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Regional thinning of the cerebral cortex in schizophrenia: Effects of diagnosis, age and antipsychotic medication

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Abstract

Morphological abnormalities of the cerebral cortex have been reported in a number of MRI-studies in schizophrenia. Uncertainty remains regarding cause, mechanism and progression of the alterations. It has been suggested that antipsychotic medication reduces total gray matter volumes, but results are inconsistent. In the present study differences in regional cortical thickness between 96 patients with a DSM-IV diagnosis of schizophrenia ($n=81$) or schizoaffective disorder ($n=15$) and 107 healthy subjects (mean age 42 years, range 17–57 years) were investigated using MRI and computer image analysis. Cortical thickness was estimated as the shortest distance between the gray/white matter border and the pial surface at numerous points across the entire cortical mantle. The influence of age and antipsychotic medication on variation in global and regional cortical thickness was explored. Thinner cortex among patients than controls was found in prefrontal and temporal regions of both hemispheres, while parietal and occipital regions were relatively spared. Some hemispheric specificity was noted, as regions of the prefrontal cortex were more affected in the right hemisphere, and regions of the temporal cortex in the left hemisphere. No significant interaction effect of age and diagnostic group on variation in cortical thickness was demonstrated. Among patients, dose or type of antipsychotic medication did not affect variation in cortical thickness. The results from this hitherto largest study on the topic show that prefrontal and temporal cortical thinning in patients with schizophrenia compared to controls is as pronounced in older as in younger subjects. The lack of significant influence from antipsychotic medication supports that regional cortical thinning is an inherent feature of the neurobiological disease process in schizophrenia.

Keywords: Schizophrenia; Cortical thickness; Magnetic resonance imaging; Freesurfer; Antipsychotic medication

1. Introduction

The human cerebral cortex is an extensively folded ribbon consisting of discrete layers of neurons. Studies in macaque monkeys have shown that neurons migrate to their destination before birth (Rakic, 1988). Recent postmortem data suggest that new neurons are generated in the adult human hippocampus (Eriksson et al., 1998; Toro and Deakin, 2007), while there is conflicting evidence regarding adult neurogenesis in the neocortex (Abrous et al., 2005). Less than half of the cortical surface

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is visible as gyri, while the majority is buried in sulci (Griffin, 1994). This complex three-dimensional shape of the cortex renders it difficult to study both from a neuropathological and neuroimaging point of view. An automated procedure has been developed to estimate cortical thickness using magnetic resonance imaging (MRI) (Fischl and Dale, 2000).

The cerebral cortex constitutes the major part of gray matter tissue within the brain. Changes in gray matter volumes could therefore imply alterations in either cortical surface area or cortical thickness. Alternatively, variation in regional folding patterns of the cortex may explain alterations in gray matter volumes. MRI-studies have shown smaller volumes of global, frontal, and temporal gray matter as well as smaller volumes of hippocampus, cerebellum, thalamus, corpus callosum, and larger volumes of the lateral ventricles among patients with schizophrenia compared to controls (Honea et al., 2005; Shenton et al., 2001; Wright et al., 2000). A number of studies have also found thinner cortex in frontal and temporal regions both in childhood-onset (White et al., 2003), first-episode (Narr et al., 2005a,b) and chronic schizophrenia (Kuperberg et al., 2003) patients when compared to controls, though negative findings have been reported (Wiegand et al., 2004). Brain abnormalities have been shown to occur in persons with a high risk of developing schizophrenia (Job et al., 2003; Pantelis et al., 2003) and among patients with a first episode of schizophrenia (Keshavan et al., 2005; Steen et al., 2006). This indicates that at least some of the brain alterations in schizophrenia are present in the early phase of the illness. The underlying pathological process as well as the clinical importance of the gray matter loss is at present poorly understood (DeLisi et al., 2006). Postmortem studies have found lower brain weight (Harrison et al., 2003) and smaller gray matter volume (Pakkenberg, 1987) in patients relative to controls. The difference may represent reduction of neuropil (Selemon and Goldman-Rakic, 1999) or loss of glia cells (Stark et al., 2004), rather than loss of neuronal cells (Pakkenberg, 1992, 1993; Harrison, 1999a; Thune et al., 2001).

Longitudinal MRI-studies of normal aging have demonstrated a heterogeneous pattern of cortical maturation in the developing brain (Thompson et al., 2005) which at least partly is related to cognitive measures (Shaw et al., 2006). Frontal and occipital regions have thinner cortex with increasing age, while this has not been shown for temporal regions (Salat et al., 2004). In a longitudinal study of childhood-onset schizophrenia spanning over five years, the patients showed reduction of gray matter volume first in parietal, and later in temporal and prefrontal cortical areas compared to the healthy children (Thompson et al., 2001). Some cross-sectional studies of patients with schizophrenia have found an interaction effect of age and diagnosis on gray matter volumes (Hulshoff Pol et al., 2002; Velakoulis et al., 2002), indicating an accelerated loss of gray matter in schizophrenia with increasing age. With regard to cortical thickness, a negative correlation was found between age and prefrontal cortical thickness in patients with first-episode schizophrenia, but not in patients with first-episode affective psychosis or controls (Wiegand et al., 2004). In contrast, other cross-sectional studies have found no interaction effect of age and diagnostic group on variation in cortical thickness among patients with first-episode (Narr et al., 2005a,b) or chronic schizophrenia (Kuperberg et al., 2003). At present there is no published study assessing longitudinal data on cortical thickness in schizophrenia.

