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The Effect of Antipsychotic Treatment on Cortical Gray Matter Changes in Schizophrenia: Does the Class Matter? A Meta-analysis and Meta-regression of Longitudinal Magnetic Resonance Imaging Studies

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ABSTRACT

BACKGROUND: Deficits in cortical gray matter (GM) have been found in patients with schizophrenia, with evidence of progression over time. The aim of this study was to determine the role of potential moderators of such changes, in particular of the amount and type of antipsychotic medication intake.

METHODS: Longitudinal magnetic resonance imaging studies comparing changes in the volume of cortical GM over time between patients with schizophrenia and healthy control subjects published between January 1, 1983, and March 31, 2014, were analyzed. Hedges' *g* was calculated for each study and volume changes from baseline to follow-up were analyzed. Meta-regression statistics were applied to investigate the role of potential moderators of the effect sizes.

RESULTS: Eighteen studies involving 1155 patients with schizophrenia and 911 healthy control subjects were included. Over time, patients with schizophrenia showed a significantly higher loss of total cortical GM volume. This was related to cumulative antipsychotic intake during the interval between scans in the whole study sample. Subgroup meta-analyses of studies on patients treated with second-generation antipsychotics and first-generation antipsychotics revealed a different and contrasting moderating role of medication intake on cortical GM changes: more progressive GM loss correlated with higher mean daily antipsychotic intake in patients treated with at least one first-generation antipsychotic and less progressive GM loss with higher mean daily antipsychotic intake in patients treated only with second-generation antipsychotics.

CONCLUSIONS: These findings add useful information to the controversial debate on the brain structural effects of antipsychotic medication and may have both clinical relevance and theoretical implications.

Keywords: Cortical gray matter, First generation antipsychotics, Magnetic resonance imaging, Schizophrenia, Second generation antipsychotics, Structural brain changes

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The presence of structural brain abnormalities in schizophrenia has been well established (1–5). Reductions in whole-brain and gray matter (GM) volume, primarily in the frontal and temporal lobes, and enlargement of the lateral ventricles are among the most replicated findings (1,3,5). These abnormalities are largely evident from the first episode of schizophrenia (6) and are detectable before illness onset in prodromal/high-risk individuals (7). Longitudinal magnetic resonance imaging (MRI) studies have shown that these brain volume abnormalities in schizophrenia are progressive, with evidence that whole-brain and cortical GM volumes decrease and lateral ventricle volumes increase over time both in first-episode and chronic schizophrenia (8–11). The nature of the pathophysiologic process underlying such progressive brain changes is still largely a matter of speculation. Genetic factors (12–16), symptom severity (17–20), duration of relapses (21) or number of weeks hospitalized (22), and poorer social functioning (18,22,23) have been associated with larger decreases in brain volume or increases in lateral ventricular volume.

The role played by antipsychotic treatment on the pathophysiologic trajectory of brain abnormalities in schizophrenia is currently a matter of lively debate. The findings from the largest meta-analysis of cross-sectional studies on schizophrenia performed to date (3) indicate that the reduction in whole-brain GM volume is associated with the dose of antipsychotics taken at the time of scanning. A longitudinal MRI investigation of a large cohort of patients from the first episode of schizophrenia followed for up to 14 years (Iowa Longitudinal Study) showed that decreases in whole-brain and GM volumes were associated with higher exposure to antipsychotics (19,21). A meta-analysis of longitudinal MRI studies showed a correlation between cumulative

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antipsychotic intake during the interscan follow-up period and the decrease in whole-brain GM volume (11). However, these studies and meta-analysis did not analyze the potential impact of first-generation antipsychotics (FGAs) and second-generation antipsychotics (SGAs) on progressive loss of brain tissue.

In fact, the relationship between antipsychotic treatment and loss of cortical GM in schizophrenia and the potential differential effect of SGAs versus FGAs on such loss is a topic of crucial clinical and heuristic interest. A number of studies have reported different impacts of SGAs versus FGAs on changes in brain volume in schizophrenia, especially GM, with SGAs being putatively associated with a lesser decrease in longitudinal GM volume than FGAs (17,24,25), although a study performed in first-episode patients over 1 year of treatment concluded that low doses of haloperidol, risperidone, or olanzapine may have similar effects on the overall change in GM volume (26). Qualitative reviews addressing the topic of brain changes in schizophrenia in relation to antipsychotic treatment have yielded inconclusive results (27–30). A recent quantitative review of longitudinal cortical GM changes in schizophrenia (10) suggested that treatment with SGAs may be associated with less progressive loss of GM, but a very rough index of intake of different classes of antipsychotics (the percentage of patients using SGAs in each study included in the review) was used.

In this article, we report the results of a meta-analysis of MRI longitudinal studies analyzing cortical GM volume in schizophrenia specifically aimed at investigating: 1) the influence of antipsychotic medications on changes in GM volume over time; 2) the possible different impact of SGAs versus FGAs on such changes; and 3) the influence of other potential moderators of longitudinal changes in cortical brain volumes (31).

