Psychological Medicine (2010), **40**, 1409–1422. © Cambridge University Press 2010
doi:10.1017/S0033291709992297

REVIEW ARTICLE

A systematic review of the effects of antipsychotic drugs on brain volume

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Background. People with schizophrenia are often found to have smaller brains and larger brain ventricles than normal, but the role of antipsychotic medication remains unclear.

Method. We conducted a systematic review of magnetic resonance imaging (MRI) studies. We included longitudinal studies of brain changes in patients taking antipsychotic drugs and we examined studies of antipsychotic-naive patients for comparison purposes.

Results. Fourteen out of 26 longitudinal studies showed a decline in global brain or grey-matter volume or an increase in ventricular or cerebrospinal fluid (CSF) volume during the course of drug treatment, including the largest studies conducted. The frontal lobe was most consistently affected, but overall changes were diffuse. One large study found different degrees of volume loss with different antipsychotics, and another found that volume changes were associated with taking medication compared with taking none. Analyses of linear associations between drug exposure and brain volume changes produced mixed results. Five out of 21 studies of patients who were drug naive, or had only minimal prior treatment, showed some differences from controls in volumes of interest. No global differences were reported in three studies of drug-naive patients with long-term illness. Studies of high-risk groups have not demonstrated differences from controls in global or lobar brain volumes.

Conclusions. Some evidence points towards the possibility that antipsychotic drugs reduce the volume of brain matter and increase ventricular or fluid volume. Antipsychotics may contribute to the genesis of some of the abnormalities usually attributed to schizophrenia.

Received 7 November 2008; Revised 7 December 2009; Accepted 8 December 2009; First published online 20 January 2010

Key words: Antipsychotics, brain volume, MRI, neuroimaging, schizophrenia.

Introduction

Neuroimaging and post-mortem studies suggest that the structure of the brain in people diagnosed with schizophrenia is subtly different from that of 'healthy controls'. In particular, numerous studies have reported that the brains of people with schizophrenia or psychosis seem to be smaller and to have less grey matter and larger ventricles and cerebrospinal fluid (CSF) spaces than brains of healthy controls (Wright *et al*. 2000). Although most of the patients involved in such studies had a history of antipsychotic treatment, the role of drug treatment in producing these abnormalities has received little attention. As some studies with first-episode patients show abnormalities of brain volume, it has been assumed that drug treatment cannot be a causal factor. However, the majority of subjects in most of these studies had received antipsychotic drugs for several weeks, and the results of recent research suggest that drug treatment may induce detectable changes within a few weeks of treatment (Dazzan *et al*. 2005; Lieberman *et al*. 2005; Schaufelberger *et al*. 2007). Several studies and reviews have suggested that typical antipsychotics may induce enlargement of basal ganglia structures and that effects of typical and atypical antipsychotics may vary (Chakos *et al*. 1995; Scherk & Falkai, 2006; Vita & De Peri, 2007; Navari & Dazzan, 2009). It remains unclear, however, whether antipsychotic drugs *per se* affect global brain structure.

This study set out to examine data from imaging studies regarding the impact of antipsychotic drug treatment on global brain structures, particularly ventricular or CSF volume, whole-brain and grey-matter volume. We looked at longitudinal studies of people treated with antipsychotic drugs, to ascertain whether there was brain volume change during a period of drug treatment. We also examined studies of patients

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who underwent brain imaging when they were drug naive, or after minimal treatment, to ascertain whether brain volume differed from controls prior to drug treatment. We looked at research on subjects at 'high risk' of psychosis who later developed psychosis and who had not received medication at the time of their scan.

Method

We identified imaging studies of people diagnosed with psychosis or schizophrenia that contained data on the effects of antipsychotic drugs on overall brain volume, grey-matter volume, lobar volumes, CSF volume, and subcortical ventricular spaces. We included recent magnetic resonance imaging (MRI) studies of people who had been taking antipsychotic medication between scans that included a group of healthy controls, also studied longitudinally. We excluded studies examining only changes in brain density, cortical surface area, or thickness. A Medline search was conducted using the terms 'longitudinal' or 'progressive' combined with 'MRI' and 'psychosis' or 'schizophrenia'. All longitudinal studies published between 1995 and April 2009 with follow-up longer than 6 months were included. These studies have usually been interpreted as indicating disease-related effects but, as many authors acknowledge, the studies cannot definitively distinguish between the effects of disease and the effects of treatment. Unlike other reviews, therefore, we considered that all studies that examine brain changes in drug-treated patients may constitute evidence of the role of drug treatment.

We searched Medline for all studies of brain structure in neuroleptic-naive patients published between 1995 and April 2009 using the terms 'neuroleptic-naive', 'antipsychotic-naive' or 'drug-naive' combined with 'MRI' and 'psychosis' or 'schizophrenia'. We also examined research on people from 'high-risk' samples who have subsequently developed psychosis, identifying the studies from citations of other reviews.

