

Gray matter changes and cognitive predictors of 2-year follow-up abnormalities in early-onset first-episode psychosis

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Abstract This study aims to examine regional gray matter (GM) changes over a period of 2 years in patients diagnosed with early-onset first-episode psychosis (EO-FEP), and to identify baseline predictors of abnormalities at the follow-up. Fifty-nine patients with EO-FEP aged 11–17 years were assessed. Magnetic resonance imaging was carried out at admission and 2 years later. Changes over time were assessed with voxel-based morphometry. Fifty-nine patients (34 schizophrenia—SCZ, 15 bipolar disorder—BP, and 10 other psychotic disorders) and 70 healthy controls were assessed. At baseline no differences were found between the EO-FEP groups and control subjects. Over time, SCZ patients presented a larger GM decrease in the orbitofrontal cortex, anterior midline frontal cortex, cingulate, left caudate, and thalamus. BP patients also had a larger GM decrease in the right putamen, right

orbitofrontal cortex, and anterior and midline region of the right superior frontal gyrus and left caudate, but with fewer areas showing significant differences than in the comparison between SCZ and controls. In the cross-sectional analysis, only SCZ patients showed differences with respect to controls in some GM areas. Significant baseline predictors of a 2-year reduction in GM were IQ and working memory. EO-FEP patients did not show differences in GM compared to controls at baseline. Both SCZ and BP patients showed a greater decrease in specific areas during the first 2 years. At follow-up, only SCZ patients differed significantly from controls in specific brain areas. The GM reduction was predicted by baseline cognitive variables.

Keywords Psychosis · Voxel-based morphometry · Early onset

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Introduction

Several studies have examined structural brain abnormalities in patients with long-duration schizophrenia (SCZ) and have shown reduced global gray matter (GM) and white matter (WM) volumes in both adults [1, 2] and children [3, 4]. Studies of patients with first-episode psychosis (FEP) offer the opportunity to detect brain abnormalities at a very early stage without the influence of potential confounding variables (i.e., medication).

Cross-sectional studies using voxel-based morphometry (VBM) neuroimaging in early-onset first-episode psychosis (EO-FEP) are scarce and have found very few abnormalities in specific areas [5–7]. Moreover, very few longitudinal studies have been conducted with EO-FEP patients, and none have used VBM methodology. Using a region of interest (ROI) methodology, Reig et al. [8] studied 21 FEP patients both at baseline and after 2-year follow-up and found a progression in frontal lobe changes, especially in male patients. Arango et al. [9], with the same methodology, found that compared with controls FEP-SCZ patients showed greater GM volume loss in the frontal lobe, total GM, and increases in the left frontal CSF and total volume during the 2-year follow-up. No differences were found between FEP-BP patients and controls during the 2-year follow-up. Brain abnormalities were related to markers of poorer prognosis such as greater GM volume loss, with more weeks of hospitalization or less improvement in PANSS negative and general subscale scores. In their meta-analysis of longitudinal MRI studies in EO-FEP patients with ROI methodology, Fraguas et al. [10] concluded that the frontal GM was the only region showing significant differences in volume change over time between patients and controls.

Some studies with adult FEP patients have found that cognitive baseline variables are good predictors of GM reduction at follow-up. In a longitudinal study, Ayesa-Arriola et al. [11] found no morphometric differences in GM at baseline between cognitively impaired and cognitively preserved FEP patients, but patients who were cognitively impaired at baseline presented greater progressive brain volume loss after 3 years in the parietal area and in total GM volume. Gutierrez-Galve et al. [12, 13], using surface-based morphometry (SBM), showed that progressive cortical thinning in the superior and inferior frontal and superior temporal cortex was predicted by lower baseline IQ and working memory.

To the best of our knowledge, no previous longitudinal studies with EO-FEP patients have used VBM methodology. Only a few follow-up studies in children and adolescent FEP samples have been carried out to date. The studies published are mainly cross-sectional and have been

conducted in young adult samples with a mean age between 18 and 24 years or with a wide age range. Analyses of predictors of GM volume are even fewer in number and those published present some methodological issues.

The aims of the present study were (1) to expand our previous global structural findings regarding progressive brain abnormalities during the first years of a psychotic episode [9] using a VBM methodology that allows for comprehensive exploration of both whole brain and specific areas and (2) to analyze whether baseline variables can predict GM reduction in specific areas at follow-up. Our hypotheses were: (1) that EO-FEP-SCZ patients would show a greater decrease in global GM volumes and in fronto-subcortical regions (i.e., orbitofrontal, anterior, and superior frontal cortex, putamen, caudate, and thalamus) than controls and that BP patients would be less differentiated from controls; and (2) that the decrease in GM in the affected areas at follow-up would be predicted by the subject's performance on IQ and working memory at baseline.

Experimental procedures

Participants

As part of the Child and Adolescent First-Episode Psychosis Study (CAFEPS) [14], MRI data were obtained from 92 patients and 94 controls at baseline. Two years later, a second neuroimaging assessment was carried out in 59 patients and 70 controls. The MRI attrition and further details about the sample and inclusion and exclusion criteria are provided in supplemental material section 1. All parents or legal guardians gave written informed consent before the study began and all patients agreed to participate.

Based on the results of the Kiddie Schedule for Affective Disorders and Schizophrenia, Present and Lifetime versions [15] at 2-year follow-up, patients were divided into three diagnostic categories: the schizophrenia spectrum group (SCZ) ($N = 34$), which included 9 patients diagnosed with schizoaffective disorder, and 25 patients diagnosed with schizophrenia; the bipolar group (BP) ($N = 15$); and the other psychosis group ($N = 10$), including 3 cases of depression with psychotic features and 7 cases of psychoses not otherwise specified.

Clinical and socioeconomic status assessment

Clinical assessment included the following scales: Kiddie Schedule for Affective Disorders and Schizophrenia, Present and Lifetime versions (K-SADS-PL) [15], the Spanish version of the Positive and Negative Symptom Scale

(PANSS) [16], and the Premorbid Adjustment Scale (PAS) [17]. We also determined the duration of untreated psychosis and estimated socioeconomic status (SES) using the Hollingshead–Redlich scale [18].

A complete description of each clinical scale is provided in supplemental material section 2.