There is some evidence for an effect of antipsychotic medication on volumes of basal ganglia, particularly of the caudate nucleus, and total brain gray matter volume (Scherk and Falkai, 2006). The effect also appears to be influenced by gender (Heitmiller et al., 2004) and type of medication (Kopelman et al., 2005). A recent study reported reduction in frontal and total gray matter volumes among first-episode patients receiving haloperidol for two years, while no change was observed among patients receiving olanzapine (Lieberman et al., 2005). A smaller study of patients receiving treatment for an acute exacerbation of psychosis observed increase in gray matter volume in response to risperidone and ziprasidone, while no change was found in response to haloperidol treatment (Garver et al., 2005).

The aims of this hitherto largest study on the topic were to investigate differences in cortical thickness between patients with schizophrenia and healthy controls, and further investigate effects of antipsychotic medication and interaction effects between age and diagnostic group. A two-step analysis was performed: First, cortical thickness was measured at numerous points across the entire cortical mantle. Second, mean cortical thickness within selected regions of the prefrontal and temporal cortex in both hemispheres was calculated and compared between groups. Interactions between age and diagnostic group on variation in cortical thickness were also investigated in two steps: First, group differences in age regression slopes at numerous points across the cortical mantle were investigated. Second, group differences in age regression slopes of mean cortical thickness within regions where patients had thinner cortex than controls were explored. The potential effect of antipsychotic medication on variation in cortical thickness was investigated by including current and estimated lifetime exposure of medication as covariates in separate analyses among patients only.

2. Materials and methods

2.1. Subject characterization

2.1.1. Recruitment and clinical assessment

Subjects were unrelated Caucasian individuals recruited in Stockholm, Sweden, between 1999 and 2003, and have been previously described (Jönsson et al., 2006). After complete description of the study, all subjects gave written informed consent to participate. The study was approved by the Research Ethics Committee at Karolinska Institutet.

Patients diagnosed with schizophrenia by their treating physician were recruited from outpatient clinics specialised in the treatment of psychoses. All centres were managed by the Stockholm County healthcare organisation and responsible for different specific geographical catchments areas in the North-Western Stockholm County. Control subjects were drawn from a population register or recruited among hospital staff members who had previously participated in clinical studies at Karolinska Institutet. Premorbid IQ was estimated using a proxy, the Wechsler Adult Intelligence Scale (WAIS) vocabulary subtest, which measures lexical knowledge (Wechsler, 1981). Highest achieved educational level was set as the total number of complete years spent in school. Subjects were assessed for lifetime psychiatric diagnoses according to Diagnostic and Statistical Manual of Mental Disorders, version III-R (American Psychiatric Association, 1987) and IV (American Psychiatric Association, 1994) using reviews of hospital case notes and semistructured interviews (Spitzer et al., 1986, 1988) performed by psychiatrists. The diagnostic procedures have been thoroughly evaluated (Ekholm et al., 2005; Vares et al., 2006). Age at onset of illness was defined as onset of psychotic symptoms according to any available source. Duration of illness was defined as the difference in years between age at onset and age at investigation. Patients' current use of antipsychotic medication was calculated on the basis of an interview and medical records. Current doses of antipsychotic medication were converted to equivalent doses of haloperidol (Kane et al., 2003). A proxy for lifetime load of antipsychotic medication was derived as the product of current medication and duration of illness. Handedness was assessed by questioning subjects about their preferred hand when using a pair of scissors. All subjects were healthy according to physical examination and biochemical screening. Exclusion criteria were a history of head trauma with loss of consciousness for more than 5 min, or somatic disorders affecting brain function.

2.1.2. Demographic and clinical data

A total of 96 patients were included, 81 fulfilling DSM-IV criteria for schizophrenia and 15 for schizoaffective disorder. The control group consisted of 107 subjects (30 from a population register and 77 among hospital staff) with no history of psychiatric illness and no psychotic illness among first-degree relatives. Mean age of all subjects was 42 years (range 17–57 years). Eighty-two patients and 90 controls were right-handed, constituting 85% in each group. Demographic and clinical data are presented in Table 1.

In the structured diagnostic interview, eight patients and two controls met DSM-IV criteria for a lifetime diagnosis of alcohol dependence, while five patients and five controls met criteria for a lifetime diagnosis of alcohol abuse. None of the participants were recruited as or receiving any treatment for alcohol or illicit drug use disorders at the time of investigation. Last years consumption of alcohol was not found to significantly influence the variation in gray matter volumes measured in a subset of the subjects in the present study (Nesvåg et al., 2007).

