Progressive Brain Changes in Children and Adolescents With First-Episode Psychosis

Celso Arango, MD, PhD; Marta Rapado-Castro, PhD; Santiago Reig, PhD; Josefina Castro-Fornieles, MD, PhD; Ana González-Pinto, MD, PhD; Soraya Otero, MD, PhD; Inmaculada Baeza, MD, PhD; Carmen Moreno, MD; Montserrat Graell, MD; Joost Janssen, PhD; Mara Parellada, MD, PhD; Dolores Moreno, MD, PhD; Nuria Bargalló, MD, PhD; Manuel Desco, MD, PhD

Context: Progressive loss of brain gray matter (GM) has been reported in childhood-onset schizophrenia; however, it is uncertain whether these changes are shared by pediatric patients with different psychoses.

Objective: To examine the progression of brain changes in first-episode early-onset psychosis and their relationship to diagnosis and prognosis at 2-year follow-up.

Design: Prospective, multicenter, naturalistic, 2-year follow-up study.

Setting: Six child and adolescent psychiatric units in Spain.

Participants: A total of 110 patients and 98 healthy controls were recruited between March 1, 2003, and November 31, 2005. Magnetic resonance imaging of the brain was performed for 61 patients with schizophrenia (n=25), bipolar disorder (n=16), or other psychoses (n=20) and 70 controls (both at baseline and after 2 years of follow-up). Mean age at baseline was 15.5 years (patients) and 15.3 years (controls).

Main Outcome Measures: The GM and cerebrospinal fluid (CSF) volumes in the total brain and frontal, parietal, and temporal lobes.

Results: Compared with controls, patients with schizophrenia showed greater GM volume loss in the frontal lobe during the 2-year follow-up (left: −3.3 vs −0.6 cm^3, $P=.004$; right: −3.7 vs −0.8 cm^3, $P=.005$) and left frontal CSF volume increase (left: 6.7 vs 2.4 cm^3, $P=.006$). In addition to frontal volume, changes for total GM (−37.1 vs −14.5 cm^3, $P=.001$) and left parietal GM (−4.3 vs −2.2 cm^3, $P=.04$) were significantly different in schizophrenic patients compared with controls. No significant differences emerged for patients with bipolar disease. Greater left frontal GM volume loss was related to more weeks of hospitalization, whereas severity of negative symptoms correlated with CSF increase in patients with schizophrenia.

Conclusions: Patients with schizophrenia or other psychoses showed greater loss of GM volume and increase of CSF in the frontal lobe relative to controls. Progressive changes were more evident in patients with schizophrenia than those with bipolar disorder. These changes in specific brain volumes after onset of psychotic symptoms may be related to markers of poorer prognosis.

Arch Gen Psychiatry. 2012;69(1):16-26

PROGRESSIVE BRAIN CHANGES have been found in adults with schizophrenia during the initial years after a first psychotic episode.[1] These progressive brain changes have been associated with poorer outcome,[2-6] although not all studies have reported such a relationship.[7] A progressive loss of cortical gray matter (GM) volume and an abnormal increase in ventricular volume have also been described in studies[8-11] of adolescent patients with childhood-onset schizophrenia (COS) with a long duration of illness conducted by the National Institute of Mental Health. Cortical GM loss in COS patients recruited at the National Institute of Mental Health appears to start in the parietal lobe, subsequently spreading through the temporal, frontal, and prefrontal cortices.[12,13]

Early-onset psychosis (EOP), defined as psychotic symptoms within a psychiatric disorder appearing before the age of 18 years, has been shown to be a marker of poor prognosis.[14,15] Patients with EOP may eventually develop schizophrenia, bipolar disorder, or other psychoses.[16] Although some studies[17,18] of COS have revealed no progressive changes during a 2- to 3-year period in prefrontal GM deficit or in the ventricular enlargement observed relative to control subjects, few longitudinal studies[17,19-22] and even fewer research teams have investigated the structural brain changes that occur in the ado-

Author Affiliations are listed at the end of this article.

lescent brain during the first few years after onset of a first psychotic episode, and the results have not been consistent. Different severity, diagnoses, age at onset, and duration of illness may have contributed to the inconsistent results in previous studies. It is unclear whether EOP patients other than those with schizophrenia show progressive brain changes during the first few years after symptom onset. A 2½-year brain imaging follow-up study comparing healthy controls and patients with psychosis not otherwise specified and COS found the greatest reduction of GM volumes in the COS group, suggesting that cortical volume loss was more evident in COS when compared with other childhood-onset psychoses.[8] In another longitudinal study by the same group, 9 children with bipolar I disorder were compared with 8 children with atypical psychosis and a matched healthy control group; the brain trajectories showed a similar pattern (cortical GM gain in the left temporal cortex and bilateral GM reduction in the anterior and subgenual cingulate cortex) in both patient groups.[23] Finally, male EOP patients (mean age, 15.8 years) showed progressive GM volume loss and CSF volume increase in the frontal lobes, regardless of a follow-up diagnosis of schizophrenia or nonschizophrenia psychotic disorder.[22]

The Child and Adolescent First-Episode Psychosis Study (CAFEPS) is a multicenter follow-up study that aims to assess clinical characteristics, prognostic factors, diagnostic specificities, and pathophysiologic changes in the brain during the first 2 years after a first psychotic episode through an integrative and translational approach.[24] Our sample includes a matched comparison group composed of healthy children and adolescents from each participating center to control for potential demographic factors known to affect neurodevelopment.[25] We report here on one of the primary aims of the study—the comparison of structural brain changes between patients with first-episode EOP and healthy controls during a 2-year period. Patients were classified into schizophrenia, bipolar disorder, and other psychoses diagnostic groups based on a 2-year follow-up clinical assessment. Thereafter, we assessed whether diagnostic subgroups differed with respect to longitudinal brain changes. We also examined the relationship of brain changes with clinical prognostic variables and antipsychotic exposure.

On the basis of our preliminary results and the previous literature on adults, our initial hypotheses were that (1) patients would show greater progressive brain changes than those seen in healthy controls, mainly in the frontal lobe, (2) progressive changes would be greater in patients who develop schizophrenia, and (3) greater progressive changes would be markers of poorer prognosis.

METHODS

STUDY PARTICIPANTS

The complete methods of the CAFEPS, a multicenter, longitudinal follow-up study of first-episode psychosis in children and adolescents, have been comprehensively described elsewhere.[24] A sample of 110 patients and 98 healthy controls matched for age, sex, and parental socioeconomic status was consecutively recruited in outpatient and inpatient units in 6 hospitals in Spain. Recruitment took place between March 1, 2003, and November 31, 2005. Inclusion criteria were age between 7 and 17 years with a first episode of psychosis of less than 6 months' duration at baseline assessment. The exclusion criteria were (1) concomitant Axis I disorder at the time of evaluation, (2) mental retardation according to *DSM-IV* criteria, (3) any neurologic or pervasive developmental disorder, (4) history of head trauma with loss of consciousness, (5) pregnancy, and (6) substance abuse or dependence but not use if psychotic symptoms persisted 14 days after a negative urine drug test result. The intention was to recruit an equal number of patients and healthy controls at each of the participating clinical centers to ensure the homogeneity of sociodemographic factors. The study was approved by all institutional review boards at each clinical center, and written informed consent was obtained from all participants and/or their parents or legal guardians. All controls and patients met magnetic resonance imaging (MRI) safety criteria.

Of the total CAFEPS sample, 92 patients and 94 healthy controls underwent MRI at baseline. Baseline differences in volume measurements have been reported for the whole sample elsewhere.[26] A subsample of 61 first-episode psychosis patients (21 girls) and 70 healthy controls (23 girls) completed both the baseline and 2-year follow-up MRI and corresponding clinical evaluations. The MRI attrition was due to loss to follow-up in 11.9% (of the total baseline sample), refusal to participate in 7.0%, technical problems in 3.8%, fear of the MRI in 2.7%, orthodontics in 1.6%, change of residence in 1.6%, and other in 0.5%. Only those patients and healthy controls who underwent the MRI and clinical assessments both at baseline and at the 2-year follow-up visit were included in the analyses. This approach allowed us to longitudinally examine brain changes in the same sample over time.

CLINICAL AND FUNCTIONAL ASSESSMENTS

Diagnosis was established according to *DSM-IV* criteria using the Spanish version of the Kiddie-Schedule for Affective Disorders and Schizophrenia, Present and Lifetime Version, a semistructured diagnostic interview designed to assess current and past psychopathologic conditions.[27,28] The interview was administered to both patients and healthy controls at baseline and follow-up. Parents, patients, and healthy controls were interviewed separately by psychiatrists or clinical psychologists trained in the use of the instrument in children and adolescents. Diagnostic consensus was achieved for those patients in whom the presence or absence of a psychiatric disorder was in doubt. For data categorization, we used the final diagnosis established at the 2-year clinical follow-up assessment. Three main diagnostic categories were established: schizophrenia, bipolar disorder, and other psychoses. According to the diagnosis at the 2-year assessment, our patient sample included 25 patients with schizophrenia, 16 with bipolar disorder, and 20 with other psychoses (including schizoaffective disorder in 11, depression with psychotic features in 3, brief psychotic disorder in 1, and psychosis not otherwise specified in 5).

