Progressive brain changes in children and adolescents with early-onset psychosis: A meta-analysis of longitudinal MRI studies

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ABSTRACT

Background: Studies on longitudinal brain volume changes in patients with early-onset psychosis (EOP) are particularly valuable for understanding the neurobiological basis of brain abnormalities associated with psychosis. However, findings have not been consistent across studies in this population. We aimed to conduct a meta-analysis on progressive brain volume changes in children and adolescents with EOP.
Methods: A systematic literature search of magnetic resonance imaging (MRI) studies comparing longitudinal brain volume changes in children and adolescents with EOP and healthy controls was conducted. The annualized rates of relative change in brain volume by region of interest (ROI) were used as raw data for the meta-analysis. The effect of age, sex, duration of illness, and specific diagnosis on volume change was also evaluated.
Results: Five original studies with 156 EOP patients (mean age at baseline MRI in the five studies ranged from 13.3 to 16.6 years, 67.31% males) and 163 age- and sex-matched healthy controls, with a mean duration of follow-up of 2.46 years (range 2.02–3.40), were included. Frontal gray matter (GM) was the only region in which significant differences in volume change over time were found between patients and controls (Hedges' g −0.435, 95% confidence interval (CI): −0.678 to −0.193, p < 0.001). Younger age at baseline MRI was associated with greater loss of temporal GM volume over time in patients as compared with controls (p = 0.005). Within patients, a diagnosis of schizophrenia was related to greater occipital GM volume loss over time (p = 0.001).
Conclusions: Compared with healthy individuals, EOP patients show greater progressive frontal GM loss over the first few years after illness onset. Age at baseline MRI and diagnosis of schizophrenia appear to be significant moderators of particular specific brain volume changes.

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1. Introduction

Recent meta-analyses assessing longitudinal brain changes over a 2- to 10-year follow-up period in patients with adult-onset schizophrenia suggest progressive decreases over time in cortical gray matter (GM) volume compared with healthy controls (Olabi et al., 2011; Vita et al., 2012; Fusar-Poli et al., 2013; Haijma et al., 2013). These changes seem to be even greater in patients with early-onset psychosis (EOP, i.e., patients with psychotic symptoms appearing before the age of 18 years and diagnosed with psychotic disorder) (Gogate et al., 2001; Vita et al., 2012), especially during the first 1–3 years after the onset of psychotic symptoms (Arango et al., 2012; Brent et al., 2013).

In particular, compared with healthy controls, patients with EOP – both those with first-episode psychosis (FEP) and non-FEP patients – show greater progressive GM volume decreases over time in total GM volume (TGV), and frontal GM and parietal GM volumes (Jacobsen et al., 1998; Rapoport et al., 1999; Thompson et al., 2001; Gogtay et al., 2004b; Reig et al., 2009a; Arango et al., 2012). EOP patients also show greater decreases in cerebellar (Keller et al., 2003a; Greenstein et al., 2011), hippocampal (Jacobsen et al., 1998; Giedd et al., 1999; Nugent et al., 2007; Mattai et al., 2011a; Johnson et al., 2013b), and thalamic volumes (Rapoport et al., 1997; James et al., 2002; Janssen et al., 2012), and greater increases in lateral ventricle volume (Rapoport et al., 1997; Giedd et al., 1999; James et al., 2004).

However, findings in EOP patients have not been consistent across longitudinal studies. One study reported loss of corpus callosum (CC) volume over time (Keller et al., 2003b), which was not reported in Johnson et al. (2013a). Several studies showed greater progressive loss of temporal GM volume over time compared with healthy controls (Jacobsen et al., 1998; Rapoport et al., 1999; Gogtay et al., 2004b;

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James et al., 2004), but see Arango et al. (2012). There were even two studies reporting an absence of progressive brain changes in patients over the first 2–3 years of follow-up (James et al., 2002; James et al., 2004).

Discrepant volumetric findings in young people may be at least partly attributable to different factors and conditions that moderate the detected pattern of structural brain changes, i.e., 1) differences in sex proportion (Lenroot et al., 2007; Janssen et al., 2012), 2) age at onset (Vita et al., 2012), 3) duration of illness (Haijma et al., 2013), 4) duration of follow-up (Vita et al., 2012; Haijma et al., 2013), 5) brain regions of interest (ROIs) under study (Arango et al., 2008), 6) use of voxel-based morphometry (VBM) versus ROI-based approaches (Giuliani et al., 2005), 7) exposure to lithium or antipsychotic treatment (Navari and Dazzan, 2009; Ho et al., 2011; Hafeman et al., 2012; Fusar-Poli et al., 2013; Haijma et al., 2013), 8) symptom presentation and severity (DeLisi et al., 1998; Strakowski et al., 2002; Nery et al., 2009; Arango et al., 2012), and 9) diagnostic heterogeneity (Arango et al., 2008; Arango et al., 2012).

