ORIGINAL ARTICLE

Widespread Reductions of Cortical Thickness in Schizophrenia and Spectrum Disorders and Evidence of Heritability

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Context: Schizophrenia is a brain disorder with predominantly genetic risk factors, and previous research has identified heritable cortical and subcortical reductions in local brain volume. To our knowledge, cortical thickness, a measure of particular interest in schizophrenia, has not previously been evaluated in terms of its heritability in relationship to risk for schizophrenia.

Objective: To quantify the distribution and heritability of cortical thickness changes in schizophrenia.

Design: We analyzed a large sample of normal controls, affected patients, and unaffected siblings using a surface-based approach. Cortical thickness was compared between diagnosis groups on a surfacewide node-by-node basis. Heritability related to disease risk was assessed in regions derived from an automated cortical parcellation algorithm by calculating the Risch λ.

Setting: Research hospital.

Participants: One hundred ninety-six normal controls, 115 affected patients with schizophrenia, and 192 unaffected siblings.

Main Outcome Measure: Regional cortical thickness.

Results: Node-by-node mapping statistics revealed widespread thickness reductions in the patient group, most pronouncedly in the frontal lobe and temporal cortex. Unaffected siblings did not significantly differ from normal controls at the chosen conservative threshold. Risch λ analysis revealed widespread evidence for heritability for cortical thickness reductions throughout the brain.

Conclusions: To our knowledge, the present study provides the first evidence of broadly distributed and heritable reductions of cortical thickness alterations in schizophrenia. However, since only trend-level reductions of thickness were observed in siblings, cortical thickness per se (at least as measured by this approach) is not a strong intermediate phenotype for schizophrenia.

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SCHIZOPHRENIA IS A HIGHLY heritable disorder that has been linked to changes in brain morphology in a wide variety of studies.[1-3] These studies have shown volumetric reductions in a number of cortical regions, particularly frontal and temporal, as well as several subcortical regions, most notably hippocampus.

The majority of these studies assess regional volumes through voxel-based approaches, estimating the volume of a given structure by summing up the number of voxels (volume elements) it encompasses. However, recent advances in morphological imaging now allow the reconstruction of structural features in a subvoxel range. This is of particular interest in cerebral cortex, where sophisticated algorithms designed to reconstruct subjects' cortical surfaces offer an exciting opportunity to study cortical thickness, surface area, and sulcal depth.[4-8] Since abnormal architecture of cortex has been identified in postmortem studies in schizophrenia[9-12] and occupies a privileged position in several influential theories of the pathogenesis of the disorder,[13-15] these measures are of particular interest for schizophrenia research. Recently emerging studies of cortical thickness in schizophrenia have in fact identified broad patterns of cortical thinning, particularly in prefrontal regions, temporal lobe, and cingulate gyrus,[16-19] although studies on this aspect of schizophrenia morphology remain far less numerous than those analyzing volume.

Since genetic factors account for the majority of schizophrenia risk, for every finding of a schizophrenia-related abnormality in brain morphology, the question immediately arises whether this change in brain structure constitutes a heritable component of the disease. If true, this structural phenotype should be enriched in subjects at risk for schizophrenia. One strategy

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for examining disease-related heritability is therefore the analysis of unaffected siblings, who share 50% of their affected sibling's genetic variants but do not themselves have schizophrenia. To our knowledge, this approach was previously pursued only in a pair of adult studies of thickness in schizophrenia, in which 19 first-degree relatives showed reduced cingulate thickness,[20] altered surface area in right cingulate and temporal regions,[20] and sulcal thickness alterations in the cingulate and superior temporal sulci.[21] A further study focused on young siblings (aged 8-28 years) of patients with childhood-onset schizophrenia and found temporal and frontal thickness reductions only in siblings younger than 20 years.[22] Observed volume differences between unaffected siblings and normal controls have varied, but a recent meta-analysis[23] reported significant reductions of hippocampal volume and cortical gray matter volume, and in a previous study of healthy siblings in our sample using voxel-based morphometry, we observed intermediate reductions in several cortical areas (including left medial frontal, left superior temporal, and left insula).[24] Other studies have reported reductions in hippocampus or other temporal areas[25-28] and frontal lobe,[28,29] though negative results have also been reported.[30-32] Given the intuitive relation between volume and thickness, there is thus reason to investigate cortical thickness as an intermediate phenotype related to schizophrenia.

In addition to being enriched in subjects at risk, a phenotype related to genetic risk must be heritable. While direct comparison of unaffected siblings with normal controls can be useful, other parameters are needed to establish this. One such measure is the Risch λ for siblings (λ_s), which compares the frequency of occurrence of a disease-related phenotype in healthy siblings of patients who exhibit that phenotype with the frequency seen in normal controls.[33-35] If the phenotype under study is heritable, siblings are more likely to exhibit the phenotype observed in their ill relative. In a previous study of brain volumetric changes, we used this measure to provide evidence of heritable components to hippocampal and overall cortical gray matter reductions in schizophrenia, whereas enlargements of the lateral ventricles and dorsal striatum did not show such familiality.[36]

To investigate the presence and heritability of cortical thickness alterations in schizophrenia, herein we applied similar methods in a large surface-based data set. One hundred ninety-six normal controls, 115 affected patients, and 192 unaffected siblings were scanned within the framework of the Clinical Brain Disorders Branch/National Institute of Mental Health Sibling Study, a study aimed at identifying schizophrenia susceptibility genes and related intermediate biologic phenotypes.[37] Brain magnetic resonance images (MRIs) were processed using an automated surface reconstruction method and then automatically parcellated into a wide range of cortical regions.[4,5,38-40] Cortical thickness was calculated at each node, and average thickness values were also extracted for each cortical region.[7,8]

We contrasted cortical thickness between normal controls, patients with schizophrenia, and unaffected siblings using a surface-based general linear model (GLM) tool to map pairwise group contrasts on a node-by-node basis. Additionally, the Risch λ was calculated using the average thicknesses for each cortical region, providing further analysis of heritability. Based on previous volumetric data[1,2] and the importance of frontotemporal processing abnormalities for schizophrenia,[41] we hypothesized that patients would exhibit heritable reductions in cortical thickness, particularly in frontal and temporal cortex. Hypothesizing that regional cortical thickness would be an intermediate phenotype for schizophrenia, we further expected unaffected siblings to show a similar but less pronounced pattern of reduction.

