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S1. Study protocol

1. Why is it important to perform this meta-analysis

Although it is known that treatment with antipsychotic medication is clinically effective in schizophrenia (i.e. reduced symptoms, relapse rates, etc.) there is no meta-analysis on effects of antipsychotics on human brain structure. Additionally, effects of other potential moderators such as illness duration, illness severity on brain structure, are of the high importance.

2. Objectives

By reviewing longitudinal structural neuroimaging studies, severity of psychotic symptoms, duration of illness, duration and doses of antipsychotic medication on brain structure in patients with schizophrenia were analyzed.

3. Electronic searches and data extraction

We provided a systematic search with terms "MRI", "neuroimaging", "psychosis", "schizophrenia", "antipsychotic" in a PubMed and Embase until the April 2012. We extracted all relevant variables reported by studies and decided which ones can be used for regression analysis according to the consistency of the data. We extracted author, center, year of publication, sample sizes, gender (proportion of females), mean age of participants, duration of follow-up, duration of illness, type of antipsychotic treatment, daily dose of antipsychotic at the follow-up MRI (chlorpromazine equivalents), previous exposure to antipsychotics, duration of the education, substance abuse, medication with antidepressants, brain volumes of the whole brain and relevant regions, severity of psychotic symptoms (as measured on the Positive and Negative Symptom Scale (PANSS), Brief Psychiatric Rating Scale (BPRS), Scale for Assessment of Positive Symptoms / Scale for Assessment of Negative Symptoms (SAPS/SANS) scores). Afterwards we calculated a random meta-regression mixed model with brain volume as dependent variable and illness severity and/or dose of antipsychotics and/or follow-up duration as independent variables.

4. Inclusion criteria

We included longitudinal studies of patients treated with antipsychotic medication compared (1) to another type of antipsychotic medication, (2) to the healthy controls, or (3) within the group before and after the antipsychotic medication. To be able to calculate meaningful meta-regression analysis we extended our initial demanding inclusion criteria (only studies reported all depended variables) and included also studies with some missing data. Additionally we included also smaller samples than 10 subjects and performed sensitivity analysis using our quality scores.

5. Types of studies

We included randomized and non-randomized longitudinal volumetric studies of patients with schizophrenia with or without healthy control groups. We decided to include longitudinal studies only, to test for brain volumetric differences during the period of treatment. Studies used voxel-based morphometry, cortical pattern matching, gray matter density, tractography were not included.

6. Types of participants

Patients fulfilled the DSM-IV or DSM-III-R criteria for schizophrenia and schizophrenia-like psychoses (schizophreniform and schizoaffective disorders).

Patients were considered as first-episode of schizophrenia (duration of illness no longer than 5 years) or chronic schizophrenia patients. Besides the adult patients' studies we included also childhood-onset of psychosis studies. As control group we considered healthy control when available.

7. Outcome measures

7.1 Primary outcome

We extracted volumetric brain changes in schizophrenia patients (outcome measures before and after treatment) as primary outcome. Volumes were extracted in cm^3 or ml as raw data or, when

only relative difference was published, we extracted the p-value and direction of difference for subsequent calculation of longitudinal volumetric changes.

7.2. Secondary outcomes

As secondary outcomes we extracted

a) Duration of illness at the baseline,
b) Duration of treatment/follow up,
c) Measures of clinical symptoms (i.e. positive and negative psychotic symptoms),
d) Antipsychotic exposure at the beginning and at the end of follow-up period or during the follow-up period.

The dose of antipsychotics was converted in chlorpromazine equivalents using the 'Antipsychotic dose conversions' supplementary table by Ho et al (Ho et al., 2011)).

8. Data extraction, collection and management

Studies from the same center with overlap more than 10% were disregarded and we selected the article with the largest sample. When studies did not report data we needed as variables in our analysis, we contacted the respective authors to collect the raw data about brain volume or type/dose of antipsychotic medication and/or become information about the psychometric rating scales. When the relevant raw data were not available in the text, but were plotted on graph in the manuscript, we extracted them using GIMP (a free software for editing and resizing of images)(Mattis and Kimball, 2008).

Brain volumes were extracted as mean and standard deviation from included whole brain or region-of interest studies. For further analysis we included only those regions where at least 3 studies reported volumetric data. Finally we include volumes of the whole brain volume (WBV), gray matter volume (GMV), white matter volume (WMV), lateral ventricle volume (LV), and caudate nucleus volume (Cd, the sum of the left and the right caudate nuclei). When the raw data were not directly available, we added difference in the volumes to the baseline value or extracted the p-values with specified direction. When intracranial volume (ICV) and not WBV were

reported we calculated them as WBV=GMV+WMV =ICV-CSF (cerebrospinal fluid).

We needed an overall measure of psychotic symptoms change during the follow-up with the studied antipsychotic medication. Most of the included studies (11) reported PANSS containing 30 items with range 0-6. Two studies used BPRS with 18 items and range 1-7 and four studies used SAPS+SANS with 50 items together and range 0-5. To assess illness severity we calculated 'mean per-item score' with baseline zero (Sherwood et al., 2006). When one study reported more than one psychometric measure (e.g. PANSS and BPRS) we decided to include PANSS in the first order and BPRS or SAPS+SANS in the second order. Data reported only part of the psychometric scores or only 'severity ratings' on some of these scores were not compatible with other extracted data and could not be entered into analysis. Because of heterogeneity of the studies and not available raw data from individual studies we could not reliably calculate Z-scores for illness severity. We transformed the total scores to a mean per-item score and calculated a "*percentage of baseline per-item score"* to follow the improvement during the antipsychotic therapy.

