Reviewer's report

Title: ADHD and Disruptive behavior scores are associated with MAO-A and 5-HTT genes and with platelet MAO-B activity in adolescents

Version: 2 Date: 13 June 2007

Reviewer: Martin Reuter

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BMC Psychiatry
Malmberg et al.: ADHD and Disruptive behavior scores are associated with MAO-A and 5-HTT genes and with platelet MAO-B activity in adolescents

The present paper investigates the relevance of the serotonergic system for ADHD and disruptive behavior in a sample of 156 twin pairs. Two polymorphisms of the candidate genes 5-HTTLPR and MAO-A and MAO-B levels were tested. Results revealed a number of sexual dimorphism: with respect to a) the relationship between MAO-B activity and Oppositional Defiant Disorder (ODD): A positive association could only be detected in girls. b) an association between the ss-genotype of 5-HTTLPR and hyperactivity only in girls. c) an association between the s-allele of MAO-A and disruptive behavior only in boys. d) a positive heterosis effect of 5-HTTLPR on Conduct Disorder (CD) only in boys.

Major Compulsory Revisions:
1) Background: Besides DRD4 and DRD5 especially the DAT gene is one of the most frequently replicated molecular correlates of ADHD!
2) Abstract: How is it possible to assess homozygosity in boys for the MAO-A VNTR when the polymorphism is located on a X-chromosome?
3) It is not clear why the data are analyzed on a parametric as well as on a non-parametric level. If possible, a parametric approach must be preferred because it has always more power and is based on the exact data.
4) The authors write that smoking affects MAO activity. Why not verifying the participants’ self report by taking cotinine levels? Smoking before taking the blood sample must be avoided and can not be controlled statistically by entering the time of the last cigarette as a covariate.
5) Statistics: The rationale for the data analysis is not clear. Why analyzing boys and girls separately when a combined two-factorial MANOVA design with the additional factor sex is possible. This strategy would yield gene x sex interactions!!! The distributional variables showed skewed distributions. Why not normalizing the data before entering them into an MANOVA model: This strategy would allow using the 5-HTTLPR as a single factor with three categories and the complex and strange method of using the LL-genotype as a reference variable (being omitted) in a GLM model could be avoided.
6) One of the major problems of the paper is that the authors do not control for zygotisity. Only one participant of each twin pair can be considered or a combination of a quantitative genetic approach with a qualitative approach must be applied.
7) Recently, it has been proposed that 5-HTT expression is not only affected by the common S/L variant of 5-HTTLPR but also by an A to G substitution (rs25531; Hu et al., 2006). Why not including this SNP into the analyses?
8) The cell frequencies for the analyses are extremely small. Often n < 5!!!
9) Ethnical stratification bias: What does “only a few individuals were of non-Caucasian origin” mean.
10) Why not including the parent into the analyses. The authors write that such data are available?
11) Why not correcting for multiple testing? Some of the significant results would not be stable after Bonferoni-correction.

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Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

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Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

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Discretionary Revisions (which the author can choose to ignore)

What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:

'I declare that I have no competing interests'