

Patterns of cortical thinning in different subgroups of schizophrenia

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Background

Alterations of cortical thickness have been shown in imaging studies of schizophrenia but it is unclear to what extent they are related to disease phenotype (including symptom profile) or other aspects such as genetic liability, disease onset and disease progression.

Aims

To test the hypothesis that cortical thinning would vary across different subgroups of patients with chronic schizophrenia, delineated according to their symptom profiles.

Method

We compared high-resolution magnetic resonance imaging data of 87 patients with DSM-IV schizophrenia with 108 controls to detect changes in cortical thickness across the entire brain ($P < 0.05$, false discovery rate-adjusted). The patient group was divided into three subgroups, consisting of

patients with predominantly negative, disorganised or paranoid symptoms.

Results

The negative symptoms subgroup showed the most extensive cortical thinning, whereas thinning in the other subgroups was focused in prefrontal and temporal cortical subregions.

Conclusions

Our findings support growing evidence of potential subtypes of schizophrenia that have different brain structural deficit profiles.

Declaration of interest

None.

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Analysis of cortical thinning from high-resolution magnetic resonance imaging (MRI) scans has contributed to a better understanding of cortical morphological effects of schizophrenia on the brain. Initial studies of people with mostly chronic schizophrenia demonstrated inferior and medial frontal as well as inferior and medial temporal cortical thinning¹ and several subsequent studies have confirmed cortical thinning in frontal and temporal areas to varying degrees; this has included first-episode^{2–5} as well as chronic patient groups.^{6,7} Several subsequent imaging studies on cortical thickness have suggested that both genetic factors and those related to progressive components in the disorder might have an impact on cortical thinning. Studies in siblings or relatives of patients have produced mixed results, with some suggesting cortical thinning in temporal and/or frontal areas^{4,8–10} and others not supporting this finding.^{11,12} However, several studies have now reported associations of cortical thinning with specific schizophrenia risk genes,^{13–18} although effect sizes and their ultimate impact on total variability of cortical thickness remains unclear. Studies using other methods for assessment of cortical brain structure, such as voxel-based morphometry (VBM), have recently demonstrated that structural deficits might vary as a function of distinct subtypes of schizophrenia. Two large studies have demonstrated that dividing schizophrenia cohorts into three groups, such that groupings are based on dominant symptoms, reveals patterns of substantial variability in frontal and temporal subregions as well as overlap across groups.^{19,20} We have also recently replicated this effect of subgroup-related variability in a measure of cortical complexity.²¹

Regarding, cortical thinning, a recent study has shown effects related to the deficit syndrome of schizophrenia,²² but it remains unclear whether these effects are related to patterns of symptomatology, and thus possibly to a distinct phenotype, or whether it is rather related to intermediate phenotype markers of the disorder. In the present study, we tested the hypothesis that subgroups of patients with schizophrenia, delineated by their symptom profiles, would show different extents of cortical

thickness changes, especially in prefrontal and temporal cortical areas. Identifying areas of overlap and divergence would highlight the role of cortical thickness as a putative intermediate phenotype.²³ In order to compare cortical thickness with other markers, we used the same approach for subdividing patients with schizophrenia as used in previous VBM studies.^{19,20}

Method

Participants

We studied a cohort of 87 patients with DSM-IV²⁴ schizophrenia and 108 healthy controls, all of whom had provided written informed consent to a protocol approved by the Ethics Committee of the Medical School of Friedrich-Schiller-University, Jena. All participants were adults and were right-handed.²⁵ The sample was drawn from a slightly larger cohort of 99 patients and 113 healthy controls, for which VBM analyses were presented previously,²⁰ and identical to a sample in a recent analysis of a novel cortical complexity measure.²¹ Although all of the initial patients and controls passed the VBM quality control protocol, 12 participants had to be excluded based on our quality control protocol for cortical surface-based measures.

