

# Patterns of Cortical Structures and Cognition in Antipsychotic-Naïve Patients With First-Episode Schizophrenia: A Partial Least Squares Correlation Analysis

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## ABSTRACT

**BACKGROUND:** Schizophrenia is associated with alterations in cortical structures and cognitive impairments, but antipsychotic medication may affect these measures. We investigated patterns of relationships between cortical structures and cognitive domains in antipsychotic-naïve patients with first-episode schizophrenia.

**METHODS:** T1-weighted 3T magnetic resonance imaging was performed in 105 patients and 136 healthy control subjects. Using FreeSurfer, we obtained measurements of cortical thickness, surface area, and mean curvature. Using an extensive neurocognitive battery including the Danish Adult Reading Test and subtests from the Cambridge Neuropsychological Test Automated Battery, we obtained estimates of premorbid intelligence, spatial working memory, spatial planning, intra-extradimensional set shifting, and reaction and movement times. With univariate analyses, we tested group differences between cortical structures and cognition. With partial least squares correlation analyses, we investigated patterns of associations between cortical structures and cognition.

**RESULTS:** Patients had significantly higher mean curvature and were impaired on 7 of 11 cognitive parameters. The between-group partial least squares correlation analysis revealed two cortical thickness/cognition patterns that differentiated patients and healthy control subjects (omnibus test,  $p = .011$ ). Most cortical regions contributed reliably to these patterns. In patients, spatial working memory, spatial planning, reaction and movement times, and premorbid intelligence contributed reliably to the pattern; in healthy control subjects, spatial planning and intra-extradimensional set shifting contributed reliably.

**CONCLUSIONS:** Antipsychotic-naïve patients with first-episode schizophrenia displayed a higher mean curvature, but no significant difference in other gray matter indices was found. Nevertheless, the pattern of associations between global cortical thickness and cognitive functions was markedly different between groups. These multivariate analyses reveal a novel linkage between regional cortical brain structure and cognitive deficits at the earliest, never-medicated illness stage.

**Keywords:** Antipsychotic-naïve, Cognition, Cortical brain structure, First-episode schizophrenia, Partial least squares correlation

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Schizophrenia is a severe mental illness associated with both structural brain changes (1,2) and cognitive impairments in an array of domains (3,4). The timing of structural brain changes in schizophrenia may differ from that of cognitive deficits, and therefore the pattern of association between these illness characteristics may be affected by, for example, illness duration and antipsychotic medication (5–7). To avoid these critical confounders, examinations of patients at their first clinical presentation with psychosis and before antipsychotic exposure are required.

As cortical thickness and surface area may have independent genetic etiologies (8), surface-based structural brain measures may be advantageous over volume-based

measures. FreeSurfer is a surface-based approach that has been widely used to obtain refined measurements of cortical structures (9,10). Reductions in cortical thickness (11) and surface area (12) and a higher mean curvature (13) have previously been reported in antipsychotic-naïve patients with first-episode schizophrenia. By means of the Cambridge Neuropsychological Test Automated Battery (CANTAB), patients with frontal lobe lesions have been found to display cognitive deficits in planning, spatial working memory (Spatial Working Memory test [SWM]), and attentional set-shifting (14,15), which are similar to deficits found in patients with schizophrenia (16). Correspondingly, marked cognitive impairments, e.g.,

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reductions in premorbid intelligence (17), working memory, processing speed, and executive functioning (4,16,18), have consistently been reported in patients with schizophrenia. In patients with schizophrenia, cortical thinning appears pronounced, particularly in frontal and temporal regions (19). Importantly, these constitute key regions for cognitive functioning (20), and in particular the frontal lobe is considered important for cognitive functioning (21). Accordingly, previous bimodal studies have shown that patients with first-episode psychosis and schizophrenia display aberrations in the cortical structure/cognition relationship (22,23), and we recently reported that higher mean curvature was associated with lower premorbid and current intelligence (13).

Group differences in brain structure between antipsychotic-naïve patients with schizophrenia and healthy control subjects are subtle (13), and higher order cognitive functions may not be isolated to one specific brain region (21). Therefore, a multivariate analysis approach may be advantageous to examine the relationship between these two modalities. Partial least squares (PLS) is a multivariate analysis method that can model complex, global patterns of associations. PLS was first introduced in functional magnetic resonance imaging (fMRI) (24), and because the method is robust against collinearity, PLS has proven to be a powerful statistical tool to assess neuropsychological hypotheses in schizophrenia (25). In addition, a recent study using sparse canonical correlation analysis suggested the use of a multivariate approach to be more informative when investigating associations with neuroimaging measures (26). In that study, the two nonimaging variables with the highest correlation with regional cortical thickness measures (i.e., frontal, insular, temporal, parietal, and visual cortex) were age and current intelligence.

By application of PLS correlation (PLS-C) analyses, we explore in the present study patterns of associations between cortical structures and core cognitive domains in a large sample of antipsychotic-naïve patients with first-episode schizophrenia. This study builds on our previous univariate report on cortical structures and global cognitive measures (13), but we have extended the study population considerably by including data from two additional independent, comparable cohorts. Regional measures of cortical structures, including cortical thickness, surface area, and mean curvature, were obtained using FreeSurfer software. The Danish Adult Reading Test (DART) was used to estimate premorbid intelligence, and CANTAB, which is sensitive to frontal lobe functions, was used to obtain measures of spatial memory, spatial planning, attentional set shift ability, and reaction and movement times.

