The course of brain abnormalities in schizophrenia: can we slow the progression?

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Abstract
There is convincing evidence that schizophrenia is characterized by progressive brain volume changes during the course of the illness. In a large longitudinal study it was shown that different age-related trajectories of brain tissue loss are present in patients compared with healthy subjects, suggesting that brain maturation that occurs in the third and fourth decade of life is abnormal in schizophrenia. Studies show that medication intake is an important confounding factor when interpreting brain volume (change) abnormalities. Atypical antipsychotics have been found to be related to smaller decreases in tissue loss. Moreover, independent of antipsychotic medication intake, the brain volume abnormalities appear associated to the outcome of the illness. Before being able to intervene with therapies and prevent the brain from shrinking, one has to understand the underlying mechanism of the progressive changes in the brains of schizophrenia patients.

Keywords
Antipsychotics, longitudinal, neuroimaging, outcome, schizophrenia

Introduction
There is consistent and convincing evidence for the presence of brain volume abnormalities in patients with schizophrenia (Shenton et al., 2001; Wright et al., 2000). Moreover, evidence for excessive tissue loss is now accumulating (Hulshoff Pol and Kahn, 2008). In one of the largest cross-sectional magnetic resonance imaging (MRI) studies across the adult age range it was shown that with age grey matter volume decreased in patients with schizophrenia compared with healthy comparison subjects, suggesting a progressive loss of cerebral grey matter in schizophrenia patients (Hulshoff Pol et al., 2002). When using a voxel-based morphometry (VBM) approach, which allowed for the investigation of distinct focal areas in the brain, it was shown that decreased grey matter density was present in the left amygdala and hippocampus, right supramarginal gyrus, thalamus, (superior) temporal, occipitotemporal, precuneus, posterior cingulate and insular gyri bilaterally. Interestingly, the left amygdala density decrease was more pronounced in the older than in the younger patients (Hulshoff Pol et al., 2001). Moreover, in the patients with schizophrenia, significant decreases in white matter density were found in the genu and truncus of the corpus callosum bilaterally, in the right anterior internal capsule and in the right anterior commissure (Hulshoff Pol et al., 2004), which may suggest aberrant inter-hemispheric connectivity in schizophrenia.

Obviously, to test whether brain volume abnormalities are static or progressive, one has to use a longitudinal design, that is, serial scanning of the same subjects. At the University Medical Centre Utrecht (UMCU), the Netherlands, MRI has been used to measure the structure of the brain in health and in schizophrenia using a longitudinal design. Here, we provide a non-systematic review specifically based on studies from the UMCU, without attempting to give an extensive and complete overview of the literature. We focus on longitudinal structural MRI studies in patients with schizophrenia. In addition, the influence of outcome of the illness and (cumulative) intake of antipsychotic medication will be addressed. Finally, we will investigate how the interaction between outcome and medication intake may play a role in explaining brain tissue loss over time in patients.

Longitudinal imaging studies have particularly focused on brain structure change in first-episode patients, showing excessive decreases in whole brain and grey matter volume (Cahn et al., 2002; DeLisi et al., 2004; Gur et al., 1998; Lieberman et al., 2001) and progressive increases in ventricular and cortical cerebrospinal fluid volumes (Cahn et al., 2002; DeLisi et al., 2004; Ho et al., 2003; Lieberman et al., 2001; but see Puri et al., 2001; Wood et al., 2001). It has been...
argued that the brain volume changes in patients with schizophrenia appear to be especially prominent in the first years of illness (Cahn et al., 2002; Ho et al., 2003; Kasai et al., 2003a, 2003b) relative to change in later stages of the illness. Although considerably fewer studies have examined brain changes over time in chronically ill patients, they provide similar findings as in first-episode patients, such as accelerated frontotemporal cortical grey matter decline and sulcal and ventricular expansion (Mathalon et al., 2001). Recent reviews of longitudinal MRI studies in patients with schizophrenia concluded that there is indeed evidence for accelerated loss of grey matter over time, not only in the early phases of the illness (Pantelis et al., 2005) but also in more chronic stages (Hulshoff Pol and Kahn, 2008). Findings so far are based on studies investigating first-episode patients or chronically ill patients as separate groups, which limits the possibility of testing the influence of age or age-related factors, such as illness duration, on brain volume change. It is of interest to investigate directly whether stage of illness is associated with the progression in brain volume decrease.

This has been done in normally developing children, and in children and adolescents with childhood-onset schizophrenia. Evidence for differential nonlinear developmental trajectories in affected and unaffected children and young adolescents has been reported, particularly in cerebral and hippocampal volumes (showing progressive decrease in patients) and lateral ventricles (showing progressive increases in patients) (Giedd et al., 1999).

