Author's response to reviews

Title: A systematic review and meta-analysis of neurological soft signs in relatives of people with schizophrenia

Authors:

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

Re: Manuscript with id MS: 4124356924016268

Thank you for the response on our manuscript (Id MS: 4124356924016268). We would be grateful if you can consider our revised manuscript now titled “A systematic review and meta-analysis of neurological soft signs in relatives of people with schizophrenia” for publication in the BMC Psychiatry. We are appreciative of the reviewers for considering our manuscript as interesting, focused and well written. The reviewers’ comments helped us to improve our work further and we would like to thank the reviewers.

In the revised version we have updated the search strategy up to April 2011. Our findings supported our hypothesis that neurological soft signs show familial association in schizophrenia. We have addressed the reviewer comments and revised the manuscript. Please find below a point-by-point response to the reviewers’ comments. We have responded to the comments of Dr Chan in our earlier correspondence dated 29th October 2010. We are pleased to submit the revised version of the manuscript along with responses to the reviewers’ comments. We hope the revised manuscript is acceptable and up to standard for consideration of publication in the BMC Psychiatry.

Reviewer: Paola Dazzan

Reviewer’s report:
The meta-analysis “Familial association of neurological soft signs in schizophrenia: a systematic review and meta-analysis” by Neelam et al, has reviewed the existing literature on neurological soft signs in patients with schizophrenia, their relatives, and healthy controls. The authors conclude that there is sufficient evidence that neurological signs are a potential endophenotype for schizophrenia.

The paper has clear aims, is focused and well written. The methodology used is sound.
Minor essential revisions:

1) The variable entered in the meta-analysis is the total neurological signs score, rather than individual subscales scores. This is understandable, since not all studies identified used the same scale. However, since there is enough evidence that different signs may have different origin, with some signs possibly more familial and other more neurodevelopmental, it would be interesting and informative to have a review and a comment as to whether there were differences in familial association across group of signs reflecting different functional areas.

Response:
1) The reviewer is correct; it would be interesting to examine the individual sub-scale scores. It was our intention. We have reviewed the included studies to extract data relating to sub-scale scores and individual signs. Of the 7 studies, three studies reported sub-scale scores and one study reported individual signs across the three groups of schizophrenia, first-degree relatives and normal controls. It is not possible to aggregate the sub-scales or individual signs as not all studies used the same scale. We have highlighted this suggestion for future research in the discussion.

“There is also evidence to suggest that certain neurological soft signs correlate with region-specific structural brain deficits in people with schizophrenia. Future research should explore the potential of these individual signs as endophenotype or biomarker of schizophrenia”

2) There is always a possibility that the higher scores found in patients are due, for some signs, to the use of antipsychotic medications. A comment on this possibility should be added to the discussion.

Response:
2) The reviewer raises an important point regarding the higher scores on some signs in patients due to use of anti-psychotic medications. In our own previous work we have shown that scores remain higher in patients despite controlling for the effects of anti-psychotic medication. However, in our manuscript we have added a comment on this in the discussion:

“A key limitation of this review was the finding of significant heterogeneity across all comparisons. Insufficient studies were available to permit investigation of this heterogeneity using meta-regression. Likewise, higher scores for some signs in patients may be due to use of anti-psychotic medication and we could not conduct moderate analysis exploring the extent of its effects”

3) The Table 1 with details of the search strategy could be moved to the additional material, while it would be important to have Table 2 (currently in the additional files) in the main body of the paper as it provides important information on the characteristics of the populations examined.

Response:
3) We agree with the suggestion to move table 1 to additional material and table 2 to the main body of the paper. However, we are bound by the BMC submission rules of the format of the table and we await editorial advice on this.

**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.

**Reviewer:** Michael Compton

**Reviewer’s report:**
The authors have conducted an interesting meta-analysis using all extant data on neurological soft signs rated across three groups, patients with schizophrenia-spectrum disorders, first-degree biological relatives, and non-psychiatric controls. The manuscript is generally well written, though it would benefit from attention to the following critiques.