At the time of investigation 89 patients received psychopharmacological treatment. Of these, 41 received atypical (clozapine, olanzapine, or risperidone), 40 typical (haloperidol, perfenazine, zuclopenthixole, or fluanxol) and seven patients received both atypical and typical antipsychotic medication. Three patients received a combination of antipsychotic medication and lithium, and one patient received a combination of antipsychotic medication and carbamazepine. One patient received

Table 1
Demographic and clinical data

	Patients ($n=96$)			Healthy subjects ($n=107$)		
Men (%)	72.9			68.2		
	Mean	SD	Range	Mean	SD	Range
Age, years	42.1	7.3	25–57	41.6	9.0	19–56
Education, years [a]	12.5	2.7	8–20	14.1	2.9	9–22
WAIS vocabulary [b]	43.3	13.3	9–66	51.2	11.0	16–69
Age at onset of illness, years	24.6	5.9	14–45			
Duration of illness, years	17.3	8.6	0–41			
Medication, mg/day [c]	4.0	3.3	0–16			

t-tests showed no significant differences ($p<0.05$) in age between patients and controls. Among patients, no significant differences in age at onset, duration of illness, or medication were found between men and women.

[a] Data available for 92 patients and 100 controls. Significant group difference ($p<0.01$).

[b] Data available for 58 patients and 70 controls. Significant group difference ($p<0.01$).

[c] Current antipsychotic medication converted to equivalent doses of haloperidol.

lithium only. Eight patients received antidepressant in addition to antipsychotic medication. Seven patients received no psychopharmacological treatment at the time of investigation.

2.2. Brain measures

2.2.1. MR scan acquisition

All subjects were examined in a 1.5 T General Electronics Signa system at the MR Research Center, Karolinska Hospital, Stockholm, Sweden. T1-weighted images were acquired using a three-dimensional spoiled gradient recalled (SPGR) pulse sequence with the following parameters: 1.5 mm coronal slices, no gap, 35° flip angle, repetition time 24 ms, echo time 6.0 ms, number of excitations 2, field of view 24 cm, acquisition matrix 256 × 192. From visual inspection, all scans were judged to be excellent without obvious motion artifacts. All scans were found to lack gross pathology when evaluated by a neuroradiologist.

2.2.2. MR scan postprocessing

The MR images were used to calculate thickness of the cerebral cortex (Dale et al., 1999; Fischl et al., 1999a, 2001) using automated procedures (FreeSurfer, http://surfer.nmr.mgh.harvard.edu/) that have been validated via histological (Rosas et al., 2002) as well as manual measurements (Kuperberg et al., 2003). Cortical thickness measures were obtained by reconstructing representations of the gray/white matter boundary and the pial surface (Dale and Sereno, 1993; Dale et al., 1999) and calculating the distance between those surfaces at numerous points (vertices) across the cortical mantle (Fischl and Dale, 2000). Vertices were arranged in a triangular grid with approximately 1 mm spacing, allowing for measures of cortical thickness at up to 160 000 points in each hemisphere. Topological defects in the gray/white matter boundary were manually fixed by laboratory assistants (listed under Acknowledgements) who were instructed and supervised by senior researchers (AMF and KBW). All analyses were performed without knowledge of subject identity. This method of estimating cortical thickness uses both intensity and continuity information from the entire three-dimensional MR volume in segmentation and deformation procedures to construct representations of the gray/white matter boundary and pial surface. The maps produced are not restricted to the voxel resolution of the original images and are thus capable of detecting submillimeter differences between groups (Fischl and Dale, 2000). Thickness measures may be mapped on the 'inflated' surface of each participant's reconstructed brain (Dale and Sereno, 1993; Fischl et al., 1999b), allowing visualization of data across the entire cortical surface without interference from cortical folding.

Maps were smoothed using a circularly symmetric Gaussian kernel across the surface with a standard deviation of 12.6 mm and averaged across participants using a non-rigid high-dimensional spherical averaging method to align cortical folding patterns (Fischl et al., 1999b). This procedure provides accurate matching of morphologically homologous cortical locations across subjects on the basis of each individual's anatomy while minimizing metric distortion, resulting in a mean measure of cortical thickness for each group at each point on the reconstructed surface. In addition, the software tools provide automatic parcellation of the cortex into 84 regions, based on anatomical landmarks and a manually labeled training set (Fischl et al., 2004).

2.3. Statistical analysis

2.3.1. Demographic and clinical data

Two-tailed *t*-tests were applied to analyze diagnostic group differences in age, education and WAIS vocabulary score, and gender differences among patients with respect to age at onset, duration of illness and antipsychotic medication.

2.3.2. Entire cortex analysis

Statistical maps were created, showing significant differences in cortical thickness between patients and controls with age and gender as covariates (Fig. 1). Statistical comparisons of global data and surface maps were generated by computing a general linear model of the effects of each predictor variable on cortical thickness at each vertex. Various covariates were contrasted to test for significant effects of gender, handedness, duration of illness, current and estimated lifetime dose and type, i.e. typical or atypical, of antipsychotic medication. All analyses were done while controlling for the effect of age, and supplementary analyses were done with age and WAIS vocabulary score as covariates. To adjust for multiple comparisons, False Discovery Rate (FDR) (Genovese et al., 2002) was applied. FDR provides posthoc calibration of *p*-values from large numbers of statistical tests. The exact threshold of significance is dependent on the data. For an FDR of 5%, our data implied an appropriate threshold of significance at $p = 0.015$ for left and $p = 0.017$ for right hemisphere. A conservative threshold for both hemispheres was set at $p = 0.010$.

