Cortical Brain Development in Nonpsychotic Siblings of Patients With Childhood-Onset Schizophrenia

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Context: Cortical gray matter (GM) loss is marked and progressive in childhood-onset schizophrenia (COS) during adolescence but becomes more circumscribed by early adulthood. Nonpsychotic siblings of COS probands could help evaluate whether the cortical GM abnormalities are familial/trait markers.

Objective: To map cortical development in nonpsychotic siblings of COS probands.

Design: Using an automated measurement and prospectively acquired anatomical brain magnetic resonance images, we mapped cortical GM thickness in healthy full siblings (n=52, 113 scans; age 8 through 28 years) of patients with COS, contrasting them with age-, sex-, and scan interval–matched healthy controls (n=52, 108 scans). The false-discovery rate procedure was used to control for type I errors due to multiple comparisons.

Setting: An ongoing COS study at the National Institute of Mental Health.

Participants: Fifty-two healthy full siblings of patients with COS, aged 8 through 28 years, and 52 healthy controls.

Main Outcome Measures: Longitudinal trajectories of cortical GM development in healthy siblings of patients with COS compared with matched healthy controls and exploratory measure of the relationship between developmental GM trajectories and the overall functioning as defined by the Global Assessment Scale (GAS) score.

Results: Younger, healthy siblings of patients with COS showed significant GM deficits in the left prefrontal and bilateral temporal cortices and smaller deficits in the right prefrontal and inferior parietal cortices compared with the controls. These cortical deficits in siblings disappeared by age 20 years and the process of deficit reduction correlated with overall functioning (GAS scores) at the last scan.

Conclusions: Prefrontal and temporal GM loss in COS appears to be a familial/trait marker. Amelioration of regional GM deficits in healthy siblings was associated with higher global functioning (GAS scores), suggesting a relationship between brain plasticity and functional outcome for these nonpsychotic, nonspectrum siblings.

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STRUCTURAL BRAIN ABNORMALITIES are an established feature of schizophrenia, characterized by decreased total gray matter (GM) volume reduction in the cortex, hippocampus, and amygdala.[1-4] Regional analyses of cortical GM, using either voxel-based morphometry or cortical thickness measures, show that most cortical GM deficits in schizophrenia are localized to the prefrontal and superior temporal cortices in adult patients with both first-episode and chronic disease.[5-7] However, it remains unclear whether the GM abnormalities in schizophrenia are familial/trait markers or are secondary to some aspect of the illness itself.[8-11] This can be addressed by studying populations at high risk for schizophrenia, typically close relatives, where most studies show smaller total and regional GM volumes[12-15] and total white matter volumes[16,17] and reduced GM volumes of the thalamus[18] and/or hippocampal-amygdalar complex.[15,19-22] However, as summarized in a recent meta-analysis,[23] the results have been inconsistent across studies with some studies showing no GM reductions in these populations.[24,25]

Several studies indicate greater brain abnormalities seen by magnetic resonance imaging (MRI) in symptomatic, high-risk subjects who arguably manifest early signs of the disorder. There are fewer studies that focus selectively on nonpsychotic full siblings of patients with schizophrenia. These have mostly measured whole-lobe brain volumes, and the results have been inconsistent,[23] finding no lobar GM deficits (mean [SD] sibling age, 35.8 [8] years)[26] or showing GM reduction in the frontal and temporal lobes (mean [SD] sibling age, 40.3 [5]

years).[27] To our knowledge, the only study to examine finer cortical GM density mapping analysis examined discordant monozygotic and dizygotic twins (20 pairs, mean [SD] age, 49 [3.9] years) and suggested that there were genetically influenced GM deficits in polar and prefrontal cortical regions and illness/environmentally based deficits in the parietal cortex.[14]

Gray matter loss in schizophrenia appears progressive over time[28-31] and is striking during adolescence for patients with childhood-onset schizophrenia (COS).[32,33] This progressive loss in COS probands plateaus and becomes more circumscribed to the prefrontal and temporal cortices by early adulthood,[34] at which time it mimics the pattern found in cortical thickness studies of adult schizophrenia. The longitudinal progression of GM loss in high-risk subjects remains largely unexplored. Although 1 study found progressive differences between high-risk subjects and controls at the 2-year follow-up,[12] to our knowledge, there are no reported studies examining progressive developmental brain changes specifically in healthy siblings of patients with schizophrenia. Siblings of patients with COS are of particular interest in this regard because the progressive nature of the GM deficits in the younger COS probands is striking and their younger-aged siblings (8-28 years) are in a period during which major brain changes are taking place.[35-38] Therefore, one would expect to find more striking, and perhaps earlier, developmental GM changes in siblings of patients with COS relative to those for siblings of patients with adult-onset disease, and if the cortical GM development is indeed under shared genetic control, one would expect siblings of patients with COS to show similar GM abnormalities and/or a similar pattern of cortical GM development over time.