Follow-up duration corresponds to the duration between the first and the second scan and is related to the extracted/calculated dose of antipsychotic in chlorpromazine equivalents. Opposite to that the duration of illness relates to the duration of the disease at the baseline (time of the first scan).

Dose of antipsychotic was extracted or calculated from the papers or received as replies from contacted authors. It was afterwards converted into daily chlorpromazine equivalent (Ho et al., 2011). Aiming to follow longitudinal changes associated with the treatment with antipsychotics we extracted or calculated cumulative dose of antipsychotics taken during the follow-up (treatment) period.

9. Calculation of the cumulative exposure to antipsychotics

We used 'Antipsychotic dose conversion table' – equivalency to 100 mg of chlorpromazine per day published by Ho et al. in Supplement Material (Ho et al., 2011) to convert other types of medication to the Chlorpromazine Equivalent per day (CPZ-EQ/d). Afterwards we multiplied the

duration of the medication in days by the maintenance (or mean or stable average) dose in CPZ-EQ/d (e.g. in the study by Gur 1998 (Gur et al., 1998)). When only dose at the follow-up date was reported, we considered 2 weeks at the beginning of the follow-up *either* for titration by antipsychotic-naïve (AN) and/or antipsychotic-free (AF) group *or* for 'washout- and titration-period' by subgroup switching from one to another medication. We subtracted these 2 weeks from the treatment/follow-up duration. When the mean dose of antipsychotics was published in a subgroup continuing the same medication, we multiplied the daily dose in CPZ-EQ by duration of treatment/follow-up. Dosages published in Haloperidol-EQ taken during interval (Boonstra et al., 2011; Saijo et al., 2001) were converted according to the Antipsychotic dose conversion table (haloperidol-EQ was converted to the CPZ-EQ). When the included study has not reported the dose of antipsychotics taken during the follow-up period, we searched in other papers published by the same group and reported data from the same population / subpopulation. Thus, searching data for study by Chakos et al. 1994 (Chakos et al., 1994), we extracted the average daily dose in fluphenazine EQ during acute treatment (24 mg, SD=15 mg) from the study by Lieberman et al. (Lieberman et al., 1992). All patients included by Chakos 1994 had remission and stayed on the same doses during the follow-up period. Thus, we converted the dose to the CPZ-EQ/d and multiplied by the duration of the follow-up period in days.

Data reported as mean dose-years at follow-up were converted according to Andreasen et al. (Andreasen et al., 2010). Dose-year formula means that 100 mg/day of CPZ-EQ = 1 dose-year. We thus multiplied dose-years by 100 mg of CPZ-EQ and by 365 (days in 1 year) to become CPZ-EQ cumulative dose during the treatment period in days.

By the study with mostly previously treated patients with the 'baseline CPZ-EQ/d' and 'change in medication dose' reported, we calculated the dose at the follow-up date and multiplied by the duration of the follow-up in days (without any titration period, as 56% of all included patients were treated previously (James et al., 2004)).

10. Assessment of risk of bias in included studies

The possibility of small publication biases in the present study was examined by visually inspecting funnel plots and applying the regression intercept of Egger (Egger et al., 1997). In this way we assessed whether there was a tendency for selective publication of studies based on the nature and direction of their results. In addition, we used the fail-safe procedure (Orwin, 1983), to generate a number of unpublished studies that would be needed to move estimates to a non significant threshold. In case of publication bias we adopted the 'trim and fill' method, which aims both to identify and correct for funnel plot asymmetry arising from publication bias (Duval and Tweedie, 2000).

11. Dealing with missing data

In case of missing data we contacted the corresponding author of each study to collect the requested information (see acknowledgments).

12. Assessment of heterogeneity

Heterogeneity among study point estimates was assessed with the Q statistics (Paulson and Bazemore, 2010) with magnitude of heterogeneity being evaluated with the I^2 index (Lipsey and Wilson, 2000). For homogeneous data, we calculated the global effect size, using a fixed effect model. In the absence of significant heterogeneity, the use of a fixed effect model is legitimate and may provide greater statistical power than the random effect model (Szoke et al., 2008). For heterogeneous data we employed random effects models which are more conservative than fixed-effect models, and appear to better address heterogeneity between studies and study populations, allowing for greater flexibility in parsing effect size variability (Cooper et al., 2009).

13. Sensitivity analysis

To assess the robustness of the results, we performed sensitivity analyses by sequentially removing each study and rerunning the analysis. We also conducted a separate analysis excluding studies with quality ratings in the lowest third to determine if potential methodological weaknesses influenced meta-analytic estimates.

S2. Supplementary table

The categories scored in the quality assessment and the range according to the reported data.

