# Evidence for Network-Based Cortical Thickness Reductions in Schizophrenia

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**Objective:** Cortical thickness reductions in schizophrenia are irregularly distributed across multiple loci. The authors hypothesized that cortical connectivity networks would explain the distribution of cortical thickness reductions across the cortex, and, specifically, that cortico-cortical connectivity between loci with these reductions would be exceptionally strong and form an interconnected network. This hypothesis was tested in three cross-sectional schizophrenia cohorts: first-episode psychosis, chronic schizophrenia, and treatment-resistant schizophrenia.

**Methods:** Structural brain images were acquired for 70 patients with first-episode psychosis, 153 patients with chronic schizophrenia, and 47 patients with treatment-resistant schizophrenia and in matching healthy control groups (N=57, N=168, and N=54, respectively). Cortical thickness was compared between the patient and respective control groups at 148 regions spanning the cortex. Structural connectivity strength between pairs of cortical regions was quantified with structural covariance analysis. Connectivity strength between regions with cortical thickness reductions was compared with connectivity strength between 5,000 sets of randomly chosen regions to establish whether regions with reductions were interconnected more strongly than would be expected by chance.

**Results:** Significant (false discovery rate corrected) and widespread cortical thickness reductions were found in the chronic schizophrenia (79 regions) and treatment-resistant schizophrenia (106 regions) groups, with more circumscribed reductions in the first-episode psychosis group (34 regions). Cortical thickness reductions with the largest effect sizes were found in frontal, temporal, cingulate, and insular regions. In all cohorts, both the patient and healthy control groups showed significantly increased structural covariance between regions with cortical thickness reductions compared with randomly selected regions.

**Conclusions:** Brain network architecture can explain the irregular topographic distribution of cortical thickness reductions in schizophrenia. This finding, replicated in three distinct schizophrenia cohorts, suggests that the effect is robust and independent of illness stage.

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Cortical thickness reductions are a consistent finding in schizophrenia (1–3). However, heterogeneity is evident between studies in terms of the extent of these reductions and the regions affected. This heterogeneity may be related to factors such as illness chronicity, symptom severity, or response to medication. Individuals with first-episode psychosis demonstrate subtle cortical thickness reductions, with changes most consistently observed in prefrontal and temporal regions (3–7). In chronic schizophrenia, cortical thickness reductions are more widespread, with pronounced reductions in frontal and temporal lobes and evidence of reductions in the parietal and occipital cortices (1, 2, 8). Individuals with chronic schizophrenia whose symptoms do not respond to antipsychotic medication are deemed to have treatment-resistant schizophrenia (9). Treatment-resistant schizophrenia is associated with cortical thickness reductions that are more widespread than reductions in patients with the same illness duration who respond to treatment (10).

Cortical thickness reductions across these illness stages are irregularly distributed across multiple loci. For example, while frontal and temporal regions exhibit pronounced cortical thickness reductions, the specific loci affected are distant from each other, resulting in patterns of thinning that

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appear sporadically distributed across the cortex. Therefore, progressive thinning, which has been observed in first-episode psychosis (11, 12), chronic schizophrenia (13), and treatment-resistant schizophrenia (14), cannot be explained by spatial proximity to putative pathological epicenters. What factors might explain the irregular cortical topography of cortical thickness reductions in schizophrenia?

One hypothesis is that cortical thickness reductions in schizophrenia extend to unaffected loci that are structurally connected to loci with existing reductions. Specifically, neural connections can propagate pathological processes to distant cortical regions or, when disrupted (15–17), result in loss of normal signaling between these regions (see the Discussion section). Under this hypothesis, we expected that cortical loci with significant cortical thickness reductions would be strongly interconnected. These reductions would therefore most likely co-occur between connected cortical regions.

We used structural covariance analysis (18–21) to assess interregional gray matter structural connectivity between regions with cortical thickness reductions. Structural covariance is an established measure of cortico-cortical connectivity that shows good correspondence with transcriptional brain networks (22) and anatomical connectivity inferred from white matter fiber tractography (23). Despite this correspondence, structural covariance is a distinct connectivity measure that is thought to specifically index mutually trophic factors between distant regions that are anatomically connected. It is hypothesized that synapses between distant neurons can have a mutually trophic effect, leading to structural covariance at the macroscale level (18). Additionally, structural covariance is sensitive to aberrant connectivity (20) and brain network organization in schizophrenia (24). Increased structural covariance between regions with cortical thickness reductions may suggest that atrophy in key illness-related regions determines the rate of atrophy in other connected regions and could provide a model for understanding progressive cortical atrophy in the disorder. We specifically hypothesized that cortico-cortical connectivity would be stronger among cortical regions with significant cortical thickness reductions compared with the connectivity between randomly selected regions.

In this study, cortical thickness was estimated in three cross-sectional schizophrenia cohorts—patients with first-episode psychosis, chronic schizophrenia, and treatment-resistant schizophrenia—and compared with corresponding healthy control groups. The aims of the study were to characterize the extent and location of cortical thickness reductions in the three cohorts and to establish whether cortico-cortical connectivity inferred from structural covariance analysis could explain the topographic distribution of reductions across the cortex. Testing our hypotheses in three schizophrenia cohorts enabled us to establish whether our findings were replicable across independent data sets and universal across different illness subtypes.

## METHODS

### Participants

Neuroimaging data were obtained for 70 patients with first-episode psychosis (schizophrenia, N=19; schizophreniform disorder, N=38; schizoaffective disorder, N=13), 153 patients with chronic schizophrenia, and 47 patients with treatment-resistant schizophrenia and for healthy control subjects corresponding with each of the three schizophrenia cohorts (N=57, N=168, and N=54, respectively). Demographic and clinical characteristics are summarized in Table 1 and in the online supplement. MRI of brain anatomy was acquired for each individual using established MRI protocols, as described in the online supplement.