We extracted data on numbers of patients and controls, duration of interscan interval where appropriate, and differences from controls in total CSF, ventricular volumes, whole-brain volume, cortical volume, grey-matter volume and regional lobar volumes, where these were recorded. We noted the results of any analysis that had been performed to assess the effects of drug treatment. In the common instances whereby a single study was reported in several different publications, we present findings from the last publication, and include previous findings only where they provide additional relevant information.

Results

Longitudinal studies

The search retrieved 279 articles. Many were not relevant because they reported functional MRI studies or receptor studies and many represented multiple publications of the same studies. Altogether, 26 longitudinal studies were identified that satisfied inclusion criteria. These studies involved a total of 767 patients experiencing a first episode of psychosis or schizophrenia and 360 patients with long-term illness (Table 1). The mean number of patients per study was 40 (range 10–161), and the average follow-up was around 34 months (range of 8 months to 10 years). Fourteen studies (58%) found that patients showed a greater reduction in whole-brain, cortical or grey-matter volume, or a greater increase in CSF or ventricular volumes compared with controls. Two further studies found effects in some patients (Nakamura *et al*. 2007; Reig *et al*. 2009).

The largest study had a sample size of 161 patients, almost five times higher than the mean sample size of the other studies, which was 35. In this study, patients were randomized after a baseline scan to take haloperidol or olanzapine (Lieberman *et al*. 2005). The study revealed significant decline in grey matter in patients on haloperidol compared to controls after 12 weeks of treatment and reduced total brain volume after 1 year. Patients on olanzapine showed no effects at 12 weeks, but after 1 year they also showed reduced grey-matter volume, although this was not statistically significant after correcting for multiple comparisons. In addition, a subsidiary analysis of different brain areas after 1 year showed evidence of reduced volume in patients taking olanzapine, and also haloperidol, in frontal, occipital and parietal lobes ($p \leqslant 0.05$). There were trend level reductions in total CSF volume in olanzapine-treated subjects compared with controls ($p = 0.07$) (Lieberman *et al*. 2005) at 1 year, but no other differences between groups in changes in total CSF, lateral or third ventricle volume. The next largest study involved a sample of 96 patients with multiple episodes followed for 5 years. This study found statistically significant reductions in cerebral and grey-matter volume and greater expansion of the lateral and third ventricles in patients compared to controls. Analysis of different lobes revealed the same trends throughout the brain, except in the cerebellum (van Haren *et al*. 2008). A study of 73 first-episode patients followed for a mean of 3 years also reported greater ventricular expansion in patients compared with controls and greater reduction in frontal lobe volume (Ho *et al*. 2003).

Studies that quantified the extent of the changes reported an increase in CSF or ventricular volumes

https://doi.org/10.1017/S0033291709992297 Published online by Cambridge University Press

of between 7.7% and 10.9% in adult patients over 1 year (Cahn *et al*. 2002*b*; Ho *et al*. 2003) compared with a 1.4% decrease in controls (Ho *et al*. 2003). Over 10 years increases were 23% to 30.1% compared with increases of 0.6% to 5.1% in controls (Saijo *et al*. 2001; DeLisi *et al*. 2004). Grey-matter, whole-brain or cerebral volume showed a decline of 1.2% to 2.9% per year in adult patients (DeLisi *et al*. 1997; Cahn *et al*. 2002*b*; van Haren *et al*. 2008) compared with 0.4% to 1% in controls (DeLisi *et al*. 1997). Over 5 years there was a 4.2–4.5% reduction in patients (van Haren *et al*. 2008; Cahn *et al*. 2009) and 2.5% in controls (van Haren *et al*. 2008). A 10-year follow-up study of cerebral volume, however, found overall decreases of 5.5–5.9% in patients but changes in controls were similar (3.9–4.1%) (DeLisi *et al*. 2004).

Three studies found that changes were confined to the frontal lobe (Mathalon *et al*. 2001; Ho *et al*. 2003; Reig *et al*. 2009), which was the most consistently affected area across studies. Many studies, however, including the two largest, found diffuse changes across different regions (Sporn *et al*. 2003; Lieberman *et al*. 2005; Whitford *et al*. 2006; Theberge *et al*. 2007; van Haren *et al*. 2008). Findings concerning the temporal lobe were contradictory, with some studies finding the greatest changes in this area (Sporn *et al*. 2003; Whitford *et al*. 2006; Nakamura *et al*. 2007) and some studies, which specifically examined the temporal lobe, finding no changes (DeLisi *et al*. 1997; Wood *et al*. 2001).

Two studies were set up to compare the effects of different drugs (Lieberman *et al*. 2005; Crespo-Facorro *et al*. 2008) and one compared brain volumes between drug-treated and non-drug-treated patients (Dazzan *et al*. 2008). Some studies rescanned drug-naive patients after a period of drug treatment and several studies looked for linear associations between brain volume changes and quantitative aspects of drug treatment such as duration of exposure and dose.

