Delayed Development of Brain Connectivity in Adolescents With Schizophrenia and Their Unaffected Siblings

Andrew Zalesky, PhD; Christos Pantelis, MD; Vanessa Cropley, PhD; Alex Fornito, PhD; Luca Cocchi, PhD; Harrison McAdams, PhD; Liv Clasen, PhD; Deanna Greenstein, PhD; Judith L. Rapoport, MD; Nitin Gogtay, MD

IMPORTANCE Abnormalities in structural brain connectivity have been observed in patients with schizophrenia. Mapping these abnormalities longitudinally and understanding their genetic risk via sibship studies will provide crucial insight into progressive developmental changes associated with schizophrenia.

OBJECTIVES To identify corticocortical connections exhibiting an altered developmental trajectory in adolescents with childhood-onset schizophrenia (COS) and to determine whether similar alterations are found in patients’ unaffected siblings.

DESIGN, SETTING, AND PARTICIPANTS Using prospective structural brain magnetic resonance imaging, large-scale corticocortical connectivity was mapped from ages 12 to 24 years in 109 patients with COS (272 images), 86 of their unaffected siblings (184 images), and 102 healthy controls (262 images) over a 20-year period beginning January 1, 1991, through April 30, 2011, as part of the ongoing COS study at the National Institute of Mental Health.

MAIN OUTCOMES AND MEASURES Structural connectivity between pairs of cortical regions was estimated using a validated technique based on across-subject covariation in magnetic resonance imaging–derived cortical thickness measurements.

RESULTS Compared with normally developing controls, significant left-hemisphere occipitotemporal deficits in cortical thickness correlations were found in patients with COS as well as their healthy siblings (P < .05). Deficits in siblings normalized by mid-adolescence, whereas patients with COS showed significantly longer maturational delays, with cortical thickness correlations between the left temporal lobe and left occipital cortex not showing evidence of development until early adulthood. The normalization of deficits with age in patients with COS correlated with improvement in symptoms. Compared with controls, left-hemisphere occipitotemporal thickness correlations in a subgroup of patients with high positive symptoms were significantly reduced from age 14 to 18 years (P < .05); however, other patients with low positive symptoms showed no significant deficits.

CONCLUSIONS AND RELEVANCE Delayed maturation of occipitotemporal connectivity appears to be a trait marker in patients with COS, with a milder endophenotype in unaffected siblings associated with resilience to developing schizophrenia. These findings indicate genetically influenced and connection-specific developmental abnormalities in the schizophrenia connectome, and lead to the hypothesis that visual hallucinations in patients with COS may be because of delayed development of the inferior longitudinal fasciculus, a prominent occipitotemporal fiber.
Schizophrenia has been considered to be a disorder of brain development.1-2 The neurodevelopmental model of schizophrenia is supported by multiple lines of evidence, including studies in brain pathology,3,4 genetics,5 environmental factors, and gene-environmental interactions.6,7 We present new evidence for late neurodevelopmental changes using sophisticated approaches in human connectomics and brain connectivity.8

Converging evidence from electrophysiological, physiological, functional, and anatomical studies suggests that brain connectivity abnormalities—disruptions to white matter axonal pathways9-10 and abnormalities in the synchronized oscillatory activity of neurons11-13—play an important role in the pathophysiology of schizophrenia. However, most of these studies have been cross-sectional, and thus unable to shed light on progressive developmental changes during the disease course. Moreover, aberrant brain connectivity may represent a schizophrenia endophenotype,14 underscoring the importance of sibship studies in characterizing the disorder's genetic and phenotypic complexity.

Childhood-onset schizophrenia (COS) is a rare but particularly severe form of the disorder, characterized by auditory and visual hallucinations, strange thoughts or feelings, and abnormal behavior.15 The onset of symptoms typically occurs before puberty, an active period of brain development during which marked changes in white matter organization take place. Studying brain connectivity development longitudinally in patients with COS and their clinically unaffected siblings is therefore of particular interest, as it enables mapping of abnormal changes during key developmental windows16 and the ability to characterize neural endophenotypes.