Childhood-onset schizophrenia (COS) is defined as schizophrenia with onset prior to age 13 years. Individuals with COS are reported to show a higher rate of pre-psychotic neurodevelopmental problems as compared with adolescent-onset cases (Hollis, 1995; Arango et al., 2008). Cross-sectional and longitudinal studies report GM volume deficits in COS that could be considered an *exaggeration* of GM development reported in typically developing subjects (Thompson et al., 2001; Greenstein et al., 2006; Burke et al., 2008), while studies in patients with late-adolescent-onset and adult-onset forms of the disease (adult-onset schizophrenia — AOS) report less marked differences in parietal GM volume and more marked differences in the later maturing prefrontal and temporal cortices as compared with their childhood-onset counterparts (Rimol et al., 2010; Rimol et al., 2012; Janssen et al., 2014a). This is also true for first-episode non-schizophrenia patients (e.g., patients with early-onset bipolar disorder) who are reported to show similar, albeit less marked and widespread, age-related GM volume abnormalities and trajectories than SSD patients (Farrow et al., 2005; Janssen et al., 2008; El-Sayed et al., 2010; Janssen et al., 2014b). This suggests a neurobiological continuum between EOP and adult-onset psychosis (AOP) (Arango et al., 2008), with the former following a more severe clinical and functional course (Driver et al., 2013; Bernardo and Bioque, 2014).

In typically developing individuals, maturation of TGV includes an increase during childhood with a peak around puberty, followed by a sustained decrease during adolescence (Gogtay et al., 2004a). However, rate and amount of GM loss varies by region and age, supposedly starting in the dorsal parietal cortices around puberty and then spreading rostrally over the frontal cortex (after reaching peak volume at 11–12 years old) and caudally and laterally over the occipital, parietal, and finally the temporal cortices (after reaching peak volume at 16–17 years old) (Gogtay et al., 2004a) and the dorsolateral prefrontal cortex, which does not reach adult dimensions until the early 20s (Lenroot et al., 2007). In fact, longitudinal trajectories suggest that the rate of cortical and hippocampal GM loss plateaus during adolescence (Giedd et al., 1999; Sporn et al., 2003). The pattern of morphological brain changes in EOP patients may thus be modulated by age (and thus stage of brain development) at illness onset.

Studies on brain volume changes in children and adolescents with psychosis seem to be particularly valuable for understanding the neurobiological basis of the illness overall (Brent et al., 2013). However, to date, a meta-analysis on progressive brain volume changes in children and adolescents with EOP has never been conducted.

The primary goal of the current meta-analysis was to examine to what extent EOP patients undergo progressive brain volume changes compared with healthy controls. We also aimed to assess the effect of factors potentially affecting brain volume change, such as age, male to female ratio, duration of illness, and specific diagnosis.

2. Methods

2.1. Selection procedures

2.1.1. Search strategies

Using the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram for literature search, a systematic two-step literature search was conducted to identify appropriate studies (Moher et al., 2009). First, a PubMed, Web of Science, and Embase search was performed to detect putative longitudinal MRI studies in EOP. The search was conducted from inception through May 2014. The following search terms were used: "magnetic resonance imaging" (MRI) (OR "MRI" OR "neuroimaging") AND "psychosis" (OR "schizophrenia") AND adolescent (OR "child") AND "longitudinal" (OR "progressive" OR "follow-up") NOT review, and combinations of the above terms. Second, the reference list of the selected articles was manually checked for any studies not identified by the computerized literature search. There was no language restriction.

2.1.2. Selection criteria

Studies were considered for review if they met the following hierarchical criteria: 1) they were published as original peer-reviewed articles; 2) they compared patients with a diagnosis of psychotic disorder (according to DSM-IV, DSM-III-R, or ICD-10) with age- and sex-matched healthy controls; 3) patients were younger than 18 years old at the beginning of the psychotic illness; 4) the studies had a longitudinal design (i.e., patients and controls were followed over a time period and underwent two or more MRI assessments); and 5) they used ROI volumetric analysis of structural MRI data (studies providing information on areas, volume estimation by means of an inadequate number of slices, VBM, cortical pattern matching, diffusion tensor imaging, tractography, or other techniques that do not provide brain volumetric data for a priori defined anatomical regions of interest were not included).

Studies were excluded if 1) there were fewer than five subjects in the EOP group and/or the control group; 2) the data overlapped with those of another publication assessing the same ROIs, in which case the publication with the largest group size was selected; 3) the data did not contribute to an ROI included in the meta-analyses (meta-analyses were conducted when at least 3 independent studies reported the volume of the specific ROI); and 4) the means and standard deviations (SDs) of the baseline and follow-up volumes of the included ROIs were not reported (or could not be extracted from the reported data or retrieved from the authors).

Supplementary Table 1 provides a summary of longitudinal MRI studies in EOP and the reason for exclusion from this meta-analysis as appropriate.