Cognitive assessment

The cognitive assessment was performed at baseline. A complete description of the methodology has been provided elsewhere [19]. The cognitive domains assessed were general intelligence quotient (IQ), working memory, verbal memory, and executive functions. Further details of each cognitive domain can be found in supplemental material section 3.

VBM analysis

Details of image acquisition and further information about VBM analysis are provided in supplemental material sections 4 and 5. All 3D images were manually re-orientated to stereotactic space (i.e., the anterior–posterior axis was parallel to the anterior commissure–posterior commissure line, and the inter-hemispheric fissure was aligned on the other two axes) using SPM8 (Statistical Parametric Mapping, Wellcome Department of Imaging Neuroscience, University College London, UK, <http://www.fil.ion.ucl.ac.uk/spm>).

Statistical analyses of images Statistics were computed using SPM8. Cross-sectional analysis was performed via two-sample *t* tests to assess GM volume differences between the control group and diagnostic groups. To assess longitudinal GM volume differences, a flexible factorial model was used between the control and diagnostic groups.

An explicit mask was calculated to select which voxels should undergo statistical analysis. The aim was to exclude any voxels that were unlikely to belong to each tissue class. A mask was created for each analysis group and GM probability map using a 0.2 threshold. The threshold was set by visual inspection of pre-processed images and assessed by visual inspection of the mask image resulting from the SPM statistical analysis. A mean image of GM was then calculated and used as an external mask after binarization. Age, sex, TIV, and scan site were used as nuisance covariates to control the potential effect of this variable on the two-sample *t* test. The statistical threshold criterion was $p < 0.001$ uncorrected, using a cutoff of $p < 0.05$, FWE (family-wise error) correction for multiple comparisons at the cluster level.

Anatomical localization was done using projection onto the corresponding whole-brain customized template.

Labels and the corresponding percentage of voxels belonging to the labeled regions were obtained for each significant GM cluster using the AAL Toolbox [20].

MRI volume calculation

Total intracranial cerebral volume (ICV), gray matter (GM), white matter (WM), and cerebral spinal fluid (CSF) were calculated using GM, WM, and CSF probability maps from the new segment tool of SPM8, using customized tissue probability maps.

Statistical analysis of numerical data

Categorical socio-demographic variables were analyzed using the χ^2 test. Continuous clinical variables were compared between groups via MANCOVA, with the variables that differed between groups (age) as covariates. Post hoc analysis was performed with the Bonferroni correction for multiple comparisons.

Volume differences between each patient group and controls at baseline and at 2-year follow-up were assessed via univariate analysis of variance, with age, sex, total intracranial volume at first scan, and site where MRI was performed as no-interest covariates. The inter-scan interval was also included as a covariate in the statistical analysis at follow-up. Longitudinal changes in clinical variables and volume measures within the patient and control groups were examined using paired *t* tests.

To assess differences in longitudinal changes in GM among the three diagnostic groups and controls, a volume change variable was calculated. This variable was the result of subtracting the follow-up volume from the baseline volume. Differences in change between each patient group and controls were tested via univariate analysis, with age, sex, total intracranial volume at first scan, site, and inter-scan interval as covariates. This methodology has been used previously [9] and is preferred to the repeated measures ANCOVA because the confounding effect of the scanner site is minimized by using the within-subjects change values. In order to test the influence of the antipsychotic medication on our results, a partial correlation analysis was conducted between the cumulative doses of chlorpromazine and all significant results. Age, sex, TIC at first scan and site where the MRI was performed were included as covariates in the analysis. To test the predictive value of baseline variables with respect to GM volume at follow-up, linear regression analyses were performed with clinical and cognitive variables as potential predictors in the patient and control

Table 1 General characteristics of the early-onset first-episode psychosis subgroups and controls

Variable	Schizophrenia (<i>n</i> = 34)	Bipolar disord. (<i>N</i> = 15)	Other psy. (<i>N</i> = 10)	Controls (<i>N</i> = 70)	Test	<i>p</i> value
Age, mean (SD)	15.2 (1.7)	16.5 (0.7)	15.3 (1.9)	15.3 (1.5)	$F_{3,125} = 2.729$	0.047 ^a
Sex, no. (%)					$\chi^2 = 0.825$	0.844
Male	24 (70.6)	9 (60.0)	6 (60.0)	48 (60.0)		
Ethnicity, no. (%)					$\chi^2 = 1.097$	0.778
White	31 (91.2)	14 (93.3)	10 (100)	66 (94.3)		
Other	3 (8.8)	1 (6.7)	0	4 (5.7)		
Parental socioeconomic status ^b , no. (%)					$\chi^2 = 9.407$	0.668
1	6 (17.6)	3 (20.0)	2 (20.0)	6 (8.6)		
2	10 (29.4)	6 (40.0)	3 (30.0)	20 (28.6)		
3	10 (29.4)	3 (20.0)	3 (30.0)	18 (25.6)		
4	4 (11.8)	2 (13.3)	1 (10.0)	6 (8.6)		
5	4 (11.8)	1 (6.7)	1 (10.0)	20 (28.6)		
Educational level, mean,(SD)	8.2 (1.9)	9.1 (1.4)	8.9 (1.9)	9.0 (1.4)	$F_{3,123} = 1.861$	0.140
Handedness, right/left/mixed, no.	29/4/0	12/3/0	8/2/0	62/6/1	$\chi^2 = 3.035$	0.804
Estimated IQ, mean (SD)	83.1 (16.1)	77.9 (20.6)	89.7 (20.1)	105.8 (16.1)	$F_{3,104} = 17.062$	<0.001 ^b
Premorbid Adjustment Scale-total score, mean (SD)	43.6 (16.5)	42.7 (19.7)	27.3 (17.3)	11.2 (7.3)	$F_{3,120} = 54.291$	<0.001 ^c
Between-scan follow-up period (mean of months (SD))	26 (3.1)	25.6 (2.4)	24.6 (0.9)	25.8 (2.6)	$F_{3,125} = 0.781$	0.507

^aPost hoc Bonferroni test: control > schizophrenia = bipolar disorder = other psychosis

^bParental socioeconomic status assessed with the Hollingshead scale. A score of 5 corresponds to the highest socioeconomic status and a score of 1 to the lowest

^cPost hoc Bonferroni test: control < other psychosis < bipolar disorder = schizophrenia

groups. All statistical analyses were performed using the SPSS 20.0 package.