Patients were recruited from in-patient and out-patient facilities of the Jena University Hospital's Department of Psychiatry, and underwent diagnostic assessment by a psychiatrist, who also rated the severity of positive and negative symptoms on the Scale for Assessment of Positive Symptoms (SAPS)²⁶ and Scale for Assessment of Negative Symptoms (SANS)²⁶ respectively at the time of scanning (same week). All patients were on stable antipsychotic medication. Healthy controls had no concurrent or previous psychiatric disorder, nor major medical or neurological conditions.

Both the SANS and SAPS scores (using single items) were used to derive a delineation of three subgroups based on factor analysis with Promax rotation. Delineation was based on the larger initial sample of 99 patients and 113 healthy controls. The three-subgroup

delineation was validated in previous studies by Liddle *et al.*^{27,28} It also is temporally stable, found even in older patients with chronic schizophrenia.²⁹

The subgroups consisted of: (a) 31 participants with predominantly negative symptoms (negative symptoms subgroup; 16 female, 15 male; mean age 35.54 years, s.d.=11.17); (b) 23 participants with predominantly disorganised symptoms (disorganised symptoms subgroup; 9 female, 14 male; mean age 35.39 years, s.d.=11.13); and (c) 33 participants with predominantly paranoid symptoms (paranoid symptoms subgroup; 14 female, 19 male; mean age 35.54 years, s.d.=11.18). These subgroups did not differ significantly from the control group (40 females, 68 males; mean age 32.16 years, s.d.=9.99) in age or gender (*t*-tests for age: control group *v.* negative symptoms subgroup, $P=0.135$; control group *v.* disorganised symptoms subgroup, $P=0.209$; control group *v.* paranoid symptoms subgroup, $P=0.126$; χ^2 for gender: control group *v.* negative symptoms subgroup, $P=0.145$; control group *v.* disorganised symptoms subgroup, $P=0.852$; control group *v.* paranoid symptoms subgroup, $P=0.578$).

Psychopathology scores for the three subgroups, as reported previously,²¹ were as follows. Negative symptoms subgroup: SAPS mean 11.5 (s.d.=11.7), SANS mean 44.6 (s.d.=14.1); disorganised symptoms subgroup: SAPS mean 24.3 (s.d.=14.0), SANS mean 35.7 (s.d.=16.5); paranoid symptoms subgroup: SAPS mean 22.6 (s.d.=18.9), SANS mean 27.8 (s.d.=17.8). Also, there was no difference between subgroups for disease duration (negative symptoms subgroup: mean 8.07 years, s.d.=8.11; disorganised symptoms subgroup: mean 10.14 years, s.d.=7.68; paranoid symptoms subgroup: mean 7.29 years, s.d.=7.44; ANOVA not significant) or age at onset (negative symptoms subgroup: mean 28.25 years, s.d.=9.27; disorganised symptoms subgroup: mean 26.13 years, s.d.=11.6; paranoid symptoms subgroup: mean 30.23 years, s.d.=9.82; ANOVA not significant).

Image acquisition and data analysis

We analysed high-resolution T_1 -weighted MRI scans, which were acquired for each participant on a 1.5 Tesla Phillips Gyroscan ASCII scanner (repetition time (TR)=13 ms, echo time (TE)=5 ms, 256 slices in sagittal orientation, field-of-view 256 mm; isotropic voxel resolution: $1 \times 1 \times 1 \text{ mm}^3$). Computation of cortical thickness was done using FreeSurfer software (v4.3 for Mac OS X) as described previously.²¹ In brief, we applied intensity normalisation, skull stripping and alignment for head position along the commissural axis, as well as labelling of cortical and subcortical structures.^{30–32} Quality control included visual inspection for gross imaging artefacts, as well as for poor quality of the extraction of the cortical surface. All scans included in this study used fully-automated extraction of the cortical surface with excellent results.

For statistical analysis, we tested differences in cortical thickness at three levels using separate general linear models (all implemented in a Matlab routine (Matlab 2010b), based on Statistical Parametric Mapping (SPM8) statistical routines): global thickness (across each hemisphere), regional thickness (across regions of interests (ROIs), defined by the Desikan atlas), and vertex-wise. For regional analysis, which constituted our main analysis, we applied a $P < 0.05$ threshold for significance with false discovery rate (FDR) to adjust for multiple comparisons, and also included gender as a nuisance variable, since this variable might induce moderate effects even in the absence of group-level differences in sample composition. Differences were first tested between the whole patient group and the control group, and then between each of the three subgroups (negative, disorganised and paranoid symptoms) and the control group ($P < 0.05$, FDR-adjusted).