2.3.3. Region-of-interest analysis

Based on previous data (Kuperberg et al., 2003; Narr et al., 2005a; Shenton et al., 2001; White et al., 2003;

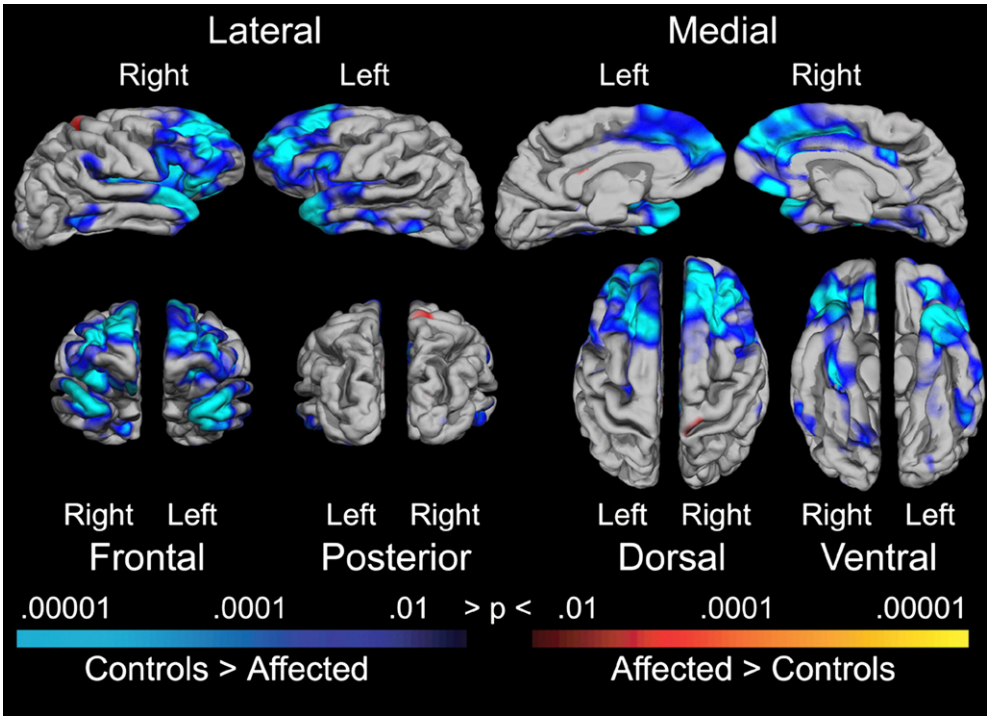

Fig. 1. Statistical maps illustrating significant differences ($p<0.01$) in cortical thickness between patients with schizophrenia and healthy subjects. Maps are produced from general linear models of cortical thickness at each vertex covarying for age and gender.

Wright et al., 2000), a number of cortical regions frequently reported to be affected in schizophrenia were a priori chosen in the prefrontal (superior and medial frontal gyrus) and temporal (superior temporal gyrus and temporal pole) cortex. Control regions with weaker association to schizophrenia were chosen in the parietal (postcentral gyrus and sulcus, angular gyrus and sulcus) and occipital (cuneus and occipital pole) cortex. These regions are among the 84 parcellations which are automatically obtained in FreeSurfer (Fischl et al., 2004). Two-tailed *t*-tests were applied to compare measures of mean cortical thickness within selected labels between groups. For regions where a significant difference in mean cortical thickness between patients and controls was found, the percentage difference from highest value was computed.

2.3.4. Interactions between age and diagnostic group

To compare the influence of age on variation in cortical thickness between diagnostic groups, we first applied a general linear model on each vertex of the entire cortical mantle, allowing for difference in age regression slopes between groups. Then, a comparison of age regression slopes for patients and controls within areas of the cortex which in Fig. 1 were shown to be significantly thinner in patients than controls was performed. This was done by manually drawing labels along the edge of each area with significant group differences in cortical thickness (Fig. 2, upper panel). Two-tailed *t*-tests were applied to compare *z*-transformed correlation coefficients of age and mean cortical thickness within each label between patients and controls.

3. Results

3.1. Demographic and clinical data

There were no significant differences with respect to age between patients and controls (Table 1). Patients had significantly less education ($t=3.91$, $df=190$, $p<0.01$) and lower score on WAIS vocabulary ($t=3.63$; $df=126$; $p<0.01$) than controls. Among patients, there were no significant gender differences in age at onset, duration of illness or dose of current medication. Among controls there were significant differences in age between subjects recruited from a population register and subjects recruited among hospital staff (mean (±SD) age 47.1 (±3.4) and 39.4 (±9.6) years, respectively; $t=4.30$; $df=105$; $p<0.01$), while these groups did not differ with respect to education or WAIS vocabulary score.