As part of an ongoing COS study at the National Institute of Mental Health, magnetic resonance imaging (MRI) of brain anatomy was prospectively performed in patients with COS, their clinically unaffected siblings, and a group of healthy controls over a 20-year period beginning January 1, 1991. Whole-brain corticocortical networks were mapped longitudinally between ages 12 and 24 years and compared between the 3 groups for connectivity differences. Previous studies of this cohort have identified delayed gray and white matter development in both patients with COS and their clinically unaffected siblings (see Discussion), leading us to hypothesize that delays in connectome development would be evident in patients with COS and their healthy siblings. In particular, we hypothesized that clinically unaffected siblings would show comparable, but milder, delays owing to shared genetic factors that are offset by influences conferring resilience to developing schizophrenia. Given that childhood manifestation of a typically adult-onset illness usually shows a more severe phenotype, we also hypothesized that connectivity disturbances would be more pronounced in patients with COS at early ages relative to patients with the adult-onset disorder. We report on connectivity development in 109 patients with COS (272 images) and 86 of their clinically unaffected siblings (184 images), comparing them with 102 unrelated healthy controls (262 images) who were matched in terms of age, sex, and MRI test interval.

**Methods**

**Patients With COS**

Through national recruitment and prescreening of more than 2000 submitted case records and in-person screening of more than 250 children, 109 patients meeting DSM-III or DSM-IV criteria for schizophrenia, with onset of psychosis before their 13th birthday, had undergone prospective MRI testing at the time this study was conducted. Patients with a history of significant nonpsychiatric medical conditions (eg, epilepsy, brain lesions), substance abuse, contraindications for MRI, or an IQ lower than 70 prior to the onset of psychotic symptoms were excluded. Most patients were treated with clozapine, with dosages sometimes adjusted between follow-ups owing to changes in symptoms; the typical dosage range was between 300 and 650 mg daily, most commonly in divided doses. Positive and negative symptoms were rated using the Scale for the Assessment of Positive Symptoms (SAPS) and the Scale for the Assessment of Negative Symptoms,17 respectively. The structured psychiatric interviews specified below were administered to diagnose Axis I and II comorbidities. Comorbidities were uncommon, but not exclusionary, in the patient group.

Cortical gray matter loss has been previously reported in a subsample of the patients with COS18 and their siblings19 studied here. Further details about patient selection are described therein and elsewhere.20 An additional 39 patients and 34 healthy siblings who underwent MRI testing since the completion of these earlier studies were included here.

**Siblings of Patients With COS**

A group of 86 healthy, full biological siblings of patients with COS participated in this study. Siblings were interviewed using structured interviews for Axis I diagnoses (using either the Schedule for Affective Disorders and Schizophrenia for adults or the Schedule for Affective Disorders for School-Age Children) and Axis II diagnoses (using the Structured Interview for the DSM-III Personality Disorders). Siblings were considered healthy if they were free from any psychotic or schizophrenia spectrum disorder, which included schizophrenia or schizoaffective disorder on Axis I, or paranoid schizotypal, schizoid, or avoidant personality disorders on Axis II. This classification minimized any risk of the sibling group comprising children with subthreshold schizophrenia-like symptoms. No sibling had ever been administered antipsychotic medications. Herein, siblings always refers to the group of clinically unaffected siblings of patients with COS.

**Controls**

A group of 102 healthy controls, unrelated to the patients with COS, was selected from a sample of community volunteers recruited as part of a prospective study of normal brain development21 and matched for sex, age, number of repeated MRI tests, and MRI testing interval. Controls were free of any lifetime medical or psychiatric disorders, as determined by clinical examination and standardized interview. Psychiatric illness in first-degree relatives was also a criterion for exclusion. Controls and siblings were followed up on average ev-
ery 2 years. Diagnosis of any Axis I disorder at follow-up was a criterion for exclusion in controls and diagnosis of any Axis I or II schizophrenia spectrum disorder at follow-up was a criterion for exclusion in siblings of patients with COS.

