Associations of Cortical Thickness and Cognition in Patients With Schizophrenia and Healthy Controls

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Associations between regional variation in cortical thickness and executive functions, memory, as well as verbal and spatial processing in patients with schizophrenia and healthy controls (HCs). We obtained magnetic resonance imaging and neuropsychological data for 131 patients and 138 matched controls. Automated cortical pattern matching methods allowed testing for associations with cortical thickness estimated as the shortest distance between the gray/white matter border and the pial surface at thousands of points across the entire cortical surface. Two independent measures of working memory showed robust associations with cortical thickness in lateral prefrontal cortex in HCs, whereas patients exhibited associations between working memory and cortical thickness in the right middle and superior temporal lobe. This study provides additional evidence for a disrupted structure-function relationship in schizophrenia. In line with the prefrontal inefficiency hypothesis, schizophrenia patients may engage a larger compensatory network of brain regions other than frontal cortex to recall and manipulate verbal material in working memory.

Key words: gray matter thickness/cognitive dysfunction/working memory/structural MRI

Introduction

Schizophrenia is characterized by considerable variation in clinical presentation and appears to have complex and possibly heterogeneous pathophysiology. A central aspect of the illness is marked cognitive impairment that is evident across the domains measured by standard neuropsychological tests. Meta-analyses have demonstrated that cognitive measures reliably distinguish a majority of schizophrenia patients from healthy controls (HCs).1,2 Although poor performance on neuropsychological tests is thought to more closely reflect cortical neuropathology than the waxing and waning of clinical symptoms, the neural determinants of cognitive deficits in schizophrenia have yet to be clearly established. Examination of brain morphology in concert with cognitive function in individuals with schizophrenia can help elucidate the relationships between disease-related changes in brain anatomy and cognitive function.3

Magnetic resonance imaging (MRI) studies in patients with schizophrenia and individuals at ultrahigh risk for schizophrenia have shown subtle gray matter volume or density reductions in multiple anatomical regions within the prefrontal and temporal cortices as well as the occipital and parietal cortices.4–9 Gray matter density and volumes of frontal and temporal lobe structures have in turn been associated with cognitive functioning (for a review see ref.10).

Due to the putative pathogenetic neurodevelopmental mechanisms currently proposed to be related to schizophrenia,11,12 cortical thickness may be of greater etiologic relevance than gray matter volume or density: Sibling and
family structural MRI (sMRI) studies provide evidence for the heritability of cortical thickness measures.\textsuperscript{13–16} suggesting that this aspect of cortical anatomy may represent a reliable intermediate phenotype for schizophrenia.\textsuperscript{17} Furthermore, these studies indicate that cortical thickness and surface area should be considered separately and that cortical thickness should be preferred over gray matter volume (which is a combination of thickness and surface parameters) in genetic imaging studies.\textsuperscript{14,18} Cortical thickness is assumed to reflect the arrangement and density of neuronal and glial cells, synaptic spines, as well as passing axons.\textsuperscript{19,20} Postmortem studies in patients with schizophrenia showed reduced neuronal size and a decrease in interneuronal neuropil, dendritic trees, cortical afferents, and synaptic spines,\textsuperscript{20–22} while no reduction in the number of neurons or signs of gliosis could be demonstrated.\textsuperscript{22,23} However, less than half of the cortical surface is visible as gyri; the majority is buried in sulci.\textsuperscript{24} The complex 3-dimensional shape of the cortex renders it difficult to study, particularly with respect to using neuroimaging data to characterize its morphology and function. An automated objective procedure (FreeSurfer) has been developed to estimate cortical thickness from MRI data.\textsuperscript{25} Using this well-validated method, several groups have shown widespread reductions of cortical thickness in frontal, temporal, and parietal regions in patients with schizophrenia.\textsuperscript{13,26–28} Reported reductions of cortical thickness in schizophrenia patients are scattered across the brain, but some frontal and temporal brain regions appear more affected than other regions. Examining the cognitive correlates of cortical morphology may be a means by which to appraise the significance of thinner cortical areas in schizophrenia. There is initial evidence for diminished executive functioning, working memory, attention, and episodic memory to be associated with prefrontal cortical volumes in schizophrenia.\textsuperscript{29–33} A recent investigation also revealed verbal learning to be related to cortical thickness of the superior and middle frontal gyri for both schizophrenia and control subjects, but verbal processing and executive functioning showed similar across group associations with thickness of frontal cortical regions.\textsuperscript{34} In the same study, cortical thickness of temporal regions was found to be related to verbal learning, verbal processing, and executive functioning, with only an association between verbal processing and temporal-occipital gyrus being unique to schizophrenia. Thus, cognitive functions that are dependent on temporal and frontal lobes appear to be most related to aspects of cortical thinning in schizophrenia, but the unique effects of the disorder on the function-structure relationship are largely unknown.

