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COMMENTARY

The effects of antipsychotics on brain structure: what have we learnt from structural imaging of schizophrenia?

A commentary on 'Do antipsychotic drugs affect brain structure? A systematic and critical review of MRI findings' by Navari & Dazzan (2009)

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Introduction

We read with great interest the article by Navari & Dazzan (2009) recently published in *Psychological Medicine*. These authors found that antipsychotic treatment may contribute to brain structural changes observed in psychosis and that antipsychotics act regionally rather than globally on the brain, with specific effects on different brain structures.

In an own systematic review on the effects of antipsychotics on the brain (Smieskova *et al*. in press) we summarized findings from structural imaging studies of schizophrenia. We focused on studies investigating schizophrenia patients using neuroimaging techniques according to antipsychotic medication and studies considering the differences in medication either in various antipsychotic medications or over the time or in various groups of patients. Overall, we found that patients with schizophrenia receiving treatment with antipsychotics had reduced grey matter (GM) volume, particularly in frontal and temporal lobes. Medication with typical antipsychotics also leads to increased volume of the basal ganglia, while atypical antipsychotics reversed the effect after switching. Studies with typical antipsychotics have reported increased GM volume in cingulate cortex, in contrast to atypical antipsychotics with the excess more often seen in thalamus volume.

Confounding effects of antipsychotics

As discussed by Navari & Dazzan (2009), the potential confounding impact of antipsychotics on progressive brain changes in schizophrenia is considered controversial (DeLisi, 2008). Although there is evidence for GM loss and ventricular enlargement from prospective studies of patients with first-episode and chronic schizophrenia (Wood *et al*. 2008), most neuroimaging studies of schizophrenia to date have not included the examination of non-medicated patients, making conclusions about medication effects on neuroimaging measures difficult. Investigation of subjects at the onset of the disease avoids potential confounders such as antipsychotic treatment (Riecher-Rossler *et al*. 2007). A clinical high-risk status for psychosis (at-risk mental state, ARMS) is associated with a set of neurofunctional abnormalities that are qualitatively similar to those observed in patients with the disorder (Fusar-Poli *et al*. 2007). As these findings are not attributable to chronic psychotic symptoms or antipsychotic treatment, they may solely represent markers of increased vulnerability to psychotic disorders. Cross-sectional structural MRI studies of non-medicated patients in a prodromal phase of psychosis or ARMS demonstrated that neuroanatomical abnormalities are already evident in the very early phase of psychosis (Wood *et al*. 2008) whereas longitudinal MRI studies found that the subset of patients who developed psychosis showed a longitudinal reduction in GM in the orbito-frontal, temporal lobe, parietal lobe and cerebellum (Pantelis *et al*. 2003; Job *et al*. 2005; Borgwardt *et al*. 2008).

Conclusions and future directions

Neuroimaging studies have provided compelling evidence that despite antipsychotic medication (both typical and atypical) there are detectable anatomical changes at the level of total and regional brain volumes. To date, it remains elusive whether the effects of antipsychotic medication on GM volume are simply

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beneficial. Experimental studies of macaque monkeys showed that chronic administration of either haloperidol or olanzapine was associated with smaller GM volume (Konopaske *et al*. 2008). These results, if confirmed, raise ethical questions on antipsychotic use. If antipsychotic medication may lead – at least in some patients – to GM volume reduction careful benefit–risk decisions have to be made for individual patients. Patients with schizophrenia should be very carefully informed about the potential risks (and of course benefits) of antipsychotic medication.

It is questionable whether the effects we are observing are the direct effects of antipsychotics or due to the illness process. Until we have more reliable studies from non-medicated patients, the potential impact of the confounding effect of medication must be borne in mind. For future studies, we therefore suggest focusing on longitudinal designs that represent the gold standard for investigation of medication effects. These studies clearly have the advantage of powerful, within-subject designs. Small sample sizes, heterogeneity in the sociodemographic characteristics of subjects, and lack of consistency between scanning parameters should be addressed by future multi-site studies that have shown the potential to overcome most of these problems and to bridge basic neuroscience with clinical psychiatry. So far, the investigation of patients at risk or with a first episode of schizophrenia seems to be the most promising alternative.

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Declaration of Interest

None.

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