Progressive losses of cortical gray matter volumes and increases in ventricular volumes have been reported in patients with childhood-onset schizophrenia (COS) during adolescence. Longitudinal studies suggest that the rate of cortical loss seen in COS during adolescence plateaus during early adulthood. Patients with first-episode adolescent-onset schizophrenia show less marked progressive changes, although the number of studies in this population is small. Some studies show that, although less exaggerated, progressive changes are also present in nonschizophrenia early-onset psychosis. The greater loss of brain tissue seen in COS, even some years after the first episode, as compared to adolescent- or adult-onset schizophrenia may be due to variables such as sample bias (more severe, treatment refractory sample of childhood-onset patients studied), a process uniquely related to adolescent development in COS, differential brain effects of drug treatment in this population, clinical outcome, or interactions among these variables. Findings from both cross-sectional studies of first-episode patients and longitudinal studies in COS and adolescent onset support the concept of early-onset schizophrenia as a progressive neurodevelopmental disorder with both early and late developmental abnormalities. Future studies should look for correlates at a cellular level and for pathophysiological explanations of volume changes in these populations. The association of risk genes involved in circuitries associated with schizophrenia and their relationship to developmental trajectories is another promising area of future research.

Key words: early-onset/MRI/children/adolescents/psychosis/neurodevelopment

Introduction

The aim of the present review is to review the longitudinal studies assessing brain progressive changes in patients with early-onset psychosis. Understanding the developmental trajectories of molecular and cellular processes in normal brain development and differences between normal and abnormal development is of key importance for the interpretation of clinical imaging studies and the search for differential physiopathology among neurodevelopment-related psychiatric disorders. Therefore, given the focus of the present review, we will briefly summarize findings of magnetic resonance imaging (MRI) studies addressing normal brain development. We will then summarize results from longitudinal studies on early-onset psychosis. Because childhood-onset schizophrenia and adolescent-onset schizophrenia seem to have differences in precursors and course, and gene expression is different depending on age groups, we will present evidence separated into 2 groups: childhood and adolescent onset. Longitudinal findings in other early-onset psychoses will be also reviewed in order to assess specificity of schizophrenia findings with other early-onset disorders with psychotic symptoms. Clinical correlates of the findings and discussion about implication will follow the summary of results. Finally suggestions for future research will be provided.

Brain Development Considerations

Cortical gray matter (GM) follows an inverted U-shape developmental course with greater regional variation than white matter. There is an increase in synaptic density above adult levels during early postnatal brain development, which goes through a process of synaptic pruning during childhood and adolescence to adult levels, with primary motor and sensory regions maturing earlier than regions serving more complex functions. This synaptic pruning is also supported by the changes in

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synaptophysin, a synaptic marker protein, during human childhood and adolescence. Other cortical glial and vascular changes parallel synaptic development; however, the relative contribution of these components to the developmental volume changes seen in brain imaging remains unknown (revised by Sowell et al). As for regional brain volumes, frontal GM volume peaks at about age 11.0 years in girls and 12.1 years in boys, whereas temporal GM volume peaks at about age 16.7 years in girls and 16.2 years in boys; then a progressive reduction in GM can be observed after the peak, possibly due to competitive elimination of redundant synapses. The dorsolateral prefrontal cortex, important for controlling impulses, is among the latest brain regions to mature, and it does not reach adult dimensions until the early 20s.

A study of 13 subjects scanned every 2 years for 8–10 years showed a clear heterochronicity in human cortical development. Low-order association cortices, such as the somatosensory and visual cortices, matured earlier while high-order association cortices matured later. GM volumes increased before puberty and decreased afterwards. Frontal and occipital poles lost GM early and, in the frontal lobe, GM maturation involved the dorsolateral prefrontal cortex only at the end of adolescence. Frontal lobe maturation progressed in a back-to-front direction, with the prefrontal cortex developing last. The frontal and occipital poles developed earlier than their corresponding central cortex. The temporal lobe showed a late maturation pattern, with the exception of the temporal pole, which also developed earlier. The sequence in which the cortex matured was in agreement with milestones in cognitive and functional development. Because of the few long-term longitudinal MRI studies with large sample sizes, the reported patterns of development are not established facts and more studies assessing normal brain development are necessary.

White matter increases during the first 4 decades in a roughly linear pattern because of axonal myelination, with minor differences in slope in the 4 major lobes. A cross-sectional study with a large number of cases (n = 600), including singletons, siblings, and twins, reported the existence of statistically significant age by heritability interactions for GM volumes, showing a reduction in heritability with increasing age (age invariance for gene and environment were 1.5 and 5.45, respectively), and the opposite for white matter, for which volume heritability increased with age (age invariance for gene and environment were 4.7 and 0.6, respectively). Regional subanalyses from the same and other studies showed that cortical thickness of areas involved in complex cognitive processes have stronger environmental influences in childhood, becoming more genetically determined later during adolescence. Genetic and environmental factors thus seem to affect cortical development in both regional- and age-specific manners, which should be taken into account when interpreting data from pediatric populations with psychiatric disorders that include patients of different ages or in which different brain areas are assessed.