As part of an ongoing COS study at the National Institute of Mental Health, all available full siblings of COS probands were scanned prospectively. Using serially acquired anatomical brain MRIs and an automated cortical thickness measurement, we report herein cortical GM development for 52 healthy siblings of patients with COS (113 scans) between ages 8 and 28 years, with no diagnosable psychotic or schizophrenia spectrum disorder or drug treatment, comparing them with 52 matched healthy controls (108 scans) matched for age, sex, and scan interval. We hypothesized that the "healthy" (defined as nonpsychotic and nonschizophrenia spectrum) siblings of patients with COS would share some pattern of GM loss with their probands and that this GM loss would be more striking than that seen in siblings of adult-onset cases. On an exploratory basis, we examined the developmental trajectories of these abnormalities in relation to their overall functioning as defined by their Global Assessment Scale (GAS) score.

METHODS

SUBJECTS

COS Probands

Since 1991, through national recruitment and prescreening of more than 2000 submitted case records and in-person screening of more than 230 subjects, 92 patients to date have met unmodified *DSM-III-R/DSM-IV* criteria for schizophrenia with onset of psychosis before their 13th birthday. Patients with a history of significant medical problems, substance abuse, or an IQ lower than 70 prior to the onset of psychotic symptoms were excluded. Further details of patient selection, including those for the COS sample used for comparison in this study, are described elsewhere.[39,40]

Siblings of Patients With COS

All available biological full siblings of patients with COS participated in the study and were scanned prospectively every 2 years along with their probands. Siblings were interviewed using structured psychiatric interviews for Axis I (using either the Schedule for Affective Disorders and Schizophrenia [SADS][41] or the Schedule for Affective Disorders and Schizophrenia for School-Age Children [K-SADS][42]) and Axis II (using the Structured Interview for the *DSM-III* Personality Disorders [SIDP][43]) diagnoses, and their GAS scores were estimated by a child psychiatrist.[44] Siblings were considered "healthy" if they were free of any psychotic or schizophrenia spectrum disorder (which included schizophrenia, schizoaffective disorder on Axis I, or paranoid, schizotypal, schizoid, or avoidant personality disorders on Axis II).[45] Additionally, symptom counts for all Axis II disorders were calculated both for individual disorders and also cumulatively for schizophrenia spectrum diagnoses. Of a total of 83 full siblings, 69 could be considered healthy, of which 52 had at least 1 MRI available for cortical thickness estimation. The remaining 17 were either not available for MRI (n=6), refused MRI (n=4), had metal objects in their body (n=3), or their scans could not pass the automated processing (n=4). To correlate GM cortical thickness with functional outcome, GAS scores were obtained on healthy siblings at the end of the study (mean [SD] age, 19.2 [7.6], at last interview) by a child psychiatrist.

CONTROL SUBJECTS

A group of 52 unrelated healthy controls was selected from a sample of community volunteers recruited as part of a prospective study of normal brain development and matched for sex, age, number of repeated scans, and scan interval. Controls were free of lifetime medical or psychiatric disorders as determined by clinical examination and standardized interview. Psychiatric illness in a first-degree relative was also exclusionary.[38]

The research protocol was approved by the National Institute of Mental Health institutional review board. Written informed consent was obtained from parents and controls and patients older than 18 years, and written informed assent was obtained from minors.

MRI ACQUISITION AND IMAGE ANALYSIS

Briefly, T1-weighted images with contiguous 1.5-mm slices in the axial plane were obtained using a 3-dimensional spoiled gradient recalled echo sequence in the steady state. Imaging parameters were echo time of 5 milliseconds, repetition time of 24 milliseconds, flip angle of 45°, acquisition matrix of 256 × 192, number of excitations equaled 1, and a 24-cm field of view. Head placement was standardized as previously described.[46] Magnetic resonance images were registered into standardized space using a linear transformation and corrected for nonuniformity artifacts.[47] Registered and corrected volumes were segmented with an advanced neural net classifier[48] and GM and white matter surfaces were fitted with a surface deformation algo-