The largest comparative randomized study suggested that different patterns of brain volume loss were associated with different drugs, as described above (Lieberman *et al*. 2005). By contrast, a smaller study found no differences in grey-matter volume changes between patients treated with either haloperidol, olanzapine or risperidone and controls. Changes in ventricle volumes were complex, with healthy controls and patients taking risperidone showing greater lateral ventricle volume increase than haloperidol-treated subjects (Crespo-Facorro *et al*. 2008). The numbers of patients taking each drug were small, however, between 16 and 18, so differences are difficult to interpret.

Preliminary results of a 6-year follow-up of 44 first-episode patients also found an association between grey-matter changes, ventricular enlargement and being on drug treatment compared to being drug free (Dazzan *et al*. 2008).

Five studies started with mostly drug-naive patients, involving 120 patients in all. Two of these demonstrated reduction of grey matter after commencement of a period of drug treatment in patients compared with controls (Cahn *et al*. 2002*b*; Theberge *et al*. 2007). One found some areas of *increased* grey matter after commencement of drug treatment, although a regression to the mean effect may have been present because the increase was strongly predicted by baseline volume (Spearman's $R = 0.62$, $p < 0.001$) (Molina *et al*. 2005). The others did not report any global or lobar volume changes (Keshavan *et al*. 1998*a*; Puri *et al*. 2001; MacMaster *et al*. 2007).

Several studies used correlation or regression analysis to test for a linear association between various estimates of exposure to antipsychotics and brain volume changes. Results were mainly negative. One study found an association between volume reductions and lifetime dose of antipsychotic medication ($r = 0.5$, $p = 0.009$) (Cahn *et al*. 2002*b*). One study found an association between treatment duration and ventricle size but no effect for cortical or hippocampal volume (Lieberman *et al*. 2001). Two studies found an association between current dose and some brain volume reductions, with one reporting correlations of 0.75 and 0.66 ($p < 0.001$) between frontal and temporal lobe volume reduction and antipsychotic dose, but only among first-episode patients (Gur *et al*. 1998). The other found that reductions in areas of the frontal lobes were associated with antipsychotic dose in an exploratory analysis (Theberge *et al*. 2007). Other analyses were negative (Lieberman *et al*. 2001; Puri *et al*. 2001; Saijo *et al*. 2001; Ho *et al*. 2003; Sporn *et al*. 2003; Nakamura *et al*. 2007; van Haren *et al*. 2008; Reig *et al*. 2009; Takahashi *et al*. 2009*a*).

One research group attempted to control for the effects of drug treatment by comparing children with childhood-onset schizophrenia with those diagnosed with 'transient psychosis and behavioural problems' (Gogtay *et al*. 2004). The authors found that the group with schizophrenia had greater loss of grey-matter volume than the comparison group, and they concluded that, as both groups had exposure to antipsychotics, their results confirmed the specificity of volume loss to schizophrenia. However, at baseline, the comparison group had a longer duration of illness, greater exposure to antipsychotics, and showed greater volume deficits than the children with schizophrenia. Over follow-up, the comparison group had less exposure to antipsychotics, with 32% not taking antipsychotics at the time of the second MRI. The volume changes over the follow-up period still left