Longitudinal Changes in Early-Onset Schizophrenia

There is evidence of abnormal structural brain changes after a first episode of schizophrenia in an adult population (see Hulshoff) as well as during the course of chronic illness. Although the study of patients with early onset (defined as onset prior to age 18) has been proposed as a useful approach for reducing the heterogeneity inherent in complex disorders, not much research has been done on early-onset schizophrenia. Lack of episodes and 85% rate of preschizophrenic neurodevelopmental problems characterize COS and are much less prevalent in adolescent onset. We also know that genes involved in brain development are expressed differentially in different age groups. For these reasons, we will present evidence from the available longitudinal studies, separated into 2 groups: childhood and adolescent onset.

Childhood-Onset Schizophrenia

Most of the evidence for longitudinal changes in early-onset schizophrenia comes from the childhood-onset study at the National Institute of Mental Health (NIMH) in which a large number of healthy children, patients, and their relatives have been scanned prospectively for the last 17 years (see table 1 for longitudinal studies of COS). Childhood-onset schizophrenia (COS) is defined as onset of schizophrenia prior to age 13. Progressive losses of cortical GM and increases in ventricular volumes have been reported in this group of patients during adolescence. Changes in cortical GM volume were examined in 15 patients with COS and 34 matched normal controls, who underwent 2 MRIs at an interval of approximately 4 years. Patients with schizophrenia showed a larger loss of frontal, parietal, and temporal GM. In a later study, 3-dimensional maps of brain changes obtained in a 5-year period showed a back-to-front cortical wave loss in 12 adolescents (mean age at first scan 13.9 years) with COS compared with matched healthy controls. An accelerated loss of GM was observed involving the prefrontal, supplementary motor, sensorimotor, parietal, and temporal cortices. In this study, only parietal and motor cortex deficits were present at baseline. Frontal and temporal GM deficits were progressive over time and were seen at 5-year follow-up. These findings were intriguing to the authors, as they began in brain regions (parietal cortex) where, in adult studies with twins discordant for schizophrenia, deficits appear to be more mediated by environmental (nongenetic) factors and then progress to regions (frontal and temporal lobes) where deficits, in those adult studies, seem to be more genetically mediated and highly heritable. An expanded sample from the
<table>
<thead>
<tr>
<th>Study Reference (Research Group)</th>
<th>n&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Age at Initial Scan in Years, Mean (SD)</th>
<th>Age at Onset in Years, Mean (SD)</th>
<th>Follow-up in Years, Mean (SD)</th>
<th>Findings&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frazier et al&lt;sup&gt;25,50&lt;/sup&gt; (NMIH)</td>
<td>8 COS, 8 controls</td>
<td>COS: 15.1 (2.3), controls: 15.4 (3.1)</td>
<td>COS 10.5 (1.3)</td>
<td>2</td>
<td>B: COS larger caudate vol, no vol differences in putamen, globus pallidus, or lateral ventricles; FU: COS significant decrease of caudate vol during FU with no vol difference at second scan. No differences in rates of vol change in putamen, basal ganglia, and lateral ventricles.</td>
</tr>
<tr>
<td>Rapoport et al&lt;sup&gt;23&lt;/sup&gt; (NMIH)</td>
<td>16 COS, 24 controls</td>
<td>COS: 14.8 (2.4), controls: 14.3 (1.9)</td>
<td>COS 10.23 (1.75)</td>
<td>2.23 (0.23)</td>
<td>B: COS smaller total cerebral vol and larger globus pallidus vol; FU: COS significant increase in lateral ventricle vol and in ventricle/brain ratio, decrease in midsagittal thalamic areas. Changes correlated with each other. No significant changes in globus pallidus, caudate, or putamen.</td>
</tr>
<tr>
<td>Rapoport et al&lt;sup&gt;18&lt;/sup&gt; (NMIH)</td>
<td>15 COS, 34 controls</td>
<td>COS 13.9 (2.3), controls 12.8 (2.9)</td>
<td>COS 10.3 (2.0)</td>
<td>4.28 (0.63), range 3–5 years</td>
<td>FU: COS significantly larger decrease in temporal, frontal, and parietal GM. No significant differences in white matter volume.</td>
</tr>
<tr>
<td>Thompson et al&lt;sup&gt;19&lt;/sup&gt; (NMIH)</td>
<td>12 COS&lt;sup&gt;c&lt;/sup&gt;, 10 PNOS, 12 controls</td>
<td>COS 13.9 (0.8), controls 13.5 (0.7)</td>
<td>About 3 years previous to first scan</td>
<td>4.6</td>
<td>B: COS severe significant loss in parietal and motor cortices (up to 20%); FU: COS significant progressive GM loss in prefrontal, supplementary motor, sensorimotor, parietal, and temporal cortices (peak values &gt;5% loss/year). Parietal and motor cortices faster loss in younger adolescents. Temporal and prefrontal cortices deficit observed only after symptom onset. PNOS: accelerated frontal GM loss relative to controls but smaller than COS, no temporal lobe vol deficits.</td>
</tr>
<tr>
<td>Keller et al&lt;sup&gt;24&lt;/sup&gt; (NMIH)</td>
<td>50 COS&lt;sup&gt;c,d&lt;/sup&gt;, 50 controls&lt;sup&gt;d&lt;/sup&gt;</td>
<td>COS 14.8 (2.5), controls 14.9 (2.4)</td>
<td>COS 10.3 (1.8)</td>
<td>Range 2–6 years&lt;sup&gt;e&lt;/sup&gt;</td>
<td>B: COS no significant differences for total cerebral vol, cerebellar measures, or vermal measures; FU: COS significant progressive decrease in total cerebellar and total cerebral vol, no significant changes in vermal area and posterior-inferior vermal vol.</td>
</tr>
<tr>
<td>Sporn et al&lt;sup&gt;22&lt;/sup&gt; (NMIH)</td>
<td>39 COS&lt;sup&gt;c&lt;/sup&gt;, 43 controls</td>
<td>COS 15.0 (2.3), controls 14.8 (2.2)</td>
<td>COS 10.2 (2.2)</td>
<td>Range 2–6 years, patients 3.4 (1.4), control 3.6 (1.6)</td>
<td>B: COS larger lateral ventricle, smaller frontal and parietal GM, no significant difference in temporal and total GM; FU: COS significant decrease in total (19.4%), frontal, and parietal GM, increase in lateral ventricles (41.3%). Steeper early frontal and parietal GM vol loss rate. Rate of cortical GM loss plateaus during adolescence.</td>
</tr>
<tr>
<td>Gogtay et al&lt;sup&gt;7,37&lt;/sup&gt; (NMIH)</td>
<td>23 COS, 19 PNOS, 38 controls</td>
<td>COS: 13.9 (2.5), PNOS: 13.3 (3.1), controls: 13.3 (3.1)</td>
<td>COS 10.13 (2.1), PNOS 7.8 (1.9)</td>
<td>2.5(0.8)</td>
<td>FU: COS significant decrease in total, frontal, temporal, and parietal GM relative to PNOS or controls. No significant vol differences between PNOS and controls.</td>
</tr>
</tbody>
</table>
Table 1. Continued