METHODS

PARTICIPANTS

A sample of 196 normal controls, 115 affected patients, and 192 unaffected siblings was included in this study. In previous studies, we analyzed local brain volume in largely overlapping but not identical samples to the one presently discussed.[24,36] Subjects were recruited nationwide as part of an ongoing family study of schizophrenia at the National Institute of Mental Health, Bethesda, Maryland, which included standard procedures such as a semistructured diagnostic interview (Structured Clinical Interview for *DSM-IV*) and a formal neurological examination. Subjects provided written informed consent and participated according to the guidelines of the National Institute of Mental Health institutional review board.

All patients met *DSM-IV* criteria for schizophrenia (79.1%) or related diagnoses including schizoaffective disorder (12.2%), psychosis (not otherwise specified) (1.7%), and schizoid, paranoid, and schizotypal personality disorders (7.0%). The majority (91.0%) were taking antipsychotic medication at the time of scan, and a minority (19.1%) had a lifetime history of comorbid mental illness or substance abuse/dependence (including alcohol). No normal controls currently had *DSM-IV* Axis I disorders, and no subjects in any group had a current history of alcohol or substance abuse within 6 months of being scanned. However, a minority of normal controls (17.3%) and unaffected siblings (41.7%) had a lifetime history of mental illness, substance abuse or dependence, personality disorders, or other disorders (**Table 1**).

For heritability analysis, 56 families were included with at least 1 affected and unaffected member, accounting for 59 affected patients and 72 unaffected siblings. The remaining patients (56) and siblings (120) did not have a relative included in the study.

IMAGING AND PREPROCESSING

Three-dimensional structural MRI scans were acquired on a 1.5-T GE scanner (GE Medical Systems, Milwaukee, Wisconsin) using a T1-weighted spoiled gradient recalled sequence (repetition time, 24 milliseconds; echo time, 5 milliseconds; number of excitations, 1; flip angle, 45°; matrix size, 256 × 256; field of view, 24 × 24 cm), with 124 sagittal slices (0.94 × 0.94 × 1.5-mm resolution). All participant groups were recruited and scanned throughout a 12-year period. Potential MRI system-specific effects were not apparent in ongoing quality control and examination of the effect of scan year using GLM-based analyses. Images were processed using the full stream in the Freesurfer stable release 3.0.2.[4-6,42,43] Preprocessing included resampling to a coronal 3-dimensional image with 1-mm isotropic voxel size, nonuniformity intensity normalization (N3),[44] an affine registration to Montreal Neurological Institute space,[45] further intensity normalization with a different algorithm, and an automated skull

Table 1. Demographic Results

	Mean (SD) [Range]		
	Normal Controls	Affected Patients	Unaffected Siblings
Age	33.51 (9.67) [18.39-60.86][a]	37.39 (10.46) [18.81-61.63]	37.49 (9.77) [17.49-58.25]
Sex			
M/F	87/109 (44.4% male)[b]	84/31 (73.0% male)[b]	76/116 (39.6% male)[b]
WAIS full-scale IQ score[c]	107.13 (9.50) [78-129]	96.95 (9.99) [78-116][a]	106.46 (11.04) [78-134]
Years of education[d]	16.84 (2.92) [12-25][a]	14.94 (2.55) [11-23][a]	16.08 (2.56) [11-27][a]
Family SES[e]	49.81 (13.06) [16-66][a]	52.86 (11.94) [13-66]	53.56 (12.50) [13-66]
Handedness,[f] %			
Right	90.1	79.8	81.8
Left	4.7	9.2	7.7
Both	5.2	11.0	10.5
Lifetime history of mental illness,[g] No. (%)	34 (17.3)	22 (19.1)[h]	80 (41.7)
Bipolar disorder,[g] No. (%)	0	1 (0.9)	1 (0.5)
Major depression,[g] No. (%)	23 (11.7)	4 (3.5)	47 (24.5)
Personality disorder,[g] No. (%)	1 (0.5)	0	10 (5.2)
Substance abuse/dependence,[g] No. (%)	6 (3.1)	16 (13.9)	12 (6.3)
Other disorders,[g] No. (%)	8 (4.1)	1 (0.9)	19 (9.9)
PANSS positive symptoms score[i]	7.04 (0.25) [7-9]	13.15 (6.01) [7-31][a]	7.07 (0.31) [7-9]
PANSS negative symptoms score[i]	8.23 (2.82) [7-20]	18.88 (9.12) [7-44][a]	8.17 (3.12) [7-26]
PANSS general psychopathology score[i]	16.44 (1.25) [16-24]	26.02 (9.97) [16-59][a]	16.93 (2.24) [16-30]

Abbreviations: PANSS, Positive and Negative Syndrome Scale; SES, socioeconomic status; WAIS, Wechsler Adult Intelligence Scale.
[a] Demographic significantly differed from both other groups based on simple contrasts.
[b] Sex (but not handedness) significantly differed among the 3 groups based on χ^2 tests.
[c] IQ scores were available for 192 controls, 112 patients, and 191 siblings.
[d] Years of education were available for 195 controls, 114 patients, and 192 siblings.
[e] Hollingshead family SES scores were available for 194 controls, 110 patients, and 191 siblings.
[f] Edinburgh handedness scores were available for 192 controls, 109 patients, and 181 siblings. Subjects scoring 0.7 or more were considered right handed and –0.7 or less, left.
[g] Some subjects had a lifetime history of multiple illnesses. No participants exhibited current substance abuse, and no normal controls exhibited current Axis I disorders.
[h] Percentage does not include primary diagnosis of schizophrenia or related disorders.
[i] Scores were available for 175 controls, 65 patients, and 166 siblings.

strip.[46] Images were then subcortically segmented as described in previous articles.[36,42,43] At this juncture, several careful visual quality checks were performed, and failures were manually corrected and reinspected as described previously.[36] These corrections were performed on 21 controls, 21 patients, and 40 siblings.