Table 1. *Longitudinal studies*

Study	Subjects	Duration of follow-up between scans	Results: Changes in CSF, ventricular, whole-brain, hemisphere, total grey-matter or lobar volumes compared with controls
DeLisi *et al*. 1997	4-year follow-up: 50 first-episode 20 controls	Change per year over 4 or more years and at 10 years	At first follow-up: greater enlargement of left ventricles ($p=0.02$), reduction of both hemispheres ($p<0.004$) and right cerebellum ($p=0.02$). No difference in temporal lobe
DeLisi *et al*. 2004	10-year follow-up: 26 patients 10 controls		Patients showed greater ventricular enlargement during the second 5 years ($p<0.05$) but no difference in change in hemisphere volumes
Nair *et al*. 1997	18 long-term 5 controls	1–4 years	Higher rate of ventricular expansion in patients ($p=0.005$)
Gur *et al*. 1998	20 first-episode 20 long-term 17 controls	Mean 30 months	Some baseline differences but no difference in CSF, whole brain, frontal lobe changes. *Less* reduction in temporal lobe volume in patients than controls ($p=0.04$)
Keshavan *et al*. 1998*a*; MacMaster *et al*. 2007	16–17 first-episode (drug-naive) 12 controls	1 year	No differences reported
Puri *et al*. 2001	24 first-episode (drug-naive) 12 controls	Mean 8 months	No difference in ventricular volume changes overall (patients showed greater variability)
Lieberman *et al*. 2001	51 first-episode 13 controls	At least 1 year. Mean 661–929 days	Baseline differences in ventricular volumes. Controls showed greater decrease in cortical volume ($p=0.01$)
Mathalon *et al*. 2001	24 long-term 25 controls	Mean 4 years	Patients showed greater expansion of right lateral ventricles ($p=0.03$), right frontal CSF ($p=0.04$), and greater reduction of right frontal, but not temporal, grey matter ($p=0.03$)
Saijo *et al*. 2001	15 long-term 12 controls	4 and 10 years	Patients showed greater expansion of lateral ventricles ($p=0.0007$)
Wood *et al*. 2001	30 first-episode 12 long-term 26 controls	Mean 1.9–2.3 years	First-episode patients ($p=0.04$) and multiple-episode patients ($p=0.002$) showed greater reduction of whole-brain volume
Cahn *et al*. 2002*b*; (mostly drug-naive)	34 first-episode 36 controls	1 year	Patients showed greater increase in lateral ventricle ($p=0.001$) and greater reduction in whole-brain volume ($p=0.001$) and grey-matter volume ($p<0.001$) but no difference in cerebellar changes
Ho *et al*. 2003	73 'recent-onset' (33 neuroleptic-naive) 23 controls	Mean 3 years	Baseline differences in whole-brain volume. Patients showed greater increase in cortical sulcal CSF, $p=0.04$. No difference in changes in lateral ventricle volumes or whole-brain volume. Patients showed greater decrease in frontal lobe volume ($p=0.05$) No difference in temporal, parietal or cerebellar volume changes
Kasai *et al*. 2003*a*,*b*	13 first-episode schizophrenia 15 first-episode affective disorder 14–22 controls	1.5 years	No differences reported
Rapoport *et al*. 1999; Sporn *et al*. 2003	39 childhood-onset schizophrenia 43 controls	Mean 3.4 years	Patients showed greater increase in lateral ventricles, greater reduction of whole-brain volume ($p=0.001$), total grey-matter ($p=0.001$–0.01), frontal ($p<0.001$), parietal ($p<0.05$) and temporal ($p<0.001$) volumes

James *et al*. 2004	16 long-term (adolescents) 16 controls	2–3 years	Baseline difference in fourth ventricle and prefrontal cortex. No difference in changes in fourth ventricle, whole-brain volume or volume of prefrontal cortex
Lieberman *et al*. 2005	161 first-episode 58 controls	1 year	Non-significantly greater increase in total CSF volume at 52 weeks in the olanzapine group compared with controls ($p=0.07$). No difference in change in lateral or third ventricle Haloperidol-treated patients showed greater reduction in whole-brain volume ($p=0.03$), total grey-matter volume ($p<0.001$) and temporal lobe volume ($p=0.03$). Olanzapine-treated patients showed greater reduction in total grey-matter volume ($p=0.03$). Both drugs showed greater reductions in frontal, parietal and occipital lobes ($p=0.05$ to <0.001)
Molina *et al*. 2005	17 first-episode (drug-naive) 12 long-term 11 controls	Mean 2 years	No change in total brain volume. Long-term patients showed *increased* grey matter ($p<0.05$). First-episode patients showed *increased* grey matter in parietal ($p=0.05$) and occipital ($p=0.02$) lobes. Long-term patients showed *increase* in frontal lobes ($p=0.04$), parietal ($p=0.004$) and occipital ($p=0.001$) lobes
Whitworth *et al*. 2005	21 first-episode 17 long-term 20 controls	2.5–3.7 years	Baseline difference in lateral ventricles, but no difference in change over time in lateral ventricles or hemisphere volumes
Khorram *et al*. 2006; Paneka *et al*. 2007	10 long-term 20 controls (10 age-matched)	Approximately 1 year	No differences reported
Whitford *et al*. 2006	25 first-episode 26 controls	2–3 years	Patients showed diffuse grey-matter loss compared with controls, concentrated in temporal and parietal cortices ($p<0.05$)
Nakamura *et al*. 2007	17 first-episode schizophrenia 21 first-episode affective psychosis 26 controls	1.5 years	Baseline differences in sulcal CSF and grey-matter volume in both groups. Schizophrenia group only showed greater expansion of left sulcal CSF ($p=0.003$) and lateral ventricle ($p<0.001$) and greater reduction in total grey-matter volume ($p=0.01$) (localized to frontal and temporal lobes). Affective group showed greater *increase* in grey matter over study ($p=0.001$)
Theberge *et al*. 2007	16 first-episode (neuroleptic-naive) 16 controls	10 months and 30 months	Patients showed reduced volume of total grey matter at 30 months ($p<0.05$), with significant reductions in frontal, temporal, parietal and limbic lobes. No changes in controls
Crespo-Facorro *et al*. 2008	52 first-episode 38 controls	1 year	No difference in changes in CSF, whole-brain, total grey-matter or lobar volumes
van Haren *et al*. 2008	96 long-term 113 controls	5 years	Patients showed greater expansion of lateral and third ventricles ($p<0.05$), greater reduction in cerebral volume ($p<0.05$) and total grey-matter volume ($p<0.05$), with trends reflected in all lobes, except cerebellum
Dazzan, 2008	44 first episode 40 controls	6.5 years	Patients showed larger increase in ventricular volume ($p=0.03$) but no difference in changes in grey-matter volume
Takahashi *et al*. 2009*a*	23 first-episode 11 long-term 26 controls	Mean 2.0–2.4 years	Greater reduction in whole-brain volume in patients compared with controls ($p<0.04$)
Reig *et al*. 2009	21 recent-onset adolescents 34 controls	2 years	Male, but not female, patients showed greater increase in left frontal CSF ($p<0.01$) No difference in total grey-matter volume changes Males but not females showed greater decrease in frontal grey matter ($p<0.05$). No differences in changes in parietal, temporal and occipital lobes

