

Effects of antipsychotics on brain structure

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Purpose of review

This review highlights the recent findings of different effects of typical and atypical antipsychotics on brain structure.

Recent findings

Studies examining the effect of treatment with typical antipsychotics on brain structure revealed a significant increase in basal ganglia volumes and decreased grey matter volume in different cortical regions. These volume changes were detectable even after a 12-week treatment. In contrast to these results, treatment with atypical antipsychotics does not seem to change basal ganglia volumes in neuroleptic-naïve patients. Moreover, switching from typical to atypical antipsychotic treatment reduces the increased basal ganglia volume to normal values compared with healthy controls. Only the volumes of thalamus and cortical grey matter increased after atypical antipsychotic treatment.

Summary

Currently, there is growing evidence that atypical antipsychotics might ameliorate structural changes caused by the disease process underlying schizophrenia and effects of typical antipsychotics. Further studies have to investigate the mechanism leading to these varying effects on brain structure.

Keywords

antipsychotics, basal ganglia, brain structure, magnetic resonance imaging

Introduction

In patients with schizophrenia, structural brain abnormalities have been extensively and consistently reported [1–3]. The most common pathomorphological finding has been demonstrated in the ventricular system and in cortical and subcortical grey matter regions in schizophrenic patients compared with healthy controls. Different longitudinal studies [4–6] revealed a progressive change in brain structure over time. These ongoing pathomorphological changes may arise from a progressive pathophysiology of the illness [7] or also from the effects of antipsychotic agents. Some preclinical studies [8,9] showed possible neurotrophic, neurogenetic and neuroprotective effects of typical and atypical antipsychotics in different brain regions.

In the present review, we will focus on the most recent literature on the effect of antipsychotics on brain structure. Articles published between July 2004 and September 2005 were identified using Medline and PubMed searches with the following keywords: ‘brain structure’, ‘schizophrenia’, ‘neuroleptics’ or ‘antipsychotics’ and ‘MRI’. This analysis revealed eight recently published studies. In addition, we will report on six prior publications on this topic based on a review we published last year in German [10]. Up to now, this topic has only been reviewed by Bilder *et al.* [11] in 1994.

Most studies used magnetic resonance imaging (MRI) and defined regions of interest analyses to obtain volumes of different brain structures. A few studies used voxel-based morphometry (VBM) to get the investigator unbiased differences in the total brain or the regional grey matter volume.

All studies included are listed in Table 1. First, we will describe the findings of cross-sectional studies that examined brain structure differences between different groups of patients. Second, we will review the results of longitudinal studies examining the same patients after treatment switches and last, we will report on the findings of longitudinal studies of neuroleptic-naïve or drug-free patients after prior antipsychotic treatment.

Cross-sectional studies on brain structural changes caused by antipsychotic treatment

Three studies investigated the effect of antipsychotic treatment on brain structure cross-sectionally. Two of them are recently published papers.

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Abbreviations

MRI magnetic resonance imaging
VBM voxel-based morphometry

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Table 1 List of all included studies