We hypothesized that patients would display cognitive impairments and brain structural alterations compared with healthy control subjects, and specifically, we aimed to explore potential relevance of regional cortical structures to specific cognitive domains. Patterns of associations were expected to differ between groups and to be pronounced between frontal cortical structures.

## METHODS AND MATERIALS

### Participants

This study included data from three consecutive, comparable cohorts of antipsychotic-naïve, first-episode schizophrenia

(Table 1 and Supplemental Figure S1). All patients were recruited from both inpatient and outpatient clinics in the Capital Region of Copenhagen, Denmark. A subsample of the current data investigating more global measures of cortical structures using a univariate approach was recently published (13). Additionally, the subjects partially overlap with previous studies investigating other modalities (see Supplemental Reference List of Previous Studies Investigating Other Modalities).

We included patients fulfilling diagnoses of schizophrenia ( $n = 101$ ) and schizoaffective disorder ( $n = 4$ ) according to Classification of Mental and Behavioural Disorders (ICD-10). Diagnoses were based on the Schedules for Clinical Assessment in Neuropsychiatry Version 2 (27). Exclusion criteria for patients were any previous lifetime exposure to antipsychotic medication or methylphenidate, current drug dependency, and serious somatic disease. All patients had normal physical and neurologic examinations. Healthy control subjects were recruited from the community through online advertisement and were reimbursed for participating. Because patients' participation included medical treatment, reimbursement was not allowed according to Danish regulations. Exclusion criteria for healthy control subjects were current or previous psychiatric illness, current drug abuse, and a first-degree relative with a psychiatric illness. Head injury with unconsciousness for more than 5 minutes was not allowed for any participants. All MRI scans were assessed by a trained radiologist.

The studies comply with the Committee on Biomedical Research Ethics (H-KF-01-78/97, H-D-2008-088, H-3-2013-149) and with the Helsinki Declaration of 1975. All studies were registered at [Clinicaltrials.gov](http://Clinicaltrials.gov) (NCT00207064, NCT01154829, and NCT02339844).

### Clinical Measures

Severity of psychopathology was assessed with the Positive and Negative Syndrome Scale, and level of functioning was assessed with the Global Assessment of Functioning. Handedness was assessed with the Edinburgh Handedness Inventory.

### Cognition

The DART was used to obtain an estimate of premorbid intelligence (28). Selected tests from CANTAB were used to obtain measures of spatial working memory (SWM), spatial planning (Stockings of Cambridge [SOC]), intra-extradimensional set shifting (IED), and simple reaction and movement times (RTI) (Table 2) (29).

### Image Acquisition and Processing

As we integrated data from three different cohorts, the MRI scanner and image acquisition differed between cohorts. For the first cohort (recruited 2004–2008), 3T high-resolution T1-weighted images were obtained from a Siemens MAGNETOM Trio (Siemens Healthcare, Erlangen, Germany) 3T MRI scanner with an eight-channel head coil (Invivo Corporation, Gainesville, FL). Images for the subsequent two cohorts (recruited 2008–2018) were obtained from a Philips Achieva (Philips Healthcare, Best, The Netherlands) 3T MRI scanner using an eight-channel head coil for the first cohort and a 32-channel head coil for the second cohort (Invivo Corporation).

**Table 1. Demographic and Clinical Characteristics of Patients With Schizophrenia and Healthy Control Subjects**

Characteristic	PT (n = 105)	HC (n = 136)	Statistics	p Value
Age, Years, Mean [Median] (SD) <sup>a</sup>	24.60 [23.00] (5.43)	24.26 [23.00] (5.42)	U = 6844.50	.58
Gender, Male/Female <sup>b</sup>	64/41	79/57	$\chi^2 = 0.20$	.65
P-SES, High/Moderate/Low <sup>b</sup>	37/53/12	52/65/15	$\chi^2 = 0.24$	.89
Handedness According to EHI Score, Right/Ambidextrous/Left <sup>b</sup>	89/8/8	123/1/12	$\chi^2 = 7.84$	.02 <sup>c</sup>
Subjects, Cohort 1/2/3 <sup>b</sup>	37/45/23	41/56/39	$\chi^2 = 1.57$	.46
Scanner Type, Siemens/Philips <sup>b</sup>	37/68	41/95	$\chi^2 = 0.70$	.40
Lifetime Substance Use				
Tobacco <sup>a</sup>	55/12/33/1/4	54/29/15/2/1	U = 4810.50	.21
Alcohol <sup>a</sup>	39/17/43/6/-	4/8/90/0/-	U = 3277.00	< .001 <sup>c</sup>
Cannabis <sup>a</sup>	53/40/7/5/-	46/49/7/0/-	U = 5238.50	.76
Opioids <sup>b</sup>	91/14/-/-/-	99/2/-/-/-	$\chi^2 = 9.26$	.002 <sup>c</sup>
Stimulants <sup>a</sup>	86/17/2/-/-	89/12/0/-/-	U = 4961.00	.20
Hallucinogens <sup>b</sup>	95/10/-/-/-	97/4/-/-/-	$\chi^2 = 2.52$	.11
PANSS, Mean (SD)				
Positive	19.24 (4.54)	—	—	—
Negative	20.32 (6.87)	—	—	—
General	39.18 (9.05)	—	—	—
Total	78.74 (16.87)	—	—	—
GAF, Mean (SD)				
	42.51 (10.89)	—	—	—
Cortical Structures, Mean (SD) <sup>d</sup>				
Intracranial volume, mm <sup>3</sup>	1,581,513.56 (208,836.07)	1,594,376.85 (176,616.58)	F <sub>1</sub> = 2.54	.11
Cortical thickness, mm				
Left hemisphere	2.56 (0.11)	2.57 (0.10)	F <sub>1</sub> = 1.02	.31
Right hemisphere	2.54 (0.11)	2.56 (0.11)	F <sub>1</sub> = 2.21	.14
Surface area, mm <sup>2</sup>				
Left hemisphere	90,338.44 (9875.96)	90,420.74 (8207.49)	F <sub>1</sub> = 0.31	.58
Right hemisphere	90,928.61 (10,048.32)	90,962.26 (8464.81)	F <sub>1</sub> = 0.29	.59
Curvature, mm <sup>-1</sup>				
Left hemisphere	0.151 (0.007)	0.148 (0.007)	F <sub>1</sub> = 22.40	< .001 <sup>c</sup>
Right hemisphere	0.149 (0.006)	0.147 (0.006)	F <sub>1</sub> = 9.99	.002 <sup>c</sup>