Results

Socio-demographic and general clinical characteristics in subgroups of EO-FEP patients and controls

The different subgroups of EO-FEP patients and controls were similar in sex, parental SES, handedness, ethnicity, and educational level (see Table 1). Differences in mean age were statistically significant, with BP patients being significantly older than controls, but not older than the SCZ or other psychosis groups. Regarding estimated IQ, all three patient groups scored lower than controls, whereas on the PAS the SCZ and BP patients showed worse premorbid adjustment than the other psychosis group, and all of them had worse scores than controls.

Comparison of EO-FEP subgroups in relation to clinical variables at baseline and at follow-up and in change on clinical scales during follow-up

Table 2 shows the comparison of EO-FEP patients with a diagnosis of SCZ, BP or other psychotic disorders at first

assessment and at the 2-year follow-up with respect to clinical variables. The duration of illness before entering the study, number of weeks hospitalized, and cumulative antipsychotic dose in chlorpromazine equivalents during the 2-year follow-up were not significantly different between the groups. The table also shows psychopharmacological treatment at both baseline and follow-up; the large majority of patients were treated with second-generation antipsychotics. At baseline there were no statistically significant differences between diagnostic groups on any PANSS subscale. At follow-up, SCZ patients scored higher on negative symptoms and on the Total PANSS score.

Comparison of EO-FEP subgroups and controls in whole-brain volumes at baseline and follow-up and in change during the follow-up period

Table 3 shows the global cerebral volumes in all groups. At baseline, the SCZ and BP subgroups had significantly more CSF volume than control subjects. There were no differences in GM or WM. The other psychosis group did not show any differences with respect to controls. During follow-up, control subjects showed a decrease in GM and an increase in WM volume. SCZ patients had a significantly larger decrease in GM and a significantly smaller increase in WM in comparison with controls. BP patients

Table 2 Comparison between subgroups of early-onset first-episode psychosis subgroups in relation to clinical variables at baseline and at follow-up

Assessment Time	Variable	Schizophrenia Mean (SD)	Bipolar disorder Mean (SD)	Other psy. Mean (SD)	F	p ^{a,b}	Post hoc ^c	
Baseline	PANSS positive score	24.5 (4.9)	25.9 (8.14)	23 (7.5)	0.304	0.739		
	PANSS negative score	20.6 (8.5)	17.7 (10.7)	22.2 (8.4)	0.505	0.606		
	PANSS general score	44.1 (9.7)	48 (15.1)	47.5 (11.8)	0.578	0.564		
	PANSS total score	89.2 (17.7)	91.6 (28.9)	92.7 (24.1)	0.098	0.907		
	Illness duration at baseline (months)	4.1 (3)	2.8 (2.4)	2.3 (1.8)	2.016	0.144		
	Treatment (No) ^d							
		Risperidone	18	7	5			
		Olanzapine	6	4	4			
		Quetiapine	8	4	3			
		Ziprasidone	2	1	0			
		Aripiprazole	1	0	0			
		Haloperidol decanoate	1	0	0			
		No antipsychotic treatment	1	0	0			
		Oxcarbazepine	0	1	0			
	Biperiden	2	0	0				
	Other ^e	5	1	0				
Follow-up	PANSS positive score	14.7 (7.2)	12.7 (5.7)	9.8 (3.1)	1.935	0.154		
	PANSS negative score	18.1 (8.1)	14.1 (7.5)	10.7 (3.1)	4.274	0.019	SCZ > O; SCZ = BP; BP = O	
	PANSS general score	31.1 (9.9)	29.7 (10.9)	23.9 (7.5)	2.135	0.128		
	PANSS total score	63.5 (22.3)	56.6 (20.8)	44.4 (11.8)	3.246	0.047	SCZ > O; CZ = BP; BP = O	
	Hospitalization (weeks)	7.7 (6.8)	4.8 (4.6)	4.7 (6)	1.628	0.206		
	Treatment (No) ^d							
		Risperidone	10	4	1			
		Olanzapine	5	4	1			
		Quetiapine	2	2	2			
		Clozapine	5	0	0			
		Ziprasidone	1	2	0			
		Aripiprazole	2	0	0			
		Haloperidol	2	0	0			
		Chlorpromazine	1	0	0			
	Amisulpride	0	1	1				
	No antipsychotic treatment	5	4	3				
	Oxcarbazepine	2	0	1				
	Valproic acid	1	2	0				
	Biperiden	1	1	0				
	Other ^e	1	0	2				
	Cumulative chlorpromazine equivalents	215375.97 (267730.54)	135684.8 (118844.59)	97271.28 (101669.61)	1.458	0.242		

PANSS Positive And Negative Syndrome Scale, SCZ schizophrenia, BP bipolar disorder, O other psychosis

^aAnalysis of variance, comparison between diagnostic groups (schizophrenia, bipolar disorder, other psychosis)

^bCovariate: age

^cPost hoc: Bonferroni

^dPatients were polymedicated, increasing the sample size for medication

^eAntidepressants or anxiolytics

Table 3 Comparison between subgroups of early-onset first-episode psychosis subgroups and controls in relation to whole-brain volumes (expressed in cubic centimeters) at baseline and at follow-up and in change during follow-up

