

## REVIEW

# Progressive loss of cortical gray matter in schizophrenia: a meta-analysis and meta-regression of longitudinal MRI studies

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Cortical gray matter deficits have been found in patients with schizophrenia, with evidence of progression over time. The aim of this study was to determine the extent of progressive cortical gray matter volume changes over time in schizophrenia, their site and time of occurrence, and the role of potential moderators of brain changes. English language articles published between 1 January 1983 and 31 March 2012 in the MEDLINE and EMBASE databases were searched. Longitudinal magnetic resonance imaging studies comparing changes in cortical gray matter volume over time between patients with schizophrenia and healthy controls were included. Hedges *g* was calculated for each study. Analyses were performed using fixed- and random-effects models. A subgroup analysis was run to explore the pattern of brain changes in patients with first-episode schizophrenia. A meta-regression statistic was adopted to investigate the role of potential moderators of the effect sizes (ESs). A total of 19 studies, analyzing 813 patients with schizophrenia and 718 healthy controls, were included. Over time, patients with schizophrenia showed a significantly higher volume loss of total cortical gray matter, left superior temporal gyrus (STG), left anterior STG, left Heschl gyrus, left planum temporale and posterior STG bilaterally. Meta-analysis of first-episode schizophrenic patients showed a more significant pattern of progressive loss of whole cerebral gray matter volume involving the frontal, temporal and parietal lobes, and left Heschl gyrus compared with healthy controls. Clinical, pharmacologic and neuroradiological variables were found to be significant moderators of brain volume changes in patients with schizophrenia. The meta-analysis demonstrates that progressive cortical gray matter changes in schizophrenia occur with regional and temporal specificity. The underlying pathological process appears to be especially active in the first stages of the disease, affects the left hemisphere and the superior temporal structures more and is at least partly moderated by the type of pharmacological treatment received.

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## Introduction

Multiple brain abnormalities in schizophrenia have been demonstrated by a large number of computed tomographic and magnetic resonance imaging (MRI) studies in the past 40 years and confirmed by a series of meta-analytic reviews.<sup>1–4</sup> A 3% decrease in whole brain volume has been found in patients with schizophrenia compared with healthy individuals; decreases were more prominent for gray matter (2%) than for white matter (1%).<sup>3</sup> The pathomorphological findings most commonly demonstrated by region of interest (ROI) MRI studies include enlargement of the ventricular system and reduction in the volume of cortical and subcortical gray matter of frontal and temporal lobes and the limbic system.<sup>5–10</sup> A more detailed examination of regional brain structural changes has been achieved by voxel-based morphometry (VBM) studies.<sup>11</sup> Meta-analytical reviews have consistently shown that schizophrenia is associated with a reduction in

gray matter volume, indicating the anterior cingulate, thalamus, frontal lobe, hippocampal–amygdala region,<sup>12</sup> superior temporal gyrus (STG) and left medial temporal lobe gray matter as key regions of structural deficits.<sup>13</sup>

The nature and meaning of such brain abnormalities, their time of occurrence and whether they are static or progressive have been investigated by cross-sectional comparisons of patients with first-episode and chronic schizophrenia and by a number of within-subject longitudinal MRI studies.<sup>14–16</sup> A recent meta-analysis of longitudinal controlled MRI studies demonstrated a significantly higher volume reduction of whole brain gray matter and enlargement of lateral ventricles in patients with schizophrenia compared with healthy controls,<sup>17</sup> thus supporting the notion that schizophrenia is associated with progressive loss of cerebral tissue. Cortical gray matter appears particularly sensitive to change.<sup>13,18–19</sup>

Given its consistent involvement in studies on brain pathology of schizophrenia and in most of the

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pathophysiological hypotheses of the disorder,<sup>20–22</sup> and also its functional relevance and implications in clinical-pathological association studies,<sup>23–26</sup> gray matter has been a focus of special attention in research on the time course of brain structural changes and their clinical significance. However, despite the extensive work carried out, debate on the time of occurrence of gray matter changes in schizophrenia and whether they progress over time is ongoing, and factors facilitating or preventing such progression are still largely unknown. The available literature data<sup>17</sup> do not allow a conclusion on whether the observed pattern of progressive changes in gray matter affects the brain uniformly or involves discrete cortical areas. Moreover, it is now well recognized that the effect of potential confounding factors such as pharmacological treatment and brain aging have to be taken into account in morphological investigations of brain volume changes over time, especially in the case of cerebral gray matter.<sup>27,28</sup> Several studies have indicated that treatment with typical antipsychotics may increase basal ganglia volume, and reduce cortical gray matter in different brain regions,<sup>29–32</sup> whereas atypical antipsychotics have been found not only to reduce<sup>33</sup> but also to retain or even increase<sup>31,34</sup> cortical gray matter volume over time.<sup>35,36</sup> A number of studies concluded that there is evidence for accelerated loss of gray matter in schizophrenia compared with healthy individuals<sup>14,15</sup> and such brain volume changes may be especially prominent in the first years of illness.<sup>37–41</sup>

A meta-analysis of all published studies can facilitate the understanding of the progression of cortical gray matter abnormalities in schizophrenia. We were interested in answering the following questions: Are gray matter abnormalities in schizophrenia progressive? Does progression uniformly affect different brain areas and structures? When progression occurs in the course of the disease? Are there differences in time and rate of such progression for different brain regions? Are there significant moderators of progression and do they differ for the different brain structures? Is there evidence of a different moderating role of first- versus second-generation antipsychotic (FGA versus SGA) treatment on such progression? To provide answer to these questions, we performed a series of updated quantitative meta-analyses of available studies that analyzed cerebral gray matter changes in schizophrenia with a longitudinal controlled design, including both the analysis of cortical subregions crucially involved in the pathophysiology of the disease not previously meta-analyzed and a subgroup analysis on studies conducted in first-episode patients, which allowed us to make inferences on the site and timing of cortical gray matter changes in schizophrenia. Finally, a series of meta-regressions were conducted to explore potential moderators of the effects detected.

## Materials and methods

**Data sources.** A systematic search was used to identify relevant studies. The MEDLINE and EMBASE databases were searched using the following Medical Subject Heading categories: ([Magnetic Resonance Imaging] OR [MRI]) AND [schizophrenia] AND ([longitudinal] OR [progressive] OR

[follow-up]) for peer-reviewed English language articles published between 1 January 1983 (when the first MRI study on schizophrenia was conducted<sup>42</sup>) and 31 March 2012. A systematic literature search using the Medical Subject Headings: ([Magnetic Resonance Imaging] OR [or MRI]) AND [psychosis] AND ([longitudinal] OR [progressive] OR [follow-up]) was also carried out to identify peer-reviewed English language articles published from 1 January 1983 to 31 March 2012 conducted with a longitudinal design comparing schizophrenia with other psychotic disorders and control groups. All the reference lists of the selected studies were reviewed to check for other references not found in the systematic search.

