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REVIEW ARTICLE

Do antipsychotic drugs affect brain structure? A systematic and critical review of MRI findings

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Background. The potential effects of antipsychotic drugs on brain structure represent a key factor in understanding neuroanatomical changes in psychosis. This review addresses two issues: (1) do antipsychotic medications induce changes in total or regional human brain volumes and (2) do such effects depend on antipsychotic type?

Method. A systematic review of studies reporting structural brain magnetic resonance imaging (MRI) measures: (1) directly in association with antipsychotic use; and (2) in patients receiving lifetime treatment with antipsychotics in comparison with drug-naive patients or healthy controls. We searched Medline and EMBASE databases using the medical subject heading terms: 'antipsychotics' AND 'brain' AND (MRI NOT functional). The search included studies published up to 31 January 2007. Wherever possible, we reported the effect size of the difference observed.

Results. Thirty-three studies met our inclusion criteria. The results suggest that antipsychotics act regionally rather than globally on the brain. These volumetric changes are of a greater magnitude in association with typical than with atypical antipsychotic use. Indeed, there is evidence of a specific effect of antipsychotic type on the basal ganglia, with typicals specifically increasing the volume of these structures. Differential effects of antipsychotic type may also be present on the thalamus and the cortex, but data on these and other brain areas are more equivocal.

Conclusions. Antipsychotic treatment potentially contributes to the brain structural changes observed in psychosis. Future research should take into account these potential effects, and use adequate sample sizes, to allow improved interpretation of neuroimaging findings in these disorders.

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Key words: Antipsychotic drugs, brain, MRI, psychosis.

Introduction

Regardless of which causes are involved in the aetiopathogenesis of psychoses, antipsychotic drugs are effective, to some extent, in alleviating the symptoms of these severe and incapacitating disorders (Seeman, 2005).

Antipsychotic drugs mostly target the dopamine D_2 receptors, and specific pharmacodynamic interactions depend on drug class (Seeman, 2002). Typical 'haloperidol-like' molecules act as dopamine D_2 receptor antagonists in the mesolimbic and mesostriatal regions. Atypical 'clozapine-like' compounds reduce dopaminergic activity in the mesolimbic system, by blocking D_1 and D_2 receptors, and have higher affinity for serotonin 5-hydroxytryptamine type 2 receptors than for D_2 receptors. Despite clinical evidence of different side-effects profiles of atypical compared to typical antipsychotics, their mechanisms of action are not fully understood.

Studies on animals, mostly rodents, suggest that antipsychotics can affect neuronal structure and function through neuroplasticity, neurotoxicity, gene expression and apoptosis (Dean, 2006). Conventional antipsychotics may be neurotoxic and induce neuronal loss and gliosis in the striatum, hypothalamus, brainstem, limbic system and cortex. Moreover, apoptosis has been documented with *in vivo* administration of haloperidol in the substantia nigra, caudate and putamen (Dean, 2006). A study of non-human primates showed that chronic therapeutic-like daily exposure to either the typical antipsychotic haloperidol or the atypical olanzapine is associated with reductions in both grey and white matter (Dorph-Petersen *et al*. 2005).

Morphological changes in brain structures, such as lateral and third ventricle enlargement and temporal regions reductions, have been reported in patients with chronic schizophrenia (Lawrie & Abukmeil, 1998;

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Table 1. *Cross-sectional studies presented in chronological order*[a]

Reference	Antipsychotic (type, dose)	Main findings
Dazzan *et al.* 2005	Typicals (32 patients): mean dose in chlorpromazine equivalents = 269 ± 245 mg/day Atypicals (30 patients): 21 on olanzapine, 14 mg/day; 5 on risperidone, 4 mg/day; 2 on quetiapine, 400 mg/day; 1 on sertindole, 16 mg/day; 1 on amisulpiride, 400 mg/day Drug-free (22 patients)	Typical *versus* drug free: putamen ↑ with typicals and ↓ frontal areas, temporal-insular areas and precuneus ($p \leqslant 0.002$) Atypical *versus* drug free: ↑ thalamus with atypicals ($p = 0.002$) Typical *versus* atypical: ↓ left middle temporal gyrus with typicals ($p = 0.002$)
Narr *et al.* 2005	Atypicals (33 patients): either olanzapine or risperidone	Patients *versus* controls: in patients ↓ cortical thickness within cingulate, occipitals and frontopolar cortices
Chakos *et al.* 2005	(*a*) Typicals (17 patients): haloperidol Atypicals (15 patients): 12 on olanzapine, 3 on risperidone Typicals and atypicals (1 patient): clozapine and molindone Unknown (1 patient)	(*a*) Atypical *versus* typical: ↑ hippocampal volumes with atypicals ($d = 1.3$, $r = 0.56$)
	(*b*) Typicals (5 patients): 3 on haloperidol, 1 on trifluoperazine, 1 on thiothixene Atypicals (15 patients): 6 on olanzapine, 8 on clozapine, 3 on risperidone	(*b*) Atypical *versus* typical: = hippocampal volumes ($F = 0.54$, $p = 0.48$)
Deicken *et al.* 2002	Mean dose in chlorpromazine equivalents = 613.6 ± 649.7 mg/day	No correlation between thalamic volume and current antipsychotic dose
Nopoulos *et al.* 2001	Cumulative antipsychotic exposure at the time of the MRI as chlorpromazine equivalents = mean dose of 40.59 ± 94.699 mg, range 0–524	If ↑ the antipsychotic exposure then ↓ the midbrain area ($r = -0.42$, $p = 0.002$)
Gur *et al.* 2000	Typicals: 24 patients Atypicals: 6 patients Typicals followed by atypicals: 11 patients	Naive *versus* previously treated patients: = prefrontal cortex volume
Velakoulis *et al.* 1999	Total antipsychotic dose in chlorpromazine equivalents: – for long-term treated patients: 21018 ± 16153 mg (mean daily dose: 656 ± 431) – for short-term treated patients: 5384 ± 7983 mg (mean daily dose: 164 ± 107)	Chronic schizophrenia patients *versus* controls: ↓ hippocampal volumes in patients (right side: $r = 0.5$, left side: $r = 0.4$) First-episode psychosis patients *versus* controls: ↓ hippocampal volumes in patients (right side: $r = 0.4$, left side: $r = 0.5$) Chronic schizophrenia patients: no associations between whole-brain volume ($r = 0.08$) or hippocampal volumes (right side: 0.02, left side: 0.09) and medication dosage First-episode psychosis patients: no associations between whole-brain volume ($r = -0.15$) or hippocampal volumes (right side: −0.17, left side: 0.04) and medication dosage