Such studies, that is, longitudinal scanning with more than two measurements in subjects across a relatively wide age range, have not been conducted in adulthood, so far. We set out to investigate age-related trajectories of brain volume change in adult-onset schizophrenia and healthy individuals (Van Haren et al., 2008). We rescanned a total of 96 patients and 113 comparison subjects between the ages of 16 and 56 years after an average of 5 years since the initial MRI scan. It was shown that the trajectory of volume change over time indeed differed between patients with schizophrenia and healthy individuals. Instead of the curved trajectory that was found for cerebral (grey) matter volume change in healthy subjects, patients showed a linear decrease over time. In addition, excessive brain volume loss in patients, particularly that of grey matter, was limited to the first two decades of the illness, that is, before 45 years of age. From this age onwards, total cerebral and grey matter volumes decreased to a similar extent in both groups. Before the age of 32 years, the progressive loss of grey matter is accompanied by a progressive increase in white matter in the patients.

Based on the findings in this study (Van Haren et al., 2008) it was calculated, using 1150 mL as a reference brain size, that it is reasonable to state that after 20 years of illness, patients show a cumulative loss of brain tissue in the order of 34.5 mL in excess of what is expected with normal aging (for details see Hulshoff Pol and Kahn, 2008). This cumulative loss of brain tissue results in a 3% overall brain volume loss after 20 years of illness. Interestingly, a meta-analysis of cross-sectional structural brain imaging studies also found a 3% volume loss in schizophrenia patients as compared with control subjects (Wright et al., 2000). Because 1.06 g of brain weight stands approximately for 1 mL (or 1 mm³) brain volume (Scharpf 1912), the excessive brain tissue loss over 20 years that patients show equals almost 37 g. In addition to this, Hulshoff Pol and Kahn (2008) calculated, based on six post-mortem studies, that the brain (weighted according the number of individuals included in the studies) weights about 38 g less in schizophrenia patients relative to controls, which is remarkably close to the 37 g found in longitudinal imaging studies.

The underlying neuropathology of excessive brain changes in schizophrenia patients is still unclear. As is well known, post-mortem studies have shown that the neuropathological abnormalities in patients with schizophrenia are most pronounced in the dorsolateral prefrontal cortex (PFC) relative to several other cortical regions (Selemon, 2001). The loss of cortical thickness in post-mortem studies of 5–10% appears due to an increase in cell packing density in the dorsolateral PFC (Brodmann areas 9 and 46) (Selemon et al., 1995). This increase in cell packing density (reduced neuropil; Selemon and Goldman-Rakic, 1999) was less pronounced in other prefrontal and temporal areas (Selemon et al., 1998). Moreover, it has been shown that the size of pyramidal neurons in deep layer 3 in the PFC is smaller in schizophrenia patients (Rajkowska et al., 1998). In addition, definitive evidence for cell loss in, for example, temporal and cingulate cortices is lacking (for review see Selemon and Goldman-Rakic, 1999). Summarizing, the excessive loss of tissue found in patients with schizophrenia could be due to a reduction of neuropil or to smaller pyramidal neurons in the cortex. However, to date post-mortem data have found limited evidence for these processes in cortical areas other than the PFC.

Another important finding in our study is that patients with poor outcome, characterized by more symptoms and a lower level of social, work or school functioning (as measured with the Global Assessment of Functioning (GAF) score) showed a larger cerebral volume decrease and more extensive lateral ventricle increases over the 5-year follow-up period than patients with good outcome (Van Haren et al., 2008). This is in line with studies in both chronically ill and first-episode patients. Davis et al. (1998) showed a larger increase in lateral ventricle volume in a group of Kraepelinian patients (i.e. poor outcome patients) as compared with non-Kraepelinian patients, while Cahn et al. (2002) found an association between larger grey matter volume change and poorer outcome in first-episode patients.

Using a VBM approach, we showed that excessive decreases in grey matter density were located in specific areas of the brain, that is, left superior frontal gyrus (Brodmann area 9/10), left superior temporal gyrus (Brodmann area 42), right caudate nucleus, and right thalamus in patients with schizophrenia as compared with healthy subjects (Van Haren et al., 2007). Interestingly, in line with the excessive cerebral (grey matter) volume decrease in poor outcome patients (GAF score), the density changes in the frontal lobe were most pronounced in patients with the poorest course of the illness (expressed as number of hospitalizations during the scan interval) (Van Haren et al., 2007).