In the present study, we aimed to examine associations of cognitive functions with cortical thickness at subvoxel resolution across the entire cortex in a large sample of schizophrenia patients and demographically similar healthy subjects. Using data from the Mind Clinical Imaging Consortium (MCIC) study, we selected cognitive measures that assessed executive functions, memory, and verbal and spatial processing because they had been previously shown to be associated with morphological indices in schizophrenia. Based on a large body of functional neuroimaging literature (for a review see ref.\textsuperscript{35}), we hypothesized that executive functioning (in particular working memory) would be correlated with cortical thickness in prefrontal regions in HCs. In schizophrenia patients, we expected more distributed associations with cortical thickness due to possibly aberrant neurodevelopmental or neurodegenerative processes and the engagement of alternative mechanisms to compensate for reduced prefrontal neuronal efficiency.\textsuperscript{36–38}

**Methods**

**Participants**

The MCIC study of schizophrenia\textsuperscript{39–41} obtained sMRI and functional MRI (fMRI) scans on a total of 328 subjects from 4 participating sites: Massachusetts General Hospital in Boston (MGH) and the Universities of Iowa (UI), Minnesota (UMN), and New Mexico (UNM). After complete description of the study to the participants, written informed consent was obtained. The institutional review boards at each of the 4 sites approved the study protocol. The patient group (SCZ) included subjects with a *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, diagnosis of schizophrenia, established through administration of structured clinical interviews and review of case files by trained clinicians. HCs were included if they had no history of a medical or Axis I psychiatric diagnosis. All participants were required to be at least 18 years of age and no older than 60 and to be fluent in English. Participants were excluded if they had a history of neurologic disease or psychiatric disease other than schizophrenia, history of a head injury, history of substance abuse or dependence within the past month, severe or disabling medical conditions, contraindication to magnetic resonance scanning, or intelligence quotient (IQ) less than 70 (based on the reading subtest from the [Wide Range Achievement Test] WRAT-III).

The final sample with complete and high-quality sMRI and neuropsychological data comprised 138 HC participants (HC) and 131 patients with schizophrenia (SCZ) for quality assurance procedures see below and ref.\textsuperscript{42}).

**Clinical Measures**

Prior to subject enrollment, clinicians from all 4 sites participated in a 2-day training session, during which cross-site inter-rater reliability for the primary diagnostic and symptom-rating scales was established (>85% concordance.
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with videotaped training materials). All study participants underwent an extensive clinical diagnostic assessment that included either the Structured Clinical Interview for DSM Disorders (SCID) Patient Edition (I/P) or Non-patient Edition (I/NP)43 or the Comprehensive Assessment of Symptoms and History (CASH 44 see also table 1 and ref. 40). Premorbid cognitive achievement was estimated by the WRAT-III 45; parental socioeconomic status (SES) was determined using the Hollingshead index 46 and handedness determined using the Annett Scale of Hand Preference.47 Severity of positive and negative symptoms was rated using the Scale for the Assessment of Positive Symptoms and the Scale for the Assessment of Negative Symptoms.48,49

Table 1. Upper Panel: Demographic and Clinical Variables; Lower Panel: Neuropsychological Variables

