Author's response to reviews

Title: Identifying Persistent Negative Symptoms in First Episode Psychosis

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Author's response to reviews: see over

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Deesha Majithia
Executive Editor
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Re: Edits to Manuscript: Identifying Persistent Negative Symptoms in First Episode Psychosis (2038010658692410)

Dear Deesha Majithia,

Please find enclosed our revised manuscript proof entitled:" **Identifying Persistent Negative Symptoms in First Episode Psychosis** ". The reviewers provided us with pertinent and important suggestions, which we believe helped significantly improve the scientific quality of the paper. We are very appreciated of all their comments and for their diligence in pointing out similar errors. We have worked hard in the last few weeks in an effort to improve our manuscript based on the comments we received. The comments were insightful and resulted in important changes to the manuscript.

The following changes have been made:

Reviewer #1:

1) Why did authors consider 3 months as a stabilization point? This is a very important issue. Though one relevant paper (44) was cited, please add more rationale or references. In the APA guideline, stabilization usually indicate 6 month after acute episode.

Response: This is a very valid point raised by the reviewer. Most articles have employed month 12 as the initial stabilization of acute symptoms in psychosis. However, more recently studies assessing the trajectory of psychotic symptoms have shown an initial stabilization of ranging from 12-14 weeks after entry into a

treatment program. Three more studies demonstrating this have been added as references on page 10 (ref 44-47).

2) On page 11, please clarify further the definition of "clinically relevant negative symptoms on the SANS scale". Global score or total score and at least one or two items ---??

Response: "Clinically relevant symptoms" were considered to be moderate to severe negative symptoms as rated by a score of 3 or greater on the SANS. This has been clarified in the paper on page 11.

3) Was this study cross-sectional design? Describe clearly how this study was designed in the Method.

Response: This point was clarified at the first sentence of our methods.
"All patients were part of a longitudinal naturalistic outcome study of first-episode psychosis and were recruited and treated through the Prevention and Early Intervention Program for Psychoses (PEPP-Montreal), a specialized early intervention service with integrated clinical, research, and teaching modules, at the Douglas Mental Health University Institute in Montreal, Canada"

4) For the reference 67, this is a review paper. Please cite more specific paper which investigated effect of rTMS on the 2ndary negative symptoms.

Response: On page 21, three new references have been added including Schneider et al. 2008. Brain Stimulation and Goyal N et al. 2007 Neuropsychiatry Clin Neurosci. Oh et al. Progress in Neuro-Psychopharmacology & Biological Psychiatry 2011 (ref 69-72)

5) In page 23, in the section of limitation, what does "REF" indicate?

Response: The reference for this statement had not been added. References have now been included on page 23.

6) In page 9, please cite the reference for CORS. The number 42 is not the right reference for the CORS.

Response: The correct reference for the CORS has been added.

6) You cited 42 as a definition for prodromal symptoms. However, in that paper, it reads that "the prodromal period is the time between onset of any psychiatric symptoms and the onset of psychosis. In other words, it does not contain "—contiguous with –" which was used in your study. Whether contiguous or not is very important. So, please cite more correct one.

Response: The reviewer is absolutely right. The term "contiguous with" was removed from the paper in order to be in line with the prodrome reference that was used.

8) When you conduct the repeated measure ANOVA, how did you handle the missing data? (Because only 140 patients obtained a SOFAS score at month 12 in page 16.). LOCF or observed case analysis?

Response: Missing data from our study is missing at random. Given this, we did not use LOCF or observed case analysis.

Reviewer #2:

Major Compulsory Revisions:

1. Bias-testing of loss of patients. The authors start the result section by reporting that in a cohort of 280 FEP patients 100 had missing data. Among the remaining 180 patients forty-four had primary negative symptoms. It would be of interest to know if there were significant differences between patients included and patients lost.

Response: The reviewer raises a valid point. Group comparisons were performed between patients excluded due to missing data and those included. No significant differences were found between groups. The following sentence was added to the paper:

Page 13: "Of note, no differences in age, DUP, DUI or prodrome were found between included patients and excluded patients due to missing data."

2. Grouping of patients The authors report in the results section the following numbers of patients meeting the three PNS-definitions: PNS_1: 44, PNS_2: 21 and PNS_H: 21. But adding the numbers meeting and not meeting the respective definitions give the following numbers: PNS_1: 160, PNS_2: 159 and PNS_H: 158. Some patients seem to be lost here, but not accounted for. Concerning PNS_1, it would give a clearer picture to have a "clean" PSN_1 group of 23 not meeting the criteria for PSN_2.