METHODS AND MATERIALS

Data Sources

We conducted a systematic literature search via the MEDLINE/PubMed (National Library of Medicine at the National Institutes of Health, Bethesda, Maryland; http://www-ncbi-nlm-nih-gov.proxy.unibs.it/pubmed) and EMBASE (Elsevier, Amsterdam, Netherlands; http://www.embase.com.proxy.unibs.it) databases for MRI studies investigating longitudinal cortical GM volume changes and the role of antipsychotic drugs on such changes in samples of patients with schizophrenia. We used the following keywords to generate a list of potentially useful studies: ([Magnetic Resonance Imaging] OR [MRI]) AND [schizophrenia] AND ([antipsychotics] OR [neuroleptics]) AND ([longitudinal] OR ([progressive]). The search was performed through March 31, 2014. All the reference lists within the selected studies, as well as the list of studies included in previous meta-analyses on similar topics, were reviewed to check for additional references.

Study Selection

Studies were included if they met the following criteria: 1) were reported in an original paper published in a peer-reviewed journal; 2) included subjects with a DSM-IV-TR, DSM-IV, DSM-III-R, or ICD-10 diagnosis of schizophrenia; 3) used longitudinal analysis of regions of interest (ROIs) of GM volume on MRI in a group of patients with schizophrenia and a group of healthy control subjects; and 4) reported the cumulative dose or the mean daily dose (MDD) of antipsychotic medication administered during the follow-up period or the same information was provided by the authors of the study. In fact, when studies did not report the data required to compute the antipsychotic dose, we contacted the respective authors to collect the individual data (cumulative or MDD of antipsychotic medication administered during the follow-up period) and avoid biases in the literature search. If no response was received from the authors, that study was excluded from the meta-analysis. Longitudinal MRI studies conducted on patients diagnosed as being in an at-risk mental state for schizophrenia or during transition to psychosis were not considered for the present meta-analysis. Studies that used voxel-based morphometry, deformation-based morphometry, or tensor-based morphometry, which cannot be included in a traditional meta-analysis, were also excluded.

Studies performed using ROI MRI were considered if they reported quantitative measurements of changes in cortical GM volume over time in terms of means and SD or as a variable that could be lead back to such values (e.g., SE values). 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. An exception to this was longitudinal studies with multiple subsequent follow-up evaluations that reported both GM volume and pharmacologic regimens of patients at each follow-up time point. In this case, even if the findings were derived from the same cohort of patients, all the follow-up intervals were included in the analysis and considered as if they were derived from independent studies. Moreover, in the case of studies that reported separately brain volumes for subgroups of patients treated with different pharmacologic treatments, we entered the results as if they were from separate studies. This technique was adopted by previous meta-analyses (8,32).

Brain regions were included when investigated in at least 10 independent study samples.

Data Recorded in the Database

The variables recorded from each article included in the meta-analysis were sample size, year of publication, mean age of participants, type of antipsychotic treatment, dose of antipsychotic at baseline and follow-up MRI scan or MDD or cumulative dose of antipsychotics during the follow-up, brain volume (baseline and follow-up means $\pm$ SD or baseline to follow-up volume mean difference $\pm$ SD), duration of follow-up (months), duration of illness at baseline MRI scan (weeks), number (or percentage) of substance abusers in the study sample, number of Tesla of MRI scanner, overall cognitive functioning (IQ), duration of untreated psychosis (DUP), and change in severity of psychotic symptoms during the follow-up (Supplement 1). The antipsychotic intake was recorded both as cumulative exposure to antipsychotics during the interscan interval and as the MDD of antipsychotics. We used the Antipsychotic Dose Conversion Table equivalency to 100 mg of chlorpromazine (19) to convert all antipsychotic doses into chlorpromazine equivalents (CPZ-Eq) (Supplement 1).

Meta-Analytical Methods and Data Analyses

Meta-analyses were carried out using the Comprehensive Meta-Analysis software, version 2 (Biostat Inc., Englewood, New Jersey). Effect sizes (ES) were calculated for each study included in the meta-analyses. As a measure of ES, Hedges' *g* was adopted and computed by subtracting the follow-up from the baseline mean volume (or using the mean volume change from baseline), divided by the standard deviation, and weighted for sample size (33). The 95% interval around the composite ES was also calculated (33). The Q statistic was used to determine between-group (patients vs. control subjects) differences. Egger's test of publication bias was used to assess whether there was a tendency for selective publication of studies based on the direction of their results (34).