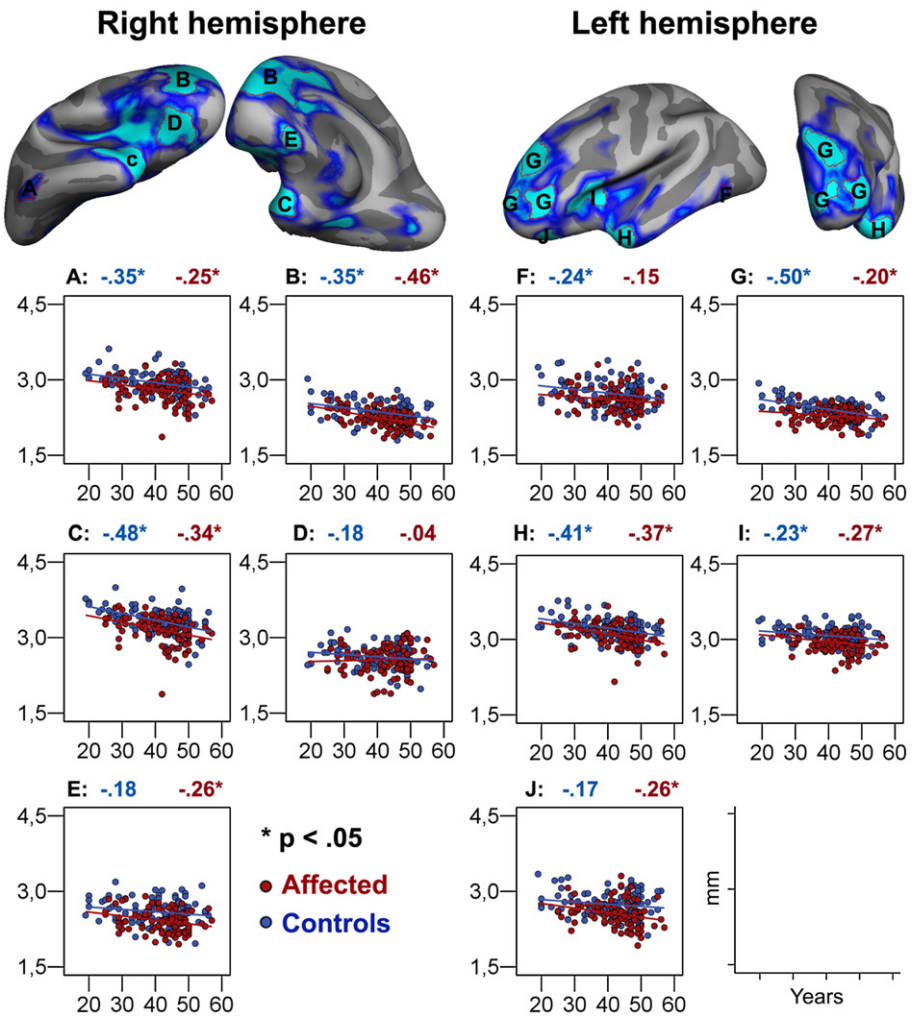

Fig. 2. Scatterplots and age regression slopes of mean cortical thickness (mm) with increasing age within selected regions of the cortex for patients with schizophrenia (red) and healthy subjects (blue). Significant correlations of age and mean cortical thickness within each region for patients and controls are marked (*). Regions are manually labeled along the edges of areas with significant group differences in cortical thickness (see upper panel).

3.2. Entire cortex analysis

Statistical maps of group differences in cortical thickness are shown in Fig. 1. These maps show a pattern of thinner cortex among patients than controls in widespread areas of the prefrontal and temporal cortex in both hemispheres, while cortical thickness in parietal and occipital areas were not significantly different between groups. Highly significant differences were found in the dorsolateral prefrontal and orbitofrontal cortex in both hemispheres, whereas no significant group difference was found for the most anterior part of the frontal pole. In the right hemisphere, patients had thinner cortex in the ventromedial prefrontal (anterior cingulate and straight gyrus) and insular cortex. In temporal regions, patients had significantly thinner cortex of the temporal pole and anterior part of superior temporal gyrus in both hemispheres. In the right hemisphere, the difference was confined to the superior temporal gyrus, whereas in the left hemisphere patients also had thinner cortex in the medial and inferior temporal gyrus. Significantly thicker cortex in patients than controls was found in the superior part of the right precentral gyrus.

When controlling for the effect of WAIS vocabulary score (available for 58 patients and 70 controls), a similar pattern of thinner cortex in patients within prefrontal and temporal regions of both hemispheres was found (pictures not shown). Group differences were restricted to the anterior part of the inferior and middle frontal gyrus, orbitofrontal gyrus, and the anterior and medial part of the