**Database study selection.** MRI studies that used ROI volumetric analysis of cerebral cortical gray matter and longitudinally analyzed its change over time in a group of schizophrenic patients and a group of healthy controls were included in the meta-analyses. Only studies that investigated patients with a formal diagnosis of schizophrenia were included. Longitudinal MRI studies on patients diagnosed as at-risk mental state for schizophrenia or during transition to psychosis were not considered for the present meta-analysis. Studies that investigated childhood-onset schizophrenia were included. Case studies, reviews, abstracts and unpublished reports were not considered. Investigations using VBM, deformation-based morphometry or tensor-based methods for measuring regional brain volumes were also excluded. We decided to focus our investigation on ROI studies because we aimed to analyze absolute brain volumes of discrete cortical regions with well-defined anatomical landmarks and brain tissue segmentation procedures. We decided not to include other indices of regional gray matter amount abnormalities derived from whole brain or cortical surface analysis, such as VBM and tensor-based methods, as they are not comparable with ROI volume measures and as they suffer from several potential biases (that is, different spatial normalization, tissue classification and spatial smoothing procedures between studies) that could be over-emphasized in a meta-analytical study. Moreover, unlike traditional meta-analyses, the Anatomical Likelihood Estimation approach (the golden standard for VBM meta-analyses) does not incorporate information from non-significant findings, thus allowing to analyze only those findings reported as statistically significant, which may lead to a relevant bias in performing meta-analysis. When repeat studies by the same research group were available, and the patients included in one study were included in a subsequent study, only the most recent or larger study was included, with the exception of data relative to brain regions investigated only in the earlier or larger study from the same group. This criterion was followed for each of the cerebral regions examined. Studies performed using MRI were considered if they reported quantitative measurements of the change in volume over time of cerebral structures in terms of means and standard deviations (s.d.) or as a variable that could lead back to such values (for example, standard error (s.e.) values). According to Furukawa *et al.*,<sup>43</sup> missing s.d.'s were calculated from the group of studies using the same outcome variables. If studies presented male and female subjects

separately, we entered the results as if they were from two separate studies, a technique adopted by previous meta-analyses of MRI volumes in schizophrenia.<sup>3</sup> Studies reporting qualitative or subjective assessments were not considered. Studies that used linear measurements were also excluded in view of the lower reliability of such measurements compared with three-dimensional measurements.<sup>44</sup>

**Data recorded in the database.** The following data were extracted from the chosen studies: number of subjects and percentage of males in the study sample; age of the patient at first MRI measurement (mean, s.d. or range, in years); duration of illness at the time of the first MRI (mean, s.d. or range, in years); interval between the two MRI scans (duration of follow-up) (mean or range, in months); type of antipsychotic medications taken during the MRI scan interval; Tesla value of the MRI scanner; MRI slice thickness (in mm); year of publication of the study; percentage change in brain tissue volume  $((\text{volume at follow-up} - \text{volume at baseline})/\text{volume at baseline}) \times 100$  (mean and s.d. or s.e.) in patients with schizophrenia and in healthy comparison group or volume (in ml) of a given cerebral structure analyzed at baseline and at follow-up scans (mean and s.d. or s.e.) in patients with schizophrenia and controls. The percent change in volume was selected to estimate the ES. If this measure was not reported, the percent change in volume over time in each study was calculated by the authors (LDP and AV) using the following formula:  $((\text{volume at follow-up} - \text{volume at baseline})/\text{volume at baseline}) \times 100$ .

**Identification of brain regions included in the meta-analysis.** To avoid bias in selecting brain regions for the meta-analysis, we recorded all cortical gray matter regions investigated by the studies included in the database. For some regions, a few studies reported left and right measurements separately, but others reported the total combined volume. In this meta-analysis, the left, right and total measurements were treated as separate measures. To ensure that the analyses were sufficiently powered, we analyzed only those cortical regions for which at least three studies were available.

**Meta-analytical methods and data analysis.** Meta-analyses were carried out using the comprehensive meta-analysis software, version 2 (Biostat Inc., Englewood, NJ, USA). The ES was calculated for each study included in the meta-analyses. As a measure of ES, Hedges'  $g$  was adopted, that is, the difference between the means of the patient and control groups, divided by the s.d. and weighted for sample size, to correct for bias from small sample sizes.<sup>45</sup> This metric is commonly used in meta-analyses and is representative of the difference in structural measurements between the control and patient distribution as indicated by the formula:

$$g = \frac{M_1 - M_2}{S_{\text{pooled}}}$$

where

$$S = \sqrt{\sum \frac{(X - M)^2}{N - 1}}$$

and

$$S_{\text{pooled}} = \sqrt{MS_{\text{within}}}$$

where  $X$  is the raw score,  $M$  is the mean and  $N$  is the number of cases.

According to the classification adopted by Cohen,<sup>46</sup> an ES of 0.8 is considered large, an ES of 0.5 is considered moderate and an ES of 0.2 is considered small. The 95% interval around the composite ES was also calculated.<sup>45</sup> To determine whether the studies could reasonably be described as sharing a common ES, a homogeneity (Cochran  $Q$ ) test of the ES was performed for each meta-analysis.<sup>45</sup> When a statistically significant heterogeneity between studies was observed, the source of such heterogeneity was investigated by testing the influence of potential moderators of the ES. The  $I^2$  statistic (the percentage of total variation across studies due to heterogeneity) was adopted to aid interpretability of between-study heterogeneity.  $I^2$  values range from 0 to 100%; values of 25%, 50% and 75% represent low, moderate, and high heterogeneity, respectively.<sup>47</sup> The pooled ES was calculated by means of a fixed-effect model when the  $Q$  test was not significant, or random-effect model in case of significant between-studies heterogeneity. Egger's test of publication bias was used to assess whether there was a tendency for selective publication of studies based on the nature and direction of their results.<sup>48</sup>

For analysis of ES, the minimum level of significance was set at 0.05. In fact, each meta-analysis for any specific area should be regarded as an independent analysis. Since a single measure for each analysis is included, a correction for multiple comparisons would be virtually not applicable or redundant and too susceptible to type II error.

**Subgroup meta-analysis.** To assess whether the findings of our analysis were confirmed or not at different time points of the lifetime trajectory of schizophrenia, a supplementary set of meta-analyses was conducted by selecting from our database those studies that investigated first-episode patients only, and analyzing them separately. To ensure that the analyses were sufficiently powered, we analyzed only those cortical regions for which at least three studies were available.

**Meta-regression analysis of demographic, clinical, treatment, neuroradiological and study quality variables.** For those cerebral structures for which a statistically significant between-studies heterogeneity was detected, meta-regression analyses were conducted to test the influence of certain potential moderators of ES. To avoid type I errors, demographic and clinical variables were chosen based on key clinical questions and the availability of the variables in the studies. The following moderators were considered: percentage of male patients in the study; mean age of patients at baseline; duration of illness at first MRI scan; age at onset of the disease; MRI slice thickness; and percentage of patients using atypical antipsychotics. The latter was adopted because only a small minority of studies detailed the amount

of antipsychotic drugs taken between scans. The number of Tesla was not considered since all studies were performed with scanners of the same magnetic field magnitude (1.5T).