Meta-regression Analyses

Meta-regression analyses were conducted to test the influence of the following potential moderators of ES: cumulative exposure to antipsychotic medication during the interscan interval (as CPZ-Eq); MDD of antipsychotics during the interscan interval (MDD CPZ-Eq); patient's age at baseline MRI scan; duration of illness at baseline; duration of MRI follow-up; change in severity of psychotic symptoms during the follow-up; and percentage of substance abusers in the study sample. Due to co-linearity between the highly correlated variables age and duration of illness, the latter was not included in the meta-regressions. The number of Tesla of MRI scanner was not included in the meta-regression analyses since all studies but one (35) were performed with 1.5 Tesla MRI scanner. Meta-regressions were performed when at least 10 independent studies were available for the outcome of interest. Thus, the potential moderating impact on GM changes of such variables as patient's IQ [reported only in three studies (20,36,37)] or DUP [reported only in three studies (26,38,39)] was not considered.

Subgroup Meta-analyses

To address the issue of a potential different impact of SGAs and FGAs on progressive loss of cortical GM, a supplementary set of meta-analyses was conducted. On the one hand, we selected from the database those studies that investigated brain morphology longitudinally in patients treated exclusively with SGAs. A separate analysis was also performed for those studies that investigated patients treated with FGAs or that included mixed antipsychotic treatments (both FGAs and SGAs) during the interscan interval. Mixed treatment means that both FGAs and SGAs were used within the patient sample, with the exception of one study (18) where a subgroup of patients was treated with both FGAs and SGAs polypharmacy. This was a heterogeneous group with respect to the relative amount of different types of antipsychotics administered, with a mean percentage of patients treated with SGAs of 43.6 ± 30.4%. Since considerably fewer studies were available on patients treated with SGAs only or with FGAs or mixed treatments, brain regions were included in the analyses when studied in at least five independent studies. Due to insufficient data, it was not conducted as a subgroup meta-analysis for studies including patients treated exclusively with FGAs [three studies available (17,24,26)].

RESULTS

Results of the Systematic Search

The selection procedure, according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (40), is shown in Figure 1.

The final database comprised 18 original independent studies suitable for analysis (Table 1) and published between 2002 and March 2014. Moreover, four studies (17,24,26,38) reported brain volumes of subgroups of patients in relation to different pharmacologic treatments (two or three arms). In these cases, as reported in Methods and Materials, we entered their results as if they were from separate studies. The same criterion was adopted for two studies (19,39) with multiple follow-up evaluations and reporting GM volume at each follow-up time point and for which antipsychotic intake between each follow-up period was derivable. Thus, a number of independent samples of patients higher than the number of original studies were analyzed. The overall sample consisted of 1155 patients with schizophrenia and 911 healthy control subjects. The following cerebral regions (GM) for which at least 10 studies were available were included in the analyses: whole brain ($n = 26$), frontal lobe ($n = 15$), temporal lobe ($n = 14$), and parietal lobe ($n = 14$).

Results of the Overall Meta-analysis

Changes in GM volume over time in patients with schizophrenia and healthy control subjects are presented in Table 2. To limit the risk of type 1 errors arising from multiple comparisons, we used the Bonferroni correction (p settled at .00625 [.05/8]).

Subgroup Meta-analyses

In the subgroup of studies analyzing patients treated with FGAs or mixed antipsychotic treatment (FGAs and SGAs), a statistically significant decrease in volume of whole-brain, frontal, temporal, and parietal lobe GM was found (Table S1 in Supplement 1). These changes in GM volume persisted after correction for multiple comparisons.

In the subgroup of patients treated only with SGAs, no decrease in whole-brain and parietal lobe GM volume was found. For frontal and temporal lobes, there was even an increase, although not statistically significant, in GM volume during the follow-up period (Table S2 in Supplement 1).

Meta-regression Analyses

A meta-regression analysis of potential moderators of the ES was performed for whole-brain GM, i.e., the cerebral region for which a statistically significant between-group heterogeneity (patients vs. control subjects) in cortical volume changes was demonstrated in the whole study sample (Table 2). The mean values of the moderators investigated are reported in Supplement 1. For computing statistical significance, the Bonferroni correction for multiple comparisons was applied (statistical significance settled at $p = .0083$ [.05/6]). The results of meta-regressions are reported in Table 3.

In all the studies analyzed, the ES of the within-subjects difference in whole-brain GM was affected by the moderator