<table>
<thead>
<tr>
<th></th>
<th>SCZ</th>
<th>HC</th>
<th>T/Chi-Square</th>
<th>df</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample (n)</td>
<td>131</td>
<td>138</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MGH/UI/UMN/UNM (n)</td>
<td>28/35/23/38</td>
<td>20/53/24/41</td>
<td>5.61</td>
<td>3</td>
<td>.123</td>
</tr>
<tr>
<td>Gender [no of female (%)]</td>
<td>32 (24)</td>
<td>48 (35)</td>
<td></td>
<td>3.45</td>
<td>.063</td>
</tr>
<tr>
<td>Age (years)</td>
<td>33.0 (11.0)</td>
<td>31.8 (11.5)</td>
<td>–0.89</td>
<td>267</td>
<td>.372</td>
</tr>
<tr>
<td>Estimated premorbid cognitive function (WRAT-III)</td>
<td>47.08 (6.44)</td>
<td>50.63 (4.36)</td>
<td>5.33</td>
<td>267</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Parental SES</td>
<td>2.81 (1.00)</td>
<td>2.68 (0.75)</td>
<td>–1.21</td>
<td>264</td>
<td>.226</td>
</tr>
<tr>
<td>Handedness (0–12)</td>
<td>1.05 (2.80)</td>
<td>0.78 (2.37)</td>
<td>–0.88</td>
<td>267</td>
<td>.379</td>
</tr>
<tr>
<td>SANS</td>
<td>7.94 (3.81)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAPS</td>
<td>4.98 (2.71)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of illness (years)</td>
<td>10.5 (10.2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cumulative antipsychotics</td>
<td>42.35 (102.14)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current antipsychotics</td>
<td>566.49 (601.17)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verbal working memory (LNS, WAIS-III)</td>
<td>9.60 (2.74)</td>
<td>12.33 (2.56)</td>
<td>8.42</td>
<td>267</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Item recognition [SIRP % correct (all loads)]</td>
<td>95.47 (4.83)</td>
<td>98.25 (1.63)</td>
<td>6.31</td>
<td>262</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Item recognition [SIRP % correct (5 item load)]</td>
<td>94.20 (6.08)</td>
<td>97.78 (2.29)</td>
<td>6.38</td>
<td>262</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Verbal processing (similarities and WAIS-III)</td>
<td>21.96 (5.83)</td>
<td>25.89 (3.78)</td>
<td>6.59</td>
<td>267</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Spatial processing (Block Design and WAIS-III)</td>
<td>39.47 (13.63)</td>
<td>50.51 (11.06)</td>
<td>7.31</td>
<td>267</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Verbal fluency (D-KEFS)</td>
<td>35.21 (11.16)</td>
<td>41.48 (10.58)</td>
<td>4.73</td>
<td>267</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Verbal learning (Hopkins Verbal Learning Test)</td>
<td>21.77 (6.08)</td>
<td>28.43 (3.69)</td>
<td>10.91</td>
<td>267</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Verbal memory discrimination (Hopkins Verbal Learning Test)</td>
<td>1.09 (1.59)</td>
<td>0.59 (0.83)</td>
<td>–3.30</td>
<td>267</td>
<td>.001</td>
</tr>
<tr>
<td>Visual memory (Benton Visual Retention Test)</td>
<td>6.21 (2.08)</td>
<td>8.10 (1.45)</td>
<td>8.68</td>
<td>267</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Face memory (Face Recognition and WMS-III)</td>
<td>35.62 (4.96)</td>
<td>39.03 (3.92)</td>
<td>6.28</td>
<td>267</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Immediate story recall (Logical memory I and WMS-III)</td>
<td>32.03 (11.84)</td>
<td>49.04 (9.00)</td>
<td>13.31</td>
<td>267</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Delayed story recall (Logical Memory II and WMS-III)</td>
<td>80.68 (19.54)</td>
<td>90.93 (10.15)</td>
<td>5.44</td>
<td>267</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Note: SCZ, patients with schizophrenia; HC, healthy controls; WRAT-III, Wide Range Achievement Test; SANS, Scale for the Assessment of Negative Symptoms; SAPS, Scale for the Assessment of Positive Symptoms; WAIS-III, Wechsler Adult Intelligence Scale—Third Edition; SIRP, Sternberg Item Recognition Paradigm; D-KEFS, Delis-Kaplan Executive Function System; WMS-III, Wechsler Memory Scale-III; LNS, Letter-Number Sequencing. Massachusetts General Hospital (MGH)/Universities of Iowa (UI)/University of Minnesota (UMN)/University of New Mexico (UNM) represent the 4 different study sites. Parental socioeconomic status (SES) was classified according to Hollingshead and handedness determined using the Annett Scale of Hand Preference. Cumulative antipsychotic drug exposures are given as dose years (1 dose year = 100 chlorpromazine equivalents/day for 1 year). Current antipsychotic drug dosages are given in chlorpromazine units. Effects involving study site (ANOVA with Scheffe’s post hoc tests if appropriate) indicated (upper panel) that the MGH site tended to use older subjects with a lower parental SES (as indicated by higher parental Hollingshead index). Furthermore (lower panel), the MGH site tended to use subjects with a lower performance on the following tasks: SIRP (only in comparison with the UI and UNM sites), spatial processing, visual memory, and face memory task (only in comparison with the UNM site). Additional study site differences were noted for the verbal learning task (UMN > UNM) and the Logical Memory I task (UI > UNM). Patients in UI had significantly higher SANS scores than patients at MGH. There were interactions of site and diagnosis for the SIRP task. Means are given with standard deviations in parenthesis.
Antipsychotic history was collected as part of a psychiatric assessment using the PSYCH instrument,50 and cumulative and current antipsychotic exposure was calculated using the chlorpromazine conversion factors (see online Supplementary materials 1.1).

