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Letter to the Editor

Are antipsychotics good or bad for the brain? A comment on Moncrieff & Leo (2010)

In a very comprehensive review of the literature, Moncrieff & Leo (2010) have examined evidence that antipsychotic medications have an effect on brain volumes. The authors focused on global brain volumes, and particularly ventricular or cerebrospinal fluid (CSF), whole-brain and grey-matter volumes. Their review suggests that antipsychotic drugs reduce brain-matter volume and increase ventricular CSF volume, but it also points to some important issues that hinder our understanding of how antipsychotics affect the brain.

That schizophrenia is associated with volume changes of several brain areas, independently from the use of medication, is not in dispute. At the same time, schizophrenia is treated with medications that affect various neurotransmitters, mostly by blocking dopamine function. Hence, it can be expected that these medications affect brain structure and function. To interpret the contribution of neuroimaging findings to our understanding of schizophrenia, it is therefore important to establish what the interaction is between brain changes related to illness pathology and those due to antipsychotics; and what the changes we see in relation to antipsychotics represent in relation to illness course.

As the authors of the review suggest, this is not an easy task. In fact, studies that have looked at the effects of antipsychotics on brain structure, including our own, have shown that antipsychotics may affect volumes of the same brain areas that are altered even in individuals with schizophrenia who have never received antipsychotics, such as temporal and frontal cortices, and the striatum (Dazzan *et al*. 2005; Ebdrup *et al*. 2010; Scheef *et al*. 2010). Additionally, some of these effects may be different for different antipsychotics, with typical antipsychotics possibly causing volume reductions, and atypicals less so (Navari & Dazzan, 2009). Furthermore, the effects may be different following prolonged, rather than acute exposure. This is an issue that may be even more difficult to disentangle. In fact, some brain changes tend to become more marked with illness progression, particularly in patients with a poorer clinical outcome (Cahn *et al*. 2006). On one side, this may be due to a longer and more marked exposure to antipsychotics in these individuals, because of their symptomatic state. On the other side, these individuals may just suffer a severe form of illness that is associated with more marked brain changes *per se*. It then becomes a circular issue as to what causes what.

Having accepted that at least some of the brain alterations found in schizophrenia may be due to antipsychotics, we need to understand what their pathophysiological substrate is, and whether they change with long-term exposure. Whether they reflect a change in gene expression, in receptor density, or in blood flow in response to receptor blockade, remains unclear. By studying the effects of these drugs in healthy individuals, it can be at least clarified whether they are due to an interaction with an underlying pathological substrate, or they are a direct effect of the drug on brain. Indeed, we are now piloting such approach. However, while conducting single dose studies in healthy individuals is acceptable, it is not possible to study the longer term effects of antipsychotics in a healthy population, where there is no therapeutic benefit to justify the exposure. The study of prolonged exposure therefore needs to continue in clinical samples, where this is justified by therapeutic benefit. Further progress can be made by obtaining sequential MRI scans at different stages of a standardized treatment. The changes observed at these various stages can then be related to both drug dosing and exposure, and clinical improvement.

More broadly, it remains unclear whether the effects of antipsychotics on the brain are damaging or alternatively protective. The possibility of a protective effect of antipsychotics on brain would be supported by evidence, from animal models of schizophrenia, that antipsychotics positively affect neurogenesis, and prevent the insurgence of brain structural changes later in life (Keilhoff *et al*. 2010; Piontkewitz *et al*. 2010). By relating longitudinal information on brain structure and function, and exposure to antipsychotic, to clinical improvement, we may be able to elucidate which of these alternatives is true.

Declaration of Interest

None.

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The authors reply

We are not as convinced as Dr Dazzan that 'schizophrenia is associated with volume changes in several brain areas' (Dazzan, 2010). As we showed in our systematic review, a large majority of studies with drug-naive patients with psychosis or schizophrenia have not found any differences in global brain or grey-matter volumes, or in total CSF or ventricular volumes between patients and controls (Moncrieff & Leo, 2010). Although some of these studies reported differences in the volumes of specific structures, such as the thalamus and the caudate nuclei, others found no differences and multiple testing suggests some of the results may be false positives.

We do agree that disentangling the effects of drug treatment and underlying pathology are difficult, but we feel that, following the Hippocratic mandate to 'first do not harm', it should be assumed that the drugs rather than the disorder are causing the effects, until proven otherwise. Similarly, although it is not impossible that antipsychotic-induced brain alterations are beneficial, it seems more prudent to assume that they might be harmful, and to direct research into assessing this possibility.

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Letter to the Editor

Early intervention in psychosis: a response to McGorry *et al*. (2010)

The Commentary of McGorry *et al*. (2010) on our Editorial in the March 2010 edition of the Journal