Author	Method	Participants	Treatment	Findings
Gur <i>et al.</i> [12]	Cross-section	21 SP 48 SP 27 SP 128 HC	Treatment-naïve Typical AP Atypical AP	Unchanged volume drug-naïve SP compared to HC Increased volumes of caudate and putamen in treated SP, positive correlation of typical AP dose and volume of caudate, putamen and thalamus
Pressler <i>et al.</i> [13*]	Cross-section	30 SP 20 HC		In previously treated SP, right insular cortical grey matter volume correlated positively with dose-years
Dazzan <i>et al.</i> [14*]	Cross-section	22 FE 32 FE 30 FE	Drug-free Typical AP Atypical AP	Increased thalamic grey matter in atypical treated FE patients Increased right lenticular nucleus and decreased grey matter volume in right insula, left paracentral lobule and left precuneus in typical treated FE patients
Scheepers <i>et al.</i> [15]	Follow-up (52 weeks)	28 SP	Switch to clozapine	Decreased volume of left caudate
Corson <i>et al.</i> [16]	Follow-up (2 years)	13 SP 10 SP	Typical AP Atypical AP	Increased basal ganglia volume in patients treated with typical AP and decreased volume in atypical treated patients
Lang <i>et al.</i> [17]	Follow-up (42–56 weeks)	10 SP, typical AP 13 SP, risperidone 14 SP, risperidone 23 HC	Switch to olanzapine Switch to olanzapine No switch	Decreased volume of putamen and globus pallidus, caudate unchanged in previous, typical treated patients Unchanged volume in risperidone to olanzapine-switched patients
Lieberman <i>et al.</i> [18**]	Follow-up (12–102 weeks)	82 SP, previously treated 79 SP, previously treated 62 healthy controls	Switch to olanzapine Switch to haloperidol	Decreased total grey matter volume (week 12) and increased caudate volume (weeks 24, 52 and 102) in haloperidol-treated patients
Chakos <i>et al.</i> [19]	Follow-up (18 months)	21 treatment-naïve SP 8 treated SP 10 healthy controls	Typical AP	Increased nucleus caudatus and unchanged ventricular or cortical volume in typical treated patients
Keshavan <i>et al.</i> [20]	Follow-up (mean, 305 days)	11 treatment-naïve PP	Typical AP	Increased nucleus caudatus and unchanged prefrontal or total brain volume in typical treated patients
Lang <i>et al.</i> [21]	Follow-up (12 months)	30 FE SP 12 chronic treated SP 23 healthy controls	Risperidone	Unchanged volume of caudate, putamen and globus pallidus in risperidone-treated patients
Heitmiller <i>et al.</i> [22]	Follow-up (mean, 30 months)	14 treatment-naïve SP 14 healthy controls	Atypical AP	Unchanged caudate volume in atypical treated patients Gender effect
Massana <i>et al.</i> [23*]	Follow-up (3 months)	11 treatment-naïve FE SP	Risperidone	Increased grey matter volume of left caudate and accumbens
Tauscher-Wisniewski <i>et al.</i> [24*]	Follow-up (12 weeks)	37 treatment-naïve FE SP 10 patients' follow-ups 37 healthy controls	Quetiapine	No difference at baseline between patients and control subjects No change in caudate volume in quetiapine-treated patients
Garver <i>et al.</i> [25**]	Follow-up (28 days)	7 SP 6 SP 6 SP 7 healthy controls	Risperidone Ziprasidone Haloperidol	No difference of cortical grey matter volume at baseline Increased cortical grey matter volume in risperidone-treated or ziprasidone-treated patients

AP, antipsychotic; FE, first-episode; HC, healthy controls; PP, psychotic patients; SP, schizophrenic patients.

Subcortical brain structures were examined in 21 neuroleptic-naïve schizophrenic patients, 48 schizophrenic patients treated with typical neuroleptics, 27 schizophrenic patients treated with typical and atypical neuroleptics and in 128 healthy controls [12]. The neuroleptic-naïve patients did not differ from the healthy controls in subcortical volumes except for decreased thalamic volume. The previously treated patient group showed an increase in the volumes of putamen and globus pallidus compared with healthy controls and neuroleptic-naïve patients. A higher dose of a typical neuroleptic was associated with higher caudate, putamen and thalamus volumes, whereas a higher dose of an atypical neuroleptic was associated only with higher thalamic volume.

A recent study [13[•]] investigated insular grey matter volume and cortical surface size in 30 patients with schizophrenia and 30 healthy controls. These authors could not observe any differences between patients and controls in either insular cortical surface or volume. The right insular cortical grey matter volume had a weak, significantly positive correlation with neuroleptic dose-years.

Dazzan *et al.* [14[•]] examined different effects of typical and atypical antipsychotics on brain grey matter in 84 first psychotic episode patients. Twenty-two patients were drug-free at examination, 32 were on treatment with typical and 30 with atypical antipsychotics. Patients treated with atypical antipsychotics compared with drug-free patients exhibited an increase in the volumes of right and left thalamus. This excess in the volumes was positively correlated with the current dose of olanzapine. Patients on typical antipsychotics in comparison with drug-free patients showed increased grey matter volume in the right lenticular nucleus and decreased grey matter volume in right insula, left paracentral lobule and left precuneus. Patients treated with typical antipsychotics compared with patients treated with atypical antipsychotics had grey matter deficit on the left middle temporal gyrus.

Follow-up studies on brain structure changes considering treatment switches

Four longitudinal studies examined volume change of brain structures after switching from typical to atypical antipsychotic treatment. Two of these were recently published papers.