### Imaging Data Acquisition

Acquisition parameters are presented in the online supplement.

### Image Processing and Cortical Thickness Estimation

To estimate cortical thickness, images were processed with the FreeSurfer software package (version 5.1 for the chronic schizophrenia group, version 5.3 for the first-episode psychosis and treatment-resistant schizophrenia groups) (https://surfer.nmr.mgh.harvard.edu). In brief, preprocessing included intensity normalization, removal of nonbrain tissue, transformation to Talairach-like space, segmentation of gray-white matter tissue, and tessellation and smoothing of the white matter boundary (25). White matter surfaces were then deformed toward the gray matter boundary at each vertex. Cortical thickness was calculated based on the distance between white and gray matter boundaries at each vertex. The entire cortex of each study subject was visually inspected, and inaccuracies in segmentation were manually edited. The cortical surface was then parcellated into 148 regions based on the Destrieux atlas (26). Finally, region-averaged cortical thickness estimates were computed by averaging across all vertices comprising each region. This yielded a vector of 148 regional cortical thickness estimates for each study subject.

### Statistical Analysis

Demographic differences between the three patient groups (first-episode psychosis, chronic schizophrenia, and treatment-resistant schizophrenia) and the three respective control groups were tested using t tests for continuous variables and chi-square tests of independence for categorical variables.

*Cortical thickness differences.* The null hypothesis of equality in cortical thickness between the three patient groups and the three respective control groups was tested independently for each of 148 cortical regions. This was performed independently for each patient group. Specifically, a general linear model was formulated to test the effect of group (patient or healthy control) on cortical thickness, while controlling for age and gender, as well as for acquisition site in the case of the chronic schizophrenia cohort. To correct

**TABLE 1. Demographic and clinical characteristics of the three schizophrenia cohorts and their respective control groups[a]**

| Characteristic | First-Episode Psychosis | | | | | Chronic Schizophrenia | | | | | Treatment-Resistant Schizophrenia | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Patient Cohort (N=70) | | Healthy Control Group (N=57) | | t or $\chi^2$ | Patient Cohort (N=153) | | Healthy Control Group (N=168) | | t or $\chi^2$ | Patient Cohort (N=47) | | Healthy Control Group (N=54) | | t or $\chi^2$ |
| | N | % | N | % | $\chi^2$ | N | % | N | % | $\chi^2$ | N | % | N | % | $\chi^2$ |
| Male | 50 | 71.4 | 34 | 59.6 | 2.43 | 110 | 71.9 | 81 | 48.2 | 18.64** | 35 | 74.5 | 36 | 66.7 | 0.47 |
| | Mean | SD | Mean | SD | t | Mean | SD | Mean | SD | t | Mean | SD | Mean | SD | t |
| Age (years) | 21.49 | 3.38 | 21.36 | 3.66 | 0.21 | 38.11 | 9.82 | 39.74 | 13.97 | 1.22 | 38.79 | 9.44 | 39.23 | 10.56 | 0.22 |
| Current IQ | 87.07 | 13.56 | 109.38 | 10.49 | 9.34** | 105.26 | 13.59 | 117.32 | 11.06 | 8.67** | –18.42 | 18.42 | 113.47 | 12.15 | 8.68** |
| Premorbid IQ | 92.58 | 13.33 | 101.28 | 10.27 | 3.99** | 99.95 | 13.89 | 107.44 | 10.79 | 5.35** | 91.36 | 13.52 | 106.36 | 9.72 | 5.84** |
| Positive symptoms (DIP) | | | | | | 1.76 | 2.6 | | | | | | | | |
| Positive symptoms (PANSS) | 22.78 | 6.56 | | | | | | | | | 16.2 | 5.71 | | | |
| Negative symptoms (SANS) | | | | | | 25.8 | 17.34 | | | | 45.64 | 17.57 | | | |
| Negative symptoms (PANSS) | 20.62 | 7.21 | | | | | | | | | 18.39 | 6.12 | | | |
| Illness duration (years) | 0.16 | 0.27 | | | | 14.16 | 8.83 | | | | 16.64 | 8.77 | | | |
| Mean cortical thickness (mm) | 2.49 | 0.08 | 2.54 | 0.1 | 3.40** | 2.5 | 0.1 | 2.6 | 0.1 | 4.66** | 2.42 | 0.09 | 2.52 | 0.08 | 5.84** |
| Total antipsychotic dose (CPZ equivalent: mg) | 216.86 | 117.37 | | | | | | | | | 915.59 | 324.16 | | | |

[a] Symptom and medication data were not available for all cohorts. CPZ=chlorpromazine, DIP=Diagnostic Interview for Psychosis, PANSS=Positive and Negative Syndrome Scale, SANS=Scale for the Assessment of Negative Symptoms.
**p<0.01.

for multiple comparisons, the false discovery rate was controlled at 5% across the 148 cortical regions using the Benjamini-Hochberg procedure (27).

*Whole-brain structural covariance analysis.* Structural covariance analysis is a robust and widely used method to infer the strength of structural connectivity between cortical regions (18–20). Structural covariance refers to the relation between the morphology of one brain region to that of another region across study subjects. This method is based on the assumption that interindividual differences in morphology covary between pairs of regions that are structurally (18, 23) and functionally connected (28, 29). Structural covariance techniques have recently been extended to map myelin (30) and resting-state glucose metabolism (31) covariance networks and to incorporate multiple anatomical indices from different neuroimaging modalities (21).