<table>
<thead>
<tr>
<th>Study Reference (Research Group)</th>
<th>n&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Age at Initial Scan in Years, Mean (SD)</th>
<th>Age at Onset in Years, Mean (SD)</th>
<th>Follow-up in Years, Mean (SD)</th>
<th>Findings&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vidal et al&lt;sup&gt;40&lt;/sup&gt; (NMIH)</td>
<td>12 COS, 12 controls, 9 PNOS</td>
<td>COS 14.1 (2.7), PNOS 13.6 (2.7), controls 13.5 (2.4)</td>
<td>Before age 13</td>
<td>4.6</td>
<td>B: COS significant decrease in medial frontal and medial parietal cortex GM. No significant differences in cingulate gyrus. PNOS significant loss in the same areas but less marked; FU: COS strongly progressive back to front bilateral deficits in superior medial frontal cortex (&gt;5% loss per year). Progressive loss in medial parietal cortices and left cingulate gyrus. PNOS accelerated GM loss in the same regions but less pervasive.</td>
</tr>
<tr>
<td>Greenstein et al&lt;sup&gt;26&lt;/sup&gt; (NMIH)</td>
<td>70 COS&lt;sup&gt;d&lt;/sup&gt;, 72 controls&lt;sup&gt;d&lt;/sup&gt;</td>
<td>COS 14.47 (2.6), controls 14.35 (2.56)</td>
<td>COS 10.17 (1.95)</td>
<td>COS up to 7.98 years, controls up to 7.38 years</td>
<td>FU: COS sign smaller cortical thickness (7.5% difference with controls) through the age range. At earlier ages, significant smaller vol in anterior and posterior regions. At ages 20–22 COS brain developmental trajectory normalizes in parietal cortex and vol deficit localizes in temporal and frontal cortices.</td>
</tr>
<tr>
<td>Nugent et al&lt;sup&gt;27&lt;/sup&gt; (NMIH)</td>
<td>29 COS, 31 controls</td>
<td>COS: 14.6 (2.4), controls: 14.6 (2.2)</td>
<td>Before age 13</td>
<td>Range 6–10 years</td>
<td>B: COS significantly smaller left and right hippocampal volumes; FU: COS no significant changes in total hippocampal volumes. Bilateral loss in anterior and posterior regions and minimal gain in the body.</td>
</tr>
</tbody>
</table>