Scheepers *et al.* [15] investigated 28 schizophrenic patients who had not responded to typical antipsychotics. Treatment was switched to clozapine, and MRI scans were processed during typical treatment and after 24 and 52 weeks of clozapine treatment. Clozapine treatment resulted in a significant reduction in left caudate volume in patients who responded to the drug but not in patients

who did not respond to clozapine at 52 weeks of treatment. The degree of reduction in left caudate volume was significantly related to the extent of improvement in positive and general symptoms but not in negative symptoms.

Another study [16] examined the change in basal ganglia volume during 2 years of follow-up in 13 schizophrenic patients treated almost exclusively with typical antipsychotics compared with 10 schizophrenic patients exposed mostly to atypical antipsychotics. The authors observed an increased mean basal ganglia volume in patients receiving predominantly typical antipsychotics while patients receiving mostly atypical antipsychotics showed a decreased mean basal ganglia volume.

A recent study [17] investigated basal ganglia volumes in chronically treated patients after switching to olanzapine. Ten patients receiving at baseline typical antipsychotics and 13 receiving risperidone exhibiting limited response were switched to treatment with olanzapine. Fourteen more patients receiving risperidone at baseline and exhibiting a good response continued treatment with risperidone. At baseline, basal ganglia volumes in patients treated with typical antipsychotics were greater than in healthy controls. After switching to olanzapine, volumes of putamen and globus pallidus decreased and did not differ from those of healthy controls at follow-up evaluation. No change of caudate volume was observed. In the patients receiving risperidone at baseline, basal ganglia volumes did not differ between those with good and poor response. No significant volume changes were observed in subjects after the switch from risperidone to olanzapine treatment.

Lieberman *et al.* [18^{••}] conducted the first longitudinal, randomized, controlled, multisite, double-blind study in 161 first-episode patients. Patients were treated with olanzapine ($n = 82$) and haloperidol ($n = 79$) and followed up for up to 104 weeks. MRI scans were processed at weeks 12, 24, 52 and 104. Haloperidol-treated patients exhibited significant decrease in grey matter volume, whereas olanzapine-treated patients did not. Most of the decline in the haloperidol group appeared to occur during the first 12 weeks. This decline in grey matter volume was significantly observed in frontal grey matter. Volume changes in temporal and parietal grey matter were not significant after correction for multi-comparison. Caudate volumes increased significantly in the haloperidol-treated patients compared with the olanzapine-treated patients in weeks 24, 52 and 104.

Follow-up studies on brain structure changes in neuroleptic-naïve or drug-free patients before and after treatment

Seven longitudinal studies examined changes of brain structure volumes in neuroleptic-naïve patients before

and after treatment with antipsychotic agents. Four studies were recently published.

The first study that reported antipsychotic-associated structural brain change was published in 1994. These authors [19] investigated volumes of nucleus caudatus, cortex and lateral ventricle in 21 treatment-naïve and eight previously treated schizophrenic patients using MRI at baseline and at 18-month follow-up. After the baseline scans, patients were treated with fluphenazine. If they did not achieve remission, patients progressed through treatment algorithm and received up to three different typical neuroleptics. The authors examined the effect of time on brain structure. Ventricular and cortical volumes did not change significantly. Caudate volume increased 5.7% in the patients during the 18-month treatment interval. Greater amounts of antipsychotic medication received prior to baseline scan and younger age were associated with a larger increase in caudate volume.

Keshavan *et al.* [20] examined volume of the caudate nuclei in a longitudinal prospective study of first-episode treatment-naïve psychotic patients. The authors obtained MRI scans at baseline and following treatment with typical neuroleptics (mean duration, 305 days). They computed caudate, prefrontal cortex and total brain volumes. Analysis revealed a significant 15% increase in caudate volumes, but no significant changes in prefrontal or total brain volume.

Volumes of caudate, putamen and globus pallidus were examined in first-episode schizophrenic patients at baseline and after 1 year of treatment with risperidone [21]. The lifetime exposure to antipsychotic medication did not exceed 8 weeks during the year of the study or 4 weeks of continuous treatment immediately before the study. Volumes of basal ganglia were unchanged after 1-year exposure to risperidone.