Category / range	0	1	2
Study design	Case-control	Open	Random-blind
Funding - role in analysis and interpretation of data	Company producing studied drug or missing	Could have	Non
Sample size *	>20	12-20	<12
Inclusion criteria	Not reported	Partly reported	Reported
Exclusion criteria + substance abuse	Not reported	Only one reported	Reported
Control group	Not included	.	Included
Gender	Not reported	.	Reported
Race /ethnic origin	Not reported	.	Reported
IQ/ educational level	Not reported	Parental education reported	Reported
Duration of illness /age of onset	Not reported	.	Reported
Previous antipsychotic medication (PAM)	Not defined	.	Defined
Duration of PAM	Not defined	.	Defined
Drop-out rate	Not reported	.	Reported
Psychopathology reported	Not reported	.	Reported
Threshold reported	Not reported	.	Reported
WB: MNI/Tal coor and/or ROI: interrater reliability	Not reported	.	Reported
max 32. **high** (80-100%) >25, **moderate-high** (60-79%): 19.5-25, **moderate** (40-59%): 12.5-19, **moderate-low** (20-39%): 6.5-12, **low** (0-19%) <6			

* One group >20 + other group <20 (1.5), one group >12 + other group <20 (0.5)

Abbreviations: PAM, previous antipsychotic medication; ROI, region of interest; WB, whole brain

S3. Supplementary table

The quality assessment of the included studies and the rating of the studies.

Author Year	Study design	Role of funding	Sample size	Inclusion criteria	Exclusion criteria + substance abuse	Control group	Gender	Race /ethnic origin	IQ/ education	Duration of illness /age of onset	PAM	Duration of PAM	Drop-out rate	Psychopathology	Threshold reported	MNI/Tal and/or ROI reliability	Sum of the scores & category	
Arango 2012(Arango et al., 2012)	1	2	2	2	2	2	2	2	1	2	2	2	2	0	0	2	24	HIGH
Boonstra 2011(Boonstra et al., 2011)	2	0	0	2	1	2	2	0	2	2	2	0	0	1	0	2	16	MODERATE
Chakos 1994(Chakos et al., 1994)	0	2	1.5	2	2	2	2	2	0	0	0	2	0	0	0	0	15.5	MODERATE
Crespo-Facorro 2008(Crespo-Facorro et al., 2008)	2	2	1.5	2	2	2	2	0	0	2	2	2	2	2	0	2	23.5	HIGH
DeLisi 2004(DeLisi et al., 2004)	0	2	2	1	0	2	2	0	0	2	0	0	2	2	0	2	15	MODERATE
Frazier 1996(Frazier et al., 1996)	2	0	0	2	0	2	2	0	0	2	2	2	2	0	0	0	16	MODERATE
Garver 2005(Garver et al., 2005)	1	0	0.5	2	2	2	2	0	0	0	0	0	0	2	0	2	11.5	MODERATE
Gur 1998(Gur et al., 1998)	0	0	1.5	1	1	2	2	0	0	0	2	2	2	1	0	0	14.5	MODERATE
Heitmiller 2004(Heitmiller et al., 2004)	1	2	1	0	0	2	2	0	0	2	2	0	0	0	0	2	12	MODERATE
Ho 2011(Ho et al., 2011)	1	2	2	2	0	0	2	0	0	2	2	2	2	2	0	2	19	MODERATE-HIGH
Ho 2003(Ho et al., 2003)	1	2	2	0	0	2	2	0	0	2	2	2	0	2	0	2	17	MODERATE
James 2004(James et al., 2004)	0	2	1	2	0	2	2	2	0	0	0	0	0	2	0	2	13	MODERATE
Keshavan 1994(Keshavan et al., 1994)	0	0	1	0	0	0	0	0	0	2	2	2	0	0	0	0	7	MODERATE-LOW
Lang 2004(Lang et al., 2004)	1	0	1.5	0	2	2	2	0	0	0	2	0	2	2	0	2	14.5	MODERATE
Lieberman 2005(Lieberman et al., 2005)	2	0	2	2	2	2	2	2	0	2	2	2	2	2	2	2	26	HIGH
Massana 2005(Massana et al., 2005)	1	2	0	2	0	0	0	0	0	0	0	0	0	0	2	2	7	MODERATE-LOW
McClure 2008(McClure et al., 2008)	0	1	0	2	2	1	2	2	2	2	2	2	0	0	2	2	20	MODERATE-HIGH
Molina 2005(Molina et al., 2005)	0	2	1.5	2	2	2	2	2	0	0	1	1	0	2	0	2	17.5	MODERATE-HIGH
Nakamura 2007(Nakamura et al., 2007)	0	2	1.5	2	2	2	2	0	2	0	2	2	0	2	0	2	19.5	MODERATE-HIGH
Puri 2001(Puri et al., 2001)	0	2	1.5	0	0	2	0	0	0	2	2	2	0	0	2	0	13.5	MODERATE
Reig 2009(Reig et al., 2009)	0	2	2	2	2	2	2	2	2	2	2	2	2	2	0	2	26	HIGH
Saijo 2001(Saijo et al., 2001)	0	2	1	2	2	2	2	0	2	2	0	0	0	0	0	2	15	MODERATE
Scheepers 2001(Scheepers et al., 2001)	0	0	2	2	2	0	2	0	0	2	1	2	2	0	0	2	15	MODERATE
Sporn 2003(Sporn et al., 2003)	0	0	2	2	2	2	2	2	0	0	2	0	0	2	0	2	16	MODERATE
Takahashi 2009(Takahashi et al., 2009)	0	2	1.5	2	2	2	2	0	2	2	2	2	0	2	0	2	21.5	MODERATE-HIGH
Tauscher-Wisniewski 2005(Tauscher-Wisniewski et al., 2005)	0	0	1.5	0	0	2	0	0	0	2	2	0	0	0	0	2	7.5	MODERATE-LOW
Tauscher-Wisniewski 2002(Tauscher-Wisniewski et	1	0	1	0	0	2	2	0	0	0	2	2	0	0	0	2	10	MODERATE-LOW

al., 2002)																		
Taylor 2005(Taylor et al., 2005)	0	2	0	2	2	2	0	0	0	1	0	0	0	2	0	2	11	MODERATE
van Haren 2008(van Haren et al., 2008)	1	0	2	0	0	2	2	0	2	2	0	0	2	1	0	2	14	MODERATE
Whitworth 2005(Whitworth et al., 2005)	0	0	2	1	0	2	2	2	0	2	1	0	1	2	0	2	15	MODERATE-HIGH