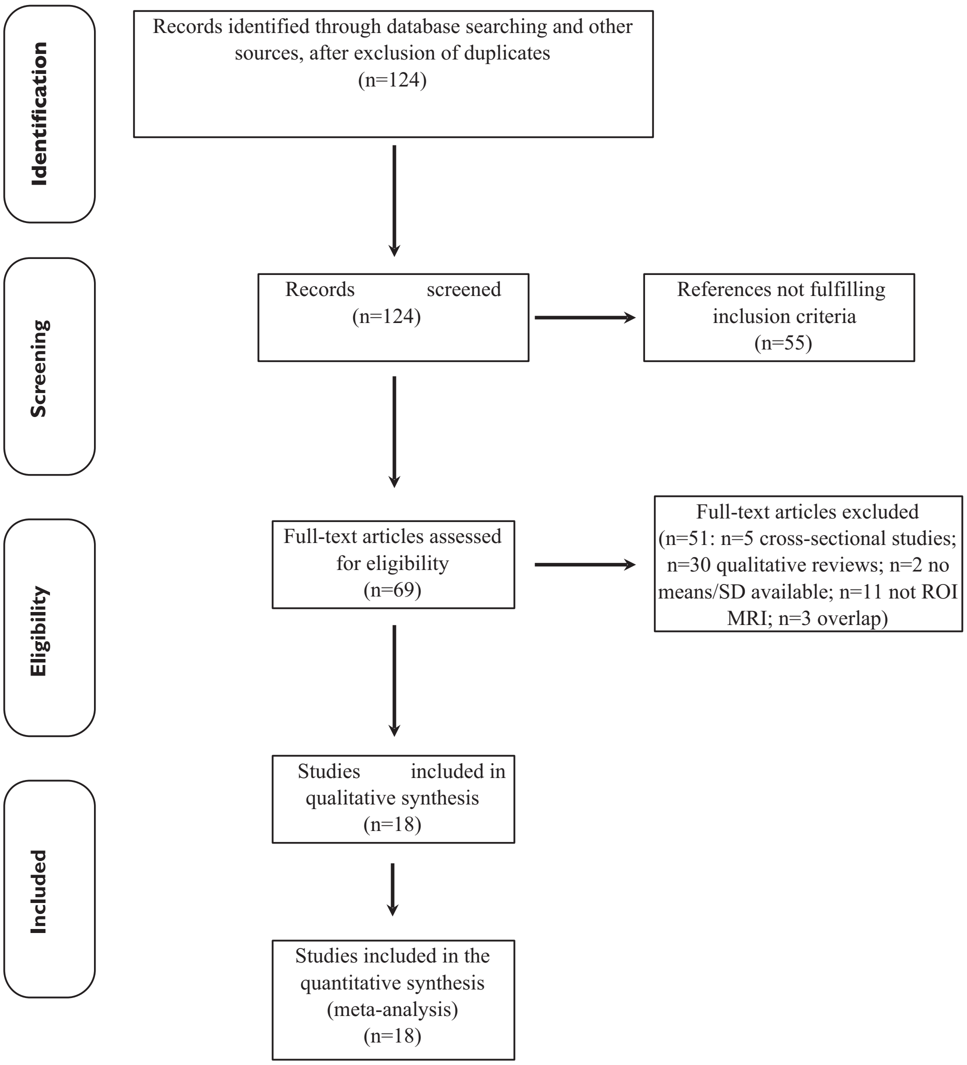

Figure 1. Study selection procedure (Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines). MRI, magnetic resonance imaging; ROI, region of interest.

cumulative exposure to antipsychotics (the greater the exposure to antipsychotics during the interscan interval, the greater the reduction in GM volume). Also, in the studies including patients treated with FGAs, the ES of whole-brain GM change was negatively affected by the cumulative exposure to antipsychotics and MDD of antipsychotics, the latter correlation persisting after correction for multiple comparisons. On the other hand, in the subgroup of studies including patients treated only with SGAs, no significant correlation emerged between whole-brain GM volume change and cumulative exposure to antipsychotics during the interscan interval. ES was even positively moderated by the MDD of antipsychotic—the higher the MDD of antipsychotics during the follow-up, the lower the reduction in GM volume, a significance persisting after correction for multiple comparisons.

The meta-regressions of time-corrected antipsychotic treatment (MDD) on whole-brain GM changes are represented in Figure 2.

DISCUSSION

This meta-analysis investigated longitudinal changes of cortical GM in schizophrenia and specifically addressed the issue of the impact of the amount and type of antipsychotic medication intake on progressive change of GM volumes.

No previous quantitative review tried to analyze separately the effects of FGAs and SGAs on cortical GM changes. In fact, the meta-analysis by Fusar-Poli *et al.* (11) reached the conclusion that antipsychotics in general may have a detrimental effect on brain structure but did not differentiate the effects of FGAs and SGAs; the other, by our group (10), suggested a possible different effect of FGAs and SGAs but used a very rough index of intake of different classes of antipsychotics (percentage of patients using SGAs in each study included), limited the analysis to a subgroup of studies, and did not analyze the effect of cumulative exposure to or mean daily dose of different classes of antipsychotics on GM changes.