Group	Variable	Control			Schizophrenia			Bipolar disorder			Other psychosis		
		Mean (SD)	F	P	Mean (SD)	F	P	Mean (SD)	F	P	Mean (SD)	F	P
Baseline ^{a,d}	Intracranial volume	1538.6 (123.1)	0.022	0.882	1542.3 (146.7)	0.022	0.882	1509.1 (117.8)	0.332	0.566	1547.2 (159.3)	0.183	0.670
	Total gray matter	762.4 (64.4)	1.012	0.317	762.2 (72.9)	1.012	0.317	740.9 (59.1)	0.715	0.400	759.8 (71.8)	2.488	0.119
	Total white matter	494.6 (40.1)	1.419	0.236	493.1 (49.3)	1.419	0.236	483.4 (42.9)	1.999	0.161	505.3 (60.6)	2.030	0.158
	Total CSF	281.6 (23.4)	4.410	0.038	286.9 (29.3)	4.410	0.038	284.8 (22.7)	4.772	0.032	282.1 (30.9)	0.000	0.990
Change ^{a,e,f}	Intracranial volume	7.08 (33.4)	5.112	0.026	-7.1 (28.3)	5.112	0.026	0.81 (35.6)	0.127	0.723	4.9 (17.5)	0.072	0.789
	Total gray matter	-6.7 ^b (15.9)	6.506	0.012	-15.6 ^b (18.5)	6.506	0.012	-11.8 ^c (17.4)	1.061	0.306	-11.1 (15.8)	0.130	0.719
	Total white matter	12.1 ^b (13.3)	10.294	0.002	3.77 ^c (10.6)	10.294	0.002	2.52 (16.1)	4.083	0.047	9.9 ^c (6.8)	0.028	0.868
	Total CSF	1.7 (11.2)	1.332	0.251	4.8 ^c (12.2)	1.332	0.251	10.1 ^c (14.7)	9.437	0.003	6.1 (11.1)	1.249	0.125
Follow-up ^{a,e}	Intracranial volume	1545.7 (128.1)	5.05	0.027	1535.2 (144.7)	5.05	0.027	1509.9 (124.5)	0.142	0.707	1552.2 (167.9)	0.070	0.793
	Total gray matter	755.7 (63.8)	8.909	0.004	746.6 (71.2)	8.909	0.004	729.1 (62.9)	2.087	0.153	748.8 (74.1)	1.524	0.221
	Total white matter	506.7 (45.1)	10.669	0.002	496.8 (47.6)	10.669	0.002	485.9 (44.9)	5.735	0.019	515.3 (61.5)	0.635	0.428
	Total CSF	283.4 (25.7)	6.525	0.012	291.8 (31.2)	6.525	0.012	294.9 (26.9)	16.144	<0.001	288.1 (38.5)	1.249	0.267

^aComparison between each diagnostic group and the control group^bPaired *t* test significant <0.001^cPaired *t* test significant <0.05^dCovariates: age, gender, total intracranial volume at baseline, center^eCovariates: age, gender, total intracranial volume at baseline, center, months between scans^fChange calculated for each participant as follow-up volume - baseline volume

had a significantly smaller increase in WM and significantly larger increase in CSF than controls. There were no differences in changes between controls and the other psychosis group. In the cross-sectional analysis at follow-up, SCZ patients showed significant differences compared with controls, specifically in terms of smaller total intracranial volume, GM and WM volumes, and more CSF. BP patients only had less global WM and more CSF than controls, while the other psychosis group showed no significant differences in cerebral volumes compared with controls. Correlations between GM, WM, CSF, and cumulative doses of chlorpromazine levels were conducted to assess the influence of the antipsychotic level and whole-brain volumes. No significant results were observed in any of the analyses.

Comparison of voxel-based regional analysis of gray matter between the EO-FEP subgroups and controls at baseline

In the regional VBM study at first assessment, there were no significant differences in GM between SCZ, BP, and other psychosis patients and control subjects.

Comparison of volume changes in the longitudinal voxel-based regional analysis of gray matter between EO-FEP subgroups and control subjects

As shown in Table 4, there was a statistically significant greater reduction in five clusters of GM in SCZ patients in comparison with controls. The largest cluster, with the

Table 4 Clusters showing significant between-group differences in the voxel-based morphometry analysis of changes in gray matter volumes

Group ^a	Change study		Anatomical label ^c	% Cluster	No. of voxels	Peak <i>t</i> score ^d	<i>p</i> value ^e
	MNI ^b Coordinate						
SCZ vs C	-34 30 11		Frontal_Sup_L	32.34	11,447	5.04	<0.001
			Olfactory_L	24.71			
			Frontal_Mid_Orb_L	19.38			
			Frontal_Sup_Orb_L	5.66			
			Cingulum_Ant_R	4.53			
	29 23 -8		Frontal_Sup_Orb_R	40.79	6185	5.01	<0.001
			Rectus_R	23.06			
			Postcentral_R	16.49			
			Frontal_Inf_Tri_R	5.40			
			Frontal_Inf_Orb_R	4.61			
	-17 -17 14		Caudate_L	45.52	4903	5.10	<0.001
			Thalamus_L	7.75			
	18 -16 15		Hippocampus_R	38.71	4281	4.81	0.001
			Thalamus_L	16.70			
	-55 -8 19			Postcentral_L	29.03	2549	5.04
			Insula_L	23.58			
			Frontal_Inf_Oper_L	11.53			
			Precentral_L	11.38			
BP vs C	54 3 8		Putamen_R	46.26	5597		<0.001
			Frontal_Sup_Orb_R	18.22			
			Rectus_R	13.26			
	-18 -25 13		Caudate_L	18.07	3270		0.003
			Occipital_Sup_L	87.49			

L left, *R* right, *Inf* inferior, *Ant* anterior, *Mid* middle, *Sup* superior, *Med* medial, *Orb* orbital, *Oper* opercular part, *Tri* triangular, *SCZ* schizophrenia patients, *BP* bipolar disorder patients, *C* control group

^aComparison between each diagnostic group and the control group

^bMontreal Neurological Institute coordinates of the voxel of maximal statistical significance within each region

^cAnatomical labels and percentages per cluster were obtained using the AAL Toolbox

^dScores for the voxel of maximal statistical significance in each region, maximal scores for a region reported in the table were significant at the two-tailed *p* < 0.0001, level, uncorrected for multiple comparisons

^eStatistical significance after correction for multiple comparisons (FWE voxel level)

highest number of voxels, involved the left orbitofrontal and olfactory cortex, the midline and anterior region of the left superior frontal gyrus, and the right anterior cingulate; the second cluster involved the midline region of the right superior frontal cortex, the inferior orbitofrontal cortex, the rectus gyrus, the right inferior frontal gyrus, and the right postcentral areas; the third cluster involved the left caudate and thalamus; the fourth cluster involved the right hippocampus and left thalamus; and the fifth involved the left inferior gyrus, the left precentral and postcentral area, and the left insula. Figure 1a shows differences in changes between SCZ patients and Controls. The BP group showed a larger decrease in GM than controls in three clusters, but with a smaller number of voxels than was observed in the two largest clusters for SCZ patients. These three clusters were as follows: one involving the right putamen, rectus gyrus, and the midline anterior part of the right superior frontal gyrus; another involving the left caudate; and a third in the left occipital area. Figure 1b shows the differences in changes between BP patients and controls. In the direct comparison between SCZ and BP patients, only one cluster showed differences between the two groups at peak level (MNI coordinate: $-55, -5, 22$), namely that in the left postcentral and precentral area ($p_{\text{FWE-corr}} = 0.016$; $T = 5.62$).