2.1.3. ROI selection and data abstraction

The following ROIs were included in the meta-analysis: total brain volume (TBV), TGV, frontal GM volume, parietal GM volume, temporal GM volume, and occipital GM volume. For each of the ROIs, brain volume changes were extracted as the primary outcome. Specifically, volume was extracted in mL, and the mean and SD of the percentage change in volume were computed as follows: [(volume at follow-up — volume at baseline) / volume at baseline] ∗ 100. Annualized rates of loss of brain volume were then estimated by dividing the percentage volume change over time in each study by the mean inter-scan interval (all included studies had a mean interval >1 year). These were the raw data used for meta-analysis (see Supplementary Table 2 for details).

When articles provided data for defined subgroups (for example, by sex or by left/right hemisphere), the data were combined (weighted by the sample size of each group) so that each study contributed only one datapoint per ROI to the meta-analysis. This was done in order to make the data from the different studies comparable.

The data extracted from the studies also included author names, year of publication, number of participants, age at baseline, proportion of male participants, handedness, diagnosis, duration of illness (as the time from the reported age at onset to MRI acquisition), and duration of follow-up (as the mean interval between MRI scans). In instances where the primary outcome measures and/or the above-mentioned demographic/clinical data could not be retrieved from the original publication, the corresponding authors were contacted by e-mail.

2.2. Statistical analysis

Data were entered into an electronic database and analyzed with a quantitative meta-analytical approach using Comprehensive Meta-Analysis (CMA) Software version 2 (Biostat, Inc., Englewood, NJ) (Borenstein et al., 2005).

The effect size was estimated by calculating Hedges' unbiased *g*. Negative values reflected greater brain volume reduction in patients compared with controls from baseline to follow-up. Standardized effect sizes were combined to produce a single summary estimate using random-effects techniques based on the method of maximum likelihood (DerSimonian and Laird, 1986). To limit the risk of false positive (type I) errors arising from multiple comparisons, we adjusted the p-value by dividing it by the number of meta-analyses conducted (corrected p = 0.0083 (0.05/6)).

To assess the heterogeneity among study point estimates, we calculated the Q statistic, with magnitude of heterogeneity being evaluated using the I^2 statistic (a measure of the proportion of variance in summary effect size attributable to heterogeneity) (Lipsey and Wilson, 2000).

Publication bias was assessed by visually inspecting funnel plots and applying Egger's regression test (Egger et al., 1997). In addition, we used Orwin's fail-safe N (Orwin, 1983). This generated the number of unpublished studies that would be needed to move estimates to a non-significant threshold. When the funnel plot or test statistics suggested publication bias, we used the Duval and Tweedie trim-and-fill method to estimate an effect size corrected for publication bias (Duval and Tweedie, 2000).

The influence of demographic and clinical variables was tested using weighted linear meta-regression analyses (mixed effects regression, unrestricted maximum likelihood), with study effect size as the independent variable and either age (as mean age of patients at baseline MRI in years), sex (as percentage of male patients), duration of illness (as time from the reported age at onset to MRI acquisition in years), and specific diagnosis (as percentage of patients with a diagnosis of schizophrenia) as the dependent variables.

3. Results

3.1. Search results

The initial literature search yielded 1047 studies. After removing 777 duplicates, 270 potential studies were fully assessed. Of the 270 studies, 21 fulfilled the inclusion criteria. Of those, 16 met at least one exclusion criterion (Supplementary Table 1). The final meta-analysis database comprised five original independent studies (Sporn et al., 2003; Gogtay et al., 2004b; James et al., 2004; Reig et al., 2009a; Arango et al., 2012). The study by Gogtay et al. (2004b) provided separate volumetric data for two independent groups of EOP patients: COS and psychosis not otherwise specified (NOS). Thus, for purposes of this meta-analysis, they were considered two different studies. The overall sample was composed of 156 EOP patients and 163 healthy controls. The mean duration of follow-up was 2.46 years (range 2.02 to 3.40). Fig. 1 shows the flowchart of the systematic literature search strategy.

3.2. Demographic characteristics

The mean age of EOP patients in each of the five included studies ranged from 13.3 to 16.6 years. The percentage of male patients in each of the five included studies ranged from 56.3% to 84.2%, with male patients outnumbering female patients overall (male patients n = 105 (67.31%), female patients n = 51 (32.69%)). Of the 156 patients, 82 (52.6%) were experiencing their first episode of psychosis. Details of the included studies are shown in Table 1.

3.3. Results of the main meta-analysis

Random effects analyses were conducted for 6 ROIs: TBV, TGV, frontal GM volume, parietal GM volume, temporal GM volume, and occipital GM volume. Results are presented in Table 2.

After correction for multiple comparisons, greater frontal GM volume reductions over time were found in EOP patients compared with healthy controls (mean Hedges' *g* −0.435, 95% confidence interval (CI): −0.678 to −0.193, corrected p < 0.001). Fig. 2 shows the forest plot for the meta-analysis of the three studies assessing longitudinal changes in frontal GM volume (Sporn et al., 2003; Reig et al., 2009a; Arango et al., 2012).