Table 1. Description of the Studies Included in the Meta-Analysis

Author (Year) (Reference)	Follow-up Duration, Months ± SD (Range)	Type of Antipsychotic	MDD (mg CPZ-Eq)	Cumulative Antipsychotic Intake (mg CPZ-Eq)	Substance Abuse: Y/N	M/F Ratio		Mean Age	
						Patients	Control Subjects	Patients	Control Subjects
Cahn *et al.* (2002) (23)	12.85 ± 1.15	Mixed (FGAs or SGAs or FGAs + SGAs)	159.57	62391.87[a]	N	29/5	30/6	26.2	24.5
Ho *et al.* (2003) (62)	40.68 ± 19.20	Mixed (FGAs or SGAs)	462.20[a]	556117.10[a]	NR	53/20	15/8	24.5	26.9
Sporn *et al.* (2003) (36)	40.80 ± 19.20	Mixed (SGAs or FGAs + SGAs)	384.26[b]	470180.54[b]	N	24/39	27/43	15.0	14.8
Lieberman *et al.* (2005) (17)	12.00	FGAs (*n* = 79, HAL)	597.82[a]	218204.30	N	136/25	40/22	23.8	25.3
	NR	SGAs (*n* = 82, OLA)	263.15[a]	96049.75					
Molina *et al.* (2005) (38)	25.60 ± 9.90 (naive)	SGAs (*n* = 17, RIS)	378.78[a]	294943.36	N	20/29	6/11	31.0 (naïve)	28.4
	28.70 ± 11.80 (chronic)	SGAs (*n* = 12, CLO)	310.18[a]	270774.21				25.6 (chronic)	
Garver *et al.* (2005) (24)	1.0	FGAs (*n* = 6, HAL)	380.43[a]	10652.04	N	13/6	5/2	33.0	29.0
		SGAs (*n* = 7, RIS)	237.62[a]	6653.36					
		SGAs (*n* = 6, ZIP)	303.03[a]	8484.84					
Molina *et al.* (2007) (63)	38.00 ± 15.00	SGAs (OLA)	324.21[a]	374731.64	N	6/5	5/6	41.0	29.8
van Haren *et al.* (2008) (18)	57.96 ± 6.60	Mixed (FGAs or SGAs or FGAs + SGAs)	338.68[b]	611656.08[b]	NR	70/26	76/37	32.2	35.2
Crespo-Facorro *et al.* (2008) (26)	12.05 ± 1.06	FGAs (*n* = 18, HAL)	244.09[a]	89464.07	Y	11/18	26/12	29.7	–
	12.03 ± 1.24	SGAs (*n* = 16, RIS)	183.65[a]	67199.83		13/16		24.9	
	12.07 ± 1.02	SGAs (*n* = 18, OLA)	289.02[a]	106107.67		13/18		28.0	
Reig *et al.* (2009) (60)	24.20 ± 1.00	Mixed (SGAs)	223.71[c]	88318.19[c]	N	16/5	21/13	15.7	15.2
Takahashi *et al.* (2010) (64)	32.40 ± 7.20	Mixed (FGAs or SGAs or FGAs + SGAs)	415.76[a]	439755.43[a]	N	12/6	11/9	23.1	23.2
Takahashi *et al.* (2010) (65)	28.80 ± 12.00	Mixed (FGAs or SGAs)	559.25[a]	489903	N	10/1	12/5	32.7	30.2
Boonstra *et al.* (2011) (66)	12.10 ± 1.20	Mixed (SGAs)	183.69[a]	67605.57[a]	Y	12/4	15/5	28.8	27.9
Andreasen *et al.* (2011) (67, data derived also from 19)	86.4 ± 45.40	Mixed	297.10[a] (1st follow-up)	332915.40	Y	148/54	66/59	24.5	29.6
			393.90[a] (2nd follow-up)	475890.28					
			479.40[a] (3rd follow-up)	680676.09					
Ebdrup *et al.* (2011) (35)	7.30 ± 1.00	SGA (QUE)	379.15[a]	84324.05	Y	15/7	21/7	26.2	28.4
Arango *et al.* (2012) (20)	26.20 ± 3.00	Mixed (FGAs or SGAs)	211.86	168840.00[a]	N	18/7	23/47	15.5	15.3
Roiz-Santiáñez *et al.* (2013) (39)	36.70 (34.50–44.90)	Mixed (FGAs or SGAs)	266.43	297420.00[a]	Y	66/109	47/76	29.4	27.8
Lappin *et al.* (2013) (37)	72.10 ± 12.00	Mixed (FGAs or SGAs)	343[c]	751170[c]	Y	15/20	14/32	25.3	29.8

CLO, clozapine; F, female; FGAs, first generation antipsychotics; HAL, haloperidol; M, male; N, no; NR, not reported; SGAs, second-generation antipsychotics; OLA, olanzapina; QUE, quetiapine; RIS, riperidone; Y, yes; ZIP, ziprasidone.

[a]Data reported in the original paper.

[b]Data derived from previous published reviews.

[c]Data provided by the authors on request.