Neuropsychological Measures

The cognitive assessments were conducted by psychometrists and were supervised by experienced neuropsychologists who had participated in an in person standardization training for the 4 sites. The instruments were chosen to sample a wide range of functions (for details see ref.42). For the current analysis, we chose 10 scales representative of key cognitive functions, which are thought to be affected in patients with schizophrenia. Wechsler Adult Intelligence Scale—Third Edition subtests31 were used to assess verbal working memory (Letter-Number Sequencing [LNS: item recall and manipulation]), verbal processing (similarities), and spatial processing (Block Design). Verbal fluency was measured using the Delis-Kaplan Executive Function System.52 Verbal learning as well as discrimination of verbal material in memory was measured using the Hopkins Verbal Learning Test-Revised53 and episodic figural memory (ie, visual memory) was assessed using the Benton Visual Retention Test.54 Wechsler Memory Scale-III55 subtests were used to measure memory for faces (Face Recognition), and immediate (ie, short-term) and delayed (ie, long-term) recall for verbally presented stories (Logical Memory I and II).

Because of the strong evidence for working memory deficits in schizophrenia,36,37 we decided to use behavioral data from a recognition memory paradigm employed in neuroimaging studies of schizophrenia58 in addition to the conventional neuropsychological measures of cognitive functions. The Sternberg item recognition paradigm (SIRP59) was administered during six 46-second blocks per run for two 360-second runs. In each block, a memory set, composed of 1 (load 1), 3 (load 3), or 5 (load 5) digits, was presented (2 blocks per load condition). The encode phase was followed by a presentation of 14 digits, one at a time (the probe phase) and participants responded to each probe to indicate whether or not the probe digit was in the memory set. The subjects were instructed to respond as quickly and accurately as possible. (For additional details about the paradigm, see ref.59). The stimuli and responses were presented during fMRI and collected using E-prime software (E-Prime v1.1; Psychology Software Tools, Inc.). For our analysis, we used the mean accuracy in percent (average across loads 1, 3, and 5) as well as the accuracy at load 5.

Structural Image Acquisition

sMRI data were acquired with either a 1.5T Siemens Sonata (MGH, UI, and UMN) or a 3T Siemens Trio (UMN). The T1-weighted structural brain scans at each of the 4 sites were acquired with a coronal gradient echo sequence: time to repetition (TR) = 2530 ms for 3T, TR = 12 ms for 1.5T; echo time (TE) = 3.79 for 3T, TE = 4.76 ms for 1.5T; inversion time = 1100 for 3T; Bandwidth = 181 for 3T, Bandwidth = 110 for 1.5T; 0.625 × 0.625 voxel size; slice thickness 1.5 mm; field of view (FOV), 256 × 256 × 128 cm matrix; FOV = 16 cm; number of excitations (NEX), = 1 for the 3T, NEX = 3 for the 1.5T. Cross-site MRI acquisition calibration and reliability were established in a preceding study using human phantoms, following guidelines developed by the biomedical informatics research network test bed for morphometry.60,61

Structural Image Data Processing

sMRI data from 3 consecutive volumes were registered, motion corrected, averaged, and analyzed in an automated manner with atlas-based FreeSurfer software suite (http://surfer.nmr.mgh.harvard.edu, Version 4.0.1). This process included volumetric segmentation, cortical surface reconstruction,25,62–65 and the estimation of total intracranial volume (ICV).66 Hippocampal volumes are a standard output of the FreeSurfer volumetric segmentation.64 The cortical surface reconstruction was performed for each hemisphere and included tessellation of the gray matter-white matter boundary, automated topology correction, and surface deformation following intensity gradients to optimally place the gray-white and gray-cerebrospinal fluid borders at the location where the greatest shift in intensity defines the transition to the other tissue class.25,67,68 Final surfaces were used to calculate cortical thickness at each vertex of the tessellated surface as the closest distance from the gray-white boundary to the pial surface.25,67 Vertices were arranged in a triangular grid with approximately 1 mm spacing (approximately 16,000 grid points) in each hemisphere. The applied method has been thoroughly evaluated and previously applied in a wide variety of settings, ie, a recent methodological study has found this approach to be reliable even across different scanner platforms both in terms of spatial localization and absolute cortical thickness measurements when assessing cortical correlates of cognitive performance.69

Segmentation and surface reconstruction quality were assured by manual inspection of all raw MRI volumes, segmented volumes in 3 planes and pial, as well as inflated volumes. Five participants’ MRI data failed the aforementioned quality assurance. The data of these subjects were then recovered with minor manual intervention following the Freesurfer user guidelines.