Clinical and functional assessments were performed at the corresponding clinical center by trained psychiatrists at different times. The rater was the same for each patient at baseline and 2-year follow-up. Severity of symptoms was measured using the Spanish validated version of the Positive and Negative Syndrome Scale (PANSS).[29,30] Interrater reliability for the PANSS was determined using the intraclass correlation coefficient, which was superior to 0.80 for all subscales and total score. Longitudinal change in all PANSS subscales and PANSS total score was estimated as measures at follow-up minus measures at baseline. The mean baseline and follow-up PANSS scores were also examined to capture traitlike individual differences in the se-

verity of the patients' clinical trajectories. Severity of disability and level of functioning in patients were determined using the Children's Global Assessment of Functioning (C-GAF) scale.[31] This scale rates the level of functioning in the past month on an ordinal scale ranging from 1 (requires supervision at all times) to 100 (high functioning). The physician completed this scale after the entire assessment visit with the patient was finished, based on his/her own clinical judgment and information given by the patient and his/her parents or legal guardians. Longitudinal change in C-GAF scores was estimated as the C-GAF score at follow-up minus the C-GAF score at baseline. In keeping with previous reports,[5] the other variable used to assess prognosis was the number of weeks hospitalized during the 2-year follow-up. Premorbid social adjustment was assessed using the Premorbid Adjustment Scale (PAS).[32] We used the PAS-1 for sociability and withdrawal where 5-item scores were obtained in each life period (childhood, early adolescence, and late adolescence), rating only those life periods considered to be premorbid with regard to age of illness onset. In the PAS, items are measured by a Likert-type scale of 0 to 6, where lower values reflect better functioning. The composite score for this domain was calculated by adding the appropriate item scores and dividing the resulting score by the maximum total score that could be obtained for the corresponding age stage and domain. Finally, the vocabulary and block design subtests of the Weschler Intelligence Scale for Children or the Weschler Adult Intelligence Scale were used to estimate the IQ of those younger than 16 years or 16 years and older, respectively.[33] The subtests were administered by experienced neuropsychologists trained in the use of these instruments. Interrater reliability determined using the intraclass correlation coefficient ranged from 0.80 to 0.99 in all cases.

The mean duration of illness was defined as the time between onset of the first symptom and enrollment. Chlorpromazine equivalents were used to derive the antipsychotic dosage and to calculate the cumulative doses taken during the interval between MRIs.[34,35]

BRAIN IMAGING

An anatomical brain MRI was performed at baseline and at the 2-year follow-up visit (mean [SD], 25.7 [2.7] months), using 5 different 1.5-T scanners (2 Siemens Symphony scanners, Siemens Healthcare; 2 General Electric Signa scanners, GE Healthcare; and 1 Philips ACS Gyroscan, Philips Healthcare). Data were collected from each center and processed at only one site. Sequences acquired were a T1-weighted, 3-dimensional gradient echo (voxel size, $1 \times 1 \times 1.5$ mm) and a T2-weighted turbo spin-echo (voxel size, $1 \times 1 \times 3.5$ mm), all in the axial plane. Full details about the acquisition parameters at each site, comparability among the machines for this study, and the limitations involved in the analysis of this multicenter data can be found elsewhere.[36] This study about compatibility among the scanners suggested that pooling of multisite data adds small error for whole brain measurements and an intersite coefficient of variation ranging from 1.8% to 5.2%, respectively, for GM and cerebrospinal fluid (CSF).[36] However, volume estimations of white matter (WM) were more prone to site-related errors than GM or CSF. On the other hand, measurement error of the occipital lobe was high, with the intersite coefficient of variation reaching 11.7% for WM and 17.3% for CSF.[36] On the basis of these findings, regional measurements of WM and of the occipital lobe were discarded for this study.

Segmentation and Region of Interest Definition

The MRIs were processed using software developed in house incorporating a variety of image processing and quantification tools.[36,37] Total GM and CSF volumes in the frontal, parietal, and temporal lobes were obtained using a method for semiautomated segmentation of the brain based on the Talairach proportional grid system.[38,39] The method follows a 2-step procedure.[37] First, an initial segmentation of cerebral tissues into GM, WM, and CSF using SPM2 (Statistical Parametric Mapping, Wellcome Institute; http://www.fil.ion.ucl.ac.uk/spm) routines for multimodal (T1 and T2) segmentation was performed. The SPM algorithm for tissue segmentation includes a method for eliminating the effect of radiofrequency field inhomogeneities.[40] Multimodal segmentation was proven to be more robust than the single modality in a multicenter setup.[36] Second, a Talairach grid was built on each edited brain MRI by manually selecting the position of the anterior and posterior commissures and establishing a third point position in the midsagittal plane. The coordinates of these points were used to calculate the transformation (rigid rotation) required to comply with the Talairach orientation (ie, setting the anterior commissure–posterior commissure line in the axial horizontal plane and the interhemispheric plane in the vertical orientation).[41] Our software application automatically finds the outer brain limits in Talairach orientation, and 3-dimensional Talairach grids are built for each brain. The Talairach grid represents a piecewise linear transformation and a tessellation of the brain into a 3-dimensional grid of 1056 cells representing homologous brain regions across study participants.[41] The region of interest (ROI) measurements were obtained by superimposing 3-dimensional tissue masks corresponding to GM, WM, and CSF onto each participant's Talairach grid, where the ROIs were defined as sets of Talairach grid cells.[36,38,39] Volume for each tissue type was measured by adding up the data from the Talairach grid cells associated with each ROI.[37]

The validity of the Talairach-based procedure as an automated segmentation and quantification tool suitable for volumetric studies has been proven,[38,39] and the tool has been used in other longitudinal studies.[2] In our implementation, all manual procedures were performed by a single operator blinded to the diagnosis and origin of each MRI, thus avoiding any potential bias or interrater variability. A detailed report about the reliability of our implementation in this multicenter setup is provided elsewhere.[36]

Regions of Interest

The ROIs included in the analysis were the frontal, parietal, and temporal lobes, defined using the boundaries previously described for the Talairach method.[38] Whole brain WM, GM, and CSF volumes were also measured. These ROIs were chosen because prior literature has shown that these regions are most likely to present volume changes over time in adolescent patients with first-episode psychosis.[36] Volumes were obtained for each ROI in both hemispheres.

Multicenter reproducibility of measurements was much higher for GM than for WM.[36] For this reason, volume data for WM was only included for total WM and not for the different brain lobes, thus reducing the dimensionality of the analysis. Intracranial volume (ICV) was obtained by adding the total GM, WM, and CSF volumes, including the cerebellum.

Measurement of Longitudinal Changes

Longitudinal change in volume was measured as the difference between the volume of each ROI at baseline and follow-up (ie, volume change = follow-up volume − baseline volume).

STATISTICAL ANALYSIS

Normality of the distributions and homoscedasticity of variance among groups were checked before the analyses. To test

for differences in demographic data between patient subgroups and controls, analysis of variance, Fisher exact, or χ^2 tests were used, depending on the type of variable.

A comparative analysis of volumetric differences at baseline between patients and controls has been reported elsewhere.[26] To test for longitudinal changes in clinical symptom scores and volume variables within patient and control groups, paired *t* tests were used. To test for longitudinal changes in volume variables among the 3 diagnostic subgroups and controls, an analysis of covariance (ANCOVA) model was used. This model included age, ICV at the first scan, interscan interval, interscan ICV change, and site as covariates of no interest. These 5 covariates were included in the model because of their potential effect on volume data, despite showing no significant differences among the groups. Assuming that ICV should not change over time, interscan ICV change (ICV2 – ICV1) was included in the ANCOVA to remove a potential effect of spurious method variance associated with change from ICV1 to ICV2. The assumption of no interaction between each of the covariates and the group factor was checked for all variables. The analysis was performed using within-subject longitudinal volume change (follow-up – baseline) as the dependent variable. When this variable showed a main effect, post-hoc Sidak tests were used to detect the pair of groups showing significant differences. This analysis was preferred over repeated-measures ANCOVA of raw data at baseline and at follow-up because the confounding effect of scanner site was minimized by using the within-subject change values. The analysis of longitudinal changes was performed using the pooled sample of boys and girls. The initial full-factorial model was tested, including sex and group × sex interaction. However, because no significant effects of sex or the interaction term were significant, sex was not included in the final model. (Results of this analysis are available on request.)

To examine the association between volumetric measurements with cumulative dose of antipsychotic medication and clinical and functional outcome scores, such as longitudinal differences in C-GAF, number of weeks hospitalized during follow-up, IQ, and premorbid social adjustment (as measured by the PAS), Pearson linear correlation coefficient was used. All statistical analyses were performed using SAS statistical software, version 9.0 (SAS Institute, Inc), and a 2-tailed $P < .05$ was considered statistically significant. We chose not to adjust *P* values to avoid type I errors due to multiple comparisons because the main goal of the study was to describe longitudinal brain changes across groups rather than drawing inferences about group membership based on the differences observed in morphometric data.