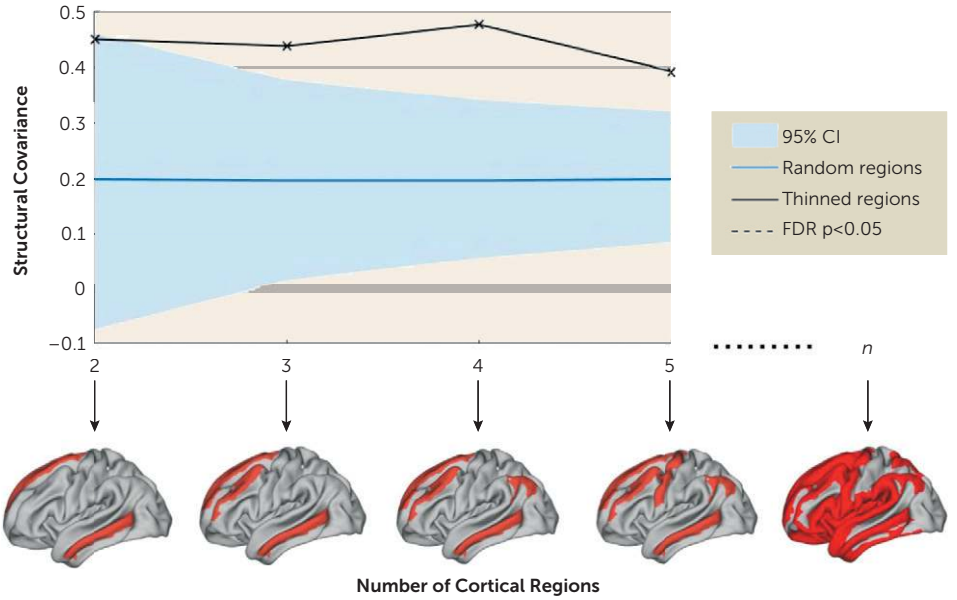
In this study, cortical thickness served as the morphological measure, and Pearson correlation was used to compute structural covariance. Partial correlation can also be used to estimate structural covariance; however, this measure can spuriously reduce the transitivity of correlation networks (32) and cannot be computed when the number of regions exceeds the sample size. The Pearson correlation coefficient was computed across the study subjects between the cortical thickness estimates for each pair of cortical regions (148 regions, 10,878 pairs of regions). Age, the square of age, and gender, as well as acquisition site in the case of the chronic schizophrenia cohort, were first regressed from the cortical thickness estimates (18, 33). The square of age corrected for possible nonlinear age effects. To improve normality, the r-to-z transformation was applied to all correlation coefficients. This yielded a separate connectivity matrix for each of the three patient groups and the respective control groups that quantified the connectivity strength (structural covariance) between all pairs of regions.

The null hypothesis of equality in structural covariance between the patient and control groups was tested independently for each of 10,878 pairs of regions using two-sample t tests. The network-based statistic (34) was used to control the family-wise error rate across the 10,878 multiple comparisons. A primary t-statistic threshold of 3 was used, with a family-wise error rate threshold of 5%. The network-based statistic was performed independently for each patient group.

*Structural covariance between regions with cortical thickness reductions.* Permutation testing was used to establish whether structural covariance was significantly stronger (or weaker) between regions with cortical thickness reductions compared with randomly selected groups of regions. Testing was performed for three separate cases: structural covariance measured in each of the three patient groups, structural covariance measured in the respective healthy control groups, and the difference in structural covariance between the patient and healthy control groups. Foremost, regions were ranked from highest to lowest according to the severity (effect size) of cortical thickness reductions. The mean structural covariance between the top-*n* regions with the most extensive cortical thickness reductions was then computed. To generate a null distribution for this mean value, the mean

structural covariance was computed between randomly chosen sets of *n* nodes. A total of 5,000 random sets of nodes were generated. The proportion of random node sets for which the mean structural covariance exceeded or equaled the mean structural covariance in the actual (nonrandom) data provided a p value for the null hypothesis of equality in structural covariance among regions of cortical thickness reductions and randomly chosen pairs of regions. This was repeated independently for n=2,…,148, and the mean structural covariance between the top-*n* regions with the most extensive cortical thickness reductions was plotted as a function of *n*. The area under this plot of mean structural covariance as a function of *n* was used to compute a global p value for all values of *n*. An overview of the structural covariance methodology and analysis is presented in Figure 1.

**FIGURE 1. Methodology of testing for increased connectivity (structural covariance) between regions with cortical thickness reductions**[a]




[a] Cortical regions were first ranked according to the effect size of cortical thickness reductions, from greatest to smallest. Cortical renderings show the top (n=2, n=3, n=4, and n=5) regions (red) in the ranked list for an example cohort. The mean structural covariance between the top-*n* ranked regions was then computed and compared with the mean structural covariance in 5,000 randomly chosen sets of *n* regions. Randomly chosen sets of regions contained regions with and without cortical thickness reductions. The proportion of random region sets for which the mean structural covariance exceeded or equaled the mean structural covariance in the actual (nonrandom) data provided a p value for the null hypothesis of equality in structural covariance among regions with cortical thickness reductions and randomly chosen pairs of regions. This analysis was repeated for all values of *n*, up to a fixed threshold, to investigate the impact of varying the smallest effect size of interest (i.e., as *n* is increased, between-group differences with smaller effect sizes were included). Crosses indicate values of *n* for which structural covariance was significantly increased ($p<0.05$) between the top-*n* regions with the most extensive cortical thickness reductions. The solid black line represents the mean structural covariance in the actual (nonpermuted) data. The blue line represents the mean structural covariance in the randomized data, averaged across 5,000 randomizations. The shaded area denotes 95% confidence intervals across the 5,000 randomizations. FDR=false discovery rate.

In ancillary analyses, we considered null models that were more constrained than randomly chosen sets of *n* nodes. Specifically, we ensured that the number of nodes within each cerebral hemisphere and the total Euclidean distance between pairs of nodes were preserved between the top-*n* regions with the most extensive cortical thickness reductions and the randomly chosen sets of *n* nodes.