The analysis for each variable has been performed on all subjects with available data: P-SES (PT = 102, HC = 132); handedness (PT = 105, HC = 136); tobacco, opioids, stimulants, and hallucinogens (PT = 105; HC = 101); alcohol and cannabis (PT = 105; HC = 102); PANSS (PT = 105); GAF (PT = 65). Subjects with EHI scores between -28 and 48 were considered ambidextrous. Subjects with EHI scores ≥48 were considered right-handed, and subjects with EHI scores ≤-28 were considered left-handed (66). Lifetime substance use was acquired on a five-level scale: 0 = never tried; 1 = tried few times; 2 = use regularly; 3 = harmful use; 4 = dependency. - indicates that there were no data to include in the analysis.

EHI, Edinburgh Handedness Inventory score; GAF, Global Assessment of Functioning; HC, healthy control subjects; PANSS, Positive and Negative Syndrome Scale; P-SES, parental socioeconomic status; PT, patients with schizophrenia.

<sup>a</sup>Mann-Whitney U test.

<sup>b</sup> $\chi^2$  test.

<sup>c</sup>p values below the significance threshold of .05.

<sup>d</sup>The p value illustrates the group effect of the analysis of variance with age, gender, and cohort 1/2/3 as covariates.

See [Supplemental MRI Parameters and Tests of Cohort-Specific Effects on Cortical Structures](#) for further information.

FreeSurfer Version 5.3.0 was used to process the acquired T1-weighted images using methods described in detail elsewhere (9,10). As all three cohorts were longitudinal studies, we applied the longitudinal processing stream, which may provide a more robust cortical segmentation (30,31). However, as recruitment in the last study is ongoing, the cortical structures were extracted for the baseline values only. All subjects with a single time point were processed in the same longitudinal processing stream (32). We applied a 3T specific option for intensity normalization (33). The Desikan-Killiany atlas in FreeSurfer was used to extract regional measures of cortical thickness, surface area, and mean curvature (34).

In FreeSurfer, cortical thickness is calculated as the distance (mm) between the pial surface and the gray/white matter boundary, and surface area is defined as the area (mm<sup>2</sup>) of the gray/white matter boundary. The mean curvature (H) is the average between the maximum (k<sub>1</sub>) and minimum (k<sub>2</sub>) principal curvature on the surface (35). Curvature is defined as the inverse radius (1/r) of an inscribed circle, as follows:

$$H = \frac{1}{2}(k_1 + k_2) = \frac{1}{2}\left(\frac{1}{r_1} + \frac{1}{r_2}\right)$$

Taken together, a higher mean curvature indicates a sharper curvature. See Jessen *et al.* (13) for further description and schematic illustration of the parameter.

**Table 2. Cognitive Tests from DART and CANTAB**

Cognition Variable	Outcome Measures	Cognitive Function Assessed
DART	Words correctly pronounced	Premorbid intelligence
CANTAB		
SWM	Strategy score	SWM strategy
	Total errors	Total SWM errors
SOC	Problems solved in minimum number of moves	Efficiency of spatial planning
	Initial thinking time, 5-move problems	Planning latency, before initiating problem solving
	Subsequent thinking time, 5-move problems	Execution latency, after problem solving had been initiated
IED	Stage completed	Number of stages completed
	Total errors (adjusted)	Total number of errors made across all stages (adjusted for stages not completed)
	EDS errors	Errors made at EDS stage
RTI	Simple reaction time	Latency in releasing press pad in response to a stimulus
	Simple movement time	Latency from releasing press pad to touching screen

CANTAB, Cambridge Neuropsychological Test Automated Battery; DART, Danish Adult Reading Test; EDS, extradimensional set shifting; IED, intradimensional/extradimensional set shifting; RTI, reaction time test; SOC, Stockings of Cambridge; SWM, Spatial Working Memory.

## Statistical Analysis

**Demographic and Clinical Analysis.** Demographic and clinical characteristics were tested for normality using both the Shapiro-Wilk test and visual inspection of histograms. Depending on the distribution of data, demographic, clinical, and cognitive variables were tested using an independent  $t$  test,  $\chi^2$  test, or Mann-Whitney  $U$  test (Table 1).