RESULTS

SOCIODEMOGRAPHIC AND CLINICAL CHARACTERISTICS

Patients and controls were not significantly different in terms of age, sex, parental socioeconomic status, years of education, race, handedness, or between-scan follow-up period (**Table 1**). Mean (SD) duration of illness for the group of patients, defined as the time between the onset of the first positive symptom and baseline MRI, was 3.3 (2.7) months (range, 1-12 months). Mean (SD) duration of antipsychotic treatment at baseline was 9.9 (11.2) weeks (range, 0-16 weeks) for the pooled group of patients. The mean (SD) daily antipsychotic dose at baseline was 270.5 (148.3) mg in chlorpromazine equivalents.[34,35] Of the final sample included, 41.0% of patients had schizophrenia, 26.2% had bipolar disorder, and 33.8% had other psychoses at the 2-year follow-up. The patient subgroups did not differ in duration of illness or duration of antipsychotic treatment at the time of MRI but differed in age, which was therefore included as covariate for comparative analyses (Table 1).

Mean (SD) cumulative antipsychotic dose during the 2-year follow-up was 168 840 (213 209) mg in chlorpromazine equivalents.[34,35] With regard to clinical measurements, all PANSS scores decreased during the 2-year follow-up (**Table 2**).

No differences were found between the patients in the general CAFEPS sample who had both the baseline and 2-year follow-up MRI assessments (n = 61) and those who did not (no baseline and/or follow-up MRI; 18 had no MRI at baseline, 26 had no MRI at the 2-year follow-up, and 5 patients had no MRI either at baseline or follow-up) with regard to age, sex, or clinical or functional characteristics at baseline. The only variable that significantly differed between the 2 groups was estimated IQ (Table 2).

DIFFERENCES BETWEEN PATIENT SUBGROUPS AND HEALTHY CONTROLS

Using the same ANCOVA model to test for overall between-group differences, post-hoc Sidak tests revealed that schizophrenic patients had significantly greater (Sidak $P < .01$) losses of whole brain GM and greater (Sidak $P < .05$) increases of left frontal CSF volumes relative to healthy controls (**Table 3**). Schizophrenic patients also had greater losses of GM volume in the frontal lobe (right: Sidak $P < .05$; left: Sidak $P < .01$) and in the left parietal lobe (Sidak $P < .05$) compared with healthy controls (Table 3). The other psychoses group also showed losses in whole brain GM volume (Sidak $P < .001$) relative to healthy controls (Table 3). These patients also had a significantly greater (Sidak $P < .05$) loss of GM in the frontal bilaterally and left parietal (Sidak $P < .01$) lobes, as well as greater increases in CSF volume in the frontal lobes (left Sidak $P < .001$; right: Sidak $P < .05$) relative to controls (Table 3). Bipolar disorder patients showed no significant differences in longitudinal volume change relative to healthy controls, although all the differences were in the same direction as other patient subgroups (Table 3 and eTable; http://www.archgenpsychiatry.com). The ANCOVA model among the 3 diagnostic subgroups revealed no significant differences (data not shown). This was still true when weeks of hospitalization or cumulative dose of treatment were included in the model as covariates (data not shown).

ASSOCIATION BETWEEN VOLUME CHANGES AND CLINICAL AND OUTCOME VARIABLES

When examining correlations among clinical and outcome variables and volume changes within diagnostic subgroups, significant correlations were observed between left frontal GM volume change during follow-up and number of weeks hospitalized ($r = -0.44$; $P = .03$) and right frontal CSF change ($r = 0.43$; $P = .04$), with more weeks hospitalized correlating with greater GM volume loss and CSF increase (**Figure**) in patients with schizophrenia.

Table 1. Sociodemographic and Clinical Characteristics of Early-Onset First-Episode Psychosis Diagnostic Subgroups and Controls

Variable	Schizophrenia (n=25)	Bipolar Disorder (n=16)	Other (n=20)	Controls (n=70)	Test[a]	*P* Value
Age, mean (SD), y	15.5 (2.0)	16.6 (0.9)	15.2 (1.8)	15.3 (1.5)	$F_{3,126}=3.2$	.03
Sex, No.					$\chi^2=1.2$	.43
Male	18	10	12	23		
Female	7	6	8	47		
Educational level, mean (SD), y	8.2 (2.2)	9.1 (1.4)	8.7 (1.6)	9.0 (1.4)	$F_{3,126}=1.6$	.18
Parental socioeconomic status, No.[b]					Fisher exact test	.93
1	4	4	3	6		
2	8	6	7	20		
3	6	3	7	18		
4	4	2	1	6		
5	3	1	2	20		
Handedness, right/left/mixed, No.	23/3/0	14/2/0	18/2/0	61/7/2	Fisher exact test	.73
Between-scan follow-up period, mean (SD), mo	26.2 (3.0)	25.6 (2.3)	24.8 (3.2)	25.8 (2.5)	$F_{3,126}=0.8$	.47
Race/ethnicity, No.					Fisher exact test	.18
White	23	15	19	66		
Other	2	1	1	4		
Duration of illness at baseline MRI, mean (SD), mo	4.3 (2.9)	2.5 (2.4)	2.8 (2.6)		$F_{2,58}=1.3$	.31
Hospitalization, mean (SD), wk	6.6 (6.2)	4.7 (4.5)	7.6 (7.4)		$F_{2,58}=1.0$	.37
Duration of treatment at baseline MRI, mean (SD), wk	11.5 (10.1)	11.9 (17.5)	6.8 (5.5)		$F_{2,58}=0.43$	.73
Treatment at baseline, No.[c]						
Quetiapine	5	4	3			
Olanzapine	6	4	3			
Risperidone	13	7	2			
Ziprasidone	2	1	0			
Aripiprazole	1	0	0			
Haloperidol decanoate	0	0	0			
No antipsychotic treatment	1	0	0			
Oxcarbazepine	0	1	0			
Biperiden	1	0	1			
Other[d]	3	1	1			
Treatment at follow-up, No.[c]						
Quetiapine fumarate	2	2	2			
Olanzapine	4	4	4			
Risperidone	6	4	6			
Clozapine	4	0	1			
Ziprasidone	1	2	0			
Aripiprazole	2	0	2			
Haloperidol	0	0	2			
Chlorpromazine	1	0	0			
Amisulpride	0	1	1			
No antipsychotic treatment	5	5	4			
Oxcarbazepine	0	0	1			
Valproic acid	1	2	0			
Biperiden	1	1	0			
Other[d]	1	0	2			
Cumulative chlorpromazine equivalents, mean (SD)	168 568 (90 011)	130 580 (116 617)	199 776 (344 057)		$F_{2,58}=0.57$	.67
PANSS negative score at baseline, mean (SD)	21.7 (8.5)	17.3 (10.5)	19.3 (8.5)		$F_{2,58}=1.2$	.31
PANSS positive score at baseline, mean (SD)	24.6 (4.3)	26.2 (8.0)	22.9 (6.8)		$F_{2,58}=1.2$	.30
PANSS general score at baseline, mean (SD)	45.3 (9.0)	47.3 (14.9)	44.6 (11.3)		$F_{2,58}=0.3$	.77
PANSS total score at baseline, mean (SD)	91.6 (16.4)	90.8 (28.2)	86.7 (21.3)		$F_{2,58}=0.3$	.74
C-GAF score at baseline, mean (SD)	34.0 (13.5)	32.4 (16.5)	37.5 (16.8)		$F_{2,58}=0.5$	.60

Abbreviations: C-GAF, Children's Global Assessment of Functioning; MRI, magnetic resonance imaging; PANSS, Positive and Negative Syndrome Scale.

[a] Analysis of variance was used for comparisons between quantitative measures, and χ^2 or Fisher exact test was used for comparisons between qualitative measures

[b] Parental socioeconomic status assessed with the Hollingshead Scale[42] (ranging from 1 to 5). A rating of 5 corresponds to the highest socioeconomic status and a rating of 1 to the lowest,

[c] Patients were polymedicated, increasing the sample size for medication. At baseline, 4 patients with schizophrenia were taking 2 antipsychotics and 3 patients with bipolar disorder were taking 2 antipsychotics, whereas only 1 patient from the other psychoses group was taking 2 antipsychotics and 1 from this group was taking 3 antipsychotics. At the 2-year follow-up, 1 patient with schizophrenia, 2 patients with bipolar disorder, and 3 patients from the others subgroup were taking 2 antipsychotics, whereas 1 bipolar patient was taking 3 antipsychotics.

[d] Other indicates antidepressants or anxiolytics. No patient was treated with lithium in this sample.

