Author's response to reviews

Title: Model-based parametric study of the frontostriatal abnormality in schizophrenia patients

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Author's response to reviews: see over
Cover Letter

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BMC Psychiatry
Editor-in-Chief
Melissa Norton, MD

Dear Dr. Norton,

MS: 1628058244277353
Model-based parametric study of the frontostriatal abnormality in schizophrenia patients.
Shoji Tanaka

I am submitting a revised manuscript of the research paper whose title is given above. According to the reviewers’ comments, I have revised all points indicated. It is now tighter related to anatomy, clinical and imaging data. The methods for testing the model have also been provided. Therefore, I believe that this article is worth publishing from BMC Psychiatry.

Number of figures: 7
Number of tables: 4

Best regards,

Shoji Tanaka

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Author's reply

Reviewer #1

This is an interesting modeling paper which uses receptor imaging data to model the effects of hypofunction of the prefrontal cortex on subcortical dopamine levels in schizophrenia. While at times the mathematical modeling was difficult to follow for someone without the background in this field the author nicely summarizes the findings of the paper.

A few discretionary revisions may help to enhance the clinical relevance of the paper. First, the author may want to comment as to which studies should be performed to test his model - would these be PET receptor imaging studies, fMRI studies, or a combination of these. It would be nice to see the predicted outcomes of the recommended studies based on this model; that way, in the future, if these studies are performed, the model would be tested.

Discussion has been revised to a great extent with new paragraphs. I tried it to be more clinically relevant. Justification of the present result and a comparison of previous findings have also been added. As for testing, multivariate analysis of a data set from the combination of PET receptor imaging and fMRI studies would be the most desirable if it will be available. Further studies on the association with symptoms and clinical outcome will be needed. An accumulation of data from either PET or fMRI studies will also be helpful to increase the reliability of the predictions from this model. These have been added.

Also, while the author does comment briefly on the effects of antipsychotic medications as they relate to the PFC, it would be interesting for him to discuss what effect reduced dopamine occupancy at the D2 receptor would have in the proposed model. See Frankle et al, Psychopharmacology 2004, for an estimation of the level of D2 occupancy by dopamine at different doses of antipsychotic medications - would there be an "optimum" occupancy of the D2 receptor which would maximize the PFC activity while improving the psychotic symptoms?

I have added the estimation of the "optimum" occupancy of the D2 receptor by antipsychotics (Sec. 3.4). By taking the effect of receptor upregulation into account (1.2 times higher than control), the optimum level was estimated to be 52%, being close to but slightly higher than the estimation by Frankle et al. (2004), which was 48%.

I appreciate the point that D2 receptor occupancy may be optimized to have the maximum PFC activity - I wish I could do it. Although this model describes the input from the PFC to the striatum, it does not include the influence of the striatum on the PFC, even via the indirect striato-pallido-thalamo-cortical circuit. Such estimation is, therefore, beyond the scope of this model, and I hope I can revise the model in the near future so as to make other interesting predictions, including this one. Thank you very much for the suggestion.

Level of interest An article of importance in its field
Quality of written English Acceptable
Statistical review No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests I declare that I have no competing interests
Reviewer #2

This paper describes a mathematical model of so-called hypofrontality in schizophrenia. While this model offers some attractive new data, further research and a more exhaustive discussion is needed to warrant validation.

1. The concept of hypofrontality stems from the finding that malfunction of NMDA receptors leads to the development of schizophrenia-like symptoms. However, this effect ultimately causes an excessive release of glutamate (hyperglutamatergia) in cortical regions. For this reason, the term hypofrontality needs a clear definition in this context.

As the author pointed out, the concept of hypofrontality contains a controversial but important issue. In this article, however, ‘hypofrontality’ means just a reduced activity of the PFC, which provides less input to the striatum. I have added this in Discussion (in the middle of the third paragraph).

2. This is further complicated by the fact that hypofrontality has been generally associated with negative (but not positive) symptoms of schizophrenia. The author fails to provide relevant literature in this respect (Wolkin et al., Arch Gen Psychiatry 1992; Whalley et al., J Affect Disord 2008; Park et al., Psychiatry Res 2009).

This point has been mentioned with the citations given above in Discussion (in the last paragraph) and in Background (in the first paragraph). Hypofrontality has also been associated with cognitive impairment but not positive symptoms. On the other hand, schizophrenia patients with higher striatal D2 receptor occupancy tended to have greater improvement of positive symptoms after antipsychotic treatments. By linking hypofrontality to striatal hyperdopaminergic neurotransmission, the frontostriatal model in this article has associated hypofrontality with the therapeutic effect on positive symptoms. This has been argued in Discussion (the last paragraph).

3. Given that the author does not measure the reduction of endogenous dopamine after AMPT (p. 5), a reference must be provided.

References have been cited (Laruelle et al. 1997; Abi-Dargham et al. 2000).

4. The manuscript would definitely benefit from some artwork depicting the circuit model described in the section 2.1.

A circuit diagram has been added (Fig. 1). Thank you very much for the suggestion.

5. Overall, the discussion fails to confront the model described with relevant clinical (and preclinical) data existing in the literature. It is surprising that only two references are provided. The discussion section is usually conceived as a justification of present data as well as a comparison of previous findings. This important action is missing in the present paper.

Discussion has been revised to a great extent with new paragraphs and many additional references. I tried it to be more clinically relevant. Justification of the present result and a comparison of previous findings have also been added. As for testing, multivariate analysis of a data set from the combination of PET receptor imaging and fMRI studies would be the most desirable if it will be available. Further studies on the association with symptoms and clinical outcome will be needed. An accumulation of data from either PET or fMRI studies will also be helpful to increase the reliability of the predictions from this model.
These have been added.

**Level of interest** An article of limited interest

**Quality of written English** Acceptable

**Statistical review** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests** I declare that I have no competing interests

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**Reply to the Comments from the Associate Editor:**

**Comments:** As suggested by the reviewers, the proposed model needs to be tighter related to anatomy, clinical and imaging data. Authors need to suggest which imaging modality will be best to test the hypotheses, what are expected imaging results, what role does the medication play in the model. Also, clinical data supporting the model needs to be discussed in more detail.

I have revised the manuscript so as to be tighter related to anatomy, clinical and imaging data. First, a circuit diagram of the frontostriatal model has been added. This is based on the anatomical study (Sesack and Carr 2002) as referred in Discussion (the first paragraph). Second, I have added the estimation of the 'optimum' occupancy of D2 by antipsychotic drugs (Sec. 3.4) and the discussion on its relevance to clinical studies. This estimation has been compared with the previous one made by Frankle et al. (2004). Third, fMRI and PET receptor imaging studies for testing the model have been referred in Discussion (the last paragraph). The receptor binding part of the model based on the data from previous receptor imaging studies (Table 3), which are limited and have large variability. By accumulating PET receptor imaging studies on the D2 binding in the striatum, one can increase the reliability of the prediction from the model. This is argued in the last paragraph of Discussion.

**Question:**

Figure 7 uses "Fig. 7 of Seeman and Tallerico (1999) [44]" with a minor modification (i.e., adding a horizontal line). Do I have to do something to get the permission to use it on my manuscript?