

Longitudinal Brain Changes in Early-Onset Psychosis

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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 relation-

ship 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,¹ 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.^{2,3} This synaptic pruning is also supported by the changes in

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synaptophysin, a synaptic marker protein, during human childhood and adolescence.⁴ 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.*⁵). 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.⁶ 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.⁶

A study of 13 subjects scanned every 2 years for 8–10 years showed a clear heterochronicity in human cortical development.⁷ 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).⁸ Regional subanalyses from the same and other studies^{9–11} 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 Hulshoff¹²) as well as during the course of chronic illness.¹³ 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 prepsychotic neurodevelopmental problems characterize COS and are much less prevalent in adolescent onset.^{14,15} We also know that genes involved in brain development are expressed differentially in different age groups.^{16,17} 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.¹⁸ 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.¹⁹ 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.²⁰ An expanded sample from the

Table 1. Volumetric Results From Longitudinal MRI Studies of Childhood-Onset Schizophrenia

Study Reference (Research Group)	<i>n</i> ^a	Age at Initial Scan in Years, Mean (SD)	Age at Onset in Years, Mean (SD)	Follow-up in Years, Mean (SD)	Findings ^b
Frazier et al ^{25,50} (NMIH)	8 COS, 8 controls	COS: 15.1 (2.3), controls: 15.4 (3.1)	COS 10.5 (1.3)	2	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.
Rapoport et al ²³ (NMIH)	16 COS, 24 controls	COS: 14.8 (2.4), controls: 14.3 (1.9)	COS 10.23 (1.75)	2.23 (0.23)	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.
Rapoport et al ¹⁸ (NMIH)	15 COS, 34 controls	COS 13.9 (2.3), controls 12.8 (2.9)	COS 10.3 (2.0)	4.28 (0.63), range 3–5 years	FU: COS significantly larger decrease in temporal, frontal, and parietal GM. No significant differences in white matter volume.
Thompson et al ¹⁹ (NMIH)	12 COS ^c , 10 PNOS, 12 controls	COS 13.9 (0.8), controls 13.5 (0.7)	About 3 years previous to first scan	4.6	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 >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.
Keller et al ²⁴ (NMIH)	50 COS, ^{c,d} 50 controls ^d	COS 14.8 (2.5), controls 14.9 (2.4)	COS 10.3 (1.8)	Range 2–6 years ^e	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.
Sporn et al ²² (NMIH)	39 COS ^c , 43 controls	COS 15.0 (2.3), controls 14.8 (2.2)	COS 10.2 (2.2)	Range 2–6 years, patients 3.4 (1.4), control 3.6 (1.6)	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.
Gogtay et al ^{7,37} (NMIH)	23 COS, 19 PNOS, 38 controls	COS: 13.9 (2.5), PNOS: 13.3 (3.1), controls: 13.3 (3.1)	COS 10.13 (2.1), PNOS 7.8 (1.9)	2.5(0.8)	FU: COS significant decrease in total, frontal, temporal, and parietal GM relative to PNOS or controls. No significant vol differences between PNOS and controls.

Table 1. Continued

Study Reference (Research Group) <i>n</i> ^a	Age at Initial Scan in Years, Mean (SD)	Age at Onset in Years, Mean (SD)	Follow-up in Years, Mean (SD)	Findings ^b	
Vidal et al ⁴⁰ (NMIH)	12 COS, 12 controls, 9 PNOS	COS 14.1 (2.7), PNOS 13.6 (2.7), controls 13.5(2.4)	Before age 13	4.6	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 (>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.
Greenstein et al ²⁶ (NMIH)	70 COS ^d , 72 controls ^d	COS 14.47 (2.6), controls 14.35 (2.56)	COS 10.17 (1.95)	COS up to 7.98 years, controls up to 7.38 years	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.
Nugent et al ²⁷ (NMIH)	29 COS, 31 controls	COS: 14.6 (2.4), controls: 14.6 (2.2)	Before age 13	Range 6–10 years	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.

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.

^aIncludes patients and controls with >1 scan unless otherwise specified.

^bAll significant findings relative to healthy controls.

^cPatients from these 3 studies come from the same sample.

^dIncluding also patients without follow-up scans.