There was also a significant association between left frontal CSF volume change during follow-up ($r=0.58$; $P=.003$) and left parietal CSF change ($r=0.45$; $P=.03$) with mea negative PANSS score in patients with schizophrenia. Le

Table 2. Comparison of Clinical and Functional Symptom Scores of Completers and Noncompleters

Variable	Completers (n=61)			Noncompleters (n=49)[a]		
	Baseline, Mean (SD)	Follow-up, Mean (SD)	Change[b]	Baseline, Mean (SD)	Baseline *t* Test[c] or χ^2 Test Score	*P* Value
Age, y	15.5 (1.7)	NA	NA	15.6 (1.8)	*t*=0.30	.77
Sex	40/21 (NA)	NA	NA	32/17 (NA)	χ^2=0.04	.66
Age at onset, y	15.8 (1.9)	NA	NA	15.9 (1.8)	t=0.00	>.99
Estimated IQ	83.9 (18.6)	NA	NA	73.0 (21.6)	*t*=3.55	.001
PAS social score	3.4 (3.2)	NA	NA	3.6 (2.8)	*t*=0.31	.76
PANSS score						
Negative	19.7 (9.1)	15.7 (7.8)	−4.25[d]	20.6 (8.5)	*t*=0.41	.68
Positive	24.5 (6.3)	13.0 (6.5)	−11.49[d]	23.3 (6.3)	*t*=1.02	.31
General	45.6 (11.4)	29.2 (10.1)	−16.22[d]	44.6 (9.5)	*t*=0.53	.60
Total	89.7 (21.4)	57.9 (21.6)	−31.97[d]	88.5 (18.1)	*t*=0.42	.67
C-GAF score	34.8 (15.5)	64.0 (22.1)	28.96[d]	31.8 (14.0)	*t*=0.97	.33

Abbreviations: C-GAF, Children's Global Assessment of Functioning; NA, not applicable; PANSS, Positive and Negative Syndrome Scale; PAS, Premorbid Adjustment Scale.

[a] Noncompleters are patients for whom we do not have a baseline or follow-up magnetic resonance imaging data or from whom the data were not good enough to be used for the study. Comparison of symptom severity and other sociodemographic factors and predictors of functional outcome for these patients and completers was performed at baseline.

[b] Absolute change (follow-up minus baseline) in symptom severity is presented for completers.

[c] Student *t* test comparative analysis between completers and noncompleters at baseline.

[d] Paired *t* test $P<.001$ for clinical and functional variables in the completers group.

frontal CSF volume change (r=0.49; P=.02) correlated with the mean PANSS total score, where more average symptoms correlated with greater CSF increase (Figure) in these patients. No other functional variables, such as C-GAF, IQ, or premorbid social adjustment, were related to volume changes in this patient subgroup.

No correlation was found between outcome or treatment variables and changes in volume measurements for the bipolar disorder or other psychoses subgroups. Antipsychotic exposure measured in chlorpromazine equivalents during the 2 years of follow-up did not correlate with any of the brain changes. With regard to clinical improvement, significant correlations were found for the schizophrenia group between the PANSS negative subscale score (r=−0.44; P=.03) and PANSS general change score (r=−0.42; P=.04) and left temporal GM loss, with less improvement correlating with larger reductions. Associations were also found between frontal right CSF and PANSS general change score (r=0.44; P=.03) and parietal right CSF and PANSS general change score (r=0.45; P=.03), suggesting that greater CSF volume increase is related to less improvement in general symptoms as measured with PANSS in schizophrenic patients. Significant correlations were found between general (r=−0.51; P=.03) and positive (r=−0.52; P=.02) and total (r=−0.51; P=.02) PANSS change scores and left parietal CSF loss in the other psychoses subgroup, suggesting that decrease in CSF volume is associated with less improvement on total score and the presence of positive psychotic symptoms during the 2-year follow-up.

COMMENT

In this longitudinal study, patients who ended up with a diagnosis of schizophrenia showed greater progressive brain changes than healthy controls in the 2-year follow-up period after the first psychotic episode. In the patients with schizophrenia, progressive volume changes in certain brain areas were related to markers of poorer prognosis, such as more weeks of hospitalization during follow-up and less improvement in negative symptoms and PANSS total score. Bipolar disorder patients did not show any significant difference when compared with healthy controls. In the control group, longitudinal brain changes were consistent with the expected pattern described for healthy adolescents.[43-45]

Some cross-sectional studies[46-48] have compared patients with bipolar disorder and schizophrenia in terms of cortical brain volume differences, with most of them showing larger reductions in the schizophrenia group. Along the same lines, a meta-analysis including studies with schizophrenic patients and studies with bipolar patients has shown that GM reductions in the schizophrenia studies are more extensive, especially in neocortical structures.[49] To the best of our knowledge, only one previous study[22] with a smaller sample size (n=16) has assessed whether progressive brain changes are diagnosis specific. In that previous study, first-episode male patients who ended up with a diagnosis of schizophrenia (and not of bipolar disorder) showed significant frontal GM reductions compared with healthy controls. We have now replicated this finding in a larger and independent sample. Our results do not support diagnosis-specific trajectories of brain volume changes in the first 2 years after illness onset because there were no significant differences in volume loss between the diagnostic subgroups. However, the schizophrenia and the other psychoses groups show different trajectories from healthy controls, whereas the bipolar disorder group does not. Patient subgroups did not differ in sociodemographic variables, duration of illness, or antipsychotic exposure with the exception of older age at the time of the MRI (schizophrenia, 15.5 years; bipolar disorder, 16.6 years). Although age was included as a covariate in the comparative analysis, this does not fully con-

Table 3. Mean (SD) Volume Measurements (in Cubic Centimeters) of Controls and Diagnostic Subgroups at Baseline and 2-Year Follow-up

Variable	Schizophrenia (n=25)			Bipolar Disorder (n=16)			Other (n=20)			Controls (n=70)			
	Baseline	Follow-up	Change[a,b]	Baseline	Follow-up	Change[a,b]	Baseline	Follow-up	Change[a,b]	Baseline	Follow-up	Change[a,b]	F[c]
Intracranial	1533.4 (158.9)	1518.7 (146.7)	−0.9	1460.8 (120.8)	1445.3 (123.4)	−1.1	1496.0 (152.2)	1482.5 (148.3)	−0.9	1498.2 (126.1)	1492.4 (124.3)	−0.4	0.9
Total gray matter	862.0 (89.0)	824.9 (75.5)	−37.1[d,e]	805.2 (66.0)	785.1 (71.4)	−20.1[f]	849.0 (75.6)	811.4 (78.6)	−37.6[d,g]	854.0 (75.8)	839.5 (70.8)	−14.5[d]	4.3[f]
Total white matter	398.5 (39.7)	411.9 (39.5)	13.4[d]	390.1 (38.4)	396.8 (39.5)	6.7[i]	389.2 (52.4)	402.2 (62.7)	13.0[d]	390.4 (38.6)	399.3 (42.1)	8.9[d]	2.1
Total CSF	272.9 (54.1)	282.0 (59.2)	9.1	265.4 (50.7)	263.4 (57.2)	−2.1	257.8 (43.7)	269.0 (43.1)	11.2	253.7 (35.5)	253.5 (37.1)	−0.2	1.7
Gray matter													
Left frontal	78.4 (8.7)	75.1 (9.8)	−3.3[i,e]	75.9 (6.3)	74.2 (8.1)	−1.7	80.4 (6.6)	76.0 (8.6)	−4.3[i,j]	80.3 (8.9)	79.7 (8.7)	−0.6	3.5[f]
Right frontal	81.4 (8.5)	77.7 (8.6)	−3.7[i,e]	78.4 (7.2)	76.7 (8.4)	−1.7	81.9 (7.4)	77.8 (8.8)	−4.2[i,j]	83.6 (8.7)	82.7 (8.5)	−0.8	2.7[f]
Left parietal	66.6 (7.1)	62.3 (9.8)	−4.3[d,j]	61.6 (6.6)	58.6 (6.8)	−3.0[d]	67.4 (8.4)	62.1 (7.4)	−5.3[d,e]	66.0 (7.5)	63.8 (7.2)	−2.2[d]	3.2[f]
Right parietal	66.7 (7.5)	63.2 (8.5)	−3.5[d]	62.3 (7.4)	59.8 (7.8)	−2.5[f]	67.1 (7.4)	61.9 (5.9)	−5.1[d,e]	66.3 (7.9)	64.0 (7.1)	−2.3[d]	2.3[f]
Left temporal	86.4 (10.5)	82.6 (9.3)	−3.8[d]	77.9 (6.6)	76.1 (6.9)	−1.8	82.4 (9.1)	79.5 (9.1)	−2.9[d]	82.2 (7.7)	80.0 (7.5)	−2.2[d]	0.4
Right temporal	84.8 (10.3)	80.6 (10.6)	−4.2[f]	77.3 (6.5)	75.3 (6.3)	−2.0[f]	82.8 (9.5)	78.2 (8.7)	−4.7[d]	81.7 (7.5)	79.5 (7.1)	−2.2[d]	1.8
CSF													
Left frontal	27.2 (7.1)	33.9 (10.0)	6.7[d,e]	28.8 (7.7)	32.8 (9.2)	4.1[i]	24.9 (4.8)	31.8 (7.0)	7.1[d,g]	25.2 (5.0)	27.7 (6.2)	2.4[d]	6.1[f]
Right frontal	28.5 (7.3)	30.6 (9.1)	2.1[f]	30.5 (7.6)	30.2 (8.2)	−0.3	27.0 (6.1)	30.1 (6.4)	3.2[d,e]	26.9 (4.7)	27.7 (5.7)	0.8	3.0[h]
Left parietal	24.6 (5.4)	27.1 (8.4)	2.5	22.7 (3.7)	24.3 (5.3)	1.5	21.6 (4.1)	23.9 (4.6)	2.8[i]	22.7 (4.5)	24.2 (4.9)	1.5[d]	0.4
Right parietal	21.9 (5.6)	22.9 (5.9)	1.0	21.9 (4.7)	21.4 (5.4)	−0.6	21.8 (6.1)	22.9 (5.6)	1.0	21.2 (4.3)	21.8 (4.6)	0.6[i]	0.5
Left temporal	23.7 (5.0)	24.4 (5.1)	0.7	21.6 (4.4)	21.4 (4.2)	−0.2	22.4 (3.9)	22.1 (3.4)	0.2	20.9 (3.9)	21.1 (4.0)	0.1	0.9
Right temporal	22.2 (5.6)	20.2 (6.2)	−2.0[i]	20.6 (4.6)	18.5 (4.8)	−2.1[f]	21.1 (4.1)	19.9 (3.9)	−1.3	20.0 (4.3)	18.5 (4.1)	−1.6[d]	0.1