The above analysis was repeated with the addition of mean cortical thickness as a covariate in order to determine the effects of global cortical thickness reductions on corticocortical connectivity. This step was taken to ensure that interregional correlations were not simply the result of individual variations in global cortical thickness (i.e., individuals with a globally thicker cortex are also more likely to have larger regional thickness estimates and vice versa), particularly those that may arise from progressive thinning in the patient groups.

## RESULTS

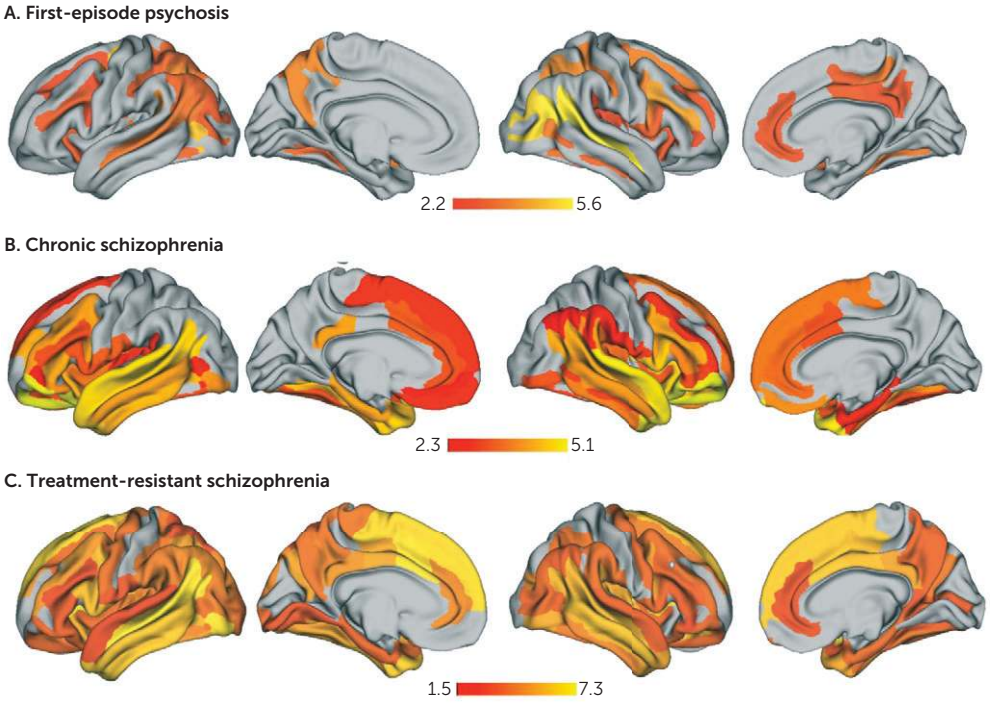
### Demographic Characteristics

Demographic data are presented in Table 1. Age did not significantly differ between the patient and control groups. Gender composition did not differ between groups for the first-episode psychosis and treatment-resistant schizophrenia cohorts. However, the chronic schizophrenia cohort comprised significantly fewer females compared with their respective control group. Patients with treatment-resistant schizophrenia had significantly greater negative symptoms than patients with chronic schizophrenia. All three patient groups demonstrated significant impairments on measures of current and premorbid IQ.

### Cortical Thickness Reductions

Compared with healthy control subjects, a total of 34, 79, and 106 regions were found to show significant cortical thickness reductions in the first-episode psychosis, chronic schizophrenia, and treatment-resistant schizophrenia groups, respectively (false discovery rate controlled at 5% across 148 regions). Effect sizes are presented in the online supplement. Increased cortical thickness was not evident in any of the three patient cohorts. Regions with significant cortical thickness reductions are illustrated in Figure 2. In chronic and treatment-resistant schizophrenia, regions with the most extensive reductions were located in the frontal and temporal lobes as well as in the insula and cingulate cortex, although

**FIGURE 2. Cortical thickness reductions in patients with first-episode psychosis, chronic schizophrenia, and treatment-resistant schizophrenia[a]**




[a] The null hypothesis of equality in cortical thickness between the three patient cohorts and matching healthy control groups was tested for the 148 cortical regions comprising the Destrieux atlas. Regions for which the null hypothesis was rejected after controlling the false discovery rate at 5% are shown in color. The color bar represents t scores. Cortical thickness maps were generated using Connectome Workbench (https://www.humanconnectome.org/software/connectome-workbench).

posterior regions also showed evidence of reductions in treatment-resistant schizophrenia. First-episode psychosis was associated with a more distributed pattern of cortical thickness reductions. We found that the number of regions with significant reductions (first-episode psychosis, n=34; chronic schizophrenia, n=79; treatment-resistant schizophrenia, n=106) and the mean effect sizes (Cohen's d) across these regions (first-episode psychosis, 0.06; chronic schizophrenia, 0.10; treatment-resistant schizophrenia, 0.30) were ordered according to putative disease severity (i.e., first-episode psychosis < chronic schizophrenia < treatment-resistant schizophrenia). Levene's test was used to test the null hypothesis that the variances in cortical thickness were equal between the patient and control groups, with no significant differences observed (false discovery rate-corrected p values >0.05).

### Whole-Brain Structural Covariance

Structural covariance, a measure of structural brain connectivity, was measured between all pairs of cortical regions. Structural covariance matrices for each cohort are shown in Figure S1 in the online supplement. The null hypothesis of equality in structural covariance between the patient and control groups was rejected for the first-episode psychosis cohort (family-wise error rate <0.05, corrected with the network-based statistic across 10,878 pairs of regions). Specifically, the network-based statistic identified a single subnetwork comprising connections with reduced structural covariance in patients with first-episode psychosis compared with study subjects in their respective control group. The majority of these connections (60.1%) were associated with temporal and frontal regions, as shown in Figure 3. The null hypothesis could not be rejected for the chronic and treatment-resistant schizophrenia cohorts.

