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COMMENTARY

Brain volume changes in schizophrenia: how do they arise? what do they mean?

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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Among the current, but not new, critical issues in schizophrenia research are finding definitive answers to the following two intertwined questions: Does the underlying disease process involve progressive changes in brain structure immediately before and after the onset of psychosis? To what extent are such changes accentuated, masked or fully explained by treatment with antipsychotic medications? The systematic review of structural magnetic resonance imaging (MRI) findings in schizophrenia by Navari & Dazzan (2009) addresses the latter question. The authors conclude that the current literature suggests that antipsychotics act regionally rather than globally on the brain, that the resulting changes in brain volume are greater with typical than atypical antipsychotics, and that antipsychotic treatment potentially contributes to the brain structural changes associated with psychosis.

The authors highlight the challenges of drawing conclusions from the existing literature both because the number and sample size of informative studies are limited and because the experimental strategies employed do not, for understandable reasons, lend themselves to incisive interpretations. A fundamental challenge in study design is the ability to distinguish between the potential effects of antipsychotic medications *versus* those of the underlying disease process on measures of brain volume. The difficulty of making this distinction reflects, in part, the absence of a comparison group of subjects who do not have schizophrenia, but who have had a similar exposure to antipsychotic medications. However, even the inclusion of such a group would leave open the possibility for a drug × diagnosis interaction on brain volume that is distinctive to schizophrenia. Given the recent advances in the identification of individuals at risk for schizophrenia (Cannon *et al*. 2008), longitudinal imaging studies of such individuals before they receive antipsychotic medications might clarify the extent to which brain volume changes reflect the disease process alone; such studies are beginning to appear (Borgwardt *et al*. 2008). However, the continued study of these individuals after conversion to psychosis and the initiation of antipsychotic medications would still leave open the question of whether any additional changes in brain volume represent the disease process, antipsychotic medications, or the interaction of the two.

Attempts to address these limitations have included controlled studies in non-human primates, using experimental strategies that mimic the early clinical treatment of schizophrenia. For example, adolescent/young adult macaque monkeys can be given typical or atypical antipsychotic medications for extended periods of time (years) using drug administration paradigms (oral or depot) at doses that produce trough serum drug levels in the range known to be therapeutic in humans, with at least some of the same adverse effects (Pierri *et al*. 1999; Dorph-Petersen *et al*. 2005). In one such study, chronic administration of either haloperidol or olanzapine was associated with smaller gray matter volume, lower glial cell number, and higher neuron density without a difference in total neuron number in the cerebral cortex, findings that parallel the results of postmortem schizophrenia studies (Konopaske *et al*. 2007, 2008). These similarities support the interpretation that at least some of the alterations in brain morphology reported in schizophrenia are attributable to the effects of antipsychotic

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medications. It is important to note, however, that all of the dependent measures in this study were made in postmortem tissue, precluding a within-subject design, and thus leaving open the possibility that the observed differences between the antipsychotic-exposed and age- and sex-matched control monkeys were present prior to drug administration. Future studies in primates that employ longitudinal assessments of brain structure using MRI, followed by postmortem evaluations of the size and number of neural elements, would address this limitation and increase the utility of the findings for interpreting studies in humans.

Such studies may also help address the challenge of determining the functional significance of brain volume changes in human structural brain imaging studies, if such changes are, in fact, due to antipsychotic medications. Do the observed structural changes actually indicate detrimental effects on brain function, or are they central to the therapeutic benefits of these medications? Might both questions be answered in the affirmative depending upon the brain region involved? Without knowing the nature of antipsychotic medication-induced changes on brain volume at the level of cells and circuits, the consequences of such changes for the activity of neural networks, and their permanence or lability, it remains difficult to discern the clinical import of such changes.

Declaration of Interest

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