Results

Patients with schizophrenia showed cortical thinning on global (hemispheric), regional and vertex-wise levels. Cortical thinning was evident across both left and right hemispheres, and was highly significant (Table 1). The effect was most pronounced for the negative symptoms subgroup.

Our main analysis of regional effects across the three subgroups (Table 2) showed that the negative symptoms subgroup showed significant cortical thinning ($P < 0.05$, FDR-adjusted) in prefrontal and temporal areas, as well as almost all other parietal and occipital cortical regions. The paranoid symptoms subgroup also showed significant thinning across several prefrontal and temporal areas, with sparing of the temporopolar, frontopolar and bilateral cuneus, whereas effects in inferior temporal and superior parietal areas varied across hemispheres. The disorganised symptoms subgroup showed the least cortical thinning, but still revealed several significantly thinner regions, including the superior and middle prefrontal, as well as temporal cortices.

Vertex-wise analyses showed a similar pattern, with the negative symptoms subgroup showing the most extensive deficits (Fig. 1). Regions of overlap of the three subgroups included left superior and inferior frontal, right superior temporal cortical areas.

Discussion

Schizophrenia subgroups

Before their removal in DSM-5,³³ clinical subtypes of schizophrenia have been a consistent feature of diagnostic classification; however, their application in biological research has seen gradual decline.^{13,34} This is at odds with the widely accepted notion that the (wider) schizophrenia definition most likely encompasses several biologically distinct disease entities. Identification of putative biological markers for schizophrenia will therefore have to consider not only variability introduced by general factors (such as disease onset, disease severity and so on), but also whether this marker relates to a common deficit or to a pathophysiological feature expressed in varying degrees across subgroups.

In this study, we provide evidence that regional variability of cortical thinning in schizophrenia is related to symptom profiles and distinct subgroups. Our findings add to an increasing body

Table 1 Global (hemisphere) analysis of cortical thickness for control and schizophrenia groups

	Cortical thickness, mm: mean (SEM)	P^a
Healthy control group		
Left hemisphere	2.4676 (0.0009)	
Right hemisphere	2.4621 (0.0009)	
Schizophrenia group		
Left hemisphere	2.3752 (0.0014)	1.0×10^{-8}
Right hemisphere	2.3773 (0.0014)	2.4×10^{-7}
Negative symptoms subgroup		
Left hemisphere	2.3420 (0.0040)	2.0×10^{-8}
Right hemisphere	2.3495 (0.0040)	6.5×10^{-7}
Disorganised symptoms subgroup		
Left hemisphere	2.3925 (0.0045)	0.001
Right hemisphere	2.3911 (0.0045)	0.003
Paranoid symptoms subgroup		
Left hemisphere	2.3941 (0.0037)	0.0004
Right hemisphere	2.3940 (0.0038)	0.002

SEM, standard error of the mean.
a. Comparison with the control group.

Table 2 Regional (ROI) analysis of cortical thickness in the control group, the schizophrenia group, and the negative, disorganised and paranoid symptoms subgroups^a