Regarding the other psychosis subgroup, there were no significant differences with respect to controls in changes in GM between baseline and follow-up assessment. Correlations between all significant clusters and chlorpromazine levels were performed and no significant results were observed.

Comparison of volumes in the voxel-based regional analysis of gray matter between EO-FEP subgroups and control subjects at the 2-year follow-up

At the follow-up assessment (Table 5), SCZ patients showed smaller volumes than controls in four clusters: one involved the right and left thalamus; a further two involved the right and left superior frontal cortex, right and left orbitofrontal cortex, and the anterior and medial part of the cingulum; and a fourth involved the right and left rectus and the orbitofrontal cortex. Figure 2 shows the differences between SCZ patients and controls at the 2-year follow-up. BP patients and the other psychosis group showed no significant differences in GM with respect to controls at the follow-up assessment. In the direct comparison between SCZ and BP patients, there were no significant differences in any specific GM area. No significant correlations were

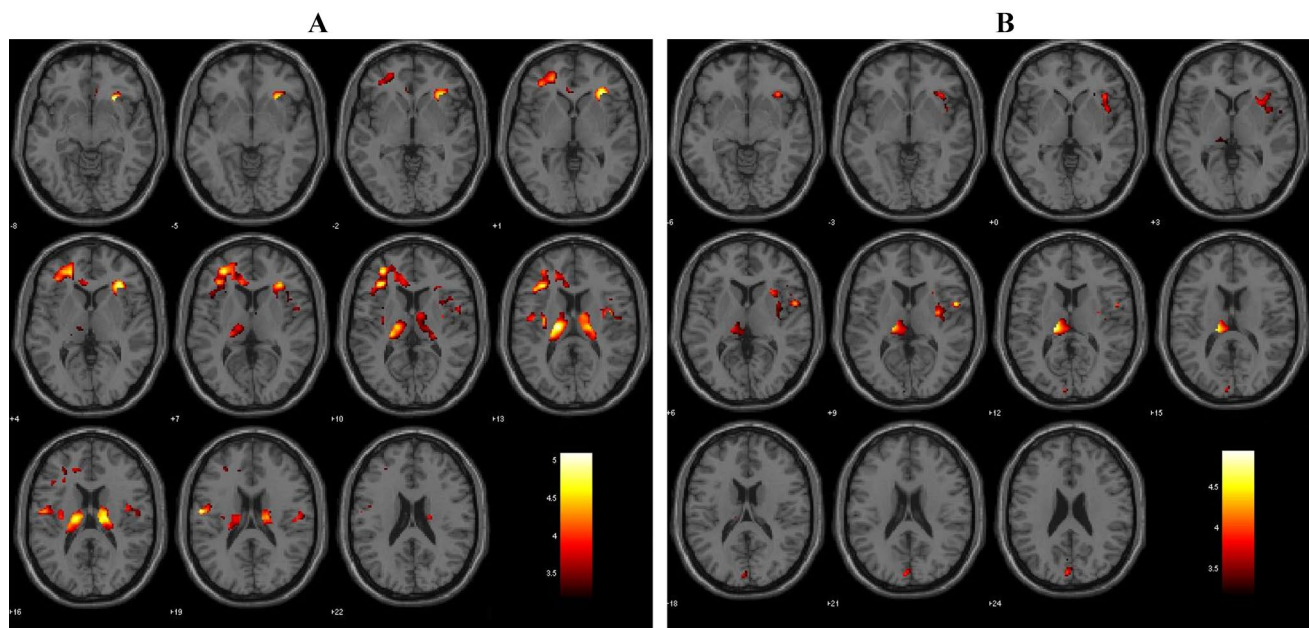


Fig. 1 Longitudinal study: Regions with a significantly greater decrease in volume in EO-FEP schizophrenia (a) and bipolar disorder (b) patients compared with control subjects during follow-up, overlaid onto the SPM8 canonical single-subject T1 image. The color bar represents the t score: yellow indicates higher statistical significance

than orange or red. The statistical parametric maps follow the standard neuroradiological representation, with the left side of the images corresponding to the left hemisphere. Maps are generated with an uncorrected $p < 0.001$

Table 5 Clusters showing significant between-group differences in the voxel-based morphometry analysis of gray matter volumes at follow-up

Group ^a	MNI ^b Coordinate	Anatomical label ^c	% cluster	No. of voxels	Peak <i>t</i> score ^d	<i>p</i> value ^e	
SCZ vs. C	8 -11 9	Thalamus_R	41.18	7010	4.68	<0.001	
		Thalamus_L	23.78				
	-2 42 37	Frontal_Sup_Medial_R	64.59	5165	4.66		
		Frontal_Sup_R	11.38				
		Cingulum_Mid_L	11.27				
		Frontal_Sup_Medial_L	11.15				
	-1 51 13	Frontal_Sup_Medial_R	48.56	3219	5.15		0.017
		Cingulum_Ant_R	16.81				
		Frontal_Med_Orb_L	10.90				
		Frontal_Med_Orb_R	10.38				
Frontal_Sup_Medial_L		9.66					
Rectus_R		46.48	2859			5.22	
Frontal_Med_Orb_R	12.24						
Frontal_Sup_Orb_L	5.56						
1 38 -20		Rectus_L	5.42				

L left, *R* right, *Ant* anterior, *Mid* middle, *Sup* superior, *Med* medial, *Orb* orbital, *SCZ* schizophrenia patients, *C* control group

^aComparison between each diagnostic group and the control group

^bMontreal Neurological Institute coordinates of the voxel of maximal statistical significance within each region

^cAnatomical labels and percentages per cluster were obtained using the AAL Toolbox

^dScores for the voxel of maximal statistical significance in each region, maximal scores for a region reported in the table were significant at the two-tailed $p < 0.0001$, level, uncorrected for multiple comparisons

^eStatistical significance after correction for multiple comparisons (FWE voxel level)

observed between significant GM clusters and chlorpromazine levels.