Images then underwent a sophisticated and validated[4,8,47] surface reconstruction algorithm.[4-6] Briefly, white matter segmentations were first produced,[4] using information from the subcortical segmentations to also fill in areas that commonly produce topological defects (such as basal ganglia and lateral ventricle). Cutting planes were used to isolate each cerebral hemisphere, and final binary white matter masks were produced. Tessellation was then performed to produce a triangle-based mesh of the white matter surface, and a smoothing algorithm was used to alleviate the voxel-based nature of the initial curvature.[4] Topological defects in the surfaces were then corrected using an automated topology fixer,[40] and the white matter surfaces were deformed outward to generate pial surfaces.[4] As mentioned, preprocessing involved a registration to Montreal Neurological Institute space, producing a transformation matrix for use in several processing steps. Notwithstanding, the surfaces produced remained in native space, allowing direct, anatomically accurate measurements of thickness but also necessitating an algorithm for surface-based intersubject registration. To achieve this, surfaces were spherically inflated,[5] and spherical surfaces for each subject were registered to a common space spherical deformation guided by automatically defined cortical features derived from a population atlas.[48]

Final surface data were then parcellated into a variety of cortical regions using an automated algorithm (**Figure 1**), which used a manually labeled training data set, as well as knowledge of curvature and the spatial relationship between regions.[38,39] The atlas used, detailed in Desikan et al,[38] included 33 gyral regions of interest, as well as 2 placeholder labels we did not analyze (corpus callosum and "unknown," which includes insula as well as diencephalon and other noncortical regions). Using combined information from the pial and white matter surfaces, cortical thickness was calculated at each node, and average thickness was also calculated for each area of cortex parcellated.[7,8] At the end of this process, each subject was again visually inspected for gross topological inaccuracies, and subjects with defects (15.8%, listed sample sizes are for final sample) were excluded from the study.

STATISTICAL ANALYSIS

Node-by-node contrasts of cortical thickness were performed for normal controls vs affected patients, controls vs unaffected siblings, and patients vs siblings. For this, an average normal control surface was generated, and thickness data from each subject were mapped to this average surface and smoothed using a 10-mm full-width-at-half-maximum gaussian filter. Finally, each contrast was entered into a node-by-node GLM including diagnosis, sex, and exact age as covariates. Results were thresholded and false discovery rate (FDR) corrected at a conservative, surfacewide $P < .05$ significance level. To ensure that lack of an intracranial volume (ICV) covariate did not confound our results, analyses were also rerun with ICV added to the model. For the purpose of generating **Figure 2** and **Figure 3**, these results were imported into SUMA (http://afni.nimh.nih.gov/afni/suma) and overlaid on the average normal control surface.

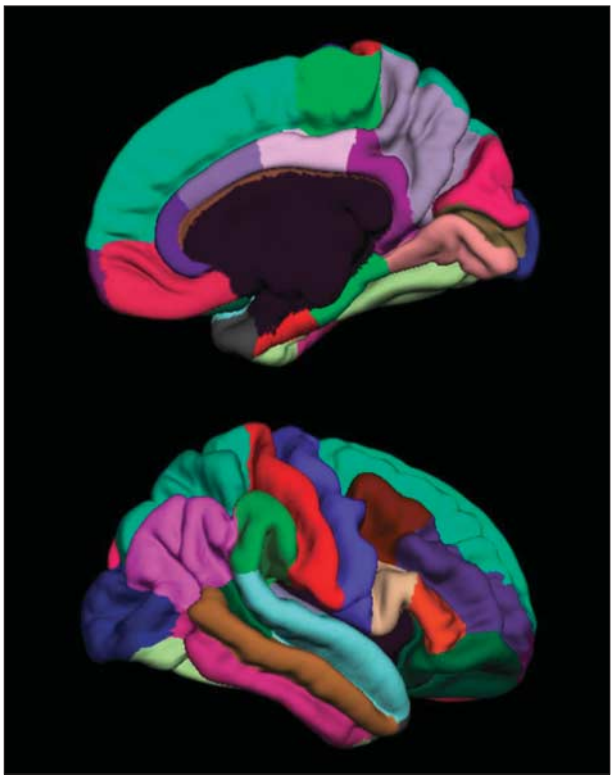

Figure 1. Average surface with overlaid cortical parcellation labels. Using an automated algorithm, labels were generated for 33 gyral regions of interest. As an example, an average pial surface for the normal control group is displayed here, with the group's average cortical parcellations overlaid.

In addition, heritability was analyzed using the Risch λ for siblings (λ_s), which quantitatively measures how frequently siblings of patients with pronounced cortical thickness reductions (the disease-associated phenotype) show such reductions themselves.[33-35] Since this measure is based on a categorical phenotype, it is necessary to determine cutoffs based on the distribution of average thickness in the normal control group. Given the sensitive nature of the heritability measure, and its lack of an inferential statistic, we chose to limit analysis to a discrete set of relatively stable regions of interest derived from an automated parcellation algorithm. Statistics of average thickness within each parcellation label were normalized to *z* scores using the mean and standard deviation of the normal controls, and subjects were assigned the reduced cortical thickness phenotype if their values were 1.5 SDs lower than the mean, corresponding to the outer 6.7% of the distribution. The Risch λ is then defined as the percentage of siblings of "patients with phenotype" who also show reductions exceeding the threshold, divided by the proportion of normal controls who show such reductions. While an inferential statistical test for this measure is not available (making this measure more similar to an effect size for heritability), nonfamilial traits are expected to have a λ_s value of 1, and relative risks of 2.0 or more are commonly considered evidence for heritability, barring shared effects of environment.[51]

RESULTS

DEMOGRAPHICS

Table 1 shows demographic data for the reported sample, which was typical overall of participants in this case-control study. To control for age and sex effects, these variables were included in all GLM analyses as confounding covariates. Furthermore, for all parcellation-based analyses, preliminary GLM tests were performed including sex × diagnosis and age × diagnosis interactions, and when significant, these interaction effects were included in the final analyses (see "Statistical Analysis" subsection).