### Structural Covariance Between Regions With Cortical Thickness Reductions

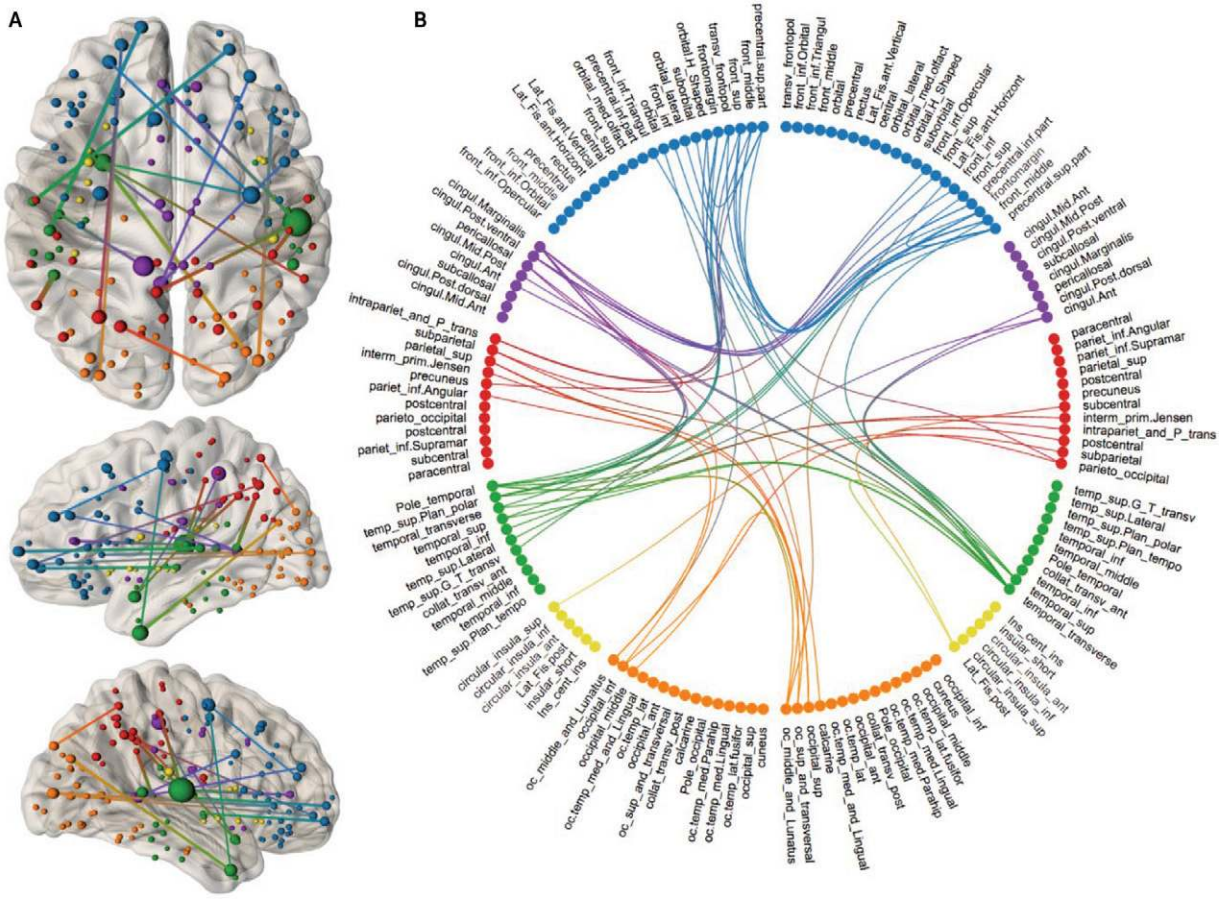
We next sought to establish with permutation testing whether structural covariance was increased among regions with cortical thickness reductions. For each of the three patient cohorts, structural covariance was significantly increased among regions with cortical thickness reductions ($p<0.0001$). This was irrespective of whether structural covariance was measured in the patient or the healthy control group. In other words, cortical regions susceptible to thickness reductions in schizophrenia were interconnected more strongly than arbitrarily chosen regions both in the general population and across different schizophrenia subtypes.

The mean structural covariance between the top-*n* regions with the most extensive cortical thickness reductions (vertical axis) as a function of *n* (horizontal axis) is illustrated in Figure 4. The shaded area in the figure denotes 95% confidence intervals for the mean structural covariance between sets of *n* randomly chosen nodes. The 95% confidence interval was exceeded for the majority of values of *n*, indicating that structural covariance was significantly increased between regions with cortical thickness reductions in all groups.

These findings were replicated when we used a more constrained null model in which the sets of *n* randomly chosen nodes were matched to the number of nodes within each cerebral hemisphere and the total Euclidean distance between pairs of nodes (for further details, see Figure S2 in the online supplement). We can therefore exclude the impact of confounders attributable to geometric effects or a potentially disproportionate number of homotopic connections in the null data.

In the above analyses, connectivity between regions with cortical thickness reductions was quantified with structural

**FIGURE 3. Whole-brain reductions in structural covariance in patients with first-episode psychosis compared with matched healthy control subjects**[a]




[a] The reductions in structural covariance are represented by brain connectivity maps (panel A) (t-statistic threshold, 3.4; the size of spheres represents the number of significant connections to a node, with larger spheres indicating more connections) and a circular connectogram (panel B) (t-statistic threshold, 3.0). Brain regions are grouped on the connectogram circumference according to lobes (frontal [blue], limbic [purple], parietal [red], temporal [green], insula [yellow], occipital [orange]). Left hemisphere nodes are shown on the left side of the connectogram. Brain connectivity maps and circular connectogram were generated using NeuroMArVL (http://immersive.erc.monash.edu.au/neuromarvl).