Gur *et al.* 1998*b*	Typicals: 44 patients Typicals + atypicals: 24 patients Mean dose in chlorpromazine equivalent units/day: typicals: 407.1 ± 25.3; atypicals (clozapine and risperidone): 334.1 ± 286.3	Long-term treated patients: ↑ putamen ($F = 4.86$, $p = 0.03$) and globus pallidus ($F = 12.58$, $p = 0.0005$) compared with controls and naive patients Patients on typicals: if ↑ dose of typicals then ↑ caudate (left side: $r = 0.38$, $p < 0.01$; right side: $r = 0.34$, $p < 0.05$) and thalamus (left side: $r = 0.55$, $p < 0.01$; right side: $r = 0.36$, $p < 0.05$) and left putamen ($r = 0.36$, $p < 0.01$) Patients on typicals and atypicals: (*a*) if ↑ dose of typicals then ↑ thalamus (left side: $r = 0.75$, $p < 0.01$; right side: $r = 0.62$, $p < 0.01$), left putamen ($r = 0.37$, $p < 0.01$) and left globus pallidus ($r = 0.46$, $p < 0.05$) (*b*) if ↑ dose of atypical then ↑ thalamus (left side: $r = 0.60$, $p < 0.01$; right side: $r = 0.59$, $p < 0.01$)
Zipursky *et al.* 1998	Haloperidol for 4 weeks (haloperidol dose was increased until the 'optimal dose' was reached) 13 patients treated with 2 mg/day ('low-dose group') 13 patients treated with doses of 5, 10 or 20 mg/day ('higher-dose group')	The low-dose group had more cortical grey matter than the higher-dose group ($t = 2.35$, $p = 0.03$) There was a trend in the same direction for the total grey matter volume ($t = 1.89$, $p = 0.07$)
Shihabuddin *et al.* 1998	Antipsychotics (type and dose not known)	Drug-free patients: ↓ caudate than controls (ventral: $d = 0.8$, $r = 0.37$; dorsal: $d = 0.9$, $r = 0.43$ and combined: $d = 0.8$, $r = 0.39$) and than drug-naive patients (ventral: $d = 0.0$, $r = 0.04$; dorsal: $d = 0.5$, $r = 0.28$ and combined: $d = 0.2$, $r = 0.12$) Drug-free patients: ↑ dorsal putamen than drug-naive patients ($d = 0.3$, $r = 0.16$) and than controls ($d = 0.3$, $r = 0.15$)

[a] An expanded version of this table is available at the Journal's website (http://journals.cambridge.org/psm).

McCarley *et al*. 1999; Shenton *et al*. 2001). Less frequently, volume reductions of frontal and parietal cortices and of subcortical structures have also been reported. There is also evidence that some of these brain changes may progress over time (Ho *et al*. 2003; Pantelis *et al*. 2003; Thompson *et al*. 2001); this may occur as part of the disease and its progression or because of treatment exposure. For example, the seminal study by Chakos *et al*. (1995) showed that when individuals were switched from a typical antipsychotic to clozapine, the basal ganglia volume decreased. This suggests that typical antipsychotics have an effect on the basal ganglia volume that is specific and also potentially reversible. These findings renewed interest in the question of whether antipsychotics affect brain structure, with an increasing number of reports documenting structural brain changes in association with use of antipsychotics. However, it has remained unclear to what extent current and previous antipsychotic drug use has influenced imaging findings.

This review addresses the following two questions: (1) is there sufficient evidence that antipsychotic medications induce changes in total or regional human brain volumes, and if so, (2) do such effects depend on antipsychotic type?

Method

Data sources

We searched Medline and EMBASE databases using the medical subject heading (MeSH) terms: 'antipsychotics' AND 'brain' AND (MRI NOT functional). The electronic search was not restricted to English language papers and included studies published up to 31 January 2007. We also searched published research with the Science Citation Index.

Studies selection

Articles were selected by the first author (S.N.) and checked by the last author (P.D.). We included studies directly reporting structural brain magnetic resonance imaging (MRI) measures in association with antipsychotic treatment, or studies that evaluated these in patients who had received at least some treatment with antipsychotics and compared them with drug-naive patients or controls.

Data extraction

Data were extracted from the studies and, when records were missing or incomplete, authors were contacted directly for clarification. For each study (Tables 1 and 2; see also expanded online versions) we recorded information on: (*a*) year of publication;

Table 2. *Follow-up studies presented in chronological order*[a]