There were no significant differences between patients and controls in changes over time in TBV, TGV, parietal, temporal, or occipital GM volumes (all p-values > 0.05, except for occipital GM volume for which significant differences were found before correction for multiple comparisons (uncorrected p = 0.047)) (see Table 2).
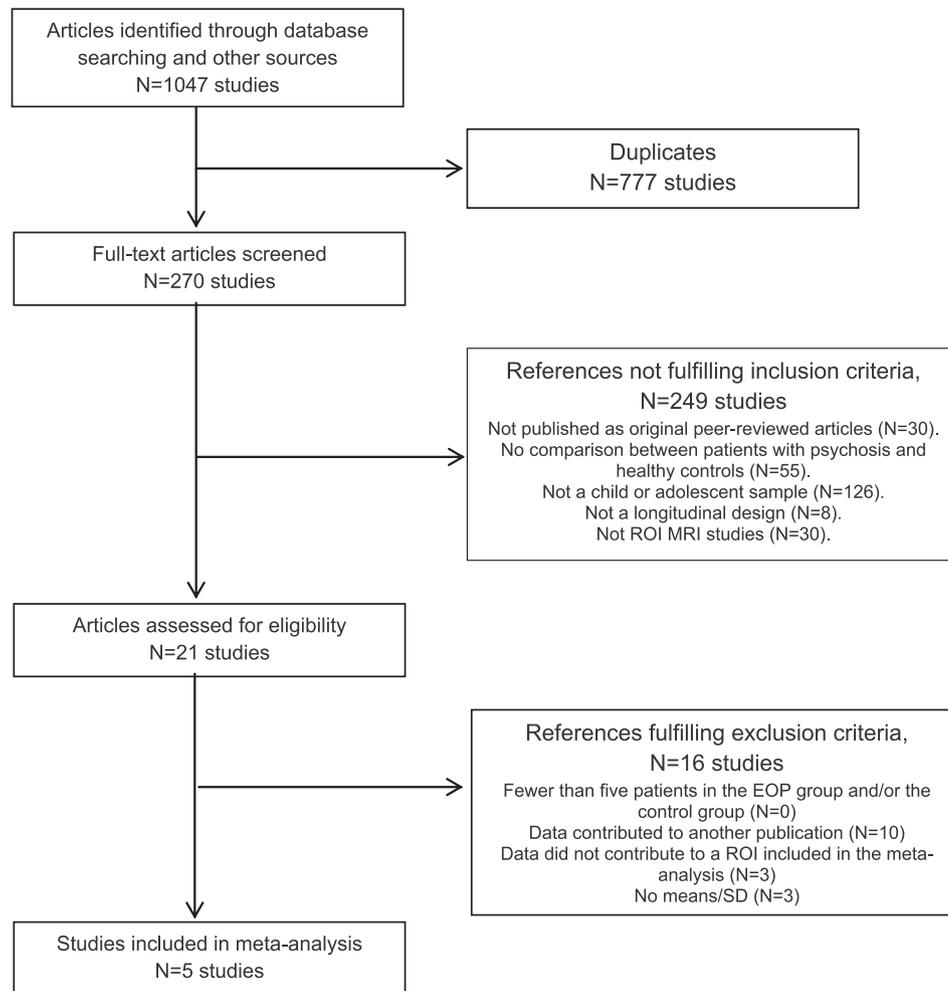
3.4. Publication bias, heterogeneity, and sensitivity analysis

Statistically significant heterogeneity was detected for temporal (Q = 9.607, I^2 = 79.18%, p = 0.008) and occipital (Q = 11.893, I^2 = 83.18%, p = 0.003) GM volumes. Egger's test indicated a presence of publication bias for TBV (p = 0.010), TGV (p = 0.049), and parietal GM volumes (p = 0.025). Indeed, trim-and-fill adjustment showed that, after correction for publication bias, differences in parietal GM volume change over time between patients and controls were significant at the uncorrected level (mean Hedges' *g* after trim-and-fill method −0.369, 95% CI −0.560 to −0.138) (see Table 2). Frontal GM volume was the only measure for which neither significant heterogeneity nor publication bias was found.

For each ROI, the modifying effects of age, male proportion, duration of illness, and diagnosis were investigated using meta-regression analyses. Two significant associations were found between these variables and effect size. First, mean age of patients at baseline MRI was associated with effect size in temporal GM, thus the younger the patient, the greater the loss of temporal GM volume over the follow-up period compared with the control group (Beta = 1.425, 95% CI: 0.427 to 2.423, p = 0.005). Second, within patients, a diagnosis of schizophrenia was related to greater loss of occipital GM volume over the follow-up period (Beta = −0.013, 95% CI: −0.021 to −0.005, p = 0.001). The effect of diagnosis (having schizophrenia vs. other psychotic disorders) on changes in TBV, TGV, and frontal, parietal, or temporal GM volumes was not significant (all p-values > 0.05). The effects of sex (proportion of males) and duration of illness on the effect size of volume changes in the assessed ROIs were not significant either. Supplementary Table 3 summarizes the meta-regression data.

