Reviewer's report

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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Reviewer: Maximilian Muenke

Reviewer's report:

The authors present a very interesting 2-week prospective placebo double-blind crossover study in order to elucidate a potential association between the serotonin transporter gene SLC6A4 and behavioral response to methylphenidate in children diagnosed with ADHD.

Comment 1
I like the way the study design was developed. It is a very straightforward way to assess a pharmacological response for one medication which an average cycle life of 4-6 hours.

Comment 2
page 12: The authors mention that the variable gender is significant when analyzing the genotypes and that for subsequent analyses this will be controlled for. However, on page 11 where they describe the linear mixed-effect model (LMEM) used for their analysis, the gender is not controlled for. What would happen with the CGI scores when controlling by gender? Several studies have shown that gender is strongly associated with ADHD and, among other results, that males are more likely to be diagnosed with the disorder. I would like to see how the results come up once you introduce the gender as a fixed effect in the LMEM.

Comment 3
Along the same lines (comment 2), I consider it important to report the coefficients of the model as well as some diagnostic measures for how well the model fits their data. In the available manuscript, the authors did not present this information. Rather than reporting the F and p-values for every single test (see page 12, for example), I suggest to refer the reader to a table with all the coefficients.

Comment 4
One of the main applications of LMEM is to capture the variability within the same sample unit, in this case a child, when it is measured several times. In the present study, each individual represents a sample unit that was measured twice: under a placebo and on medication. In LMEM one of the assumptions is the correlation structure for the sample unit. Did the authors assume any particular correlation structure for the analysis? If yes, which one?
Comment 5
On page 12, “Behavioral response to clinical intervention”, the authors present two p-values, each of them corresponding to different tests. Which cutoff was used for those p-values? (p<0.05, p<0.001, p<0.0001 instead of p<0.00 or is this just a typo?).

Comment 6
In the Result section the authors mention that no significant difference in IQ was found among groups. Why did not the authors refer to Table 1 for the results? Neither in Table 1 nor anywhere else in the manuscript is there any mention of p-value / statistical tests of IQ measures.

Comment 7
In the beginning of the “Behavioral response to clinical intervention” the authors write that “Irrespective of genotype, a significant behavioral response during the week of treatment… was observed” and then refer the reader to Figure 1. However, the explanation of their findings both does not correspond to what the p-values are showing and are not clear at all. In addition, it is hard to conclude their statement from Figure 1. Perhaps either a better representation of the data or a different analysis could help to elucidate this point. On the other hand, if the authors found that the genotype is significant, why did they not include this effect to conclude about this on this paragraph?

Comment 8
What do the authors mean by “significant genotype by treatment 2-way interaction” on page 12? Do these results correspond to the CGI-Parents or CGI-Teachers score? Also, based on the hierarchical principle of modeling, I would suggest to review the fact of commenting on individual effects of a covariate when a 2-way interaction is present.

Comment 9
On page 13 the authors mention “the Tukey’s Honestly significant differences” and then mention that term again on the next page using an acronym (HSD) not defined anywhere else before.

Comment 10
What do “the same model of analysis” on page 13 mean? Is that model the same the authors use with the change scores between the week of treatment with placebo and the week of treatment with methylphenidate?

Comment 11
For the first time in the manuscript the authors mention a correction for multiple tests on page 14. Did the authors use any correction by multiple tests on the other p-values? How would their results change if these corrections were performed?
Comment 12

One of the points mentioned by the authors in the discussion was that patients with the s’s’ and s’l’ genotypes tend to exhibit more anxiety disorders compared to patients with the l’l’ genotype. However, from the manuscript I did not see any results supporting this notion.