Reviewer’s report

Title: Behavioural patterns of ADHD in a large multicentre study. Part 2: Dimensional questionnaire data and intelligence measures in probands and unselected siblings of the IMAGE project.

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Reviewer: Rosemary Tannock

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Overall assessment: The authors are courageous to undertake this investigation of factors that might potentially contribute to the marked heterogeneity of ADHD, particularly because it highlights the grey-zones of diagnosis of mental health conditions. That is, although the rationale is based on potential problems of diagnostic procedures and tools for genetic analyses, the clinical implications are rather concerning. This second manuscript focuses on a different subset of data from the IMAGE project from those used for the first manuscript (i.e., parent and teacher questionnaires analyzed at subscale level, IQ test, as opposed to parent interview and parent and teacher questionnaires analyzed at the item level). However, the analyses herein also examine the same factors as used in the first manuscript (age, gender, informant, centre, tools). The major results indicate differential effects of the proposed factors (age, gender, child-status (proband, sibling), informant, instrument, and diagnostic centre) on the questionnaire-based and IQ data (small gender and status effects on IQ scores, but large effects on questionnaire scores). The results are interpreted primarily from the perspective of the resultant risk for quantitative genetic analyses based on these standardized diagnostic measures. Major strengths of this study on which the analyses are based, include the large sample of probands and siblings amassed across 8 countries, the use of standardized inclusion/exclusion criteria and the same assessment tools. Of course, the present data set will also reflect any shortcomings in the design or implementation of the IMAGE study itself (e.g., marked differences in sample sizes contributed by the various diagnostic centres/countries; use of assessment tools that may not have been fully adjusted and validated for cross-cultural differences).

Shortcomings of this second manuscript include lack of clarity of the primary aims of the study, the confounding of ‘diagnostic centres’ and countries, the lack of attention to the clinical implications, and the complex statistical analyses (although seemingly robust) will render the results inaccessible to much of the readership of the Journal. Also, in its present state, the manuscript cannot stand alone (i.e., without the first manuscript) because key information about the diagnostic procedure and assessment tools are not included herein. Thus one key issue is to what extent the two manuscripts need to be independent of each other and whether two manuscripts are warranted on this topic and justified by the breadth of diagnostic behavioral data generated by the IMAGE study and the importance of the findings.
Major Compulsory Revisions

1. The major aims of the study need to be clarified and written consistently in the Abstract, Introduction, and Discussion. For instance, the overall aim was implied in the Discussion, by the sentence: “AN important question was whether the gain in power due to the large sample size was at least partly lost by [inadvertently] increasing heterogeneity of the sample.” The specific aim was then stated as being to determine possible sources of heterogeneity.

2. The rationale for the study presented in the Introduction must be clarified. Reflecting on both manuscripts, this issue has wide-spread implications that go beyond the concerns for molecular genetic analyses. That is, there is increasing pressure from funding agencies to engage in multisite large-N studies, with the implicit assumption that larger is better. To me, the current set of analyses put this assumption under the microscope – at least for child mental health field.

3. At present, the Introduction is not well-organized and the underlying logic for the current set of analyses is not clearly stated. By contrast to manuscript #1, the introduction is too short and the reader arrives at the methods section without a solid understanding of the issues to be investigated or of the rationale for the approach. For example, it is unclear why IQ scores are included along with behavior questionnaires, and why the SCQ is included. From a design perspective, the inclusion of IQ measures are advantageous for several reasons: By contrast to the questionnaires, IQ tests are administered to the child under controlled and standardized conditions by a trained psychometrist; performance is scored using strict criteria that minimize subjectivity; the scores index the child’s actual performance that day as opposed to perceived behavior over the past months as rated by significant others; and are normed for age and thus would not be expected to be influenced by age or informant (parent, teacher) etc.

4. As in the first manuscript, the issue of ‘centre’ versus ‘country/culture’ requires clarification in both the text and analyses. If I understand correctly, two countries contribute samples from 2 diagnostic centres (Netherlands, Germany), whereas other countries contribute participants from just one centre. Moreover, Netherlands contribute 765 participants which is the largest sample from a country (30% of the total sample). From a design perspective, the predominant unit would appear to be best described as country rather than centre. This issue poses problems for interpretation of findings., because it is not at all clear whether ‘centre-based’ differences reflect possible cultural differences or centre-based issues.

5. The Discussion needs to be drastically shortened and better focused. It is currently 10 pages!

6. Clinical implications must be discussed. For example, how should clinicians and researchers view the Conners versus the SDQ in terms of clinical and research use? Are the contrast effects important in terms of clinical diagnosis when there are twins or siblings involved?

Minor Essential Revisions
1. The whole manuscript will benefit from rigorous editing to correct some understandable problems with English written expression and incorrect statements (e.g., Introduction “Furthermore, intellectual abilities often are impaired in ADHD.” – by definition IQ scores must be in the ‘normal’ range – not impaired as in Intellectual Disability. Research often indicates that IQ scores a a few points lower than controls but they are still within the normal range).

2. The methods section needs to include all of the essential information to understand the study design. The study design, diagnostic protocol and diagnostic procedure should be summarized briefly, with a cross-reference to more detailed descriptions in another manuscript (if appropriate). Under Measures, specify the number of probands, siblings to have the WAIS (versus the WISC). Also a comment is warranted on the validation of translated versions of the questionnaires and WISC/WAIS in the participating countries.

3. The diagnostic protocol requires some clarification. Under “Diagnostic protocol for probands” the authors state that the proband must meet DSM-IV criteria based on CTRS-R:L and the PACS. The CTRS threshold (T-score) and specific subscale(s) need to be specified. Also, clarify why pervasiveness was based on the threshold of “2” symptoms on CTRS and without any mention of impairment. Could the 2 symptoms on the CTRS be unique – that is, not endorsed on the PACS interview?

Discretionary revisions

1. Results: report the male: female ratio is a more standard format (eg. 7.2: 1, instead of 938:130). Clarify to which tables figures you are referring (sometimes difficult to tell whether the table is in additional material or in the manuscript (eg Table 1a, doesn’t seem to exist but Table A1 does and is part of additional material)

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Needs some language corrections before being published

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:

I declare that I have no competing interests.