To investigate illness-related demographic variables that may have confounded or modulated observed reductions in our patient group, post hoc GLMs were performed for medication status (taking medication/not taking medication), years of illness, age at onset, and scores on the 3 major Positive and Negative Syndrome Scale symptom scales. Each variable was modeled along with age and sex, and effects were thresholded at $P < .05$, FDR corrected. The results were broadly negative, with only 1 small suprathreshold cluster appearing for Positive and Negative Syndrome Scale general psychopathology (in left superior temporal gyrus).

NODE-BASED ANALYSIS OF THICKNESS

Average thickness maps for normal controls, affected patients, and unaffected siblings are shown in Figure 2. Maps of the 3 groups show good correspondence to the classic postmortem thickness maps reported by Von Economo,[49] and reductions of prefrontal and lateral temporal cortical thickness are readily visible in the patient group.

Statistical contrasts of mean cortical thickness between diagnostic groups (Figure 3), thresholded at $P < .05$ and surfacewide FDR corrected for multiple comparisons, showed significant thickness reductions throughout the cortex in the patient group compared with controls. Differences were most pronounced in the frontal lobe but were also found in temporal, parietal, occipital, and limbic regions. Temporal lobe differences appeared especially pronounced in the right hemisphere, though we did not explicitly test for group × hemisphere effects. At the threshold applied, affected patients did not show increased cortical thickness in any brain area. Unaffected siblings, however, did not significantly differ from normal controls and showed relatively few effects even prior to FDR correction (eFigure 1, http://www.archgenpsychiatry.com). The pattern of reductions in patients compared with unaffected siblings was similar to that seen compared with normal controls, but less pronounced. While our statistical model did not account for the relatedness of some of the subjects, supplemental analyses using only the 120 unaffected siblings without a relative in the study showed equivalent results (eFigure 2). Similarly, adding ICV as a covariate did not appreciably alter our results (eFigure 3).

Effects of age and sex on cortical thickness are displayed in eFigure 4 and eFigure 5. Briefly, in each of the 3 groups (normal controls, affected patients, and unaffected siblings) similar widespread age effects were seen, most prominently including decreases in thickness with age in lateral frontal lobe, as well as lateral temporal areas, cingulate, precentral and postcentral gyrus, and parts of the parietal lobe. Interestingly, differences were less pronounced in the patient group, perhaps because of increased variance. Only a few sex effects were seen, which seemed most significant in the unaffected sibling group.

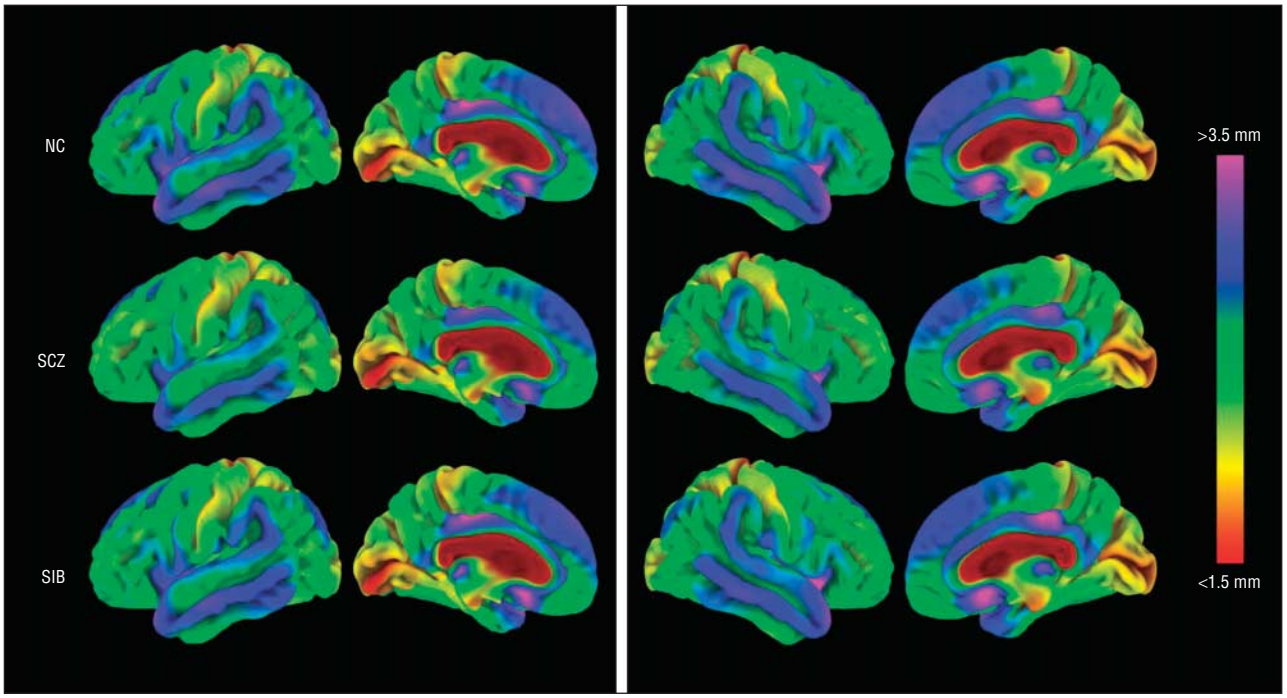

Figure 2. Mean thickness maps for normal controls (NC), patients with schizophrenia (SCZ), and siblings (SIB). For each subject, cortical thickness values were calculated on a node-by-node basis. Results were then mapped to a mean surface generated based on the NC group, and average thicknesses for each diagnosis group were calculated. For display purposes, average thickness maps were imported into SUMA (http://afni.nimh.nih.gov/afni/suma) and overlaid on the NC's average surface. Mean thickness maps for each diagnosis group were similar both to each other and the maps reported by Von Economo.[49,50] Purple represents areas of highest thickness (>3.5 mm), whereas red indicates areas of lowest thickness (<1.5 mm). Results in the corpus callosum and midbrain were not meaningful.