For all participants, socioeconomic status was estimated using the Hollingshead scale, where higher scores reflect lower socioeconomic status. Intelligence was measured using the vocabulary-scaled score component of the age-appropriate version of the Wechsler Intelligence Scales.

The research protocol was approved by the National Institute of Mental Health Institutional Review Board. Written informed consent was obtained from participants older than 18 years and parents of minors. Children younger than 18 years also signed an assent form.

Longitudinal MRI Acquisition
T1-weighted images with contiguous 1.5-mm slices in the axial plane were obtained using a 3-dimensional spoiled gradient recalled echo sequence on a 1.5-T General Electric Signas scanner (GE Healthcare). Imaging parameters were echo time, 5 milliseconds; repetition time, 24 milliseconds; flip angle, 45°; acquisition matrix, 256 × 192; and a 24-cm field of view. Head placement was standardized as described previously.

Cortical Thickness Estimation
Magnetic resonance images were registered into standardized space using a linear transformation and corrected for non-uniformity artifacts. Registered and corrected volumes were segmented with a neural net classifier. Gray and white matter surfaces were then fitted with a surface deformation algorithm, which first determines the white matter surface, then expands outward to find the intersection between gray matter and cerebrospinal fluid. As a result, gray and white matter surfaces were nonlinearly aligned using a template surface registration so that each vertex of the white matter surface corresponded to a gray matter surface counterpart. Cortical thickness measurements, defined as the distance between linked vertices of the gray and white matter surfaces using a 30-mm surface-based blurring kernel, were calculated in native space at 40 962 cortical points. While our method is robust and popular, alternative cortical thickness estimation methods such as FreeSurfer and Advanced Normalization Tools can be used.

Cortical Network Mapping
Cortical networks were mapped at the coarse resolution of brain lobes, followed by a finer-grained regional mapping to localize any effects identified at the level of lobes. A total of 66 cortical regions (23 per hemisphere) were delineated according to the Desikan-Killiany atlas, with each region representing a node of the cortical network. Regions were clustered to form 10 brain lobes (5 per hemisphere) for the coarse-grained analysis: frontal, parietal, temporal, occipital, and cingulate. Regional cortical thickness was determined by averaging vertex-level thickness measurements across all vertices comprising a region. Lobe cortical thickness was estimated by averaging regional measurements analogously. The motivation for this dual-resolution approach was 2-fold: it led to (1) a substantial reduction in the number of multiple comparisons and (2) superior signal-to-noise ratio of cortical thickness estimates.

Corticocortical connectivity was determined based on group-level covariation in cortical thickness between pairs of regions (or lobes). This measure of structural connectivity is usually quantified with the Pearson correlation coefficient between paired thickness estimates across a population, computed after regressing age, sex, socioeconomic status, vocabulary-scaled score, and total gray matter volume from the thickness estimates. Our study, the same approach was followed, but the weighted Pearson correlation coefficient was used instead to enable mapping cortical connectivity prospectively across the lifespan. Connectivity was mapped between ages 12 and 24 years at every other year (ie, 12, 14, 16, 18, 20, 22, and 24 years). The age distribution of MRI tests was such that 12 and 24 years corresponded to approximately 1 SD away from the mean age within each group, hence justifying this age range. To compute thickness correlations for a desired age of n years, an MRI test performed at an age of k years was downweighted according to the Gaussian scaling expression where was set to 0.1. As such, the influence of MRI results was reduced exponentially as a function of the difference between the specific age of interest and the age at which the MRI test was performed. For example, a 1-year difference was downweighted by a factor of 0.90, while a 2-year difference was downweighted by 0.40. This approach yielded 3 group-level connectivity matrices of dimension 66 × 66 (regional) and 10 × 10 (lobes) at each of 7 ages.

