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# Complex pattern of cortical thinning in schizophrenia: Results from an automated surface based analysis of cortical thickness

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ABSTRACT

A considerable body of evidence from structural brain imaging studies suggests that patients with schizophrenia have significant alterations of gray matter density. Additionally, recently developed surface-based analysis approaches demonstrate reduced cortical thickness in patients with schizophrenia. However, the number of studies employing this relatively new method is still limited. Specifically, little is known about changes in cortical thickness in schizophrenia patients whose duration of illness is relatively short. Therefore, the present study sought to examine cortical thickness in a large sample of patients with adult onset schizophrenia and an average duration of illness of 4.4 years, using an automated analysis method over the entire cortex. A significantly decreased cortical thickness in prefrontal and temporolimbic regions as well as parieto-occipital cortical areas was hypothesized. A sample of 58 patients with schizophrenia and 58 age- and sex-matched healthy controls was investigated using high-resolution magnetic resonance imaging (MRI) and an automated algorithm for extraction of the cortical surface in order to assess local cortical thinning across the entire cerebrum. Significant reduction of cortical thickness in schizophrenia was found in a spatially complex pattern of focal anatomical regions. This pattern comprised the dorsolateral prefrontal cortex as well as the medial prefrontal cortex, lateral temporal cortices, left entorhinal cortex, posterior cingulate cortex, precuneus and lingual cortex, bilaterally. A complex fronto-temporo-parietal pattern of reduced cortical thickness in schizophrenia was observed. This pattern is consistent with a disruption of neurofunctional networks previously implicated in the pathophysiology of schizophrenia.


## 1. Introduction

There is a broad base of evidence suggesting morphologic alterations in patients with schizophrenia. According to recent reviews and meta-analyses, the left temporal and frontal areas seem to be predominantly affected by decreases in gray matter density (Honea et al., 2005; Williams, 2008). However, there are also a substantial number of studies which could not detect any alterations in a subset of regions including the medial temporal lobe (Ananth et al., 2002) and medial frontal gyrus (Wright et al., 1999).

Recently, automated surface-based approaches have developed in order to allow for a closer examination of cortical surface characteristics between patient and control groups. These approaches take into account the intrinsic two-dimensional structure and highly folded geometry of the cortex (Dale et al., 1999; Fischl et al., 1999). Thus, whereas the voxel based morphometry (VBM) approach is primarily directed towards gray matter density, surface-based analysis complements the available analysis strategies by including morphological shape analysis either in terms of thickness or curvature. Measurement of cortical thickness is of great interest for the investigation of morphological alterations that are attributed to putative pathogenetic neurodevelopmental mechanisms currently proposed to be related to schizophrenia (Rapoport et al., 2005; Fatemi and Folsom, 2009). Automated methods for regional parcellation and surface-based cortical shaping analyses efficiently extract information about the entire cortex. While a region of interest analysis is restricted to an a priori defined search space of potential anatomical alterations, entire cortex analyses can examine the entire surface for morphological changes in an exploratory manner. In addition, the quantification of cortical thinning across the entire cortex sheds light on how strongly the different brain regions are affected.

In first episode schizophrenia, cortical thinning was previously demonstrated in frontal, cingulate, temporal, occipital, and parietal cortices (Narr et al., 2005a,b). Venkatasubramanian et al. (2008) demonstrated prefrontal cortical thinning in antipsychotic-naive patients with schizophrenia utilising a surface-based approach. In addition, first episode patients investigated using a surface-based method demonstrated cortical thinning in the anterior cingulate cortex (Fornito et al., 2008).

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To date, few studies have examined cortical thickness in multi-episode, adult onset schizophrenia. They demonstrated decreased cortical thickness mainly in prefronto-temporal areas (Kuperberg et al., 2003; Nesvag et al., 2008). However, these studies showed some heterogeneity regarding the affected anatomical regions. While the study of Nesvag et al. (2008) demonstrated cortical thinning in superiorfrontal regions, this area was mostly spared according to the study of Kuperberg et al. (2003). Conversely, the entire cortex analyses of Kuperberg et al. (2003) revealed lateral occipital regions to be affected, which were not affected in Nesvag et al. (2008). These heterogeneities might be attributable to scanner modalities such as differences in MRI sequences as well as clinical and demographic characteristics of the study group.

Nesvag et al. (2008) and Kuperberg et al. (2003) investigated chronic patients with a duration of illness of 16 years or longer. The investigation of cortical thickness of patients with schizophrenia in the short/medium course of the illness might therefore extend our knowledge of cortical thickness aberrations in schizophrenia. In order to detect and quantify even subtle cortical alterations in the short/medium term of schizophrenia, the present study sought to examine cortical thickness in a larger sample of patients with adult onset schizophrenia in the short/medium course of the illness using an entire cortex analysis and an automated surface-based approach. Based on the previous literature (Kuperberg et al., 2003; Narr et al., 2005a,b; Nesvag et al., 2008), it was hypothesized that cortical thinning in schizophrenia patients would be detectable predominantly in prefronto-temporal as well as parieto-occipital regions.