Abbreviations: PAM, previous antipsychotic medication; ROI, region of interest

S4. Supplementary table

Excluded studies which full text was inspected and the reason why they were excluded.

Author & Year	Reason why excluded
Arango 2008	Cross-sectional study
Bakalar 2009	Cortical thickness
Cahn 2002	Overlap with van Haren 2008
Cahn 2009	Overlap with van Haren 2008
Chakos 1995	Overlap with Chakos 1994
Christensen 2004	Overlap with Garver 2005
Corson 1999	Overlap with Heitmiller 2004
Crespo-Facorro 2004	No relevant regions
Dazzan 2005	Cross-sectional study, VBM
DeLisi 2005	No relevant regions - only STG
DeLisi 1997	Overlap with De Lisi 2004
Douaud 2009	VBM
Ehrlich 2011	Cross-sectional study
Girgis 2006	VBM
Gogtay 2004	Overlap with Sporn 2003
Gur 1998	Cross-sectional study
James 2002	Overlap with James 2004
Kasai 2003	No relevant regions + MEDI + DOI
Keshavan 1998	Cross-sectional study
Lang 2001	Cross-sectional study
Lieberman 2001	Overlap with Lieberman 2005
Mathalon 2001	ICV, no WBV + MEDI
McClure 2006	Overlap with McClure 2008
McCormick 2005	No relevant regions
Nair 1997	No relevant regions
Pressler 2005	No relevant regions
Rapoport 1999 & 1997	Overlap with Sporn 2003
Stip 2008	GMD + MEDI
Theberge 2007	VBM
Thompson 2009	Overlap with Lieberman 2005
van Haren 2007	Overlap with Haren 2008 + VBM
Vidal 2006	Gray and white matter cortical maps
Whitford 2006	VBM
Wood 2001	Overlap with Takahashi 2009

S5. Supplementary table

Included studies with treatment duration, original dose, and calculated cumulative doses in chlorpromazine equivalents.

Author & Year	Type of antipsychotic	Schizophrenia patients N + subgroups	Length of treatment in weeks	SD - length of treatment in weeks	Daily CPZ Eq.	SD - daily CPZ Eq.	Cumulative CPZ Eq. during the interval between MRIs (10^3 units)	SD -cumulative CPZ Eq.
Arango 2012(Arango et al., 2012)	MIX	25	104.80	12.00	209.18	NA	168.57	90011
Boonstra 2011(Boonstra et al., 2011)	ATYP	8 FE AF	57.27	8.55	190.20	NA	62.87	NA
	ATYP	8 FE	54.00	0.84	176.60	NA	29.75	NA
Chakos 1994(Chakos et al., 1994)	TYP	29	72.00	NA	1363.63	NA	687.27	NA
Crespo-Facorro 2008(Crespo-Facorro et al., 2008)	TYP	18 Hal	54.60	4.60	244.09	NA	11.68	NA
	ATYP	18 Olan	55.30	4.20	289.02	NA	14.04	NA
	ATYP	16 Risp	53.70	3.50	183.65	NA	8.63	NA
DeLisi 2004(DeLisi et al., 2004)	MIX	26	520.00	NA	.	.		.
Frazier 1996(Frazier et al., 1996)	CLOZ/MIX	8	104.00	NA	377.00	NA	269.18	NA
Garver 2005(Garver et al., 2005)	TYP	6	4.00	NA	760.00	NA	21.28	NA
	ATYP	13	4.00	NA	272.80	NA	7.64	NA
Gur 1998(Gur et al., 1998)	MIX	20 FE	69.60	32.40	259.90	165.6	126.62	NA
	MIX	20 Ch	78.80	56.40	515.30	224.00	284.24	NA
Heitmiller 2004(Heitmiller et al., 2004)	ATYP	14	120.80	NA	297.32	NA	269.37	NA
Ho 2011(Ho et al., 2011)	MIX	211	374.40	202.80	91.65	220.45	240.19	NA
Ho 2003(Ho et al., 2003)	MIX	73	171.00	83.20	462.20	NA	556.12	494284.50
James 2004(James et al., 2004)	CLOZ/ATYP	9 M	130.00	NA	175.00	NA	159.25	NA
	CLOZ/ATYP	7 F	130.00	NA	140.00	NA	127.40	NA
Keshavan 1994(Keshavan et al., 1994)	TYP	11	43.57	NA	121.80	NA	37.15	NA
Lang 2004(Lang et al., 2004)	ATYP	10	56.00	17.10	170.00	64.00	64.26	NA
	ATYP	14	52.10	6.90	84.00	52.00	30.63	NA
	ATYP	13	42.20	12.10	150.00	10.70	42.21	NA
Lieberman 2005(Lieberman et al., 2005)	TYP	79	52.00	NA	202.70	NA	73.78	NA
	ATYP	82	52.00	NA	250.00	NA	91.00	NA
Massana 2005(Massana et al.,	ATYP	11	9.00	NA	458.33	NA	28.87	NA