	Left hemisphere					Right hemisphere				
	Control group	Schizophrenia group	Negative symptoms subgroup	Disorganised symptoms subgroup	Paranoid symptoms subgroup	Control group	Schizophrenia group	Negative symptoms subgroup	Disorganised symptoms subgroup	Paranoid symptoms subgroup
Banks of the superior temporal sulcus	2.611	2.510	2.461	2.494	2.567	2.438	2.324	2.307	2.313	2.347
Caudal anterior cingulate	2.904	2.802	2.782	2.869	2.776	2.846	2.750	2.702	2.788	2.769
Caudal middle frontal	2.680	2.552	2.526	2.543	2.584	2.785	2.706	2.678	2.710	2.729
Corpus callosum	1.054	1.028	0.996	1.057	1.037	2.736	2.631	2.578	2.677	2.648
Cuneus	1.953	1.900	1.876	1.961	1.881	2.568	2.461	2.461	2.464	2.460
Entorhinal	3.219	3.163	3.080	3.108	3.279	3.013	3.023	3.022	2.939	3.084
Fusiform	2.671	2.565	2.478	2.591	2.630	2.619	2.530	2.496	2.522	2.567
Inferior parietal	2.558	2.472	2.435	2.487	2.497	2.180	2.113	2.066	2.159	2.124
Inferior temporal	2.805	2.701	2.653	2.657	2.779	2.362	2.291	2.263	2.288	2.320
Isthmus cingulate	2.842	2.792	2.720	2.858	2.813	2.825	2.723	2.679	2.742	2.752
Lateral occipital	2.292	2.222	2.190	2.236	2.243	2.345	2.295	2.295	2.310	2.284
Lateral orbitofrontal	2.897	2.778	2.749	2.757	2.821	2.898	2.780	2.748	2.798	2.797
Lingual	2.151	2.062	2.011	2.135	2.058	2.864	2.758	2.755	2.740	2.772
Medial orbitofrontal	2.519	2.432	2.382	2.500	2.430	3.076	2.959	2.939	2.974	2.969
Middle temporal	2.892	2.773	2.729	2.773	2.815	2.068	1.986	1.966	1.983	2.006
Parahippocampal	2.623	2.491	2.419	2.513	2.545	2.920	2.824	2.816	2.800	2.849
Paracentral	2.433	2.356	2.314	2.384	2.376	2.003	1.941	1.877	1.958	1.989
Pars opercularis	2.723	2.592	2.567	2.594	2.615	2.850	2.732	2.754	2.685	2.744
Pars orbitalis	3.007	2.890	2.903	2.853	2.902	2.757	2.697	2.709	2.658	2.712
Pars triangularis	2.673	2.558	2.561	2.581	2.538	2.739	2.642	2.645	2.642	2.640
Pericalcarine	1.711	1.693	1.667	1.753	1.675	2.709	2.604	2.615	2.605	2.592
Postcentral	2.094	2.002	1.971	2.023	2.017	2.312	2.247	2.214	2.279	2.254
Posterior cingulate	2.819	2.738	2.722	2.778	2.726	2.708	2.594	2.553	2.595	2.633
Precentral	2.444	2.329	2.300	2.343	2.346	2.643	2.553	2.514	2.577	2.572
Precuneus	2.440	2.344	2.311	2.406	2.332	2.525	2.443	2.417	2.463	2.455
Rostral anterior cingulate	2.868	2.759	2.717	2.807	2.765	2.840	2.682	2.634	2.700	2.716
Rostral middle frontal	2.576	2.477	2.481	2.467	2.481	2.678	2.582	2.568	2.569	2.605
Superior frontal	2.970	2.884	2.848	2.908	2.900	2.579	2.467	2.449	2.468	2.483
Superior parietal	2.202	2.131	2.116	2.160	2.124	2.258	2.200	2.157	2.227	2.221
Superior temporal	2.866	2.742	2.728	2.728	2.766	1.285	1.217	1.177	1.232	1.244
Supramarginal	2.653	2.541	2.481	2.564	2.580	2.423	2.352	2.343	2.380	2.341
Frontal pole	3.010	2.944	2.863	3.020	2.968	2.922	2.807	2.814	2.782	2.818
Temporal pole	3.743	3.685	3.623	3.637	3.777	2.576	2.458	2.312	2.436	2.612
Transverse temporal	2.382	2.263	2.223	2.303	2.272	0.024	0.037	0.040	0.035	0.036

a. Results in bold indicate values significantly different (compared with the control group) at a threshold of $P < 0.05$, false discovery rate-adjusted.

of research highlighting the biological heterogeneity of schizophrenia, which could provide important hints to delineating universal *v.* specific pathological pathways.^{22,35}