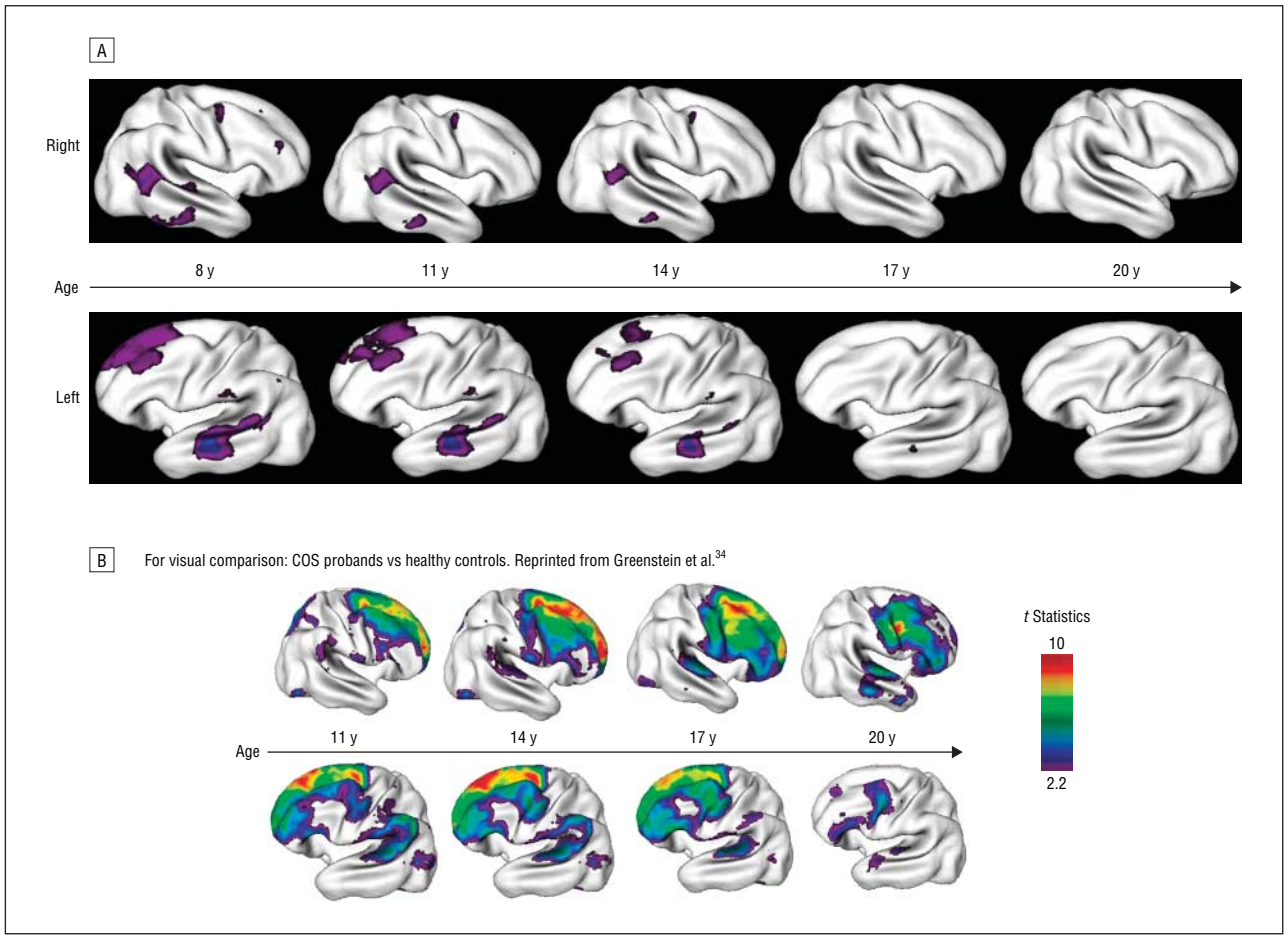

Figure 1. Cortical gray matter (GM) thickness of healthy siblings of patients with childhood-onset schizophrenia (COS) (A) and COS probands (B) vs age-, sex- and scan interval–matched healthy controls. A, Cortical GM thickness in healthy siblings of patients with COS (n=52; 113 scans) compared with healthy controls (n=52; 108 scans) between ages 8 through 28 years. Healthy siblings show significant GM deficits in the left prefrontal and bilateral temporal cortices and smaller deficits in the right prefrontal and inferior parietal cortices. These deficits in healthy siblings normalize with age, with no abnormalities remaining by age 20 years. The color bar shows the *t* statistic with the threshold to control for multiple comparisons using the false-discovery rate procedure with q=0.05. B, Gray matter thickness of COS probands (n=70; 162 scans) compared with healthy controls (n=72; 168 scans) between ages 7 through 26 years. Gray matter cortical thickness is adjusted for mean cortical thickness. These data are published elsewhere[34] (reprinted with permission from Blackwell Publishing) and are used here only for visual comparison with the GM developmental pattern in healthy siblings (Figure 1A).