As the most rapid clinical changes, including deterioration in functioning, are seen in the first (symptomatic) years of the schizophrenic illness (Fenton and McGlashan, 1991; McGlashan, 1988), investigating the association between
brain volume (change) and outcome is particularly relevant in first-episode patients. In a longitudinal multicentre study, where we investigated whether brain volume at illness onset can predict outcome in recent-onset schizophrenia after a follow-up of approximately 2-years, no associations were found (Van Haren et al., 2003). The lack of relationship between brain volume measures at illness onset and outcome may be a consequence of the relatively short follow-up period. Indeed, studies did find brain volume measures to predict outcome after 7 and 4 years, respectively (Van Os et al., 1995; Wassink et al., 1999). Although it has been suggested that the first 5 years after the first psychosis are characterized by the largest decline in functioning, followed by a relatively stable clinical period (Davidson and McGlashan, 1997), this also indicates that the disease is still very active during this time period, and outcome may be particularly unstable and reach a plateau only later.

Alternatively, measuring brain volume at one time point might not provide sufficient information to predict prognosis. Indeed, if brain changes progress over time, one would expect the changes to be particularly pronounced during the early phase of the illness. We examined cerebral grey matter volume change after a 1-year interval in patients with first-episode schizophrenia (Cahn et al., 2002). Cerebral grey matter volume significantly declined and lateral ventricle volume increased over the 1-year interval in patients relative to healthy subjects. Important in this respect was that these volume changes in the first year of illness appeared significantly related to functional outcome 2 years after the baseline MRI measurement (Cahn et al., 2002). Moreover, we clinically re-examined the same individuals 5 years after the initial evaluation, using various outcome measures (Cahn et al., 2006). Again, those patients who had the largest decrease in grey matter volume in the first year had the highest negative symptom scores, and were less likely to live independently 5 years after the first evaluation. This suggests that indeed, in contrast to static brain volumes, dynamic brain measurements could be more useful in predicting both functional and symptomatic outcome in schizophrenia. However, it is important to note that there are also studies showing the opposite relationship, that is, larger ventricles and smaller hemispheres were related to clinical improvement (DeLisi et al., 1998; Gur et al., 1998).

Evidence that the volume deficits are functionally important is not only provided by associations with symptoms or impairments in daily life functioning, but also by associations with cognitive function (Antonova et al., 2004; Crespo-Facorro et al., 2007).

**Antipsychotic medication**

A major confounding factor in neuroimaging studies in general, and in studies investigating brain volume change over time in particular, is the (cumulative) intake of antipsychotic medication. It is difficult to establish whether these (changes in) structural brain abnormalities are caused by the disease or are an effect of treatment.

One of the best-replicated findings regarding the effect of antipsychotic medication is the increase in caudate nucleus volume in patients treated with typical antipsychotics, which is consistent with the high density of dopamine receptors in this structure (Chakos et al., 1994; Keshavan et al., 1994; Wright et al., 2000). Interestingly, typical and atypical antipsychotic medication appears to affect basal ganglia volume differently. Decreases in basal ganglia volume are generally reported in patients that shift from typical to atypical antipsychotic treatment (Chakos et al., 1995; Scheepers et al., 2001; Westmoreland Corson et al., 1999).

Both in our 1-year follow-up of first-episode patients and in our 5-year follow-up of patients across the age range we showed significant associations between brain changes over time and cumulative medication intake during the interval. During the very first year of illness this association was negative, that is, larger volume decreases were associated with higher cumulative medication intake. The majority of included patients were medication naive at baseline measurement, and half of the patients used typical antipsychotics during the first year of treatment (Cahn et al., 2002). In contrast to the findings in our first-episode sample, the association between brain volume change and medication intake was positive, at least for atypical antipsychotic medication intake. All patients were medicated at baseline and the majority of patients used atypical antipsychotic medication exclusively, or changed from typical to atypical medication during the interval (Van Haren et al., 2008). Moreover, in a cross-sectional VBM study Dazzan et al. (2005) showed that both typical and atypical antipsychotics are associated with brain changes. However, typical medication seemed to affect more extensively the putamen (enlargement) and cortical areas, such as lobulus paracentralis, anterior cingulate gyrus, superior and medial frontal gyri, superior and middle temporal gyri, insula, and precuneus (reductions), while atypical antipsychotics were associated with enlargement of the thalami. However, in chronically ill patients that were randomly assigned to haloperidol or clozapine for 10 weeks, no differences in hippocampal, caudate, prefrontal grey or white matter volumes were observed (Arango et al., 2003).