References	Antipsychotic (type, dose)	Main findings
Girgis *et al*. 2006	Risperidone (mean dose 2.67 mg/day)	Patients: ↑ in left superior temporal gyrus and middle temporal gyrus and ↓ in left rectal gyrus and corpus callosum Controls: no changes over time
Khorram *et al*. 2006	Typicals for at least 1 year before the first MRI then atypicals until the second MRI	If ↑ dosage of typical antipsychotics at baseline then ↓ thalamus after switching to olanzapine ($r=0.7$, $p=0.0$)
McClure *et al*. 2006	Placebo *versus* typicals and atypicals	Drug-withdrawal group: both with ROI and VBM, no effect of treatment status and antipsychotic type on brain volumes Chronic stable treatment group: both with ROI and VBM, no effect of treatment on brain volumes
Taylor *et al*. 2005	Haloperidol (2 patients); risperidone (7 patients), mean dose 4 mg/day; ziprasidone (2 patients)	Patients: ↑ in striatal tissues (left side: $d=0.3$, $r=0.1$; right side: $d=0.3$, $r=0.1$)
Garver *et al*. 2005	First 7 patients assigned to risperidone at 4 mg/day and subsequent 12 patients randomly assigned to: ziprasidone, 120 mg/day (6 patients); haloperidol, 7 mg/day (6 patients)	Patients on atypicals: diffuse ↑ cortical grey matter without differences between ziprasidone ($d=0.3$, $r=0.1$) and risperidone ($d=0.5$, $r=0.2$) Patients on haloperidol: =cortical grey matter ($d=1.1$, $r=0.5$)
Lieberman *et al*. 2005	Haloperidol (79 patients) 2–20 mg/day; olanzapine (82 patients) 5–20 mg/day	Olanzapine *versus* haloperidol: (*a*) whole-brain grey matter: ↓ in the haloperidol group (week 12: $d=1.6$, $r=0.6$). Frontal grey matter: ↓ in the haloperidol group (week 52: $d=2.6$, $r=0.79$). Temporal and parietal grey matter: ↓ in the haloperidol group (week 52: $d=1.1$, $r=0.5$ and $d=1.2$, $r=0.5$ respectively) (*b*) caudate volumes: ↑ in the haloperidol group (week 24 $d=1.3$, $r=0.5$; week 52: $d=2.3$, $r=0.76$; week 104: $d=0.2$, $r=0.13$) Patients *versus* controls: (*a*) whole-brain grey matter: ↓ in the haloperidol group (week 12: $d=3$, $r=0.1$; week 52: $d=2.3$, $r=0.7$) whereas=in the olanzapine group (week 12: $d=3$, $r=0.1$; week 52: $d=0.17$, $r=0.0$). Frontal grey matter: ↓ in the haloperidol group (week 12: $d=2.1$, $r=0.7$; week 52: $d=3.3$, $r=0.8$) Temporal grey matter: ↓ in the haloperidol group (week 52: $d=0.9$, $r=0.4$) Parietal grey matter: ↓ in the haloperidol group (week 52: $d=1.3$, $r=0.5$)
Massana *et al*. 2005	Risperidone (no fixed dose; mean dose of 6.05 mg/day)	↑ left nucleus accumbens ($T=4.26$, $p=0.00$) and the left caudate ($T=3.68$, $p=0.02$)

Lang *et al*. 2004	10 patients under typicals (mean dose/day, chlorpromazine equivalents 360 ± 263.7) switched to olanzapine (mean dose/day, chlorpromazine equivalents 170 ± 64); 27 patients under risperidone: 13 switched to olanzapine (mean dose/day, chlorpromazine equivalents 132 ± 44 → 150 ± 10.7) and 14 continuing with risperidone (mean dose/day, chlorpromazine equivalents 92 ± 44 → 84 ± 52)	Patients on typicals switched to olanzapine. (*a*) at baseline, patients on typicals ↑ basal ganglia than controls (differences were statistically significant for putamen: $d = 0.7$, $r = 0.3$ and globus pallidus: $d = 1.4$, $r = 0.5$) (*b*) at follow-up, basal ganglia volume ↓ in patients (caudate: $d = 0.04$, $r = 0.02$; putamen: $d = 1.2$, $r = 0.5$; globus pallidus: $d = 1.06$, $r = 0.4$) and patients *versus* controls: = basal ganglia (caudate: $d = 0.2$, $r = 0.1$; putamen: $d = 0.1$, $r = 0.08$; globus pallidus: $d = 0.5$, $r = 0.2$) Patients on risperidone: (*a*) at baseline, risperidone-treated patients subsequently switched to olanzapine *versus* those continuing risperidone: = basal ganglia volumes (caudate: $d = 0.4$, $r = 0.2$; putamen: $d = 0.08$, $r = 0.04$; globus pallidus: $d = 0.1$, $r = 0.07$) (*b*) at follow-up, risperidone patients *versus* olanzapine patients: = basal ganglia volumes (caudate: $d = 0.00$, $r = 0.00$; putamen: $d = 0.08$, $r = 0.00$; globus pallidus: $d = 0.4$, $r = 0.2$)
Heitmiller *et al*. 2004	Atypicals (risperidone: mean dose 3.625 mg/day, olanzapine, quetiapine, clozapine) Mean dose-years at follow-up, chlorpromazine equivalents = 7.38 ± 5.53	Patients *versus* controls: = amount of change caudate ($d = 0.00$, $r = 0.001$) However, the female patients had a negative correlation between drug exposure and volume change (total volume: $r = -0.6$, $p = 0.1$) whereas the male patients had a positive correlation (total volume: $r = -0.5$, $p = 0.2$)
Christensen *et al*. 2004	Risperidone (7 patients) at 4 mg/day, ziprasidone (6 patients) at 120 mg/day, haloperidol (6 patients) at 7 mg/day	Risperidone *versus* ziprasidone *versus* haloperidol: = change in white matter (paired t: 1.561, $p = 0.1$)
Cahn *et al*. 2002	Typicals (5 patients) Atypicals (15 patients) Typicals + atypicals (14 patients) Cumulative lifetime dose in haloperidol equivalents: $T_0 = 65.9 \pm 157.6$ mg $T_1 = 2077.5 \pm 962.7$ mg	If ↑ cumulative dose of antipsychotic medication (typical or atypical) between T_0 and T_1 then ↓ in global grey matter volume ($r = -0.45$, $p = 0.00$)
Tauscher-Wisniewski *et al*. 2002	Typicals (4 patients): haloperidol at mean dose of 2 mg/day (2 patients); loxapine at mean dose of 10 mg/day (2 patients) Atypicals (9 patients): clozapine (3 patients) Typicals + clozapine (2 patients)	At baseline, naive *versus* treated patients: = caudate ($F = 0.18$, $p = 0.68$) At follow-up, controls and patients = caudate ↓ of 9% (controls: $d = 0.6$, $r = 0.3$; patients: $d = 0.5$, $r = 0.2$; clozapine: $d = 0.4$, $r = 0.2$; atypicals: $d = 0.09$, $r = 0.04$; typicals: $d = 2.1$, $r = 0.7$; clozapine + typicals: $d = 0.2$, $r = 0.1$)
Scheepers *et al*. 2001*b*	Clozapine: mean dose 346 ± 61 mg/day	↓ left caudate at week 24 if on clozapine (left side: $F = 3.9$, $p < 0.05$; right side: $F = 2.4$, $p = 0.1$)
Scheepers *et al*. 2001*a*	Clozapine: mean dose 345.57 ± 63.44 mg/day (range 200–600)	↓ caudate if on clozapine ($d = 0.2$, $r = 0.1$); = whole-brain volume if on clozapine ($F = 3.85$, $p = 0.6$)