**Univariate Analyses.** Before statistical analysis, standardized  $z$  scores for mean thickness, total surface area, and mean curvature for both hemispheres were calculated. Subjects with a value of  $\pm 2$  were visually inspected for segmentation errors in Freeview (part of the FreeSurfer package). The images were excluded if the image quality was judged to be of poor quality (see Consolidated Standards of Reporting Trials diagram in Supplemental Figure S1 for reasons for attrition).

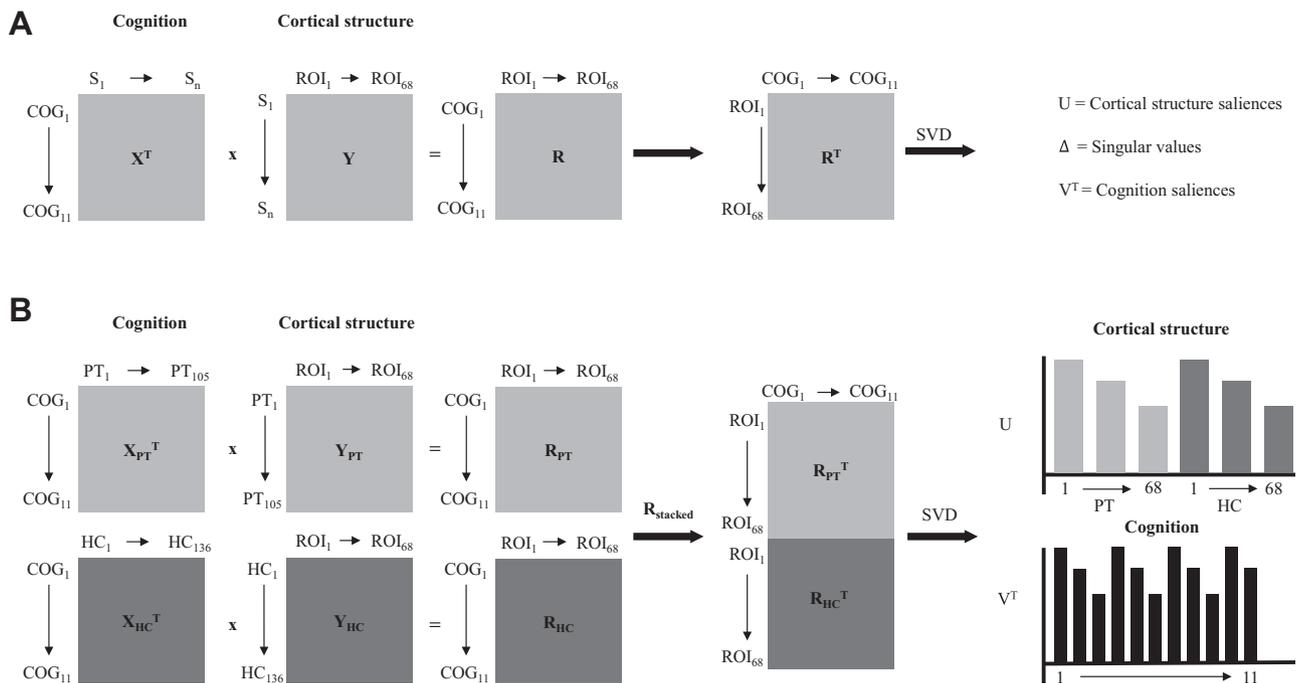
Group differences in global measures (cortical thickness, surface area, and mean curvature) and regions (68 independent regions of interest) were tested using univariate analysis of variance, covaried for age, gender, and cohort. Tests of global measures are presented in Table 1. Regional measures are presented on Manhattan plots (Supplemental Figures S2–S4). Depending on distribution of data, group differences in cognitive variables were tested with an independent  $t$  test or Mann-Whitney  $U$  test.

**PLS Analysis.** PLS-C was used to analyze the patterns of associations between regional cortical structures (cortical thickness, surface area, and mean curvature) extracted from the Desikan-Killiany atlas in FreeSurfer (34) and the 11 cognitive variables. Both within-group and between-group PLS-C analyses were performed, and results are presented accordingly. The primary PLS-C outcome for the present study was the between-group analysis (Figure 1B). As planned secondary tests, we performed two separate within-group analyses for patients and healthy control subjects, respectively (Figure 1A). The analysis process has been described in detail elsewhere (36,37) and is briefly

described here. Also, we have recently applied a similar PLS approach in a sample of individuals at ultrahigh risk of psychosis (38).

For the within-group PLS-C analyses (Figure 1A), the cognitive and cortical structural parameters were stored in matrices denoted  $X$  and  $Y$ , respectively. Each row represented the subjects, and columns of  $X$  and  $Y$  matrices represented the cognitive and structural parameters. Both  $X$  and  $Y$  were centered and normalized. Next, the correlations between the  $X$  and  $Y$  matrices were computed resulting in a cross-block correlation matrix ( $R$ ). The  $R$  matrix was then decomposed by singular value decomposition. The left ( $U$ ) and right ( $V^T$ ) singular vectors described the structural and cognitive saliences, respectively. The latent variables (LVs), which described the maximum covariance, were derived from  $U$  and  $V^T$ . The three cortical measures were analyzed in three separate PLS-C analyses. Before running the PLS analyses, the structural data were corrected for age, gender, and cohort, and the cognitive variables were corrected for age and gender.