1. I think that the term “familial association” in the title is a little unclear. It is not until the Abstract that the reader really understands the question being addressed by the meta-analysis. I think the title would be clearer by replacing this term with something about “neurological soft signs in first-degree relatives of patients with schizophrenia.”

**Response:**
1) We have amended the title from

“Familial association of neurological soft signs in schizophrenia: a systematic review and meta-analysis”

to

“A systematic review and meta-analysis of neurological soft signs in relatives of people with schizophrenia”

2. In the last sentence of the Conclusions portion of the Abstract, the authors suggest that neurological soft signs may have value as a simple clinical test for helping to identify people in the prodrome of schizophrenia. However, to do so, there would need to be evidence that such signs are specific to schizophrenia, as opposed to attentional disorders, mood disorders, anxiety disorders, etc. Since the article does not comment on the specificity of soft signs, I think that this suggestion may be over-stated. The same is true for the last paragraph of the Discussion section, which also comments on the issue of “increasing pre-test probability that an individual was developing prodromal symptoms…”

**Response:**
2) The reviewer raised the issue of specificity of soft signs. We agree the article does not comment on the specificity of soft signs. It was not within the scope of the meta-
analysis to test the specificity of soft signs. We have changed the emphasis of our statement in both the abstract and discussion.

We have amended the abstract. We have deleted text reading:

“neurological soft signs may have value as a simple clinical test for helping to identify people in the prodrome of schizophrenia”

and replaced with

“they may have value when used in conjunction with prodrome assessment tools for improving the detection of prodrome of schizophrenia”.

We have amended the last paragraph of the Discussion section. We deleted text reading:

“increasing pre-test probability that an individual was developing prodromal symptoms…”

and replaced with:

“The presence of higher rates of soft signs has the potential to augment the predictive power of psychopathological tests for the prodrome,”

3. In the second paragraph of the Background section, it would be helpful to provide parenthetical explanations of what is mean by “co-segregation” and “heritability.”

Response:
3) We have added explanation for all the criteria of endophenotype. This section of the article now reads as,

“(i) association with illness (higher rates of endophenotype in people with the illness than that found in the general population); (ii) state independence (presence of endophenotype irrespective of the disease state); (iii) familial association (the endophenotype is present at higher rates in unaffected family members than in the general population) ; (iv) co-segregation (higher prevalence of the endophenotype in ill relatives of ill probands than in well relatives of ill probands); and (v) heritability (the extent of variation of the endophenotype that is attributable to the genetic variation)”

4. In the sentence that follows that sentence, I think that “gene expression than psychopathology” would be clearer as “gene expression than is psychopathology” (add “is”).

Response:
4) We have changed the text: from

“gene expression than psychopathology”
“gene expression than is psychopathology”

5. At the end of the third paragraph of the Background section, the authors note that neurological soft signs meet the criterion of being state-independent. But does “because they do not vary with duration of illness, or receipt of neuroleptic medication” really provide any evidence state independence? Those don’t seem to be tests of state independence. State independence would indicate that soft signs are traits, present whether or not the illness is active.

Response:
5) We have changed the description of state independence in parenthesis to the actual definition of state independence. The end of third paragraph of the Background section reads as

“state-independence (because they are present whether or not the illness is active)”

6. In the last paragraph of the Background section, the authors present their hypothesis around familial association. What about research looking at correlations between patients’ scores and their respective relatives’ scores? Wouldn’t that also get at the issue of familial association?

Response:
6) The reviewer is correct; correlations between measures from patients and relatives can and are used in describing familial association. Particularly with measures relating to magnetic resonance imaging scans between the groups. In our meta-analysis we used the mean score of neurological soft signs between patients, relatives and controls as the outcome measure. On clinical measures (e.g. scores from soft signs rating scales) correlations are usually not reported if a same scale is used. Correlations on such clinical measures are reported if two different scales are used to test the relationship between the scales. However, none of the studies available for the review with three group comparisons used these methods.