Table 2
Regional cortical thickness measures in patients and controls

Region	Structure	Side	Patients (n=96)	Controls (n=107)	t (df=1, 201)	p [a]	% [b]
Frontal	Middle f. gyrus	Right	2.32 (0.22)	2.45 (0.22)	4.24	.000	5.3
		Left	2.42 (0.21)	2.50 (0.23)	2.77	.006	3.2
	Superior f. gyrus	Right	2.65 (0.24)	2.83 (0.26)	5.04	.000	6.4
		Left	2.80 (0.22)	2.94 (0.27)	3.93	.000	4.8
Temporal	Superior t. gyrus	Right	2.68 (0.31)	2.80 (0.31)	2.79	.006	4.3
		Left	3.21 (0.30)	3.49 (0.28)	6.78	.000	8.0
	Temporal pole	Right	3.31 (0.35)	3.57 (0.32)	5.52	.000	7.3
		Left	3.25 (0.37)	3.56 (0.31)	6.39	.000	8.7
Parietal	Postcentral gyrus	Right	2.19 (0.24)	2.21 (0.21)	0.43	n.s.	
		Left	1.96 (0.19)	2.00 (0.19)	1.41	n.s.	
	Postcentral sulcus	Right	1.79 (0.18)	1.80 (0.18)	0.14	n.s.	
		Left	2.02 (0.18)	2.06 (0.21)	1.36	n.s.	
	Angular gyrus	Right	2.49 (0.22)	2.55 (0.21)	1.87	n.s.	
		Left	2.48 (0.19)	2.50 (0.19)	0.57	n.s.	
	Angular sulcus	Right	2.42 (0.22)	2.43 (0.21)	0.64	n.s.	
		Left	2.45 (0.19)	2.48 (0.18)	1.28	n.s.	
Occipital	Gyrus cuneus	Right	1.95 (0.17)	2.00 (0.17)	0.16	n.s.	
		Left	1.96 (0.18)	1.95 (0.18)	1.65	n.s.	
	Occipital pole	Right	1.87 (0.16)	1.88 (0.17)	0.57	n.s.	
		Left	1.86 (0.20)	1.90 (0.20)	1.20	n.s.	

Mean cortical thickness in mm (SD) within selected brain regions automatically parcellated by FreeSurfer.
[a] Significant group differences (p<0.05) based on t-tests, not adjusted for multiple comparisons.
[b] Significant group differences shown as percentage difference from highest value.

middle temporal gyrus in both hemispheres. In separate regression analyses, subjects' gender, handedness and durations of illness did not significantly affect variation in cortical thickness.

3.3. Region-of-interest analysis

Mean cortical thickness measures within selected parcellated regions are shown in Table 2. The pattern of thinner cortex among patients compared to controls in prefrontal and temporal, but not parietal and occipital regions in both hemispheres, remained. The difference was largest in the left superior temporal gyrus and the left temporal pole. The p-values for group differences in mean cortical thickness (Table 2) were not adjusted for multiple comparisons. However, when applying the conservative Bonferroni correction, all reported differences in prefrontal and temporal parcellated regions remained significant (p<0.05), except left middle frontal gyrus and right superior temporal gyrus (p=0.12 for both).

3.4. Influence of antipsychotic medication

Current dose or type of antipsychotic medication did not significantly affect variation in cortical thickness. The derived proxy for lifetime load of antipsychotic medication did not affect cortical thickness when controlling for age.

3.5. Interactions between age and diagnostic group

The initial vertex-wise analysis revealed no group differences in age regression slopes between patients and controls when adjusting for FDR. Results from the comparison of correlation coefficients of mean cortical thickness and age in areas of the cortex that were thinner among patients than controls are shown as scatterplots in Fig. 2. A significant group difference was found in the left prefrontal cortex (Fig. 2, panel G) with a steeper downward directed age regression slope among controls compared to patients (z=2.43; p=0.008). For other regions, the age regression slopes were not significantly different between diagnostic groups.

4. Discussion

The main finding of this study was reduced cortical thickness in widespread areas of the prefrontal and temporal brain regions of both hemispheres among patients with schizophrenia compared to a group of age and gender matched control subjects. These results are in concordance with findings from a previous study using the same methodology on a smaller subject group (Kuperberg et al., 2003), and a series of volumetric studies showing involvement of frontal and temporal cortical regions in schizophrenia (Honea et al., 2005;

Narr et al., 2005a; Shenton et al., 2001; White et al., 2003; Wright et al., 2000).

4.1. Putative pathological mechanisms

The underlying pathophysiological mechanism of the observed cortical thinning is at present poorly understood. Postmortem data points to reduced neuronal size and arborization of dendrites in prefrontal cortical regions as key findings in schizophrenia (Harrison, 1999a; Selemon and Goldman-Rakic, 1999), while no reduction in number of neurons in prefrontal cortex has been found (Thune et al., 2001). A meta-analysis of brain weight in schizophrenia found a slight, but significant, reduction of 2% in 540 patients as compared to 794 controls (Harrison et al., 2003). Absence of gliosis in postmortem brain tissue (Arnold et al., 1998) argues against a view of schizophrenia as a neurodegenerative disease. Impaired connectivity between frontal and temporal cortical areas has been a suggested pathological mechanism for the disorder (Davis et al., 2003; Friston and Frith, 1995). Findings from diffusion tensor imaging (DTI) studies have provided support for this theory (Kubicki et al., 2002; Wang et al., 2004), while postmortem studies have found no difference in myelinated fiber length in prefrontal cortex (Marner and Pakkenberg, 2003) or area, fibre density or number in the uncinate fasciculi (Highley et al., 2002). At this point, it is not clear if abnormal development of white matter fiber bundles may explain the cortical abnormalities in the brain of patients with schizophrenia. The only published study of combined DTI and structural MRI data in schizophrenia showed significantly reduced fractional anisotropy (FA) in the entorhinal cortex among patients, while volume of the entorhinal cortex was not significantly reduced (Kalus et al., 2005). Studies combining DTI with functional MRI (Schlösser et al., 2007) and proton magnetic resonance spectroscopy (Steel et al., 2001) have not shown functional changes in regions with FA, or vice versa, indicating a weak relationship between structure and function. A thinner cortex in prefrontal and temporal regions may reflect disruptions in the white matter bundles connecting them, or impaired connectivity may be a consequence of an abnormal maturation of the cortex. Regionally thinner cortex and impaired connectivity may also be independent features of the disorder.

