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Severity of Cortical Thinning Correlates With Schizophrenia Spectrum Symptoms

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Abstract

Objective—This study investigated the relationship between regional cortical gray matter thinning and symptoms of schizophrenia spectrum personality disorders (PDs) in siblings of patients with childhood-onset schizophrenia (COS).

Method—66 siblings of patients with COS were assessed for symptoms of schizophrenia spectrum PDs (avoidant, paranoid, schizoid, schizotypal). Structural magnetic resonance images were obtained at approximately 2-year intervals from the siblings and from 62 healthy volunteers, matched for age, sex, ethnicity, and handedness. Cortical thickness measures were extracted. Mixed effect regression models were used to test the relationship between symptoms and cortical gray matter thickness. Cortical thinning was also tested longitudinally in healthy volunteers and siblings.

Results—Cortical thinning was found to correlate with symptoms of schizotypal and, to a lesser extent, schizoid PDs. Thinning was most pronounced in the left temporal and parietal lobes and right frontal and parietal regions. Gray matter loss was found to be continuous with that measured in COS. Longitudinal thinning trajectories were found not to differ between siblings and healthy volunteers.

Conclusion—The present investigation of cortical thinning in siblings of patients with COS indicates that symptoms of schizophrenia spectrum PDs correlate with regional gray matter loss. This finding supports the idea of cortical thinning as a schizophrenia endophenotype.

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Keywords

schizophrenia spectrum; cortical thinning; childhood-onset schizophrenia; psychosis; schizotypal personality disorder

INTRODUCTION

The concept of schizophrenia and other psychotic illnesses as categorical entities has increasingly yielded to the notion of psychosis as a dimensional construct.[1] Genetic, neural, and behavioral features are shared across diagnostic lines, and diseases do not fall into the binary categories of “present” and “absent.” The need for a dimensional approach is particularly clear in childhood-onset schizophrenia (COS), defined as onset of symptoms before age 13, as this form of the illness is accompanied by highly prevalent familial abnormalities.[2-4] The presence of a range of symptoms along the schizophrenia spectrum in COS family members highlights the dimensional nature of schizophrenia.

One way to investigate the range of psychosis from a neurobiological perspective is to measure structural brain changes in patient groups with varying levels of psychosis severity. In previous research, we described the incremental relationship between psychosis symptomatology and gray matter (GM) deficits in children with psychopathology without evidence of psychosis, psychosis not otherwise specified (PNOS) without Axis I comorbidities, PNOS with other Axis I diagnoses, and COS.[5] Our results showed increasing gray matter deficits corresponding with increased levels of psychosis, with patients with COS exhibiting the most significant thinning.

To further assess the biological underpinnings of psychosis dimensionality, siblings of patients with COS may be of particular interest due to the shared genetic makeup between relatives. Siblings of patients with schizophrenia have a greater genetic liability for schizophrenia than the average population, which may contribute to higher than average levels of psychosis symptomatology.[6,7] Indeed, siblings of adult patients with schizophrenia have been found to have higher rates of all schizophrenia spectrum personality disorders (PDs) than siblings of healthy volunteers.[8] However, despite the shared genetic profile and some symptomatology in siblings, the siblings do not develop schizophrenia. Determining whether phenotypes such as abnormal brain structure are present in both patients and siblings can help indicate whether the abnormalities are trait markers (endophenotypes) or disease-related.[9]

Our group has assessed biological evidence of increased genetic liability to schizophrenia over the course of development in siblings of patients with COS who are free of any psychotic or schizophrenia spectrum disorder, including schizotypal, schizoid, paranoid, or avoidant PDs.[10] In COS, GM loss in the prefrontal and superior temporal cortices and in parietal regions progresses through adolescence until reaching a plateau in early adulthood. In siblings without psychosis, we detected thinning in prefrontal and superior temporal areas, which gradually lessened over the course of adolescence and disappeared by age 17. In a follow-up study, we confirmed that GM loss in siblings without psychosis converges with that seen in control participants, with thinning in controls being an expected function of

age.[11] This neurodevelopmental trajectory implicates early prefrontal and temporal GM deficits as potential endophenotypes in COS, and the cortical normalization in siblings without psychosis between childhood and late adolescence may suggest the presence of protective factors preventing the development of psychosis.[12]