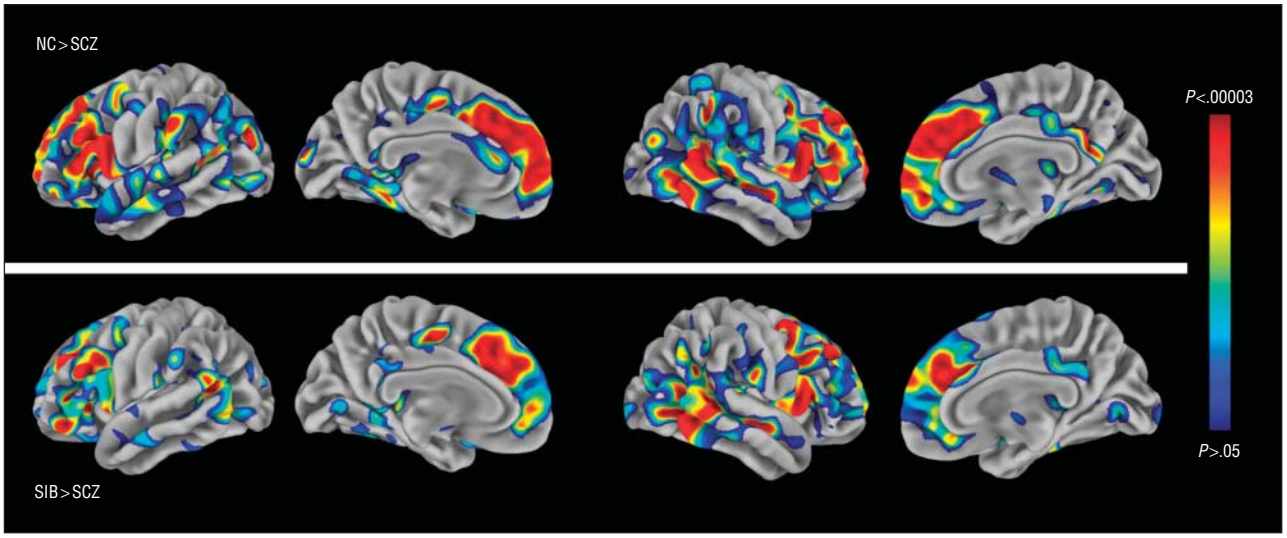

Figure 3. Node-based contrasts of thickness between diagnosis groups. A surface-based general linear model approach was used to contrast thickness values between diagnosis groups on a node-by-node basis. Thickness values for each subject were mapped to an average surface of the normal control (NC) group and smoothed using a 10-mm full-width-at-half-maximum gaussian filter. Group contrasts were then performed, covarying for age and sex. Results were thresholded at $P<.05$, false discovery rate corrected, and display images were generated in the same fashion as Figure 2. Between-group contrasts of thickness revealed widespread reductions in patients with schizophrenia (SCZ) compared with NCs, most pronouncedly in frontal and temporal lobes. Comparison of the affected patients with unaffected siblings (SIB) revealed similar, but far less pronounced, reductions. The SIB vs NC contrast showed no significant results and is therefore not displayed.

HERITABILITY ANALYSIS

The Risch λ was calculated for each parcellated region as a measure of heritability. In numerous areas, siblings of patients with pronounced thickness reductions indeed exhibited such reductions themselves, as shown in **Table 2**. Risch λ values of 2 or more, generally viewed as evidence for heritability, were seen in the majority of brain regions, and values as high as 7.88 were observed. **Figure 4** and **Figure 5** depict heritability results, as well as distributions of average thickness, for selected brain regions of special interest. With very few exceptions, re-

Table 2. Risch λ (λ_s) in Cortical Parcellation Regions[a]

Region	Left Risch λ (λ_s)[b]			Right Risch λ (λ_s)[b]		
	No./Total No.			No./Total No.		
	Siblings With Phenotype	Controls With Phenotype (n = 195)	λ_s	Siblings With Phenotype[c]	Controls With Phenotype (n = 195)	λ_s
Superior frontal gyrus	3/18	15	2.17	3/20	17	1.72
Rostral middle frontal gyrus	4/21	13	2.86	3/14	12	3.48
Caudal middle frontal gyrus	4/17	10	4.59	1/18	14	0.77
Inferior frontal gyrus, opercular	5/24	11	3.69	1/22	11	0.81
Inferior frontal gyrus, triangular	3/13	14	1.76	2/7	12	2.17
Inferior frontal gyrus, orbital	2/17	13	3.21	2/15	12	4.64
Lateral orbitofrontal cortex	1/3	12	5.42	2/10	10	3.90
Medial orbitofrontal cortex	1/10	9	2.17	2/21	13	1.43
Precentral gyrus	5/14	14	4.97	2/17	16	1.43
Frontal pole	0/4	16	0	1/13	15	1.00
Superior temporal gyrus	8/26	15	4.00	4/19	21	1.95
Middle temporal gyrus	4/22	13	2.73	2/11	13	2.73
Inferior temporal gyrus	2/13	10	3.00	2/19	17	1.21
Entorhinal cortex	0/2	13	0	2/6	10	6.50
Parahippocampal gyrus	2/10	13	3.00	0/11	14	0
Fusiform gyrus	1/5	15	2.60	2/9	13	3.33
Lingual gyrus	0/7	13	0	0/9	13	0
Banks of the superior temporal sulcus	5/21	12	3.87	1/16	12	1.02
Transverse temporal	4/14	14	3.98	2/14	12	2.79
Temporal pole	0/1	17	0	0/5	11	0
Superior parietal lobule	2/8	10	4.88	2/12	11	2.95
Inferior parietal lobule	3/20	11	2.66	1/15	18	0.72
Supramarginal gyrus	1/14	18	0.77	4/15	13	4.00
Cuneus	1/8	9	2.71	1/10	12	1.63
Precuneus	2/10	10	3.90	5/19	14	3.67
Postcentral gyrus	3/13	11	4.09	1/7	11	2.53
Paracentral lobule	2/21	14	1.33	3/17	14	2.46
Rostral anterior cingulate	2/10	14	2.79	3/15	14	2.79
Caudal anterior cingulate	5/18	15	3.61	4/26	15	2.00
Posterior cingulate	6/23	13	3.91	3/13	16	2.81
Isthmus/posterior cingulate	2/9	16	2.71	2/9	11	3.94
Lateral occipital lobe	1/9	12	1.81	3/13	18	2.50
Pericalcarine	3/12	12	4.06	4/9	11	7.88

[a] Risch λ was calculated as a measure of heritability in each region. For Risch λ, $\lambda_s = 1$ is the expected value for nonfamilial traits, while $\lambda_s > 2.0$ is considered evidence for familiality.

