Author's response to reviews

Title: Morphological correlates to cognitive dysfunction in schizophrenia as studied with Bayesian regression

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Author's response to reviews: see over
Comments to the reviewers regarding the revised manuscript

“Morphological correlates to cognitive dysfunction in schizophrenia as studied with Bayesian regression” by Lawyer, Nyman, Agartz, Arnborg, Jönsson, Sedvall, Hall

General comments

Thank you for taking the time to review our manuscript. Your many suggestions have proved invaluable in revising the manuscript.

We have noticed that you were bothered by one overriding difficulty in our previous submission, the lack of a clear aim. The paper has now been substantially rewritten with strict emphasis on the aim identifying morphological covariates to cognitive skill tests, and testing for where this relationship differs in schizophrenia. Following the advice from Professors Kruggel and Shenton, the investigation has been placed in the wider context of the ongoing debate on relationships between morphology and cognition in psychosis. Professor Friston gave detailed suggestions on statistical approaches to this question; his advice has been closely followed. The correlation analysis has been dropped. The sharpened focus and improved statistical approach have allowed us to simplify the presentation of results. The discussion has been expanded, and placed in the context of the theories mentioned in the introduction.

Enclosed please find individual replies giving a more detailed response to your specific points. We trust that the readers of BMC Psychiatry will appreciate the improvements arising from your recommendations.

Professor Friston

We are grateful for your encouraging review. Many of your specific concerns dealt with method, including detailed suggestions on how we could improve our statistical analysis. Following your advice, a new method has been implemented in the current study. We have otherwise amended our work in response to your comments as follows.

1) I think you have to motivate data-mining in a more compelling way...Perhaps you could provide one or two examples where this sort of informatics approach has been useful previously in schizophrenia research.

We have revised our introduction to frame our investigation in terms of conflicting theories of morphological covariates to cognitive skill deficits in schizophrenia. We then discuss how a data mining approach can shed more light on this important debate. The revised discussion includes a short presentation of the advantages of a data mining approach, including some references to work where it has provided a clear benefit.

2) The second motivation issue relates to the aim of the paper. Is your aim to compare a classical (re-randomisation) approach with a Bayesian model selection approach to data-mining? Or is it to reveal some interesting empirical observations in schizophrenia using these techniques.

We have clarified the presentation and execution of the paper’s aim. It is to reveal some interesting observations using a model selection approach.

3) You have chosen to compare a simple pair-wise correlation analysis with a model selection approach based upon a multiple linear regression model. This is not appropriate.

Your advice has been taken, and both the pairwise analysis and the comparison have been dropped.

4) I think you need to explain your Bayesian covariate selection approach more thoroughly ...In short, I think you need to describe the benefits of the Bayesian approach and how it differs from classical model selection.
You will now find a presentation of this in the statistics section of the methods. You will find additional comments in the discussion, which contains a brief presentation of the benefit of this style of analysis.

5) I do not understand ...your ...model? ...If you were interested in how schizophrenia affects brain structure-function relationships ...this would entail modelling the diagnosis times structure interactions in explaining the psychological responses. ...You should be using a multivariate linear model where the response variable is multivariate and covers all the psychological responses.

Your suggestions factored greatly in our new choice of methods. We have added interaction effects for diagnosis to the model, and the method chosen uses a multivariate response.

We depart from your suggestion slightly in that while our response variable is multivariate, each model covers only one functional domain. The method used in the current manuscript selects one set of covariates to explain the full multivariate response. We did not expect the same morphological covariates to be involved in, say, hand-eye coordination as in verbal learning.

6) I think you should ...remove the correlation analysis.
Done.

7) On page 9 you say gender was a significant determinant in verbal memory and that this could be due to the differences in the sample. How could this happen?
By careless editing on our part.

The remark referred to findings in the correlation analysis. Having dropped the correlation analysis and the remark, we hope that this is no longer an issue.

8) When you refer to the probability estimates greater than 99% ...Are they the posterior probability that the regression co-efficient is greater than zero?
Yes, or, more precisely, not equal to zero.

We have worked to make the figures and tables in the revision clear and legible. The figure legends have been expanded, and the presentation of the results is phrased to demonstrate how to interpret the figures.

9) On page 14 you say that traditional acceptance levels for p-values have not been established in Bayesian statistics. This is not true. There is an accepted and established semantics regarding Bayes factors ...
   The comment has been removed. Our current method does not rely on Bayes factors.

Professor Kruggel

As we mentioned above, we are grateful to you for your guidance regarding the motivation for selecting our morphological covariates. Our investigation is now presented in the context of the wide debate (to use your term) regarding morphological differences and their functional correlates.

Before replying to your major points of concern, note that we have also paid close attention to the points you list as minor when you reviewed the work. The phrases you objected to have either been modified as you suggested or dropped. We have clarified the tables, and the figure to which you referred has been removed.

1. The motivation of selecting these 16 anatomical structures is unclear, at least, without referring to previous publications. Assist the reader in understanding why these structures are important.

The revised manuscript refers explicitly to the debate surrounding morphology and cognition, including references to some key papers within it, as a motivation for the anatomical structures we studied. This debate has also provided structure to the discussion, which is now longer and contains more references.
2. In addition, the motivation of selecting (just) these two statistical tests is unclear.