Statistical Analysis
Demographic differences between the 3 groups were tested using F tests for continuous variables and χ² tests of independence for categorical variables. Patients with COS were compared with the healthy control group independently of their siblings. Comparisons were first performed at the coarse resolution of lobes, using a mass univariate approach based on the Fisher method for comparing correlation coefficients. Thickness correlations were r-to-z transformed. The difference in the resulting r-to-z values between the 2 groups was normalized by the appropriate degrees of freedom to yield a z score that tested the null hypothesis of equality in thickness correlations between the 2 groups. This approach yielded a total of 45 z scores, one for each pair of lobes. Permutation testing was performed to control familywise errors (FWEs) across the set of 45 lobe pairs. This testing involved randomizing the 2 groups so that patients with COS were randomly relabeled as healthy controls and vice versa, yielding 2 groups comprising random combinations of patients with COS and controls. The entire cortical network mapping process described above was then repeated for the randomized data. The maximum z score across all 45 pairs of lobes was stored for each of 10 000 such randomizations. A 1-tailed, FWE-corrected P value for a given pair of lobes was then given by the proportion of randomizations for which the maximum z score exceeded or equaled the true z score observed in the data with no randomization. This testing was repeated independently for each of the 7 ages, controlling the FWEs across the 45 lobe pairs within each age, but not across ages.

The above statistical analysis was performed identically on the fine-grained regional networks. The number of mult-
tiple comparisons became formidable at the regional level, with 2145 distinct pairs of regions to test across 7 ages. To reduce the number of multiple comparisons, regions were omitted a priori if they were not within a lobe where a significant effect was found using the coarse analysis. A hierarchical approach was therefore used, consisting of an initial coarse analysis to identify lobes between which connectivity deficits were evident, followed by a more circumscribed, fine-grained analysis aimed at regionally localizing these effects.

![Figure 1. Corticocortical Connectivity Deficits Mapped Throughout Adolescence and Early Adulthood](image)

Corticocortical connectivity deficits are mapped for patients with childhood-onset schizophrenia (COS) and their healthy, unaffected siblings (COSSIB), relative to a group of normally developing controls (NV). Matrices of z scores are shown for each age and oriented in the shape of a diamond so that the right (R) half represents the contrast of NV - COS, while the left (L) represents NV - COSSIB. Significant connectivity differences are shown as solid lines between pairs of brain lobes represented on an axial cross-section for each age ($P < .05$, familywise errors corrected across 45 pairs of lobes). The axial cross-sections thus indicate corticocortical connections associated with significant $z$ scores.

### Results

Sample demographics are shown in the Table. The samples were well matched on all variables with the exception of socioeconomic status and vocabulary-scaled score. Post hoc tests indicated both patients and their siblings had significantly lower socioeconomic status relative to controls, whereas only patients had significantly lower vocabulary-scaled scores ($P < .05$).

### Table. Demographics of Patients With Childhood-Onset Schizophrenia, Their Healthy Siblings, and Normally Developing Controls

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>COS (n = 109)</th>
<th>COSSIB (n = 86)</th>
<th>NV (n = 102)</th>
<th>Test Statistic</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at psychosis onset, y, mean (SD)</td>
<td>10.1 (2.0)</td>
<td>11.4 (3.6)</td>
<td>11.9 (2.9)</td>
<td>$F = 78$</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Socioeconomic status score, mean (SD)*</td>
<td>60.8 (29.6)</td>
<td>54.6 (26.0)</td>
<td>40.6 (19.8)</td>
<td>$F = 16.3$</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Vocabulary-scaled score, mean (SD)</td>
<td>6.3 (3.4)</td>
<td>11.4 (3.6)</td>
<td>11.9 (2.9)</td>
<td>$F = 78$</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Male/female, No.</td>
<td>62/47</td>
<td>42/44</td>
<td>60/42</td>
<td>$\chi^2 = 2.1$</td>
<td>.15</td>
</tr>
<tr>
<td>Ethnicity, No.</td>
<td></td>
<td></td>
<td></td>
<td>$\chi^2 = 3.2$</td>
<td>.79</td>
</tr>
<tr>
<td>White</td>
<td>54</td>
<td>47</td>
<td>57</td>
<td></td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td>30</td>
<td>17</td>
<td>26</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>9</td>
<td>7</td>
<td>8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>16</td>
<td>15</td>
<td>11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total MRI tests, No.</td>
<td>272</td>
<td>184</td>
<td>262</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: COS, childhood-onset schizophrenia; COSSIB, healthy, unaffected siblings of patients with COS; MRI, magnetic resonance imaging; NV, normally developing controls.