Table 2 (*cont.*)

References	Antipsychotic (type, dose)	Main findings
Puri *et al*. 2001	Still naive (3 patients) Risperidone (4 patients) Typicals (27 patients) Cumulative medication dose in chlorpromazine equivalents: T_0 = mean 6677.45 ($\pm$6994.73) T_1 = mean 68365.96 ($\pm$53879.50)	Patients *versus* controls: = ventricular volume at baseline ($d=0.4$, $r=0.2$) and follow-up ($d=3.2$, $r=0.8$) and = ventricle brain ratios at baseline ($d=0.5$, $r=0.2$) and follow-up ($d=0.5$, $r=0.2$) No correlations between ventricular size at presentation and cumulative medication dose ($r=-0.2$) or duration of treatment ($r=-0.1$) No correlations between change in ventricular size and total duration of treatment ($r=0.2$) or total cumulative medication dose ($r=0.05$)
Lieberman *et al*. 2001	Open therapy with a standardized treatment algorithm composed largely of conventional antipsychotic drugs (used ultimately clozapine for treatment refractory patients)	Patients *versus* controls: $\downarrow$ caudate in patients; $\downarrow$ anterior hippocampus and cortical volume in controls; = ventricles volumes No association between cumulative dose of antipsychotic treatment in the interscan interval and ventricular, cortical, hippocampal or caudal volumes Association between longer duration of treatment with typicals during the interscan interval and smaller ventricular volumes in patients both at baseline and follow-up scan ($F=5.73$, $p=0.2$)
Lang *et al*. 2001	At baseline patients treated with risperidone (dose range 1–6 mg/day, mean 2.7 mg/day). They took risperidone continuously for $\geqslant$6 months	At follow-up, both patients and controls = basal ganglia than at baseline (for all comparisons $p>0.2$)
Corson *et al*. 1999	Typicals: 13 patients; 8 treated only with typicals and 5 minimally exposed also to atypicals. Mean dose years, chlorpromazine equivalents = 9.05 ± 6.89 Atypicals: 10 patients; 6 treated only with atypicals and 4 minimally exposed also to typicals. Mean dose years, chlorpromazine equivalents = 10.96 ± 9.14	Patients on typicals: $\uparrow$ basal ganglia ($t=2.93$, $p<0.02$) Patients on atypicals: $\downarrow$ basal ganglia ($t=1.98$, $p<0.04$)
Gur *et al*. 1998*a*	Mainly typicals + atypicals Follow-up daily dose in chlorpromazine equivalents: drug-naive: mean dose 259.9 ± 165.6 drug-free: mean dose 515.3 ± 224.0	Drug-naive *versus* drug-free patients: in drug-naive patients more $\downarrow$ in left hemispheric frontal lobes ($T=0.17$, $p=0.02$) and in temporal lobes bilaterally ($T=0.12$, $p=0.05$) Drug-free patients: if $\uparrow$ medication dose then $\downarrow$ in frontal and temporal volumes ($r=-0.75$ and -0.66 respectively; $p<0.001$) Drug-naive patients: no association between medication dose and $\downarrow$ in frontal and temporal volumes ($r=0.03$ and 0.16 respectively)
Frazier *et al*. 1996	Patients were under typicals for about 2 years before the first MRI All patients were under clozapine at the time of the second MRI (mean dose 400 ± 128.9 mg/day)	Caudate: $\downarrow$ in patients ($F=4.96$, $p=0.02$) Putamen: $\downarrow$ in patients ($F=2.32$, $p=0.08$) Globus pallidus: $\downarrow$ equally in patients and controls ($F=21.74$, $p=0.00$) Lateral ventricles: $\uparrow$ in patients ($F=2.38$, $p=0.07$)

Chakos *et al.* 1995	(*a*) Patients were under typicals before the first MRI, then switched to clozapine before the second MRI (*b*) Patients were under typicals at the time of the first and the second MRI	(*a*) Patients on clozapine: caudate ↓ 10% at second scan ($d=0.9$, $r=0.4$) (*b*) Patients on typicals: caudate ↑ 8% at second scan ($d=0.5$, $r=0.2$)
Chakos *et al.* 1994	Standardized typical antipsychotics regimens (fluphenazine up to 20 mg/day for 6 weeks. If not improved, patients progressed through the treatment algorithm receiving full trials of up to 3 different typical antipsychotics)	Patients: caudate ↑ 5.7% ($d=0.3$, $r=0.1$) Controls: caudate ↓ 1.6% ($d=0.09$, $r=0.04$) A higher daily dose received prior to the first MRI was associated with larger ↑ in caudate ($r=0.4$, $p<0.02$)
Keshavan *et al.* 1994	Typicals: mean maintenance dose in haloperidol equivalents 2.24±1.2 mg/day	↑ in right ($d=1$, $r=0.44$), left ($d=0.68$, $r=0.32$) and total caudate ($d=0.86$, $r=0.39$) None of the other MRI parameters changed

[a] An expanded version of this table is available at the Journal's website (http://journals.cambridge.org/psm).