Statistical Analyses

Group differences of basic demographics were examined with Student’s t-tests and chi-square tests using SPSS 17.0.
Entire cortex vertex-wise analyses of cortical thickness were performed with FreeSurfer. Briefly, spherical cortical thickness data from all subjects were mapped to an average subject using surface-based registration methods (http://surfer.nmr.mgh.harvard.edu/fswiki/FsAverage, #1330).62,63 This procedure provides accurate matching of morphologically homologous cortical locations across subjects on the basis of each individual’s anatomy while minimizing metric distortion. Cortical thickness maps were smoothed using a Gaussian kernel with a full-width-at-half-maximum of 10 mm. Finally, statistical maps were generated by computing general linear models of the effects of each predictor variable on cortical thickness at each vertex. Because of known confounding effects and in line with similar studies, we included age, gender, and acquisition site into the models as control variables.13,26,27,70–72 All cortical thickness results were corrected for multiple comparisons using a Monte-Carlo simulation (uncorrected results were not reported). This procedure includes the following steps: (1) The initial vertex-wise threshold (VWT) was set to $P = .05$ to form spatially contiguous areas of association (referred to as “cluster”). (2) The likelihood that a finding (cluster) of this size and magnitude (difference in thickness as specified by the VWT) would appear by chance, ie, when using repeated random sampling, was tested using Monte-Carlo simulation with 10 000 repeats. This results in a cluster-wise probability (CWP), which is reported as $P$ values throughout the “Results” section. In addition, CWP values were corrected for the number of tested neuropsychological scales in our main analysis using the Bonferroni method. Furthermore, we performed the following exploratory analyses: (1) In order to control for false positive results due to brain asymmetry caused by handedness, we reran all models on a sample limited to right handed participants ($n = 240$). (2) We tested relationships between the neuropsychological scales and right and left hippocampus volumes in separate ($2 \times 11$) multiple regression analyses controlling for age, gender, ICV, and acquisition site.

**Results**

**Sample Characteristics**

Patients with schizophrenia and HCs did not differ in age, parental SES, handedness score, and the distribution of gender or the distribution across acquisition sites (table 1). Patients had a significantly lower estimated premorbid cognitive function than controls and impaired performance on all 12 cognitive measures (table 1). The clinical characteristics of the schizophrenia cohort are also listed in table 1.

**Widespread Reductions of Cortical Thickness in Schizophrenia**

In accordance with previous studies,13,27,71 and using the same technique, entire cortex vertex-wise statistics revealed widespread bilateral thickness reductions in schizophrenia patients, most pronouncedly in the frontal lobe, temporal cortex, inferior parietal lobe, and occipital cortex (figure 1). There were no regions where cortical thickness was increased when compared with HCs.

**Significant Associations Between Cortical Thickness and Cognitive Functioning**

Associations between cortical thickness at each vertex and the level of cognitive functioning were tested separately in the groups of schizophrenia patients and HCs. After correction for multiple comparisons at the cluster level using Monte-Carlo simulation, the following associations between cortical thickness and cognitive measures remained significant: verbal working memory (item recall and manipulation, LNS; for patients and controls, see figure 2), working memory as measured by the SIRP (item recognition; for patients and controls, see figure 3A), verbal processing (only in the patient group, see figure 3B), verbal fluency (only in HCs: left rostral middle frontal cortex CWP = 0.0327), and spatial processing (only in the patient group: right rostral middle frontal, pars triangularis, and pars orbitalis CWP = 0.0194).
When controlling for multiple comparisons at the level of the neuropsychological scales using Bonferroni correction (12 scales, i.e., \( P < 0.05/12 = 0.0042 \)), none of the associations with verbal fluency or spatial processing remained significant. Similarly, some of the associations of cortical thickness with working memory as measured by the SIRP (item recognition) and verbal processing did not survive this form of correction (see figures 3 and 4). The most robust associations with cortical thickness were the following: (1) verbal working memory (LNS) in the bilateral caudal middle frontal gyrus for HCs and the right middle and superior temporal gyrus for schizophrenia patients, (2) working memory as measured by the SIRP (item recognition) in the left rostral middle frontal gyrus for HCs, and (3) verbal processing in the right middle and inferior frontal gyrus for schizophrenia patients. Many of these regions overlap with the regions of overall reduced cortical thickness in schizophrenia patients (compare figure 1 and see online Supplementary figures 1 and 2).