Baseline predictors of volume reductions at follow-up in the longitudinal voxel-based regional analysis of gray matter in SCZ patients

In SCZ patients, low IQ at baseline predicted GM reductions at follow-up in the right and left rectus and orbitofrontal cortex (cluster 1 38 -20; $R^2 = 0.205$; $F_{1,30} = 7.745$; $p = 0.009$) and in the right and left superior frontal and orbitofrontal cortex (cluster -1 51 13 $R^2 = 0.246$; $F_{1,30} = 9.775$; $p = 0.004$). Low performance in the working memory domain was a significant predictor of a GM volume decrease in the right and left superior and orbitofrontal cortex at the 2-year follow-up (cluster -1 51 13; $R^2 = 0.218$; $F_{1,30} = 8.631$; $p = 0.006$). These associations were not present in the healthy control group, except for lower working memory performance and GM volume decrease in the right and left superior and orbitofrontal cortex (cluster -1 51 13; $R^2 = 0.061$; $F_{1,67} = 4.360$; $p = 0.041$), although in the control group working memory explained only 6.1% of the variance, whereas in the SCZ group it explained 24.6% (Fig. 3). Other baseline variables such as negative symptoms (PANSS), premorbid

adjustment, verbal memory, or executive function were not significant predictors of GM reduction at follow-up. Correlations between GM reduction at follow-up in the different voxels and cumulative antipsychotic dose in chlorpromazine equivalents were not significant.

Discussion

The main findings in this longitudinal study with children and adolescents are that SCZ EO-FEP patients present larger decreases in GM than control subjects, and especially in the orbitofrontal cortex, anterior midline frontal cortex, cingulate and left caudate and thalamus, and that BP EO-FEP patients also present larger decreases of GM than controls in the right putamen, right orbitofrontal cortex and anterior and midline region of the right superior frontal gyrus, left caudate and left occipital area, but with less extensive differences than in the comparison between SCZ and controls. After the 2-year follow-up, only SCZ patients showed regional differences with respect to controls in the orbitofrontal cortex, the anterior and midline areas of the superior frontal cortex and thalami, and these abnormalities were predicted by lower IQ and working memory performance at baseline.

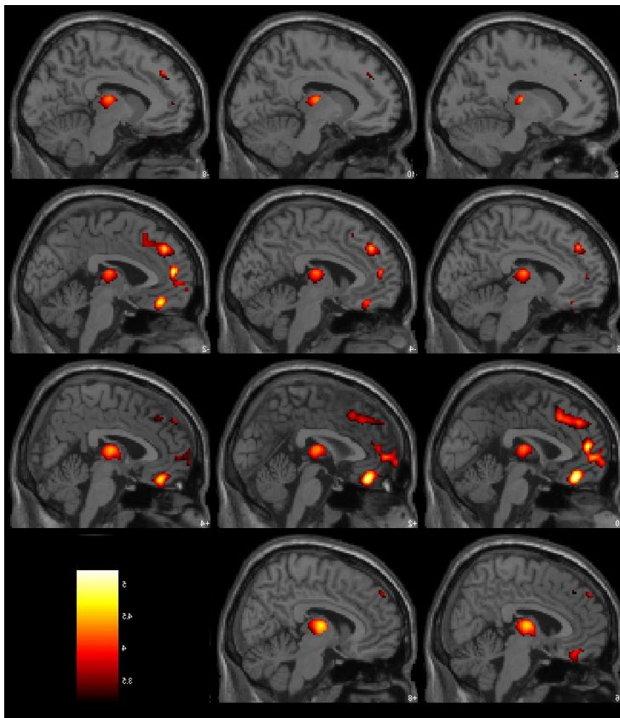


Fig. 2 Regions of decreased gray matter volume at the 2-year follow-up in EO-FEP schizophrenia patients compared with control subjects are overlaid onto the SPM8 canonical single-subject T1 image. The color bar represents the *t* score: Yellow indicates higher statistical significance than orange or red. The statistical parametric maps follow the standard neuroradiological representation, with the left side of the images corresponding to the left hemisphere. Maps are generated with an uncorrected $p < 0.001$

In our study, the assessment of whole-brain volumes was included to test the progress of GM, WM, CSF in FEP and healthy controls and to include these results as covariates in some of the following statistical analyses. Thus, at first assessment, SCZ and BP subgroups had significantly more CSF volume than control subjects, but there were no differences in global GM or WM. This is in agreement with some other studies that did not find global GM or WM differences between FEP patients and controls at baseline (cross-sectional analysis) at these young ages and with a very short duration of the disorder [5, 7, 21].

In the regional VBM study, at the first assessment there were no significant differences in GM between SCZ, BP or other psychosis patients and control subjects. This result corroborates the findings of Pagsberg et al. [5] who, also using VMB methodology, found no abnormalities in specific areas in adolescent FEP patients. Nevertheless, other authors have found small significant differences with respect to controls. Janssen et al. [6] showed lower GM volumes in the left medial frontal gyrus in FEP-SCZ and BP and also in the left middle frontal gyrus in SCZ patients in comparison with controls, while in a study of EO-FEP-SCZ

patients with a duration of illness of 9 months Tang et al. [7] found that patients only had lower GM volume in a small voxel at the left and middle and superior temporal gyrus. In contrast, in adult cross-sectional studies with VMB, a reduction in GM has been observed in different frontal and medial regions, anterior cingulate, and fronto-subcortical regions such as medial frontal, caudate, thalamus, cingulate gyrus, parahippocampal gyrus, hippocampus, insula and putamen [22–24]. These differences in the results at baseline between adolescent and adult FEP patients in cross-sectional studies may be because the disorder duration may be longer in adult samples even if long-term symptoms are not clinically obvious and therefore patients are not referred to treatment. Recruiting adolescent samples probably ensures that the duration of sub-threshold psychosis before baseline assessment is indeed short. Moreover, the idea that the duration of disorder is crucial to find structural abnormalities is underscored by the finding of the reduction during the 2-year follow-up in the present study, which was significantly higher in EO-FEP-SCZ and BP patients than in control subjects.