* For socioeconomic status, higher scores reflect lower status.

** Degrees of freedom were computed as the sum of the weights used to compute weighted correlation coefficients (see Methods).
Delayed Brain Connectivity Development in Adolescents With Schizophrenia

Regional Comparisons
The occipitotemporal deficits identified at the coarse resolution of lobes were localized in finer detail by parcelling the left temporal lobe and left occipital cortex into 13 cortical regions and repeating the analysis at this regional scale. Compared with controls, regional thickness correlations were significantly reduced in patients between 6 regions: the pericalcarine and lingual gyrus in the occipital cortex and the fusiform, inferior, middle, and superior temporal gyrus ($P < .05$, FWEs corrected across 78 pairs of regions; Figure 4). These deficits diminished with age, with no significant deficits evident after age 18 years. Siblings also showed a significant reduction in thickness correlations between the pericalcarine gyrus and both the fusiform and superior temporal gyrus (Figure 4). However, this deficit was only significant at age 12 years.

Clinical Associations
As shown in Figure 5, positive and negative symptoms were both negatively correlated with age ($r = −0.3$, $P < .001$). We hypothesized that deficits in occipitotemporal cortical thickness correlations would be greater in patients with more severe positive symptoms, particularly those with visual hallucinations (see Discussion). To test this hypothesis, patients were subdivided into high ($n = 33$) and low SAPS subgroups ($n = 30$). The high SAPS subgroup comprised patients with SAPS scores consistently greater than the mean SAPS scores averaged across all patients at each age considered; the low SAPS subgroup comprised patients with SAPS scores consistently lower than the mean SAPS scores. Compared with controls, left hemisphere occipitotemporal thickness correlations in the high SAPS subgroup were significantly reduced from ages 14 to 18 years ($P < .05$); however, the low SAPS subgroup showed no significant deficits relative to controls at any age (Figure 5C; results shown for age 14 years).

Lobar Comparisons
Using a data-driven, hypothesis-free approach, evidence for delayed development of occipitotemporal cortical thickness correlations in patients was identified in whole-brain networks mapped at the coarse resolution of brain lobes. Compared with controls, correlation in cortical thickness measurements between the left occipital cortex and left temporal lobe was significantly reduced in patients from ages 12 to 22 years ($P < .05$, FWEs corrected across 45 pairs of lobes; Figure 1). Between ages 16 and 20 years, connectivity between the right occipital cortex and left temporal lobe was also significantly reduced. These deficits normalized markedly in early adulthood, with differences in occipitotemporal thickness correlations diminishing at age 22 years and failing to reach significance by age 24 years. Increased thickness correlations were not found in patients at any age.

Healthy siblings of patients with COS showed a similar pattern of deficits. Most notably, correlation in cortical thickness measurements between the left occipital cortex and left temporal lobe was also significantly reduced in siblings. However, while significant at age 12 years, this deficit normalized in siblings during adolescence to levels comparable with that seen in controls. Siblings also showed significant increases in cortical thickness correlations at ages 16 and 18 years between the right cingulate and right temporal lobe as well as the right cingulate and right parietal lobe. The increase at the latter pair of regions was reduced to a trend ($P < .10$) when controlling for socioeconomic status and vocabulary-scaled score. Figure 1 provides a summary of these findings. Matrices of $z$ scores are shown for each age and oriented in the shape of a diamond so that the right half represents the contrast of controls minus patients with COS, while the left half represents controls minus siblings. Left-right symmetry in the $z$ score matrix is evident at age 12 years but diminishes by mid-adolescence, at which time siblings catch up to controls and continue along a normal developmental trajectory, whereas patients with COS continue to have such deficits until early adulthood.