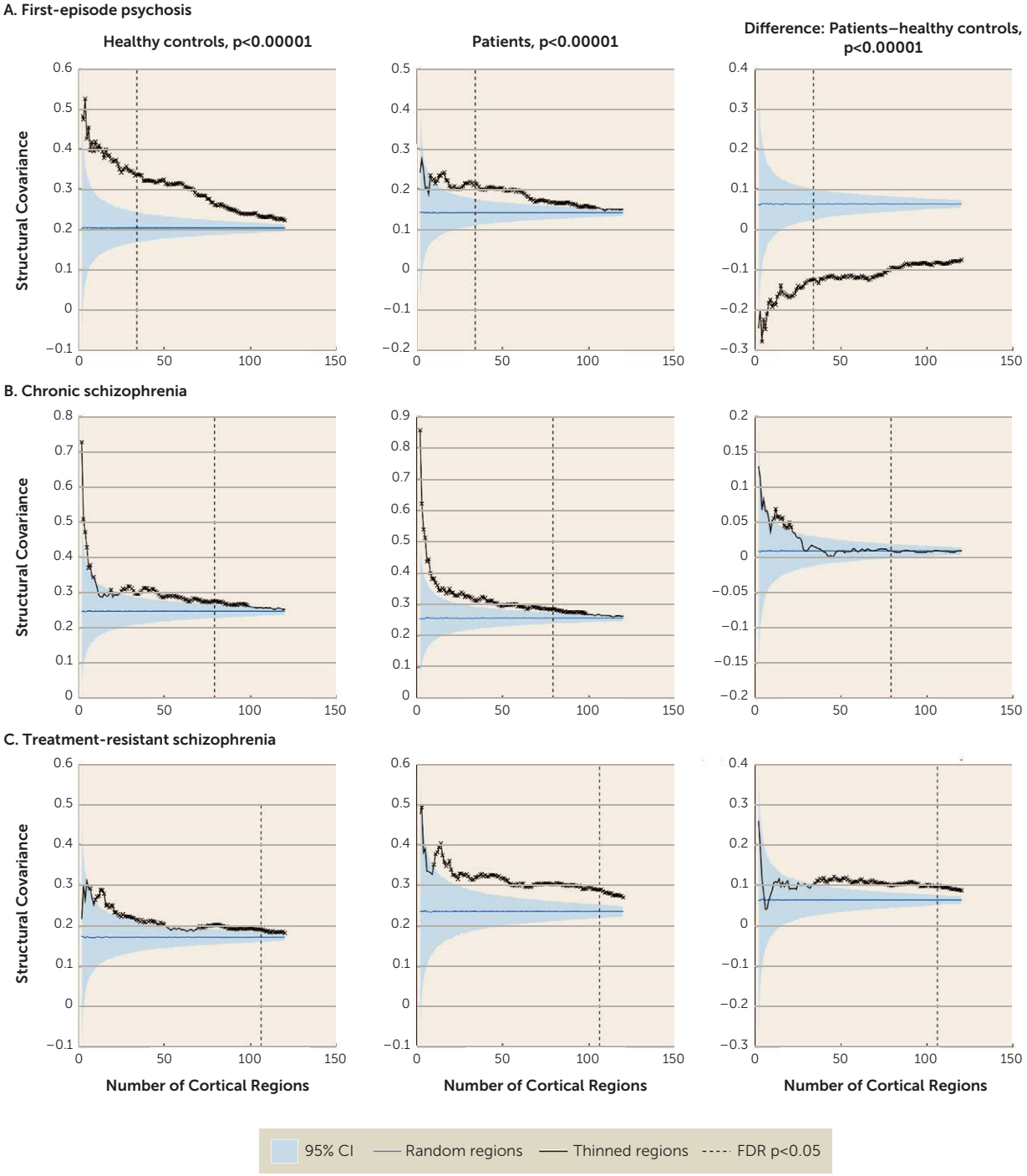
covariance computed in the control groups and in the patient groups separately (Figure 4A–4C). In the final analysis, the between-group difference in structural covariance between regions with thickness reductions was investigated. Structural covariance in the chronic and treatment-resistant schizophrenia cohorts was significantly stronger between regions with reductions when compared with healthy control subjects ($p<0.00001$) (Figure 4B and 4C). Conversely, patients with first-episode psychosis had significantly weaker structural covariance than their respective healthy control group in regions with thickness reductions ($p<0.00001$) (Figure 4A). Thus, structural covariance between thinned cortical regions was found to increase with increasing illness severity among patients compared with healthy control subjects.

We repeated the above analyses with mean cortical thickness included as a covariate for structural covariance analysis (for further details, see Figure S3 in the online supplement). After correcting for this potential confounder, structural covariance measured in either the patient groups or the healthy control groups remained significantly increased between regions with cortical thickness reductions ($p<0.0001$). However, for all patient cohorts and respective control groups, the difference in structural covariance between patients and control subjects was no longer significantly increased between regions with thickness reductions ($p>0.05$). These results remained unchanged when potentially spurious negative correlations were removed from the analyses.

### Supplementary Analyses

In supplementary analyses, 81 regions (55%) were found to have significant cortical thickness reductions in at least two of the three cohorts. This level of overlap could not be attributed to chance ($p=0.006$). Consistent with our primary analyses, structural covariance was significantly increased among these 81 regions in both patients and healthy control subjects for all three cohorts compared with the structural covariance between randomly chosen sets of 81 regions (for further details, see Table S5 in the online supplement).