Note: COS, childhood-onset schizophrenia patients; PNOS, psychosis not otherwise specified patients medication matched with COS; GM, gray matter; vol, volume; B, baseline; FU, follow-up.

<sup>a</sup>Includes patients and controls with >1 scan unless otherwise specified.
<sup>b</sup>All significant findings relative to healthy controls.
<sup>c</sup>Patients from these 3 studies come from the same sample.
<sup>d</sup>Including also patients without follow-up scans.
<sup>e</sup>Those analysis performed with data from 36 COS and 34 controls with more than one scan.
Thompson et al (2001) report on 60 cases of COS, which include the 15 patients from the former study, provided additional support for a parietal-frontal progression of GM volume reduction during adolescence. In the latter study, rate of GM reduction was assessed using developmental trajectories for total and regional brain volumes derived from follow-up scans acquired at approximately 2-year intervals in 39 subjects with COS. The longitudinal trajectories suggested that the rate of cortical loss seen in COS during adolescence plateaus during early adulthood. The same NIMH group has reported progressive increases in ventricular volume and ventricle-brain ratio and reductions in the midsagittal thalamic area after 2 years of follow-up, as well as loss of cerebellar volume. However, in a study with 8 cases of COS on treatment with clozapine and 8 healthy controls scanned after 2 years, there were no differences between groups in rates of volume change in the putamen, basal ganglia, or lateral ventricles. More recently, reduced cortical thickness has been reported with repeated scans in 70 patients, ages 7–26, diagnosed with COS. The brain development trajectory converged with controls in the parietal regions while remaining divergent in the anterior (frontal and temporal) regions, with a pattern similar to that seen in adults with schizophrenia. The authors speculate that patients with adult-onset schizophrenia may have undergone a similar process of parietal-frontal wave loss during development prior to onset of illness and that patients with COS have an exaggeration of the progressive pattern of normal posterior-anterior development so that, as COS patients get older, their brains resemble those of adult-onset patients. Finally, in another longitudinal study by the same group in 29 children with COS, scanned every 2 years for 6–10 years, total hippocampal volume was 9%–10% smaller at baseline compared with normal controls and remained consistently smaller between ages 9 and 26. However, there were differences among different hippocampal subunits, with patients losing more anterior and posterior hippocampal volume and gaining more hippocampal body volume.

Healthy full siblings (ages 8–28 years) of patients with COS showed greater prefrontal and temporal GM loss compared to matched healthy controls. Importantly, these cortical reductions did not progress in adolescence (unlike the progression described for this same group in COS) and the differences between groups disappeared by age 20 years. In this study, GM thickness, especially in the prefrontal and temporal cortices, increased with higher global assessment scale scores. This may suggest a compensatory plastic response in these very well adjusted healthy siblings. In longitudinal studies in an adult population, the larger GM decrease was restricted to the first 2 decades and was similar to controls thereafter.

We are not aware of any study of first-episode child-onset schizophrenia. However, the rarity of episodes in this population makes it difficult to date a first episode. In fact, out of 100 cases of COS recruited in the NIMH cohort, only 2 cases had clear first episodes (J. Rapoport, unpublished data). All other cases had a very insidious onset with various neurodevelopmental problems years before the appearance of psychotic or negative symptoms.

**Adolescent-Onset Schizophrenia**

There are very few longitudinal studies in adolescent early-onset patients (see table 2). Although some first-episode schizophrenia studies include adolescents together with adults in their cohorts, they do not report separately on the subset of late adolescence patients and the patients are usually above the age of 16. Adolescent-onset schizophrenia is closer to adult-onset schizophrenia in that a first episode is usually recognizable. In purely adolescent cohorts, decreased frontal (but not parietal or temporal) GM volumes and increased total cerebrospinal fluid (CSF) and frontal sulcus CSF in a group of 23 patients with first-episode early-onset psychosis (8 schizophrenia, 15 other psychoses) with a mean age at onset of 15.2 years have been reported with progression of GM deficits over the first 2 years of the disease. It is noteworthy that these studies assessed patients with early-onset psychosis, not only schizophrenia, and had small sample sizes. James et al assessed 16 adolescents (mean age at onset 15.1 years) with first-episode schizophrenia at baseline (a mean of 18 months after onset of illness) and after 2–3 years of follow-up. Although patients had smaller prefrontal cortices at the baseline assessment, there was no evidence of progression over time compared with normal controls. Patients also had smaller thalamic and larger fourth ventricle volumes at baseline, again with no evidence of progressive changes.

