activation (Honey et al., 2003). The three-factor model holds particularly well for chronic patients, as studied in our sample, and

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can be applied reliably also in geriatric populations (Sauer et al., 1999). Some more recent data imply that the three-factor solution might be linked to underlying genetical predisposition, as shown in twin studies (Cardno et al., 2001). This lends additional validity to this approach of subtyping a complex disorder. Yet, delineation of subgroups based on cross-sectional psychopathological data has inherent limitations for several reasons. Even though we chose chronic patients, for which the three-factor model holds best, and limited ourselves to stabilised patients, we cannot exclude effects of medication, especially in the basal ganglia, which are known to be prone to these, but also for cortical reasons. As psychopathology changes over time (especially when psychosis flares up) one might therefore argue that correlating a mostly state-related parameter with a presumably trait-related marker such as brain structure might could lead to an excess of both false-positive and false-negative results. However, we should argue that neither of these parameters is purely state or trait related. In our patient cohort, for example, we chose chronic patients, well past their first years of illness onset, who had developed a stable psychopathology. All of them were well outside an acute episode of their psychosis and at a stage where psychopathology enters a residual phase with moderate fluctuations in both positive and negative symptoms. It might therefore be assumed that we identified time points that are most stable (and thus possibly most characteristic) for each individual patient's disease course. There is limited data on the time course of symptoms in the different three subsyndromes. Lack of longitudinal data did not allow us to assign patients to either Kraepelinian (deficit) or non-Kraepelinian subtypes—an alternative recently proposed subtyping, for which differing patterns of brain pathology have been shown (Heckers et al., 1999; Mitelman et al., 2003). Brain structure, on the other hand, cannot be assumed to be a purely trait-related marker. Although there is good evidence that some structural changes occur at the point of disease onset or even before (Pantelis et al., 2003), there is now good evidence for disease progression and even changes with acute phases of psychosis. Hence, despite these limitations, the study can serve as a paradigm to disentangle the effects of phenotypic variation on brain structure as a putative endophenotype.

Regarding our second hypothesis of this study, we could not confirm the proposed pattern of hippocampus, thalamus, and prefrontal cortex as a set of core abnormalities characterising all schizophrenia patients irrespective of subgrouping. We identified grey matter reduction in all of these structures (as well as the superior temporal gyrus and the cerebellum) in the schizophrenia vs. healthy controls comparison, thus replicating the most stable findings in one of the largest VBM samples so far (Honea et al., 2005). Overall, the morphometric results in the subgroups are consistent with the previous classical imaging studies by Liddle et al. (1992) on the three-subgroup model of schizophrenia, which closely resembles our factor solution as well as more recent VBM data (Koutsouleris et al., 2008). However, there was marked heterogeneity among the three subgroups in these regions. For the hippocampus, it was the disorganised subgroup and (to lesser extent) also the paranoid subgroup (esp. in the anterior hippocampus and amygdala) that showed prominent changes. For the thalamus, the reductions were most prominent in the negative symptoms subgroup. For the cerebellum, this is the first study to identify the disorganised (and to lesser extent the negative) subsyndromes of schizophrenia to show volume deficits in this region. The former is of particular interest in view of the concept of formal thought disorder linked to cognitive dysmetria, which has been proposed as a general model for schizophrenia (Andreasen and Pierson, 2008). On the other hand, the medial temporal lobe structures have often been linked to delusions, which makes the lack of more wide-spread findings in this region in the paranoid subgroup somewhat surprising. Interestingly, the area of greatest convergence or spatial overlap is the prefrontal cortex, and in particular the right ventrolateral and lower dorsolateral cortices and the medial prefrontal areas bilaterally. For our results, it appears that alterations of all subtypes converge in these areas, with negative patients showing greatest spatial extent of changes.

We should also point out that several of the spatial components of the brain structural patterns resemble previous findings of correlations with single symptoms or groups of single psychopathological items. For example, negative symptoms have repeatedly been linked to grey matter reductions in prefrontal cortex (Sanfilipo et al., 2000), yet another study found a positive correlation in the thalamus in an early onset sample (Yoshihara et al., 2008), which would not be in line with our thalamus findings in chronic patients. A more recent study found delusions to be correlated to medial prefrontal cortex, close to the area of the clusters seen in our paranoid subgroup (Whitford et al., 2009). However, there is also considerable heterogeneity in studies on structure–symptom correlations, owing to a number of confounding factors such as patient group studied (symptom distribution, first-episode vs. chronic patients), medication status, etc.

Finally, we need to consider limitations of the study such as potential effects of antipsychotic medication (past and current). All our patients were on stable antipsychotic medication with wither a first- or second-generation antipsychotic. Experiments in monkeys have demonstrated that chronic exposure to antipsychotics leads to histologically evident volume reductions in brain grey and white matter, which might have both a generalised component as well as regional variation of effects (Dorph-Petersen et al., 2005). Inpatient samples, changes of brain volumes related to antipsychotic exposure have been shown especially for basal ganglia, where first-generation antipsychotics lead to volume increases (Navari and Dazzan, 2009), which might be reversible by atypical agents such as clozapine. More recent studies, however, have also shown first-generation antipsychotic haloperidol to lead to cortical volume loss after one year of treatment, but not olanzapine, which is a second-generation antipsychotic (SGA) (Lieberman et al., 2005). Also, SGAs might lead to partial reversal of cortical atrophy by inducing subtle expansion of grey matter (Garver et al., 2005), possibly an effect closely related to the functional properties regarding blood flow and metabolism (Molina et al., 2005). A major conclusion from the available literature (Navari and Dazzan, 2009) is therefore that medication effects (especially of SGAs) might be quite variable across different cortical areas. Even if medication dosage is converted to a comparable standard such as chlorpromazine equivalents, we still need to consider the fact that there is considerable non-adherence to antipsychotic medication in patients (Lindenmayer et al., 2009), which limits the value of using these indicators of antipsychotic exposure.

Taken together, this study provides biological evidence on the plausibility and face validity of a combination of overlapping and differing brain structural pathology in psychopathologically delineated subgroups of schizophrenia. It also rejects the notion that all patients might share pathology of a core network.

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