Abbreviation: CSF, cerebrospinal fluid.

[a] Within-group paired *t* test. Rate of volume change was calculated for each study participant as follow-up – baseline volume (see the "Methods" section), and mean values are shown for each group. Negative values indicate volume decrease and vice versa.

[b] Post-hoc Sidak test appears in the "Statistical Analysis" subsection in the "Methods" section.

[c] *F* values, *df*=120.3, analysis of covariance model among the 4 groups (see the "Methods" section).

[d] $P<.001$, within-group paired *t* test.

[e] $P<.01$, post-hoc Sidak test.

[f] $P<.01$, within-group paired *t* test.

[g] $P<.001$, post-hoc Sidak test.

[h] $P<.001$, *F* value, analysis of covariance.

[i] $P<.05$, within-group paired *t* test.

[j] $P<.05$, post-hoc Sidak test.

[k] $P<.05$, *F* value, analysis of covariance.

trol for these variables if the trajectories are age dependent. In addition, data from the other psychoses group should be interpreted with caution because this group is a heterogeneous group in which some of the patients may end up developing schizophrenia or bipolar disorder in the long run. We have shown that, contrary to the diagnostic stability found in first-episode patients with schizophrenia and bipolar diagnoses at these ages, the stability of the other psychoses group is low.[16]

Progressive reduction in frontal GM volume and increase in frontal CSF volume have been reported during the initial years after the onset of schizophrenia in young adults[1,2,50] and later in the illness.[51] This has also been reported in very early-onset schizophrenia (mean age at the time of assessment, 16.3 years) who showed a progressive decrease in frontal-parietal growth rates in the left hemisphere during 5 years of follow-up.[52] We report progressive brain changes during adolescence, with greater loss of frontal GM volume in patients compared with controls in an EOP cohort with a mean age of approximately 15 years at onset. All these results suggest a continuum between early-onset and adult-onset psychotic disorder.

Compared with most published studies, our sample has a very short duration of illness before baseline assessment. In fact, most of the previous studies[13,53] in early-onset schizophrenia or early-onset psychoses are not with first-episode patients because patients included in those studies are usually referred to the participating institu

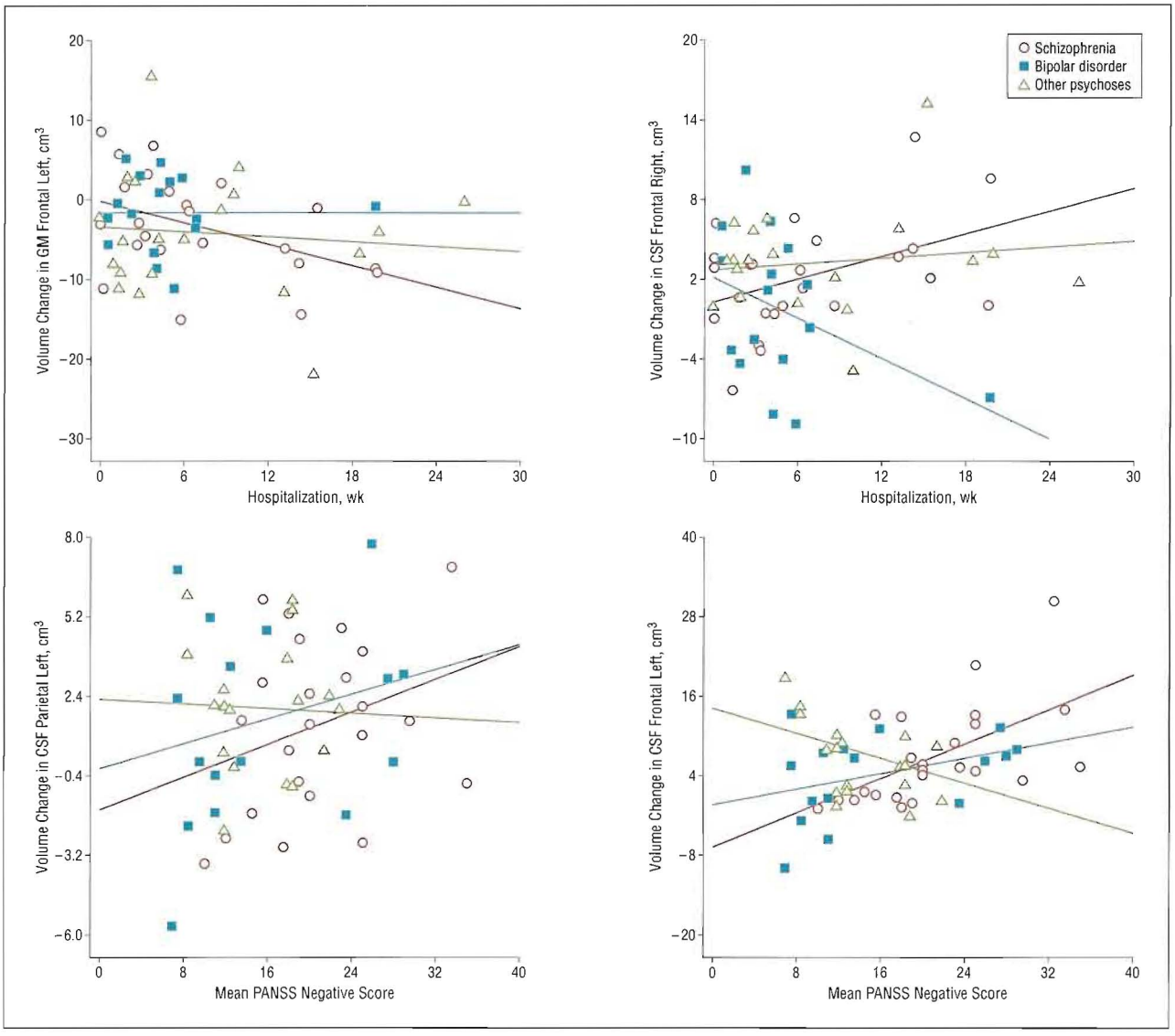

Figure. Relationship between the number of weeks hospitalized and the mean baseline and follow-up Positive and Negative Syndrome Scale (PANSS) score and gray matter (GM) and cerebrospinal fluid (CSF) volume changes within diagnostic subgroups.

tions for refractoriness after some years in treatment. Considering this short duration of illness at the baseline MRI (mean, 3.3 months) and short time of exposure to antipsychotics (mean, 9.9 weeks) in our sample, the baseline structural changes might seem to have occurred before the onset of the positive symptoms. However, based on our data, we cannot determine when frontal lobe changes first occurred. The smaller volume in patients at baseline, shortly after the onset of the first positive symptoms, may reflect a disruption of developmental processes taking place before the appearance of the first psychotic symptoms (eg, neuronal migration[54] or synaptic pruning[55,56]). Although the progressive decrease in frontal GM and the increase in frontal CSF in our sample might be interpreted as a consequence of the toxic effect of psychosis on brain structures, perhaps through an indirect mechanism such as increased cortisol produced by increased stress,[57] some researchers have argued against explanations based solely on volume differences in the absence of concurrent and consistent evidence of neuronal death and acceleration of clinical progression.[58,59] As an alternative, structural brain disease in patients with psychosis may be due to disrupted neurodevelopmental mechanisms starting after illness onset (eg, impaired synaptic plasticity[58]) and continuing during the first few years of illness. In any case, brain maturation continues until early adulthood, and any event occurring before completion of maturation, such as the progressive brain changes that we observe in this study, could be conceptualized as neurodevelopmental in nature.