**Longitudinal Changes in Other Early-Onset Psychoses**

A comparison of 23 COS patients and 19 patients with psychosis not otherwise specified (NOS), matched for age, gender, IQ, and drug treatment with a control group, after 2.5 years of follow-up, showed that the reduction in GM volumes in the COS group was greater than in either the psychosis NOS or the normal control group. The psychosis NOS and control groups did not differ significantly from each other in baseline volumes or volume changes during follow-up. The patients with psychosis NOS had been ill for a longer period of time (age at onset of psychosis 7.8 years vs 10.1 for COS), so changes could have taken place earlier in the course of the disease for the NOS group. However, this is not likely as, at baseline, the brain volumes in this group were not significantly different from the normal control group. The authors argued that cortical loss may be
diagnostically specific to COS in contrast to other child-
onset psychoses. At a 2- to 10-year follow-up after ini-
tial assessment of a group of children with atypical psy-
chosis, none had a diagnosis of schizophrenia, but 40%
met criteria for bipolar type I disorder. When 9 chil-
dren with bipolar I were compared with 8 children with
atypical psychosis and a matched healthy group, the
brain trajectories showed a pattern of cortical GM
gain in the left temporal cortex and bilateral GM reduc-
tion in the anterior and subgenual cingulate cortex. This
pattern, usually shared by patients with a persistent
diagnosis of atypical psychosis, was considered to be
different from COS.

Twelve patients from the NIMH COS cohort were
assessed to map GM loss rates across the medial hemi-
sphere surface. Patients, healthy controls, and medica-
tion- and IQ-matched subjects with psychotic symptoms
not fulfilling criteria for schizophrenia were scanned
5 years apart. The medial frontal cortex was already af-
fected at baseline in both hemispheres in COS patients.
On the contrary, the cingulate was preserved at baseline.
At follow-up, frontal deficits were progressive and there
was significant GM reduction in the left cingulate in
the schizophrenia group. GM loss occurred over the
course of the study in a dorsal-to-ventral medial surface
pattern, irrespective of gender. The control patients with
psychosis NOS with transient psychosis symptoms who
nevertheless received treatment with antipsychotics
and continued to have mood and behavioral problems
during the 5-year follow-up exhibited a pattern similar to
patients with schizophrenia. The Thompson et al study,
they also used a psychosis NOS medication-matched
comparison group and, at follow-up, reported accelerated frontal GM loss relative to controls (with less
magnitude than COS) with no temporal lobe volume
changes. A recent 2-year longitudinal study followed 21 adolescents with very recent onset of psychosis (mean 3.2
months) and short duration of antipsychotic treatment
(mean 3.7 weeks) and 34 healthy controls matched
with patients for age, gender, race/ethnicity, handedness,
and years of education. The group of patients with
schizoaffective disorder, depressed, and atypical psychoses. Patients with
schizophrenia and with atypical psychoses, and with
patients for age, gender, race/ethnicity, handedness,
and years of education. The group of patients with
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### Table 2. Volumetric Results From Longitudinal MRI Studies of Adolescent-Onset Psychosis

<table>
<thead>
<tr>
<th>Study Reference</th>
<th>n</th>
<th>Duration of Illness</th>
<th>Age at Initial Scan, Mean (SD)</th>
<th>Follow-up, Mean (SD)</th>
<th>Findingsa</th>
</tr>
</thead>
<tbody>
<tr>
<td>James et alb, c</td>
<td>16 patientsb, 16 controls</td>
<td>M: 1.95 yrs., F: 1.04 yrs.</td>
<td>Patients 16.6 (1.9) yrs., controls 16.0 (2.0) yrs.</td>
<td>Patients 2.7 (1.7) yrs., controls 1.7 (0.5) yrs.</td>
<td>B: Significant generalized ventricular enlargement (greater in males), greater left temporal horn, and smaller left amygdala; FU: no evidence of progressive structural brain changes.</td>
</tr>
<tr>
<td>James et alc</td>
<td>16 patientsb</td>
<td>Same as above</td>
<td>Same as above</td>
<td>Same as above</td>
<td>B: Smaller prefrontal cortex and thalamus vol, larger fourth ventricle vol, no significant changes in cerebellum vol; FU: no progressive changes except decrease in the posterior-inferior vermis vol.</td>
</tr>
<tr>
<td>S. Reig, C. Moreno, D. Moreno, M. Burdalo, J. Janssen, M. Parellada, A. Zabala, M. Desco, C. Arango, submitted</td>
<td>21 patientsc, 34 controls</td>
<td>3.2 (3) mo.</td>
<td>Patients 15.7 (1.7) yrs., controls 15.2 (1.4) yrs.</td>
<td>Patients 24.2 (1.0) mo., controls 24.2 (0.5) mo.</td>
<td>B: smaller frontal GM vol and larger frontal CSF vol in both hemispheres in males; FU: significant decrease in right and left frontal GM and increase in frontal left CSF in males.</td>
</tr>
</tbody>
</table>