CSF, Cerebrospinal fluid.

the comparison group with smaller volumes than controls in all areas, and smaller or comparable volumes to children with schizophrenia.

In addition to the large randomized comparative trial (Lieberman *et al*. 2005), one study of 96 long-term patients also found that a lesser degree of cerebral grey-matter loss was associated with a higher cumulative dose of olanzapine, although the association just failed to reach statistical significance ($p = 0.07$) (van Haren *et al*. 2008). However, another study did not report any differences after a switch from older antipsychotics to olanzapine, except for a reduction in thalamic volume, which had been increased at baseline (Khorram *et al*. 2006; Panenka *et al*. 2007). Other studies also found no difference in volume changes in patients taking typical and atypical antipsychotics (Cahn *et al*. 2002*b*; Ho *et al*. 2003; Sporn *et al*. 2003).

Drug-naive studies

Locating drug-naive studies was difficult as subjects in some studies that are presented as drug naive had taken antipsychotics for short periods, and some studies with drug-naive patients did not identify themselves as such. As some longitudinal and cross-sectional studies show possible changes after only short periods of treatment (Dazzan *et al*. 2005; Lieberman *et al*. 2005), it was decided to include only studies in which patients had had $\leqslant 4$ weeks of antipsychotic treatment. Three studies that were presented as drug-naive studies were therefore excluded because patients had taken antipsychotic medication for a mean of around 5 weeks (Ettinger *et al*. 2001; Moreno *et al*. 2005; Crespo-Facorro *et al*. 2008). Two of these did not report any evidence of differences in total brain volume, ventricular volume or grey-matter volume (Ettinger *et al*. 2001; Crespo-Facorro *et al*. 2008). The third detected differences in total CSF and frontal lobe grey-matter volumes in males only, which may not have been detected had male and female patients been combined because female patients showed opposite trends (Moreno *et al*. 2005). One study that specified that patients had not had any 'significant neuroleptic treatment' was included (Bottmer *et al*. 2005) because this was specified as less than 2 weeks of treatment in a previous paper (Bachmann *et al*. 2004). Two other studies in which patients had had a mean or median of between 1 and 3 weeks of antipsychotic treatment were also included (Puri *et al*. 2001; Nakamura *et al*. 2007).

The Medline search produced 94 papers and 21 studies were identified that met inclusion criteria (Table 2). Other papers were not relevant or represented multiple publications. The studies included a total of 657 principally drug-naive patients. Most involved young people with a first psychotic episode prior to the commencement of medication. The majority of studies did not report any differences in volumes of whole brain, total grey matter or CSF spaces between patients and controls, including the largest study involving 68 patients.

Five out of 21 studies reported some differences between patients and controls in volumes of interest (Chua *et al*. 2007). One of these studies involved a sample of patients with first-episode schizophrenia and affective psychosis who had taken antipsychotic drugs for up to 24 weeks. Hence, drug use cannot be entirely excluded as a cause of the observed differences (Nakamura *et al*. 2007). Another study reported reductions in global grey-matter and CSF volume in an initial publication involving 18 subjects (Jayakumar *et al*. 2005), but did not report global differences in a larger sample of 51 patients (Venkatasubramanian *et al*. 2008). A study from Hong Kong found no difference in absolute volumes, except for the right lateral ventricle, but did find differences in ratios of grey matter, white matter and CSF to whole-brain volume (Chua *et al*. 2007). Another study reported a difference in the third ventricle only (Cahn *et al*. 2002*a*). One further study reported a trend level reduction in whole-brain volume (John *et al*. 2009) and another reported that patients had smaller cerebellar volumes (Bottmer *et al*. 2005).

One study involved 31 chronically ill, untreated patients in India. This study found no differences between patients and controls in the volume of both cerebral hemispheres, the ventricles and the caudate nuclei. A subgroup of patients without dyskinetic movements had a larger ventricle to hemisphere ratio on the right side ($p = 0.01$) (McCreadie *et al*. 2002). Two other studies involved patients whose mean duration of illness was 4 to 5 years (Buchsbaum *et al*. 1996; Ichimiya *et al*. 2001). Neither of these studies reported any difference in global volumes. Hence, the only three studies of patients whose duration of illness is comparable to patients who have taken antipsychotic drug treatment for some time report no major differences in global cerebral, grey-matter, ventricular or CSF volumes.