The current study returned to assessing cortical thinning in siblings, but with an emphasis on the symptomatology that some siblings do show rather than a focus on the absence of psychosis in siblings. We performed an analysis of GM deficits in siblings as they relate to symptoms of schizophrenia spectrum PDs: schizotypal, schizoid, paranoid, and avoidant. Siblings with psychotic disorders on Axis I were not included in the analysis, but a diagnosis of a schizophrenia spectrum PD did not disqualify sibling participants. We had previously seen that siblings who neither exhibit psychosis nor have a PD diagnosis display GM loss through early adolescence. For siblings who show behavioral features along the psychosis spectrum, we hoped to determine whether those features increase proportionally to the severity of GM reductions, and whether the trajectory of thinning over time is the same as seen in previous studies. We hypothesized that gray matter reductions would increase in severity along with increasing symptoms on the psychosis spectrum, most likely in frontal and temporal cortical areas. We further hypothesized that the spectrum disorder symptoms closest to those of the schizophrenia phenotype (i.e., schizotypal PD symptoms)[13,14] would show the strongest correlation between symptom count and schizophrenia-like GM abnormalities.

METHOD

Participants

Participants included 66 full siblings of patients with COS recruited in a longitudinal study of the disorder that has been ongoing since 1991 at the National Institute of Mental Health. Siblings have been followed since the initial admission of their relatives with COS. Selection and exclusion criteria for the COS study have been described elsewhere.[10,15] Siblings were excluded for psychiatric diagnoses of autism, schizophrenia, bipolar disorder, or other primary psychotic disorders, but not for any schizophrenia spectrum PD diagnoses (only diagnosable in those age 18 and older). Siblings were included in analysis if they had complete *DSM-III* or *DSM-IV* Axis II symptom ratings and at least one structural magnetic resonance imaging (MRI) scan that displayed no significant motion artifacts upon visual inspection.

Participants also included 62 healthy volunteers (HVs) who were matched with sibling participants for age, sex, and socioeconomic status (SES). HVs and siblings were also matched for vocabulary score, which was used as a proxy for IQ. Vocabulary was assessed using the Wechsler Adult Intelligence Scale–Revised (WAIS-R), Wechsler Intelligence Scale for Children–Revised (WISC-R), WAIS-III, WISC-III, Wechsler Preschool and Primary Scale of Intelligence–III (WPPSI-III), or Wechsler Abbreviated Scale of Intelligence (WASI), depending on which was both most current at the time of interview and age-appropriate for the participant. Healthy volunteers were recruited from the community and screened for neurological and psychiatric illnesses, as described by Giedd et al.[16] These participants were included for the purpose of examining whether this sibling cohort followed

the same age trajectory as in our previous studies, which showed that cortical thinning in COS siblings without psychosis normalizes relative to that of controls by late adolescence.[11]

Symptom Assessment

Schizophrenia spectrum symptoms were assessed once per participant using either the Structured Interview for DSM-IV Personality (SIDP-IV) or the Structured Clinical Interview for DSM-III Axis II Disorders (DSM-III SCID-II), depending on which version was more current at the time of interview.[17,18] Symptoms included in this analysis were those of the schizophrenia spectrum PDs: avoidant, paranoid, schizoid, and schizotypal.[7,8] Similar symptoms between disorders were not excluded in the total symptom count analysis, allowing for a maximum possible total symptom score of 28 symptoms, with 7 constituting avoidant PD, 5 for paranoid PD, 7 for schizoid PD, and 9 for schizotypal PD.