*Note: M, males; F, females; CSF, cerebrospinal fluid; yrs., years; mo., months.

*aAll significant findings relative to healthy controls.

bAdolescent-onset schizophrenia.

cIncludes schizophrenia and nonschizophrenia psychotic disorders.
Clinical Correlates of Progressive Changes

Ventricular enlargement at 2-year follow-up has been related to worse premorbid adjustment and higher brief psychiatric rating scale (BPRS) scores at follow-up in COS.\textsuperscript{23} Higher rates of loss in the frontal cortex correlated with more severe negative symptoms, while faster temporal loss was significantly associated with greater severity of positive symptoms.\textsuperscript{19} On the contrary, larger GM reduction in COS has been related to greater clinical improvement (measured as percent improvement in BPRS and scale for assessment of negative symptoms scores) at follow-up.\textsuperscript{22} However, in the same study, greater severity of clinical symptoms at baseline and poorer premorbid functioning were related to larger GM reduction, in the expected direction. The relationship between improvement in symptomatology and greater GM reduction was unexpected and did not seem to depend on the type of medication received by patients or on the severity of symptoms at baseline or follow-up.\textsuperscript{22} One speculative reason suggested by the authors for this finding was the existence of compensatory synaptic and cellular pruning of malfunctioning neurons. Similarly, although GM loss was not predictive of functioning at baseline, probably due to small sample size \( (n = 12) \), worse symptoms at follow-up were related to higher GM volume in the frontal and medial cingulate cortices in a 5-year longitudinal study in the same group.\textsuperscript{41} The opposite has been reported in adults with cortical representations. However, pruning usually takes place at younger ages than those reported in early-onset schizophrenia.\textsuperscript{2,44-46}

Age at onset is not associated with degree of GM deficits in most adult population cross-sectional studies.\textsuperscript{47-50} Age at onset is also not related in COS\textsuperscript{22} although Thompson et al\textsuperscript{19} found that loss of GM in the right parietal and sensorimotor cortices was faster in younger adolescents.

We are not aware of any study assessing the clinical correlates of progressive changes in early-onset psychosis other than schizophrenia.

Discussion of Findings

The few studies of first-episode adolescent-onset schizophrenia\textsuperscript{34,37} are not very consistent with studies of COS (in which clear episodes are seldom seen). On the one hand, some of the COS studies do not report changes in frontal lobe volumes,\textsuperscript{19,23,51} even some years after the onset of psychotic symptoms that are already present in the first-episode early-onset studies.\textsuperscript{34,37} This lack of significant findings in the frontal lobe in COS may be due to a lack of statistical power because of small sample sizes and high variability in the measurements. For instance, in a study by Kumra et al\textsuperscript{52} the right and left prefrontal volumes were 71.1 and 70.5 cc, respectively, in COS patients and 79.5 and 75.9 cc, respectively, in controls. Despite differences exceeding 10\%, they did not reach statistical significance. On the other hand, in the follow-up, the amount of brain loss seemed to be more marked in the COS studies, with reported rates of GM loss up to 5\% annually in the parietal, motor, temporal,\textsuperscript{19} and frontal regions.\textsuperscript{41} In the study by Reig et al, rates of frontal GM loss in adolescent-onset psychosis were 2.0% and 2.9% for right and left lobes, respectively, during the first 2 years of illness. The greater loss of brain tissue seen in COS, even some years after the first episode, may be due to a sample bias (toward the more severe, treatment refractory sample of patients), a process uniquely related to adolescent development in COS, differential brain effects of drug treatment in this population, clinical outcome, or interactions among these variables. Given the larger amount of GM loss some years after the onset of positive symptoms, it would be interesting to know what changes took place in the brains of the COS patients in the initial years after the first episode and what changes will take place in the first-episode adolescents a few more years after the first episode (to date, the longest duration of follow-up reported is 2 years), in order to reconcile the data from these 2 groups of patients.