**Additional Analyses**

To examine the effect of larger working memory loads, associations were computed between cortical thickness and performance on the 5-item condition of the SIRP. In contrast to the average performance across loads of 1, 3, and 5 items, we found a large and highly significant cluster spanning from the left rostral middle frontal to the left caudal middle frontal gyrus (CWP \( = 0.0001 \)) and less significant clusters in the temporal lobe (CWP \( = 0.032 \)) and the right superior frontal gyrus in HCs (CWP \( = 0.0054 \)) in HCs (see online supplementary figure 3). Associations in the patient group were not significant.

Further analyses were conducted to control for possible effects of handedness. We reran the models for our main findings excluding all non-dextral participants (final sample size = 240). The associations of cortical thickness with verbal working memory (LNS) remained significant for the left frontal lobe in HCs (CWP \( = 0.0094 \)) and right temporal lobe in schizophrenia patients (CWP \( = 0.0001 \)). None of the associations of cortical thickness with working memory as measured by the SIRP (item recognition) remained significant after Monte-Carlo simulation when non-dextral subjects were excluded. Similarly, the association between thickness and verbal processing in the frontal lobe for schizophrenia patients was lost (CWP \( = 0.0864 \)), but the cluster in the right superior temporal gyrus remained significant (CWP \( = 0.0012 \)).
Due to the prominent role of the hippocampus in schizophrenia, we also explored relationships between hippocampal volumes and all neuropsychological scales. In schizophrenia patients, but not in HCs, hippocampal volumes were significantly positively related to verbal working memory, verbal processing, verbal learning, visual memory, and immediate story recall (Logical Memory I). Associations between left hippocampus volumes and logical memory seemed to be larger (higher standardized betas) than with the other neuropsychological scales (table 2). In HCs, the only association was a weak negative relationship between verbal fluency and left hippocampus volume.

**Discussion**

**Summary of Results**

Using a rater-independent and well-validated analytic approach for measurement of cortical thickness across the brain, we identified associations between cognitive deficits and regional thinning of the cortical ribbon in schizophrenia. In comparison with HCs, schizophrenia patients performed significantly worse on all cognitive measures. Working memory assessed by measures of verbal item recall and manipulation (LNS) as well as item recognition (SIRP) showed robust associations with cortical thickness in lateral prefrontal cortex in HCs, whereas patients exhibited associations between verbal working memory item recall and cortical thickness in the right middle and superior temporal lobe. Verbal processing was associated with cortical thickness in the right middle and inferior frontal gyrus in schizophrenia patients. Furthermore, we confirmed findings of previous studies, demonstrating substantially reduced cortical thickness in frontal, temporal, occipital, and parietal areas in patients with schizophrenia.

**Brain Regions**

Relationships between the lateral prefrontal cortex and working memory have been suggested by numerous fMRI studies demonstrating disturbed prefrontal activation patterns and connectivity in association with impaired working memory and executive processing in patients with schizophrenia (for reviews see ref.38,74,75). Our data

**Table 2. Associations Between Hippocampus Volumes and Neuropsychological Functioning in Schizophrenia Patients**

<table>
<thead>
<tr>
<th>Cognitive Function</th>
<th>Left Hippocampus</th>
<th>Right Hippocampus</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Beta (Standardized Beta)</td>
<td>t</td>
</tr>
<tr>
<td>Verbal working memory</td>
<td>30.131 (0.176)</td>
<td>2.386</td>
</tr>
<tr>
<td>Verbal processing</td>
<td>12.242 (0.152)</td>
<td>2.11</td>
</tr>
<tr>
<td>Verbal learning</td>
<td>16.115 (0.209)</td>
<td>2.951</td>
</tr>
<tr>
<td>Visual memory</td>
<td>36.670 (0.162)</td>
<td>2.123</td>
</tr>
<tr>
<td>Logical memory I</td>
<td>66.833 (0.173)</td>
<td>2.517</td>
</tr>
</tbody>
</table>

