Reduced Anterior Cingulate Cognitive Activation Is Associated with Prefrontal–Temporal Cortical Thinning in Schizophrenia

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Background: The anterior cingulate cortex plays a central role in altered processes of cognitive control in schizophrenia. However, the cortical foundations of disturbed anterior cingulate cognitive activation are poorly understood. Therefore, this study investigated the association of anterior cingulate cognitive activation and cortical thickness in schizophrenia combining functional magnetic resonance imaging (fMRI) and surface-based morphometry.

Methods: Fifty-three patients with schizophrenia according to DSM-IV and 53 age- and sex-matched healthy subjects were included and underwent fMRI and high-resolution T1-weighted MRI. fMRI data was analyzed using SPM5. Cortical thickness was calculated using an automated computerized algorithm (Freesurfer Software). Statistical cortical maps were created correlating anterior cingulate activation and cortical thickness on a node-by-node basis covering the entire cortex in schizophrenia and healthy control subjects.

Results: Patients demonstrated a significantly reduced anterior cingulate cognitive activation. Significantly differing associations of anterior cingulate activation and cortical thickness were found in a pattern of dorsolateral prefrontal, superior frontal–anterior cingulate, and superior temporal cortical regions, where patients but not healthy control subjects demonstrated a significant association of reduced anterior cingulate activation and cortical thinning. A direct comparison of cortical thickness between the diagnostic groups revealed a significantly reduced cortical thickness of these prefrontotemporal regions in schizophrenia.

Conclusions: To our best knowledge, this is the first study indicating that prefrontotemporal cortical thinning constitutes a relevant cortical pathomechanism for altered cognitive activation in schizophrenia. Our data additionally reveal a profound disruption of structural and functional integration in the prefrontotemporal system in schizophrenia.

Key Words: Anterior cingulate cortex, cognitive control, cortical thickness, entire cortex analysis, fMRI, multimodal, schizophrenia, surface based morphometry

Working memory (WM) deficits are a major feature of altered cognition in schizophrenia (1). They have been shown to be linked to genetic liability (2,3). Thus, WM deficits are widely assumed to constitute a trait marker for schizophrenia. The characteristics of neuronal activation regarding WM deficits in schizophrenia have been explored intensively by functional magnetic resonance imaging (fMRI) studies. A recent meta-analysis (4) indicated that the anterior cingulate cortex (ACC) plays a pivotal role in disturbed processes of cognitive control and associated WM deficits in schizophrenia. Alterations of cognitive activation of the ACC even occurred in antipsychotic-naive patients (5), demonstrating that altered ACC activation is not an artifact of antipsychotic drug exposure. As a putative neuroanatomic basis for the observed functional activation deficits in schizophrenia, recent meta-analyses of voxel-based morphometry (VBM) studies (6,7) consistently revealed structural alterations of the ACC. Furthermore, evidence for heritability of ACC gray matter alterations was provided by studies in unaffected relatives by means of cortical thickness (8) and additionally surface area and volume (9). Moreover, cortical thinning and volume loss of the ACC have been found in high-risk subjects (10–12). Because the ACC is known to be a core module in a larger prefrontotemporal neuronal network subserving major functions of cognitive control (13), these functional and structural abnormalities of the ACC might be of critical relevance for the integrity of prefrontotemporal circuitry. Accordingly, a failure of functional ACC network integration has been shown to be of major relevance for disturbed cognitive processes in schizophrenia (14,15).

However, the neuroanatomic basis of altered ACC activation remains largely unclear although the examination of this structure–function relationship can be assumed to extend our knowledge about the etiology of core cognitive deficits in schizophrenia. Recent studies explored the relationship between neurocognitive test performance and structural and functional alterations in schizophrenia. Schobel *et al.* (16) found an association of cognitive deficits and hippocampal and orbitofrontal volume. Using proton magnetic resonance spectroscopy, Ohmann *et al.* (17) illustrated a significant correlation between *N*-acetylaspartate and glutamate/glutamine in the ACC and learning potential. Koutsouleris *et al.* (18) demonstrated an association of prefronto-temporo-cerebellar volume and executive functioning in high-risk subjects. Surface-based methods allow determination of whether cognitive dysfunction is related to particular cortical shape parameters. Several studies demonstrated cortical thinning in schizophrenia (8,19–22) in mainly frontotemporal regions. In a recent study by Gutierrez-Galve *et al.* (23), surface area of the frontotemporal cortex was associated with IQ measures, whereas working memory span was associated with surface area of the frontal cortex in first-episode schizophrenia. Hartberg *et al.* (24) demonstrated a positive correlation of several cognitive measures and frontotemporal cortical thickness in patients and healthy control subjects with a disrupted correlation in

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Table 1. Demographic and Clinical Data

