Author's response to reviews

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

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Author's response to reviews: see over
To the editors:

Re: manuscript 1585685614432932
   Theories of schizophrenia: Need for an inflammatory/vascular component?
   Hanson & Gottesman

We found all of the comments by Drs. Mueller and Manji to be most helpful and we have revised the manuscript in several ways. Our responses to the reviewers are itemized below:

Dr. Mueller’s comments:

1) Hypothesis statement with regards to whether we are dealing with the currently defined syndrome of schizophrenia or a subpart.
   We have added a paragraph at the end of the hypothesis section (p11) trying to clarify that our hypothesis may explain only a part of the current syndrome and, if the theory is correct, may lead to redefinitions based on pathophysiology rather than behavioral symptoms.

2) Distinguishing vascular inflammation vs. parenchymal inflammation
   We have added a paragraph in the hypothesis section (p10) attempting to clarify the distinction. On the same page, we also make brief mention of the relationship between parenchymal and vascular inflammation but did not attempt to provide extensive discussion both for space and focus reasons.

3) Negative association between schizophrenia and rheumatoid arthritis.
   Our unconvincing statement about strain differences as an explanation lies in our failure to adequately represent the literature. Indeed, strain differences are the most widely accepted explanation for why some strep infections lead to rheumatic fever and in other cases cause, for example, kidney damage. We have extended our comments and added additional references to document this assertion.

4) Neuropath findings in schizophrenia including inflammation
   This is a huge topic worthy of entire articles. We have enhanced our discussion of the topic, in conjunction with #2 above, in the hypothesis section by discussing the topic of gliosis and some of the newest approaches to the subject including work on S100B (pp10-11). We added references to point the reader to up-to-date reviews.

5) We appreciate being directed to several relevant references and have included them as suggested.

6) We also appreciate (and are chagrined by) the spelling errors and typos and have corrected them.
Dr. Manji’s comments
1) Specificity of our hypothesis
   We have added a section on specificity at the end of the paper (pp27-28). In the same section we mention the issue of epiphenomena and made additional reference to the issue on p.7

2) Confounds such as medication effects
   We added an acknowledgement of this issue toward the end of the top paragraph p.7.

3) Brain changes in affective illness
   We made reference to these in the section on specificity. The possible impact of stress/glucocorticoids is inserted in this section as well as on p7.

4) Are any current genes implicated in schizophrenia also involved in inflammatory responses?
   We answered this question by referencing linkage studies showing an association between schizophrenia and inflammation modulating genes (p23, references 237-239).

5) The request for an overview of how our hypothesis might be tested formed the basis for a new section on ‘future directions’ (p 24).

6) We have attempted to improve flow by reducing redundancy though the format with abstract, body of article, conclusions invariably leads to some redundancy.

7) We do not believe that any of our ‘broad statements’ about other neuropsychiatric disease are factually wrong but are necessarily brief and are used for illustrative purposes. Elaborate discussions of these conditions would consume much space and would distract from our main point.

PLEASE NOTE: DRH will be on holiday 2 Jan 05 through 9 Jan 05 and will have limited access to e-mail. Please cc any urgent communications to IIG at e-mail address on title page. Thanks. Happy New Year.