The results support the notion that the pattern of GM volume loss in very early-onset schizophrenia resembles the normal developmental pattern but at an exaggerated rate. Findings from both cross-sectional studies of first-episode patients and longitudinal studies in COS and adolescent onset support the concept of early-onset schizophrenia as a progressive neurodevelopmental disorder with both early and late developmental abnormalities.\textsuperscript{53} (S. Reig, C. Moreno, D. Moreno, M. Burdalo, J. Janssen, M. Parellada, A. Zabala, M. Desco, C. Arango submitted). However, not all studies support this view because some baseline studies of COS do not find differences some years after the first episode compared with normal controls.\textsuperscript{19} In this study, there are baseline parietal differences, but the differences are not consistent with known adult schizophrenia deficits, and some longitudinal studies do not find progressive changes.\textsuperscript{37} These discrepancies could be due to genetic diversity and heterogeneity in response to neurotrophic factors that can determine important differences in each patient’s adaptation to the malformative disorders at different stages of development.\textsuperscript{54,55}

Despite evidence of prenatal and perinatal factors associated with schizophrenia, the emergence of symptoms in adolescence or early adulthood may have to
do with a second wave of genetic and environmental factors and their interaction with earlier developmental abnormalities.\textsuperscript{46,56,57}

Changes reported in COS seem to be more marked than those reported in adults (effect size for ventricular enlargement was 0.89 for COS vs 0.18–0.65 in studies of adult-onset schizophrenia).\textsuperscript{58} In addition, effect sizes for cross-sectional studies using z scores show a smaller cerebral volume in COS as compared to adult-onset schizophrenia.\textsuperscript{51} However, there are no direct comparisons of the magnitude of changes in COS and adult-onset subjects in the same study using the same methodology or direct comparisons assessing these 2 cohorts assessed at the same age. In the study by Sporn et al\textsuperscript{22} the rate of progressive changes reached a plateau after the age of 18. The smaller volumes at baseline and larger progressive losses may represent a more severe and/or earlier phenotype. On the other hand, the plateauing of effect observed by Sporn et al would predict that young adult or late adolescent studies would need longer time periods and larger samples to observe this attenuated effect. That is, it predicts that progressive change lessens with age, even for childhood-onset cases.\textsuperscript{26} Most studies in adults have failed to find a relationship between age at onset and volume deficits (see above). However, this may be the result of an insult—genetic or environmental—occurring in a critically early developmental period, correlating with greater structural abnormalities. Longitudinal studies in adults with very early-onset psychosis will be informative regarding this issue. Early developmental histories of patients with very early and early-onset schizophrenia show more striking impairment in language and motor development than that reported in adult-onset schizophrenia, as well as more neurological signs than other early psychotic diagnoses.\textsuperscript{15,59} The more marked failure of normal maturation may be related to exaggerated progressive changes in this population. Another important issue derived from the greater progressive changes seen in COS is that the effect size for relative brain changes seems to be smaller after age 18, and studies should have larger samples to assess brain changes in an adult population.

Abnormalities in either the degree or the spatiotemporal pattern of basic developmental processes may underlie neurodevelopmental disorders. Early insults may affect developmental and maturational processes in brain regions, as is also the case with modifications in genes known to play a role in prenatal processes (such as cell migration and axonal navigation) with clear influences on processes occurring later during brain maturation.\textsuperscript{17,60–63} Early and late maturational processes, eg, regressive or pruning processes, result in dynamic changes in the structure of the brain occurring well into the second and third decade of life.\textsuperscript{64} It may be the case that these normal maturational events, which lead to decreased cortical volume, are exaggerated in patients with schizophrenia and even more exaggerated in early-onset schizo-

The overall profile of progressive frontal GM loss reinforces the notion of a neurobiological continuum between COS and later-onset illness. Much less is known about early-onset affective psychosis, but preliminary results suggest that some of the progressive changes may not be disease specific, as they are found in other early-onset psychoses\textsuperscript{41} (S. Reig, C. Moreno, D. Moreno, M. Burdalo, J. Janssen, M. Parellada, A. Zabala, M. Desco, C. Arango, submitted). This lack of difference with other psychotic symptoms could also be mediated by an antipsychotic effect as, in both studies, all patients with psychoses other than schizophrenia received treatment with antipsychotics. In this respect, significantly greater cortical GM loss has been reported in subjects with COS than in medication-matched controls with other psychoses, making the argument that the deficits were not attributable to the antipsychotics.\textsuperscript{38} Whether brain changes represent a trait marker or a plastic response to the disease process, which may be mediated by medication, is still unknown.