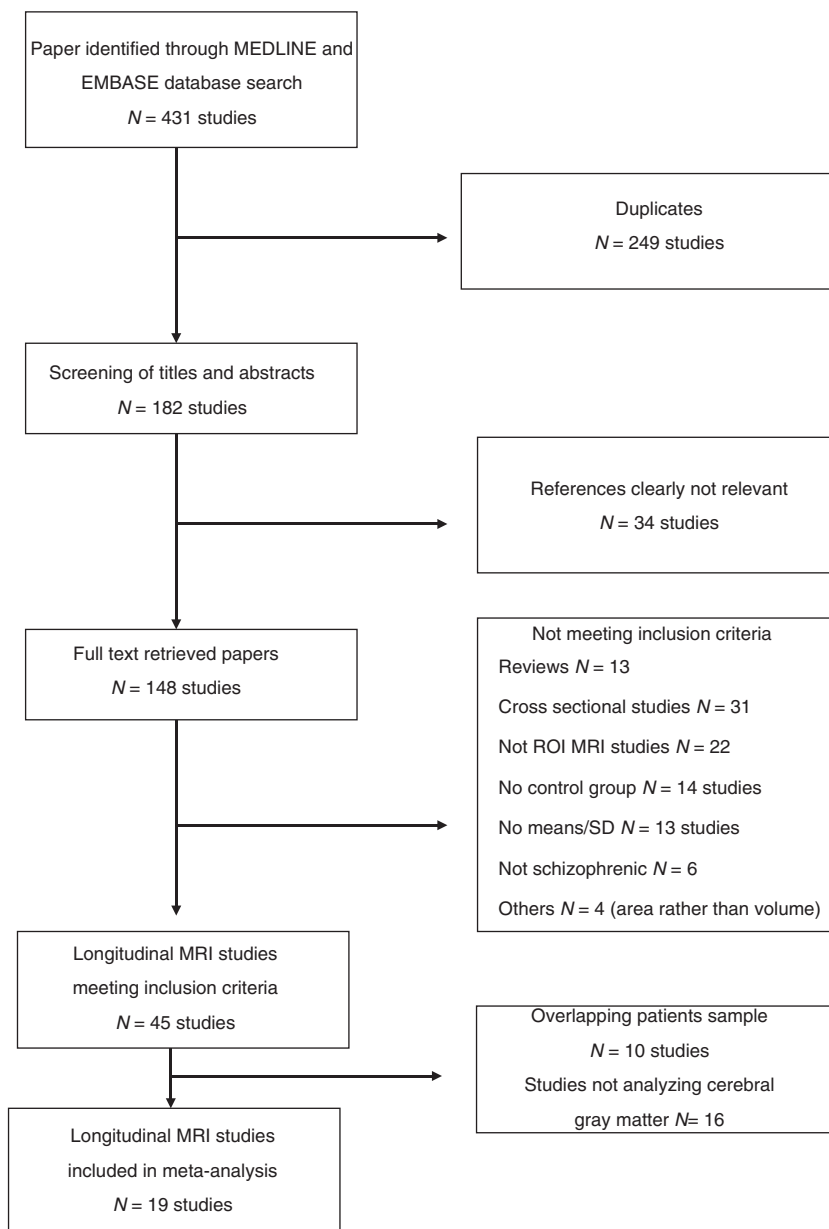
We also tested whether the ES was modulated by the quality of the studies. Study quality was scored in six key areas by two independent investigators (LDP and AV), with disputes resolved by consensus. One point was given for each of the following categories: age matching (not stated/significant difference = 0; matched = 1), sex matching (not stated/significant difference = 0; matched = 1), control subjects with no psychiatric illness (not stated = 0; no psychiatric illness = 1), same MRI scanner and sequence at each follow-up time point for each subject (different scanner or sequence = 0; same scanner and sequence = 1), good reliability of measures (intraclass correlation coefficient/

$k < 0.8$ /not stated = 0; intraclass correlation coefficient/  $k \geq 0.8 = 1$ ) and small slice thickness ( $\geq 4$  mm = 0;  $> 1.5$  mm and  $< 4$  mm = 0.5; and  $\leq 1.5$  mm = 1).

For analysis of the effects of moderators, the minimum level of significance was set again at 0.05. In fact, meta-regressions were intended to be exploratory analyses with the aim to generate hypotheses, to be tested in new primary studies, and correction for multiple comparisons would have been unduly conservative.

## Results

**Results of the systematic search.** The selection procedure is shown in Figure 1. A total of 19 studies were identified



**Figure 1** Flowchart of study selection.



**Table 1** Summary of studies included in meta-analysis

First author (year) <sup>ref.</sup>	Diagnostic criteria	Diagnosis	M/F ratio		Mean age		MRI		Mean duration of inter-MRI interval (years)	
			Patients	Controls	Patients	Controls	Tesla	Thickness (mm)	Patients	Controls
Jacobsen <i>et al.</i> <sup>52</sup>	DSM-III R	Early-onset schizophrenia	7/3	13/4	15.2	14.2	1.5	1.5	2.0	2.0
Keshavan <i>et al.</i> <sup>5</sup>	DSM-III R	First-episode schizophrenia	6/5	7/5	24.0	24.0	1.5	2.6	1.0	1.0
Rapoport <i>et al.</i> <sup>54</sup>	DSM-III R	Early-onset schizophrenia	6/9	17/17	13.9	12.8	1.5	2	4.2	4.3
Mathalon <i>et al.</i> <sup>56</sup>	DSM-III R	Schizophrenia	24/0	25/0	39.4	40.7	1.5	5	3.6	4.2
Kasai <i>et al.</i> <sup>59</sup>	DSM-IV	First-episode schizophrenia	10/3	13/1	27.2	25.6	1.5	1.5	1.4	1.6
Kasai <i>et al.</i> <sup>8</sup>	DSM-IV	First-episode schizophrenia	10/3	20/2	27.3	25.0	1.5	1.5	1.4	1.6
Sporn <i>et al.</i> <sup>55</sup>	DSM-III R/DSM-IV	Early-onset schizophrenia	24/39	27/43	15.0	14.8	1.5	1.5	4.6	2.7
Lieberman <i>et al.</i> <sup>34</sup>	DSM-IV	First-episode schizophrenia	136/25	40/22	23.8	25.3	1.5	1.5–3	2.0	2.0
Molina <i>et al.</i> <sup>57</sup>	DSM-IV	First-episode schizophrenia/schizophrenia	20/29	6/11	25.6/31.0	28.4	1.5	1.1–1.5	2.2	2.3
Nakamura <i>et al.</i> <sup>60</sup>	DSM-IV	First-episode schizophrenia	24/5	31/5	24.3	22.9	1.5	1.5–3	1.5	1.5
Salisbury <i>et al.</i> <sup>61</sup>	DSM-IV	First-episode schizophrenia	17/3	22/10	24.5	24.1	1.5	1.5–3	1.7	1.4
van Haren <i>et al.</i> <sup>49</sup>	CASH	Schizophrenia	70/26	76/37	32.2	35.2	1.5	1.2	4.8	4.9
Takahashi <i>et al.</i> <sup>9</sup>	ICD-10	First-episode schizophrenia	12/6	11/9	23.1	23.2	1.5	1	2.7	2.6
Yoshida <i>et al.</i> <sup>40</sup>	DSM-III R	Schizophrenia	16/0	20/0	38.6	40.9	1.5	1.5–3	3.1	1.4
Reig <i>et al.</i> <sup>51</sup>	K-SADS-PL	First-episode schizophrenia	16/5	21/13	15.7	15.2	1.5	1.5–3.5	2.0	2.0
Takahashi <i>et al.</i> <sup>41</sup>	DSM-IV	Schizophrenia	10/1	12/5	32.7	30.2	1.5	1	2.4	2.4
Boonstra <i>et al.</i> <sup>50</sup>	DSM-IV	First-episode schizophrenia	12/4	15/5	28.8	27.9	1.5	1.2–1.6	1.0	1.0
Andreasen <i>et al.</i> <sup>53</sup>	DSM-IV	First-episode schizophrenia	148/52	66/59	24.5	29.6	1.5	1.5–3	7.2	—
Arango <i>et al.</i> <sup>62</sup>	DSM-IV	First-episode (early-onset) schizophrenia	18/7	23/47	15.5	15.3	1.5	1.5–3.5	2.4	2.4

Abbreviations: CASH, Comprehensive Assessment of Symptoms and History; DSM-III R, Diagnostic and Statistical Manual of Mental Disorders, third edition, revision; ICD-10, International Classification of Disease, 10th revision; SADS, Schedule for Affective Disorders and Schizophrenia; K-SADS-PL, Schedule for Affective Disorders and Schizophrenia for School Age Children Present and Lifetime version; —, not reported. Studies references<sup>5,34,49,50,51</sup> included also patients with diagnosis other than schizophrenia (see Results section for details).

as suitable for analysis (Table 1). The following cerebral regions (gray matter), for which at least three studies were available, were included in the analyses: whole brain, frontal lobe, temporal lobe, parietal lobe, occipital lobe, right and left STG, right and left anterior STG, right and left posterior STG, right and left Heschl gyrus (HG) and right and left planum temporale (PT).