(*b*) study design; (*c*) sample characteristics; (*d*) duration of treatment with antipsychotic drugs before the first MRI and time to follow-up MRI [data on length of treatment before the first MRI scan were not available for one study (Corson *et al*. 1999*b*), for which plausible estimates based on length of illness were imputed]; (*e*) type and dose of antipsychotic drug; (*f*) brain region/s evaluated; (*g*) methods for estimating brain volumes and slice thickness; and (*h*) any reported association or lack of association between brain volume and antipsychotic treatment. If information on the strength of the association (either Pearson's *r*, or Cohen's *d*, correlation coefficient) was reported, this was included in the tables. When this was not the case but the data were available in the original paper, we calculated the effect size (*d*) (Cohen, 1992). When data were not sufficient to calculate the effect size, we reported the statistical test with the *p* value quoted in the original study.

As length of exposure to antipsychotic treatment can be associated with different brain changes, we classified studies first according to design (cross-sectional *versus* longitudinal). Then, within each study design, studies were classified according to duration of treatment prior to first MRI scan: (1) studies conducted in drug-naive (never-treated) and drug-free (not treated for the previous 3 weeks) subjects. These two groups were considered together according to the existing literature on antipsychotic washout (Farde *et al*. 1986; Miller *et al*. 1997*a*, *b*, 2001); (2) studies conducted in subjects receiving short-term treatment (⩽12 weeks); and (3) studies conducted in subjects receiving long-term treatment (>12 weeks). This makes it easier to discriminate between brain changes that are potentially due to a specific treatment effect and those that are related to the illness itself and its progression (Dazzan & Murray, 1999).

Method of analysis

Published reports did not provide sufficient information across studies to allow a meta-analytical quantitative summary; therefore, data were used for a systematic review and critical literature analysis.

Results

We identified 33 papers investigating the association between antipsychotic drug treatment and brain structure: 10 cross-sectional and 23 longitudinal studies. We report on the effects on any regional or global brain volume. For studies with the same design, we first present findings at a regional level, following brain anatomy from cortical to subcortical structures (basal ganglia and thalamus). We then present findings on

global volumes (grey and white matter, whole brain, ventricles).

Cross-sectional studies

Cross-sectional studies evaluated brain structure and its association with concomitant antipsychotic treatment in terms of dosage and type of antipsychotic used at a single time-point (Table 1).

Studies conducted in drug-naive and drug-free subjects

Such studies are extremely valuable in understanding brain changes at illness onset and also the possible effect of previous medication on brain structure. Only three studies were available on patients either drug-naive or drug-free at MRI.

A single report compared cortical volumes in drug-naive patients, long-term treated patients, and controls (Gur *et al*. 2000). Both patient groups showed reduced prefrontal cortex volume, particularly in the dorsolateral sector. The authors concluded that reduced prefrontal volume is not a by-product of treatment and might represent a neuroanatomical abnormality already present at illness onset.

Nopoulos *et al*. (2001) studied a sample of male patients at their first episode of psychosis; all 45 drug-free patients had previous exposure to typicals and four of these had been additionally exposed to atypicals. The cumulative dose of antipsychotic medication was negatively correlated with the size of the midbrain, indicating that the greater the antipsychotic exposure, the smaller the midbrain area. When the authors compared subjects naive ($n=5$) and with minimal antipsychotic exposure ($n=9$) to those medicated, they found that the medicated group had a smaller midbrain area. Treatment with typicals seemed to induce a reduction in the midbrain area that was still present 3 weeks after withdrawal.

Shihabuddin *et al*. (1998) looked at volume of striatum in a small sample of naive and drug-free schizophrenia patients in comparison to healthy individuals. They found a significant group (drug-naive *versus* drug-free *versus* controls) by level (ventral *versus* dorsal side) by structure (putamen *versus* caudate) interaction. The largest difference was a larger dorsal putamen volume in drug-free patients *versus* controls and, to a minor extent, *versus* drug-naive patients. Findings on the caudate size were in the opposite direction, with drug-free patients showing a smaller caudate volume than both drug-naive patients and controls. The authors suggested that the post-treatment enlargement might last longer after treatment discontinuation for the putamen than for the caudate, possibly because of a higher density of D_2 receptors in the putamen. The difference between the drug-naive and drug-free subjects in putamen and caudate volumes might be more likely to reflect the effect of never-medicated *versus* previously medicated status than that of age or illness severity.

More investigations on drug-naive and drug-free patients are required to clarify the timing of brain changes and the possible relationship between causality and antipsychotic treatment.

Studies conducted in subjects receiving short-term treatment ($\leqslant$*12 weeks*)

Studies on patients at the initial stages of psychosis, when treatment would have occurred only for a short time, can provide information on the occurrence and timing of structural brain changes; such studies can help to disentangle changes caused by a specific class of antipsychotics from those due to the illness and its progression.

Our group (Dazzan *et al*. 2005) has evaluated a sample of first-episode psychosis patients treated with typical or atypical antipsychotics for a relatively short period of time (mean 8.5 weeks). Patients who received typicals, but not those on atypicals, compared to drug-free patients showed cortical grey matter reduction in frontal areas, temporal-insular areas and precuneus. As there were no clinical differences between the groups that could explain the brain morphological differences, these results support the hypothesis that these brain changes could be at least in part explained by the different treatment received. A potential effect of haloperidol on cortical volume has also been suggested by another study (Zipursky *et al*. 1998). Here, first-episode psychosis patients treated with higher doses of haloperidol had significantly smaller total cortical grey matter volumes than subjects on lower doses. Therefore, more marked brain structural changes may represent a dose-dependent effect of haloperidol on cortical grey matter. Alternatively, individuals with more marked structural abnormalities may also be those less responsive to treatment, and hence receiving higher antipsychotic doses.

Narr *et al*. (2005) reported that both patients receiving short-term treatment (mean length 8 days) with atypical antipsychotics and drug-naive patients, when compared to controls, had significant cortical thinning of cingulate, occipitals and frontopolar cortices, suggesting that brain changes at this level predate illness onset. This is an important issue to consider when evaluating potential medication effects, and it may be at least partially addressed by comparing patients on treatment with those who are drug free, the approach used by our group (Dazzan *et al*. 2005).