rithm,[49,50] which first determines the white matter surface, then expands outward to find the GM–cerebrospinal fluid intersection. As a result, GM and white matter surfaces with more than 80 000 polygons each are fit and nonlinearly aligned using a template surface registration so each vertex of the white matter surface corresponds to a GM surface counterpart, thereby generating linked polygons on the GM and white matter surfaces.[51] Cortical thickness measurements, defined as the distance between linked vertices of the GM and white matter boundaries using a 30-mm surface-based blurring kernel (which has been shown to maximize statistical power), have been previously validated and were calculated in native space at 40 962 cortical points.[52]

STATISTICAL ANALYSIS

Statistical analyses examined the data from only the healthy siblings and their matched control groups. The COS data have been published elsewhere[34] and are shown (**Figure 1**B) only for visual comparison of GM changes between COS probands and healthy siblings of patients with COS.

Differences in sibling/control group demographics were tested using *t* tests or Mann-Whitney *U* tests (if assumptions were violated) for continuous variables, χ^2 tests of independence for categorical variables, and the Fisher exact test for categorical variables if there was an expected cell count less than 5. Mixed-model regression was used to examine cortical thickness development and was chosen over traditional methods (ie, repeated-measures analysis of variance, fixed-effects regression models) because it permits the inclusion of cross-sectional as well as longitudinal data, thus allowing multiple measurements per person, missing data, and irregular intervals between measurements, thereby increasing statistical power.[53] There were 14 siblings and 14 controls with only 1 scan and 38 siblings and 38 controls with more than 1 scan. Thirteen of 35 families contributed more than 1 sibling. Controls were unrelated. Because multiple siblings per family and multiple scans per person over time were included in the analyses, 2 random intercepts were included for all analyses: one intercept to model within-family dependence and one intercept to model person within-family dependence. The regression model was fit at every cortical point regressing cortical thickness against group, age (centered at the sample average age), and group × age. A straight-line fit was deemed adequate to model cortical thickness development because the combined contribution of quadratic age terms for both groups was not a significant contribu-

Table. Sample Demographics for Siblings of Patients With Childhood-Onset Schizophrenia and Healthy Controls

	Siblings (n = 52; 113 Scans)	Healthy Controls (n = 52; 108 Scans)	Test Statistic	*P* Value
Men/Women, No.	29/23	29/23	$\chi^2_1 = 0$	.99
No. of scans at			$\chi^2_3 = 0.54$	.92
Time 1	52	52		
Time 2	38	38		
Time 3	16	12		
Time 4	7	6		
Age at scan, y, mean (SD) [range]				
All scans	17.93 (7.35) [4.25-38.29]	17.48 (7.29) [4.16-39.39]	$t_{219} = 0.45$	.65
Time 1	16.21 (7.526)	16.26 (7.39)	$t_{102} = -0.03$	.97
Time 2	18.91 (7.21)	18.71 (7.16)	$t_{74} = 0.12$	.91
Time 3	18.76 (7.22)	21.29 (7.75)	$t_{26} = -0.88$	.39
≥Time 4	16.98 (4.95)	18.40 (4.47)	$t_{11} = -0.55$	.59
Cortical thickness (all scans),[a] mm, mean (SE)	4.38 (0.07)	4.36 (0.07)	$t_{85} = 0.31$	.75
Vocabulary scaled score, mean (SD)	10.87 (2.87)	10.80 (2.56)	$t_{88} = 0.13$	.87
Socioeconomic status[b]	53.94 (25.08)	44.55 (18.48)	$t_{100} = 2.15$	.03
Ethnicity			Fisher exact test = 2.33	.52
White	36	30		
African American	11	12		
Hispanic	2	5		
Other	3	5		
Comorbid Axis I disorders (lifetime) in nonpsychotic siblings				
Anxiety disorder	14			
Alcohol/substance abuse	14			
Behavioral disorder	10			
MR or LD	5			
Bipolar disorder	0			
Depressive disorder (major/minor depression, dysthymia)	31			

Abbreviations: MR, mental retardation; LD, learning disability.
[a] Results from mixed-effect regression, showing diagnostic differences after accounting for age effects.
[b] Socioeconomic status was measured using the Hollingshead scale.[55] Higher scores reflect lower socioeconomic status.

tor to the explanatory power of the model across the cortical surface after using a false-discovery rate correction. Cortical thickness was measured in native space and the siblings and controls did not differ in either total cerebral volume ($P=.30$) or mean cortical thickness ($P=.75$), based on mixed-effect regression contrasts of group intercepts at the average age. As such, we did not correct for interindividual differences in brain size.