Three studies of people considered to be at high risk for developing schizophrenia or psychosis due to genetic loading or subclinical symptoms have been conducted. None have reported any differences in global grey matter, whole-brain, lobar, CSF or ventricular volumes in high-risk patients as a whole, or in the subgroup who progress to psychosis compared to controls (Lawrie *et al*. 2001; Borgwardt *et al*. 2007; Takahashi *et al*. 2009*b*, *c*). Longitudinal follow-up of the Australian cohort suggested reduction of the superior temporal gyrus and insular cortex, but most

of the sample were treated with antipsychotics (Takahashi *et al*. 2009*b*,*c*). In the Scottish study, individuals in the high-risk group with psychotic symptoms showed greater right temporal lobe reduction than those who were unsymptomatic, but they did not differ from controls (Lawrie *et al*. 2002).

Discussion

The data presented here raise two important questions. First, does treatment with antipsychotic drugs cause a reduction in brain volume? Second, does antipsychotic drug treatment contribute to some of the features of brain structure that are usually attributed to schizophrenia, particularly reduced brain size and enlarged ventricles?

Some evidence suggests that there is progressive reduction of brain size and enlargement of brain spaces in people who are taking antipsychotic drugs. Fourteen studies found evidence of reduced brain or grey-matter volume or increased ventricular or CSF volume in patients compared with controls during a period of drug treatment. The two largest studies, one conducted in first-episode patients (Lieberman *et al*. 2005) and one in patients with long-term illness (van Haren *et al*. 2008), both found global brain volume reductions, suggesting that some of the negative studies may have suffered from being underpowered. One of these studies found differential rates of volume reduction with different drugs (Lieberman *et al*. 2005).

Evidence from longitudinal studies has traditionally been interpreted as showing the progressive nature of the neuropathology of schizophrenia. The finding that some studies with first-episode patients showed the same patterns of volume loss was thought to demonstrate that drug treatment could not be responsible for the changes. However, authors of a systematic review of first-episode studies stress that antipsychotic drug effects cannot be discounted (Steen *et al*. 2006). Most studies of drug-naive patients examined here did not report or detect differences in total brain volume, global grey-matter volume or CSF volumes between patients and controls, including three studies of untreated patients with long-term illness. These results are particularly remarkable, given the difficulty of selecting a comparable control group in these studies. The results suggest that the brain changes found in some first-episode studies may also be attributable to drug treatment, especially because some studies suggest that structural changes may occur after only short periods of treatment (Lieberman *et al*. 2005).

The literature examined in this review is inconsistent, however, with almost half of the longitudinal studies failing to detect or report progressive changes, for example. We attempted to ascertain whether use of lower doses of medication might account for negative findings in some studies, but information on dose was scant and did not enable comparisons. The dose range of haloperidol in the negative comparative drug trial by Crespo-Facorro *et al*. (2008) was lower than the dose range for the larger trial (Lieberman *et al*. 2005), and the mean daily dose of haloperidol used was <5 mg, but no mean doses are given for the larger study.

Analyses of the relationship between the degree of exposure to antipsychotics and brain volume changes also gave mixed results, and only a minority of studies detected a linear association between measures of drug use and brain volume changes. However, this may partly reflect the difficulty of accurately ascertaining previous drug intake. In addition, the effects of drugs may be nonlinear in nature. If, for example, the impact of drug treatment occurs when a certain threshold of exposure is reached, which may vary between individuals, then it is unlikely that a linear association would be seen. Drug-induced effects may also vary as a function of the stage of exposure and age of recipients. One study found, for example, that the association between duration of illness and brain volume decrease was better described by a logarithmic than a linear function, with brain volume decreasing at a faster rate in the early years of illness than later on (Molina *et al*. 2004). Studies that quantified the extent of brain volume loss also suggested that it was highest during the first year of follow-up. By contrast, however, there was little evidence in the studies examined here that changes varied between first-episode and long-term patients. Of the three studies that included both multiple-episode and first-episode patients, two found no differences in volume changes between the patient groups (Wood *et al*. 2001; Whitworth *et al*. 2005) and only one found greater reductions of frontal and temporal lobe volumes in first-episode patients compared with long-term patients (Gur *et al*. 1998). Some authors have also suggested that brain volume changes may be exaggerated in children and adolescents compared to adults (Arango *et al*. 2008).

