Author's response to reviews

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

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

Thank you for giving us the opportunity to revise our manuscript. We believe it has benefited from the constructive comments provided by reviewers.

**General change to manuscript:**

A) All comments have been taken into account and the appropriate changes have been made to the manuscript.

B) Data was reanalyzed using a larger sample.

C) New measures of executive function performance were added:

- Tower of London scores performance on all 12 difficulty levels
- Self Ordered Pointing Task performance on all 4 difficulty levels
- Wisconsin Card Performance Test number of categories completed
- Wisconsin Card Performance Test number of trials to complete first category
- Wisconsin Card Performance Test perseverative errors
- Wisconsin Card Performance Test non-perseverative errors
- WISC-III arithmetic subtest
- WISC-III digit span subtest

D) New content was added to the discussion that takes into account new findings

E) Figures have been replaced by a summary table

**Specific responses to Dr. Langley:**

1- **Response to general comments:**

A) The Tower of London is now included in the manuscript.

B) A wider range of measures has now been included in the manuscript. See Table 2.

C) It was the opinion of the majority of authors that an FBAT analysis would indeed not have added much to the manuscript (as alluded to by the reviewer). As it is less powerful than the statistical tests implemented here, it was felt that the sample was not yet large enough. We intend to implement such an analysis as soon as our sample becomes large enough. It is noteworthy that the two genotype groups had almost identical demographic characteristics and were both constituted by approx. 90% Caucasians from Quebec. This would make less likely that our findings may be due to
spurious population stratification. Due to all the above and to the large amount of time it would take to create the appropriate file for an FBAT analysis, it was decided not to implement it now. Note that the file used in the COMT manuscript recently sent by colleagues of ours was based on a slightly smaller sample with no DAT1 gene information. All this being said, we are willing to add such an analysis if Dr. Langley insists.

2- Response to major compulsory revision comments:

A) The a priori hypothesis has been modified in light of the comments (see end of introduction). Further, Barkley et al’s work has been qualified as requested (ie results supporting that the 9/10 fair worse than the 10/10 in psychopathological measures rather than in executive function tasks). See last paragraph of page 4 as well as the 2nd paragraph of page 13.

3- Response to minor essential revision comments:

A) Figures have been removed. The reason for this is that we decided to add the Tower of London test (TOL) and analyze both the TOL and SOPT using a repeated measures general linear model in order to increase sensitivity. As the SOPT has 4 levels of difficulty and the TOL has 12, it was felt that representing this in a graph would have been unwieldy. For this reason, a second table has been added, summarizing results.

B) Sample size issues have been clarified. See Table 1 as well as second paragraph of page 11. The initial confusion was simply due to the fact that we had inadvertently added the 9/9 group sample in our calculation of sample size.

C) Ns have now been added to the sections where only proportions were provided. Male and Female proportions had indeed been inverted. This has now been corrected.

D) We now explicitly state that there are no statistically significant differences between groups in demographics and in other pertinent variables.

E) Final sample size has now been added at the end of the paragraph of page 11.

F) With our larger sample it became apparent that ADHD subjects from both genotype groups scored at least slightly below average in performance. For this reason the section about scoring within the normal range has been removed.

G) Proportion of those having been administered the WISC-III at school has now been added in the methods section. Unfortunately, we do not have data regarding medication status for these children (which comprise approximately 15% of both groups).
4- Response to discretionary revisions

It was decided that only this manuscript would be presented as combining the papers proved rather difficult. Regarding a noted discrepancy between the COMT and the present DAT1 manuscripts: an error was made in the COMT manuscript and subjects were indeed without medication for at least a week as initially stated in the present manuscript.

Specific responses to Dr. Tannock

1- Response to general comments:

A) Neuropsychological measures have now been added to help better uncover links between genotype and behavior. Results from Arithmetic, Digit Span, WCST perseverative errors, and others have now been added to the manuscript and have indeed clarify the message for the manuscript. See table 2.

2- Response to major compulsory revision comments:

A) Reported frequencies in the text are for alleles instead of genotype while table 1 reports genotype frequencies. Giving allele frequency in the text was simply done to provide Hardy-Weinberg equilibrium calculation details. As the goal was a calculation of the Hardy-Weinberg equilibrium, it was preferred to base it on the total sample of those with the 9 or 10 alleles (ie including those with the 9/9 genotype). Table 1 only reports data for the 9/10 and 10/10 genotype groups. Clarification is now added in the first paragraph of the results section of page 12.

B) With our larger sample it became apparent that ADHD subjects from both genotype groups scored at least slightly below average in performance. For this reason the section about scoring within the normal range has been removed. We now further provide scaled FFDI values.

C) We have added scatter plots for all statistically significant findings or trends. However, these are for review purposes and are not aimed for inclusion in the paper (unless asked to do otherwise). The reason for this is that we decided to add the Tower of London (TOL) and analyze both the TOL and SOPT using a repeated measures general linear model in order to increase sensitivity. As the SOPT has 4 levels of difficulty and the TOL has 12, it was felt that representing this in a scatter plot would have been unwieldy. For this reason and in order to be consisted for all tests, a second table has been added to summarize results and all graphs have been removed. Mean could not easily be added to scatter plot in SPSS. As this is only for review purposes and as the means can now easily be obtaining in the summary, means were not added.
included in the graphs. If this is problematic, we are willing to create new graphs that include the means.

Regarding findings from the scatter plots: essentially, when there may be outliers, it will be noted that they tend to go in the opposite direction one would expect if findings were due to them. For instance, in the TOL scatter plot, the lowest scorers are in the 10/10 group and the highest scores are in the 9/10 groups yet the mean is higher for the 10/10 group. This is rather incompatible with findings being due to outliers. A comment to that effect has been added in the Results section.

D) All requested WCST measures have now been added and due to the larger sample the trend that we had for the WCST essentially waned.

We hope these responses are satisfactory.

Cordially,

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