4. Discussion

Findings from the present meta-analysis suggest that, compared with age- and sex-matched healthy controls, patients with EOP exhibit greater progressive loss in frontal GM, but not in TBV, TGV, parietal GM volume, temporal GM volume, or occipital GM volume over the first few years after illness onset. These results suggest that progressive cortical GM changes in EOP occur with regional specificity.

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┌─────────────────────────────┐
│ Articles identified through  │
│ database searching and       │
│ other sources                │──────────────┐
│ N=1047 studies               │              ▼
└──────────────┬──────────────┘        ┌──────────────────┐
               │                        │ Duplicates        │
               │                        │ N=777 studies     │
               ▼                        └──────────────────┘
┌─────────────────────────────┐
│ Full-text articles screened  │
│ N=270 studies                │───────────────┐
└──────────────┬──────────────┘               ▼
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References not fulfilling inclusion criteria, N=249 studies

Not published as original peer-reviewed articles (N=30).
No comparison between patients with psychosis and healthy controls (N=55).
Not a child or adolescent sample (N=126).
Not a longitudinal design (N=8).
Not ROI MRI studies (N=30).

Articles assessed for eligibility N=21 studies

References fulfilling exclusion criteria, N=16 studies

Fewer than five patients in the EOP group and/or the control group (N=0)
Data contributed to another publication (N=10)
Data did not contribute to a ROI included in the meta-analysis (N=3)
No means/SD (N=3)

Studies included in meta-analysis N=5 studies

Fig. 1. Flowchart of study selection (according to PRISMA flow diagram for literature search). *Abbreviations*: EOP: early-onset psychosis. MRI: magnetic resonance imaging. ROI: region of interest. SD: standard deviation.

Recent meta-analyses in adult patients with schizophrenia (Olabi et al., 2012; Haijma et al., 2013) have reported larger decreases over time in TGV, frontal GM volume, temporal GM volume, parietal GM volume, and occipital GM volume in patients relative to healthy controls. These results have been replicated in mixed samples of adolescent and adult patients with schizophrenia (Vita et al., 2012) as well as in original

studies in EOP patients (Jacobsen et al., 1998; Rapoport et al., 1999; Thompson et al., 2001; Arango et al., 2012). Nevertheless, these findings have not been consistent across studies (e.g., it has been reported that occipital GM volume shows a positive annualized percentage of change both in patients and controls) (Vita et al., 2012). Even though our meta-analysis found a pattern of GM loss for TGV, frontal GM, parietal GM, and

Table 1
Summary of the studies included in the meta-analysis.

Author, year	EOP patients									Controls				MRI[a]	Follow-up[b]
	n	% M	Age[c]	% RH	Diagnostic criteria	% SCZ	CPZ equiv.	Duration of illness until MRI (years)		n	% M	Age[c]	% RH		
James et al. (2004)	16	56.3	16.6	94.1	DSM-III-R	100	281.3	1.55		16	56.3	16.0	58.8	1.5, 3	2.11
Sporn et al. (2003)[d]	39	61.5	15.0	NA	DSM-III-R or DSM-IV	100	NA	4.60		43	62.8	14.8	NA	1.5, 1.5	3.40
Gogtay et al. (2004b) (COS)[e]	23	82.6	13.9	78.3	DSM-III-R or DSM-IV	100	NA	3.77		38	84.2	13.3	94.7	1.5, 1.5	2.51
Gogtay et al. (2004b) (psychosis NOS)[e]	19	84.2	13.3	89.5	DSM-III-R or DSM-IV	0	NA	5.50		38	84.2	13.3	94.7	1.5, 1.5	2.60
Reig et al. (2009a)	21	76.2	15.7	90.5	DSM-IV	38.10	NA	0.27		34	61.2	15.2	85.3	1.5, 1.5	2.02
Arango et al. (2012)	61	65.6	15.3	91.7	DSM-IV	40.98	217.2	0.28		70	32.9	15.3	87.1	1.5, 1.5	2.13

Abbreviations: COS: childhood-onset schizophrenia. CPZ equiv.: chlorpromazine equivalents (mean daily dose of antipsychotic during follow-up). EOP: early-onset psychosis. M: males. MRI: magnetic resonance image. NA: not available. NOS: not otherwise specified. RH: right-handed. SCZ: schizophrenia.

[a] MRI: Tesla, slice thickness (mm).
[b] Duration of follow-up (years).
[c] Mean age at initial MRI (years).
[d] Patients evaluated in Sporn et al. (2003) were also evaluated in Gogtay et al. (2004b) (COS). Here, they were used to conduct different meta-analyses: Sporn et al. (2003) for total brain volume, total gray matter volume, frontal gray matter volume, parietal gray matter volume, and temporal gray matter volume, and Gogtay et al. (2004b) (COS) for occipital gray matter volume.
[e] Healthy controls included in Gogtay et al. (2004b) (COS) and Gogtay et al. (2004b) (psychosis NOS) were also included in Sporn et al. (2003).