Recent studies have established that regional cortical thinning is not only present at disease onset in schizophrenia, but also is evident in high-risk individuals in some areas.⁴ In addition, several recent studies have addressed the influence of certain clinical factors of disease and genetic risk on cortical thinning in schizophrenia.^{16,18,36} Yang *et al* have demonstrated that cortical thinning might also be observed in non-psychotic relatives of people with schizophrenia, although those with the disease had more pronounced thinning, especially in frontal and temporal areas.¹² Although this establishes both alterations related to disease liability or general phenotypic variation, there is rather little data on the heterogeneity of cortical thickness within participant groups with schizophrenia that would reflect possible subgroups within the disease entity. There is recent evidence of an association between the deficit subtype of schizophrenia and regional cortical

thinning, but the results have been mixed. Whereas one found a significant difference in anterior cingulate thickness and volume,²² another study found mostly overlapping regional thinning in patients with and without deficits compared with a control group.³⁵ Therefore, cortical thickness may be unable to separate those subtypes, albeit other morphometric markers did diverge.

Compared with the subtypes used in our study, the deficit syndrome relies mostly on outcome, *i.e.* longitudinal aspects. Although this might result in higher temporal stability of subgrouping, it remains to be clarified whether the deficit subtype truly correlates with a distinct biological endophenotype or merely represents a more severe disease form. Before the introduction of DSM-5, schizophrenia subtypes in DSM-III-R³⁷ and DSM-IV²⁴ have been based on clinical prototypes rather than biological parameters. Their validity on biological grounds has been insufficiently supported by (biological) research.¹³ Although our approach has also been based on psychopathology as a clinical phenotype, it has not utilised prototypes or assignment to a