All studies analyzed patients with schizophrenia, but some also included patients with related diagnoses. van Haren *et al.*<sup>49</sup> included diagnoses of schizophrenia and schizoaffective disorder; Keshavan *et al.*,<sup>5</sup> Lieberman *et al.*<sup>34</sup> and Boonstra *et al.*<sup>50</sup> included diagnoses of schizophrenia, schizophreniform disorder and schizoaffective disorder. Reig *et al.*<sup>51</sup> included patients diagnosed with schizophrenia, psychotic mood disorder and atypical psychosis. In these studies, the percentage of patients with schizophrenia ranged from 50<sup>50</sup> to 96%.<sup>49</sup>

From 19 studies, 1531 subjects were included ( $n=813$  patients;  $n=718$  healthy controls). In the patient group, sample size ranged from 10<sup>52</sup> to 202<sup>53</sup> patients with schizophrenia. Four of 19 studies investigated childhood-onset<sup>52,54,55</sup> or adolescent-onset<sup>51</sup> schizophrenia. The mean age of patients in the whole sample ranged from 13.9 years (childhood schizophrenia study from Rapoport *et al.*<sup>54</sup>) to 39.4 years.<sup>56</sup> The percentage of male patients in each study ranged from 37<sup>52</sup> to 100%;<sup>40,51,56,57</sup> male patients outnumbered female patients overall ( $n=586$  males;  $n=227$  females). As just one study presented data for male and female patients separately,<sup>51</sup> it was not possible to directly compare gray matter volume changes between sexes; gender

was therefore considered among the potential moderators of the ES (see below).

Two of 18 studies reported brain volumes only in terms of milliliters at baseline scan and at follow-up (mean and s.d. or s.e.) rather than percentage volume change and, in these cases,<sup>5,52</sup> the percentage volume change in brain tissue was computed by the authors as described earlier. The studies included in the meta-analysis were published from 1998 to 2012.

For the subgroup analysis, studies that investigated a group of patients with first-episode schizophrenia and a group of controls were included. In all, 12 studies were identified as suitable for the longitudinal analysis of brain volume in patients with first-episode schizophrenia. We carefully evaluated the criteria adopted in the studies to define first-episode patients. In most studies, first episode was operationally defined as the first psychiatric hospitalization.<sup>8,53,58–61</sup> Other authors refer to first contact with psychiatric services or patients receiving treatment for an episode of psychosis for the first time.<sup>5,34,50,51,56,62</sup> Mean duration of illness since the onset of psychotic symptoms (6–12 months at baseline scan) was used to define first-episode schizophrenia in a few studies.<sup>9,51,62</sup> We restricted our analysis of first-episode schizophrenia to those patients analyzed within 24 months from illness onset (no chronic cases were included). Thus, in this subgroup analysis, we did not include the studies by Molina *et al.*,<sup>57</sup> Keshavan *et al.*<sup>5</sup> and Boonstra *et al.*<sup>50</sup> because the duration of illness at baseline scan was 27, 36 and 40 months, respectively. The pool of studies included in the analyses of first-episode patients consisted of nine

studies<sup>8,9,34,51,53,59–62</sup> and covered the following gray matter volumes: whole brain, frontal, temporal, parietal and occipital lobes and left and right HG.

**Results of the main meta-analysis.** Table 2 compares the change in brain volume over time in patients with schizophrenia and healthy controls. Relative to controls, patients with schizophrenia showed a significantly higher volumetric decrease over time of whole brain gray matter, left STG, left anterior STG, left posterior STG, right posterior STG, left HG and left PT gray matter. None of the other brain regions considered showed significantly different changes between patients with schizophrenia and healthy controls.

The Cochran *Q* test showed a significant between-studies heterogeneity in the analysis of the following brain regions: whole brain gray matter, frontal, temporal, parietal and occipital lobe gray matter, right and left STG, right and left

anterior STG, left posterior STG, left HG and left PT gray matter. The potential sources of heterogeneity detected in the analysis of such brain structures have therefore been further considered in meta-regression analyses (detailed below).

Table 2 lists the *P*-values for the Egger test for publication bias for each brain region. No evidence of possible publication bias for the cerebral structures investigated was found, except for frontal lobe and right and left anterior STG gray matter volume change, with higher ES detected in earlier studies.

Table 3 shows the estimation of percentage of change (per year) of brain volumes in patients and controls for different gray matter structures.

**Results of the meta-analysis in first-episode schizophrenia.** Brain volume change over time for first-episode patients and healthy controls is shown in Table 4. Patients with first-episode schizophrenia showed a significantly larger decrease in volume not only of whole brain gray matter but

**Table 2** Summary of the main meta-analysis

Region (volume)	No. of studies	No. of patients/ controls	Effect size	Effect size:	Heterogeneity <i>I</i> <sup>2</sup>		Egger test:
			(95% CI)	<i>P</i> -value	%	<i>P</i> -value	<i>P</i> -value
Total GM	13	532/552	-0.50 (-0.80, -0.20)	0.001	78	<0.001	0.33
Frontal GM	7	362/304	-0.18 (-0.48, 0.12)	0.24	65	0.009	0.02
Temporal GM	7	362/304	-0.24 (-0.57, 0.08)	0.14	70	0.003	0.38
Parietal GM	6	345/278	-0.06 (-0.43, 0.30)	0.71	74	0.002	0.06
Occipital GM	6	321/269	0.14 (-0.26, 0.55)	0.48	76	0.001	0.13
STG (right)	6	79/100	-0.35 (-1.13, 0.42)	0.37	84	<0.001	0.42
STG (left)	6	79/100	-0.80 (-1.55, -0.04)	0.03	83	<0.001	0.18
STG (right anterior)	5	81/96	-0.32 (-0.82, 0.18)	0.21	65	0.02	0.04
STG (left anterior)	5	81/96	-0.71 (-1.23, -0.20)	0.006	63	0.02	0.04
STG (right posterior)	5	81/96	-0.62 (-0.92, -0.32)	<0.001	39	NS	0.20
STG (left posterior)	5	81/96	-1.14 (-1.67, -0.62)	<0.001	62	0.03	0.06
HG (right)	4	53/72	-0.13 (-0.48, 0.21)	0.44	0	NS	0.47
HG (left)	4	53/72	-1.05 (-1.68, -0.43)	0.001	63	0.04	0.45
PT (right)	3	42/59	-0.37 (-0.76, 0.02)	0.06	0	NS	0.33
PT (left)	3	42/59	-1.18 (-2.13, -0.23)	0.01	79	0.008	0.35

Abbreviations: CI, confidence interval; GM, gray matter; NS, nonsignificant; PT, planum temporal; STG, superior temporal gyrus. Included are only regions for which at least three studies were available (see Materials and methods).