2005)								
McClure 2008(McClure et al., 2008)	ATYP/CLOZ	10	12.00	NA	534.10	NA	37.39	NA
Molina 2005(Molina et al., 2005)	ATYP	49	102.40	39.60	378.80	151.5	266.22	NA
	CLOZ	29Ch	114.80	47.20	240.70	204.6	190.06	NA
Nakamura 2007(Nakamura et al., 2007)	ATYP	17 FE	72.40	46.40	252.00	NA	124.19	NA
Puri 2001(Puri et al., 2001)	MIX	24	22.69	NA	388.39	NA	61.69	NA
Reig 2009(Reig et al., 2009)	CLOZ/ATYP	21	104.00	NA	.	.	.	.
Saijo 2001(Saijo et al., 2001)	TYP	18	520.00	NA	2255.40	NA	8178.08	NA
Scheepers 2001(Scheepers et al., 2001)	CLOZ	29	24.00	NA	320.00	NA	49.28	NA
Sporn 2003(Sporn et al., 2003)	MIX	39	176.80	72.80	384.26	NA	470.18	NA
Takahashi 2009(Takahashi et al., 2009)	MIX	23 FE	105.04	39.52	193.50	198.9	139.57	NA
	MIX	11Ch	125.32	50.44	626.00	NA	540.39	NA
Tauscher-Wisniewski 2005(Tauscher-Wisniewski et al., 2005)	ATYP	14	12.00	NA	347.89	NA	24.35	NA
Tauscher-Wisniewski 2002(Tauscher-Wisniewski et al., 2002)	MIX	15	260.00	NA	353.33	NA	638.11	NA
Taylor 2005(Taylor et al., 2005)	MIX	11	4.00	.	.	.	.	.
van Haren 2008(van Haren et al., 2008)	MIX	96	260.00	NA	338.68	156.92	611.66	NA
Whitworth 2005(Whitworth et al., 2005)	MIX	21 FE	132.10	41.60	.	.	.	.
	MIX	17Ch	171.10	63.40	.	.	.	.

. missing data

Abbreviations: AF, antipsychotic free; ATYP, atypical antipsychotic, CLOZ, clozapine; Ch, chronic; CPZ Eq., chlorpromazine equivalent; F, female; FE, first episode; GM, gray matter; Hal, haloperidol; M, male; MIX, both typical and atypical antipsychotics; N, amount of individuals; NA, not announced; Ola, olanzapine; Ris, risperidone; TYP, typical antipsychotic.

S6. Supplementary table

Included studies with duration of illness and measures of clinical symptoms.

Author & Year	SCZ N + subgroups	DOI in weeks at baseline (SD)	PANSS Total baseline (SD)	PANSS Total follow-up (SD)	BPRS Total baseline (SD)	BPRSS Total follow-up (SD)	SAPS+SANS baseline (SD)	SAPS+SANS follow-up (SD)	Mean per-item score baseline	Mean per-item score follow-up	% of baseline per-item
Arango 2012(Arango et al., 2012)	25	17.20 (10.60)	91.60 (16.40)	59.63 (NA)	.	.	.	.	2.05	0.99	48
Boonstra 2011(Boonstra et al., 2011)	8 FE AF	172.10 (NA)	45.85	.	.	.	.	.	0.53	.	.
	8 FE		49.26	.	.	.	.	.	0.64	.	.
Chakos 1994(Chakos et al., 1994)	29	.	.	.	.	.	.	.	.	.	.
Crespo-Facorro 2008(Crespo-Facorro et al., 2008)	18 Hal	103.20 (111.20)	.	.	.	.	17.73 (NA)	5.35 (NA)	0.35	0.11	30
	18 Olan	91.60 (120.80)	.	.	.	.	19.56 (NA)	6.28 (NA)	0.39	0.13	32
	16 Risp	118.00 (104.40)	.	.	.	.	22.45 (NA)	7.20 (NA)	0.45	0.14	32
DeLisi 2004(DeLisi et al., 2004)	26	104.00 (NA)	.	.	40.12 (11.24)	32.60 (12.85)	.	.	1.23	0.81	66
Frazier 1996(Frazier et al., 1996)	8	239.00 (NA)	.	.	.	.	.	.	.	.	.
Garver 2005(Garver et al., 2005)	6	.	.	.	.	.	81.30 (NA)	40.70 (NA)	1.63	0.81	50
	13	.					90.60 (NA)	33.80 (NA)	1.81	0.68	37
Gur 1998(Gur et al., 1998) *	20 FE	145.60 (197.60)	.	.	.	.	.	.	.	.	54
	20 C	442.00 (286.00)	.	.	.	.	.	.	.	.	70
Heitmiller 2004(Heitmiller et al., 2004)	14	184.00 (201.4)	.	.	.	.	.	.	.	.	.
Ho 2011(Ho et al., 2011)	211	22.46 (NA)	.	.	.	.	.	.	.	.	.
Ho 2003(Ho et al., 2003)	73	104.00 (NA)	.	.	.	.	.	.	.	.	.
James 2004(James et al., 2004)	9 M	.	73.89 (7.68)	54.78 (NA)	.	.	.	.	1.46	0.83	56
	7 F	.	68.50 (5.58)	50.36 (NA)	.	.	.	.	1.28	0.68	53
Keshavan 1994(Keshavan et al., 1994)	11	.	.	.	.	.	.	.	.	.	.
Lang 2004(Lang et al., 2004)	10	577.30 (478.50)	64.60 (15.80)	59.40 (16.10)	.	.	.	.	1.15	0.98	85
	14	38.50 (16.10)	49.90 (18.50)	48.50 (19.10)	.	.	.	.	0.66	0.62	93
	13	58.50 (15.40)	67.20 (23.10)	56.20 (13.70)	.	.	.	.	1.24	0.87	70
Lieberman 2005(Lieberman et al., 2005)	79	77.33 (61.10)	73.57 (17.50)	59.35 (16.63)	.	.	.	.	1.45	0.98	67
	82	54.11 (50.70)	75.90 (18.10)	55.85 (16.52)	.	.	.	.	1.53	0.86	56
Massana 2005(Massana et al., 2005)	11	.	.	.	.	.	.	.	.	.	.