The associations between brain volume change and medication intake become even more complicated when taking outcome into account. Since patients are usually medicated continuously, it is difficult to disentangle the effects from outcome and medication on brain volume (change). Cahn et al. (2002) showed that cerebral grey matter decrease in the first year of illness was related to both outcome and antipsychotic medication intake. Larger loss of brain tissue was associated with poorer outcome and, independent of that, with larger cumulative medication intake during this year. Moreover, in our longitudinal study across the adult age range we found that treatment with atypical antipsychotic medication (clozapine and olanzapine; expressed as cumulative dose per year scan during the scan interval) attenuated the loss of grey matter density in medial superior frontal gyrus. Excessive decrease in this same area was associated with an increased number of hospitalizations, which can be interpreted as an estimation of number of psychotic relapses during the scan interval. Again, these associations were independent from each other, that is, number of hospitalizations could not explain the association between excessive grey matter density decrease and medication intake. Based on these findings it could well be that although progressive brain volume
change is related to both outcome and medication intake, the two processes act independently and do not explain each other.

The only MRI study so far that was set up to investigate the effects of medication on the brain, using random assignment of first-episode patients to either treatment with olanzapine or haloperidol, was done by Lieberman et al. (2005). In 263 randomized patients, of whom 161 had a baseline and at least one follow-up MRI scan, the authors showed that haloperidol-treated patients showed significant decreases in grey matter volume, whereas olanzapine-treated patients did not, relative to control subjects. Interestingly, in the original sample it was suggested that improvement in symptomatology was associated with less lateral ventricular volume increase only in the olanzapine group. In contrast, more improvement in neurocognitive functioning was associated with less decrease in grey matter volumes only in haloperidol-treated patients. Using time-lapse maps in a subgroup of patients that had at least four MRI scans, it was shown that intensified normal cortical maturation, that is, a rapidly advancing parietal-to-frontal deficit trajectory, was present in haloperidol-treated patients (Thompson et al., 2009).

Whether the lack of, or diminished, excessive brain changes that are associated with atypical medication reflect either reduced neurotoxicity or neuroprotection cannot be addressed with neuroimaging (Thompson et al., 2009). So far, evidence from volumetric MRI studies in monkeys is not consistent with human studies, that is, the administration of both haloperidol and olanzapine to macaque monkeys over a 2-year period resulted in a significant overall brain tissue loss in both grey and white matter across several brain regions (Dorph-Petersen et al., 2005; Konopaske et al., 2007). Although this work is in monkeys, and it might be that primate brains react differently to these compounds, these important and remarkable findings cannot be ignored. However, one has to bear in mind that before the introduction of antipsychotic medication in the early 1950s, pneumoencephalography had already shown that the ventricles are enlarged in patients with schizophrenia. Moreover, a progressive enlargement across the course of the illness was reported (Haug, 1962). In addition, first-degree relatives of patients with schizophrenia (siblings and twins) (Brans et al., 2008a, 2008b; Gogtay et al., 2007) and genetically or symptomatically high-risk individuals (Lawrie et al., 2008; Wood et al., 2008), not (yet) treated with antipsychotics, show progressive changes in the brain. This indicates that if antipsychotic medication causes the brain to shrink, the brain volume abnormalities cannot be fully explained by this.

Based on the above, one has to conclude that the relationship between outcome, antipsychotic medication and brain volume (change) needs to be clarified further. So far, the lack of consistent significant correlations between these three domains raises the question whether the association between intake of atypical antipsychotics and a smaller tissue loss is clinically relevant.

**Limitations of longitudinal studies**

When running large longitudinal MRI studies, some difficulties are unavoidable; however, some potential issues can be avoided. For example, in our longitudinal study across the age range, effects of alcohol and drug abuse or dependence were ruled out. Abuse and dependency were exclusion criteria at baseline, and only three patients received a DSM-IV diagnosis of drug abuse or dependence at follow-up. Moreover, all MRI scans were obtained on the same scanner running the identical scan protocol at both visits. All images were processed using the same processing pipeline, including methods that have been thoroughly validated. Still, several limitations need to be taken into account when interpreting our findings. First, it is not possible to rule out a selection bias. Indeed, at baseline, patients and comparison subjects that participated in the follow-up were younger than the patients and comparison subjects that did not take part in the follow-up. Moreover, at baseline, the patients included at follow-up had a shorter duration of illness and fewer negative symptoms than the patients who did not complete the follow-up. In our sample, no interactions between negative symptoms and age were found, suggesting that there was no association between age and negative symptoms at baseline in patients that were included at follow-up and in patients that did not participate at follow-up (Van Haren et al., 2008).