In our study, whole-brain GM change at the 2-year follow-up decreased more and WM increased less in SCZ patients than in healthy controls. GM results obtained in this study are in line with those obtained by the study with the ROI methodology [21]. Nevertheless, although Arango et al. found a significant increase in WM volume in all samples (FEP and healthy controls), their study failed to find significant differences between FEP groups and controls. Differences in WM results between our study and Arango's study may be due to methodological issues, since the authors used software developed in-house [25, 26] and stated that with this methodology the multicenter reproducibility of measurements was much higher for GM than WM. As has been well established by previous literature [27, 28], in the general population as well as in our control sample, GM undergoes a pre-pubertal increase and a post-pubertal decrease due to synaptic pruning processes, while WM increases over time as a result of myelination processes [29]. Thus, some authors have hypothesized that in SCZ samples, the GM loss pattern is the same, but is abnormally accelerated [28]. An overall difference with respect to controls in GM changes during the first 2 years of the disorder, especially in the frontal and parietal lobes, has already been reported in Arango et al. [21] and support the idea that SCZ or BP causes deviations from normal brain development, suggesting a neurodevelopmental basis for these disorders.

Regarding voxel-based region analysis of change at the 2-year follow-up, the present study is the first one to use this methodology in EO-FEP patients and indicates some of the regions that show greater decreases than in controls during these two first years in SCZ and BP adolescents. Regarding

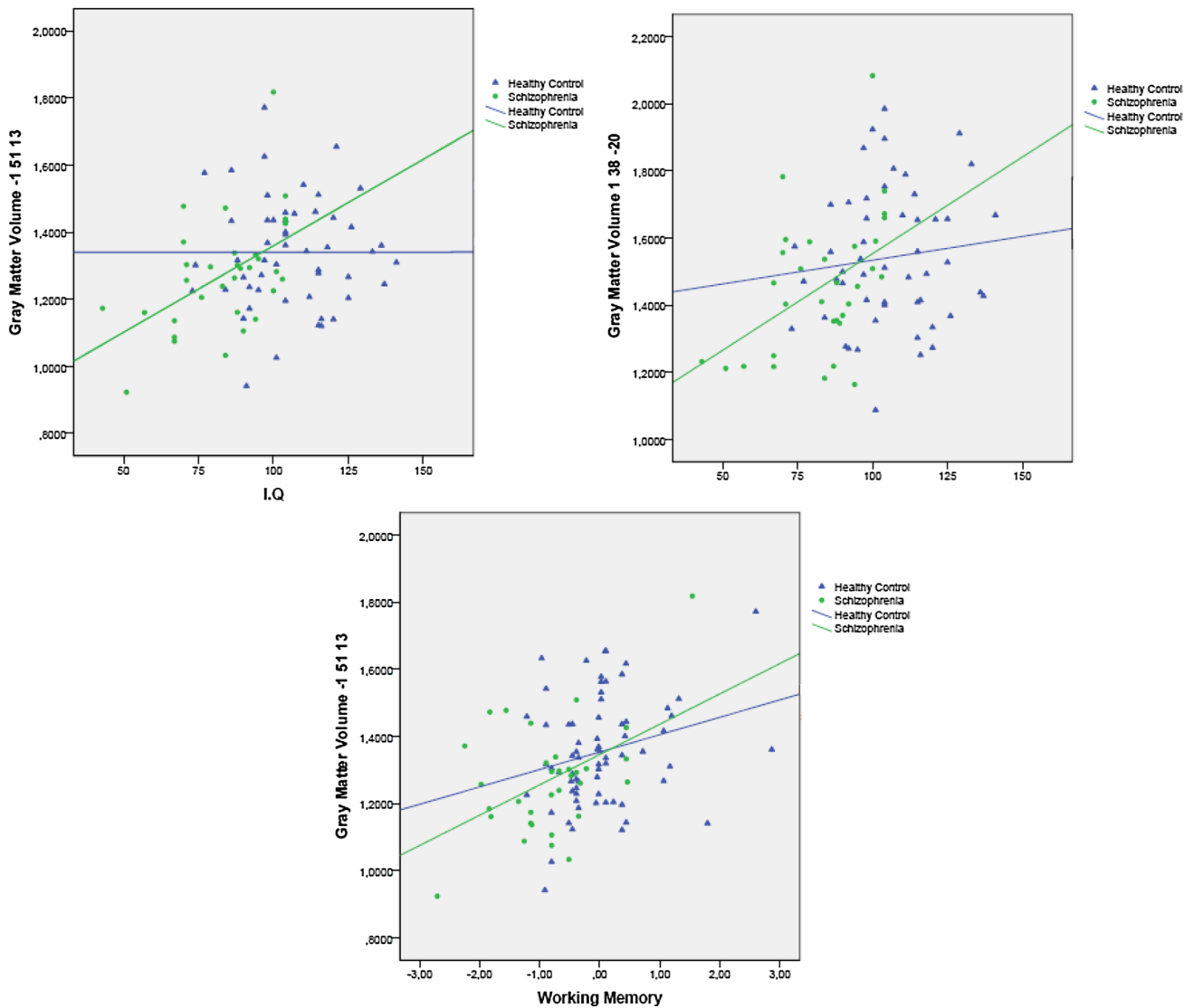


Fig. 3 Scatter plots of the associations between IQ and working memory at baseline with the specific GM areas that showed differences between SCZ patients and controls at follow-up

SCZ patients, the areas affected are both orbitofrontal cortices, the anterior and midline area of the left superior frontal gyrus and the precentral and postcentral gyrus, the right superior and inferior frontal gyrus, the right postcentral area, the left caudate and thalamus and the right hippocampus. These areas are quite similar to some of the already mentioned areas that have been found to be decreased in adult FEP-SCZ patients in cross-sectional studies with VBM [22–24]. In a longitudinal study with adults using VBM, Mane et al. [30] studied FEP-SCZ patients, and after 4 years found an excessive GM decrease in FEP-SCZ patients in the left superior temporal gyrus and right orbitofrontal gyrus. So in view of the previous literature, our

results might suggest that the changes observed could be an early biomarker in schizophrenia [31].

As we hypothesized at the 2-year follow-up, BP patients showed less extensive differences with respect to controls with smaller voxel sizes showing a decrease of GM than SCZ patients. The regions that showed a greater decrease than controls during follow-up were in the frontal and limbic structures; the decreases were more marked in SCZ patients, though the difference was not great. In their cross-sectional study, Watson et al. [24] pointed out that FEP-BP did not differ from controls in any area, and our study with ROI methodology [21] found no differences between controls and FEP-BP patients. With regard to the group

of other psychosis patients, there were no differences with respect to controls in their GM changes during the 2-year follow-up.