McClure 2008(McClure et al., 2008)	10	551.20 (NA)	.	.	.	.	.	.	.	.	.
Molina 2005(Molina et al., 2005)	49	119.60 (5.60)	.	.	.	.	61.30 (NA)	52.50 (NA)	1.23	1.05	86
	29Ch	395.20 (208.00)	.	.	.	.	68.00 (NA)	38.10 (NA)	1.36	0.76	56
Nakamura 2007(Nakamura et al., 2007)	17 FE	3 (NA)	.	.	41.50 (13.70)	27.80 (6.70)	.	.	1.31	0.54	42
Puri 2001(Puri et al., 2001)	24	59.69 (94.22)	.	.	.	.	.	.	.	.	.
Reig 2009(Reig et al., 2009)	21	12.80 (12.00)	86.90 (18.40)	58.30 (16.20)	.	.	.	.	1.90	0.94	50
Saijo 2001(Saijo et al., 2001)	18	785.20 (301.60)	.	.	.	.	.	.	.	.	.
Scheepers 2001(Scheepers et al., 2001)	29	638.00 (456.40)	78.00 (NA)	61.00 (NA)	.	.	.	.	1.60	1.03	65
Sporn 2003(Sporn et al., 2003)	39	239.20 (104.00)	.	.	.	.	103.10 (NA)	61.40 (NA)	2.06	1.23	60
Takahashi 2009(Takahashi et al., 2009)	23 FE	9.36 (14.56)	84.80 (NA)	80.00 (NA)	.	.	.		1.83	1.67	91
	11Ch	624.00 (361.90)	76.20 (NA)	64.60 (NA)	.	.	.		1.54	1.15	75
Tauscher-Wisniewski 2005(Tauscher-Wisniewski et al., 2005)	14	59.60 (71.20)	82.60 (7.90)	54.50 (9.90)	.	.	.	.	1.75	0.82	47
Tauscher-Wisniewski 2002(Tauscher-Wisniewski et al., 2002)	15	.	.	.	.	.	.	.	.	.	.
Taylor 2005(Taylor et al., 2005)	11	.	.	.	.	.	.	.	.	.	.
van Haren 2008(van Haren et al., 2008)	96	569.40 (532.00)	70.81 (16.40)	53.71 (16.26)	.	.	.	.	1.36	0.79	58
Whitworth 2005(Whitworth et al., 2005)	21 FE	33.20 (70.80)	122.90 (21.39)	62.76 (24.17)	.	.	.	.	3.10	1.09	35
	17Ch	374.80 (290.40)	115.06 (33.85)	66.50 (17.19)	.	.	.	.	2.84	1.22	43

* Published the severity ratings on the SANS and SAPS

. missing data

Abbreviations: AF, antipsychotic free; BPRS, Brief Psychiatric Rating Scale; Ch, chronic; DOI, duration of illness at the baseline; F, female; FE, first episode; Hal, haloperidol; M, male; MIX, both typical and atypical antipsychotics; NA, not announced; Ola, olanzapine; PANSS, Positive and Negative Symptom Scale; Ris, risperidone; SAPS, Scale for Assessment of Positive Symptoms; SANS, Scale for Assessment of Negative Symptoms; SCZ N, number of schizophrenia patients; SD, standard deviation.

REFERENCES

Andreasen, N.C., Pressler, M., Nopoulos, P., Miller, D., Ho, B.C., 2010. Antipsychotic dose equivalents and dose-years: a standardized method for comparing exposure to different drugs. Biol Psychiatry 67, 255-262.

Arango, C., Rapado-Castro, M., Reig, S., Castro-Fornieles, J., González-Pinto, A., Otero, S., Baeza, I., Moreno, C., Graell, M., Janssen, J., Parellada, M., Moreno, D., Bargalló, N., Desco, M., 2012. Progressive brain changes in children and adolescents with first-episode psychosis. Arch Gen Psychiatry 69, 16-26.

Boonstra, G., van Haren, N.E., Schnack, H.G., Cahn, W., Burger, H., Boersma, M., de Kroon, B., Grobbee, D.E., Hulshoff Pol, H.E., Kahn, R.S., 2011. Brain volume changes after withdrawal of atypical antipsychotics in patients with first-episode schizophrenia. J Clin Psychopharmacol 31, 146-153.