Most of the differences found in our study were between the group on typicals and the drug-free group. This suggests a different effect of antipsychotic type, which could not be estimated in the report by Narr *et al*. (2005), where all patients were taking atypicals. It remains unclear whether medications act on cortical volume or on cortical thickness. Changes in cortical thickness may reflect cytoarchitectural abnormalities more closely related to illness onset than volumetric abnormalities (Thompson *et al*. 2003).

Data on the basal ganglia in patients on short-term treatment are limited to a single report from our group (Dazzan *et al*. 2005). Typical antipsychotics were found to be specifically associated with increased putamen volume in comparison to drug-free status. Of note, we found no differences in basal ganglia volumes when patients on typicals and atypicals were compared directly. This suggests that atypicals also act on these structures, although to a lesser extent. This finding may also reflect a lack of statistical power, and a larger sample size could have clarified if indeed basal ganglia enlargement is an effect specific to typical antipsychotics. Our study is also the only report on thalamus volume in patients on short-term treatment (Dazzan *et al*. 2005). We found that only patients treated with atypicals showed an enlargement of the thalami in comparison with drug-free patients.

Finally, one study (Velakoulis *et al*. 1999) specifically evaluated the relationship between hippocampal volume and antipsychotics, albeit indirectly. Here, the smaller hippocampal volume identified in patients at their first episode of psychosis in comparison to controls was not related to the cumulative dose of antipsychotics received prior to MRI.

Studies conducted in subjects receiving long-term treatment (*>12 weeks*)

Findings from these studies are difficult to interpret because subjects may have been treated with different antipsychotics at different doses for many years. Therefore, brain modifications due to medication are difficult to distinguish from those due to illness progression.

We identified four studies that included patients treated for >12 weeks, and most have evaluated the effect of antipsychotics on the basal ganglia and thalamus. Data from a sample of males with schizophrenia found no differences in thalamic volumes between patients and controls and no association between thalamic volume and antipsychotic dose at time of MRI (Deicken *et al*. 2002). By contrast, Gur *et al*. (1998*b*) found that a total higher lifetime dose of typicals was associated with larger caudate, putamen and thalamus volumes whereas a higher dose of atypicals was associated only with larger thalamic volume. These data on chronic patients are consistent with the findings from Dazzan *et al*. (2005), who described thalami enlargement following short-term treatment with atypicals, and enlargement of the putamen in relation to use of typicals.

In the study by Velakoulis *et al*. (1999) on long-term patients with schizophrenia, hippocampal volume was found to be significantly smaller than in controls. Similar to their findings in subjects on short-term treatment, they found no correlation between hippocampal volume and cumulative antipsychotic dose. Only one study evaluated hippocampal volume in relation to type of antipsychotic used, with negative findings (Chakos *et al*. 2005). However, patients had received long-term treatment with both typical and atypical antipsychotics, and it could have been difficult to distinguish specific effects of drug type. To better investigate the effects of different antipsychotics on hippocampal volume, Chakos *et al*. (2005) randomly assigned male patients to treatment with either an atypical (olanzapine or risperidone) or a typical (haloperidol) antipsychotic. They found a larger hippocampal volume in patients treated with atypicals than in those taking haloperidol, suggesting that male patients, treated early in the course of illness with atypicals rather than typicals, might be protected against hippocampal volume reduction. Despite the randomized design, the sample evaluated was relatively small.

The cross-sectional studies reviewed used different designs to test the relationship between antipsychotics and brain structure (Table 1): three are drug-type (typicals and/or atypicals); five are dose-correlation (chlorpromazine equivalents range: from 40.59 ± 94.96 mg for drug-naive and drug-free patients to 21018 ± 16153 mg for long-term treated patients); and one is dose-correlation for drug-type (chlorpromazine equivalents for typicals: 407.1 ± 25.3 mg and for atypicals: 334.1 ± 286.3 mg). Finally, two are comparisons between drug-free and drug-naive patients *versus* controls (for one of them neither the type nor the dose of antipsychotic used was reported, and for the other one only the number of patients taking which type of antipsychotic was reported). Indeed, as cross-sectional studies evaluate brain structure at a single time-point, it is difficult to understand the role of antipsychotics in determining brain changes if type and dose used are not reported systematically, as either could be responsible for any effect observed. Even taking into account these limitations, the cross-sectional studies reviewed suggest that antipsychotics, typicals in particular, affect the basal ganglia even after short-term treatment. They also provide

preliminary evidence of an early action at cortical level that may be drug specific.

Longitudinal studies

A longitudinal design allows a better understanding of the timing and progression of changes in brain structures and of the effects of antipsychotics on these changes, making it possible to speculate on causality.

Studies conducted in drug-naive and drug-free patients

We identified eight longitudinal studies on drug-naive and drug-free patients. Keshavan *et al*. (1994), in naive first-episode psychosis patients, found that the prefrontal cortex did not change significantly over 1 year of treatment with typicals. By contrast, Gur *et al*. (1998*a*, *b*) found, over approximately 2 years, a more pronounced reduction in frontal and temporal lobes in drug-naive patients at their first psychotic episode than in drug-free patients treated previously for more than 12 weeks (mainly with typicals). The differences between these studies might be related to the slightly different brain areas investigated, and to the subjects receiving different antipsychotics at different doses. Indeed, Garver *et al*. (2005) found that, even after a short period (28 days) of antipsychotic use, patients treated with haloperidol did not show any change in cortical grey matter volume whereas patients treated with atypicals showed an increase in cortical grey matter volume. These data support a different effect of typical *versus* atypical antipsychotics, even after a short period of treatment.

