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Letter to the Editor

A comment on 'A systematic review of the effects of antipsychotic drugs on brain volume' by Moncrieff & Leo (2010)

Moncrieff & Leo (2010) provide an excellent overview of the literature on the association between antipsychotic medication intake and global brain volume changes. The authors build the case that at least some of the brain abnormalities that are found in schizophrenia patients are not a consequence of the illness itself but result from antipsychotic medication. Indeed, being ill is in the majority of cases linked to the intake of antipsychotic medication, which is known to interact with the brain. The underlying mechanisms of how the structure of the brain is influenced by antipsychotic medication are largely unknown. Trying to understand these mechanisms is important in order to put the findings from structural magnetic resonance imaging (MRI) studies into perspective.

Two issues are important to take into account when interpreting the longitudinal MRI studies that include medicated patients. First, as antipsychotic medication interacts with neurotransmitter systems it is not unlikely that it affects the brain focally, as was also suggested by Navari & Dazzan (2009) in their overview of the literature on this topic. By investigating global brain volumes no conclusion can be drawn on focal abnormalities. Second, as different antipsychotic drugs act on different neurotransmitter systems it would not be surprising that type of medication is a crucial factor. Indeed, two of the largest follow-up MRI studies (including the only randomized trial) (Lieberman *et al*. 2005; van Haren *et al*. 2008) found evidence for differential effects from different kinds of antipsychotics on global brain volumes. This is of particular interest since it was suggested that typical antipsychotics were related to a more pronounced loss while atypical medication (olanzapine in particular) was related to less pronounced loss. This was not only the case in first-episode patients (Lieberman *et al*. 2005) but also in a sample consisting of first-episode and chronically ill patients who had all been medicated for more than a few weeks at baseline measurement (van Haren *et al*. 2008). Moreover, to investigate the effects of medication in an unbiased fashion randomized control trials are essential; therefore, it is justified to place more weight on the results of the only large randomized trial, even though it was funded by the manufacturers of olanzapine.

It is even more important to realize that not finding brain volume abnormalities in medication-naive patients does not necessarily indicate that the brain abnormalities occur as a result of starting antipsychotic medication, even though the timing might suggest this. Much of the argument that loss of brain tissue is related to intake of medication is built on this assumption. It might well be that the brain starts to change at illness onset, that it progresses during the course of the illness, and is actually a consequence of being ill. The medication-naive studies cannot provide evidence for either one of these hypothesis.

Many studies found strong evidence for brain volume abnormalities to be related to outcome. Those patients with a poorer outcome show more pronounced loss of brain tissue compared to those with a better outcome. This indicates that the illness process itself is at least associated (not to say responsible). Indeed, based on some of our own findings that the effects of outcome on brain volume appear to be independent of the intake of medication (Cahn *et al*. 2006; van Haren *et al*. 2008), it could be that progressive brain volume change is indeed related to both outcome and medication intake independently.

The authors suggest that future studies should randomize first-episode patients to either treatment with antipsychotic medication or to withhold antipsychotic treatment for a few weeks. Studies like this are extremely difficult to perform. It is easier, and not less informative, to perform randomized controlled trials like the one that has been done by Lieberman *et al*. (2005) and compare patients using different types of medication in a longitudinal fashion or study the effects of (randomized) discontinuation of medication.

Declaration of Interest

None.

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NEELTJE VAN HAREN, RENÉ KAHN
Rudolf Magnus Institute of Neuroscience, Department of Psychiatry, University Medical Centre Utrecht, Utrecht, The Netherlands
(Email: N.E.M.vanHaren@umcutrecht.nl)

The authors reply

Drs van Haren and Cahn make several interesting comments. The most interesting comment concerns the 'assumptions' of the neuroimaging field. It is these assumptions about medication which are the heart of the question, or disagreement, when it comes to interpreting the imaging data. Our paper called into question a strongly held assumption in the schizophrenia imaging field (Moncrieff & Leo, 2010), namely, that any observed difference between the brains of patients and controls can be attributed to an organic pathology. Yet studies using only medicated patients cannot provide evidence of an organic pathology, that is, unless one makes the prior assumption that the medications are not a confounding variable.

They point out in their letter the problem with interpreting results from patients who are medication naive at the point of initial scan, and show volume reductions following a course of antipsychotic medication. Are the observed reductions due to the natural course of the disease or to the medications? We agree that without well-designed trials the results of these studies are hard to interpret, which is why we suggested the need for more well-developed studies.

Data on clinical outcomes and brain-volume changes are also difficult to interpret, and may also reflect medication-induced effects, since people with worse outcomes may receive more medication. In the neuroimaging field indications of brain volume reduction over time were found to be associated with poor outcome in several of the longitudinal studies examined (Davis *et al*. 1998; Lieberman *et al*. 2001; Mathalon *et al*. 2001; Cahn *et al*. 2002; Ho *et al*. 2003; Nakamura *et al*. 2007), although others found no effect or opposite effects (Sporn *et al*. 2003; DeLisi *et al*. 2004). Other factors that may reflect exposure to antipsychotic treatment, such as longer duration of hospital admission, duration of illness and increased number of hospital admissions, were also associated with reduced brain volume in several of these studies (Mathalon *et al*. 2001; DeLisi *et al*. 2004; van Haren *et al*. 2008).

The study cited to support the argument that neuroimaging studies still provide evidence of an organic pathology, examined brain-volume changes over a 5-year period (Cahn *et al*. 2006). But in this study all of the patients received medication during the 5-year period between scans (confirmed by an email to one of the authors). Without a medication-naive group of patients it seems problematic to assume that the medications did not play a role in the observed volume reduction in a group of people exposed to antipsychotic medications for 5 years. No data on the association between antipsychotic exposure and brain volumes at 5-year follow-up has yet been published, but 1-year follow-up of this cohort showed that cumulative dose predicted loss of grey-matter volume (Cahn *et al*. 2002).

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JOANNA MONCRIEFF[1], JONATHAN LEO[2]
[1] *Department of Mental Health Sciences, University College London, UK*
[2] *Lincoln Memorial University-DeBusk, College of Osteopathic Medicine, Harrogate, TN, USA*
(Email: j.moncrieff@ucl.ac.uk)

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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.