[b] Risch λ measurements were taken using a threshold of $z > 1.5$.

[c] For each region, Risch λ analysis includes only siblings of patients beyond the threshold. Thus, the denominator for siblings differed in each region (see "Statistical Analysis" subsection of "Methods" section.

gions noted earlier for especially pronounced thickness reductions also showed evidence for heritability.

COMMENT

The present study examined the heritability of cortical thickness changes associated with schizophrenia in a large cohort of normal controls, affected patients, and unaffected siblings analyzed using sophisticated surface extraction and cortical parcellation procedures. The study demonstrated marked thickness reductions in the patient sample, most notably in frontal and temporal lobes, and provided evidence for widespread heritability of these cortical alterations. Since no significant thickness reductions were found in unaffected siblings in this large sample, reduced cortical thickness per se is unlikely to be a major neural signature of the genetic risk architecture of schizophrenia. However, this conclusion must be considered in light of the technical limitations of MRI as an anatomical research method.

Perhaps the most striking thickness effects were seen in the frontal lobe, where patients showed widespread reductions. Prefrontal cortex is one of the most consistently implicated regions in morphometric studies of schizophrenia,[1-3] and previous studies of cortical thickness have likewise shown widespread thinning in this area,[16,17,19] although 1 study (using a non–surface-based method) found no reduction among first-episode patients.[52] Furthermore, unaffected siblings showed widespread relative risk for thickness reductions within the frontal lobe, consistent with reports associating schizophrenia susceptibility genes with altered prefrontal structure[53] and function,[54] as well as studies showing intermediate prefrontally linked functional phenotypes in the first-degree relatives of patients with schizophrenia.[55]

The temporal lobe has likewise exhibited reduced volume in a wide range of studies, particularly in the supe-

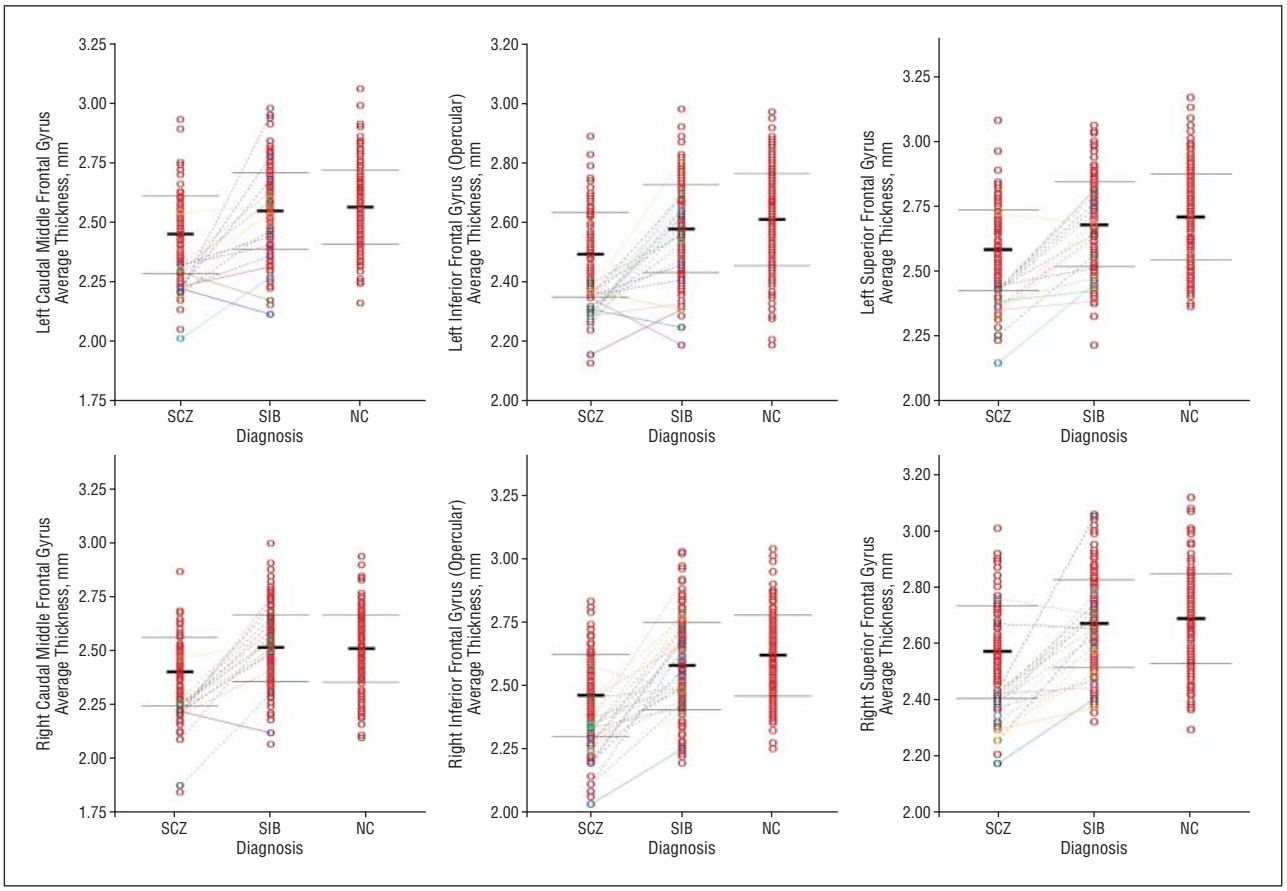

Figure 4. Average thickness distributions and heritability results for selected frontal regions. Thickness was also analyzed on a regionwide basis using automated cortical parcellations. Here, results are displayed for the 3 frontal regions in which patient thicknesses were most reduced. Red circles show the distribution of average thicknesses for subjects in each region, and error bars show the mean and standard deviation. Lines connect patients with schizophrenia (SCZ) expressing each phenotype (ie, having scaled volumes >1.5 SDs from the mean in the direction of our hypothesis) to their unaffected siblings (SIB). Solid lines represent cases where the SIB also expressed the phenotype, whereas dotted lines indicate cases where the SIB did not. According to Risch λ tests (λ_s), SIB showed heritability for thickness reductions in the left hemisphere for all 3 regions. NC indicates normal controls.