7. In the section on Study Selection, I think that “between were resolved” should be “between them were resolved” (add “them”).

Response:
7) We have amended the text: from

“between were resolved”

to

“between them were resolved”

8. In the second paragraph of the Data Extraction section, it may be clearer to change “data were accepted from all three” to “data were included if any of these three measures were used.”
8) We have amended the text: from
“data were accepted from all three”
to
“data were included if any of these three measures were used.”

9. Although the authors consider the issue of whether the studies’ raters were blinded to group allocation, I think they need to acknowledge that when patients with schizophrenia are involved, blinding can be very difficult due to the behavioral manifestations of the illness. It is really difficult to ever ensure blinding to patient status when doing a neurological examination. Thus, there may be a bias that is very difficult to remove.

Response:
9) We have acknowledged this by adding a phrase in parenthesis.

“In addition, each included study was rated on three quality criteria: evidence of inter-rater reliability on the ratings of soft signs; rater blind to the status of the participant (although adequate blinding is difficult to establish and this bias cannot be fully eliminated); and degree of age matching between comparison groups”.

10. On page 9, the terminology “the control group of first-degree relatives” would be clearer as “the group of first-degree relatives” so that the term “control” is reserved for describing the non-psychiatric controls

Response:
10) We have amended the text: from
“the control group of first-degree relatives”
to
“the group of first-degree relatives”

11. In the Results section, each time the authors present data from the sensitivity analyses, I think it would be helpful to explicitly state the number of studies involved and the number of participants involved. That way, it is clearer to the reader to what extent the loss of significance may be related to a much smaller sample size in the subsequent analyses.

Response:
11) We have explicitly stated the number of studies used in the sensitivity analyses and the number of participants involved in the subsequent analyses.

12. On page 12, the authors state, “Thus, in summary, soft signs appear to be...consistent with the inheritance of a polygenic trait.” However, it is not clear how the preceding sentences led the authors to conclude anything about a polygenic trait.
I think some of the reasoning here is missing such that the reader may not see how the authors arrived at this conclusion based on these results.

Response:
12) We have amended the text from “Thus, in summary, soft signs appear to be distributed across people with schizophrenia and their first-degree relatives in a manner that is consistent with the inheritance of a polygenic trait.” to “Thus, in summary, soft signs appear to be distributed across people with schizophrenia and their first-degree relatives in a manner that is consistent with familial association.”

13. There is inconsistency in the formatting of the references; for example, the title of reference #6 is capitalized whereas the others are not.

Response:
13) We have re-formatted the references and ensured they are consistent with the BMC style.

14. In reference #24, the names of the three authors appear to be duplicated.

Response:
14) We have rectified the error with the reference management system. We have re-formatted the references and removed the duplicated names.

15. Throughout the references, the authors should go back to the original articles as they were published and confirm the initials of all authors. There are many instances in which only the author’s first initial is given, even though the published article used both first and middle initial. This is important for indexing purposes. Additionally, authors may be offended if the reference list does not accurately represent the authors’ names as published in the original articles (i.e., both first and middle initials).

Response:
15) We agree with the comments. We have now referred to the original articles and re-checked the initials of the authors in the references. We reviewed all the references and ensured they are accurate and consistent with the BMC style of referencing.

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.

Reviewer: Marie-Odile Krebs

Reviewer’s report:
First there is a similar paper now published by Chan et al (Neurosci Biobehav Rev. 2010 May;34(6):889-96. Epub 2009 Nov 27)

Response:
1) In our previous letter to the editor we have highlighted the differences between our paper and the one published by Chan et al. The three key differences between our paper and the one published by Chan et al are: First, our paper demonstrates that there is an association between the degree of relatedness and the level of neurological soft signs. Our methodology of using studies with three group comparison allowed us to demonstrate that level of neurological soft signs is associated with the amount of shared genetic material between people with schizophrenia and their relatives. This is important because it suggests that genetic factors are critical determinants of neurological soft signs.