Progressive prefrontal volume loss has been reported in adolescents with bipolar disorder.[60] The former study did not include a schizophrenia comparison group, and participants had a wider age range than ours (10-21 years for bipolar disorder patients and 11-19 for healthy controls). Use of imaging techniques such as voxel-based morphometry[48] could help delineate GM volume differences more specifically among diagnostic groups.[12,60]

Some of the progressive brain changes could be secondary to antipsychotic exposure, although there were

no differences in cumulative exposure to antipsychotics among the 3 diagnostic subgroups during the 2 years of follow-up that could explain the larger brain changes seen in the schizophrenia subgroup compared with the healthy controls. Because previous studies[61] with nonhuman primates show a reduction in brain volume after exposure to antipsychotics and because antipsychotic exposure was found to be related to smaller GM volumes and larger decreased WM volume in a recent longitudinal study[62] of patients with first-episode schizophrenia, the role of antipsychotics in progressive brain changes in humans should be addressed in future studies. Almost all patients in this cohort were treated with second-generation antipsychotics. Therefore, our results do not seem to support previous suggestions that second-generation antipsychotics may counteract progressive deteriorative effects by enhancing synaptic plasticity and cellular resilience, or at least if they do so, they do not completely prevent excess volume loss.[1,63] This was a naturalistic study; we therefore cannot compare the effect of first- and second-generation antipsychotics on brain volume changes because we did not have a group of patients treated only with first-generation antipsychotics.

The underlying mechanisms of brain volume changes in schizophrenia and other psychotic disorders are not yet understood. Previous longitudinal studies in adult schizophrenia patients have correlated brain volume changes with duration of untreated psychosis,[64] poorer function at follow-up,[4,6] number of hospitalizations,[5,51] hospitalization time,[65] and worsening of neuropsychological performance.[66-68] The relationship with symptoms is more controversial, with some studies showing a direct inverse relationship between brain volume changes and symptom changes at follow-up and some studies not showing any such relationship (for a review, see the article by Hulshoff Pol and Kahn[1]). In the present study, we showed a correlation between different GM volume changes and changes in symptoms as measured by PANSS. In all cases the relationship was in the expected direction, with less improvement related to larger losses of GM volumes. There are few studies of clinical correlates of progressive changes in pediatric psychosis populations. Ventricular enlargement at 2-year follow-up has been related to higher scores on the Brief Psychiatric Rating Scale at follow-up in COS.[9] Higher rates of GM volume loss in the frontal cortex have been correlated with more severe negative symptoms and faster temporal loss with greater severity of positive symptoms in COS.[12] On the contrary, greater GM volume reduction in COS has been related to greater clinical symptom improvement at follow-up.[11] The relationship between improvement in symptoms and greater GM reduction in the former study was unexpected and did not seem to depend on the type of medication or severity of symptoms at baseline or follow-up. One speculative reason suggested by the authors for this finding was the existence of compensatory synaptic and cellular pruning of malfunctioning neurons.

Some of the limitations of the present study include the following. First, our analysis protocol is restricted to brain lobes, which limits findings to large-scale brain changes. Second, the smaller sample sizes when the patients are subdivided into different diagnostic groups may be responsible for type II errors (eg, lack of significant differences between bipolar disorder patients and healthy controls or lack of significant differences among the 3 diagnostic subgroups). Third, all patients with bipolar disorder had psychotic symptoms, usually with a first manic episode, which suggests that our group of bipolar patients is probably biased toward a severe group. Fourth, adjusting *P* values to avoid type I errors due to multiple comparisons might have eliminated some of the differences we observed. However, we have provided the *P* values obtained to allow the reader assessment of this limitation. One of the strengths of the study is the short duration of illness and short antipsychotic treatment before the first MRI and the homogeneity of sociodemographic factors in the patient and control samples. The length of the follow-up period was also carefully set the same for all participants, thus reducing the effect of other possible confounding factors on the analysis of longitudinal changes.

In conclusion, we found progression of GM volume loss after a 2-year follow-up in patients who ended up with a diagnosis of schizophrenia but not bipolar disease compared with healthy controls. One or more active pathophysiologic processes seem to be occurring in the brains of children and adolescents after a first psychotic episode, especially in those with schizophrenia. Findings from cross-sectional and longitudinal studies examining patients with adolescent-onset psychosis support the concept of EOP as a progressive neurodevelopmental disorder with both early and late neurodevelopmental abnormalities.[52,69] Progressive brain changes seem to be more marked in those patients ending up with a diagnosis of schizophrenia, although progressive changes were present in other psychoses. Some of these pathophysiologic processes seem to be markers of poorer prognosis. To develop therapeutic strategies to counteract these pathologic progressive brain changes, future studies should focus on their neurobiological underpinnings. The correlates of volume changes at a cellular level and the study of risk genes involved in circuitries associated with different psychoses and their relationship to developmental trajectories may be promising areas of research.

Submitted for Publication: January 19, 2011; final revision received July 18, 2011; accepted July 21, 2011.
Author Affiliations: Department of Child and Adolescent Psychiatry (Drs Arango, Rapado-Castro, C. Moreno, Parellada, and D. Moreno), Medical Imaging Laboratory, Hospital General Universitario Gregorio Marañón, CIBERSAM (Drs Reig, Janssen, and Desco), Bioengineering and Aerospatial Engineering, University Carlos III of Madrid (Dr Desco), and Psychiatry and Psychology Section, Hospital Infantil, Universitario Niño Jesús, CIBERSAM (Dr Graell), Madrid, Spain; Image Diagnostic Center (Dr Bargalló), Department of Psychiatry and Clinical Psychobiology, University of Barcelona, Hospital Clinic de Barcelona, Institut d'Investigacions Biomèdiques August Pi Sunyer, CIBERSAM (Drs Castro-Fornieles and Baeza), Barcelona, Spain; Stanley Institute International Mood-Disorders Research Center, Hospital Santiago Apóstol de Vitoria, CIBERSAM, Vitoria, Spain (Dr González-Pinto); and Child Psychiatry Unit, Hospital Universitario Marqués de Valdecilla, CIBERSAM, Santander, Spain (Dr Otero).

Correspondence: Celso Arango, MD, PhD, Department of Child and Adolescent Psychiatry, Hospital General Universitario Gregorio Marañón, Centro de Investigación Biomédica en Red de Salud Mental, CIBERSAM, C/ Ibiza 43, 28009 Madrid, Spain (carango@hggm.es).

Financial Disclosure: Dr Arango has been a consultant to or has received honoraria from AstraZeneca, Bristol-Myers Squibb, Janssen-Cilag, Lundbeck, Otsuka, Pfizer, Roche, Servier, and Schering-Plough. Dr Castro-Fornieles has been a consultant to Lilly. Dr C. Moreno has served as a consultant to AstraZeneca, Otsuka, and Bristol-Myers Squibb. Dr Parellada has received travel support from AstraZeneca and Juste. Dr González-Pinto is employed by the University of the Basque Country and has been a consultant for the Ministry of Science of Spain and the Basque Government. Dr González-Pinto also gives conferences, acts as consultant to, or receives grants from Lilly, Janssen, MSD, Lundbek, AstraZeneca, Almirall, sanofi-aventis, BMS, Novartis, and Pfizer. The rest of the authors declare no conflicts of interest.

Funding/Support: This study was supported by the Spanish Ministry of Health and Social Policy, Spanish Ministry of Science and Innovation, Instituto de Salud Carlos III, Centro de Investigación Biomédica en Red de Salud Mental, CIBERSAM, Red Temática de Investigación Cooperative Sanitaria RD06/0011 (Red de Enfermedades Mentales y Trastornos Afectivos y Psicóticos Network), Fundación Alicia Koplowitz, and by grants PI02/1248, PI05/0678, and G03/032 from the Spanish Ministry of Health and Social Policy, Institute of Health Carlos III (Madrid, Spain), Centro para el Desarrollo Tecnológico e Industrial (CDTI) under the Consorcios Estratégicos Nacionales en Investigación Técnica (CENIT) programme Advanced Molecular Imaging Technologies (AMIT) project and supported by the Spanish Ministry of Science and Innovation.

Previous Presentations: Presented as a poster at the 12th International Congress of Schizophrenia Research; March 31, 2009; San Diego, California. The abstract was published in *Schizophrenia Bulletin* (2009;35[suppl 1]:219) and was presented as a poster at the Second Biennial Schizophrenia International Research Conference; April 12, 2010; Florence, Italy. The abstract was published in *Schizophrenia Research* (doi:10.1016/j.schres.2010.02.605) and presented at the 57th Annual Meeting of the American Academy of Child and Adolescent Psychiatry; October 28, 2010; New York, New York; and published in *The Scientific Proceedings of the 2010 Annual Meeting of the American Academy of Child and Adolescent Psychiatry* (2010;37:247).

Online-Only Material: The eTable is available at http://www.archgenpsychiatry.com.

Additional Contributions: Jose de Arriba, MSc, of the Department of Child and Adolescent Psychiatry, Hospital General Universitario Gregorio Marañón, and Centro de Investigación Biomédica en Red de Salud Mental, CIBERSAM, Madrid, Spain, provided data management.