Our main goal was to investigate differential patterns between the cortical structures and the cognitive parameters (Figure 1B) (36). For each group separately (patients with first-episode schizophrenia and healthy control subjects), the cognitive and cortical structural parameters were stored in matrices denoted as  $X_{PT}$ ,  $X_{HC}$ ,  $Y_{PT}$ , and  $Y_{HC}$ . The  $X$  and  $Y$  for each group were also centered and normalized.  $R$  matrix was computed for each group ( $R_{PT}$  and  $R_{HC}$ ) and stacked vertically ( $R_{stacked}$ ). Singular value decomposition was applied to  $R_{stacked}$  and determined the corresponding singular values, MRI saliences and cognition saliences, and LVs. For the present analysis, we investigated differential patterns in cortical structures (i.e., between groups) in relation to the cognitive parameters. By default, the saliences of the structural parameters (i.e., by group) are presented in bar graphs, but for visual and interpretational purposes, we projected the MRI saliences onto a standard brain derived from the Desikan-Killiany atlas in FreeSurfer. The cognitive parameters are presented in bar graphs with confidence intervals.



**Figure 1.** (A) Standard within partial least squares correlation analysis (36). (B) Partial least squares correlation analysis pipeline used to test for differential patterns between the cortical structures and cognitive parameters. The saliences of the structural parameters (i.e., by group) are presented in bar graphs (B), but for visual and interpretational purposes, we projected the saliences onto a standard brain derived from FreeSurfer. Refer to text for details. COG, cognitive variable; HC, healthy control subjects; PT, patients; R, cross-block correlation matrix; ROI, region of interest; S, subjects; SVD, singular value decomposition; X, matrix of cognitive parameters; Y, matrix of structural parameters.

Permutations (100,000) were used to compute the distribution of singular values over the null. The overall association between the cortical structural and cognitive parameters was considered significant if the sum of singular values exceeded the upper fifth percentile of the distribution found during permutations (omnibus test) (37). Thus, the omnibus test investigates whether the overall pattern is significant. The LV was deemed significant when its singular value was found in the upper 5% of the distribution. Only LVs with a cross-block covariance larger than 5% were reported (39). The reliability of the saliences for both structural and cognitive parameters was determined using bootstrap resampling, which provided confidence intervals for the saliences (100,000 bootstraps) (36).

The following post hoc PLS-C analyses were conducted: 1) the CANTAB variables were corrected for premorbid intelligence, 2) the cortical structures and cognitive variables were corrected for recreational alcohol and opioid use, and 3) the PLS-C analyses were repeated after excluding the 6 patients receiving antidepressants (results provided in Supplemental Post Hoc PLS Analysis).

IBM SPSS Statistics for Windows, Version 22.0 (IBM Corp., Armonk, NY) was used for analyses of demographics and clinical characteristics as well as for the univariate analyses. The PLS-C analyses and analysis of variance Manhattan plots were performed in MATLAB R2017b (The MathWorks, Inc., Natick, MA). A significance threshold for all analyses was set to .05 (two-tailed), and false discovery rate correction was performed for univariate analyses of regional cortical structures and cognitive variables.

## RESULTS

### Demographics and Clinical Characteristics

The combined sample of the three cohorts (Table 1) comprised 178 patients and 175 healthy control subjects, but after exclusions the final subject sample yielded 105 patients and 136 healthy control subjects; see Supplemental Figure S1 for reasons for attrition. Patient and healthy control groups did not differ in age, gender, or parental socioeconomic status, but significant group differences were found for handedness (i.e., more healthy control subjects were right-handed). Regarding lifetime substance use, group differences were found for alcohol and opioids but not for tobacco, cannabis, stimulants, or hallucinogens. Six patients had alcohol use that was deemed harmful, and 5 patients had cannabis use that was deemed harmful according to ICD-10. No significant group differences were found between scanner type and cohort.

### Univariate Analyses

Neither global cortical thickness nor surface area revealed differences between patients and healthy control subjects (Table 1). However, patients displayed a higher mean curvature in both the left hemisphere (LH) ( $F_1 = 22.40$ ;  $p < .001$ ) and the right hemisphere (RH) ( $F_1 = 9.99$ ;  $p = .002$ ). In post hoc analyses, each cohort was analyzed independently. These separate cohort analyses revealed no group difference in cortical thickness ( $p > .195$ ) or in surface area ( $p > .410$ ). However, in all three separate cohort analyses, we replicated the finding of

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significantly higher mean curvatures in patients (except for the RH in cohort 2) (cohort 1, LH,  $p = .008$ ; RH,  $p = .027$ ; cohort 2, LH,  $p = .026$ ; RH,  $p = .600$ ; cohort 3, LH,  $p = .001$ ; RH,  $p = .001$ ).

No regional group differences were found for cortical thickness or surface area (Supplemental Figures S2 and S3). In patients, higher mean regional curvatures (Supplemental Figure S4), which survived false discovery rate correction, were identified in frontal (left paracentral, superior and bilateral precentral), temporal (left entorhinal, superior, transverse, and middle), parietal (left inferior, superior and right precuneus), and occipital (left lateral) lobes. In 7 of 11 cognitive measures, patients performed significantly more poorly than healthy control subjects (Table 3).