Response: The reviewer is correct. There were errors in our results. Upon revision, we have made the following corrections to our prevalence's. The following prevalence's were found: 44 patients met the criteria for PNS_1 while 114 patients did not meet the criteria for PNS_1. 21 patients met the criteria for PNS_2 and PNS_H, while 137 did not meet the criteria for PNS_2 or PNS_H.

Furthermore, Figure 1 (Classification of FEP patients based on negative symptoms) depicting patient groups has been edited in order to clarify patient classification.

Furthermore, in an attempt to make it clearer, we have also edited the section entitled" *Supplementary Analysis of the PNS_1 group"* and added the following sentence "To obtain a "clean" PNS_1 group, specific patients in the PNS_1 group were extracted and re-named as the "liberal" group."

3. Recommended definition of PSN The authors conclude in the section "Characterization of the PNS cohort": "Given that PNS_1 allows for the maximum number of patients to be included in the PNS-cohort and showed a strong association with poor functional outcome, it would be recommended to apply this PNS- definition." I find it hard to follow this advice. For, as the authors state in the beginning of the discussion: "Interestingly, when patients who met the criteria solely for our PNS_1 definition were extracted, this "liberal" definition did not show any significant associations with functional outcome at the one-year follow-up." In my opinion this indicates the PNS_2 definition is the best one. (A detail: There were 21 patients meeting the criteria for PNS_2 and exactly the same number meeting the criteria for PNS_H. All results for PNS_2 and PNS_H show identical numbers, suggesting that the same 21 patients are included. If that is the case, it ought to be stated, and the result presentation simplified.)

Response: The reviewer has raised an important and valid point. Indeed, PNS_2 and PNS_H are the same group. We believe that this information is relevant because it means that when a patient has 2 negative symptoms they always seem to fit in either of the 2 categories of the hybrid (diminished expression or amotivation). We have edited what we recommend in this section of the discussion.

It now reads: "Choosing which PNS definition to employ may be dependent on the research question being asked. From an intervention perspective, the number of patients needs to be maximized to have a stronger conclusion determining the efficacy of a given intervention. Hence, applying our PNS_1 definition may be more appropriate. Interestingly, all patients who met the criteria for PNS_2 also met the criteria for either of the two domains of the hybrid definition (diminished expression or amotivation). Future research should focus on identifying the neurobiological and physiological determinants of PNS_1 and PNS_2 in order to determine whether they are distinct or share similarities."

4. Figure 3. The graphs of PNS _1 and PNS_2 ought to be combined by showing three lines: Non-PNS_1, PNS_1 only and PNS_2. The graph of PNS_H is so close to PNS_2 that it can be dropped without substantial loss of information.

Response: This was a great suggestion by the reviewer. As suggested, we combined part A, B and C of figure 3 into 1 figure (Figure 3).

Minor essential revisions:

1. Transformation of DUI In the method section transformation of several variables is described. I miss a description of transformation of DUI.

Response: The reviewer is correct. Upon revision of our statistics, it was observed that DUI transformation had been unintentionally left out from the results section. This correction has been made in the manuscript.

2. One-way analysis of age differences. In the same section is stated that differences in age between PNS and non-PNS is tested by use of a one-way analysis of variance. Why isn't simply a t-test used?

Response: This correction was made in Table 1. A sentence was also added in the statistical analysis section of the paper.

3. Frequency of patients with schizoaffective disorder. In the result section it is stated that "the majority of patients in the PNS_2 and the PNS_H groups were diagnosed as being schizoaffective". This is inaccurate, as only one third of the groups have this diagnosis. Furthermore, at least in my opinion, a diagnosis is something a patient has, not something a patient is. I suggest: "In the PNS_2 and the PNS_H groups schizoaffective disorder was the most common disorder".

Response: The reviewer is correct. Edits were made to the paper and this sentence now reads, "On the other hand, a greater number of patients in the PNS_2 and PNS_H groups were diagnosed with either schizoaffective disorder or schizophrenia (undifferentiated)."

A small detail Table 1
There is a strange symbol with two question marks. Should it be chi square? If the above revisions are made, I clearly recommend publication

Response: We have verified our original manuscript and the chi square symbol seems to be fine. However, there may have been an error when it was converted to a .pdf file.