Table 2
Summary of the meta-analyses.

Brain region (ROI)	No. of studies	No. of patients	No. of controls	Mean annualized percentage of change in ROI volume		Effect size (Hedges' g)[a]			Test for heterogeneity			Publication bias		
				Patients	Controls	Mean (95% CI)	Z-value	p-Value[b]	Cochran's Q	I² (%)	p-Value	ERT	FSN	Trim and fill, mean (95% CI)
TBV	3[c]	74	97	−0.29%	−0.17%	−0.019 (−0.321 to 0.283)	−0.124	0.901	0.414	0	0.813	0.010	0	−0.105 (−0.351 to 0.141)
TGV	4[d]	140	147	−1.36%	−0.71%	−0.091 (−0.311 to 0.128)	−0.818	0.414	1.108	0	0.775	0.049	0	−0.135 (−0.339 to 0.068)
Frontal GM volume	3[e]	121	147	−1.83%	−0.65%	−0.435 (−0.678 to −0.193)	−3.522	0.000	1.726	0	0.422	0.383	6	−0.435 (−0.678 to −0.193)
Parietal GM volume	3[e]	121	147	−2.29%	−1.46%	−0.238 (−0.479 to 0.002)	−1.944	0.052	1.578	0	0.454	0.025	0	−0.369 (−0.560 to −0.138)
Temporal GM volume	3[e]	121	147	−1.29%	−0.86%	−0.027 (−0.578 to 0.525)	−0.095	0.924	9.607	79.18	0.008	0.201	0	−0.027 (−0.578 to 0.525)
Occipital GM volume	3[f]	63	72	−1.24%	+0.43%	−0.796 (−1.583 to −0.010)	−1.984	0.047	11.893	83.18	0.003	0.052	15	−0.796 (−1.583 to −0.010)

Abbreviations: CI: confidence interval. COS: childhood-onset schizophrenia. ERT: Egger's regression test. GM: gray matter. Psychosis NOS: psychosis not otherwise specified. ROI: region of interest. TBV: total brain volume. TGV: total gray matter volume.

[a] Comparison of patients versus controls. Negative values reflected greater brain volume reduction in patients as compared with controls during follow-up.

[b] Adjusted p for multiple comparisons (6 meta-analyses, corrected p = 0.0083 (0.05/6)).

[c] Sporn et al. (2003), Gogtay et al. (2004b) and James et al. (2004). Patients from Gogtay et al. (2004b) were those with psychosis NOS.

[d] Sporn et al. (2003), Gogtay et al. (2004b), Reig et al. (2009a) and Arango et al. (2012). Patients from Gogtay et al. (2004b) were those with psychosis NOS.

[e] Sporn et al. (2003), Reig et al. (2009a) and Arango et al. (2012).

[f] Gogtay et al. (2004b) and Reig et al. (2009a). Patients from Gogtay et al. (2004b) were those with both psychosis NOS and COS.

temporal GM for both EOP patients and controls, and occipital GM loss for patients only, that loss was significantly larger only in the frontal lobe for patients compared with controls.

A type II error, i.e., a failure to detect an effect that is present, may underlie our regional-specific findings. In our study, the difference in volume loss over the follow-up period between patients and controls in both occipital GM and parietal GM showed a trend towards significance (p = 0.047, and p = 0.052, respectively). Indeed, after correction for publication bias, differences in parietal GM volume change reached statistical significance (although this finding did not survive multiple comparison correction, see Table 2). In this context, frontal GM would be merely the ROI that showed the most marked difference between patients and controls during follow-up. This is congruent with findings in adult patients with schizophrenia showing the greatest effect size for frontal volume loss as compared with the other lobes (Olabi et al., 2012; Vita et al., 2012; Haijma et al., 2013). Furthermore, it is consistent with a recent study showing decreased frontal cortical thickness and increased sulcal width in adolescents with psychoses who were diagnosed with schizophrenia or bipolar disorder with psychotic symptoms after a two-year clinical follow-up when compared with controls (Janssen et al., 2014a). In addition, although our meta-analysis did not find a significantly greater loss of temporal GM volume in EOP patients compared with controls, it showed that mean age of patients at baseline MRI was associated with the effect size in this ROI, thus the younger the patient, the greater the loss of temporal GM volume over the follow-up period compared with controls. This effect of age could partly explain the heterogeneous temporal GM volume findings in previous studies.