### PLS-C Analyses

The main between-group PLS-C analysis including cortical thickness revealed a significant cortical thickness/cognition pattern between patients and healthy control subjects (omnibus test,  $p = .011$ ) with two significant LVs (LV1<sub>between-group</sub> and LV2<sub>between-group</sub>). LV1<sub>between-group</sub> explained 47.37% of the cross-block covariance ( $p = .027$ ), and LV2<sub>between-group</sub> explained 26.62% ( $p = .004$ ) (Figure 2). LV1<sub>between-group</sub> comprised a pronounced cortical thickness/cognition pattern in patients, which involved most cortical regions. The involved regions contributed reliably to the pattern and were positively associated with SWM, SOC (i.e., except SOC initial thinking time), RTI, and DART. Conversely, LV2<sub>between-group</sub> comprised a pronounced cortical thickness/cognition pattern in healthy control subjects, which involved most cortical regions. The involved regions that contributed reliably to the pattern were positively associated with IED and negatively associated with SOC initial thinking time. In general, increased cortical thickness was associated with better cognitive performance in both groups. The two between-group PLS-C analyses including surface area and mean curvature did not reveal significant patterns (omnibus test,  $p = .090$  and  $p = .735$ , respectively).

## DISCUSSION

In this large cross-sectional study of antipsychotic-naïve patients with first-episode schizophrenia, we investigated patterns of associations between cortical structures and cognitive measures using both conventional univariate analyses and PLS-C, a multivariate analysis approach. The univariate analyses revealed that patients had higher mean curvature values compared with healthy control subjects, but cortical thickness and surface area did not differ between groups. Therefore, we have now replicated our previous finding of higher mean curvature in three independent, consecutive cohorts of antipsychotic-naïve patients with a first psychotic episode (13). A higher curvature has been found regionally in the parahippocampal, lingual, and visual cortex in medicated patients with schizophrenia (40,41) but not in the anterior cingulate cortex (42). We speculate that the sharper curvature could reflect aberrations in early neurodevelopment (43). Moreover, our current sample confirms the well-established findings of a lower premorbid intelligence (DART) in patients with first-episode schizophrenia (17) as well as impairments in spatial working memory (SWM), planning efficiency (SOC), attentional set shifting (IED), and reaction and movement times (RTI) in patients with schizophrenia (4,16,18,44,45).

Compared with other studies investigating cortical thickness in first-episode of psychosis, illness severity in our patients was comparable (46,47). Nevertheless, one study in antipsychotic-naïve patients reported higher Positive and Negative Syndrome Scale scores and demonstrated widespread cortical thinning (11,48). However, low rates of lifetime recreational substance use may explain the absence of group differences in cortical thickness and surface area in our data.

The multivariate PLS-C analyses identified significant patterns of associations with cognitive measures, including widespread cortical regions. This global cortical involvement contrasted our hypothesis of a predominantly frontal impairment. In both patients and healthy control subjects, greater cortical thickness was generally associated with better cognitive performance. Interestingly, PLS-C revealed two

**Table 3. Group Differences in the Cognitive Measures**

Cognitive Measure	Patients With Schizophrenia	Healthy Control Subjects	Statistics <sup>a</sup>	$p$ Value
IED Stages Completed	8.70 [9.00] (0.71)	8.85 [9.00] (0.51)	$U = 6600.50$	.08
IED Total Errors, Adjusted	19.32 [11.00] (17.78)	13.98 [9.00] (12.79)	$U = 5681.00$	.006 <sup>b</sup>
IED EDS Errors	7.86 [3.00] (9.33)	4.83 [2.00] (6.79)	$U = 5250.50$	<.001 <sup>b</sup>
SOC Problems Solved in Minimum Moves	9.50 [10.00] (1.79)	10.05 [10.00] (1.60)	$U = 5805.50$	.01 <sup>c</sup>
SOC Initial Thinking Time	9760.90 [8021.50] (6983.57)	10,626.62 [9469.00] (6674.42)	$U = 6338.00$	.14
SOC Subsequent Thinking Time	720.62 [158.29] (1216.20)	498.75 [78.54] (963.44)	$U = 6498.00$	.21
SWM Strategy	28.78 [30.00] (6.49)	24.76 [23.00] (5.50)	$U = 4563.00$	<.001 <sup>b</sup>
SWM Total Errors	15.80 [8.00] (18.05)	6.88 [4.00] (9.43)	$U = 5011.50$	<.001 <sup>b</sup>
RTI Reaction Time	331.41 [314.67] (82.27)	301.40 [295.83] (43.45)	$U = 5756.00$	.01 <sup>b</sup>
RTI Movement Time	461.69 [418.00] (169.99)	391.82 [370.44] (118.83)	$U = 5215.00$	<.001 <sup>b</sup>
DART	22.23 (8.02)	24.96 (7.13)	$t = 2.80^d$	.006 <sup>b</sup>

Values are presented as mean [median] (SD) or mean (SD).