**Table 3** Annual percentage of change of brain volumes in patients and controls

Region (volume)	Patients		Controls	
	Mean percentage change (%)	(95% CI)	Mean percentage change (%)	(95% CI)
Total GM	-0.66	(-0.74, -0.58)	-0.15	(-0.20, -0.10)
Frontal GM	-0.20	(-0.37, -0.03)	-0.16	(-0.22, -0.10)
Temporal GM	-0.11	(-0.22, 0.00)	0.28	(0.19, 0.37)
Parietal GM	-0.10	(-0.29, 0.09)	-0.48	(-0.59, -0.37)
Occipital GM	1.0	(0.76, 1.40)	0.27	(0.19, 0.35)
STG (right)	0.83	(-0.36, 2.02)	0.76	(0.39, 1.13)
STG (left)	-0.61	(-1.76, 0.54)	0.67	(0.06, 1.28)
STG (right anterior)	-0.99	(-1.31, -0.67)	0.22	(0.06, 0.38)
STG (left anterior)	-2.03	(-2.49, -1.57)	0.38	(0.12, 0.64)
STG (right posterior)	-1.62	(-1.88, -1.36)	-0.19	(-0.26, -0.12)
STG (left posterior)	-2.83	(-3.41, -2.25)	-0.38	(-0.55, -0.21)
HG (right)	-0.13	(-0.28, 0.02)	-0.40	(-0.56, -0.24)
HG (left)	-2.76	(-3.34, -2.18)	-0.39	(-0.56, -0.22)
PT (right)	-0.54	(-0.69, -0.39)	0.37	(0.31, 0.43)
PT (left)	-2.35	(-3.13, -1.57)	0.12	(0.01, 0.23)

Abbreviations: CI, confidence interval; GM, gray matter; HG, Heschl gyrus; PT, planum temporal; STG, superior temporal gyrus.

**Table 4** Summary of the meta-analysis in first-episode schizophrenia

Region (volume)	No. of studies	No. of patients/controls	Effect size	Effect size:	Heterogeneity $I^2$		Egger test:
			(95% CI)	P-value	%	P-value	P-value
Total GM	7	341/337	-0.58 (-0.90, -0.26)	<0.001	66	0.006	0.16
Frontal GM	4	294/239	-0.39 (-0.57, -0.22)	<0.001	0	NS	0.29
Temporal GM	4	294/239	-0.37 (-0.71, -0.04)	0.028	63	0.04	0.19
Parietal GM	3	277/213	-0.30 (-0.48, -0.12)	0.001	0	NS	0.41
Occipital GM	3	277/213	0.13 (-0.31, 0.05)	0.15	0	NS	0.02
HG (right)	3	42/55	-0.14 (-0.53, 0.25)	0.48	15	NS	0.46
HG (left)	3	42/55	-1.33 (-1.77, -0.90)	<.001	63	0.04	0.46

Abbreviations: CI, confidence interval; GM, gray matter; HG, Heschl gyrus; NS, nonsignificant. Included are only regions for which at least three studies were available (see Materials and methods).

also of frontal lobe, temporal lobe and parietal lobe gray matter. Moreover, they showed larger decrease in gray matter volume of the left HG.

The Cochran *Q* test showed a significant between-studies heterogeneity for the following brain regions: whole brain and temporal lobe, and left HG.

No evidence of possible publication bias was found, with the exception of occipital lobe gray matter ( $P=0.02$ ).

**Meta-regression of demographic, clinical, treatment, neuroradiological and study quality variables on ES of differential gray matter volume change over time.** A number of clinical, pharmacological and neuroradiological variables were found to be significant moderators of ES of differences of brain volume changes between patients with schizophrenia and healthy controls. The summary of findings are presented in Table 5.

Variables found to be significant moderators of ES of differential brain volume changes between patients with first-episode schizophrenia and healthy controls are also presented in Table 5.

The following variables that resulted significantly correlated with ESs (explanation of the correlations presented in Table 5 legend).

As for total brain gray matter volume, the ES of the difference between groups was affected by the moderators 'age of onset' ( $Z=3.73$ ,  $P=0.0001$ ), 'percentage of patients treated with atypical antipsychotics' ( $Z=2.24$ ,  $P=0.024$ ) and 'MRI slice thickness' ( $Z=2.05$ ,  $P=0.040$ ).

The ES of frontal lobe gray matter resulted to be affected by the moderator 'duration of illness at baseline' ( $Z=2.21$ ,  $P=0.027$ ). A similar correlation was also found for occipital lobe gray matter ( $Z=2.45$ ,  $P=0.014$ ).

Parietal lobe ES resulted to be affected by the moderator 'patients' mean age at baseline scan' ( $Z=2.68$ ,  $P=0.007$ ).

As for temporal lobe gray matter, significant correlations between the ES and the moderators, 'percentage of patients treated with atypical antipsychotics' ( $Z=2.39$ ,  $P=0.016$ ) and 'patients' mean age at baseline scan' ( $Z=2.44$ ,  $P=0.014$ ), were demonstrated.

Left STG ES were affected by the moderators 'duration of illness' ( $Z=2.45$ ,  $P=0.013$ ), 'MRI slice thickness' ( $Z=2.92$ ,  $P=0.003$ ) and 'quality of the study' ( $Z=-2.36$ ,  $P=0.018$ ). Right STG ES were affected by the moderators

'slice thickness' ( $Z=3.49$ ,  $P=0.0004$ ), 'age of onset' ( $Z=2.70$ ,  $P=0.006$ ), 'mean age at baseline' ( $Z=1.98$ ,  $P=0.04$ ) and 'quality of the study' ( $Z=-4.03$ ,  $P=0.0006$ ). As for the left anterior STG, a significant correlation between ES and the variables 'percentage of males in the study sample' ( $Z=2.46$ ,  $P=0.013$ ), 'patients' mean age at baseline scan' ( $Z=3.11$ ,  $P=0.001$ ) and 'duration of illness at baseline' ( $Z=2.97$ ,  $P=0.002$ ) were demonstrated. The ES of right anterior STG resulted to be affected by the moderator 'patients' mean age at baseline scan' ( $Z=2.67$ ,  $P=0.007$ ) and 'age of onset' ( $Z=2.23$ ,  $P=0.025$ ). Left posterior STG ES that resulted correlated with the variable 'duration of illness at baseline' ( $Z=2.21$ ,  $P=0.026$ ).

With respect to left HG, a significant correlation was demonstrated between ES and the moderator 'duration of illness at baseline' ( $Z=2.57$ ,  $P=0.009$ ). Such a correlation was also demonstrated for left PT ( $Z=2.82$ ,  $P=0.004$ ). Moreover, for left PT, statistically significant correlations emerged also for the following moderators: 'patients' mean age at baseline scan' ( $Z=2.44$ ,  $P=0.014$ ), 'age of onset' ( $Z=-2.78$ ,  $P=0.0005$ ), 'duration of illness at baseline' ( $Z=2.82$ ,  $P=0.004$ ), MRI slice thickness ( $Z=2.44$ ,  $P=0.014$ ) and 'quality of the study' ( $Z=2.44$ ,  $P=0.014$ ).

In first-episode schizophrenia, the meta-regressions, which were restricted to total gray matter ES, that resulted correlated with the variables 'patients' mean age at baseline scan' ( $Z=2.10$ ,  $P=0.035$ ) and 'MRI slice thickness' ( $Z=2.33$ ,  $P=0.019$ ).

## Discussion

Patients with schizophrenia, compared with healthy controls, show a significantly higher progressive reduction in cortical gray matter volume over time. A substantial progressive loss of total gray matter volume, with a moderate ES ( $g=-0.50$ ), was demonstrated. However, the pattern of gray tissue loss does not affect the brain uniformly but is specific to discrete cortical areas, which appear to be affected by such progression at different stages of the disease. For the first time with a meta-analytic approach, and at variance with other quantitative reviews on the time course of brain abnormalities in schizophrenia,<sup>17,63</sup> we demonstrated a selective, rather than generalized, involvement of cortical gray matter in the trajectory of brain tissue loss.