Some of the discrepancies between previous results of meta-analyses of longitudinal MRI studies (e.g., Olabi et al., 2012; Vita et al., 2012; Haijma et al., 2013), and our findings could be partially explained by the particular developmental stage of patients included in our study and their region-related brain development pattern. The mean age of patients of the five studies included in the present meta-analysis ranged from 13.3 to 16.6 years. At that developmental stage, frontal and occipital poles are likely to be the ones that are most affected and show greater differences compared with controls, as they are actually undergoing active maturation at these ages, while the temporal lobe shows a later maturation pattern (Arango et al., 2008). Our results would thus support the hypothesis that, in EOP, there is an exaggeration of the *normal* brain GM loss that takes place in adolescence, a physiological process in which volume loss (Gogtay et al., 2004a) and flattening of cortical GM appear to be greatest in the frontal and occipital regions as compared with other cortical regions (Aleman-Gomez et al., 2013). In fact, purely adolescent EOP cohorts are reported to show frontal (but not parietal or temporal) GM volume deficits compared with age-matched healthy individuals, both in cross-sectional (Moreno et al., 2005) and longitudinal studies (Reig et al., 2009a). Of note, mean age at scan of the patients of the five studies included in this meta-analysis (13.3 to 16.6 years) should not be considered equal to mean age at onset of psychosis. Indeed, duration of illness (and thus patient age at onset) varied among studies (from 0.27 years in adolescent-onset psychosis studies to 5.50 years in COS studies). Thus, age-related findings in our study could be potentially confounded by a time-of-measurement effect. That said, the effect of duration of illness on brain volume changes over the follow-up period was not significant for any of the ROIs.

The mechanisms that lead to an *exaggeration* of progressive GM loss in EOP patients may include anomalous neurodevelopmental processes (most likely glial and vascular rather than purely neuronal changes (Rapoport and Gogtay, 2008), excessive and aberrant synaptic pruning with a reduction of neuropil rather than a deficit in the total number of neurons (Whitford et al., 2007; Cannon et al., 2015), aberrant neurogenesis, axonal growth, myelinization, or synaptogenesis, and GM disorganization (van Os et al., 2010; Mauney et al., 2013)), dopamine sensitization (Howes and Murray, 2014), epigenetic changes (van Os et al., 2010), oxidative damage (Fraguas et al., 2012), and pro-inflammatory status (Garcia-Bueno et al., 2014). According to the
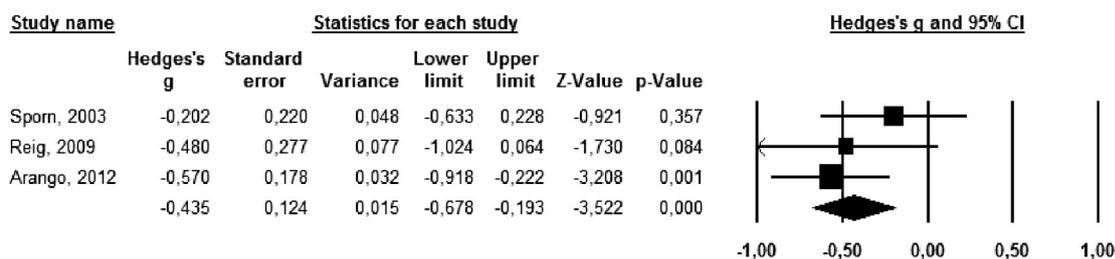
Meta Analysis

Study name	Statistics for each study							Hedges's g and 95% CI
	Hedges's g	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	
Sporn, 2003	-0,202	0,220	0,048	-0,633	0,228	-0,921	0,357	
Reig, 2009	-0,480	0,277	0,077	-1,024	0,064	-1,730	0,084	
Arango, 2012	-0,570	0,178	0,032	-0,918	-0,222	-3,208	0,001	
	-0,435	0,124	0,015	-0,678	-0,193	-3,522	0,000	

Fig. 2. Forest plot for the meta-analysis of the three studies assessing longitudinal changes in frontal gray matter volume.

two-hit hypothesis, early GM loss in EOP patients would be due to the interaction of genetic or very early vulnerabilities (first *hit*) with a second *hit* around adolescence (typical age of onset of psychosis) (Maynard et al., 2001; Brown, 2011). These *hits* could trigger or maintain pathophysiological mechanisms that would lead to abnormal brain development and may pre-date illness onset (Rapoport et al., 2012). The two-hit hypothesis appears to be supported by prospective neuroimaging studies of non-psychotic full siblings of COS patients. These individuals show a pattern of frontal and temporal GM deficits in childhood that appear to *normalize* by the time they reach late adolescence (Raznahan et al., 2011). The normalization of cortical GM loss would represent a *resilient phenotype* in siblings. Early GM loss in siblings would be due to genetic vulnerabilities (first *hit*), but the second *hit* around adolescence would be absent or overcome by a plastic response of *normalization* of the early GM abnormalities. Conversely, EOP patients would represent a group in which the *two-hits* are present so they do not develop this *resilient phenotype* (Rapoport et al., 2012). This observation was recently replicated in a *non-overlapping* sample of healthy siblings and matched healthy controls (Mattai et al., 2011b).

