Reviewer's report

Title: Dopamine transporter 3'UTR VNTR genotype is a marker of performance on executive function tasks in children with ADHD

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Reviewer: Kate Langley

Reviewer's report:

General

This paper investigates possible association between the COMT Val 108/158 Met Polymorphism and measures of executive functioning in a sample of children with ADHD. This paper is well written and concise. The length of the paper seems adequate whilst the accompanying tables are helpful without there being too many. The authors find some significant associations, although considering the number of tests undertaken it seems unlikely that they would stand up to correction for multiple testing. The authors state their findings well, without overstating them and pointing out the relevant advantages and limitations of the study.

I have been asked to review a second paper by the same group concurrently (Dopamine transporter 3'UTR VNTR genotype is a marker of performance on executive function tasks in children with ADHD). There are a number of factors and methods which have been addressed in the accompanying paper which it seems odd not to have included in this paper –

The main issue is about the correction for multiple testing; in the DAT1 paper, such corrections have been performed but they have not been performed here.

Second, the measures analysed for each task are also different; the DAT1 paper makes an argument that, in order to test the four factors of executive batteries, only the total scores for each of the tests used should be analysed. This paper suggests that a variety of measures should be included. The two manuscripts should be more consistent in their arguments for the measures analysed and why such decisions were made.

The actual tests included in each paper also differ; this paper does not include the Freedom From Distractibility measure from the WISC III which is analysed in the DAT1 paper. The reason for this being left out is not clear and justification (either for its exclusion here, or its specific inclusion in the DAT1 paper) should be made clear.

These points should be viewed as issues which need to be addressed before a decision on this manuscript can be taken.
Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

1). The main issue with this manuscript is that the authors do not correct for multiple testing in their analyses. They perform analyses on 13 different measures within their three tasks (8 from the WCST) and this should be taken into account. I suspect that, should corrections be made, that the significant findings (p=0.04 for the perseverative error score on the WCST) would no longer be significant.

Incidentally, the paper states in the methods that 8 measures were analysed for the WCST but only 4 are reported in the text and table.

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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)

1). For the SOPT, the authors mention there seems to have been some typos in the description of the results (page 10). The results for the raw error scores are in Table 4, not Table 2 whilst the genotype by task difficulty interaction findings do not seem to be in Table 4 as stated.

2). For the family based association analysis, the authors noted that 295 parents were available for the analysis. It would be helpful to have further information regarding this data; how many participants was parental data available for? What proportion of individuals had information available from both parents and what proportion only 1 parent? It would also be helpful to know if there are any demographic or behavioural differences between those with and without parental genotyping data if there are such individuals – any differences may help explain the lack of association. Also, the paper states that 145 were heterozygous using M & F to denote proportions of each. Are M and F for Mother and Father, or Male and Female?

3). In the results section (page 8) the authors say that the demographic and behavioural measures were “similar” for each genotype group. As this has been analysed statistically (table 1) it seems prudent to mention that there are not statistically significant differences.

4). In the introduction section (page 1) there seems to be a typo in the 3rd paragraph – it should read “metabolism of catecholamines, especially dopamine” (rather than specially).

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Discretionary Revisions (which the author can choose to ignore)

ADDITIONAL ISSUES FOR REVIEW THAT I HAVE BEEN ASKED TO CONSIDER:
As part of this review, I have been specifically asked to comment on whether or not these separate manuscripts by the same research group should be resubmitted as a single paper.

There are a number of similarities between the two papers;

1). both address the same question – are there associations between executive function measures and specific genotypes in individuals with ADHD? (albeit different variants).
2). they also use the same sample
3). they use the same tests of executive function (well almost, the DAT1 paper uses one test that the COMT paper does not – see specific comments for each paper)
4). the analyses utilised is essentially the same (except for some additional FBAT analysis in the COMT paper).
5). Both papers come from the same research group and have the same senior author (R. Joober)

However, there are also a number of distinct differences between the papers;

1). each paper uses the majority of the introduction to specifically discuss the different genotype analysed, with specific justification. Each individual justification does not make the other invalid (or reflect on it in any way), but by putting the papers together, the introductions would either have to be changed quite substantially, or would be prohibitively long.
2). the tests utilised do differ to some extent (see above) although in my specific review of each paper, I do question these differences and if there are no explanations, this should no longer be the case.
3). The sample sizes for the papers are slightly different, but presumably this is due to differences in genotyping and so would not be an issue if the papers were merged.
4). similarly, the two papers analyse different measures within the same tests of executive function. This doesn’t seem to be differently justified (see review of the COMT paper) and may be altered, but at present they are different.
5). Despite the fact the two papers come from the same research group and have the same senior author, the actual authors for each paper do not wholly overlap. For the COMT paper, there are 9 authors one of whom is not on the DAT1 paper. For the DAT1 paper, there are 12 authors, 3 of whom are not on the COMT paper. I doubt that this would make a major difference if the papers were put together, but this is another issue to consider.

If the papers were to be made into one single paper, I doubt that it would be excessively increased in length (with the exception of the introduction mentioned above and also the tables and figures which may have to be at least reorganised).
I think that these papers could be presented either as a single paper or as the separate papers as currently submitted. If separate papers, they should probably be accompanying papers as the methods, concept and samples are very similar. I am assuming that, whether a single or two separate papers, that the methodological differences between the papers will be altered.

If they are separate papers (especially if accompanying) there are a couple of differences which should be standardised (other than those previously mentioned). For example, in the DAT paper, the prevalence of ADHD is cited as 8-12% whilst in the COMT paper, it is 2-9%. Although both have been referenced, if the papers were presented together, this difference may seem a little odd. Similarly, in the DAT paper it is stated that the participants were off medication for at least one week before testing, whilst in the COMT paper, it states a medication break of 3-5 days. These inconsistencies should be altered.

The decision as to whether or not these papers should be merged needs to be addressed before a final decision on this manuscript can be made.

**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:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

'I declare that I have no competing interests