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Review

Confounders of excessive brain volume loss in schizophrenia

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ABSTRACT

There is convincing evidence that schizophrenia is characterised 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 to healthy subjects, suggesting that brain maturation that occurs in the third and fourth decade of life is abnormal in schizophrenia. However, studies show that medication intake and cannabis use are important confounding factors when interpreting brain volume (change) abnormalities. Indeed, continues use of cannabis, but not cigarette smoking, is associated to a more pronounced loss of grey matter in the anterior cingulated and the prefrontal cortex. 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.

Contents

1. Progressive brain volume loss in schizophrenia

There is substantial evidence for the presence of brain volume abnormalities in patients with schizophrenia (Wright et al., 2000; Shenton et al., 2001), and evidence for excessive tissue loss is now accumulating (Hulshoff Pol and Kahn, 2008; Pantelis et al., 2005; Kempton et al., 2010; Olabi et al., 2011). In one of the largest cross-sectional magnetic resonance imaging (MRI) study across the adult age range it was shown that with age grey matter volume decreased in patients with schizophrenia compared to healthy comparison subjects, suggesting a progressive loss of cerebral grey matter in schizophrenia patients (Hulshoff Pol et al., 2002). Focal analyses, using a voxel-based morphometry approach (VBM), 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, 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 in schizophrenia patients (Hulshoff Pol et al., 2004), suggesting aberrant inter-hemispheric connectivity in schizophrenia.

Obviously, to test whether brain volume abnormalities are static or progressive one has to use a longitudinal design, i.e., serial scanning of the same subjects. At the University Medical Centre Utrecht (UMCU), the Netherlands, Magnetic Resonance Imaging (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 based on studies from the UMCU, without attempting to give an extensive and complete overview of the literature. In addition, the influence of potential confounders, such as the outcome of the illness, (cumulative) intake of antipsychotic medication, smoking and cannabis use will be addressed.

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The majority of longitudinal imaging studies involved the measurements of structural brain changes in first-episode patients, providing evidence for 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 (CSF) 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,b) relative to change in later stages of the illness. Although considerably fewer studies have examined brain changes over time in chronically ill patients, they show 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 to test the influence of age or age-related factors, such as illness duration on brain volume change. It is important to test directly whether stage of illness is associated to the progression in brain volume decrease by including both groups in one study.

This has been done in normally developing children and in children and adolescent 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, i.e. 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 after an average of five 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, i.e., 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. In the patients the increase in white matter volume diminished with increasing age while the trajectory of volume increase in the control subjects remained stable across the age range.

It has been suggested that the regionally specific remodelling of grey and white matter that takes place into the third decade of life (Sowell et al., 2003) underlies some of the structural and functional changes that lead to the development of psychiatric disorders such as schizophrenia (for review see Höistad et al., 2009). The fact that the prefrontal cortex matures last and that myelination is not complete until late adolescence (Paus et al., 2001; Lenroot & Giedd, 2006) may be significant, as the timing coincides with the typical onset of symptoms in schizophrenia. This suggests that a dysfunctional myelination process could underlie the pathogenesis of schizophrenia. This is in line with previous diffusion tensor imaging (DTI) studies showing decreases in fractional anisotropy (FA)—which reflects microstructural directionality and to a certain extent fiber integrity—in schizophrenia (for reviews, see Kanaan et al., 2005; Kubicki et al., 2007; Konrad and Winterer, 2008).

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 mm^3) brain volume (Scharpff, 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 postmortem studies that the 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.

2. Outcome

An import finding in our study is that poor outcome patients, 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 good outcome patients (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 to non-Kraepelinian patients while Lieberman et al. (2001) found an association between a larger increase in the ventricles and poorer outcome in first-episode patients.

When focussing on the location of the excessive grey matter loss we showed that excessive decreases in grey matter density (using a voxelbased morphometry approach) were located in the 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 to healthy subjects (Van Haren et al., 2007). In line with this are our findings on excessive cortical thinning in widespread areas on the cortical mantle, being most pronounced bilaterally in the temporal cortex and in the left frontal area (Van Haren et al., 2011). Interestingly, consistent 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). In addition, poor outcome in patients was associated with more pronounced cortical thinning (Van Haren et al., 2011).

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 multi-centre study, where we investigated whether brain volume at illness onset can predict outcome in recent-onset schizophrenia after a follow-up of approximately two 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