4.2. Regional specificity

Mechanisms underlying the selective vulnerability of prefrontal and temporal cortex and the relative preservation of parietal and occipital cortex in schizophrenia remain to be clarified. According to the neurodevelopmental model of schizophrenia, early pre- or perinatal insults may interfere with normal brain development and entail subtle brain abnormalities (Rapoport et al., 2005). As symptoms of schizophrenia in general do not manifest themselves until early adulthood it has been proposed that additional events taking place in the later stages of brain maturation may be superimposed upon these early insults (Pantelis et al., 2005). In this respect, it is of interest to note that in the developmental trajectory of the cerebral cortex prefrontal and temporal regions mature later than parietal and occipital regions (Thompson et al., 2005). The observed regional thinning of the cortex in schizophrenia may thus reflect a disruption in the later stages of cortical maturation, such as excessive synaptic pruning. Although the evidence for adult neurogenesis in the human cerebral cortex is controversial (Abrous et al., 2005) aberrant expression of developmental genes in the adult cortex may play a role in the neuropathological process of schizophrenia (Toro and Deakin, 2007).

4.3. Age

In the present study, a significantly steeper downward directed age regression slope in healthy subjects compared to patients with schizophrenia was found in the left prefrontal cortex. Examination of the regression slopes, however, revealed that the intercept is lower for patients than controls, and that the regression lines almost intersect in the higher age range (Fig. 2, panel G), indicating that the difference in age regression slope is due to a lower offset in patients than controls. For other regions, the decrease in mean cortical thickness with increasing age was similar in patients and controls. This is in concordance with the cross-sectional study using the same method on a smaller sample (Kuperberg et al., 2003), but not with the larger study showing a slightly steeper regression slope of gray matter volume with increasing age among patients than controls (Hulshoff Pol et al., 2002). In accordance, progressive loss of gray matter volume with increasing age in patients relative to controls has been reported in a number of longitudinal studies of first-episode (Cahn et al., 2002; Farrow et al., 2005; Whitford et al., 2006) and chronic schizophrenia patients (Mathalon et al., 2001), while some studies have not found such a progression (Ho et al., 2003; Lieberman et al., 2001). So far, the results on possible loss of gray matter (typically measured as volumes or cortical thickness) with increasing age and duration of illness are inconsistent (Weinberger and McClure, 2002). Some of the discrepancies may be due to clinical subject heterogeneity, reflected in the finding of a more pronounced volume loss in patients with a severe

outcome than in patients with a better outcome of the disease (Ho et al., 2003; Lieberman et al., 2001). Notably, since patients have a thinner cortex even in their first episode of psychosis (Keshavan et al., 2005; Steen et al., 2006) a direct comparison of longitudinal brain changes between patients and controls may not be appropriate.

4.4. Antipsychotic medication

In the present study, neither type, nor dose of current or estimated lifetime load of antipsychotic medication significantly influenced the variation in cortical thickness. In a previous study we reported only a trend level association between smaller volumes of frontal lobe gray matter and antipsychotic medication using a different segmentation method on a subset of the present subject material (Nesvåg et al., 2007). Lieberman et al. (2005) have reported reduction of total and frontal gray matter volumes, and increase in ventricular and caudate volumes, in response to treatment with haloperidol, but not olanzapine, from a randomized controlled study of 161 first-episode patients repeatedly investigated over two years. Most of the reduction had occurred after 12 weeks of treatment. In accordance a cross-sectional voxel-based morphometry study comparing 32 patients receiving typical, 30 patients receiving atypical antipsychotic medication and 22 drug-free patients showed significant differences in brain volumes between medicated and non-medicated patients (Dazzan et al., 2005). Typical antipsychotic medication was related to larger volume of putamen and reduced volume of discrete parts of the prefrontal and temporal cortex, while atypical medication was related to larger volume of thalamus. However, when comparing the two groups of medicated patients, only one cluster (left middle temporal gyrus) showed grey matter deficit among patients receiving typical as compared to patients receiving atypical medication. A study of 19 acutely admitted patients reported an increase in gray matter volumes in response to four weeks of treatment with risperidone and ziprasidone, but not haloperidol (Garver et al., 2005). Furthermore, in a study of healthy macaque monkeys given olanzapine or haloperidol with serum levels equal to treatment of patients with schizophrenia, both types of medication were associated with reduction in postmortem weight and volume of the brain when compared to monkeys given placebo (Dorph-Petersen et al., 2005). Concurring with results from the present study, antipsychotic medication has not previously been found to influence cortical thickness (Kuperberg et al., 2003; Narr et al., 2005a,b; Wiegand et al., 2004). Thus the effect of antipsychotic medication on cerebral cortex morphology remains elusive. While there is consistent evidence for an association between typical antipsychotic medication and larger volumes of basal ganglia, foremost the caudate (Dazzan et al., 2005; Keshavan et al., 1994; Lieberman et al., 2005), more conflicting results have come from studies of associations between basal ganglia volumes and atypical antipsychotic medication (Dazzan et al., 2005; Heitmiller et al., 2004; Lang et al., 2001). A recently published review concluded that different effects of typical and atypical medication on variation in cortical and subcortical volumes may be explained by different mechanisms of action (Scherk and Falkai, 2006). Preclinical and postmortem studies have shown associations between antipsychotic medication and ultrastructural morphological changes, indicative of synaptic plasticity, in the caudate and prefrontal cortex, while there is no evidence for gliosis or neurotoxic effects of antipsychotic medication (Dean, 2006; Harrison, 1999b). Some of the MRI-based studies showing morphological change in response to antipsychotic medication have been performed in patients with first-episode schizophrenia (Lieberman et al., 2005) or in patients with an acute exacerbation of psychosis (Garver et al., 2005). The effect of medication may be confined to the early phase or acute psychotic state of the disorder, and possibly is of less importance among patients with chronic, stable schizophrenia, as was the case for patients in the present study.