Table 2. Summary of the Meta-analyses

Brain Region	Number of Studies	Groups	Number of Patients or Control Subjects	Effect Size (95% CI)	Effect Size: *p* Value	Heterogeneity (Between-Groups Comparison) *Q*	Heterogeneity (Between-Groups Comparison) *p* Value	Egger Test: *p* Value
Whole-Brain GM	26	CTRL	883	−.10 (−.17 to −.02)	**.006**[a]	5.62	**.018**	.348
		SCZ	1102	−.24 (−.33 to −.15)	<**.001**[a]			
Frontal Lobe GM	15	CTRL	542	−.11 (−.27 to .04)	.163	.43	.511	.193
		SCZ	891	−.18 (−.33 to −.03)	**.013**			
Temporal Lobe GM	14	CTRL	519	−.02 (−.17 to .07)	.574	.44	.503	.460
		SCZ	818	−.08 (−.18 to .02)	.149			
Parietal Lobe GM	14	CTRL	519	−.18 (−.32 to −.04)	**.008**	.05	.816	.390
		SCZ	818	−.21 (−.32 to −.09)	<**.001**[a]			

CI, confidence interval; CTRL, control subject; GM, gray matter; SCZ, schizophrenia. Bold text indicates statistically significant values.
[a]Statistically significant after correction for multiple comparisons ($p = .00625$).

One main finding of the present meta-analysis is that longitudinal changes in whole-brain cortical GM volume in schizophrenia are related to exposure to antipsychotic medication during the MRI follow-up. The effect sizes detected were small to moderate, but the consistency of the findings are strengthened by the results of the statistics for within-group heterogeneity and those for publication bias, both nonsignificant for all cortical regions. A significant between-group (patients vs. control subjects) difference in GM volume loss was demonstrated, however, only for whole-brain GM, with higher volume reduction in patients.

The meta-regression analyses showed that both the cumulative exposure and the MDD of antipsychotics were associated with greater whole-brain cortical GM decreases in the entire patient sample, although the latter regression did not maintain statistical significance after applying a conservative correction for multiple comparisons. Other variables, such as illness severity, age, substance use, and duration of follow-up, were not significant moderators of longitudinal GM changes.

However, a different impact of SGAs and FGAs on cortical GM changes in schizophrenia based on the amount of antipsychotic intake during the MRI follow-up interval did emerge. In fact, whole-brain GM volume reduction was inversely correlated with exposure to antipsychotic treatment only in patients treated with FGAs or mixed treatments; on the other hand, in the sample of studies including patients treated only with SGAs, the cumulative exposure to antipsychotics did not correlate with GM volume changes over time and was not associated with cortical tissue loss. The different impact of SGAs versus FGAs on longitudinal cortical GM changes became even more evident when considering the MDD of antipsychotic intake during the follow-up period. In this case, a robustly significant negative correlation emerged for patients who were administered FGAs or mixed treatments, while a reversed, statistically highly significant, positive correlation was detected in studies including patients treated only with SGAs—the higher the MDD of antipsychotics taken, the lower the reduction of whole brain GM volume over time. It is worth noting that MDD corrects the cumulative intake of antipsychotics for the different durations of follow-up between the study groups (although not statistically significant in our analysis) and may reflect, more than the cumulative dose of antipsychotics taken, the patient's continuous level of exposure to drug treatment. It may also indicate whether the drug is prescribed at therapeutic, subtherapeutic, or even excessive dose and may be considered an indicator of the degree of probability of a given drug to exert its biological effects on the patient's brain. It could be argued that it may be also an indirect index of severity of patient's psychopathology, since a higher daily dose of antipsychotics is expected to be

Table 3. Meta-regression of Gray Matter Volume Changes Over Time in Patients with Schizophrenia: Treatment, Clinical, and Study Variables

	Mean Daily Dose of Antipsychotics (CPZ-Eq)	Cumulative Exposure to Antipsychotics (CPZ-Eq)	Age of Patients	Severity of Psychotic Symptoms	Substance Abuse	Interscan Interval
Whole-Brain GM (Entire Sample)						
Z	**−2.19**	**−2.63**	1.13	.29	.17	**−2.20**
p	**.028**	**.008**[a]	.255	.770	.866	**.027**
Whole-Brain GM (FGAs + SGAs)						
Z	**−2.88**	**−2.31**	.88	.05	**−2.01**	−1.51
p	**.003**[a]	**.020**	.373	.958	**.044**	.128
Whole-Brain GM (Only SGAs)						
Z	**2.95**	.78	1.11	1.73	−1.03	−.38
p	**.003**[a]	.439	.267	.083	.299	.701

CPZ-Eq, chlorpromazine equivalents; FGAs, first-generation antipsychotics; GM, gray matter; SGAs, second-generation antipsychotics.
[a]Statistically significant after correction for multiple comparisons ($p = .0083$). Bold text indicates statistically significant values.