**FIGURE 4. Comparison of the average structural covariance between the top-*n* cortical regions with cortical thickness reductions[a]**




[a] The graphs show patients with first-episode psychosis (panel A), chronic schizophrenia (panel B), and treatment-resistant schizophrenia (panel C) with the average structural covariance in 5,000 randomly chosen sets of *n* regions. Comparisons are shown separately for matched healthy control subjects, patients, and between-group differences. The vertical axis shows structural covariance, which is an r-to-z-transformed Pearson correlation coefficient. Dashed vertical lines represent the boundary between regions with and without cortical thickness reductions based on a false discovery rate threshold of 5%. Values of *n* marked with a cross indicate that structural covariance was significantly increased between the top-*n* regions with the most extensive cortical thickness reductions ($p<0.05$). The solid black line represents the mean structural covariance in the actual (nonpermuted) data. The blue line represents the mean structural covariance in the randomized data, averaged across 5,000 randomizations. The shaded area denotes 95% confidence intervals across the 5,000 randomizations. FDR=false discovery rate.

In addition, to evaluate the impact of variation in sample size across the cohorts, five subsamples were randomly drawn from the largest cohort according to sample size (chronic schizophrenia and respective control), such that each random subsample comprised the same number of patients and control subjects as the smallest cohort (treatment-resistant schizophrenia and respective control). Structural covariance among regions with cortical thickness reductions was highly consistent between the full sample and each random subsample (for further details, see Table S6 in the online supplement), suggesting that intercohort sample size variation did not introduce bias.

## DISCUSSION

We sought to identify regions with cortical thickness reductions in three distinct schizophrenia cohorts (first-episode psychosis, chronic schizophrenia, and treatment-resistant schizophrenia) and to establish whether structural connectivity between these regions was increased relative to randomly selected regions. Significant cortical thickness reductions were found in all three patient cohorts, and these reductions increased with increasing illness severity. Critically, we found that structural covariance was significantly increased among regions with the most extensive thickness reductions, irrespective of whether it was measured in patients or healthy control subjects, suggesting that cortico-cortical connectivity can provide an explanation for the irregular topographic distribution of thickness reductions across the cortex. Notably, this increase in structural covariance was observed only when analyses were constrained to regions in which thickness reductions were present, with no difference in average whole-brain structural covariance observed between patients and healthy control subjects. Replicating our findings across three independent schizophrenia cohorts increases the robustness of our findings and demonstrates that our analyses are reproducible. We have shown that the link between connectivity and cortical thickness reductions can be found across different illness stages of schizophrenia and different MRI acquisitions. We consider this a major advantage of our study, given the need for reproducible and transparent neuroimaging research (35).

Shafiei et al. (36) recently reported further evidence supporting the link between connectivity and gray matter pathology. The investigators used diffusion MRI and tractography to directly estimate whole-brain cortico-cortical connectivity and found that connectivity significantly shaped spatial patterns of cortical pathology in schizophrenia. Their study replicates and builds on our findings with an explicit measure of structural connectivity.

The finding of increased structural covariance in healthy control subjects between regions of increased cortical thickness reductions found in patients is particularly important, because it suggests that regions that are affected in patients are part of networks that are present in healthy individuals. We thus posit that the cortical topography of thickness reductions in schizophrenia is shaped by network topology. In this context, topography refers to the spatial arrangement of cortical regions on the cortical surface, whereas topology refers to the patterns of connectivity between these regions.

While we posit that brain network topology shapes and constrains the cortical topography of cortical thickness reductions, it is important to note that cortical topography may influence well-known topological disruptions associated with schizophrenia (18, 37). However, given that structural covariance measured in each of the three healthy control groups was significantly increased among regions with cortical thickness reductions, we can specifically posit that network topology explains the cortical topography of these reductions. If the effect had been evident only in the patient groups, then we would have only been able to suggest that topology and topography are associated. Thus, our most noteworthy finding is the evidence of increased structural covariance in healthy control subjects among regions that show thickness reductions in schizophrenia patients.

In addition to structural covariance (connectivity strength), topological properties of brain networks provide insight into the topography of cortical thickness reductions. For example, regions with a high degree of connectivity (hub nodes) are more likely to be affected by pathology in a range of brain disorders, including schizophrenia (38). Our findings suggest that regions with cortical thickness reductions in schizophrenia may not only be hubs but may also be interconnected with each other significantly more strongly than would be expected by chance.

### Characterizing Cortical Thickness Reduction Across Distinct Schizophrenia Cohorts

First-episode psychosis was associated with a diffuse but mild pattern of cortical thickness reductions, with the frontal, temporal, and parietal heteromodal association cortices most consistently affected. In contrast, chronic schizophrenia was associated with significant thickness reductions in more than half of the regions tested. Regions with the greatest reductions in the chronic schizophrenia group included the prefrontal, temporal, insular, and cingulate cortices, whereas the occipital and parietal lobes were only minimally affected. In treatment-resistant schizophrenia, reductions were widespread, encompassing more than 70% of the investigated regions and extending posteriorly into large sections of the parietal and occipital cortices. These findings are consistent with previous cross-sectional studies, which have typically found small but diffuse thickness reductions in patients with first-episode psychosis (3, 6, 7, 39) and more widespread reductions in patients with chronic (1, 2, 8) and treatment-resistant (10) schizophrenia, although some studies have also reported cortical thickness increases in first-episode psychosis (39).

### Network-Based Cortical Thickness Reductions

Structural covariance analysis revealed significantly increased cortico-cortical connectivity between regions with

cortical thickness reductions in first-episode psychosis, chronic schizophrenia, and treatment-resistant schizophrenia. Notably, increased structural covariance between thinned regions was observed not only in patients but also in healthy control subjects. These findings are consistent with the hypothesis that cortical networks may propagate local pathological processes involved in schizophrenia (e.g., aberrant neuronal signaling, disruption to neurotransmitter systems), resulting in cortical thickness reductions at distant cortical locations to which these processes propagate. This provides an explanation for why the distribution of thickness reductions in the cortical surface is irregular and not contiguous, supposing that these reductions are shaped by connections that can interconnect distant regions.