To ensure that possible results were not better accounted for by comorbid, non-spectrum symptomatology, sibling participants were also assessed for Axis I symptoms according to the Structured Clinical Interview for DSM-IV-TR Axis I Disorders (SCID) or the Kiddie-Schedule for Affective Disorders and Schizophrenia-Present and Lifetime Version (K-SADS-PL), depending on which was age-appropriate for the participant.[19,20]

Image Acquisition and Processing

Participants were scanned on a 1.5-T MRI scanner (Signa; General Electric, Milwaukee, WI, USA) at the National Institutes of Health Clinical Center in Bethesda, Maryland. 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 as previously described,[21] with the following imaging parameters: echo time 5 milliseconds, repetition time 24 milliseconds, flip angle 45°, acquisition matrix 256 × 192, number of excitations 1, and field of view 24 cm. Cortical surface extraction was carried out using the Montreal Neurological Institute (MNI) CIVET pipeline, version 1.1.10, and raw scans were masked using the Brain Extraction Tool method.[22] Magnetic resonance images were registered into standardized stereotaxic space (MNI-ICBM152 non-linear sixth generation symmetric target) using a nine-parameter linear transformation and corrected for non-uniformity artifacts.[23] Effort was made to obtain follow-up scans for each patient and their immediate family every 2 years after initial admission to the NIMH study. Each participant in this analysis had up to 5 scans at 2-year intervals. T1-weighted scans were visually inspected for artifacts by a trained rater, and only those with the highest quality control rating were included in analysis. Cortical surfaces were inspected for quality assurance using the verify and CLASP output of CIVET.

Statistical Analysis

Demographic differences between the HV group and the matched sibling group were assessed using t-tests for continuous variables and chi-square tests for categorical variables.

Mixed effect regression models were used to test the relationship between symptoms and cortical GM thickness at each of the 40,962 GM points per hemisphere using the number of symptoms to predict variance in GM and controlling for age and sex. As some siblings were

from the same family and most participants had multiple scans, each analysis included two random intercepts, one to model within-family dependence and one for within-person dependence. Mixed model analyses were conducted in R using the nlme (Linear and Nonlinear Mixed Effects Models) package.[24] Type I error was controlled per hemisphere and per analysis using the false discovery rate (FDR) procedure with q set at 0.05.[25] This approach controls the FDR within a set of results corresponding to a model and does not control the FDR globally across all models with a single threshold. Analyses were conducted for symptom counts of each schizophrenia spectrum PD, total symptoms across all PDs, each Axis I diagnosis, and total symptoms across all Axis I diagnoses.

In order to examine whether our sibling cohort had any differences in age-related GM trajectory from that which our group previously observed, we performed a mixed effects regression model at each cortical vertex, with GM thickness as the dependent variable. Fixed effects included group, age (centered at the average age for the sample), group × age, and sex. For this analysis, we included only scans for which participants were between the ages of 10 and 30, as the limited data beyond this range might have led to unreliable results.

RESULTS

Demographics

Of the 66 siblings included in analysis, 50% were female (Table 1). At the time of symptom assessment, siblings ranged in age from 14.82 to 33.44 (mean = 20.20, SD = 3.71). Each participant was scanned at up to 5 different time points at 2-year follow-up visits, resulting in each sibling having an average of 2.44 scans (range = 1 to 5, SD = 1.33). The mean age at first scan was 18.44. Of 225 total sibling scans of sufficient quality, 161 corresponded to participants with complete SIDP ratings.

Sibling participants had an average of 2.88 total schizophrenia spectrum PD symptoms (SD = 3.40), ranging from 0 to 14 with a median of 2. Means, SDs, and ranges for the individual PDs were as follows: avoidant, 0.76 (1.30), 0-6; paranoid, 0.56 (1.02), 0-5; schizoid, 0.82 (1.26), 0-6; schizotypal, 0.74 (1.21), 0-5. Medians were 0 for each individual PD. There was no relationship between age and symptom counts ($r = 0.02$, $p = .9$).

For the age trajectory analysis, scans were included if the participant was between ages 10 and 30 at the time of the scan. Excluding scans outside this range left 63 siblings (137 scans) and 62 healthy volunteers (138 scans) (Table 1). The 62 HVs and 63 siblings were matched for age, sex, and vocabulary score. The sibling group had lower SES (p = .03), but when we included SES as a covariate in the analyses comparing HV and sibling longitudinal cortical thickness, the pattern of results was the same (data not shown).