**Table 5** Meta-regression of differential gray matter volume changes over time between patients with schizophrenia and healthy controls: demographic, clinical, treatment, neuroradiological and study quality variables

	MRI slice thickness	Mean age of patients at baseline	Duration of illness at first MRI	Age at onset of the disease	% Of male patients in the study	% Of patients using atypical antipsychotics	Study quality
Total GM	Z=2.05 <sup>a</sup> P=0.040	Z=1.67 P=0.094	Z=-1.51 P=0.128	Z=3.73 <sup>b</sup> P=0.0001	Z=1.74 P=0.081	Z=2.24 <sup>c</sup> P=0.024	Z=-0.65 P=0.514
Frontal GM	Z=-1.24 P=0.214	Z=1.85 P=0.063	Z=2.21 <sup>d</sup> P=0.027	Z=0.87 P=0.380	Z=1.42 P=0.154	Z=0.58 P=0.559	Z=0.47 P=0.633
Temporal GM	Z=-0.77 P=0.436	Z=2.44 <sup>a</sup> P=0.014	Z=0.56 P=0.573	Z=1.49 P=0.135	Z=0.79 P=0.428	Z=2.39 <sup>e</sup> P=0.016	Z=-0.64 P=0.520
Parietal GM	Z=-1.62 P=0.105	Z=2.68 <sup>e</sup> P=0.007	Z=1.73 P=0.082	Z=1.71 P=0.087	Z=1.16 P=0.244	Z=1.31 P=0.189	Z=0.78 P=0.431
Occipital GM	Z=-1.12 P=0.184	Z=1.67 P=0.092	Z=2.45 <sup>d</sup> P=0.014	Z=1.58 P=0.111	Z=0.67 P=0.501	Z=1.72 P=0.084	Z=0.85 P=0.352
STG (right)	Z=3.49 <sup>a</sup> P=0.0004	Z=1.98 <sup>e</sup> P=0.046	Z=0.81 P=0.413	Z=2.70 <sup>b</sup> P=0.006	Z=0.69 P=0.486	Z=-0.08 P=0.929	Z=-4.03 <sup>f</sup> P=0.0006
STG (left)	Z=2.92 <sup>a</sup> P=0.003	Z=1.62 P=0.104	Z=2.45 <sup>d</sup> P=0.013	Z=-0.18 P=0.853	Z=1.21 P=0.222	Z=-0.16 P=0.870	Z=-2.36 <sup>f</sup> P=0.018
STG (right anterior)	Z=0.72 P=0.470	Z=2.67 <sup>e</sup> P=0.007	Z=1.83 P=0.067	Z=2.23 <sup>b</sup> P=0.025	Z=1.40 P=0.159	Z=-1.91 P=0.055	Z=-95 P=0.340
STG (left anterior)	Z=1.56 P=0.118	Z=3.11 <sup>e</sup> P=0.001	Z=2.97 <sup>d</sup> P=0.002	Z=1.42 P=0.155	Z=2.46 <sup>g</sup> P=0.013	Z=-1.36 P=0.172	Z=-1.39 P=0.162
STG (left Posterior)	Z=0.10 P=0.915	Z=1.85 P=0.063	Z=2.21 <sup>d</sup> P=0.026	Z=0.19 P=0.847	Z=1.08 P=0.279	Z=-0.34 P=0.729	Z=0.44 P=0.658
HG (left)	Z=-0.47 P=0.634	Z=1.45 P=0.146	Z=2.57 <sup>d</sup> P=0.009	Z=-1.80 P=0.071	Z=1.06 P=0.287	Z=0.26 P=0.794	Z=1.58 P=0.112
PT (left)	Z=2.44 <sup>a</sup> P=0.014	Z=2.44 <sup>e</sup> P=0.014 <sup>e</sup>	Z=2.82 <sup>d</sup> P=0.004	Z=-2.78 <sup>h</sup> P=0.0005	Z=0.75 P=0.452	Z=0.70 P=0.483	Z=2.44 <sup>i</sup> P=0.014
<i>First-episode schizophrenia</i>							
Total GM	Z=2.33 <sup>a</sup> P=0.019	Z=2.10 <sup>e</sup> P=0.035	Z=0.73 P=0.461	Z=1.73 P=0.082	Z=-1.03 P=0.301	Z=1.67 P=0.093	Z=0.95 P=0.337
Temporal GM	Z=0.92 P=0.356	Z=-0.45 P=0.648	Z=0.48 P=0.626	Z=1.38 P=0.126	Z=-0.84 P=0.403	Z=1.93 P=0.053	Z=-1.10 P=0.268
HG (left)	Z=-0.21 P=0.830	Z=0.05 P=0.955	Z=-0.40 P=0.683	Z=-0.17 P=0.861	Z=-0.37 P=0.703	Z=0.63 P=0.524	Z=0.21 P=0.830

Abbreviations: Ctrl, control; GM, gray matter; HG, Heschl gyrus; MRI, magnetic resonance imaging; pts, patients; STG, superior temporal gyrus.

<sup>a</sup>Larger MRI slice thickness lower pts/ctrls volume change differences.

<sup>b</sup>Later age of onset lower pts/ctrls volume change differences.

<sup>c</sup>Higher percentage of pts. in atypicals lower pts/ctrls volume change differences.

<sup>d</sup>Longer duration of illness lower pts/ctrls volume change differences.

<sup>e</sup>Higher mean age lower pts/ctrls volume change differences.

<sup>f</sup>Higher quality of the study greater pts/ctrls volume change differences.

<sup>g</sup>Higher percentage of males lower pts/ctrls volume change differences.

<sup>h</sup>Younger age of onset lower pts/ctrls volume change differences.

<sup>i</sup>Higher quality lower pts/ctrls volume change differences.

In particular, we detected a significantly more pronounced decrease of gray matter volume in the STG and STG subregions (HG and PT) in patients with schizophrenia: the magnitudes of the ES for the left STG ( $g = -0.80$ ), left HG ( $g = -1.05$ ) and left PT ( $g = -1.18$ ) were large; on the other hand, several other cortical subregions did not exhibit such a large reduction in volume over time. The role of superior temporal lobe structures in the pathophysiology of schizophrenia was intensely debated in the 1990s, but has not been systematically addressed by later studies. This is a case where traditional ROI methodology may be more informative than more sophisticated techniques that rely on automated computation of surface or whole gray matter volumes, with which the opportunity to detect subtle, localized or deep brain alterations is lost. Changes in STG volume have been related to positive symptom severity, especially of thought disorder (posterior STG)<sup>6,64,65</sup> and hallucinations (anterior and middle STG);<sup>66-69</sup> HG volume abnormalities have been correlated to severity of formal thought disorder<sup>70,71</sup> and PT alterations to language and thought disorder of schizophrenia.<sup>64,71</sup> The higher involvement of these areas in the trajectory of

progression of brain abnormalities strengthens the hypothesis of a specific relevance of these brain regions in the pathophysiology of the disorder or, in turn, of the centrality of thought and language disorders in schizophrenia, according to a relevant, still actual, phenomenological literature,<sup>72</sup> only partly incorporated in the current diagnostic criteria of the disease (Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision (DSM-IV TR) and International Classification of Disease, 10th revision (ICD-10)).