*Note:* Results of independent multiple regression models controlling for the effects of age, gender, intracranial volume, and acquisition site. The P values are not corrected for multiple comparisons. In healthy controls, verbal fluency was associated with left hippocampus volume (beta = −0.376, standardized beta = −.170, t = −2.368, P = .019).
indicate that structural alterations in these areas might also contribute to the behavioral and functional abnormalities associated with the disorder. With marked prefrontal dysfunction in schizophrenia, other brain regions may be tapped in response to cognitive demands. Associations between cognitive performance and cortical thickness that are only evident in schizophrenia patients may reflect such a compensatory process. Thus, individuals with schizophrenia may engage a larger network of cortical regions to compensate for reduced neural signal-to-noise stemming in part from prefrontal cortical dysfunction. This might explain why working memory performance was associated with cortical thickness in temporal regions in schizophrenia patients. Interestingly, a recent fMRI study confirmed that schizophrenia patients but not HCs activated the bilateral middle temporal gyrus significantly for increased accuracy during working memory. Hence, it is possible that schizophrenia patients more heavily rely on cortical regions other than lateral frontal cortex for recalling and manipulating orally presented verbal material in working memory. Furthermore, genes involved with cell migration, cell proliferation, axonal outgrowth, myelination, synaptogenesis, and apoptosis that are implicated in schizophrenia might interact with environmental factors and cause neurodevelopmental abnormalities, such as changes in the organization of the cortical layers, which may ultimately lead to the activation of pathologic neural circuits during adolescence or young adulthood.

The only other published study comparing relationships between cortical thickness and cognitive performance in patients with schizophrenia spectrum disorder (n = 67) and HCs (n = 62) found similar relationships of cortical thickness with verbal learning and executive functioning but a diminished association between thickness in temporoparietal areas and verbal fluency in patients compared with HCs. Although in this study the discrepancies between patients and controls were less pronounced (which may be due to a different statistical model which uses a 2-step approach to constrain the search space for the final analyses), the authors also interpret their findings as a disruption of structure-function relationships in schizophrenia patients.

Among HCs, the associations of prefrontal cortical thickness with working memory performance differed depending on which of the specific measures employed by this study was investigated. Associations with item recall and manipulation (LNS) were localized to the motor, dorsal-premotor, and lateral prefrontal cortices (Brodmann area 6), whereas item recognition performance (SIRP) showed correlations with thickness in more anterior and ventral parts of the right frontal cortex (Brodmann areas 10, 46, and 47). This is in line with recent studies of brain lesions and fMRI experiments, which have provided support for a functional organizing principle along the rostro-caudal axis of the frontal lobes. In particular, posterior frontal regions are thought to support control involving temporally proximate concrete action representations, while the anterior prefrontal cortex supports operations involving temporally extended representations. Due to its use in the fMRI environment, the SIRP task of item recognition includes a long retrieval phase (38 seconds) with delays of 1.54 seconds (on average) between each probe. In that sense, participants performing this task engage in temporally extended control processes, which might rely on more anterior parts of the prefrontal cortex. In contrast, LNS requires the immediate reproduction of stimulus material, which may engage more posterior prefrontal regions. However, associations between cortical thickness and the SIRP task also differed by working memory load, ie, excluding the relatively easy loads (1 and 3), the main cluster spanned the entire rostral middle frontal gyrus.

**Significance of Associations Between Cognitive Functioning and Thickness**

Regional differences in associations of cortical thickness with cognitive functioning may also be due to abnormal neuronal activity in frontal and temporal cortical areas and the resulting functional connectivity changes between the areas in schizophrenia patients as compared with healthy subjects. Interestingly, early positron emission tomography (PET) studies demonstrated that speeded word generation increases prefrontal and decreases superior temporal lobe activity in HCs but patients fail to modulate the superior temporal gyrus, leading to abnormally increased activity in this brain region. A more recent study investigating functional connectivity using fMRI found reduced functional connectivity between the dorsolateral prefrontal cortex (DLPFC) and temporal lobe areas during verbal encoding in patients with schizophrenia. Data obtained in the same schizophrenia cohort as the present study are also consistent with impaired frontal and temporal structural connectivity. Thus, correlations of verbal working memory performance and cortical thickness in the superior and middle temporal gyrus instead of prefrontal areas might be an expression of fronto-temporal network dysfunction in schizophrenia.