Reviewer #3

1. Is the question posed by the authors well defined?
The questions put in the abstract are well defined. However, on reading the actual manuscript, the introduction is muddled, and the questions that lead on from the introduction, seemed a bit confusing. For e.g. "The main objectives of this paper were two-fold. First, we set out to explore various PNS criteria in order to determine if any one definition was more clinically relevant than the others".
What does "clinical relevance" mean? While this is the broad "aim" of the paper, the objectives should be more focused and specific. In fact, the whole of the introduction would benefit from being focused and succinct.

Response: The objectives in the introduction have been simplified and made clearer. The term "clinically relevant" has been changed to "clinically significant" and has been described on pages 7 and 11 (having a score of 3 or more on SANS global items). Some edits have also been made to the introduction to help make it more succinct.

2. Are the methods appropriate and well described?
Yes. However, there are a number of areas that are not clear. For e.g. when were the PNS criteria applied to the sample? Were they done retrospectively? The temporal relationship between assessments and when the data for this particular analysis was derived was not clear.

Response: This is a great point raised by the reviewer. On page 10, our description of our "methods for identifying PNS" was changed. More information was added regarding when our definition was applied. It now reads, "Upon completing 12 months of the treatment program, clinical data were obtained and the PNS definition was applied retrospectively from the first assessment, months 1,2,3,6,9 and 12."

3. Are the data sound?
The data are showing some inconsistencies. Inconsistent reporting of bonferroni correction. What was the rationale behind the multiple testing corrections? Why

was it done in some places, but not reported in others (for example in repeated measures statistics?). Why were paired t tests and repeated measures ANOVA done in different places? Why not do the same type of statistical analysis?

There are several inconsistencies in the data presentation and analysis. For example –
Pg 14 - "PNS_1 Definition: Forty- four patients (27.8%) were identified with PNS and 116 (73%) were not." The percentages here add to more than 100%.

Response: The reviewer is correct. There was no reason for multiple testing corrections. These have been removed. Regarding the ANOVA and t-test. An ANOVA was originally applied for age differences. This has now been changed to a t-test. Regarding other t-tests and ANOVA's in our analysis, we used t-tests for group differences and one-way ANOVA's for between group analysis at 2 time points. We have also corrected the inconsistences made in our results regarding prevalence's. We thank the reviewer for noticing this error.

Pg 15 – PNS_1 analysis shows the number of participants as 44/116 (see above comment). PNS_2 and PNS_H seem to show exactly the same result, with the same degrees of freedom. While this is possible, the number of people in the analysis does not add up. For e.g. - 21/138 (total 159) in PNS_2 and 21/137 (total 158) in PNS_H group. Why was this?

Response: This was a great point raised by the reviewer and was a similar concern with reviewer 1. As stated above, these corrections have been made. There were errors in the final numbers but this has now been corrected. The following prevalence's were found: 44 patients met the criteria for PNS_1 while 114 patients did not meet the criteria for PNS_1. 21 patients met the criteria for PNS_2 and PNS_H, while 137 did not meet the criteria for PNS_2 or PNS_H.

Also, some of the p values ($p<0.052$) have been reported as significant. While traditionally $p<0.05$ is considered significant, why was it considered to be 0.052 in this case?

Response:

"Trend" statistics have been reported, while none have been done.
Page: 17 "However, although there was a trend towards a significant [time x group] interaction using the entire PNS_1 cohort, isolation of the "liberal" group from this definition failed to reveal any significant [time x group] interactions ($F1,82=0.879$, $p=0.351$)."

Response: This was an error in the manuscript. "a trend towards" was removed.

4. Does the manuscript adhere to the relevant standards for reporting and data deposition?

The above mentioned inconsistencies have to be sorted out.

5. Are the discussion and conclusions well balanced and adequately supported by the data?

The data has to be sorted out clearly, and the analysis reported clearly and consistently.

6. Are limitations of the work clearly stated? Yes
7. Do the authors clearly acknowledge any work upon which they are building, both published and unpublished? Yes
8. Do the title and abstract accurately convey what has been found? Yes
9. Is the writing acceptable? The manuscript could be much more focused and succinct.

Discretionary revisions
To be extremely finicky as a reviewer, the term "golden standard" is not right – while this term has been used in other papers, the right term is "gold standard" – see below the history of this term in BMJ.
Classen J. The gold standard: not a golden standard. BMJ 2005;330:1121

Response: This change has been made. We thank the reviewer for this information.