To explore the relationship between cortical thickness and sibling functioning, cortical thickness was regressed on GAS score using GAS scores as a continuous measure and controlling for the effects of age, using all scans from siblings for whom we had obtained GAS scores (n=51) using the model:

cortical thickness = intercept + B1 (GAS score) + B2 (age),

where B1 is a fixed effect and presents the change in thickness associated with a 1-point change in GAS score (controlling for the effects of age). We also ran a model that interacted age and GAS score; however, for unknown reasons, this resulted in problems with model convergence for numerous vertices, and there were no significant interaction effects after we applied a false-discovery procedure. Scans with a mean cortical thickness value less than 2.0 (a cutoff chosen to exclude unrealistic values) were considered outliers and deleted from the sample. This resulted in 1 control scan being omitted because the mean cortical thickness (averaged across all 40 962 points) was less than 2.0 (an unrealistic value). One other control scan was of insufficient quality to yield cortical thickness measurements and could not be included.

We pooled *P* values for all terms excluding the intercept (age, diagnosis, and age × diagnosis) because none of the terms were considered confounds but rather effects of interest. We also chose this approach in an attempt to be more conservative by keeping the ratio of falsely rejected hypotheses to all rejected hypotheses at 0.05 (the q we chose for our false-discovery rate procedure) for each regression analysis rather than for 1 term in the model.[54]

AGE RECENTERING

These analyses entailed the same model as in the "Statistical Analysis" subsection but recentered age at approximate 3-year intervals within the middle 80% of the age range. This approach permits interpretation of the intercept and group differences at the centered age (instead of at age zero). It also permits maximal use of the entire data set without separating participants into age groups and thereby diminishing statistical power. Thus, the differences that are visually represented at different ages are essentially snapshots of the differences between the 2 groups' regression lines at the specified age, where all scans are informing all pictures in Figure 1.

RESULTS

Sample demographics are shown in the **Table**. As seen in the Table, the samples are well matched on all the variables with the exception of socioeconomic status, which was lower for siblings of patients with COS than for the unrelated healthy controls ($P=.03$)

There were no significant mean cortical thickness differences between the healthy siblings and their matched controls. When cortical GM development was visual-