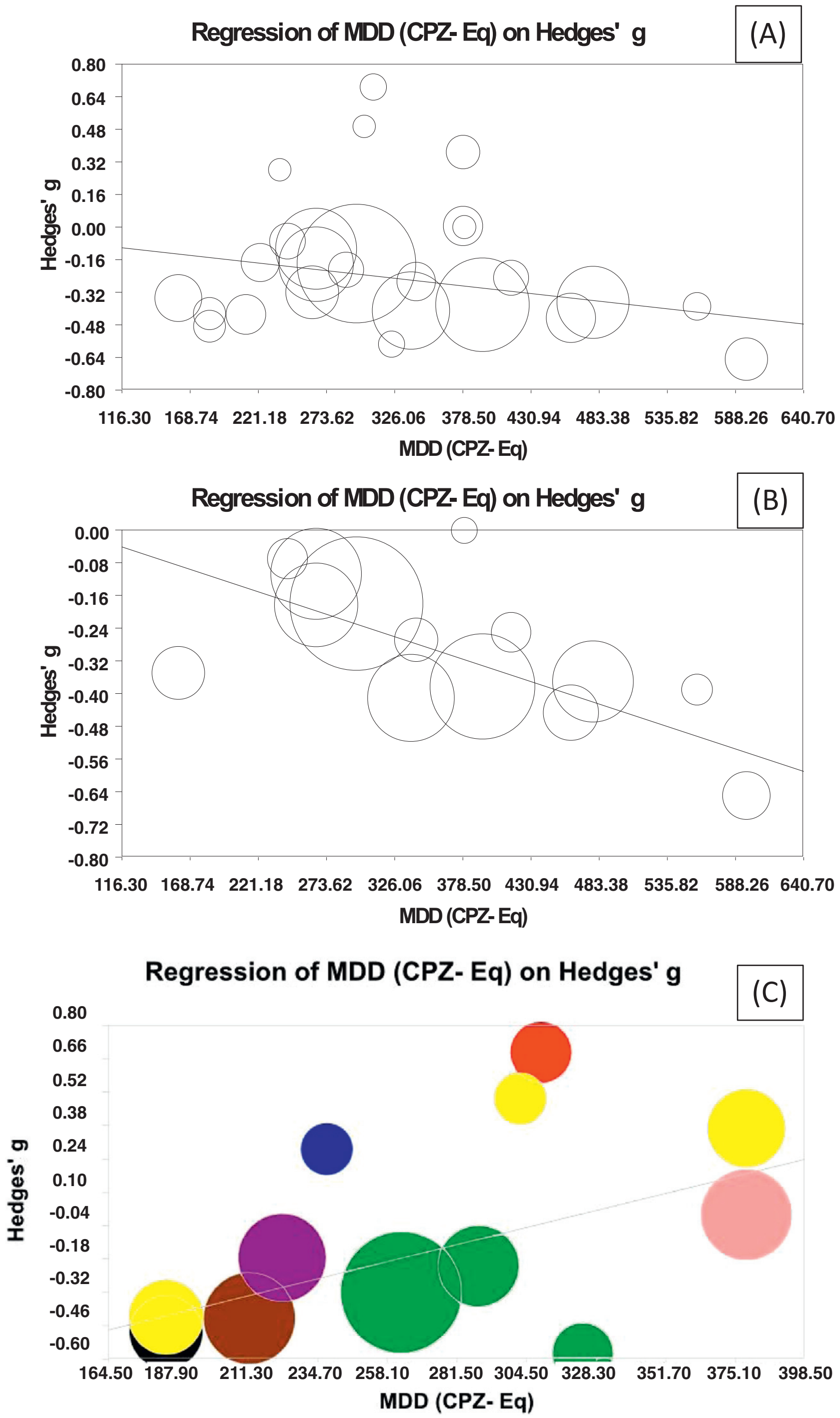

Figure 2. Meta-regression analyses. GM volume changes and mean daily dose (MDD) of antipsychotic medication administered to patients during the interscan interval: **(A)** in the whole sample ($Z = -2.19$, $p = .028$); **(B)** in the subgroup of patients treated with first-generation antipsychotics or mixed treatment (second-generation antipsychotics [SGAs] + first-generation antipsychotics) ($Z = -2.88$, $p = .003$); and **(C)** in the studies including patients treated exclusively with SGAs ($Z = 2.95$, $p = .003$). The size of the circles reflects the sample size of the study. **(C)** The colors indicate the different SGAs used as follows: red: clozapine; green: olanzapine; pink: quetiapine; yellow: risperidone; blue: ziprasidone; black: more atypicals (risperidone or olanzapine or quetiapine); brown: more atypicals (risperidone or olanzapine or quetiapine or ziprasidone or aripiprazole or clozapine); violet: more atypicals (risperidone or olanzapine or quetiapine or clozapine). CPZ-Eq, chlorpromazine equivalents.

prescribed in more severe illness. Although we could not explore directly this possibility, we analyzed a variable that may be considered a proxy of such psychopathological severity, i.e., the change over the follow-up period of different scales of symptom severity, an approach already used by other authors (11). The latter resulted, however, totally unrelated to the ES of GM volume changes, so excluding that the effect of antipsychotic intake on brain morphology could be entirely mediated by the clinical severity of the disease during the follow-up. Rather, it could be inferred that the higher the MDD, the more evident is the divergent effect of different categories of antipsychotics on cerebral GM. Nor could these differences be attributable to different duration of follow-up in the groups of patients, since the meta-regressions of interscan interval on cortical GM changes were not significant both in the mixed and the pure SGA groups.