Regarding the basal ganglia, Heitmiller *et al*. (2004) followed up naive patients treated with different atypical antipsychotics for 2 years. They found that patients had a very small increase in caudate volume, almost identical to that of the controls. This replicates findings from cross-sectional studies suggesting that exposure to atypicals affects the caudate volume less than exposure to typicals. By contrast, a study by Massana *et al*. (2005) on naive schizophrenia patients treated with risperidone reported an increase in left caudate and left accumbens volumes, with a positive correlation between dose and volume. Considering the large body of evidence of an increase in caudate volumes after treatment with typicals (Chakos *et al*. 1994, 1995; Keshavan *et al*. 1994; Corson *et al*. 1999*a*, *b*; Lang *et al*. 2001; Scheepers *et al*. 2001*a*, *b*), it is possible that the increase in caudate volume seen at higher doses of risperidone reflects an action more like that of a typical antipsychotic (Nyberg *et al*. 1999). Finally, Taylor *et al*. (2005) found an increase of striatal volumes following 4 weeks of treatment with either atypicals or typicals in schizophrenia patients but not in healthy controls. The small sample size did not allow an evaluation of antipsychotic-type differences on striatal volume.

In the study by Christensen *et al*. (2004), white matter did not change significantly following 4 weeks of treatment (typicals or atypicals) in schizophrenia subjects. Indeed, Keshavan *et al*. (1994) reported no change in brain volume even after 1 year of treatment with typicals in drug-naive patients at their first psychotic episode. By contrast, Girgis *et al*. (2006) found, in naive first-episode psychosis patients, a decrease in white matter and an increase in grey matter volumes after 6 weeks of treatment with the atypical risperidone. Differences between studies might be related to the characteristics of the subjects and to the different treatment received (type and dose of antipsychotics).

In conclusion, studies on drug-naive and drug-free subjects have been mostly conducted on small samples (between 11 and 19), and this may have affected the power of such studies to identify significant differences. Studies on larger samples would allow testing the hypothesis of an antipsychotic-type effect not only on basal ganglia but also on cortical grey and white matter.

Studies conducted in subjects receiving short-term treatment ($\leqslant$*12 weeks*)

These studies take into account the treatment received prior to, and in between, MRI scans. Chakos *et al*. (1994) studied drug-naive and short-term treated patients with first-episode schizophrenia and did not find any cortical volume change following treatment with typical antipsychotics. These findings are consistent with two other studies that also found no longitudinal changes in total cortical and prefrontal cortex volumes over a period of 2.5 years (Lieberman *et al*. 2001) and 1 year (Keshavan *et al*. 1994) respectively. It is possible that treatment may prevent the volume loss potentially associated with disease progression. However, a later study with a randomized design (Lieberman *et al*. 2005) reported a drug-type effect of antipsychotics on cortical grey matter over 2 years. Subjects treated with haloperidol, but not with olanzapine, lost frontal grey matter between weeks 12 and 24, suggesting that typical and atypical antipsychotics have differential effects also at the cortical level.

As far as the basal ganglia are concerned, two studies have found increased basal ganglia volumes following short-term treatment with typicals (Chakos *et al*. 1994; Lieberman *et al*. 2001). By contrast, Tauscher-Wisniewski *et al*. (2002) reported a 9% reduction in caudate volumes over 5 years in first-episode schizophrenia patients mostly treated with atypicals and

low-dose typicals (about one-tenth of the doses received in the study by Chakos *et al*. 1994). This would suggest an effect related to both dose and type of antipsychotic. A drug-type effect of antipsychotics on basal ganglia was also reported by Lieberman *et al*. (2005), who found a caudate volume increase in haloperidol-treated but not in olanzapine-treated subjects. Similarly, Corson *et al*. (1999*b*) found an increase in basal ganglia volumes in patients receiving mostly typicals, whereas the opposite was observed in patients receiving mostly atypicals. Of interest, the use of the atypical risperidone at low doses has been associated with no basal ganglia volume change over time (Lang *et al*. 2001), in contrast with the volume increase observed when risperidone is administered at higher doses (Massana *et al*. 2005), when is thought to have a more typical-like action.

Only one study specifically examined hippocampal volume, in patients mostly treated with typicals (Lieberman *et al*. 2001). Anterior hippocampal volume remained unchanged in patients, independently from cumulative antipsychotic dose, whereas it decreased over time in controls.

Regarding total grey matter, Cahn *et al*. (2002) found a 3% volume decrease over 1 year, positively correlated with cumulative antipsychotic dose. These authors did not find any association between grey matter decrease and antipsychotic type. The small size of the typical antipsychotic group could limit this conclusion, which contrasts with evidence from Lieberman *et al*. (2005) that subjects treated with haloperidol, but not with olanzapine, lose grey matter over 2 years.

As far as ventricular volumes are concerned, Puri *et al*. (2001) found that patients on antipsychotic treatment (mostly with typicals) did not show any significant change in ventricular volume over time in comparison with controls. These results are consistent with data from short- and long-term treated patients showing no significant changes in lateral and third ventricular volume over time (Frazier *et al*. 1996; Lieberman *et al*. 2001).

This evidence is in accordance with data from studies on drug-free and drug-naive patients, suggesting that even after short-term treatment, typical and atypical antipsychotics differentially affect brain structure not only at the subcortical but also at the cortical level.

Studies conducted in subjects receiving long-term treatment (*>12 weeks*)

The existing literature on chronically treated patients mostly evaluated basal ganglia volume and the reversibility of volume changes in these structures.