**Verbal Processing and Altered Laterality in Patients With Schizophrenia**

The lateralization of certain brain functions, ie, located in the right or left side of the brain, and its relations to right- or left-handedness has been subject to broad generalization often made in popular psychology. While spatial attention is commonly lateralized to the right hemisphere, 95% of the population shows left-hemispheric dominance for language functions. However, even among strong left-handers, only about 27% show right-hemispheric dominance.
language dominance. A number of postmortem and in vivo neuroimaging studies suggest leftward asymmetry in frontal and temporal brain regions and a rightward asymmetry in occipital regions of the healthy brain (cerebral torque). In patients with schizophrenia as well as their unaffected relatives, decreased or reversed anatomical asymmetry, in particular in the temporal lobe, has been reported. This has been interpreted as evidence for an (epi-)genetically disturbed lateralization during neurodevelopment and as a common origin of psychosis and language-related cognitive symptoms in schizophrenia. Further substantiating this hypothesis in the present study, verbal processing in schizophrenia patients was associated with cortical thickness in the right frontal lobe and right superior temporal gyrus, whereas we did not find any associations with this measure in HCs. After the exclusion of all non-dextral participants, the association in patients in the right superior temporal gyrus remained highly significant. Similarly, working memory item recall was associated with cortical thickness in the right middle and superior temporal gyrus in schizophrenia patients. Altered laterality and hemispheric asymmetry of this neocortical structure, which has been consistently implicated in studies of schizophrenia, may constitute a biological risk factor for psychotic illness.

**Associations With Hippocampal Volumes**

In accordance with a large number of studies employing more conventional morphometric methods, none of the scales measuring long-term verbal memory recall (as opposed to working memory) showed significant associations with thickness in cortical areas. In contrast to that, our exploratory analyses provided evidence for significant positive associations between hippocampal volumes and verbal learning, logical memory (immediate story recollection), and visual memory for figures. Our findings are in line with previous studies, which demonstrated positive correlations between hippocampal volumes and memory for stories as well as verbal and spatial memory in schizophrenia. Volume reduction of the hippocampi is one of the most widely replicated structural neuroimaging findings in schizophrenia patients. The hippocampus has been traditionally thought of as the principal structure responsible for the consolidation of short-term memory into long-term memory but has also been associated with the functions commonly attributed to the integrity of the frontal lobes, such as executive processes in schizophrenia. Our finding of associations of hippocampal volume with verbal learning and recall of stories and figures are consistent with the role of hippocampus in consolidation of episodic memory, but associations with verbal processing and working memory also support a general role of the structure with verbal material.

**Limitations**

The present findings must be interpreted within the context of the study limitations. First, abnormal patterns of associations between cortical thickness and cognitive functioning in schizophrenia patients may be influenced by the effects of antipsychotic medications. Due to the absence of a comparison group of subjects who do not have schizophrenia, but who have had a similar exposure to antipsychotic medications, we and others are currently unable to distinguish between the potential effects of antipsychotic medications vs those of the underlying disease process on measures of brain volume. However, cognitive dysfunction and reduced cortical gray matter density and thickness have been shown to occur in persons with a high risk of developing schizophrenia and among neuroleptic-naïve and very young patients with a first episode of schizophrenia, implying the involvement of disturbed neurodevelopmental mechanisms. Second, the absence of highly significant correlations between cortical thickness and some cognitive domains might be attributed to a limited sensitivity of the employed neuropsychological measures, in particular for the group of HCs. In accordance with our results, a previous study in healthy adults also failed to demonstrate significant relationships between verbal learning and cortical thickness. Some correlations between cognitive performance (eg, long-term memory) and cortical thickness or gray matter volume may only be evident in schizophrenia patients. Third, our approach of using quantitative morphometric data, collected at multiple acquisition sites, is associated with advantages and possible disadvantages. The rapid collection of data from a large cohort of subjects provided increased statistical power, which enabled us to isolate neural correlates of cognitive dysfunction in an unbiased manner, ie, without averaging across predefined a priori regions of interest. A possible disadvantage of this design is that our results could have been influenced by differences in MR scanner field strength. However, several groups have studied the robustness of cortical thickness measurements using the same technology as in our study. Measurements across field strengths were found to be highly reliable and only slightly biased. We co-varied for the effects of acquisition site in all statistical models.

**Conclusions**

In conclusion, the present study revealed differential patterns of association between cognitive functions and cortical thickness for HCs and patients with schizophrenia. While some of these differences are possibly related to compensatory mechanisms in schizophrenia patients, others may reflect a structural abnormality selectively associated with functional impairment in the disorder.
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Supplementary Materials


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