Developmental trajectories for occipitotemporal thickness correlations are quantified in Figure 2 and Figure 3. In Figure 2, correlation in cortical thickness measurements between the left occipital cortex and left temporal lobe are shown from ages 12 to 24 years for patients with COS, siblings, and controls. Occipitotemporal thickness correlations are strong ($r > 0.5$) and remain relatively stable throughout normal adolescent development but are absent in patients with COS and their siblings until adulthood and mid-adolescence, respectively. Figure 3 shows scatter plots of cortical thickness measurements in the left temporal lobe and the left occipital cortex. Lines of best fit are positively sloped for controls, consistent with strong thickness correlations, which are not evident in patients until age 24 years.
Using cortical thickness estimates derived from prospectively acquired MRI tests, corticocortical connectivity was mapped across an age range of active brain development in a large sample of patients with COS, their clinically unaffected siblings, and a matched group of healthy unrelated controls. Evidence was found for delayed maturation of occipitotemporal connectivity in the left hemisphere of patients with COS. Specifically, compared with healthy controls, cortical thickness correlations between the left temporal and occipital lobes were significantly weaker throughout adolescence for patients with COS, suggesting a lack of mutually trophic factors, possibly owing to aberrant axonal wiring between these 2 cortices.36,37

Figure 3. Scatterplots Showing Cortical Thickness Correlations Between the Left Temporal Lobe and Left Occipital Cortex for Patients With Childhood-Onset Schizophrenia (COS), Patients’ Unaffected Siblings (COSSIB), and Normally Developing Controls (NV)

Each x represents an individual’s magnetic resonance imaging results acquired at an age within approximately ±2 years of the specific age of interest. Solid lines represent lines of best fit. Positively sloped lines of best fit suggest strong occipitotemporal connectivity. Correlations are statistically significant (P < .05) for all ages in the NV group and for ages 16 to 24 years in the COSSIB group. Correlations are not significant for all ages in patients with COS.

Figure 4. Left-Hemisphere Occipitotemporal Connectivity Deficits Mapped at the Resolution of Regions for Patients With Childhood-Onset Schizophrenia (COS) and Their Healthy, Unaffected Siblings (COSSIB), Relative to Normally Developing Controls (NV)

Significant interregional connectivity deficits are shown as solid lines between pairs of cortical regions represented on a flattened cortical surface (P < .05, familywise errors corrected across 78 pairs of regions). Flattened surfaces represent temporal and occipital regions of the left hemisphere. Regions are labeled according to the Desikan-Killiany atlas.30 Inf. indicates inferior; Mid., middle; and Sup., superior.
Occipitotemporal connectivity deficits in the left hemisphere were also found in the clinically unaffected siblings of patients. Deficits in siblings normalized by mid-adolescence, whereas patients with COS showed longer maturational delays, with cortical thickness correlations between the left temporal lobe and left occipital cortex not showing evidence of development until early adulthood. This finding suggests that delayed development of occipitotemporal connectivity may be under genetic control and represents a familial or trait marker. Delays in the maturation of this circuit might therefore increasesusceptibility for developing psychosis in individuals with a genetic risk for schizophrenia. A milder endophenotype in siblings might confer resilience to developing schizophrenia.