Second, the relationship between excessive brain changes in patients and the type and dose of antipsychotic exposure, as examined in this study, is subject to several caveats. We estimated cumulative dose of all antipsychotic medication that was prescribed during the interval between the scans in haloperidol equivalents. These were summed for both typical and atypical antipsychotics. However, in case a relatively large number of patients had been on a particular medication, dose in mg was used. This has another advantage as the conversion rates used to convert atypical antipsychotic dose to haloperidol equivalents are by no means generally accepted. We were able to calculate cumulative olanzapine and clozapine intake in mg per year during the scan interval, and these figures were used in the analyses without converting them to haloperidol equivalents. However, patients differed in the amount of medication that they had used prior to inclusion in the study, and reliable information was unavailable on their lifetime cumulative medication use. Moreover, most patients changed medication during the scan interval, making it difficult to reliably investigate the effects of different types of antipsychotics. Only 10 patients were exclusively taking olanzapine during the scan interval, therefore it cannot be excluded that the protective effect can be explained by the release of exposure to typical antipsychotics. Also, no information was available about the compliance to the prescribed medication.

**Conclusion**

There is sufficient evidence to suggest that schizophrenia is a progressive brain disease. Interestingly, our data suggest that the largest decline of cerebral (grey matter) volume takes place during the first year of illness. This can possibly be explained by initiation of pharmacological treatment, since the majority of the patients in our longitudinal first-episode study were medication naive at inclusion in the study. In addition, after the first year, the brain changes found in the patients with schizophrenia might be due to an abnormality
in brain maturational processes (Van Haren et al., 2008). First, the progressive changes in schizophrenia were limited to the first 10 (for white matter) to 20 years (for cerebrum, grey matter and lateral ventricle volumes) of the illness. In addition, grey matter volume loss in the patients is mainly characterized by the absence of the normal curved trajectory of volume change with age that we observed to be present in healthy subjects. Grey matter decreased in a linear fashion in patients, failing to show the relative diminution in grey matter loss before the age of 30, as was seen in controls. After the age of approximately 45 years, the age-related progression in brain tissue loss, that is, the effect of aging, was similar in patients with schizophrenia and healthy subjects. These different age-related trajectories of brain tissue loss, in our view, suggest that the brain maturation that occurs in the third and fourth decade of life to be abnormal in schizophrenia. However, one has to bear in mind that prodromal and clinically high-risk individuals show structural brain changes during, and possibly before, transition into psychosis (Smieskova et al., 2010), so the exact timing of the aberrant brain changes are not yet determined.

Both the presence of more symptoms as well as poorer social and daily functioning are associated with larger decreases in brain volume over time. We and others showed that medication intake is a confounding factor when interpreting brain volume (change) abnormalities. However, what has become clear is that cumulative dose of antipsychotic medication cannot cause the brain volume abnormalities. It only explains a portion of the detectable abnormalities in volume (change); see Figure 1.

So far, there is a lack of consistent significant correlations between brain volume change, outcome of the illness and cumulative medication intake. Before being able to intervene with (antipsychotic) therapies and prevent brain shrinkage, one has to understand the underlying mechanisms of the progressive changes in the brains of patients with schizophrenia. Most studies in adulthood have only acquired two measurements. What is needed are large (multicentre) studies with a longitudinal set up, following subjects over an extensive period of time with regular visits. Such studies have been done in childhood-onset schizophrenia at the National Institute of Mental Health (NIMH); however, it remains unknown how these findings can be extrapolated to adulthood schizophrenia. Moreover, the use of multimodal imaging across neurochemical, functional, and structural imaging modalities, combined with animal modelling of the cellular and molecular mechanisms of brain changes is what is required to address the issue of what is going on in the brain maturational processes (Van Haren et al., 2008). The trajectory of volume change over time differs between patients and healthy individuals. Instead of the curved trajectory that was found for cerebral (grey) matter volume change in healthy subjects, patients showed a linear decrease over time. Evidence suggests that symptom severity, level of functioning and antipsychotic medication intake influence brain volume change over time in patients. How these influences are interrelated remains unclear.

Figure 1. The graphs represent a diagram of our findings of aberrant neurodevelopment in the brain of patients with schizophrenia (data taken from Van Haren et al., 2008). The trajectory of volume change over time differs between patients and healthy individuals. Instead of the curved trajectory that was found for cerebral (grey) matter volume change in healthy subjects, patients showed a linear decrease over time. Evidence suggests that symptom severity, level of functioning and antipsychotic medication intake influence brain volume change over time in patients. How these influences are interrelated remains unclear.
brain over time before and during the illness. Structural brain imaging by itself is limited in its ability to fully answer these questions.

**Funding**

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

**Conflict of interest**

The authors declare that they have no conflicts of interest.

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