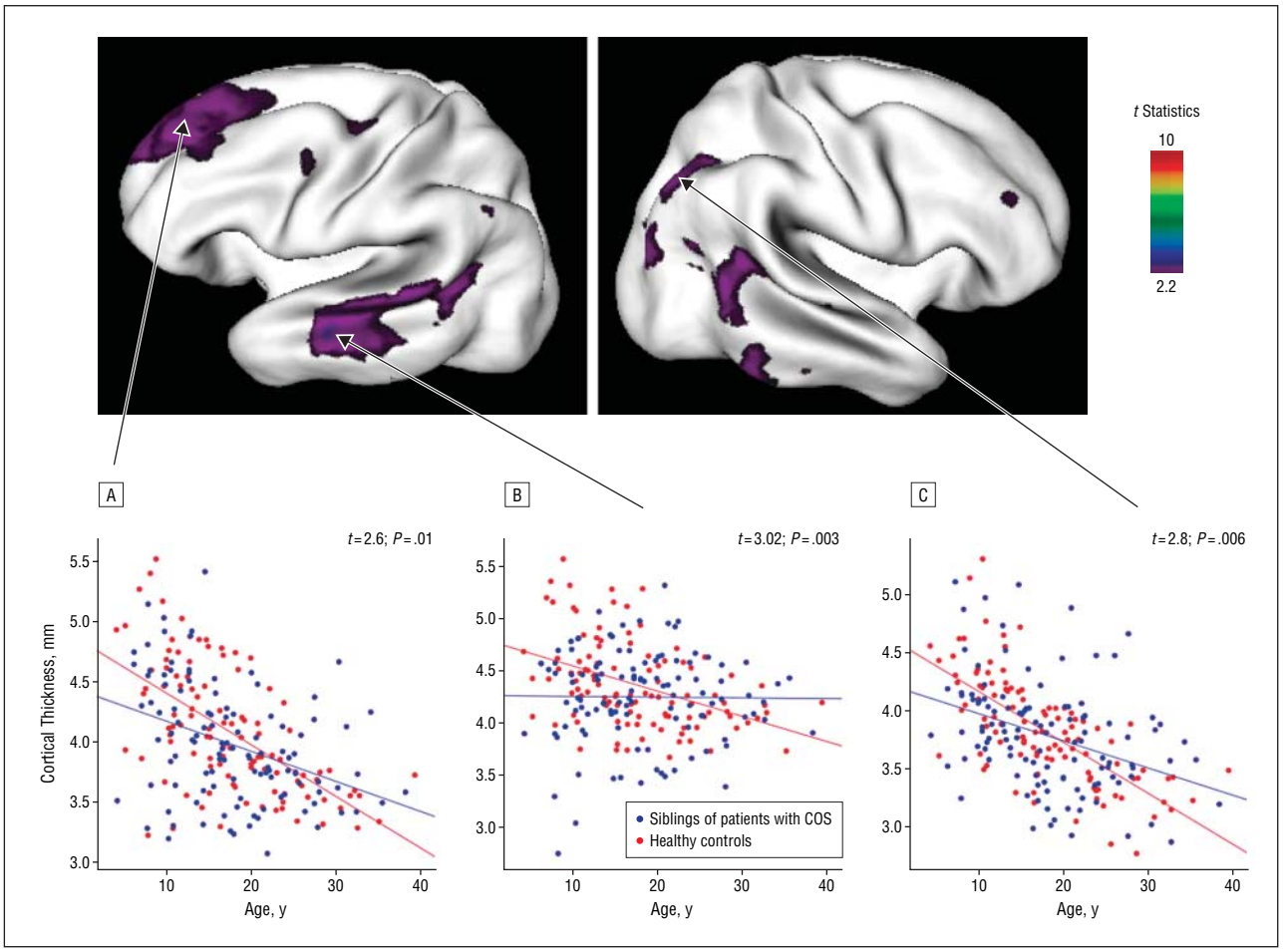

Figure 2. Longitudinal trajectories (slopes) of selected regional cortical gray matter thickness in siblings of patients with childhood-onset schizophrenia (COS) compared with those for the same regions for healthy controls, showing group × age interaction effects. Siblings of patients with COS "normalize" by age 20 years (by slower thinning) in the prefrontal (A) and superior temporal (B) cortices and by age 17 years in the inferior parietal cortex (C). The graphs represent region of interest analyses at selected regions. The color bar shows the *t* statistic with the threshold to control for multiple comparisons using the false-discovery rate procedure with q=0.05.

ized between ages 8 and 28 years, healthy siblings showed a more restricted pattern of GM loss compared with their probands, which was still localized to the prefrontal and superior temporal cortices (Figure 1). The GM deficits appeared at age 8 years, mainly in the prefrontal (superior and middle frontal gyri) and temporal cortices (superior and middle temporal gyri), most prominently on the left side, but gradually lessened through adolescence and disappeared by age 20 years (Figure 1). There was no significant parietal GM loss except for a small region in the inferior parietal cortices (Figure 1, left side of the brain, and **Figure 2**C), which was not apparent by age 17 years (Figure 2C).

Analyses of GM trajectories of COS probands (compared with matched controls) are provided in Figure 1B. These are published elsewhere[34] and shown here only for visual comparison of the patterns.

Visual comparison of the GM deficit patterns of patients with COS and siblings of patients with COS over time shows a broad pattern of early deficits, which somewhat improve with age and localize to the prefrontal and temporal cortices in patients with COS but disappear in healthy siblings by age 20 years (Figure 2). The GM developmental trajectory appears to be shifted to earlier ages (shift to left) in healthy siblings of patients with COS possibly because the controls have a steeper slope of GM loss than in the siblings in these areas (Figure 2).

When cortical thickness was regressed with GAS scores of healthy siblings, significant positive relationships between GAS score and thickness were noted. Cortical thickness increased with higher GAS scores in the bilateral frontal and temporal cortices (**Figure 3**). Additionally, the GAS scores also showed positive correlation with the mean cortical thickness at initial scan in healthy siblings.