The present findings accord with a previous study of this cohort reporting delayed white matter growth rates in the clinically unaffected siblings of patients with COS, although delays were localized to the parietal and occipital lobes, without involvement of temporal regions. The absence of temporal deficits in this previous study may reflect the analysis of a fundamentally different measure that indexes growth rates on a voxel by voxel basis. Interestingly, cortical thickness deficits in frontal and temporal gray matter normalized with age in siblings but not in patients with COS. Therefore, while measures of structural connectivity, cortical thickness, and white matter growth all point to normalization of deficits in siblings, the precise location of neural deficits appears to depend on the type of neuroimaging measure analyzed. Frontotemporal deficits are most consistent, with a recent magnetoencephalography study (N. Vyas, PhD, D. Y. Rubinstein, BS, F. W. Carver, PhD, unpublished data, 2014) and a study map-
Fusion MRI, Ashtari and colleagues reported reduced fractional anisotropy, a direct measure of white matter integrity, in the left ILF of young patients with schizophrenia, particularly those with a history of visual hallucinations. Using similar techniques, Ortibus and colleagues reported a loss of ILF integrity in children with visuoperceptual impairment, and found correlations between decreased fractional anisotropy in the ILF and impaired object recognition. Evidence of disrupted ILF integrity has also been found in other neurodevelopmental disorders associated with visuospatial deficits. Nevertheless, cortical thickness correlations have been shown to correspond reasonably well with direct measures of fiber connectivity derived from tractography as well as functional connectivity.

There has been interest in characterizing the functional role of the ILF, particularly in developmental disorders. Using diffusion MRI, Ashtari and colleagues reported reduced fractional anisotropy, a direct measure of white matter integrity, in the left ILF of young patients with schizophrenia, particularly those with a history of visual hallucinations. Using similar techniques, Ortibus and colleagues reported a loss of ILF integrity in children with visuoperceptual impairment, and found correlations between decreased fractional anisotropy in the ILF and impaired object recognition. Evidence of disrupted ILF integrity has also been found in other neurodevelopmental disorders associated with visuospatial deficits.

Taken together, these findings support the hypothesis that delayed development of the left ILF may underlie visual hallucinations, which are commonly reported in adolescents with schizophrenia.

Positive and negative symptoms significantly improved with age (Figure 5), which may be associated with treatment interventions and is consistent with the normalization of occipitotemporal deficits seen in early adulthood. Moreover, deficits were greatest in patients with the most severe positive symptoms, suggesting that delayed ILF development may indeed underlie hallucinations, among other positive symptoms.

Several limitations should be noted. First, statistical power was lowest at the upper and lower ends of the age range considered owing to the fact that fewer MRI tests were performed before adolescence and in early adulthood. As such, it can be argued that the absence of significant connectivity deficits in early adulthood might be caused by a reduction in statistical power, thus opposing the notion of delayed maturation in favor of a chronic occipitotemporal connectivity deficit; that is, patients experience developmental arrest, rather than development lag. However, cortical thickness correlations at age 24 years were significantly stronger than at age 20 years in the patient group ($z = 1.8$, $P < .05$), providing explicit evidence for development of this connection in early adulthood. Second, many of the healthy siblings were not past the age of risk for schizophrenia. However, the stringent definition of healthy in this group makes it unlikely that they will develop a psychotic or schizophrenia spectrum illness in the future. Finally, investigating the effect of antipsychotic medication in this longitudinal design was difficult owing to complex dosing regimens that sometimes varied between follow-ups.

Conclusions

We have identified significant differences in structural brain connectivity in individuals with COS and their unaffected siblings. Crucially, connectivity deficits in the unaffected siblings normalized by mid-adolescence and were absent in early adulthood. Normalization with age might therefore represent a putative resilience endophenotype. It may be that the unaffected siblings benefit from protective network factors that are weaker in the patients and absent in the general population: namely, circuit-based intermediate phenotypes conferring resilience to developing schizophrenia. Future work will investigate resilience-associated intermediate phenotypes, which may have counterbalanced familial risk and illness effects in the unaffected siblings. We will also confirm the current findings using a direct measure of white matter connectivity.