Heitmiller *et al.* [22] investigated in a recent study caudate volumes in neuroleptic-naïve schizophrenic

patients at baseline and at a follow-up (mean duration, 30.2 months) after atypical treatment. The authors observed no difference between patients and controls in the amount of change during this time in the volume of the caudate. Female patients showed a negative correlation between drug exposure and volume change while male patients had a positive correlation. Hence this study revealed a significant gender effect on the relationship between atypical antipsychotic exposure and caudate volume.

A more recent study [23^{*}] examined 11 first-episode neuroleptic-naïve schizophrenic patients. MRI scans were processed at baseline and after 3 months of continuous treatment with risperidone. Regions of interest-based VBM analyses revealed increased grey matter volume for the left caudate nuclei and for the left accumbens after the treatment with risperidone. This result is in contrast to prior findings.

Another recent study [24^{*}] investigated volumes of caudate nuclei in first-episode neuroleptic-naïve psychotic patients compared with healthy controls and after 12 weeks of treatment with quetiapine. No difference in the caudate volume between baseline and endpoint was observed.

A further study [25^{**}] examined the volume of cortical grey matter in drug-free schizophrenic patients at baseline and at 28-day follow-up after treatment with atypical or typical antipsychotics. This study revealed that cortical grey matter volume expanded after treatment with risperidone or ziprasidone. Patients receiving haloperidol and healthy controls showed no change in cortical grey matter volume after 28 days of treatment.

Conclusion

The majority of studies used regions of interest analyses – in particular, of the nucleus caudatus, globus pallidus, putamen and thalamus. Only two studies used VBM and examined the total brain grey matter for voxel-cluster differences.

Table 2 Number of studies that reported volume changes in brain structures

	Increased volume	Decreased volume	Unchanged volume	Summary
Typical antipsychotics				
Cortex	–	2	3	↔
Nucleus caudatus	6	–	–	↑
Globus pallidus	3	–	–	↑
Putamen	3	–	–	↑
Thalamus	2	–	–	↑
Atypical antipsychotics				
Cortex	1	–	1	↔
Nucleus caudatus	1	2	3	↓
Globus pallidus	–	2	1	↓
Putamen	–	2	1	↓
Thalamus	2	–	–	↑

All studies on multiepisodic schizophrenia that examined the effects of treatment with typical antipsychotics revealed a significant increase in basal ganglia volumes, in particular nucleus caudatus, and decreased grey matter volume in different cortical regions (Table 2), predominantly in frontal grey matter volume. These volume changes were detectable even after a 12-week treatment. In contrast to these results, treatment with atypical antipsychotics do not seem to change basal ganglia volumes in previously neuroleptic-naïve patients. Moreover, switching from typical to atypical antipsychotic treatment reduces the increased basal ganglia volume to normal values compared with healthy controls. Only the volumes of thalamus and cortical grey matter increased after atypical antipsychotic treatment (Table 2).

Brain structural changes over time in schizophrenia are in general a matter of debate [26]. Although there is growing evidence for grey matter loss and ventricular enlargement in studies of patients with first episode schizophrenia, the extent and the nature of these changes are vividly debated. The mechanism of this remarkable different effect of typical and atypical antipsychotics remains unclear. The volume changes detected by MRI may simply be due to changes in tissue perfusion, fat or water content [26]. Other mechanisms have, however, been discussed to explain the increase in basal ganglia volume by typical antipsychotics. Owing to their high density of dopamine D2 receptors, basal ganglia are a major target of dopaminergic pathways. The strong antagonistic effect on D2 receptors of typical antipsychotics may chronically lead to a proliferation of these receptors resulting in an increased metabolism, blood flow and size of these structures [27]. This hypothesis is in accordance with findings in rat brains that were exposed to typical antipsychotics. In these studies enlargement of striatal structures was observed as well [28,29]. Atypical antipsychotics also have antagonistic effects on D2 receptors, but they have smaller affinity and occupancy on this receptor than typical antipsychotic agents.

The observed changes in brain structure may, however, reflect progressive neuropathological changes suggested in at least a subform of schizophrenia [30]. According to this, atypical antipsychotics may slow down or stop this process, whereas typical antipsychotics may not. Via agonism on *N*-methyl-D-aspartate receptors [31,32], increased expression of neurotrophic factors [33,34] and stimulating of neurogenesis [35,36] atypical antipsychotics may improve the pathophysiology and the neuronal degeneration process in schizophrenia.

Up to now there are no published post-mortem studies in schizophrenic patients treated with atypical antipsychotics.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 216–219).

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