The cohort effects observed were quite prominent, as shown in Figure 4. While it may be tempting to draw quantitative conclusions about these intercohort differences, it is important to note that data for the three schizophrenia cohorts were acquired using MRI scanners with different magnet strengths, and thus the intercohort differences may potentially reflect data acquisition differences.

In some degenerative brain disorders, unaffected regions at greatest risk of future atrophy are directly connected to atrophied regions via white matter fiber bundles (40–43). This suggests that white matter may inauspiciously facilitate proliferation of pathological processes, through transneuronal or transsynaptic spread (41, 44). Alternatively, and perhaps a more probable mechanism in schizophrenia, rather than white matter providing a conduit that facilitates the progression of pathology, progressive disruption to white matter connectivity may result in loss of normal neuronal signaling or reduced trophic support to vulnerable regions, leading to postsynaptic dendrite retraction and eventual atrophy as a consequence (45, 46). Although our study does not allow for investigation of these potential mechanisms, white matter disruptions are known to be associated with cortical thickness reductions in schizophrenia (47–50).

In the first-episode psychosis cohort, structural covariance between regions with cortical thickness reductions was significantly reduced in patients compared with healthy control subjects. Late adolescence to early adulthood—when the onset of psychosis typically occurs—is a period during which synaptic connections continue to be refined and cortical thickness continues to decrease (51, 52), and our findings in first-episode psychosis are therefore best interpreted within a neurodevelopmental framework. Given the high degree of structural covariance observed in the youngest healthy control group, it is possible that these individuals were still undergoing refinement of their brain networks, resulting in increased connectivity between brain regions that may no longer be connected in older healthy individuals. This notion is consistent with previous findings indicating a shift away from distributed patterns of interregional gray matter covariance and increased global efficiency in younger healthy individuals, toward increased localization of brain network topology across a number of brain regions in older individuals (53, 54). However, in patients with first-episode psychosis, maladaptive processes, including abnormal (i.e., excessive) synaptic pruning and reduced brain plasticity, may have led to disruptions in the normal maturation of higher-order regions, such as the prefrontal and parietal cortices and the superior temporal gyrus (55), which could account not only for the greater cortical thickness reductions in these regions in patients with first-episode psychosis but also for the decreased structural covariance observed in patients with first-episode psychosis compared with younger healthy control subjects. This is consistent with previous longitudinal studies showing that compared with healthy control subjects, cortical surface retraction occurs at a faster rate in early psychosis (including in individuals with first-episode psychosis and high-risk individuals) (56, 57) and that individuals with childhood-onset schizophrenia exhibit an accelerated rate of cortical thickness reduction in cingulo-fronto-temporal brain modules during adolescence (58).

Conversely, structural covariance between regions with cortical thickness reductions was significantly increased in patients compared with control subjects in the chronic and treatment-resistant schizophrenia cohorts. The increased structural covariance observed in regions with thickness reductions in these groups may reflect progressive neurodevelopmental brain abnormalities in psychotic illnesses (59). That is, as the illness progresses, connected brain regions that thin at a similar rate may become more closely correlated in size. This could result in the increased structural covariance observed in patients with chronic schizophrenia and with treatment-resistant schizophrenia and would explain why patients with treatment-resistant schizophrenia demonstrate the greatest increase in structural covariance compared with healthy control subjects.

**Limitations and Future Directions**

A noteworthy limitation of this study was its cross-sectional design. While it is possible to hypothesize about progressive cortical thinning in our sample, given that cortical thickness reductions increased with illness duration and severity (i.e., first-episode psychosis < chronic schizophrenia < treatment-resistant schizophrenia), this requires confirmation with a longitudinal sample. It was also impossible in this study to determine whether apparent cortical thickness reductions may actually have been the result of variations in the microstructural properties of brain tissue, including myelination, iron, and water content (60), across our cohorts. Additionally, magnetic field strength and FreeSurfer version differed between the three cohorts examined. Because these variations can potentially affect the accuracy and reliability of cortical thickness estimates (61, 62), we did not combine MRI data across different cohorts for any quantitative or statistical analyses. Thus, we did not quantitatively evaluate the impact of disease severity on the relation between connectivity and cortical thickness reductions, because this would have required combining MRI data that were

acquired with different scanners and processed with different FreeSurfer versions, thereby introducing several potential confounders. Despite this limitation, replicating our findings across different scanner strengths and FreeSurfer versions highlights the robustness and reproducibility of our findings. Inconsistencies in symptom and medication data across cohorts and a lack of antipsychotic dosage information for the chronic schizophrenia cohort also made it difficult to compare these measures across groups and to assess their influence on cortical thickness reductions. However, the aim of our study was not to investigate the cause of thickness reductions but rather the mechanism through which thinning may occur, and therefore the potential effects of medication and illness severity on thickness reductions are beyond the scope of this study. Finally, it is noteworthy that our analyses were somewhat circular, because the same data used to map thickness reductions were also used to measure structural covariance. However, it is critical to remember that structural covariance measured in healthy control subjects was increased between cortical thickness reductions mapped in the schizophrenia patient groups, and thus the cortical thickness reductions in patients and the structural covariance in healthy control subjects were derived separately.

In summary, we found that cortical connectivity networks can explain the irregular topographic distribution of cortical thickness reductions across the cortex in schizophrenia. We replicated this finding in three distinct schizophrenia cohorts, suggesting that the effect is robust and universal across illness stages. By using a robust measure of structural brain connectivity, we observed significantly stronger connectivity between regions with cortical thickness reductions compared with arbitrarily chosen regions. If thickness reductions are progressive in the disorder, our findings suggest that regions most vulnerable to future degeneration are most likely structurally connected to regions already affected by such reductions. Our findings provide evidence for network-based thickness reductions in schizophrenia and yield new knowledge about how neuropathological processes may be constrained by the human connectome. Future work will include longitudinal investigation of cortical thickness reductions and cortical networks as well as evaluation of this relation in distinct diagnostic subtypes and other disorders.

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