Chakos, M.H., Lieberman, J.A., Bilder, R.M., Borenstein, M., Lerner, G., Bogerts, B., Wu, H., Kinon, B., Ashtari, M., 1994. Increase in caudate nuclei volumes of first-episode schizophrenic patients taking antipsychotic drugs. Am J Psychiatry 151, 1430-1436.

Cooper, H., Hedges, L., Valentine, J., 2009. Handbook of Research Synthesis and Meta-Analysis. Russell Sage Foundation, New York.

Crespo-Facorro, B., Roiz-Santiáñez, R., Pérez-Iglesias, R., Pelayo-Terán, J.M., Rodríguez-Sánchez, J.M., Tordesillas-Gutiérrez, D., Ramírez, M., Martínez, O., Gutiérrez, A., de Lucas, E.M., Vázquez-Barquero, J.L., 2008. Effect of antipsychotic drugs on brain morphometry. A randomized controlled one-year follow-up study of haloperidol, risperidone and olanzapine. Prog Neuropsychopharmacol Biol Psychiatry 32, 1936-1943.

DeLisi, L.E., Sakuma, M., Maurizio, A.M., Relja, M., Hoff, A.L., 2004. Cerebral ventricular change over the first 10 years after the onset of schizophrenia. Psychiatry Res 130, 57-70.

Duval, S., Tweedie, R., 2000. Trim and fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. Biometrics 56, 455-463.

Egger, M., Davey Smith, G., Schneider, M., Minder, C., 1997. Bias in meta-analysis detected by a simple, graphical test. BMJ 315, 629-634.

Frazier, J.A., Giedd, J.N., Kaysen, D., Albus, K., Hamburger, S., Alaghband-Rad, J., Lenane, M.C., McKenna, K., Breier, A., Rapoport, J.L., 1996. Childhood-onset schizophrenia: brain MRI rescan after 2 years of clozapine maintenance treatment. Am J Psychiatry 153, 564-566.

Garver, D.L., Holcomb, J.A., Christensen, J.D., 2005. Cerebral cortical gray expansion associated with two second-generation antipsychotics. Biol Psychiatry 58, 62-66.

Gur, R.E., Cowell, P., Turetsky, B.I., Gallacher, F., Cannon, T., Bilker, W., Gur, R.C., 1998. A follow-up magnetic resonance imaging study of schizophrenia. Relationship of neuroanatomical changes to clinical and neurobehavioral measures. Arch Gen Psychiatry 55, 145-152.

Heitmiller, D.R., Nopoulos, P.C., Andreasen, N.C., 2004. Changes in caudate volume after exposure to atypical neuroleptics in patients with schizophrenia may be sex-dependent. Schizophr Res 66, 137-142.

Ho, B.C., Andreasen, N.C., Nopoulos, P., Arndt, S., Magnotta, V., Flaum, M., 2003. Progressive structural brain abnormalities and their relationship to clinical outcome: a longitudinal magnetic resonance imaging study early in schizophrenia. Arch Gen Psychiatry 60, 585-594.

Ho, B.C., Andreasen, N.C., Ziebell, S., Pierson, R., Magnotta, V., 2011. Long-term antipsychotic treatment and brain volumes: a longitudinal study of first-episode schizophrenia. Arch Gen Psychiatry 68, 128-137.