REFERENCES

1. Hulshoff Pol HE, Kahn RS. What happens after the first episode? a review of progressive brain changes in chronically ill patients with schizophrenia. *Schizophr Bull.* 2008;34(2):354-366.
2. Ho BC, Andreasen NC, Nopoulos P, Arndt S, Magnotta V, Flaum M. Progressive structural brain abnormalities and their relationship to clinical outcome: a longitudinal magnetic resonance imaging study early in schizophrenia. *Arch Gen Psychiatry.* 2003;60(6):585-594.
3. Cahn W, van Haren NE, Hulshoff Pol HE, Schnack HG, Caspers E, Laponder DA, Kahn RS. Brain volume changes in the first year of illness and 5-year outcome of schizophrenia. *Br J Psychiatry.* 2006;189:381-382.
4. van Haren NE, Cahn W, Hulshoff Pol HE, Kahn RS. Schizophrenia as a progressive brain disease. *Eur Psychiatry.* 2008;23(4):245-254.
5. van Haren NE, Hulshoff Pol HE, Schnack HG, Cahn W, Mandl RC, Collins DL, Evans AC, Kahn RS. Focal gray matter changes in schizophrenia across the course of the illness. *Neuropsychopharmacology.* 2007;32(10):2057-2066.
6. van Haren NE, Hulshoff Pol HE, Schnack HG, Cahn W, Brans R, Carati I, Rais M, Kahn RS. Progressive brain volume loss in schizophrenia over the course of the illness. *Biol Psychiatry.* 2008;63(1):106-113.
7. van Haren NE, Cahn W, Hulshoff Pol HE, Schnack HG, Caspers E, Lemstra A, Sitskoorn MM, Wiersma D, van den Bosch RJ, Dingemans PM, Schene AH, Kahn RS. Brain volumes as predictor of outcome in recent-onset schizophrenia: a multicenter MRI study. *Schizophr Res.* 2003;64(1):41-52.
8. Gogtay N, Sporn A, Clasen LS, Nugent TF III, Greenstein D, Nicolson R, Giedd JN, Lenane M, Gochman P, Evans A, Rapoport JL. Comparison of progressive cortical gray matter loss in childhood-onset schizophrenia with that in childhood-onset atypical psychoses. *Arch Gen Psychiatry.* 2004;61(1):17-22.
9. Rapoport JL, Giedd J, Kumra S, Jacobsen L, Smith A, Lee P, Nelson J, Hamburger S. Childhood-onset schizophrenia: progressive ventricular change during adolescence. *Arch Gen Psychiatry.* 1997;54(10):897-903.
10. Rapoport JL, Giedd JN, Blumenthal J, Hamburger S, Jeffries N, Fernandez T, Nicolson R, Bedwell J, Lenane M, Zijdenbos A, Paus T, Evans A. Progressive cortical change during adolescence in childhood-onset schizophrenia: a longitudinal magnetic resonance imaging study. *Arch Gen Psychiatry.* 1999;56(7):649-654.
11. Sporn AL, Greenstein DK, Gogtay N, Jeffries NO, Lenane M, Gochman P, Clasen LS, Blumenthal J, Giedd JN, Rapoport JL. Progressive brain volume loss during adolescence in childhood-onset schizophrenia. *Am J Psychiatry.* 2003;160(12):2181-2189.
12. Thompson PM, Vidal C, Giedd JN, Gochman P, Blumenthal J, Nicolson R, Toga AW, Rapoport JL. Mapping adolescent brain change reveals dynamic wave of accelerated gray matter loss in very early-onset schizophrenia. *Proc Natl Acad Sci U S A.* 2001;98(20):11650-11655.
13. Vidal CN, Rapoport JL, Hayashi KM, Geaga JA, Sui YH, McLemore LE, Alaghband Y, Giedd JN, Gochman P, Blumenthal J, Gogtay N, Nicolson R, Toga AW, Thompson PM. Dynamically spreading frontal and cingulate deficits mapped in adolescents with schizophrenia. *Arch Gen Psychiatry.* 2006;63(1):25-34.
14. Häfner H, Nowotny B, Löffler W, an der Heiden W, Maurer K. When and how does schizophrenia produce social deficits? *Eur Arch Psychiatry Clin Neurosci.* 1995;246(1):17-28.
15. Huber G. The heterogeneous course of schizophrenia. *Schizophr Res.* 1997;28(2-3):177-185.
16. Fraguas D, de Castro MJ, Medina O, Parellada M, Moreno D, Graell M, Merchán-Naranjo J, Arango C. Does diagnostic classification of early-onset psychosis change over follow-up? *Child Psychiatry Hum Dev.* 2008;39(2):137-145.
17. James AC, James S, Smith DM, Javaloyes A. Cerebellar, prefrontal cortex, and thalamic volumes over two time points in adolescent-onset schizophrenia. *Am J Psychiatry.* 2004;161(6):1023-1029.
18. James ACD, Javaloyes A, James S, Smith DM. Evidence for non-progressive changes in adolescent-onset schizophrenia: follow-up magnetic resonance imaging study. *Br J Psychiatry.* 2002;180:339-344.
19. Arango C, McMahon RP, Lefkowitz DM, Pearlson G, Kirkpatrick B, Buchanan RW. Patterns of cranial, brain and sulcal CSF volumes in male and female deficit and nondeficit patients with schizophrenia. *Psychiatry Res.* 2008;162(2):91-100.
20. Bakalar JL, Greenstein DK, Clasen L, Tossell JW, Miller R, Evans AC, Mattai AA, Rapoport JL, Gogtay N. General absence of abnormal cortical asymmetry in childhood-onset schizophrenia: a longitudinal study. *Schizophr Res.* 2009;115(1):12-16.
21. Douaud G, Mackay C, Andersson J, James S, Quested D, Ray MK, Connell J, Roberts N, Crow TJ, Matthews PM, Smith S, James A. Schizophrenia delays and alters maturation of the brain in adolescence. *Brain.* 2009;132(pt 9):2437-2448.
22. Reig S, Moreno C, Moreno D, Burdalo M, Janssen J, Parellada M, Zabala A, Desco M, Arango C. Progression of brain volume changes in adolescent-onset psychosis. *Schizophr Bull.* 2009;35(1):233-243.
23. Gogtay N, Ordonez A, Herman DH, Hayashi KM, Greenstein D, Vaituzis C, Lenane M, Clasen L, Sharp W, Giedd JN, Jung D, Nugent TF III, Toga AW, Leibenluft E, Thompson PM, Rapoport JL. Dynamic mapping of cortical development before and after the onset of pediatric bipolar illness. *J Child Psychol Psychiatry.* 2007;48(9):852-862.