Earlier research is sometimes thought to have ruled out drug-induced effects on brain volume. A cross-sectional study using computed tomography that included a small number of patients who had not received antipsychotic treatment found no association between categories of antipsychotic use and ventricular–brain ratio among long-term in-patients with schizophrenia. Nevertheless, the fact that an association between ventricular volume and involuntary movements was detected suggests that drug treatment may have played a contributory role (Owens *et al*. 1985). A previous review of drug-naive research suggested that differences in the brains of drug-naive

https://doi.org/10.1017/S0033291709992297 Published online by Cambridge University Press

Table 2. *Imaging studies of brain structure in antipsychotic-naive patients*

Study	Subjects	Results: differences in CSF, ventricular, whole-brain, hemisphere, total grey-matter or lobar volumes compared with controls
Buchsbaum *et al*. 1996	20 long-term schizophrenia (mean duration 4.6 years) 15 controls	No differences reported
Keshavan *et al*. 1998*a*, *b*; Gilbert *et al*. 2001; Prasad *et al*. 2004*a*, *b*; Lacerda *et al*. 2007; Upadhyaya *et al*. 2007	16–51 first-episode 17–55 controls	No differences reported
Ichimiya *et al*. 2001	20 long-term (mean duration 5.1 years) (men) 20 male controls	No difference in hemisphere volumes or cerebellum
Puri *et al*. 2001 (treated for a mean of 20 days, S.D. = 20.7)	24 first-episode 12 controls	No significant difference in total ventricular volume or ventricular–brain ratio
Cahn *et al*. 2002*a* (sample described as mostly drug naive)	34 first-episode 36 controls	Patients had larger third ventricle ($p = 0.01$). No differences in lateral ventricle, whole-brain, grey-matter or cerebellar volume
Joyal *et al*. 2002, 2003	18 first-episode 22 controls	No differences reported
McCreadie *et al*. 2002	31 long-term 31 controls	No difference in lateral ventricle or hemisphere volumes
Salgado-Pineda *et al*. 2003	13 first-episode, men 13 controls	No difference in total CSF and total grey matter
Molina *et al*. 2004	22 first-episode 44 controls	No differences in prefrontal CSF volumes
Narr *et al*. 2004, 2005	Subsample of 38 drug-naive first-episode 60 controls	No differences reported
Bottmer *et al*. 2005 (< 2 weeks of drug treatment)	37 first-episode 18 controls	Patients had reduced left and right cerebellar volumes ($p < 0.001$). No other differences reported
Davatzikos *et al*. 2005	32 first-episode 79 controls	Patients had higher ventricular CSF volume ($p = 0.01$) and lower grey-matter volume ($p = 0.005$)
Jayakumar *et al*. 2005	18 first-episode 18 controls	First sample of patients had larger global CSF volumes ($p = 0.009$) and smaller grey-matter volume ($p = 0.001$)
Venkatasubramanian *et al*. 2008	51 first-episode 47 controls	No differences reported
Tauscher-Wisniewski *et al*. 2005	37 first-episode 37 controls	No differences reported
Chua *et al*. 2007	26 first-episode 38 controls	No difference in global CSF, whole-brain or grey-matter volume. Patients had larger right lateral ventricle ($p = 0.02$) and raised CSF to whole brain ratio ($p = 0.007$). Grey matter to whole brain ratio reduced in patients ($p = 0.03$)
Glenthoj *et al*. 2007	19 first-episode 19 controls	No difference in whole-brain volume
Nakamura *et al*. 2007 (treated for a median of 3 weeks, range 0–24 weeks)	29 first-episode schizophrenia 34 first-episode affective disorder 36 controls	Both patient groups showed larger sulcal CSF ($p = 0.004$) and lateral ventricles ($p = 0.05$) and smaller total grey matter ($p = 0.001$)
Okugawa *et al*. 2007	14 first-episode 16 controls	No differences reported
Theberge *et al*. 2007	16 first-episode 16 controls	No difference in total grey-matter volume or any regional volumes

https://doi.org/10.1017/S0033291709992297 Published online by Cambridge University Press

Table 2 (*cont.*)

Study	Subjects	Results: differences in CSF, ventricular, whole-brain, hemisphere, total grey-matter or lobar volumes compared with controls
John *et al*. 2009	23 first-episode 23 controls	Patients showed trend for lower whole-brain volume ($p < 0.08$)
Lui *et al*. 2009	68 first-episode 68 controls	No differences reported

CSF, Cerebrospinal fluid, S.D., standard deviation.

patients with schizophrenia had been demonstrated (Torrey, 2002). However, this conclusion was based on pneumo-encephalography studies from the mid-twentieth century conducted on chronically institutionalized patients who had received many other types of drugs and physical treatments and two small computerized tomography studies from the 1980s that involved only 17 drug-naive patients in total (Schulz *et al*. 1982; Weinberger *et al*. 1982). Moreover, most of the drug-naive studies examined in the current paper were published subsequent to this review.