4.5. Gender

The present study showed no significant effect of gender on variation in cortical thickness. Among healthy subjects larger intracranial volume in men and gender-specific differences in the degree of lateralization have been reported (Good et al., 2001; Nopoulos et al., 2000). No differences, however, have been found with respect to cortical surface anatomy in long-term treated patients (Nopoulos et al., 2000). When investigating gender differences of brain morphology among first-episode schizophrenia patients, thicker cortex in right ventromedial frontal regions has been reported among men, and higher concentration of gray matter in posterior parietal cortical regions among women (Narr et al., 2005a). In a study of patients with chronic schizophrenia, larger ventricular volumes were found only among male patients relative to controls (Nopoulos et al., 1997). The male patients also had a longer duration of illness and greater load of medication than female patients, but neither of these variables significantly correlated with ventricular size.

4.6. Lateralization

Certain brain functions are lateralized. Pierre Paul Broca first identified a functional asymmetry related to language in the left hemisphere (Broca, 1861), and more recent work has shown that language is generated in the left hemisphere in about 95% of the population, and even so in 70% of subjects with a dominant left hand (Capozzoli, 1999). Recent MRI-studies have shown leftward asymmetry in frontal and temporal regions, and a rightward asymmetry in occipital regions of the healthy brain (Barrick et al., 2005; Luders et al., 2006), also referred to as the cerebral torque. Morphological studies of the brain in schizophrenia have shown a reduced and even reversed asymmetry of the planum temporale among patients relative to healthy subjects (Sommer et al., 2001). This has been held as evidence for a genetically disturbed lateralization during neurodevelopment in schizophrenia (Crow, 1999, 2004; Esiri and Crow, 2002; Mitchell and Crow, 2005). In the present study, in which 85% of both patients and controls were right-handed, no significant effect of handedness on variation in cortical thickness was found. Furthermore, a left-larger-than right pattern in mean cortical thickness of inferior frontal gyrus and superior temporal gyrus was found both among patients and healthy subjects (Table 2). The distribution of significant difference in cortical thickness showed some hemispheric specificity when evaluated qualitatively (Fig. 1). Patients had thinner cortex in parts of the insula, anterior cingulate, precentral and straight gyrus in the right hemisphere, and in parts of the medial and inferior temporal gyrus in the left hemisphere.

4.7. Strengths and limitations

The major strength of this study was the comparatively large group of participants who were subjected to careful clinical characterization. MR measures were obtained using methods that have been thoroughly validated. Potential effects of alcohol consumption on the gray matter had been carefully ruled out. The same calibrated MR system was used for all investigations without upgrading or other uncontrolled changes throughout the study period.

The issue of false positive findings resulting from multiple comparisons in the vertex-wise general linear model analyses was considered using a conservative threshold of significance ($p=0.01$) with an expected rate of false positive findings of less than 5%.

Given the aim of investigating effects of antipsychotic medication on brain cortical thickness, the study would have benefited from detailed data on lifetime load of antipsychotic medication. A full history of antipsychotic medication was, however, not available for all patients and the derived proxy for lifetime load of antipsychotic medication provides only a rough estimate.

Years of education and WAIS vocabulary score were significantly lower in patients than controls (Table 1). Among the subjects for whom data on WAIS vocabulary were available, group differences in cortical thickness were still present, though less widespread than in the entire group analysis. Information on parental education would have been helpful to further control for socio-demographic group differences.

A cross-sectional design is an obvious limitation for detecting effects of age on variation in morphological brain measures. Cross-sectional data may reveal interaction effects, but caution is warranted when inferring any conclusions regarding longitudinal changes.

5. Conclusion

The cortex is significantly thinner in prefrontal and temporal brain regions in both hemispheres among patients with schizophrenia compared to age and gender matched control subjects, while parietal and occipital regions are relatively spared. The influence of age on variation in regional cortical thickness is similar in patients and controls. Dose or type of antipsychotic medication has no significant effect on variation in cortical thickness among the patients. The results suggest that regional cortical thinning is an inherent feature of the disease process in schizophrenia.

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Contributors

RN, GL, AF and IA designed the study. IA organized magnetic resonance imaging and EGJ performed clinical assessment of study participants. RN, GL, KV, AMF and KBW performed statistical analyses of the data. AF supervised the statistical analyses. RN performed literature search and wrote the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest

All authors declare that they have no conflict of interest.

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