Second, unlike Dr Chan's work our paper has applied quality criteria excluding poorer quality studies that are likely to have confounding effects.

Third, the search strategy in our paper has been updated up to April 2011. In our paper we have also considered the implications of the findings for early detection research in schizophrenia.

Second, meta analysis might not be the best way to address the question since it overlook a number of pitfalls: for instance, the heterogeneity of explored populations (siblings, offspring, parents) while there is indication of age effect and heterogeneity of the scoring (qualitative rating as present/absent or semi quantitative).

Response:
2) Systematic review and meta-analysis is a widely accepted method of synthesizing data from scientific studies. We agree with the pitfalls identified by the reviewer. We have addressed the pitfalls in our meta-analysis. We looked at the effects of age by conducting a sensitivity analyses and have now reported the actual results on these analyses with standardized mean difference (SMD), number of participants and number of studies that had more than 10 years of age difference between the groups.

In terms of the scoring of soft signs the included studies in our meta-analysis have all used a validated rating scale. The included studies used three rating scales for soft signs including Neurological Evaluation Scale, Standardised Neurological Examination and Condensed Neurological Examination. We extracted the total score of the wide range of soft signs giving a quantitative measure of soft signs. A moderator analyses did not show any difference in effect size based on the rating scale used.

We recognize heterogeneity across comparisons and have highlighted it in the discussion section as below:

“A key limitation of this review was the finding of significant heterogeneity across all comparisons. Insufficient studies were available to permit investigation of this heterogeneity using meta-regression. Likewise, higher scores for some signs in
patients may be due to use of anti-psychotic medication and we could not conduct moderate analysis exploring the extent of its effects. However, all studies in the review had the same direction of effect, and the findings were stable to analysis using a random effects model. Moreover, with the exception of one comparison (first degree relatives versus controls, where the effect size remained stable but no longer statistically significant), the findings were also stable to a rigorous sensitivity analysis which ruled out those studies with poor age matching of controls, lack of reliability testing, and unblinded raters”.

Third, it cannot be definitively concluded on familial transmission only by comparing first degree relative to patients and controls. Actually a true familial transmission can only be explored by exploring intra familial transmission while in the considered studies the first degree relatives are not always related to the patients. These two latter points should be directly addressed and documented the discussion.

Response:
3) The reviewer raises two important points. First, the reviewer highlights the need to clarify the meaning of “familial association” and second point about the actual relatedness of first degree relatives and patients in the considered studies.

We would like to clarify that our meta-analysis aimed at establishing if neurological soft signs meet one of the five criteria of an endophenotypic marker, i.e. Familial association. There is a slight overlap among the five criteria of the endophenotype when explicitly applied to complex concepts of mental illness. “Familial transmission” as commented by the reviewer is slightly different from the familial association we examined in our meta-analysis. Familial transmission or intra familial transmission is used to explore another criterion of endophenotype, namely “Heritability”. We have added the meaning of all the five criteria of endophenotype in the introduction, so that the reader clearly understands the criteria of endophenotype.

“(i) association with illness (higher rates of endophenotype in people with the illness than that found in the general population); (ii) state independence (presence of endophenotype irrespective of the disease state); (iii) familial association (the endophenotype is present at higher rates in unaffected family members than in the general population); (iv) co-segregation (higher prevalence of the endophenotype in ill relatives of ill probands than in well relatives of ill probands); and (v) heritability (the extent of variation of the endophenotype that is attributable to the genetic variation)”

The second point raised by the reviewer has been explicitly addressed in our meta-analysis. We used a robust methodology in our meta-analysis that only included studies in which the first degree relatives are always related to the patients. It is an important difference between our paper and the paper published by Chan et al 2009 as highlighted in the previous letter to the editor and as response to the reviewers first comment.