A significant effect of hemisphere has also been clearly demonstrated in this meta-analysis for volume loss of temporal gray matter. The anterior STG, HG and PT appeared to show excessive tissue loss over time in the left, but not the right hemisphere. This may explain the finding of abnormalities in cerebral asymmetries frequently, but inconsistently reported in previous literature on the brain pathology of schizophrenia.<sup>73-76</sup> The progression of cortical volume changes seems to affect especially the left hemisphere: this could justify the finding of abnormal asymmetries reported particularly in chronic, rather than first-episode cases, when this phenomenon may be less detectable. A reduced



lateralization of cortical structures has been recently reported also at the onset of schizophrenia, before medical treatment is initiated, most prominent in the inferior frontal gyrus (part of Broca's area) and the STG (part of Wernicke's area).<sup>77</sup> Moreover, a reduction in normal cerebral asymmetries, particularly in superior temporal structures, has been proposed as a trait marker of schizophrenia by some authors.<sup>78–80</sup> According to the existing literature<sup>81,82</sup> and our own findings, however, this reduction may be even more relevant over time, after progressive tissue loss affected the two hemispheres differently. Our findings therefore confirm that the left (dominant) hemisphere may be involved in the pathophysiology of schizophrenia, and may also be particularly sensitive to the trajectory of pathological progressive brain changes characterizing this disease. Consistently with this hypothesis, a polymorphism of *NRG1* gene has been found to be involved in determining STG size in schizophrenia, and suggested to have a role in the neurogenetic basis of the language disturbances seen in this disorder.<sup>83</sup> Analyses of the subsample of studies that selectively investigated first-episode patients gave us the opportunity to make some more specific inferences about the time of occurrence of such progressive loss of cortical gray matter.

In the case of first-episode patients, larger ESs than those detected in the whole sample for the difference in brain tissue loss between patients and controls were detected for all brain regions considered in the analyses. This strongly supports the hypothesis that progressive tissue loss is especially active in the first phases of the illness. Such an early tissue loss affects diffuse cerebral regions and indicates a process that may lead at a later stage (that is, in chronic samples) to a decrease in whole brain volume.<sup>17</sup> The latter may be consistent also with the notion of progressive ventricular enlargement acknowledged by most, although not all, studies,<sup>30,37,84–90</sup> and quantitatively reviewed by Kempton *et al.*,<sup>63</sup> who demonstrated a larger than normal increase in the volume of lateral ventricles over time in chronic schizophrenia. Although not directly investigated by our meta-analysis, this could be compatible with the evidence of progressive loss of white matter volume over the disease course,<sup>91</sup> which may determine, or parallel, cerebral ventricular enlargement. On the other hand, the most divergent trajectory of cortical structural changes between patients with schizophrenia and normal subjects arises during the very first phases of the disease, when there is evidence of accelerated gray matter loss; at a later stage, the decrease in gray matter volume is likely to be similar to what appears to be a physiological correlate of aging.

The notion of a different trajectory of brain changes over time between patients and controls is also supported by the results of the few original longitudinal studies with three or more MRI measurements for the same cohorts. The largest such study from Andreasen *et al.*<sup>53</sup> showed that reductions in brain tissue volume in patients with first-episode schizophrenia were greatest during the first interscan interval (2 years) when patients had significantly greater reductions than healthy volunteers in nearly all gray matter measures. Conversely, changes in brain volume in patients during the second (3–4 years after the second scan) and third (3–4 years after the third MRI measurement) interscan intervals did not

differ significantly from those found in healthy volunteers. The results of our meta-regression analysis between the ES of the differences in gray matter loss between patients and controls and the duration of illness at first MRI scan confirms this hypothesis; the longer the duration of illness, the lower the difference in volume change over time detected between patients and controls. This may be again somewhat specific to defined brain areas, involving the frontal and occipital lobes, and, only in the left hemisphere, STG, the anterior and posterior portions of STG, HG and PT.

Since the definition we used for first episode, including patients who had the first scan within 24 months from onset, may be somehow misleading because many of such patients could have been exposed to long-term psychotropic drugs, we conducted a supplemental meta-analysis of first-episode cases limited to those patients with a duration of illness no longer than 12 months. In fact, adopting this more conservative approach, the magnitude of the differences between volumetric changes in schizophrenic and control groups became even larger as for the only cortical brain region that could be investigated according to our inclusion criteria (at least three study suitable for analysis), that is, whole brain gray matter ( $g = -0.61$ ; confidence interval =  $-0.87$  to  $-0.37$ ;  $P < .001$ ). Moreover, our findings relative to left HG in first-episode schizophrenia derived from studies that recruited only patients within their 1st year of illness.

Meta-regression analysis between the ES of the differences in gray matter loss between patients and controls and the age of patients at baseline scan showed lower ES in older patients for temporal and parietal lobes, for STG and its anterior component only in the right hemisphere and for left PT. This indicates that the trajectory of gray matter changes may be affected differently by the disease process and aging, the former being more active in the left hemisphere and the latter involving cerebral gray matter more generally.

Our findings are consistent, and complementary, to those obtained in recent meta-analyses of VBM studies in anti-psychotic naïve subjects at high risk of psychosis and first-episode schizophrenia patients, which indicate that gray matter reductions in the anterior cingulate may be a marker of genetic liability to psychosis, while reductions in the STG can be interpreted as markers of first onset schizophrenia.<sup>92,93</sup>

Taken together, the results of our study provide useful information about the time and site of occurrence of progressive gray matter changes in schizophrenia, substantially refining and shaping the hypothesis of schizophrenia as a general progressive brain disease.<sup>17,53</sup> A number of hypotheses, not mutually exclusive, may be advocated to explain the different time course of brain structural changes over the lifespan between patients with schizophrenia and healthy individuals. The existence of a cortical neurodegenerative process acting differently at different stages of the disease, particularly detectable around the onset and the first phases of overt illness, can be proposed. It is also possible to speculate on the existence of a pathological maturational program determining both early (pre- or perinatal) neurodevelopmental anomalies and later development of abnormal brain processes during adolescence and early adulthood, leading to, or paralleling, the onset of the disease. It is also

plausible that there is an interaction between the two, that is, that anomalous neurodevelopmental processes may interact with other factors occurring around the onset of psychosis leading to accelerated tissue loss, which adds to the earlier abnormalities, to determine the ultimate brain pathology possibly relevant to the clinical manifestations of schizophrenia. This accelerated tissue loss may be especially active in the first phases of the disease and progressively less evident as the disease stabilizes, and may be counteracted by continuous treatment. Consistent with this possibility, it has been claimed that some of the brain abnormalities found at the onset of psychoses may be at least in part reversible.<sup>94</sup> Even if the cause of the observed pattern of progressive brain changes during the course of schizophrenia remains largely unclear, it is possible to state that certain brain areas are involved in substantial alteration just around the time of onset and during the early course of the disease.