Gray Matter and Schizophrenia Spectrum Symptoms

Schizotypal PD symptoms were significantly negatively associated with gray matter thickness (more symptoms = thinner cortex) in the left inferior temporal lobe, left paracentral lobule, right prefrontal cortex, and bilateral supramarginal gyri (Figure 1). Symptom counts for schizoid PD were also significantly negatively associated with gray matter except in a small area located in the left inferior temporal lobe. Symptoms of

avoidant and paranoid PDs were not significantly associated with cortical thickness (data not shown).

To test the stability of the relationship between schizotypal PD symptom counts and gray matter, we limited the data to the single scan closest in time to each participant's symptom rating (median time between symptom assessment and scan = 3 months). Using only one scan per participant, rather than multiple longitudinal scans, did not substantially alter the results, leaving significant correlations in the left inferior temporal lobe and right prefrontal cortex.

To ensure that the schizotypal PD results were not artifacts of relationships with global brain measures, we controlled for total brain volume and mean cortical thickness in two separate analyses using all scans. The results of these two analyses were very similar, yielding slight reductions in the strength of results but no meaningful alteration in the overall pattern of results.

To make sure the relatively few observations associated with five schizotypal PD symptoms were not unduly influencing the relationship with cortical thickness measures, we also tested the schizotypal PD effect by making the schizotypal PD symptom variable an ordered factor with counts equal to 0, 1, 2, or 3+. The general pattern of results was the same with the exception of the small area in the right prefrontal cortex.

Thinning was visually compared with that seen in childhood-onset schizophrenia. COS gray matter loss was analyzed by our group in 2012 using a cohort of patients who were scanned close to the time of diagnosis.[5] Demographic characteristics of the COS cohort were similar to that of the current participant groups, with the exception of age, which was lower for the COS patients. Scans were collected using the same 1.5-T scanner as in the current study. The COS analysis used a general linear model to test for differences in cortical thickness from controls. Figure 1 reveals that the frontal and temporal areas associated with symptoms of schizotypal PD reported above tend to overlap with areas of thinning seen in COS, with the exception of the left paracentral lobule.

The relationship between cortical gray matter thickness and Axis I symptoms was also examined to ensure that Axis I conditions (depression; anxiety; mood disorders, comprising the sums of depression, mania, and hypomania symptoms) did not better account for the relationships between spectrum symptoms and gray matter. Mood and depression symptoms had significant negative (more symptoms = thinner cortex) relationships with GM. However, there was no spatial overlap between these findings and the aforementioned findings for schizoid PD symptoms, schizotypal PD symptoms, and COS (data not shown). No significant GM associations were found for anxiety disorder symptoms.

Sibling Versus HV Cortical Gray Matter Trajectories

We next asked if this group of siblings had patterns of developmental GM loss similar to what we previous reported in nonpsychotic siblings, with attenuated loss in the left inferior temporal lobe and right prefrontal cortex relative to controls.[11] Results showed no difference

in either the height or the slope of the trajectories between the sibling and HV groups in the hypothesized regions.

DISCUSSION

In this study of cortical thinning in siblings of patients with COS, we found that symptoms of schizoid and schizotypal PDs correlate with gray matter deficits. These deficits in cortical thickness are similar to, but less striking than, those found in COS, with the most notable coincidence of GM loss correlating with schizotypal PD symptoms and localized to the left inferior temporal lobe and bilateral inferior parietal regions, particularly the supramarginal gyri. By considering the current work in light of our group's previous research, it is clear that schizophrenia spectrum disorders present anatomically on a gradient with PNOS and COS.[5]

The continuity of cortical thinning between participants who display symptoms of schizotypal PD and those with COS supports the perspective of psychosis as a dimensional construct. Our current findings extend those of our own group and other researchers who established continuity across clinical populations with schizophrenia and related disorders in terms of, for example, sensory gating[26] and white matter integrity.[27] The variety of techniques used to place disorders like schizotypal PD on a gradient with schizophrenia indicates that the “spectrum” nature of psychosis applies across modalities.