^eThose 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.^{21,22} 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,²³ as well as loss of cerebellar volume.²⁴ 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.²⁵ More recently, reduced cortical thickness has been reported with repeated scans in 70 patients, ages 7–26, diagnosed with COS.²⁶ 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 development²⁶ 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 26.²⁷ 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.²⁸ 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.²⁹

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,^{30–33} 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 psychosis) with a mean age at onset of 15.2 years³⁴ have been reported with progression of GM deficits over the first 2 years of the disease.³⁵ It is noteworthy that these studies assessed patients with early-onset psychosis, not only schizophrenia, and had small sample sizes. James et al^{36,37} 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.³⁷ Patients also had smaller thalamic and larger fourth ventricle volumes at baseline, again with no evidence of progressive changes.³⁶

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.³⁸ 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

Table 2. Volumetric Results From Longitudinal MRI Studies of Adolescent-Onset Psychosis

Study Reference	n	Duration of Illness	Age at Initial Scan, Mean (SD)	Follow-up, Mean (SD)	Findings ^a
James et al ³⁵	16 patients ^b , 16 controls	M: 1.95 yrs., F: 1.04 yrs.	Patients 16.6 (1.9) yrs., controls 16.0 (2.0) yrs.	Patients 2.7 (1.7) yrs., controls 1.7 (0.5) yrs.	B: Significant generalized ventricular enlargement (greater in males), greater left temporal horn, and smaller left amygdala; FU: no evidence of progressive structural brain changes.
James et al ³⁴	16 patients ^b , 16 controls	Same as above	Same as above	Same as above	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.
S. Reig, C. Moreno, D. Moreno, M. Burdalo, J. Janssen, M. Parellada, A. Zabala, M. Desco, C. Arango, submitted	21 patients ^c , 34 controls	3.2 (3) mo.	Patients 15.7 (1.7) yrs., controls 15.2 (1.4) yrs.	Patients 24.2 (1.0) mo., controls 24.2 (0.5) mo.	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.

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.

diagnostically specific to COS in contrast to other child-onset psychoses.³⁸ At a 2- to 10-year follow-up after initial assessment of a group of children with atypical psychosis,³⁹ none had a diagnosis of schizophrenia, but 40% met criteria for bipolar type I disorder.⁴⁰ When 9 children 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 reduction 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.⁴⁰

Twelve patients from the NIMH COS cohort were assessed to map GM loss rates across the medial hemisphere surface.⁴¹ Patients, healthy controls, and medication- and IQ-matched subjects with psychotic symptoms not fulfilling criteria for schizophrenia were scanned 5 years apart. The medial frontal cortex was already affected 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 frontal and cingulate GM loss in the same areas, although to a lesser degree than patients with schizophrenia. Differences between patients with schizophrenia and psychosis NOS did not reach statistical significance. In 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.¹⁹

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 (S. Reig, C. Moreno, D. Moreno, M. Burdalo, J. Janssen, M. Parellada, A. Zabala, M. Desco, C. Arango, submitted). The group of patients comprised 8 patients with schizophrenia and 13 with “nonschizophrenia psychotic disorders” (including bipolar disorder, depression with psychotic features, brief reactive episodes, and atypical psychoses). Patients with schizophrenia and with nonschizophrenia psychotic disorders showed a similar pattern of change relative to controls (S. Reig, C. Moreno, D. Moreno, M. Burdalo, J. Janssen, M. Parellada, A. Zabala, M. Desco, C. Arango, submitted).

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.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.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.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.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.⁴¹ The opposite has been reported in adults with poorer outcome associated with greater brain tissue loss,²⁹ although other adult studies agree with the counterintuitive results in COS.^{42,43} Different brain development stages at the time of first episode could account for the difference between adult- and early-onset schizophrenia in terms of the relationship between progressive changes and clinical correlates. For instance, excessive pruning in those adolescents could represent an appropriate response to a dysfunctional mechanism for establishing cortical representations. However, pruning usually takes place at younger ages than those reported in early-onset schizophrenia.^{2,44-46}

Age at onset is not associated with degree of GM deficits in most adult population cross-sectional studies.⁴⁷⁻⁵⁰ Age at onset is also not related in COS²² although Thompson et al¹⁹ 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^{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,^{19,23,51} even some years after the onset of psychotic symptoms that are already present in the first-episode early-onset studies.^{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 al⁵² 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,¹⁹ and frontal regions.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 abnormalities⁵³ (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.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.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.^{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.^{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).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.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*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.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.^{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.^{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.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-

phrenia, and lead to larger than expected decreases in cortical volume and compensatory increases in CSF, in the absence of neurodegeneration markers.