Another finding of the present meta-analysis is that the type of antipsychotic treatment may be a significant moderator of the time course of brain abnormalities in schizophrenia. In particular, treatment with atypical antipsychotics seems to reduce or at least, in part, counteract the progressive loss of cortical gray matter tissue in the whole brain, especially in the temporal lobe. Treatment with antipsychotic medications has been considered to be an important potential confounder of the progressive changes in brain volume detected in schizophrenia by other authors.<sup>15,27</sup> Our finding is consistent with that of a controlled longitudinal MRI study comparing the effects of an SGA (olanzapine) and an FGA (haloperidol) on gray and white matter volumes in first-episode schizophrenia, reporting substantial progressive (global) gray matter loss over a 1-year period in the patients on haloperidol, but not in those treated with olanzapine.<sup>34</sup> It has been hypothesized that SGAs may have a neuroprotective effect in schizophrenia, either increasing the expression of neurotrophic factors<sup>95</sup> or stimulating neurogenesis,<sup>96</sup> or interacting with and increasing the activity of *N*-methyl-D-aspartate glutamate receptors.<sup>97</sup> Conversely, the excess reduction in cortical gray matter observed in patients treated with FGAs may be attributable to a direct neurotoxic effect secondary to oxidative stress and/or excitotoxic phenomena, which have been well documented in animals treated with haloperidol<sup>98–100</sup> or may indicate a hypothetical lower capacity of FGAs to interfere with the natural pathophysiological trajectory of the disease, which may also be reflected in the different impact on cerebral blood flow and metabolism of FGAs versus SGAs.<sup>101–103</sup> A recently published MRI longitudinal study<sup>33</sup> reported progressive brain tissue loss in patients with schizophrenia followed for up to 14 years and related such loss to antipsychotic drug use. However, it seems likely that the results of this uncontrolled study could not distinguish between the highly intercorrelated variables of illness severity and antipsychotic dose taken. In fact, it is now well known that brain abnormalities are present even before the onset of schizophrenia, in the prodromal stage of the disease or in first-episode drug-naïve patients<sup>4,18</sup> independently of drug treatment, and that these anomalies show progression over time even during the phase of transition to psychosis,<sup>104</sup> again without or with little potential effect of pharmacotherapy. Alternatively, morphological abnormalities in the brain, and their progression over time,

may represent a significant correlate of poor outcome of schizophrenia, for which a larger prescription and use of antipsychotic drugs may be considered an epiphenomenon. Early<sup>105–107</sup> and more recent<sup>108</sup> literature confirm that the most consistent clinical correlate of structural brain abnormalities and their progressive change is poor clinical outcome of the disease.

Age at onset of schizophrenia was a significant moderator of change of whole brain gray matter, of right STG (and its anterior component) and left PT gray matter loss ES. This suggests that the trajectory of cortical gray matter loss is more pronounced in early-onset schizophrenia. That is not surprising given the large literature reporting a different severity of clinical presentation and course of early- versus late-onset schizophrenia.<sup>109,110</sup> The ratio of male to female patients included in the studies was not a significant moderator of ES, with the only exception of a more pronounced tissue loss in left anterior STG in female patients, compatible with a higher prevalence of hallucinations and positive versus negative symptoms in female than in male patients.<sup>111</sup> Slice thickness of MRI scans was a significant moderator of the ES for whole brain and STG gray matter, indicating more evident differences between patients and controls detected in technologically more sophisticated studies. We also calculated a composite index of overall quality of the study, and this was found to be a significant moderator of ES for STG, the higher the study quality, the higher the differences detected between patients and controls, and for PT (left) in the opposite direction. Study quality may therefore affect MRI findings from different brain structures differently, especially in those discrete areas that present difficult or controversial segmentation procedures.

This study suffers from several limitations. First, common to all meta-analyses, a complete control of the quality of the primary studies, that is, on the possibility that certain biases were present in the original studies, was not possible. For instance, most of the studies considered in the meta-analysis included both schizophrenia and schizophrenia spectrum disorders patients without presenting separate results for these subgroups; others investigated both drug-naïve and previously treated first-episode subjects again without presenting separate data for the subgroups. We tried to address the issue of the quality of primary studies, assigning them a 'value' reflecting the degree of rigorousness and reliability of methods and results, and analyzing this as a potential moderator of ESs. The presence of significant results for this moderator indicates that weaknesses of the studies might have a role in the findings of each original study. Second, the choice of performing analyses without correction for multiple comparisons could have generated type I errors in the results. However, the independence of each meta-analysis on different brain structures, each driven by a single hypothesis, and the exploratory nature of meta-regressions, which were performed not to confirm but to elicit new testable hypotheses, justified the choice and the risk to obtain results that could be not confirmed by specifically addressed new research. Third, in general, our analysis was limited to the variables reported in the original studies. This was particularly evident for the description of the pharmacological regimen of patients during the study period, with only a small minority of studies reporting

the amount of antipsychotic drugs taken between scans and therefore limiting the possibility to investigate more carefully this variable. In fact, the moderator 'percentage of patients using atypical antipsychotics' is a very rough index of actual intake of specific antipsychotic drugs. However, there was no better way to analyze this issue since the studies available did not report either the cumulative dose of different classes of antipsychotics or of specific drugs taken. The correlation of the ES of different cortical gray matter changes and the proportion of patients treated with SGAs versus FGAs may be in any case meaningful. Rather than allowing any conclusive interpretation on the relationship between type of antipsychotic taken and cortical brain changes, such findings may indicate the need for further studies specifically aimed at clarifying the issue. Fourth, the number of published papers eligible for the analysis was small, so that some brain regions potentially implicated in the pathophysiology of schizophrenia, such as the prefrontal cortex or cingulate gyrus gray matter, could not be investigated. Fifth, the largely unbalanced sex distribution in the studies did not allow to analyze in a definitive manner the role of gender on brain structural changes and progressive tissue loss in schizophrenia, even if the moderator variable analyzed (percentage of males in the sample) did not result significant in explaining the heterogeneity of ESs. Sixth, the course over time of cerebral lateralized structures could be inferred but not directly analyzed, as no study reported laterality indices for individual subjects or group of subjects. Finally, the results of both ES and meta-regressions were not corrected for multiple comparisons, so they may have been vulnerable to type I error. We carefully considered the relative costs of detecting versus failing to detect significant effects and decided to avoid statistical corrections. In fact, each meta-analysis on any specific brain region should be considered a separate analysis for which any statistical correction should be questionable; moreover, also applying a more stringent level of significance (that is,  $<0.01$ ), all but one ES remained significant. On the other hand, meta-regressions, there were in any case limited *a priori* in number, were intended to be exploratory analyses with the aim to generate, rather than prove, hypotheses, so that correction for multiple comparisons would be too restrictive, particularly for revealing otherwise elusive effects.

In conclusion, with all the above-mentioned limitations in mind, the picture emerging from this series of meta-analyses could be useful to generate new hypotheses and suggests the need for further studies specifically aimed to test them. A more refined progressive brain pathology hypothesis of schizophrenia is emerging, with meaningful regional and temporal specificity of the pathological brain process. Whether preceded by substantial early brain changes, genetic or environmental in origin, the time around the onset and the first phases of the disease seem crucial for a rapid, progressive, cortical tissue loss that could partly determine the clinical and outcome severity of the disorder. This process is especially active in the left hemisphere and in the superior temporal structures, the same structures that are involved in the mediation of core psychotic symptoms of schizophrenia and/or their severity. The time and type of antipsychotic treatment seem to counteract partially such process, but are not able to arrest it. Future studies should address some specific issues

raised by these results, such as the course over time not only of the volume of cortical gray matter but also of other brain components before the onset of schizophrenia compared with well-matched healthy controls, in relation to potential moderators such as specific genetic polymorphisms or the presence or absence of crucial environmental factors. Even short-term longitudinal studies may be informative, since the longer the follow-up the greater the number of potential confounders of the effects analyzed. Further studies will be required to better understand how the progressive brain changes affect the morphological lateralization of the schizophrenic brain, an issue of potentially high heuristic value. The clinical correlates of tissue loss in specific brain areas in the different phases of illness are largely unknown. The hypothesis of schizophrenia as a progressive generalized brain disease is far less established than believed by many authors, and requires further, more specific, straightforward and thoughtful search.

### Conflict of interest

The authors declare no conflict of interest.

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