Our finding of the most severe cortical deficits correlating with schizotypal PD is in accordance with our hypothesis. Of all the PDs examined, only in schizotypal PD do people experience “unusual perceptual experiences” and “odd thinking and speech,”[28] which align with the pronounced psychotic symptoms of schizophrenia. The inferior parietal lobule has been implicated in both perceptual dysfunction and thought disorder in schizophrenia,[29-31] so the thinning in the supramarginal gyrus in schizotypal PD may similarly be the locus of the perceptual abnormalities and odd thinking frequently reported in the disease.

Connections have been made between populations with schizophrenia and those who are healthy but at high risk. Researchers use first-degree relatives to investigate which elements of schizophrenia are state markers—tied to the disease itself—and which are trait markers, derived from genetic factors that have some relation to the disease but not necessarily indicative of the presence of the illness.[9] Work with siblings has given conflicting results regarding cortical thickness, sometimes indicating no difference from control participants[32,33] or decreases even greater than those in schizophrenia.[9,34] The discrepancies in findings indicate a need to account for the range in symptom presentations in siblings, a concern that our work addresses.

Cortical thinning can be present without schizophrenia, which raises the question of what differentiates members of a family who develop schizophrenia from those who do not. One hypothesis is that siblings possess neuroprotective factors that prevent the development of psychosis. Alternately, siblings may lack additional factors that promote psychosis. The existence of neuroprotective factors is still largely hypothetical, but research has begun to implicate particular genes that may promote psychosis if mutated. These include the major histocompatibility complex region on chromosome 6[35,36] and, particularly in childhood-

onset schizophrenia, 22q11.[36,37] Heat shock proteins have been shown to be involved in neuroprotection; antibodies against them may inhibit that protection.[38] These examples of factors that may be involved in the development of schizophrenia, or in the maintenance of health, indicate the wide range of relevant biochemistry and the breadth of work that remains to be done.

Our age trajectory analysis indicated no differences in cortical thickness changes over time in frontal and temporal areas in this sibling sample relative to HVs. As the goal of this study was to look at GM as it related to symptoms of schizophrenia spectrum PDs, we excluded young siblings who had not been rated for symptoms at any study visit. As a result, the age range for the current study (10-30) is slightly higher than that of the cohort previously studied by our group (5-26),[11] and there was a much lower density of younger scans in the current sample (sibling average age at scan 1 for this study was 18.44, while for the prior study, the average age at scan 1 was 13.36). The reduced number of scans at earlier ages likely diminished our power to detect earlier GM differences.

Limitations of this study included the lack of longitudinal data for symptom counts, preventing us from assessing the relationship of changes in symptom count to changes in gray matter thickness over time. PDs are defined as being “stable over time,”[28] so it is possible that PD symptoms are similarly stable, which has been corroborated by recent evidence in schizotypal PD.[39] Since PDs are not typically diagnosed for young teenagers, their stability between adolescence and adulthood has not been ascertained. Some work has shown moderate stability in schizotypal PD symptoms between early (ages 11–13) and middle (ages 14–16) adolescence.[40] Other work bridged the gap between adolescence (age 16) and adulthood (age 25) in high-risk and non–high-risk populations, showing moderate to high predictive value of schizotypal features at the first time point in predicting symptoms at the second point.[41] In our sample, PD symptom counts were generally taken in the late teenage years or later; mean age at symptom assessment was 20.20 with an SD of 3.71. We can expect symptoms in our cohort to be moderately stable, which still leaves considerable room for change over time. It would be illuminating to determine whether individuals’ symptom trajectories match gray matter trajectories, which would bolster the evidence for the two factors being causally connected.

Another limitation deriving from our lack of follow-up data on symptoms is that we do not have formal evidence that our participants did not go on to develop psychosis. However, any sibling who presented with a diagnosed psychotic disorder at any follow-up visit was excluded from the study. This does not preclude the possibility that some siblings might still end up becoming psychotic in the future.

Our sample of siblings in the age trajectory analysis had a low density of younger scans, limiting our ability to detect differences in gray matter between siblings and controls at younger ages.