Most studies consistently suggest that switching from long-term treatment with typical antipsychotics to clozapine results in a significant decrease in basal ganglia volume (Chakos *et al*. 1995; Frazier *et al*. 1996; Scheepers *et al*. 2001*a*). This has been most often shown for the caudate (Chakos *et al*. 1995; Frazier *et al*. 1996; Scheepers *et al*. 2001*a*), and to a lesser extent for the putamen (Frazier *et al*. 1996). The volume of the globus pallidus has also been reported as decreasing over time both in patients switching from typicals to atypicals and in healthy individuals (Frazier *et al*. 1996). Switching from haloperidol to olanzapine is also reported to be associated with putamen and globus pallidus volume reduction (Lang *et al*. 2004). By contrast, switching from risperidone to olanzapine (pharmacologically more similar to clozapine than risperidone) is not associated with a decrease in basal ganglia volume (Lang *et al*. 2004). This suggests that atypical antipsychotics could induce basal ganglia volume normalization, rather than reduction, in patients previously treated with typicals, and supports the notion that atypical antipsychotics also act on basal ganglia, albeit differently from typicals (Heitmiller *et al*. 2004). Indeed, Khorram *et al*. (2006) found that switching from typicals to olanzapine also resulted in a reduction in thalamic volumes, with higher baseline dosage being associated with a greater reduction over time. These changes would therefore represent a normalization of previously larger volumes associated with the dosage of typicals administered. These findings are in contrast to data from cross-sectional studies suggesting an association between increased thalamic volume and atypical antipsychotic treatment (Gur *et al*. 1998*b*; Dazzan *et al*. 2005). These inconsistencies could be due to methodological issues and differences in sample characteristics.

McClure *et al*. (2006) explored whole-brain volume changes with both region of interest (ROI) and voxel-based morphometry (VBM) methods in subjects scanned before and after antipsychotic withdrawal, and in subjects scanned at two time-points during stable antipsychotic treatment. Both methods found no volume changes in either group. The authors concluded that these findings may be explained by the small sample size, the low statistical power, and the brief follow-up period.

Finally, only one study looked at lateral ventricular volume changes, following switch to clozapine (Frazier *et al*. 1996), and found a trend for an increase in lateral ventricle volume compared to controls.

In conclusion, findings from studies on long-term treated patients, already exposed to different antipsychotics at baseline, are limited by the implicit difficulties in interpreting the nature of the

relationship between brain structure and antipsychotic treatment.

Conclusions

The studies reviewed suggest that antipsychotic drugs act regionally rather than globally on the brain, with different effects on different brain structures. An estimate of the effect sizes of these volumetric changes suggests that they are of a greater magnitude in association with typical than with atypical antipsychotics.

The studies reviewed also suggest an early action of antipsychotics on the basal ganglia, and possibly on the thalamus, with typicals specifically increasing the volume of the basal ganglia and atypicals increasing the volume of the thalamus. Moreover, they suggest that antipsychotics also affect cortical grey matter, with typicals reducing global grey matter volume, possibly with a dose-dependent effect, and atypicals potentially retaining/increasing cortical grey matter over time.

Whether there are progressive brain changes after the onset of schizophrenia remains debatable (Mathalon *et al*. 2001; Ho *et al*. 2003). Some changes could precede illness onset and may progress in the course of the disease. Should this be the case, we might expect these changes to be associated with measures of illness severity but this association remains controversial (Hulshoff Pol & Kahn, 2008). It is also possible that antipsychotic treatment interacts with the underlying pathophysiology of the illness, co-determining structural brain changes or playing a protective role against the progression of the illness itself (Ho *et al*. 2003). Indeed, in this perspective, the potential reversibility of antipsychotic effects has to be considered, as observed, for example, for the caudate enlargement induced by typicals and reversed by clozapine (Chakos *et al*. 1995; Frazier *et al*. 1996).

The potentially different effects of typical and atypical antipsychotics on brain structures could be due to different mechanisms of action (Lieberman *et al*. 2005; Scherk & Falkai, 2006). Atypical drugs, such as clozapine and olanzapine, could increase cellular resilience and therefore act on the pathophysiology of psychosis through an agonistic effect on *N*-methyl-D-aspartate (NMDA) receptors (Duncan *et al*. 1999; Millan, 2005), increasing the expression of trophic factors (Fumagalli *et al*. 2004; Angelucci *et al*. 2005) and stimulating neurogenesis (Halim *et al*. 2004; Wang *et al*. 2004). Moreover, typical antipsychotics such as haloperidol may have a potentially toxic effect, and induce oxidative stress and excitatory neurotoxicity (Post *et al*. 1998; Wright *et al*. 1998). The potential confounding effect of dose also has to be considered. For example, low doses of typicals may produce effects similar to those of atypicals (Oosthuizen *et al*. 2004), although the data reviewed did not support such effects.

Changes in MRI volume measurements can also be produced by alterations in neuronal and non-neuronal tissue compartments, in addition to physiological alterations in brain tissue (e.g. changes in tissue perfusion, fat and water content) and in body weight, alcohol intake, steroid administration and hormonal status (Weinberger & McClure, 2002). An additional issue, implicit to all MRI studies, is that measurements can be affected by differences in image acquisition and analysis techniques. The studies reviewed certainly used several different parameters, which made comparability of findings difficult.

The interpretation of findings can be difficult when these are negative, and when the raw data are not presented. The significance of the p value is often overestimated, and a critical interpretation of the data in terms of effect size would be more informative and improve comparability. Indeed, it would be useful if authors systematically reported the median of the dose of antipsychotic used, and also the type of antipsychotic, to allow more meaningful comparisons on the association between typical and atypical antipsychotics and changes in brain structures. These issues make it difficult to discern to what extent findings are comparable, and to interpret the meaning of volume changes at a neuroanatomical, clinical and prognostic level.

Implications for future research

This is, to our knowledge, the first systematic review on the effects of past and current antipsychotic drug use on brain structure. The evidence reviewed supports the notion that treatment represents one of the factors among those potentially contributing to the wide range of brain structural modifications in psychosis, and it should be considered in the interpretation of neuroimaging findings.

Studies accounting for structural brain changes over time, in first-episode psychotic patients, possibly drug-naive or short-term treated, with randomized assignment of medications and dose, would be desirable. Finally, evaluating measures such as the shape of brain structures could provide a complementary approach to volumetric methods. In fact, volume changes may not be uniform over a specific structure but rather localized to specific parts.

Declaration of Interest

None.

Note

Supplementary material accompanies this paper on the Journal's website (http://journals.cambridge.org/psm).

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