Parameter	Control Subjects ($n = 53$)	Range	Patients ($n = 53$)	Range	p
M/F	35/18	NA	35/18	NA	
Age (years)	27.8 (8.1)	19–51	28.1 (9.0)	18–49	.830
Education (years)	11.6 (0.9)	9–13	10.9 (1.2)	9–13	.001
PANSS Total Score	NA	NA	72.2 (24.3)	34–155	
PANSS Positive	NA	NA	16.9 (8.2)	7–47	
PANSS Negative	NA	NA	18.4 (6.2)	7–35	
Duration of Illness (years)	NA	NA	4.8 (7.4)	1–30	
Age at Onset (years)	NA	NA	23.5 (5.8)	17–44	
No. of Hospitalizations	NA	NA	2.9 (4.7)	1–30	
Medication Status	NA	NA	3 un; 9 typ; 41 atyp	NA	

Data expressed as mean (SD) and ranges (minimum-maximum) p values resulting from two-sample t test.

atyp, atypical antipsychotics; F, female; M, male; NA, not applicable; PANSS, Positive and Negative Syndrome Scale (77); un, unmedicated; typ, typical antipsychotics.

temporal and occipital regions in schizophrenia. Cognitive test deficits reflect cognitive dysfunction at the level of performance, whereas fMRI allows elucidating the underlying disturbed pattern of neuronal activation. Rasser *et al.* (25) demonstrated positive correlations of global blood oxygen level dependent response and cortical thickness in prefrontotemporal and parietal regions in 10 male patients with schizophrenia and healthy subjects performing the Tower of London task. These correlations were partly reversed in healthy control subjects. Thus, to examine specifically the association of altered ACC activation during cognitive control with cortical structure might be a promising approach to shed light on the cortical foundations of disturbed ACC activation in schizophrenia and might additionally identify altered structural–functional coupling of the engaged frontotemporal networks.

On the basis of these considerations, we explored the association of cognitive activation of the ACC and fine grained node-by-node cortical thickness of the entire cortex combining fMRI and surface-based morphometry in a large cohort of patients with schizophrenia and healthy control subjects, extending our previous work on neuronal activation (26) and cortical thickness alterations (22, 27) in schizophrenia. We focused on the dorsal ACC (dACC) for two reasons: 1) the ACC has been revealed to be one of the most prominent cerebral nodes in disturbed neuronal networks of WM retrieval in schizophrenia (4). 2) Recent studies suggest that disturbed dACC activation in schizophrenia occurs independently from performance aspects (26), and appears to be a consistent finding over a wide range of cognitive tasks including Stroop and verbal fluency tasks (13). Hence, disturbed dACC activation might be regarded as an authentic feature of altered neuronal activity of central cognitive processes in schizophrenia. Because it is known that the ACC is highly involved in WM retrieval and that the retrieval phase demands important processes of cognitive control such as source monitoring and response execution (4), we focused on the association of neuronal activation of the retrieval phase. Thus, examining the association of disturbed ACC activation and cortical thickness might provide important clues to functional and neuroanatomical underpinnings of disturbed cognitive control in schizophrenia.

On the basis of the foregoing cited studies showing structural and functional alterations of the ACC and a failure of functional ACC integration in frontotemporal networks in schizophrenia we hypothesized the following: 1) reduced ACC activation in schizophrenia; 2) disturbed structure–function relationship in patients in mainly prefrontotemporal regions; and 3) cortical thinning in these regions of a disturbed structure–function relationship in patients with schizophrenia as potential structural correlate.

Methods and Materials

Participants

We studied 53 patients with schizophrenia and 53 healthy control subjects closely matched for age and sex, all of whom were right-handed (28). Diagnoses were established by a clinical psychiatrist (MR) based on the Structured Clinical Interview for DSM-IV and were confirmed by two independent psychiatrists (RS and CCS). All patients met DSM-IV criteria for schizophrenia and had no second psychiatric diagnosis. In particular, none of the patients fulfilled DSM-IV criteria for substance abuse or dependence. Of the 53 patients, 3 were unmedicated, 9 were medicated with typical antipsychotics (8 haloperidol, 1 promethazine), and 41 were medicated with atypical antipsychotics (6 amisulpride, 2 aripiprazole, 6 clozapine, 14 olanzapine, 6 quetiapine, 7 risperidone). Healthy volunteers were screened for major medical, neurologic, and psychiatric history. None of the healthy subjects had a current or history of a psychiatric disorder or first-degree relatives with a psychiatric disorder according to DSM-IV. Exclusion criteria for all participants were neurological disease or damage, and medical disorders potentially influencing neurocognitive function. All participants gave written informed consent to the study, which was approved by the Ethics Committee of Friedrich-Schiller University. Sociodemographic and psychopathological data are given in Table 1.

High-Resolution Structural MRI Acquisition

We acquired high-resolution anatomic T1-weighted brain scans on a 1.5-T Siemens (Erlangen, Germany) Magnetom Vision scanner (for details, see Supplement 1).

All scans were inspected for motion artifacts, and two patients were excluded for such artifacts. A neuroradiologist confirmed absence of gross pathologic findings. The final number of patients included in the analyses was 53.

MR Scan Processing

We used the FreeSurfer software package (version 4.0.5, http://surfer.nmr.mgh.harvard.edu) for image processing (29,30). The implemented processing stream provides removal of nonbrain tissue (31), transformation to Talairach-like space, and segmentation of gray/white matter tissue (32,33). The white and gray matter boundary is tessellated and topological defects are automatically cor-