When we tested the effect of schizotypal PD symptoms by making it an ordered factor with counts equal to 0, 1, 2, and 3+, the pattern of results was the same with the exception of the

small area in the right prefrontal cortex (PFC). As such, we have less confidence in the right PFC finding.

The resolution of our anatomic images, obtained on a 1.5-T scanner in 1.5-mm slices, limited to some degree the precision of mapping of cortical thickness, which was unavoidable given the machine available for use throughout this longitudinal study.

Our results indicated that cortical thinning was not significantly correlated with symptoms of avoidant or paranoid PDs. As avoidant PD is sometimes grouped more with anxiety than psychosis,[28] the absence of cortical abnormalities in relation to avoidant PD symptoms was not surprising. As paranoid, schizoid, and schizotypal PDs are all typically associated with psychotic disorders, the lack of correlation between paranoid PD symptoms and GM loss was more unexpected. In our sibling cohort, the average number of symptoms for each of avoidant, schizoid, and schizotypal PDs was higher than the mean number of paranoid PD symptoms. The lower incidence of symptoms for paranoid PD could have prevented us from detecting a relationship with cortical thinning if one does exist.

Future directions for this work include the incorporation of information regarding genetic variants. Patients with COS carry a higher number of risk-related copy number variants (CNVs) than does the general population.[37] While the patients are more likely to carry CNVs than their siblings, some healthy siblings do possess these CNVs, indicating incomplete penetrance; future work could examine the relationship between CNVs and cortical thinning both in patients and in their relatives. Symptom counts in healthy volunteers suggest another fruitful avenue for future research, adding the dimension of cortical thickness in adolescents who are not at high risk to existing research on subclinical psychosis symptoms.[42,43] While one source of value in studying siblings is the shared genetic profile with patients with COS, examining people with no family history of schizophrenia can show the relationship between cortical abnormalities and schizophrenia spectrum symptoms in the absence of significant genetic loading.

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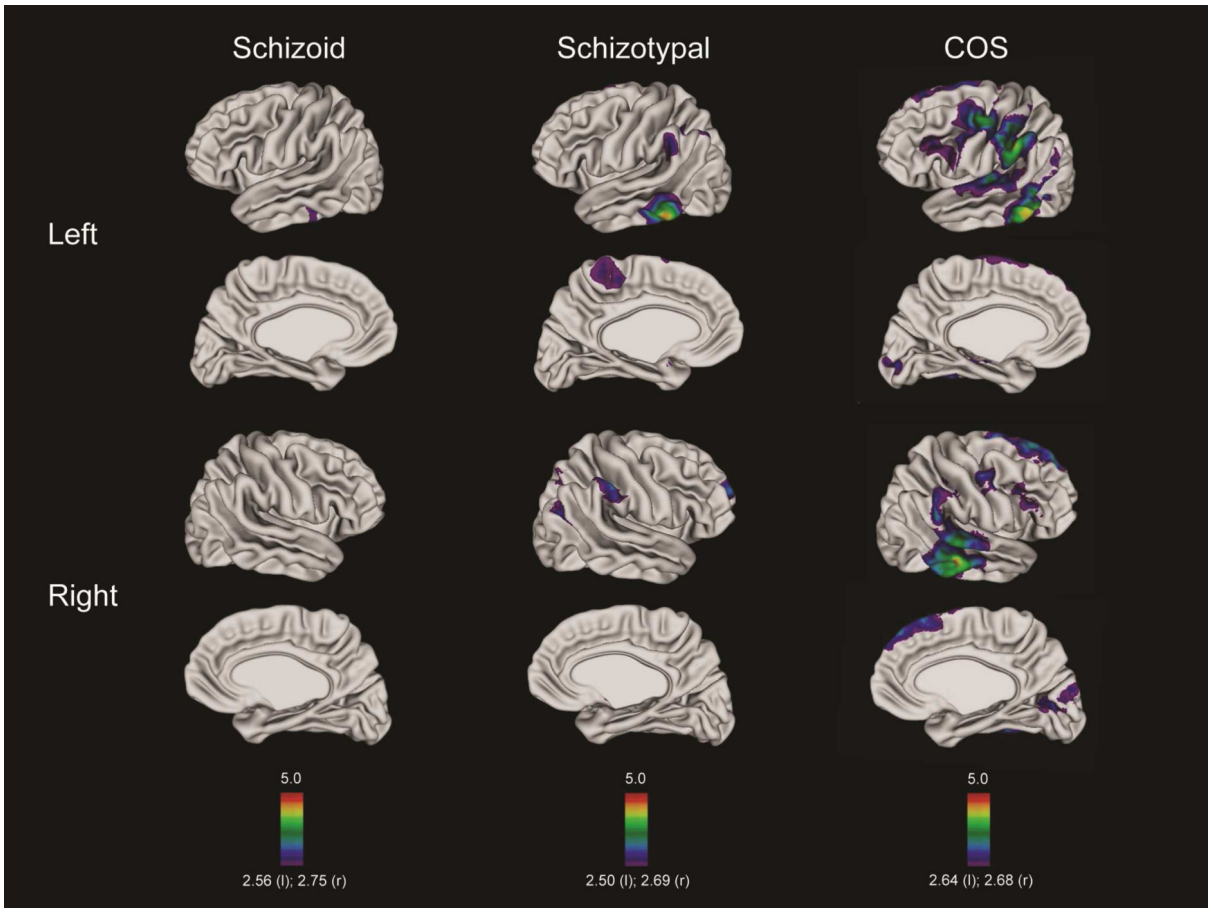