The revised introduction discusses how the method used can shed light on the debate regarding morphology and cognition.

3. Using pairwise correlation does not disentangle well-known correlation among covariates...so why not using regression models (perhaps stepwise selected models)?

As both you and Professor Friston suggest, our current submission is based on a regression model with interaction terms and a multivariate response. The analysis of the model uses an approach very like stepwise regression, this is discussed in the methods section.

Your comment was specifically concerned with the comparison of pairwise correlation with the RJMCMC analysis, which was, as you say, inappropriate. The pairwise analysis has been dropped, and with it attempts to compare findings from multiple approaches.

4. Why were variables age of onset, duration of illness and medication not used as covariates? Here, disease is used as a classifier only. A developmental vs. degenerative (and/or medication-induced) influence might be discriminated.

We sought to identify morphological covariates to cognitive function that differ in schizophrenia. As you observe, disease was used as a classifier. Given that we also control for age, which is in our data associated with duration and lifetime medication exposure, the inclusion of these additional covariates would dilute the information carried in the diagnostic classification, which could have consequences for the covariate selection which was the main aim of the paper.

The questions you raise are certainly important to understanding the relationships we present evidence for. We have included them in the discussion. Answering them, however, seemed beyond the scope of this current work.

5. Discuss how much test scores just reflect a disease/medication induced attention deficit. How much depend scores on session time? Was the same temporal sequence of tests used or were they randomized (in both groups)?

We now included answers to these important methodological questions when presenting the neuropsychological tests in the methods section.

6. Is the relatively small sample size an issue when using this Bayesian method?

This has now been taken up in the statistical background in the methods section of the paper.

7. The relatively non-overlap between results of the correlation tests and the Bayesian method requires a more in-depth discussion - at least, from a data-mining perspective. As presented now, there is little discussion about the neurobiological meaning of the results.

The correlation analysis has been removed. Discussion is focused on the neurobiological meaning of the results. Your opening remark has been a great asset in framing this discussion.

Professor Shenton

Thank you for your suggestions as to how we could improve our submission to BMC Psychiatry. They have proved helpful in turning a rather unfocused work into something that we hope will prove quite interesting to the community.

As we understood your review, the main weakness you saw in the study was the application of several methods without any a priori hypotheses, making the comparisons of findings across methods difficult in the absence of a validation sample. The revised manuscript’s introduction presents three differing theoretical frameworks that link morphological characteristics and cognitive function in schizophrenia. These provide several hypotheses regarding the data used in the investigation. Attempts to compare methods have been eliminated, the work now focuses exclusively on the neurobiological findings.

You also provided a list of more specific recommendations, which we have addressed as follows:
The issue of gender differences between groups has not been adequately addressed. This issue is now introduced in the materials section, and the methods section discusses how the approach used can account for gender bias when it exists.

A discussion of the number of variables has not been adequately reviewed with respect to the power needed to detect associations in pairs of data.

Thank you for suggesting such a discussion, as it has added to the comprehensibility of the manuscript. Please see the subsection “power of the test” in the methods section of the manuscript.

The word “change” for brain morphology is not appropriate, as brains over time are not being evaluated. A better word would be “morphological abnormalities” rather than “morphological changes”. Similarly, the word “reduction” in reference to volume is misleading, as there is no indication of reduction per se.

The word brain “abnormalities” has now been substituted for “changes”. Likewise, we now use the term “smaller” since reductions, as pointed out, are not demonstrated with this method.

Further information regarding the selection of the two statistical methods for data mining, including a further rationale, is needed. Specifically, because there are many data mining tools, why did the investigators select these two?

The revised introduction discusses how the method used can improve understanding of morphology relationships to cognition in schizophrenia. The methods section mentions some advantages of the specific approach taken.

The results are very hard to follow. For example, why list all of the variations of neuropsychological tests that show differences? That is, is there one measure among the WCST that is most informative? Also the acronyms used are not defined in the table. Finally, the figures are quite confusing and the display chosen does not at all elucidate the findings but instead obfuscates them. A different approach to showing the main findings of the study is needed.

Given that the aim of the previous manuscript was so vaguely expressed, it follows that the results were poorly presented. We hope that the current revision, with its sharper focus, has remedied this. We have redone all of the figures and tables.

You refer specifically to the table of neuropsychological test results. Following your suggestion, the table legend has been re-written to give readers without a deep interest in neurocognitive testing a summary of the results. The reference to the previous table, which explains the test acronyms, has been made more explicit.

The table itself, however, is quite difficult to shorten. Each test score highlights a different aspect of performance. In general, none of the sub tests within a domain can be considered the most informative. As these are new findings, not presenting them in full would give an incomplete picture to those readers with a deep interest in this specialty.

When all is said and done, what does this study add to what we know about brain morphology abnormalities and their association with cognitive function in schizophrenia? We now provide a broader context for our work, which also gives structure to the discussion. You will notice heavy revisions in both the introduction and the discussion of the new manuscript.

A native English speaker should go over the manuscript, as there are some odd uses of language. Agreed. The author list has been re-ordered. The current first author is a native English speaker, and he has changed the language where he found it odd.