On the whole, our results indicate that the putative contributory role of antipsychotic treatment in reducing the volume of cortical GM in schizophrenia cannot be generalized and appears to be less evident for SGAs, which seem to be associated with less loss of brain tissue. The evidence of a different impact of SGAs on brain tissue over time is reinforced by the absence of any progressive decrease in whole-brain GM observed in this subgroup of patients with respect to healthy control subjects (between-group comparison: $Q = .002$; $p = .965$), at variance with what was observed for the whole patient sample.

Obviously, only studies directly comparing GM changes in patients randomly assigned to FGAs or SGAs for the same period of time could give a definitive answer to the question raised by the results of our analysis. At present, only three ROI MRI studies (17,24,26) had such design and demonstrated less GM volume loss (or even increase) in patients treated with SGAs as compared with those treated with FGAs. A description of these studies and a subgroup meta-analysis on their results is reported in Supplement 1.

Any interpretation of the main result of this meta-analysis, i.e., a different moderating effect of SGAs taken alone and of FGAs or mixed treatment on cortical GM tissue loss in schizophrenia, are speculative at this time. It has been hypothesized that SGAs may have a neuroprotective effect, either increasing the expression of neurotrophic factors (41) or stimulating neurogenesis (42) or interacting with and increasing the activity of *N*-methyl-D-aspartate glutamate receptors (43). Conversely, the excessive reduction in cortical GM 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 (44–48). It may also indicate a hypothetical lower capacity of FGAs to interfere with the natural pathophysiologic trajectory of the disease, which may also be reflected in the different impact on cerebral blood flow and metabolism of FGAs versus SGAs (49–55). It is not even possible to exclude that the metabolic effects and weight gain related to the treatment with some SGAs (56) may have had a role in mediating such relationship between higher SGA dose and less GM loss, an hypothesis warranting further exploration. Given the limited number of studies, it was not possible to investigate whether different SGA compounds had different effects on GM volume. The qualitative inspection of the degree of correlation between daily drug exposure to individual compounds and changes in GM volume (Figure 2) suggests that more favorable effects on cortical structures could apply to the whole class of SGAs. The most marked positive effect on GM volume over the follow-up was detected in a study including only patients treated with clozapine, an SGA for which there is much evidence, although not univocal, of neurogenesis or neurotrophic effects in animal models (39,57–59).

This study has several limitations. First, common to all meta-analyses, a complete control of the validity and quality of the primary studies was not possible. Second, our analysis was limited to the variables reported in the original studies. Few studies reported the amount of the individual antipsychotic drugs taken between scans, and we could obtain these data from the authors in a minority of cases. We relied on the cumulative dosage or MDD of different classes of antipsychotics taken but could not investigate the effect of each drug on brain morphology. Similarly, insufficient data were available to conduct an analysis of brain volumes for male or female subjects separately [only one study available (60)] or a meta-regression with IQ or DUP or other potential moderators of GM changes that should be the object of future research. Third, insufficient information was available to analyze separately patients treated with FGAs and SGAs in the studies including both treatments. Even in the case of detailed information reported in the article or provided by the authors about the number of patients treated with each class of antipsychotics and the amount of treatment given, it was impossible to link such medication intake with the individual MRI data in the follow-up. Fourth, there is little empirical foundation for converting SGA doses in CPZ-Eq; however, this is the conversion more frequently used and that allows direct comparison with previous analyses. Moreover, even different methods of dose conversion (61) may present problems of applicability to SGAs and FGAs. In any case, also applying an olanzapine equivalent conversion (61), we confirmed that in the group of studies including patients treated only with SGAs, the cumulative dose of antipsychotics taken was not a significant moderator of cortical GM change ($Z = -.0905$, $p > .05$), so excluding that our results might be an artifact of the CPZ-Eq conversion. Finally, the relationship between antipsychotic exposure and change in GM volume could be not linear and so might be better captured by more sophisticated and complex data analysis procedures.

In conclusion, there is evidence to suggest that antipsychotic treatment may have a contributory role in reducing the volume of cortical GM in schizophrenia, but this effect cannot be generalized and appears to be far less evident for SGAs, which results in being associated with less loss of brain tissue. More longitudinal studies specifically designed to directly test the hypothesis of a different effect on regional brain volumes of FGAs and SGAs, conducted with adequate methodology on samples allowing sufficient statistical power, are warranted. Whether different drugs may have varying effects on brain structure or whether their effects on the brain vary as a function of the patient's age and stage of illness or may occur only when a certain threshold of exposure (daily dose or cumulative dose) is reached will also require specifically designed studies. Clarification of these issues will have crucial importance in the clinical management of schizophrenia and will allow a better understanding of the mechanisms underlying the progression of structural brain abnormalities in schizophrenia and the effects of antipsychotic medication on such progression.

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