COMMENT

This is a prospective study mapping longitudinal GM development in healthy siblings of patients with COS in spatiotemporal detail. This sample was of particular interest because the age range (8-28 years) encompassed periods of active brain development and organization. Beginning at an early age, healthy siblings of patients with COS showed GM loss, which did not progress during adolescence (unlike the progression seen in COS probands) and disappeared by age 20 years. The GM loss in siblings was most prominent in the prefrontal and tem-

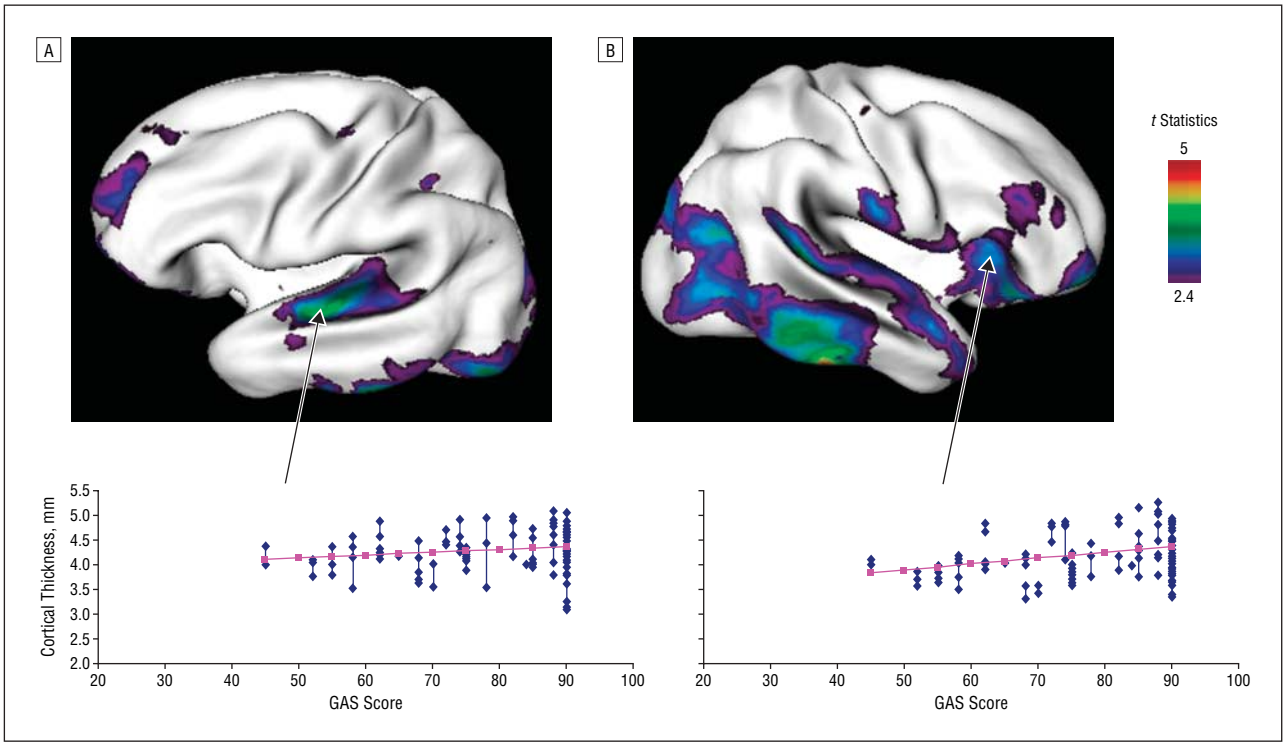

Figure 3. Within-group analyses of the relationship between gray matter (GM) cortical thickness and Global Assessment Scale (GAS) scores. The areas of cortex that display a positive relationship between GM cortical thickness and GAS score obtained by regressing GM cortical thickness with GAS scores are shown. The graphs show an increase in cortical thickness with higher GAS scores using region of interest analyses. The color bar shows the *t* statistic with the threshold to control for multiple comparisons using the false-discovery rate procedure with q=0.05. A, Left superior temporal gyrus as the region of interest. GAS score slope, *P*=.09. B, Right inferior frontal gyrus as the region of interest. GAS score slope, *P*=.008.

poral cortices as has been seen in COS probands, but unlike that seen in probands, siblings did not show parietal GM loss at younger ages (except for a small region in the inferior parietal cortex). This GM loss in siblings of patients with COS appeared more prominent than that seen for the discordant dizygotic twin sample in the Cannon et al study,[14] which also used fine GM density mapping, although comparisons across methods cannot be quantified. Furthermore, although the GM deficits in healthy siblings did not progress in a "back-to-front" pattern, seen in COS probands, visual comparison of the process of age-related amelioration of deficits did follow a somewhat similar pattern in both probands and siblings. This leads us to speculate that the younger age of our sibling group and lack of associated schizophrenia spectrum pathology may account for this plastic response (apparent inhibition of cortical thinning) in siblings as supported by the fact that within the healthy sibling group, cortical thickness increased with higher overall functioning as measured by the GAS.