Fourth, 7 studies might not be enough to truly take advantage from meta analysis as this limited number hamper some detailed analysis. An intrinsic limitation that is correctly addressed in the discussion.
Overall, the discussion could be improved. The suggestions at the end of the discussion are out of the topic since the paper does not bring any information on NSS in prodromal subjects. In addition the discussion of endophenotype vs biomarker (and the possibility that NSS are not only related to genetic transmission) is somewhat contradictory. It could be further address by quoting the studies truly exploring intra familial transmission. Actually, there is indication in the literature that some markers of developmental markers (MPA, dermatoglyphic) may be more related to environment or gene x environment while NSS appear related to genetic transmission. If resubmitted, this paragraph should be modified or deleted

Response:
The reviewer raises important point about the use of neurological soft signs in prodromal subjects. We agree the study does not bring data relating to prodromal subjects, but our findings of NSS being a marker for schizophrenia has an important implication in the growing field of prodrome research. In our discussion we propose the idea of an important clinical use of NSS in the detection of prodrome of schizophrenia that needs to be clarified in future research. We added further references of studies on developmental markers relating to the genetic and environmental effects. We modified and improved the whole paragraph in the discussion section.

“Hence, the findings of this review add weight to the idea that neurological soft signs are an endophenotype of schizophrenia. Contrary, to other developmental markers such as ‘minor physical anomalies’ were early environmental factors are indicated, soft signs reflect familial association [26]. However, there are alternative explanations. For example, the findings are also consistent with the possibility that soft signs are not an endophenotype, but a biomarker. The term “biomarker” encompass a wider category of diagnostically valuable physical parameters that includes not only endophenotypes but also parameters that are wholly or partially environmentally determined [7]. For example, soft signs would be a biomarker for schizophrenia, if they reflected an underlying defect in neural integration that had arisen from the interaction of a genetic predisposition and an environmental insult in utero [31]. There is also evidence to suggest that certain neurological soft signs correlate with region-specific structural brain deficits in people with schizophrenia [33, 34]. Future research should explore the potential of these individual signs as endophenotype or biomarker of schizophrenia.”

“Paradoxically, if soft signs were a biomarker, they might be of greater clinical utility than a true endophenotype. Because soft signs can be elicited quickly, reliably and cheaply [13], they could be used in ordinary clinical settings to establish that an individual had progressed along the neurodevelopmental pathway to schizophrenia. There is evidence to suggest association of neurological soft signs in relatives with schizotypal personality scores, symptom severity and neuropsychological measures [30]. The presence of higher rates of soft signs has the potential to augment the predictive power of psychopathological tests for the prodrome, such as: the SIP/SOPS [35], Comprehensive Assessment of At Risk Mental States (CAARMS) [36], or Basic Symptoms [37]. Our meta-analysis highlights the meaning of neurological soft signs in the context of neurodevelopmental theory of schizophrenia. Neurological soft signs have important clinical implications and they open an avenue for future research.”
Minor points: first the authors are advised to included 2010's studies. It is unclear why the authors selected Gourion 2003 rather than Gourion 2004 which included the 3 groups with larger sample size.

Response:
We have updated the search strategy and reviewed studies until April 2011. Since the original search of September 2009 the last 2 year updated search retrieved 1399 articles. We further screened these articles retrieved full texts of articles that were thought to have potentially met the inclusion criteria. We amended the text and the flowchart of studies. We have amended the table 1 search strategy and included the updated retrieval of all the studies. We have also updated the figure 1 highlighting the identification, screening, eligibility and included studies of the systematic review and meta-analysis. In second paragraph of the methods section we added:

“The original search performed in September 2009 was updated again in April 2011 (see table 1).”

We selected Gourion 2003 rather than Gourion 2004, because Gourion 2003 explicitly reported the NSS scores among all the three groups. Whilst Gourion 2004 although had larger sample size divided the first-degree relatives group into presumed carriers and presumed non-carriers. The Gourion 2004 did not report the combined total NSS score for the first-degree relatives group.

We hope the responses on the reviewers’ comments are acceptable. Thank you for considering the revised manuscript for publication in BMC Psychiatry.

Yours sincerely,

Dr Kishen Neelam
Consultant Psychiatrist