rior temporal gyrus and medial temporal lobe.[1-3] Not surprisingly, therefore, and as hypothesized, thickness was found to be reduced in a variety of temporal regions in our present data, most pronouncedly on the lateral surface, replicating previous reports of temporal thickness reductions in schizophrenia.[16,17,19] Furthermore, relative risk for reduced thickness was seen in a variety of temporal regions, suggesting a role of schizophrenia risk genes in temporal lobe cortical architecture.

Intriguingly, despite the prevalence of middle temporal lobe reductions in volumetric studies of schizophrenia,[1-3,36] our sample did not show significant thickness reductions in parahippocampal gyrus or entorhinal cortex. The lack of results in this area could indicate that medial temporal volume reductions are limited to subcortical regions (hippocampus and/or amygdala). Alternatively, since thickness is not directly synonymous to volume, cortical reductions could exist in the form of reduced cortical area or some other morphometric difference, such as abnormal cytoarchitecture. Previous results in the parahippocampal gyrus have been equivocal, with at least 1 study reporting reduced thickness[16] but others failing to find thinning in first-episode schizophrenia[18] or over the first 5 years of childhood-onset schizophrenia.[56]

Beyond these a priori hypothesized regions, thickness reductions were seen in lingual gyrus, supramarginal gyrus, inferior parietal lobule, right precuneus, lateral occipital lobe, postcentral gyrus, paracentral lobule, and most of the cingulate gyrus. As with temporal and frontal lobe, many of these regions showed evidence of heritability of volume reductions. Cortical abnormalities in the cingulate might be a structural correlate of convergent reports of abnormal error-related processing in this region in schizophrenia.[57] Thus, while dorsolateral prefrontal and lateral temporal regions are generally the most strongly implicated in schizophrenia, morphometric effects were not exclusive to these regions, again mirroring findings using other methods, such as regional volumes.[1,24,36] This supports the idea that the predominant functional impairment of prefrontal and medial temporal structures in schizophrenia may not be exclusively due to localized structural-functional effects, but also mediated through the extensive interconnections that these regions maintain with the rest of the brain.[11,41,58] The majority of patients were treated with antipsychotic medications at the time of scanning. While supplemental analysis did not show any significant effects of medication use on cortical thickness (see the "Demographics" subsection in the "Results" section), it is impossible to fully rule