There are a number of limitations in the studies assessing progressive changes in early-onset psychosis. Most studies come from the same group at NIMH assessing severely ill patients referred for treatment nonresponse. Patients studied in the NIMH childhood-onset study have a mean length of illness greater than 3 years and cannot be considered first episodes. Changes occurring immediately after the onset of psychotic symptoms are therefore not known in this cohort. Another limitation is that most studies have small sample sizes, which reduces the validity of the study findings, increasing the possibility of type I error in those studies. In addition, some studies use the same sample to report findings in different areas (see table 1). Although there are increasing data on normal development from longitudinal MRI studies in children and adolescents, we still need more data on normal brain development, especially on different brain structures (and not just gross volumes of gray, white, and CSF compartments). Most studies examine lobar volumes with no specificity at the sublobar level. A limitation of this review is the fact that different groups use different imaging techniques (see the multiple assessment technique used in NIMH studies), which makes it difficult to replicate/compare results (see table 3). For instance, we cannot directly compare studies using region of interest vs dynamic cortical mapping. There are some longitudinal studies in first-episode schizophrenia in adult populations controlling for medication showing differential treatment effects on brain morphology.\textsuperscript{65,66} Studies with early-onset cases need to control for these differential treatment effects. Also, most studies on early-onset psychosis do not take into account the known gender differences in developmental trajectories of the brain.\textsuperscript{6,67}
<table>
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<td>Total cerebral volume, lateral ventricle volume, ventricle/brain ratio, basal ganglia (caudate, putamen, and globus pallidus), and midsagittal thalamic area</td>
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<td>Sporn et al(^{22})</td>
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<td>Total brain, cerebral volume, cerebellar volume, lateral ventricle (L, R), third ventricular volume, fourth ventricular volume, temporal WM (L, R), temporal horn (L, R), temporal lobe (L, R), hippocampuses (L, R), and amygdala (L, R)</td>
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Separate analyses by gender would allow an assessment of whether the timing of brain changes is gender specific.

**Future Research**

Results of studies are controversial regarding which specific brain structures in children and adolescents with psychosis abnormally change over the course of development. Most studies examine volumes of lobes and ventricles with scant analysis at a sub-lobar level. Indeed, volumetric studies focus on brain macroarchitecture but offer little data on brain microarchitecture. Observed changes are most likely glial and vascular rather than purely neuronal. In fact, it has been recently suggested that reduction in GM may primarily reflect a reduction of neuropil rather than a deficit in the total number of neurons. Furthermore, brain regions do not mature in parallel, and the interaction between onset of symptoms and brain areas affected needs to be disentangled. In this sense, diffusion tensor imaging (DTI) reports on white matter structure represent an interesting contribution.

The time course of GM maturation varies by region, suggesting dynamic patterns of overproduction and regression. Developmental trajectories may vary according to gender, intelligence, and other variables. Thus, the inclusion of other variables such as specific diagnosis, IQ, antipsychotic and other types of treatment, presence of psychotic symptoms, duration of untreated psychosis, and normal control groups matched for education, parental socioeconomic status, race, height, and other potential confounding variables may offer new insights into the meaning of longitudinal brain abnormalities in children and adolescents with psychosis.

Additionally, COS should be compared with adolescent-onset data. In this sense, controlling for confounding variables, as well as longer duration of follow-up and larger sample sizes, will provide validity to the specificity of the findings for early-onset schizophrenia compared with other early-onset mental disorders. Furthermore, research on brain development changes in early-onset schizophrenia should explore whether abnormal brain function in children and adolescents with psychosis is related to brain volume abnormalities.

Research on the etiology of brain changes should be linked with research on pathophysiological mechanisms that explain how longitudinal brain abnormalities are produced. Our group is currently working on this topic. For example, we have recently found that enlargement of lateral ventricles in children and adolescents with first-episode schizophrenia is directly related to oxidative stress damage (D. Fraguas, S. Reig, O. Rojas, unpublished data). Future studies should look for correlates at a cellular level and for pathophysiological explanations of
volume changes. Finally, the genetics of normal and abnormal brain development seems to be a promising area of research. Much of brain development requires modification of gene expression and protein production. Most developmental genes are expressed differentially depending on age and brain region, and genetic and environmental factors seem to relate to cortical development in both a regional and age-specific manner. Similarly, many of the genes associated with schizophrenia seem to have functional roles throughout the lifespan and, for a complex disorder such as this, an ongoing interplay of genetic, epistatic, and environmental factors is likely to take place. A question of great interest is whether brain developmental trajectories will be better intermediate phenotypes than static regional volumes or densities at a given point in time. Pilot data with candidate genes such as GAD1 and neuregulin suggest that this may be the case. The association of risk genes involved in circuitries associated with schizophrenia and their relationship to developmental trajectories is another promising area of future research.

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