With regard to the cross-sectional analysis at the 2-year follow-up, only SCZ patients showed differences with respect to controls in specific GM regions, such as the superior frontal, orbitofrontal cortex and the anterior and medial part of the cingulum and thalamus. These regions partially correspond to the already mentioned areas found in cross-sectional studies of adult patients as mentioned elsewhere [22–24]. No significant differences were detected in the VBM analysis of BP samples. These data may be in line with those obtained by McDonald et al. [32] who hypothesized that bipolar psychosis may be predominantly a WM disorder, while schizophrenia involves both GM and WM disturbances. Moreover, methodological issues such as the size of our BP sample may have meant that our study lacked the statistical power to show significant differences in GM in the VBM analysis.

Regarding the prediction of GM change in specific regions according to baseline clinical and cognitive variables, only IQ and performance in working memory tasks were significant predictors of GM reductions in the superior frontal, orbitofrontal cortex and anterior and medial part of the cingulum and thalamus in SCZ patients. In control subjects only working memory was a significant predictor of GM volume in the orbitofrontal cortex and anterior and medial part of the cingulum areas, but the variance explained was much lower than in SCZ patients. The majority of studies assessing the relationship between cognitive variables and GM reduction are cross-sectional, but a few studies in adult FEP patients have shown that some baseline cognitive variables predict GM reduction at follow-up. In a longitudinal study, Ayesa-Arriola et al. [11] found that patients classified as cognitively impaired with a global measure, including major cognitive domains of verbal and working memory, executive functions, speed of processing and attention at baseline, presented greater progressive brain volume loss after 3 years. In another study, Gutierrez-Galve [12] showed that cortical changes in the superior and inferior frontal and in the lower extent superior temporal cortex were predicted by baseline IQ and working memory. Intelligence as a global measure is closely related to the frontal and parietal areas, and patients with schizophrenia have lower premorbid IQ than controls [33]. Our findings show that lower IQ, as a measure of lower cognitive reserve, can predict a more severe disorder in relation to GM abnormalities. Other clinical variables at baseline such as premorbid adjustment, duration of illness or negative PANSS score did not predict reduction of GM in any specific area. Some adult patient studies did not find any relationship between symptom severity or duration of illness and cortical abnormalities [13, 34], although other studies

with longer duration of illness in their sample did find a correlation with gray matter abnormalities [35]. Moreover, in view of previous reports of a relationship between higher doses of antipsychotic treatment and smaller GM and WM volumes [36], we conducted a correlation analysis between all our significant results and cumulative doses of chlorpromazine (almost exclusively of second-generation antipsychotics). No association was observed in our samples. Therefore, this is an issue that should be further analyzed in future studies.

The present study has some limitations. The main one is the small sample size in the subgroups of BP and other psychotic disorders; this may have introduced type II errors and so further replication with larger samples is necessary. The group of BP patients all had psychotic symptoms with a first manic episode and the results are limited to this subgroup, (probably more severe) and cannot be extrapolated to all BP patients. The strengths of the study include the very short duration of disorder at baseline, the uniformity of patients regarding age and duration of disorder, its longitudinal design using a control group of similar age, the re-evaluation after 2 years in all cases to better establish the diagnosis, and the use of a longitudinal voxel-based method to map the progression of changes after follow-up both in patients and controls.

These results, which showed no differences at baseline when the disorder is just starting and a larger reduction in GM areas specifically in SCZ patients during the first 2 years of disease, indicate that the disorder has an important influence on GM abnormalities in these patients. In contrast, the impact in BP patients seems to be lower. It is also important to stress that in cases in which no definite diagnosis of SCZ or BP could be reached after 2 years, changes in GM were similar to those in control with a lower degree of severity both clinically and in neuroimaging studies. The prediction of GM decrease in cortical and subcortical areas by baseline IQ and working memory may help clinicians to detect SCZ patients who are going to have more neuroimaging abnormalities during the course of their disorder, and the intensification of strategies to counteract the progression of cognitive and brain abnormalities such as cognitive rehabilitation may improve prognosis in more severe young patients. Further studies with EO patients with longer follow-up periods are needed to determine whether these abnormalities progress over the years and whether in some patients they can be stabilized.

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Compliance with ethical standards

Conflict of interest Dr. Rapado Castro was supported by a Sara Borrell Health Research Fellowship from the Institute of Health Carlos III, Spanish Ministry of Economy and Competitiveness, an Alicia Koplowitz Research Grant, an Alicia Koplowitz Short-Term Visiting Fellowship from the Alicia Koplowitz Foundation and an IiSGM Fellowship Award for Short-Term Placements from the Health Research Institute from the Hospital Gregorio Marañón (IiSGM) (Madrid, Spain). Dr. Gonzalez-Pinto has received grants and served as consultant, advisor or CME speaker for the following entities: Almirall, AstraZeneca, Bristol-Myers Squibb, Cephalon, Eli Lilly, Glaxo-Smith-Kline, Janssen-Cilag, Jazz, Johnson & Johnson, Lundbeck, Merck, Otsuka, Pfizer, Sanofi-Aventis, Servier, Shering-Plough, Solvay, the Spanish Ministry of Science and Innovation (CIBERSAM), the Ministry of Science (Carlos III Institute), the Basque Government, the Stanley Medical Research Institute, and Wyeth. Dr. Graell was received honoraria or grants from Eli Lilly and Shire. Dr. Arango has been a consultant to or has received honoraria or grants from Abbot, AMGEN, AstraZeneca, Bristol-Myers Squibb, Caja Navarra, CIBERSAM, Fundación Alicia Koplowitz, Instituto de Salud Carlos III, Janssen-Cilag, Lundbeck, Merck, Ministerio de Ciencia e Innovación, Ministerio de Sanidad, Ministerio de Economía y Competitividad, Mutua Madrileña, Otsuka, Pfizer, Roche, Servier, Shire, Schering Plough and Takeda.

Ethical Standards The study was approved by the institutional review board at each clinical center. All parents or legal guardians gave written informed consent before the study began and all patients agreed to participate.

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