James, A.C., James, S., Smith, D.M., Javaloyes, A., 2004. Cerebellar, prefrontal cortex, and thalamic volumes over two time points in adolescent-onset schizophrenia. Am J Psychiatry 161, 1023-1029.
Keshavan, M.S., Bagwell, W.W., Haas, G.L., Sweeney, J.A., Schooler, N.R., Pettegrew, J.W., 1994. Changes in caudate volume with neuroleptic treatment. Lancet 344, 1434.
Lang, D.J., Kopala, L.C., Vandorpe, R.A., Rui, Q., Smith, G.N., Goghari, V.M., Lapointe, J.S., Honer, W.G., 2004. Reduced basal ganglia volumes after switching to olanzapine in chronically treated patients with schizophrenia. Am J Psychiatry 161, 1829-1836.
Lieberman, J.A., Alvir, J.M., Woerner, M., Degreef, G., Bilder, R.M., Ashtari, M., Bogerts, B., Mayerhoff, D.I., Geisler, S.H., Loebel, A., et al., 1992. Prospective study of psychobiology in first-episode schizophrenia at Hillside Hospital. Schizophr Bull 18, 351-371.
Lieberman, J.A., Tollefson, G.D., Charles, C., Zipursky, R., Sharma, T., Kahn, R.S., Keefe, R.S., Green, A.I., Gur, R.E., McEvoy, J., Perkins, D., Hamer, R.M., Gu, H., Tohen, M., Group, H.S., 2005. Antipsychotic drug effects on brain morphology in first-episode psychosis. Arch Gen Psychiatry 62, 361-370.
Lipsey, M., Wilson, D., 2000. Practical Meta-analysis. Sage Publications, Thousand Oaks, CA.
Massana, G., Salgado-Pineda, P., Junqué, C., Pérez, M., Baeza, I., Pons, A., Massana, J., Navarro, V., Blanch, J., Morer, A., Mercader, J.M., Bernardo, M., 2005. Volume changes in gray matter in first-episode neuroleptic-naive schizophrenic patients treated with risperidone. J Clin Psychopharmacol 25, 111-117.
Mattis, P., Kimball, S., 2008. Gimp, the GNU image manipulation program.
McClure, R.K., Carew, K., Greeter, S., Maushauer, E., Steen, G., Weinberger, D.R., 2008. Absence of regional brain volume change in schizophrenia associated with short-term atypical antipsychotic treatment. Schizophr Res 98, 29-39.
Molina, V., Reig, S., Sanz, J., Palomo, T., Benito, C., Sánchez, J., Sarramea, F., Pascau, J., Desco, M., 2005. Increase in gray matter and decrease in white matter volumes in the cortex during treatment with atypical neuroleptics in schizophrenia. Schizophr Res 80, 61-71.
Nakamura, M., Salisbury, D.F., Hirayasu, Y., Bouix, S., Pohl, K.M., Yoshida, T., Koo, M.S., Shenton, M.E., McCarley, R.W., 2007. Neocortical gray matter volume in first-episode schizophrenia and first-episode affective psychosis: a cross-sectional and longitudinal MRI study. Biol Psychiatry 62, 773-783.
Orwin, R., 1983. A fail-safe N for effect size in meta-analysis. J Edu Stat 8, 157-159.
Paulson, J.F., Bazemore, S.D., 2010. Prenatal and postpartum depression in fathers and its association with maternal depression: a meta-analysis. JAMA 303, 1961-1969.
Puri, B.K., Hutton, S.B., Saeed, N., Oatridge, A., Hajnal, J.V., Duncan, L., Chapman, M.J., Barnes, T.R., Bydder, G.M., Joyce, E.M., 2001. A serial longitudinal quantitative MRI study of cerebral changes in first-episode schizophrenia using image segmentation and subvoxel registration. Psychiatry Res 106, 141-150.
Reig, S., Moreno, C., Moreno, D., Burdalo, M., Janssen, J., Parellada, M., Zabala, A., Desco, M., Arango, C., 2009. Progression of brain volume changes in adolescent-onset psychosis. Schizophr Bull 35, 233-243.
Saijo, T., Abe, T., Someya, Y., Sassa, T., Sudo, Y., Suhara, T., Shuno, T., Asai, K., Okubo, Y., 2001. Ten year progressive ventricular enlargement in schizophrenia: an MRI morphometrical study. Psychiatry Clin Neurosci 55, 41-47.
Scheepers, F.E., de Wied, C.C., Hulshoff Pol, H.E., van de Flier, W., van der Linden, J.A., Kahn, R.S., 2001. The effect of clozapine on caudate nucleus volume in schizophrenic patients previously treated with typical antipsychotics. Neuropsychopharmacology 24, 47-54.

Sherwood, M., Thornton, A.E., Honer, W.G., 2006. A meta-analysis of profile and time-course of symptom change in acute schizophrenia treated with atypical antipsychotics. Int J Neuropsychopharmacol 9, 357-366.
Sporn, A.L., Greenstein, D.K., Gogtay, N., Jeffries, N.O., Lenane, M., Gochman, P., Clasen, L.S., Blumenthal, J., Giedd, J.N., Rapoport, J.L., 2003. Progressive brain volume loss during adolescence in childhood-onset schizophrenia. Am J Psychiatry 160, 2181-2189.
Szoke, A., Trandafir, A., Dupont, M.E., Meary, A., Schurhoff, F., Leboyer, M., 2008. Longitudinal studies of cognition in schizophrenia: meta-analysis. Br J Psychiatry 192, 248-257.
Takahashi, T., Wood, S.J., Soulsby, B., McGorry, P.D., Tanino, R., Suzuki, M., Velakoulis, D., Pantelis, C., 2009. Follow-up MRI study of the insular cortex in first-episode psychosis and chronic schizophrenia. Schizophr Res 108, 49-56.
Tauscher-Wisniewski, S., Tauscher, J., Christensen, B.K., Mikulis, D.J., Zipursky, R.B., 2005. Volumetric MRI measurement of caudate nuclei in antipsychotic-naive patients suffering from a first episode of psychosis. J Psychiatr Res 39, 365-370.
Tauscher-Wisniewski, S., Tauscher, J., Logan, J., Christensen, B.K., Mikulis, D.J., Zipursky, R.B., 2002. Caudate volume changes in first episode psychosis parallel the effects of normal aging: a 5-year follow-up study. Schizophr Res 58, 185-188.
Taylor, S., Christensen, J.D., Holcomb, J.M., Garver, D.L., 2005. Volume increases in striatum associated with positive symptom reduction in schizophrenia: a preliminary observation. Psychiatry Res 140, 85-89.
van Haren, N.E., Hulshoff Pol, H.E., Schnack, H.G., Cahn, W., Brans, R., Carati, I., Rais, M., Kahn, R.S., 2008. Progressive brain volume loss in schizophrenia over the course of the illness: evidence of maturational abnormalities in early adulthood. Biol Psychiatry 63, 106-113.
Whitworth, A.B., Kemmler, G., Honeder, M., Kremser, C., Felber, S., Hausmann, A., Walch, T., Wanko, C., Weiss, E.M., Stuppaeck, C.H., Fleischhacker, W.W., 2005. Longitudinal volumetric MRI study in first- and multiple-episode male schizophrenia patients. Psychiatry Res 140, 225-237.