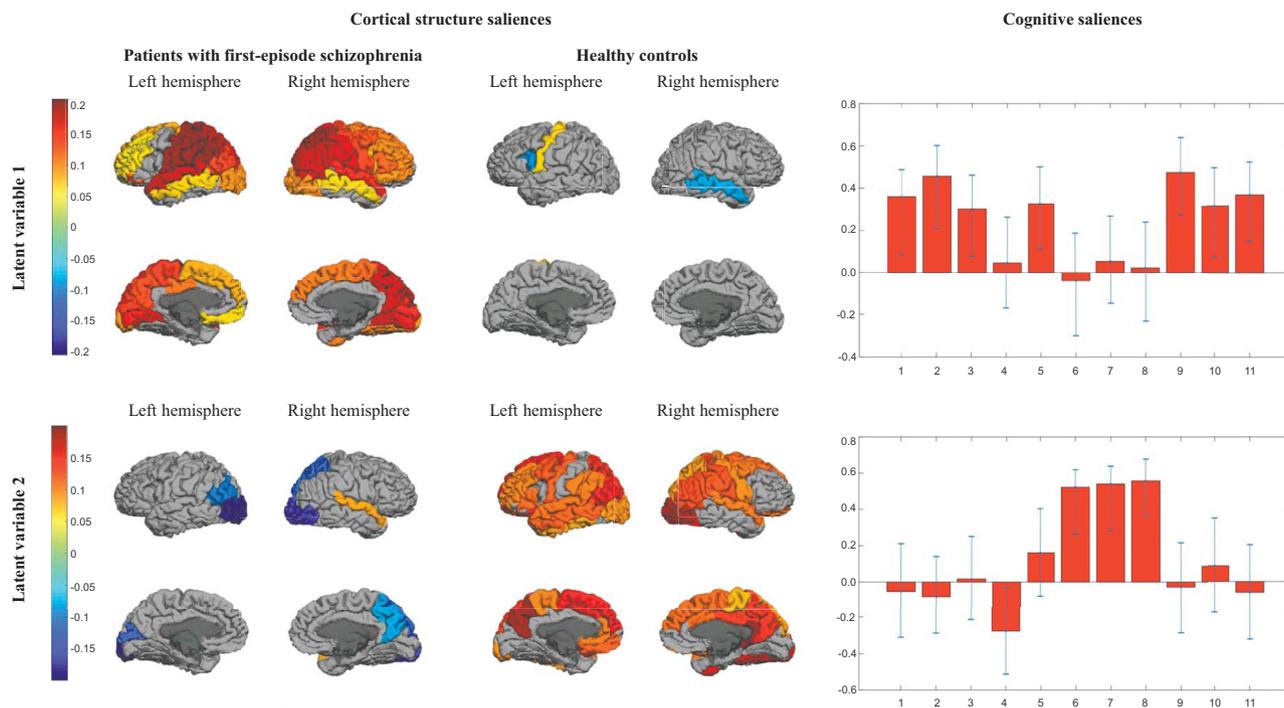
DART, Danish Adult Reading Test; EDS, Extradimensional Set Shift; IED, Intra-Extradimensional Set Shift; RTI, Reaction Time; SOC, Stockings of Cambridge; SWM, Spatial Working Memory.

<sup>a</sup>Mann-Whitney  $U$  test was applied owing to violations of normality, unless specified otherwise.

<sup>b</sup> $p$  values below the significance threshold of .05, which survived false discovery rate correction.

<sup>c</sup>Indicates trend-level significance.

<sup>d</sup>Independent  $t$  test.



**Figure 2.** Differential patterns of associations between cortical thickness and cognition between patients with schizophrenia and healthy control subjects. (Left panel) The cortical thickness salience pattern is shown on magnetic resonance imaging in patients and healthy control subjects. Cortical regions in gray do not contribute reliably to the pattern. The color bar indicates the salience (i.e., blue = negative salience and red = positive salience). (Right panel) The cognitive salience pattern is shown with a bar graph. The y-axis illustrates saliences. Latent variable 1 shows a cortical thickness/cognition pattern, which is pronounced in patients with first-episode schizophrenia. A differential pattern is found for latent variable 2, which shows a cortical thickness-cognition pattern that is pronounced in healthy control subjects. Confidence intervals, which do not cross the zero line, indicate reliable contributing variables. Cognitive variables listed on x-axes are as follows: 1, Spatial Working Memory, strategy score; 2, Spatial Working Memory, total errors; 3, Stockings of Cambridge, problems solved in minimum moves; 4, Stockings of Cambridge, initial thinking time, 5-move problems; 5, Stockings of Cambridge, subsequent thinking time, 5-move problems; 6, Intra-Extradimensional Set Shift, stages completed; 7, Intra-Extradimensional Set Shift, total errors (adjusted for stages not completed); 8, Intra-Extradimensional Set Shift, errors at the extradimensional set shift stage; 9, simple reaction time; 10, simple movement time; 11, Danish Adult Reading Test.

distinct and differential cortical thickness/cognition patterns in patients and healthy control subjects. In patients, premorbid intelligence (DART total score), spatial working memory (SWM strategy scores and total errors), planning efficiency and latency (SOC problems solved in minimum moves and subsequent thinking time), and reaction and movement times (RTI simple reaction and movement times) contributed to the pattern, and in healthy control subjects, initial planning latency (SOC initial thinking time) and attentional set shifting (IED stages completed, total errors adjusted, and IED extradimensional set shifting errors) contributed to the pattern (Figure 2). However, the cortical thickness/cognition pattern for healthy control subjects ( $LV2_{\text{between-group}}$ ) should be interpreted with caution, as the overall pattern for the analysis within healthy control subjects was nonsignificant (results provided in Supplemental Post Hoc PLS Analysis).

