Author's response to reviews

Title: The 5-HTTLPR polymorphism of the serotonin transporter gene and short term behavioral response to methylphenidate in children with ADHD

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Author's response to reviews: see over
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Dr. Sabina Alam  
Senior Scientific Editor  
BMC series journals

Re: MS: 4979311912392369 – ‘The 5-HTTLPR polymorphism of the serotonin transporter gene and short term behavioral response to methylphenidate in children with ADHD’

Dear Dr. Alam,

Please find enclosed a revised version of the above manuscript as well as itemized answers to the reviewer comments below:

**Response to Comment #1:**
In response to this comment, we think that mixed models are ideally suited for crossover studies as the latter include both fixed (treatment, gender, genotype, period, carry-over) and random effects (subjects). Moreover, mixed-models procedure allows greater flexibility than traditional ANOVA or GLM in modeling residual covariance structures, i.e. the non-independence of residuals owing to correlation of scores over time and correlation between dependent variables. Finally, mixed models are more flexible for handling missing data.
Secondly, we were only interested in a genotype by treatment interaction, thus we did not include a gender by treatment interaction and a period by treatment interaction.
Next, the model suggested by the reviewer does not account for the baseline scores (CGI-parents baseline, CGI-teachers baseline) and in studying outcome, it is important to control for these baseline scores.
In sum, we believe that the mixed model approach is a state of the art approach and is more appropriate and flexible than the general model for the purpose of our study.

**Response to Comment #2:**
The total sample was of 157 children (df error = 154). For the CBCL scores, data were missing for 5 subjects ($F_2,149$) and for the WISC variable, data were missing for 10
subjects (F$_2$, 144). We have added a line in the legend of Table 1 stating that there are some data points missing for both these variables:

‘Number of observations varied some times with regard to variables (eg. CBCL, WISC-III). Variation n number of observation is reflected in the degrees of freedom.’

Response to Comment #3:
We have omitted the section on effect sizes and Table 2.

Response to Comment #4:
The Hardy Weinberg Equilibrium is a strategy used to ensure that the genotypic frequencies in our sample are in equilibrium.

We hope that the manuscript will be acceptable for publication in its revised form and we would like to thank the reviewers for their help in improving the manuscript and hope they will find the answers to their concerns satisfactory.

Thank you again for your consideration.

Sincerely,

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