Other recent reviews have highlighted regional drug-induced effects and differences between typical and atypical antipsychotics (Scherk & Falkai, 2006; Vita & De Peri, 2007; Navari & Dazzan, 2009). One of these suggests that typical antipsychotics, but not atypicals, may reduce global grey-matter volume (Navari & Dazzan, 2009), but this and other reviews place much weight on the results of the large randomized trial, funded by the manufacturers of olanzapine, which reported that haloperidol, but not olanzapine, was associated with reduced grey-matter volume at 1 year. Similar trends were apparent for olanzapine-treated subjects, however, both in global grey-matter volume and in several regional volumes (Lieberman *et al*. 2005). The authors of a review of structural changes in long-term patients suggested that drug treatment may even reverse underlying changes (Hulshoff Pol & Kahn, 2008), but this conclusion was based on a small number of studies and depended on the finding of a non-significant trend association between olanzapine dose and smaller brain volume loss in one study (van Haren *et al*. 2008). The evidence on typicals and atypicals from the present review was inconsistent and overall it was not possible to conclude that they have differential effects.

Most post-mortem studies confirm that the brains of people who have received long-term treatment for schizophrenia are lighter, smaller and have larger ventricles than control brains (Harrison, 1999*b*). Studies of antipsychotic-treated rats conducted in the 1970s and 1980s found changes in neuronal density and volume attributable to antipsychotic drug treatment in the striatum but not in the cortex (Harrison, 1999*a*). However, a recent study of macaque monkeys treated with olanzapine or haloperidol for 18 months found an 8–11% reduction in mean fresh brain weight compared to controls (Dorph-Petersen *et al*. 2005). The deficit was present throughout the brain but was most significant in the frontal and parietal lobes.

Further evidence is provided by a recent meta-analysis of studies of people diagnosed with bipolar disorder, which found that antipsychotic use correlated with reduced grey-matter volume compared to controls across studies (Arnone *et al*. 2009).

The mechanism by which antipsychotic drugs cause brain volume reduction, if they do, is uncertain, including whether changes are permanent or reversible. A small withdrawal study suggested that drug-induced volume changes are reversible over short periods of time, leading the authors to suggest that they represent physiological rather than permanent anatomical changes (McClure *et al*. 2006). However, experimental neuropathological studies demonstrate that antipsychotics can cause neurotoxicity and apoptosis (Dean, 2006). Human and animal brains demonstrate neuropathological effects such as gliosis in the brain stem and striatum (Harrison, 1999*a*), and some studies report more generalized gliosis (Bruton *et al*. 1990; Selemon *et al*. 1999).

The clinical significance of the structural changes is a further important question, and several longitudinal and cross-sectional studies find evidence of an association between impaired intellectual performance and brain volume changes (Sullivan *et al*. 1996; Gur *et al*. 1998, 1999; Ho *et al*. 2003). A recent study of patients with bipolar disorder found a significant correlation between IQ reduction and grey-matter density loss in the temporal lobe in patients and controls (Moorhead *et al*. 2007). By contrast, DeLisi *et al*. (1991) found no association between neurocognitive measures and brain volume loss.

https://doi.org/10.1017/S0033291709992297 Published online by Cambridge University Press

This review is limited by the fact that few studies have been designed primarily to investigate the effects of drug treatment on brain structure. Existing studies are highly heterogeneous with respect to outcomes measured, sample size, length of follow-up and analysis of drug exposure, where this was conducted. Hence, it was not possible to conduct a meta-analysis of studies. The fact that many studies had small samples raises the possibility that they were underpowered to detect volume changes or effects of antipsychotic exposure. Studies of drug-naive patients may also have missed differences between patients and controls because of their small size. By contrast, studies may have selectively highlighted chance positive findings, especially where multiple tests were conducted.

Further studies that are specifically designed to investigate drug-induced effects on brain volume are needed. Randomized trials with drug-naive patients allocated to antipsychotic treatment and non-drug treatment and compared with well-matched healthy controls would be the ideal design. Although withholding drug treatment for a long period would be ethically problematic, it may be possible to do so for a few weeks. Given the importance of clarifying the impact of drug treatment, we suggest that such studies need to be conducted. Such studies would also clarify how rapidly drugs start to affect brain structure, which would aid the interpretation of imaging research in first-episode schizophrenia. Naturalistic comparisons between patients treated continuously and those who remain wholly or largely drug free would also be interesting, but factors such as illness course and severity may confound results. Further investigation is needed into the differential effects of different classes of antipsychotic drugs and of the impact on brain volume of incidental effects of schizophrenia such as use of illicit substances, institutionalization and poor physical health.

Conclusion

Overall, there seems to be enough evidence to suggest that antipsychotic drug treatment may play a role in reducing brain volume and increasing CSF or ventricular spaces. Further research is urgently required to clarify this possibility. The issue is clinically important as some studies suggest that there is a correlation between reduced brain volume and cognitive function. Although it remains possible that the underlying disease process also causes brain volume changes, we suggest that antipsychotic drug treatment may be responsible for some of the changes that are usually attributed to schizophrenia.

Declaration of Interest

No specific financial support was received for this study. J.M. is the co-chairperson of the Critical Psychiatry Network.

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