There are several limitations to this study that should be taken into account when interpreting the results. Firstly, we assessed patients with EOP, which is a diagnostically heterogeneous group. The small sample size limited the capacity of analysis for a specific diagnosis, such as schizophrenia. To reduce the consequences of this limitation, we conducted a meta-regression with specific diagnosis (percentage of patients with a diagnosis of schizophrenia) as the dependent variable. Within the group of EOP patients, a diagnosis of schizophrenia was related only to greater loss of occipital GM volume during follow-up, while effect of a diagnosis of schizophrenia on the other ROIs was not significant. Although the pioneering studies assessing progressive cortical loss in COS as compared with other childhood-onset psychoses suggested that progressive cortical loss may be diagnostically specific to the former group (Gogtay et al., 2004b), our results suggest that differences between schizophrenia and affective psychosis are more quantitative than qualitative, with observed morphometric measures for bipolar patients positioned between healthy controls and schizophrenia patients (Arango et al., 2014). Since some of these brain abnormalities seem to predict outcome, they may represent a marker of severity rather than of specific psychosis diagnosis. Indeed, excessive GM loss in the early stages of psychotic illness may be considered a marker of poorer prognosis (e.g., it has been associated with longer duration of hospitalization during follow-up and with less improvement in psychotic symptoms) (Arango et al., 2012). In this sense, the schizophrenia finding may be an epiphenomenon driven by severity and/or medication (Arango et al., 2014).

Secondly, within the group of EOP patients, we did not distinguish between childhood-onset (i.e., onset before 13 years old) and adolescent-onset cases and, given the limited sample size, we did not conduct specific subanalyses for childhood-onset patients (who seem to follow a clinical and neurobiological continuum with the adolescent- and adult-onset cases (Arango et al., 2008; Driver et al., 2013)).

Thirdly, it has been suggested that progressive GM volume decreases in schizophrenia patients are associated with exposure to antipsychotic treatment (Vita et al., 2012; Fusar-Poli et al., 2013; Haijma et al., 2013). However, antipsychotic dose over the follow-up period was not available for 3 out of the 5 studies included in the meta-analysis. This is relevant because young people may be especially sensitive to antipsychotic-related adverse effects (e.g., extrapyramidal side effects, sedation, prolactin elevation, weight gain) (Kumra et al., 2008), and it is not known if the heightened sensitivity also moderates the putative relationship between antipsychotic drugs and brain volume changes. However, a recent study examining lobar cortical thickness and surface area width in healthy controls, EOP–schizophrenia and EOP–bipolar disorder with psychotic symptoms found no within-patient correlation between anatomical variation and dose of chlorpromazine equivalents used (Janssen et al., 2014a).

Fourthly, although data annualization allows comparison between studies, it makes the assumption that brain volume loss is equivalent over all years of follow-up. However, it is unlikely that this loss is linear over time (Weinberger and McClure, 2002).

Fifthly, different brain imaging acquisition and processing techniques may have an impact on observed effect sizes. A study assessing the increase in variability when combining volumetric data from different scanners showed that occipital lobe volumes had greater intersite coefficient of variation than frontal, parietal, or temporal lobes (Reig et al., 2009b). Although this may be due to a size effect, i.e., small variations in smaller regions have a greater effect than small variations in larger regions, significant heterogeneity in temporal GM volume and occipital GM volume may be a consequence, at least in part, of greater intersite coefficient of variation. Furthermore, we did not control for slice thickness of MRI scans. In the meta-analysis by Vita and colleagues, slice thickness of MRI scans was a significant moderator of effect size for whole brain and superior temporal gyrus GM, indicating more evident differences between patients and controls detected in technologically more sophisticated studies (Vita et al., 2012). That said, all but one of the studies included in this meta-analysis used the same slice thickness (i.e., 1.5 mm).

Sixthly, we were not able to investigate the effect of left/right asymmetry. This is a controversial topic. The meta-analysis by Vita and colleagues reported that progressive cortical changes more markedly affect the left hemisphere (Vita et al., 2012). However, the meta-analysis by Haijma and colleagues concluded that significant differences in effect sizes between the left and right hemispheres were observed only for the planum temporale, without significant effects for frontal, parietal, or occipital regions (Haijma et al., 2013). Moreover, including separate left and right measures in this meta-analysis would have resulted in a need to increase the number of comparisons with a derived increased risk of finding false positive associations.

Seventhly, effect of intelligence quotient (IQ) on brain volume changes was not investigated. The largest cross-sectional meta-analysis of brain volume in adult schizophrenia patients did not find a significant moderating effect of IQ on brain volume differences between patients and controls (Haijma et al., 2013).

In conclusion, this meta-analysis revealed that, during the first few years after illness onset, children and adolescents with EOP show greater progressive frontal GM loss compared with healthy controls. Future studies should focus on the neurobiological underpinnings of these pathologic progressive brain changes. The correlates of volume changes at cellular and network levels and the study of neurodevelopmental trajectories associated with different psychotic disorders may be promising areas of research for developing new therapeutic tools.

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