Author's response to reviews

Title: Family-based clusters of cognitive test performance in familial schizophrenia

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Author’s response to reviews: see over
Dear Editor,

Attached is the revised manuscript MS: 1091371093418903 (Family-based clusters of cognitive test performance in familial schizophrenia) which we resubmit for your consideration of being published in the BMC Psychiatry.

Please find below the point-by-point description of the changes we made to our manuscript (Version 3) in response to the new comments of the referees. We thank all the reviewers for all their comments.

Please note the answer to comment 5. of prof. Jeremy Miles: If the Journal finds it desirable, the supplement files (in http://www.rni.helsinki.fi/~fjh/supplement.html), including the movies, may be copied to the BMC website. If you decide to do so, please change the web address in the text to be correct.

Sincerely yours,

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Responses to the referees comments

I.I. Gottesman

1. I suggest a specific mention-sitation of R.W. Heinrichs 2001 OUP book and a comment about those neuropsychological tests meeting or failing to meet the simple criterion of separating schizophrenics from normals that are also listed in your Tables 3 and 4 (and Fig). Perhaps an asterisk and brief comment is sufficient.

2. Although Erlenmeyer-Kimling et al. results (e.g. 2000 Arch.Gen Psychiat.) have been mentioned in previous work by Ms. authors, it might be appropriate to cite the findings that converge with those here -- the traits and trait clusters that distinguished the actual schizophrenic-to-be from other high risk children. Of course the strategy was different and therefore the convergence is all the more interesting.

Taking into account these two essential comments does clearly improve the discussion of the present study. Thus we have included these issues in the Discussion section instead of the Tables. Unfortunately, we did not have access to the book by R.W. Heinrichs, but instead, we have referred the article by Heinrichs and Zakzanis (1998), which addresses the same issues that prof. Gottesman suggests. In addition, we have referred the paper by Erlenmeyer-Kimling et al. (2000) at this same point. The following chapter has now been added to the Discussion, on page 11.

“Global verbal memory, including the story recall from the WMS-R (Wechsler 1987) and verbal learning from the CVLT (Delis et al. 1987), were among the measures that
differentiated well the clusters. This is in line with results by Heinrichs and Zakzanis (1998), who found the best effect sizes in these functions in differentiating schizophrenia patients from controls. However, against a background of global dysfunction, any selective impairments such as those in verbal memory, are only relative (Heinrichs and Zakzanis, 1998). The present study suggests that it is possible to characterize families with convergent cognitive performance using variables from several domains of cognition, such as attention, verbal memory, executive functioning, and intelligence. In efforts aiming at sample homogeneity, the best method may be using multiple endophenotypic measures. In part, our results are also comparable to those by Erlenmeyer-Kimling et al (2001), who found that impairments in multiple cognitive measures best predicted future schizophrenia in high risk subjects.”

William Horan

1. The authors now emphasize certain diagnostic differences in probands and family members in an effort to validate the clusters. Specifically, “…the impaired cluster did not include any subjects with affective psychotic disorders, whereas in the well-performing and in the intermediate cluster, these diagnoses were assigned for 14% and 11% of the family members, respectively. Furthermore, the impaired cluster comprised merelt those patients from the schizophrenia spectrum that suffered from pure schizophrenia, along with their unaffected family members.” It would be useful to report whether the rates of affective psychotic disorders were statistically different across clusters. It might also be useful to discuss how these findings could be interpreted as supporting the validity of the clusters.

As the percentages Prof. Horan refers to on page 9 in the subsection “Demographic and Clinical Characteristics” include also schizoaffective patients, we have changed the sentence next to the last to be the following:

“The impaired cluster did not include any patients with schizoaffective disorder, bipolar disorder or other affective psychotic disorders, while in the well-performing and intermediate clusters, these diagnoses were assigned to 14% and 11% of the subjects, respectively.”

Furthermore, we have replaced the text that Prof. Horan refers above with the following, on page 10:

“We tested the differences in the diagnostic class distributions (including those with no diagnosis), and although the differences did not reach statistical significance, we find it interesting that none of the subjects with schizoaffective disorder, bipolar disorder, or other affective psychotic disorders ended up into the impaired cluster. We consider this as supporting the validity of particularly the poor cluster, which seems to represent a subsample of core schizophrenia with the most defected cognitive functioning. This cluster included the same proportion of unaffected subjects than the other two clusters, and based on the clustering algorithm, these family members without any psychiatric diagnoses during their lifetime performed generally poorly, too.”
2. Figure 1 has been added to help the reader understand the clustering procedure. I did not find this new figure added much to the generally clear description of the overall steps that the analyses follow. The stage in the process that I find more difficult to grasp is exactly how the inter-cluster distance is determined. On p. 6 the authors write: "In the sense of this distance measure, two clusters are close when all subjects in both clusters are close." If the authors choose to conduct further text revisions, this particular aspect of the procedure might be more fully described.

We have now added the word "members" in to the sentence right after the formula for d_r, on page 6.

Jeremy Miles

1. The abstract refers to clustering analysis, however I would prefer to see it referred to as cluster analysis.

We have replaced "clustering analysis" with "cluster analysis".

2. The section called "subjects" might be better termed "subjects and data collection", or might be split into two sections.

We have changed the title of the section to "Subjects and data collection".

3. I am not sure that the title and abstract reflect what is really interesting about this paper (or at least all of what is interesting). I think the title and/or abstract should mention the application of the visually aided cluster algorithm.

We preferred to keep the old Title, because we find that the psychiatric aspect is relevant considering the Journal. Instead, we have added to the Abstract, section Conclusions, the words "visually aided…"

4. Table 1 could include sex percentages, as well as numbers.

As the figures are so similar between the sexes, we think the numbers give the sufficient information.

5. Could the movie files be added as supplementary files to the BMC website?

If the Journal finds it desirable, you may copy the supplement files (in http://www.rmi.helsinki.fi/~fjh/supplement.html), including the movies, to the BMC website. If you decide to do so, please change the web address in the text to be correct.