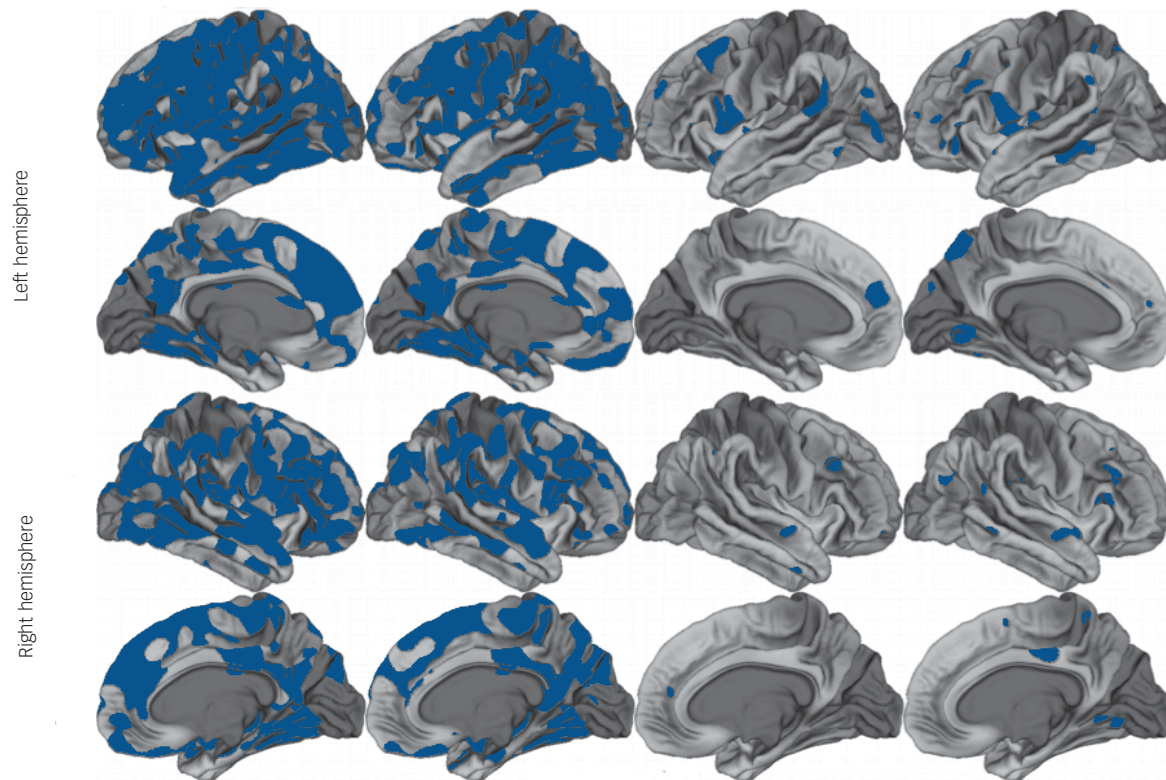


Fig. 1 Vertex-wise analysis ($P < 0.05$, false discovery rate-adjusted) of cortical thickness and statistical comparison (*v.* control group) of the entire schizophrenia group (left column), the negative symptoms subgroup (second column), disorganised symptoms subgroup (third column) and paranoid symptoms subgroup (last column).

subgroup by clinical decision, but rather has used psychometric aspects of symptom ratings to develop a more stable clinical phenotype, which is less susceptible to clinical rating biases.

Differences in our findings between subgroups

The regional patterns in frontal, temporal and cingulate areas across our three subsamples merit some attention. Our findings in the negative symptoms subgroup most closely resemble a pattern of widespread cortical thinning, almost lacking regional specificity, as seen in some recent large samples.⁶ Probably the greatest overlap between our three subgroups was seen in prefrontal regions, where all three groups showed convergence in areas covering both the orbitofrontal cortices (except left medial orbitofrontal cortex for the disorganised symptoms subgroup, which did not reach significance), superior and rostral middle frontal (again, except left superior frontal cortex for the disorganised symptoms subgroup) and right frontal pole regions. In contrast, temporal areas, such as the temporal pole, fusiform cortex and even superior temporal showed less convergence, as none of these areas showed thinning across all three groups. This was also the case for the medial temporal areas (parahippocampal and entorhinal). Our study did not include a detailed analysis of hippocampal thickness, which requires other analytical approaches to address the more convoluted topography.³⁸

Considering the three subgroups in terms of how many regions showed reduction of cortical thickness, it is noteworthy that the disorganised symptoms subgroup showed the least deficits, which is consistent with recent VBM studies, where the extent of deficits was also smallest in this subgroup.^{19,20} Overall, the pattern of the negative symptoms subgroup showing the most widespread pathology is consistent with our previous study assessing cortical complexity,²¹ although cortical complexity

variation (both reduction and increase) in the negative symptoms subgroup was not as widespread and extensive as the cortical thickness deficit.

Limitations

The study has some limitations. Given that this is a cross-sectional study with patients well past their first episode, the effects of disease progression, which might diverge between subgroups,³⁹ cannot be controlled for. Subgroups might also have varied disease severity, which is difficult to assess, especially in the absence of unequivocal unidimensional markers. This is also the case for antipsychotic medication, which might at least have some subtle effects on cortical thickness (including frontal areas), although recent studies in psychosis are not suggestive of very strong effects⁴⁰ and actually demonstrate some reversibility of cortical thinning during short-term treatment.⁴¹ In participants with chronic schizophrenia, cumulative intake of antipsychotics is often difficult to assess, and given potential non-adherence to treatment, is also difficult to assess retrospectively. Chlorpromazine equivalents, which are often used in clinical studies to calculate simple dose equivalents between different antipsychotics, are likely not to be useful for this type of study, since brain structural effects of antipsychotics are probably not only related to dopamine D₂ receptor occupancy or other pharmacological factors important for assessment of clinical efficacy. Finally, we also cannot rule out effects of alcohol intake or illicit substances. These effects are difficult to track, especially when assessed retrospectively.

Implications

We conclude from our findings, that although cortical thickness is reduced in schizophrenia across multiple areas, especially the prefrontal cortex, the spatial extent and effect size are variable

across subgroups delineated by predominant symptoms. Our results warrant further exploration of the notion that different patterns of regional thinning might be related to different biological subtypes, which might then be used as different intermediate phenotypes for the dissociation of genetically distinct forms of the disease.

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