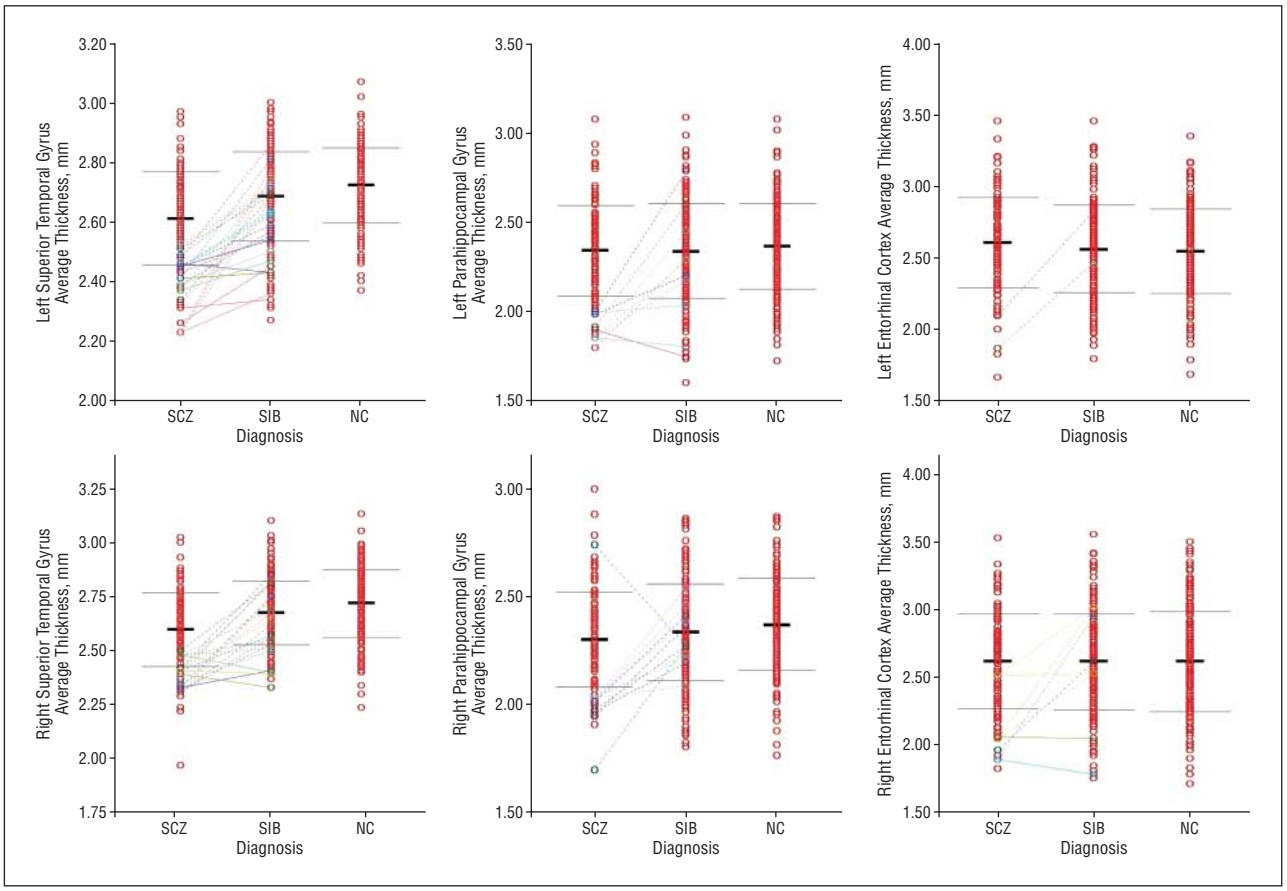

Figure 5. Average thickness distributions and heritability results for selected temporal regions. Similar to Figure 4, thickness distribution and heritability results are displayed for superior temporal gyrus, as well as regions of the medial temporal lobe (parahippocampal gyrus and entorhinal cortex), in which affected patients (SCZ) did not significantly differ from normal controls (NC). Red circles show the distribution of average thicknesses for subjects in each region, and error bars show the mean and standard deviation. Lines connect SCZ expressing each phenotype (ie, having scaled volumes >1.5 SDs from the mean in the direction of our hypothesis) to their unaffected siblings (SIB). Solid lines represent cases where the SIB also expressed the phenotype, whereas dotted lines indicate cases where the SIB did not. Risch λ tests (λ_s) revealed heritability for thickness reductions in left superior temporal gyrus, left parahippocampal gyrus, and right entorhinal cortex.

out medication effects in the context of this study design. Indeed, studies in monkeys treated long-term with antipsychotic drugs have demonstrated that cortical volume is reduced by these agents.[59]

The Risch λ, the measure of heritability used in this study, has previously been used in a variety of schizophrenia studies, including analyses of *N*-acetylaspartate level[60] and local brain volume,[36] among others. In a previous study, our group used this method in an analysis of brain morphology using automated subcortical segmentations. Importantly, while this study provided evidence for heritable reductions in cortical gray matter as a whole and hippocampus in particular, it also demonstrated that marked and well-replicated phenotypes such as ventricle and dorsal striatal enlargements (the latter of which has been linked primarily to use of typical antipsychotics) did not show increased relative risk using this measure,[36] illustrating that the Risch λ can be used to help dissect heritable disease-related factors from those that are environmental.[36]

In terms of cortical thickness, the Risch λ indeed showed evidence for heritability of thickness reductions in a wide variety of brain areas studied. Therefore, cortical thickness reduction as measured herein has a significant heritable component. Cortical thickness reductions do not necessarily reflect a loss of neurons but could also be related to a loss of local circuit connections and cortico-cortical connections through reductions in neuropil volume. This has indeed been suggested by previous postmortem studies of prefrontal cortex[61] and conforms with the "dysconnectivity" concept discussed earlier. However, postmortem evidence of cortical thickness reductions is not consistent and the possibility that changes observed with MRI reflect changes that are not related to cellular elements, eg, changes in fluid compartments or vascularity, cannot be ruled out. Methodologically, one strength of the present study is the large sample assessed through a reliable semiautomated technology. Even so, the robustness of the Risch λ varies depending on the distribution of thickness values in each region and can depend on very few siblings exceeding the chosen phenotype-defining threshold. However, even using an excessively stringent limit to the most robust analyses (for the sake of example, those containing ≥20 siblings), areas of marked heritability were seen throughout the brain. These included findings in left superior and middle temporal gyrus, rostral middle frontal gyrus, inferior frontal gyrus (opercular part), banks of the supe-

rior temporal sulcus, inferior parietal lobule, and posterior cingulate and right caudal anterior cingulate, highlighting the majority of regions hypothesized at the onset of the study. While the use of parcellation labels may have obscured effects that did not conform to gyral anatomy, we feel false negatives are unlikely given the multitude of our positive findings.

Widespread heritability of cortical thickness reductions alone does not demonstrate that reduced thickness is a reflection of the risk architecture of schizophrenia, because findings like the ones presented herein could also be obtained if the siblings of healthy subjects with thin cortices were examined. To show that reduced thickness is also a marker of increased genetic risk for schizophrenia, it has to be enriched in the sample of people who are at increased genetic risk for this disease, ie, the sibling group. In our data, thickness reductions in siblings did not exceed the chosen surfacewide threshold, although smaller studies[20-22] did find reductions in siblings, and in our sample, differences between the sibling and patient groups were consistently less pronounced than those between controls and patients, suggesting that siblings did occupy an intermediate position between patients and controls. Even larger samples might still uncover a significant reduction of thickness in healthy subjects at risk, or intermediate thickness reductions may be observed in subjects assessed to be at particularly high risk for the disorder.[62]

However, at the present time, while our data clearly show that reduced cortical thickness is heritable, our findings do not support the presence of thin cortex per se as a strong intermediate phenotype, or endophenotype, related to genetic risk for schizophrenia. This raises the question of the intermediate phenotype status of gray matter structure in schizophrenia in general. While the evidence is variable, some studies, including our own in this sample, have found heritable reductions in gray matter volume in first-degree relatives of schizophrenic patients. If it is accepted that volume can be reduced while thickness is unaltered in genetically high-risk individuals, this could indicate a reduction in cortical area, possibly as a signature of abnormal neurodevelopment, and it would be of interest to examine this feature of brain structure. If on the other hand one takes a more skeptical view of the literature regarding gray matter volume reduction, one could also conclude that gray matter structure, while heritable, lies outside the core genetic risk architecture of schizophrenia and would then be more related to peristatic and environmental effects related to illness state. In support of this latter skeptical view, significant structural differences in monozygotic twins discordant for schizophrenia are well established.[63,64] Further studies should examine the effects of specifically disease-related allelic variation on cortical thickness, analogous to studies performed using regional brain volume as the phenotype,[53,65-67] and investigate the effect of illness-related variables, such as treatment and duration of illness, on the phenotype in patients.

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