Figure 1.

Cortical gray matter deficits increase with schizophrenia spectrum personality disorder symptoms and show continuity with childhood-onset schizophrenia (COS). Note: colored bars indicate t statistics; all comparisons adjusted for age and sex, false discovery rate. Figure based on *Schizophrenia Research*, 140, Gogtay N, Weisinger B, Bakalar JL, et al., Psychotic symptoms and gray matter deficits in clinical pediatric populations, pp. 149–154, Copyright 2012, with permission from Elsevier.

Table 1

Characteristics of Siblings for Assessment of Gray Matter Thinning and Healthy Volunteers (HV) for Age-Trajectory Analysis

	Sibling			HV			Test statistic (df)[b]	*P* value
	n[a] or Mean	SD	Total *n*	*n* or Mean	SD	Total *n*		
Sex			66			62	$X^2_{(1)}=0.01$	>0.05
Female	33			33				
Male	33			29				
Race			66			62	$X^2_{(4)}=2.50$	>0.05
White	41			45				
Black	12			9				
Hispanic	6			4				
Asian	1			0				
Other	6			4				
Handedness			61			62	$X^2_{(2)}=0.57$	>0.05
Right	54			54				
Left	3			4				
Mixed	4			4				
Vocabulary score	10.94	3.46	54	11.77	2.74	61	$t_{(111)}=1.10$	>0.05
SES	55.91	25.75	66	45.71	19.81	62	$t_{(123)}=2.23$	<0.05*
Age at symptom assessment (Range)	20.20 (14.82 – 33.44)	3.71	66					
Age at scan								
Scan 1	18.44	6.86	66	17.50	4.81	62	$t_{(123)}=0.38$	>0.05
Scan 2	20.44	7.78	43	19.60	5.01	38	$t_{(72)}=0.52$	>0.05
Scan 3	21.87	6.68	31	21.76	4.60	23	$t_{(45)}=0.46$	>0.05
Scan 4	23.77	6.86	16	22.81	2.13	11	$t_{(19)}=0.69$	>0.05
Scan 5	21.97	4.28	5	24.12	4.02	4	$t_{(6)}=0.21$	>0.05

Note: Vocabulary and socioeconomic status (SES) were assessed at Scan 1. SES was measured using the Hollingshead scale. Higher scores reflect lower SES.

[a] Three participants, and several scans for additional participants, excluded from age trajectory analysis because participant was over age 30 at time of scan. Age range for siblings in age analysis: 10.56 – 29.33. Age range for HVs: 10.55 – 28.7.

[b] Comparisons made only with sibling participants and scans used for age analysis.

* $p < .05$