Young, nonpsychotic siblings of patients with COS showed GM deficits mainly in the prefrontal and superior temporal cortices, regions with the most consistent cortical thickness deficits in adult subjects with schizophrenia[5-7,56,57] and where GM deficits remain in COS probands as they become young adults.[34] Prior studies in high-risk populations show cortical GM deficits[12,19,58,59] that correlate with later development of psychosis,[12,60,61] and unaffected first-degree relatives (including siblings and twins) also exhibit GM deficits.[14,23,62-66] Fewer studies have focused specifically on siblings and report a modest smaller total GM volume (effect size, 0.18; 95% confidence interval, 0.01-0.35) but better agreement on decreased volume of the hippocampus or hippocampal-amygdalar complex.[15,18,20,22,23,26,27,67] The findings for regional cortical GM deficits, however, remain inconsistent. For instance, as seen in some studies of unaffected relatives[13] and our pilot study on healthy siblings,[68] Cannon et al[27] found frontal and temporal GM loss in siblings, while others have found no reduction in individual lobar GM volumes.[25,26] Because the healthy siblings in this study show no phenotypic manifestations of the illness, GM abnormalities in the frontal and temporal regions are most likely to be familial/trait markers influenced by shared genetic factors. On the other hand, siblings showed minimal GM deficits in the parietal cortex, only at early ages and with little overlap with that seen for COS probands (Figure 1B), suggesting that GM loss for most of the parietal cortex (with the possible exception of the inferior parietal region) may be more under environmental- or illness-related influence. These findings are supported by the only comparable study, to our knowledge, of cortical mapping in discordant dizygotic twins with schizophrenia where prefrontal and polar cortices showed strong genetic liability while the parietal cortex appeared illness related.[14]

The degree of cortical normalization by age 20 years in siblings is surprising. Prior adult studies on high-risk populations and first-degree relatives show GM deficits

well beyond age 20 years. There could be several reasons for this. In most adult sibling studies, brain abnormalities are most consistently seen in deeper cortical structures, which were not measured in the current study. The 2 prior adult sibling studies (both from the same group) that showed frontal and temporal GM deficits at later ages using either whole-lobe measures in siblings[27] or cortical density maps in discordant twins[14] (mean [SD] age, 40.7 [5.8] and 48.3 [2.9] years, respectively) included siblings with schizophrenia spectrum disorders in their analyses, which may have influenced their GM findings. Although subanalysis suggested this not to be the case in 1[27] of these 2 studies, our unpublished data suggest that the GM deficits in "spectrum siblings" (n=12, 20 scans vs 40 controls with 61 scans) are more robust than those seen in healthy siblings and indeed appear to normalize at a later age (N.G. et al, unpublished data, 2007). Finally, in COS probands, the GM developmental trajectory appears to show a "shift to left" (deficits appearing in early ages, which improve by young adult age) compared with the adult subjects with schizophrenia with early parietal GM loss progressing during the adolescent years with relative improvement and localization to the adult pattern of frontal and temporal GM loss as subjects mature. It is possible that siblings of patients with COS may be showing a similar pattern of GM development as evidenced by early GM loss and early normalization. Thus, it may be possible that longer-term follow-up of high-functioning healthy adult siblings of patients with schizophrenia will ultimately show similar normalization of the deficits.

When cortical thickness was regressed with overall GAS scores, GM thickness increased with higher GAS scores, most prominently in bilateral prefrontal and temporal cortices (Figure 3). This direct relationship between normalization of cortical thickness and GAS scores would suggest that in the absence of core schizophrenia spectrum pathologic features or other confounding factors such as medication exposure, restitutive "normalization" of GM deficits (particularly in the prefrontal or temporal areas) in healthy siblings is closely related to their overall functioning. Better social and cognitive "competence" is associated with normalization (by inhibition of the regional GM loss). Whether this relationship between GM thickness and GAS score reflects cause or effect, or influence of yet another factor, remains unknown.

There are several limitations to this study. Many of our healthy siblings are not yet past the age of risk for schizophrenia (28 siblings were still younger than 20 years at last scan) and age at onset for Axis II disorders remains, for the most part, undetermined. However, the uniquely stringent definition of "healthy" in this group makes it unlikely that they will develop a psychotic or schizophrenia spectrum illness (mean [SD] age at last interview, 19.2 [7.6] years) and their GM deficit normalization may reflect this fact. Second, while all subjects had 2 scans, relatively few had 3 or more scans. Thus, although partially longitudinal, the group of siblings did not overlap with those at younger ages and the study remains susceptible to unknown cohort effects. Ongoing studies of new and extended follow-up of healthy siblings as well as siblings with schizophrenia spectrum diagnoses, which also include mapping of the deeper cortical structures, will continue to address some of these issues.

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