24. Castro-Fornieles J, Parellada M, Gonzalez-Pinto A, Moreno D, Graell M, Baeza I, Otero S, Soutullo CA, Crespo-Facorro B, Ruiz-Sancho A, Desco M, Rojas-Corrales O, Patiño A, Carrasco-Marin E, Arango C; CAFEPS Group. The child and adolescent first-episode psychosis study (CAFEPS): design and baseline results. *Schizophr Res.* 2007;91(1-3):226-237.
25. Lenroot RK, Giedd JN. Brain development in children and adolescents: insights from anatomical magnetic resonance imaging. *Neurosci Biobehav Rev.* 2006; 30(6):718-729.
26. Reig S, Parellada M, Castro-Fornieles J, Janssen J, Moreno D, Baeza I, Bargallo N, Gonzalez-Pinto A, Graell M, Ortuno F, Otero S, Arango C, Desco M. Multicenter study of brain volume abnormalities in children and adolescent-onset psychosis. *Schizophr Bull.* 2011;37(6):1270-1280.
27. Kaufman J, Birmaher B, Brent D, Rao U, Flynn C, Moreci P, Williamson D, Ryan N. Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL): initial reliability and validity data. *J Am Acad Child Adolesc Psychiatry.* 1997;36(7):980-988.
28. Soutullo C. Traducción al Español de la Entrevista Diagnóstica: Kiddie-Schedule for Affective Disorders & Schizophrenia, Present & Lifetime Version (K-SADS-PL, 1996). http://www.cun.es/la-clinica/departamentos-yservicios-medicos/psiquiatria-y-psicologia-medica/mas-sobreel-departamento/unidades/psiquiatria-infantil-y-adolescente;1999. Accessed May 2003.
29. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull.* 1987;13(2):261-276.
30. Peralta Martín V, Cuesta Zorita MJ. Validation of positive and negative symptom scale (PANSS) in a sample of Spanish schizophrenic patients. *Actas Luso Esp Neurol Psiquiatr Cienc Afines.* 1994;22(4):171-177.
31. Shaffer D, Gould MS, Brasic J, Ambrosini P, Fisher P, Bird H, Aluwahlia S. A children's global assessment scale (CGAS). *Arch Gen Psychiatry.* 1983;40(11):1228-1231.
32. Cannon-Spoor HE, Potkin SG, Wyatt RJ. Measurement of premorbid adjustment in chronic schizophrenia. *Schizophr Bull.* 1982;8(3):470-484.
33. Satler J. *Assessment of Children Cognitive Applications.* 4th ed. San Diego, CA: San Diego State University Publisher Inc; 2001.
34. Rey MJ, Schulz P, Costa C, Dick P, Tissot R. Guidelines for the dosage of neuroleptics, I: chlorpromazine equivalents of orally administered neuroleptics. *Int Clin Psychopharmacol.* 1989;4(2):95-104.
35. Woods SW. Chlorpromazine equivalent doses for the newer atypical antipsychotics. *J Clin Psychiatry.* 2003;64(6):663-667.
36. Reig S, Sánchez-González J, Arango C, Castro J, González-Pinto A, Ortuño F, Crespo-Facorro B, Bargalló N, Desco M. Assessment of the increase in variability when combining volumetric data from different scanners. *Hum Brain Mapp.* 2009; 30(2):355-368.
37. Desco M, Pascau J, Reig S, Gispert JD, Santos A, Benito C, Molina V, Garcia-Barreno P. Multimodality image quantification using Talairach grid. In: Sonka M, Hanson KM, eds. Proceedings from the International Society for Optical Engineering; February 18-22, 2001; San Diego, CA.
38. Andreasen NC, Rajarethinam R, Cizadlo T, Arndt S, Swayze VW II, Flashman LA, O'Leary DS, Ehrhardt JC, Yuh WTC. Automatic atlas-based volume estimation of human brain regions from MR images. *J Comput Assist Tomogr.* 1996;20(1): 98-106.
39. Kates WR, Warsofsky IS, Patwardhan A, Abrams MT, Liu AMC, Naidu S, Kaufmann WE, Reiss AL. Automated Talairach atlas-based parcellation and measurement of cerebral lobes in children. *Psychiatry Res.* 1999;91(1):11-30.
40. Ashburner J, Friston K. Multimodal image coregistration and partitioning: a unified framework. *Neuroimage.* 1997;6(3):209-217.
41. Talairach J, Tournoux P. *Co-planar Stereotaxic Atlas of the Human Brain.* New York, NY: Thieme; 1988.
42. Hollingshead AB, Redlich FC. Schizophrenia and social structure. *Am J Psychiatry.* 1954;110(9):695-701.
43. Jernigan TL, Trauner DA, Hesselink JR, Tallal PA. Maturation of human cerebrum observed in vivo during adolescence. *Brain.* 1991;114(pt 5):2037-2049.
44. Lenroot RK, Gogtay N, Greenstein DK, Wells EM, Wallace GL, Clasen LS, Blumenthal JD, Lerch J, Zijdenbos AP, Evans AC, Thompson PM, Giedd JN. Sexual dimorphism of brain developmental trajectories during childhood and adolescence. *Neuroimage.* 2007;36(4):1065-1073.
45. Sowell ER, Peterson BS, Thompson PM, Welcome SE, Henkenius AL, Toga AW. Mapping cortical change across the human life span. *Nat Neurosci.* 2003;6 (3):309-315.
46. Molina V, Galindo G, Cortes B, de Herrera AG, Ledo A, Sanz J, Montes C, Hernandez-Tamames JA. Different gray matter patterns in chronic schizophrenia and chronic bipolar disorder patients identified using voxel-based morphometry. *Eur Arch Psychiatry Clin Neurosci.* 2010;261(5):313-322.
47. Rimol LM, Hartberg CB, Nesvåg R, Fennema-Notestine C, Hagler DJ Jr, Pung CJ, Jennings RG, Haukvik UK, Lange E, Nakstad PH, Melle I, Andreassen OA, Dale AM, Agartz I. Cortical thickness and subcortical volumes in schizophrenia and bipolar disorder. *Biol Psychiatry.* 2010;68(1):41-50.
48. Janssen J, Reig S, Parellada M, Moreno D, Graell M, Fraguas D, Zabala A, Garcia Vazquez V, Desco M, Arango C. Regional gray matter volume deficits in adolescents with first-episode psychosis. *J Am Acad Child Adolesc Psychiatry.* 2008; 47(11):1311-1320.
49. Ellison-Wright I, Bullmore E. Anatomy of bipolar disorder and schizophrenia: a meta-analysis. *Schizophr Res.* 2010;117(1):1-12.
50. Gur RE, Cowell P, Turetsky BI, Gallacher F, Cannon T, Bilker W, Gur RC. A follow-up magnetic resonance imaging study of schizophrenia: relationship of neuroanatomical changes to clinical and neurobehavioral measures. *Arch Gen Psychiatry.* 1998;55(2):145-152.
51. Mathalon DH, Sullivan EV, Lim KO, Pfefferbaum A. Progressive brain volume changes and the clinical course of schizophrenia in men: a longitudinal magnetic resonance imaging study. *Arch Gen Psychiatry.* 2001;58(2):148-157.
52. Gogtay N, Lu A, Leow AD, Klunder AD, Lee AD, Chavez A, Greenstein D, Giedd JN, Toga AW, Rapoport JL, Thompson PM. Three-dimensional brain growth abnormalities in childhood-onset schizophrenia visualized by using tensor-based morphometry. *Proc Natl Acad Sci U S A.* 2008;105(41):15979-15984.
53. Jacobsen LK, Rapoport JL. Research update: childhood-onset schizophrenia: implications of clinical and neurobiological research. *J Child Psychol Psychiatry.* 1998;39(1):101-113.
54. Cannon TD, Mednick SA, Parnas J. Genetic and perinatal determinants of structural brain deficits in schizophrenia. *Arch Gen Psychiatry.* 1989;46(10):883-889.
55. Huttenlocher PR, Dabholkar AS. Regional differences in synaptogenesis in human cerebral cortex. *J Comp Neurol.* 1997;387(2):167-178.
56. Keshavan MS, Anderson S, Pettegrew JW. Is schizophrenia due to excessive synaptic pruning in the prefrontal cortex? the Feinberg hypothesis revisited. *J Psychiatr Res.* 1994;28(3):239-265.
57. Arango C, Kirkpatrick B, Koenig J. At issue: stress, hippocampal neuronal turnover, and neuropsychiatric disorders. *Schizophr Bull.* 2001;27(3):477-480.
58. McGlashan TH. Is active psychosis neurotoxic? *Schizophr Bull.* 2006;32(4):609-613.
59. Weinberger DR, McClure RK. Neurotoxicity, neuroplasticity, and magnetic resonance imaging morphometry: what is happening in the schizophrenic brain? *Arch Gen Psychiatry.* 2002;59(6):553-558.
60. Kalmar JH, Wang F, Spencer L, Edmiston E, Lacadie CM, Martin A, Constable RT, Duncan JS, Staib LH, Papademetris X, Blumberg HP. Preliminary evidence for progressive prefrontal abnormalities in adolescents and young adults with bipolar disorder. *J Int Neuropsychol Soc.* 2009;15(3):476-481.
61. Dorph-Petersen KA, Pierri JN, Perel JM, Sun Z, Sampson AR, Lewis DA. The influence of chronic exposure to antipsychotic medications on brain size before and after tissue fixation. *Neuropsychopharmacology.* 2005;30(9):1649-1661.
62. Ho BC, Andreasen NC, Ziebell S, Pierson R, Magnotta V. Long-term antipsychotic treatment and brain volumes: a longitudinal study of first-episode schizophrenia. *Arch Gen Psychiatry.* 2011;68(2):128-137.
63. Lieberman J, Chakos M, Wu HW, Alvir J, Hoffman E, Robinson D, Bilder R. Longitudinal study of brain morphology in first episode schizophrenia. *Biol Psychiatry.* 2001;49(6):487-499.
64. Cahn W, Rais M, Stigter FP, van Haren NE, Caspers E, Hulshoff Pol HE, Xu Z, Schnack HG, Kahn RS. Psychosis and brain volume changes during the first five years of schizophrenia. *Eur Neuropsychopharmacol.* 2009;19(2):147-151.
65. DeLisi LE, Hoff AL. Failure to find progressive temporal lobe volume decreases 10 years subsequent to a first episode of schizophrenia. *Psychiatry Res.* 2005; 138(3):265-268.
66. Antonova E, Sharma T, Morris R, Kumari V. The relationship between brain structure and neurocognition in schizophrenia: a selective review. *Schizophr Res.* 2004; 70(2-3):117-145.
67. Rüsch N, Spoletini I, Wilke M, Bria P, Di Paola M, Di Iulio F, Martinotti G, Caltagirone C, Spalletta G. Prefrontal-thalamic-cerebellar gray matter networks and executive functioning in schizophrenia. *Schizophr Res.* 2007;93(1-3):79-89.
68. Sanfilipo M, Lafargue T, Rusinek H, Arena L, Loneragan C, Lautin A, Rotrosen J, Wolkin A. Cognitive performance in schizophrenia: relationship to regional brain volumes and psychiatric symptoms. *Psychiatry Res.* 2002;116(1-2):1-23.
69. Arango C, Moreno C, Martínez S, Parellada M, Desco M, Moreno D, Fraguas D, Gogtay N, James A, Rapoport J. Longitudinal brain changes in early-onset psychosis. *Schizophr Bull.* 2008;34(2):341-353.