## 2. Subjects and methods

### 2.1. Participants

A total of 58 patients with schizophrenia and 58 matched healthy controls matched for age and gender were included in the study. All subjects were right-handed (Annett, 1967). Diagnoses were established by a clinical psychiatrist (M. R.) based on the Structured Clinical Interview for DSM-IV, and these diagnoses were subsequently confirmed by two independent psychiatrists (R. S. and C. S.). All patients met the DSM-IV criteria for schizophrenia and had no second psychiatric diagnosis. Patients were in the short/medium term of the disease with an average duration of illness of 4.4 years. Patients were in remission from a psychotic episode and clinically stabilized. They were treated with clinically typical doses of second-generation antipsychotics (9 patients with amisulpiride, dose range of 600–800 mg; 4 patients with aripiprazole, dose range of 10–30 mg; 8 patients with clozapine, dose range of 200–400 mg; 15 patients with olanzapine, dose range of 12.5–20 mg; 9 patients with quetiapine, dose range of 450–800 mg and 13 patients with risperidone, dose range of 2–6 mg).

Healthy volunteers were screened for a history of major medical, neurological, and psychiatric disorders. None of the healthy subjects had first-degree relatives with a psychiatric disorder according to DSM-IV. Exclusion criteria for all participants were neurological disease or damage, or medical disorders potentially influencing neurocognitive function. All participants gave written informed consent to participate in the study, as approved by the Ethics Committee of the Friedrich-Schiller University. Sociodemographic and psychopathological data are given in Table 1.

**Table 1**
Data expressed as mean (SD). *P*-values resulting from two-sample *t*-test. $df = 114$. a.: Not applicable; PANSS: Positive and Negative Syndrome Scale (Kay et al., 1987).

| Parameter | Controls ($n = 58$) | Patients ($n = 58$) | *P* |
|---|---|---|---|
| M/F | 41/17 | 41/17 | |
| Age (year) | 28.5 (8.8) | 30.5 (10.1) | 0.252 |
| Education (year) | 11.4 (0.9) | 10.7 (1.3) | 0.001 |
| PANSS total | n.a. | 70 (25.8) | |
| PANSS positive | n.a. | 16.8 (8.9) | |
| PANSS negative | n.a. | 18.2 (7.4) | |
| Duration of illness (year) | n.a. | 4.4 (5.9) | |

### 2.2. MRI acquisition

High-resolution anatomical T1-weighted scans were acquired on a 1.5 T Siemens Magnetom Vision whole-body MRI system using a three-dimensional spoiled gradient echo sequence: 1 mm sagittal slices with TR = 15 ms, TE = 5 ms, flip angle 30°, FOV = 256, matrix = 256 × 256, number of sagittal slices = 192. All scans were inspected for motion artifacts and a neuroradiologist confirmed the absence of gross pathological findings.

### 2.3. MR scan processing and calculation of cortical thickness

The FreeSurfer software package (version 3.3, http://surfer.nmr.harvard.edu) was used for image data preprocessing and analysis (Dale et al., 1999; Fischl et al., 1999). The implemented processing stream included removal of non-brain tissue, transformation to Talairach-like space, and segmention of gray/white matter tissue. The white and gray matter boundary was tessallated and topological defects were automatically corrected. After intensity normalization, the gray/white matter and pial boundaries were detected by finding the greatest shift in intensity as the surface is deformed. The entire cortex of each subject was then visually inspected and any inaccuracies in segmentation were manually edited. After creation of the cortical representations, the cerebral cortex was parcellated into anatomical structures. Cortical thickness was computed by finding the shortest distance between a given point on the estimated pial surface and the gray/white matter boundary and vice versa. These two values were then averaged (Fischl and Dale, 2000). As the generated cortical maps were not limited to the voxel resolution of the original data, they were capable of detecting sub-millimeter differences between diagnostic groups. Measurements of cortical thickness have been previously validated against manual measurements in schizophrenia (Kuperberg et al., 2003).

### 2.4. Quantification of cortical thinning

In order to quantify cortical thinning, the authors manually traced all focal regions that demonstrated significant differences ($P < 0.05$, False Discovery Rate (FDR) threshold) in the statistical cortical maps and which constitute anatomically relevant networks in schizophrenia (Mitelman et al., 2005a,b). These areas were traced from the FreeSurfer average template, and then automatically transferred as an anatomical label to all individual brains for the quantification of cortical thickness differences between the study groups. Finally, the mean cortical thickness of those regions of interest was automatically calculated for each subject using the FreeSurfer software package.

### 2.5. Statistical analysis

#### 2.5.1. Statistical cortical maps

The thickness measurement of each vertex of the subject's surface was mapped onto a common spherical coordinate system using a spherical transformation. Maps were smoothed using a Gaussian kernel of 10 mm. A general linear model controlled for the effect of age in the estimatation of differences in cortical thickness between the groups at each vertex of the surface.

The right and left hemispheres were tested separately. All results for the statistical maps were corrected for multiple comparisons using the False Discovery Rate (FDR) adjustment for *P*-values (Genovese et al., 2002). FDR controls the expected proportion of false positives among