Our univariate analyses indicated that cortical thickness did not differ between patients and healthy control subjects. Nevertheless, our bimodal multivariate approach revealed differential cortical thickness/cognition patterns in the two groups. This finding could therefore represent a disruption in the relationship between brain structure and cognitive function

in patients with first-episode psychosis. The fact that the cortical thickness/cognition pattern was significant only in patients further supports this notion. Intriguingly, without being volumetrically different from healthy control subjects, most cortical regions contributed to the cortical thickness/cognition pattern. Whereas frontal regions are generally considered to play a key role in executive functioning, disruptions in other cortical and subcortical regions may also impair cognition (21). A similar global notion is found for measures of intelligence, which appear to rely on multiple regions distributed throughout the brain (49). Additionally, structural alterations in both frontal and other regions outside of the frontal lobe have been associated with poorer executive functions, such as SWM and IED performance (22).

Our observation of involvement of most brain regions in the specific pattern of cognitive disturbances suggests a global brain structural disruption, which may be related to the widespread gray matter aberrations related to a subgroup of patients with schizophrenia with both a low premorbid and current intelligence (49). In fact, the changes may also be related to the widespread disruptions in white matter that have been recently observed in large-scale studies (50,51). As working memory

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and executive functions in patients with schizophrenia may not be directly associated with volumetric alterations in prefrontal and anterior cingulate cortices (52), more general cognitive deficits at the earliest stages of disease may be not directly reflected in the volume of cortical regions. Hence, the cortical thickness/cognition dysfunction observed in the present study may be partly explained by other underlying mechanisms, such as a disruption in white matter integrity (53).

Cognitive deficits are considered core features of schizophrenia, and the deficits appear to manifest long before the first episode of frank psychosis (54). It is controversial whether cognitive deficits progress after the prodromal stage (55). However, after illness onset, some cognitive functions may remain relatively stable despite progressive cortical thinning (56,57), whereas other cognitive functions appear to deteriorate with time (58). For example, normative data have suggested that IED ability matures during early puberty (59). IED appears to be one of few cognitive domains preserved in the early stage of schizophrenia, but in later stages of schizophrenia IED is impaired (60). Interestingly, the current data-driven analyses revealed that IED performance was the only cognitive domain that did not contribute reliably to the cortical thickness/cognition pattern in patients. Thus, our data support that varying maturational trajectories of cognitive functions may be affected differentially at different illness stages (61).

In contrast to the cognitive impairments, the progressive brain changes that have been widely described in schizophrenia (62) may be more closely associated with other features of the illness, such as symptomatic and functional outcome (63,64). Specifically, our findings suggest that IED abilities are less affected by cortical thickness/cognition dysfunctions at the early stages of psychosis.

This study has several strengths. First, all included patients were antipsychotic naïve, and thus we have avoided potentially confounding effects of antipsychotic medication on the observed cortical thickness/cognition patterns. Second, our large sample of 105 patients and 136 healthy control subjects underwent both structural neuroimaging and an extensive neurocognitive battery. Third, the multimodal and PLS-C method allowed for investigation of complex global patterns of associations, whereas conventional univariate analyses would have been challenged by multiple comparison issues. Lastly, we investigated cortical thickness, surface area, and mean curvature.

Some limitations should be considered. In addition to premorbid intelligence and CANTAB measures, inclusion of measures of current intelligence may have further refined the understanding of the complex patterns between cortical structures and cognition. Also, measures of memory functions were not included in the current analyses. Future analysis may benefit from inclusion of cognitive tests targeting functions relevant to temporal lobe structures, such as the Paired Associates Learning task from the CANTAB (58). These variables were not included because measures were obtained by slightly different methods between cohorts. Lastly, cohort-specific effects were found for cortical thickness and mean curvature, which is an inherent limitation when pooling data from across different cohorts.

Furthermore, the post hoc analysis showed that the cortical thickness/cognition pattern in patients was nonsignificant

when controlling for premorbid intelligence (results provided in [Supplemental Post Hoc PLS Analysis](#)). This could indicate that premorbid intelligence is a key factor to consider for future investigations. Although intelligence may be closely related to working memory (in contrast to, for example, tasks of inhibition and set shifting), executive functions are not exclusively explained by current intelligence (65). Nevertheless, as more structural alterations have been found in patients with schizophrenia with impaired premorbid and current intelligence (49), it could be speculated that stratification of patients based on premorbid intelligence may have revealed refined cortical thickness/cognition patterns.

Expanding the PLS-C analyses to include other modalities, such as functional MRI and diffusion tensor imaging, may further clarify the potential involvement of alterations in underlying neural networks and/or white matter integrity, which may explain why SOC initial thinking time and IED functions appeared to be related to brain structure only in healthy control subjects. Finally, the cortical thickness/cognition patterns are likely to change with disease development. Thus, analyses of patients with ultrahigh risk of psychosis as well as patients with chronic schizophrenia may provide important knowledge about dynamically changing brain structure/cognition patterns across illness stages.

In conclusion, our univariate analyses detected higher mean curvature in antipsychotic-naïve patients with first-episode schizophrenia compared with matched healthy control subjects, but we found no group differences in other gray matter indices. Nevertheless, the pattern of associations between global cortical thickness and cognitive functions was markedly different between groups. Therefore, these bimodal and multivariate analyses reveal a novel linkage between regional cortical brain structure and cognitive deficits at the earliest, never-medicated illness stage.

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