Reviewer's report

Title: Theories of Schizophrenia: An Inflammatory/Vascular Component?

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Reviewer: Husseini Manji

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General

--Theories of Schizophrenia: An Inflammatory/Vascular Component?
By Hanson and Gottesman

This is a very interesting article that proposes an ‘inflammatory/vascular’ hypothesis for the etiology of schizophrenia. The authors posit that the physiologic abnormalities leading to illness involve disruption of the regulation of the delivery of energy and oxygen required for normal brain function. They further theory propose that abnormalities of CNS metabolism arise because genetically modulated excessive inflammatory reactions damage the microvascular system of the brain in reaction to environmental agents, including infections, hypoxia, and physical trauma. Overall, the authors have done a very good job of synthesizing the salient information, and the paper should be of interest to a broad scientific/medical readership. However, several issues need to be addressed:

§ The major potential problem with the manuscript is the lack of specificity of the proposed hypothesis. In the manner presented, the findings are not associated solely with schizophrenia but with a broader spectrum of psychoses and psychotic-like symptoms. A careful comparison of findings between pathologies in which the inflammatory/vascular component plays a role (pointing out the specific ones in schizophrenia) will help the authors to better establish their proposal.

§ As the authors are aware, many of the postmortem and neuroimaging studies are confounded by medication effects, medication withdrawal effects, etc. These should be acknowledged.

§ When considering the potential role of glial cell dysfunction, the role of these changes in affective disorders also needs to be addressed. Important clues regarding the basis of the finding may be provided by the consistency of the finding of glial cell loss in major depression, and the data suggesting that, among schizophrenic subjects, those with affective symptoms are particularly likely to show these changes. In light of this, some have hypothesised that many of the brain changes seen in major depression, schizophrenia and bipolar disorder may be epiphenomenon of the diseases, for they may be secondary to the depressive symptoms and elevated glucocorticoid levels which accompany the illnesses.

§ Do any of the currently known genes implicated in schizophrenia play a clear role in inflammatory/vascular responses?

§ An overview of how the authors proposed that this hypothesis may be tested would be very useful. This may include a systematic review of epidemiological data, for example, when experimental evidence is not available.
Some information is repeated several times throughout the text -- this interferes greatly with the appropriate flow.

Similarly, there are broad statements regarding the etiology of several neuropsychiatric diseases (not only schizophrenia) that may not be completely accurate.