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 psychoses⁴¹ (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.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.^{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.^{6,67}

Table 3. Methodological Issues of Longitudinal MRI Studies

Study Reference	Areas Assessed	Methods of Measurement	Imaging Techniques
Frazier et al ^{25,51}	Lateral ventricle volume, basal ganglia (caudate, putamen, and globus pallidus) volume	Automated procedure (lateral ventricular vol), mouse-driven tracing tool (basal ganglia)	1.5-T scanner ^a , ROI analyses
Rapoport et al ²³	Total cerebral volume, lateral ventricle volume, ventricle/brain ratio, basal ganglia (caudate, putamen, and globus pallidus), and midsagittal thalamic area	Automated procedure (lateral ventricular vol), mouse-driven tracing tool (basal ganglia), and manual outlining (midsagittal thalamic area)	1.5-T scanner ^a , ROI analyses
Rapoport et al ¹⁸	Regional cortical (temporal, frontal, parietal, and occipital) GM and WM volume	Automated procedure separates GM, WM, and CSF and separates cortex into anatomically defined lobar regions	1.5-T scanner ^a , ROI analyses
Thompson et al ¹⁹	Cortical GM volume	Automated procedure separates cortical GM, WM, and CSF	1.5-T scanner ^a , generation of brain mapping algorithms (dynamic cortical mapping) ^b
Keller et al ²⁴	Total cerebral volume, cerebellar volume (total, R, and L), vermal midsagittal area, and posterior-inferior vermal volume	Automated procedure (total cerebral and cerebellar volumes) and manual outlining (midsagittal vermal area and posterior inferior vermal lobe)	1.5-T scanner ^a , analysis of longitudinal data from all available scans (108 scans from 50 patients and 101 scans from 50 controls) with polynomial growth models, ROI analyses
Sporn et al ²²	Total cerebral volume, total and regional (F, P, T) GM volume, and ventricular volume	Automated procedure separates GM, WM, and CSF and separates cortex into lobar regions	1.5-T scanner ^a , analysis of longitudinal data from all available scans (131 scans from 60 patients and 140 scans from 64 controls) with polynomial growth models, ROI analyses
Gogtay et al ^{7,38}	Total cerebral volume and total and regional (F, P, T, O) GM volume	Automated procedure separates GM, WM, and CSF and separates cortex into lobar regions	1.5-T scanner ^a , ROI analyses
Vidal et al ⁴¹	Interhemispheric medial cortical surface	Automated method generates maps of cortical GM, WM, and CSF	1.5-T scanner ^a , generation of brain mapping algorithms (dynamic cortical mapping) ^b
Greenstein et al ²⁶	Cortical regions (except R and L insula, R cuneus, and R parahippocampus)	Automated method measures cortical thickness at 40 962 points across the cerebral hemispheres	1.5-T scanner ^a , analysis of longitudinal data from all available scans (162 scans from 70 patients and 168 scans from 72 controls) with mixed model regression; ROI analyses
Nugent et al ²⁷	Hippocampi (R, L, and subregional level)	Manual outlining by a single individual. Anatomical mesh modeling methods to match equivalent surface points across subjects.	1.5-T scanner ^a , generation of ratio maps at each age (dynamic sequence) ^c
James et al ³⁷	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), hippocampues (L, R), and amygdala (L, R)	Manual outlining, hierarchical semiautomated method of segmentation of GM and WM in the temporal lobes	1.5-T scanner, ROI analyses

Table 3. Continued

Study Reference	Areas Assessed	Methods of Measurement	Imaging Techniques
James <i>et al</i> ³⁶	Total brain volume, prefrontal cortex volume, cerebellum volume, thalamus volume, vermis volume, and fourth ventricle volume	Manual outlining	1.5-T scanner, ROI analyses
S. Reig, C. Moreno, D. Moreno, M. Burdalo, J. Janssen, M. Parellada, A. Zabala, M. Desco, C. Arango, submitted	Total intracranial volume, total and regional (F, P, T, O) GM volume, total and regional (F, P, T, O) CSF volume, and total WM volume	Semiautomated segmentation	1.5-T scanner, ROI analyses

Note: ROI, region of interest; R, right; L, left; WM, white matter; CSF, cerebrospinal fluid; F, frontal; T, temporal; P, parietal; O, occipital.

^aAll scans obtained with the same 1.5-T scanner.

^bThe 3-dimensional distribution of GM in the brain was computed from one scan to the next with a computational cortical pattern matching strategy that aligns corresponding locations on the cortical surface across time and across subjects. A local measurement of GM density was made in each subject and averaged across equivalent cortical locations. This procedure allows to pool maps of individual GM loss over time.

^cRatio maps at each age obtained by dividing the average hippocampal size of patients at a given age at each hippocampal point by the size at the corresponding hippocampal point of the control group at the matched age. Mixed model regression analyses at each of 30 000 hippocampal points were used to test for differences in longitudinal hippocampal development in patients vs controls.

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.¹¹ 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.⁶⁸ 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.^{69,70} Although DTI has been applied to the study of pediatric populations,^{71,72} there are no longitudinal studies in children assessing white matter development.

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.¹¹ 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.⁷³ Most developmental genes are expressed differentially depending on age and brain region,¹⁶ and genetic and environmental factors seem to relate to cortical development in both a regional and age-specific manner.¹¹ 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.⁷⁴ 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.¹¹ 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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