Reviewer's report

Title: Functional serotonin transporter gene polymorphisms and anxiety personality traits: new study and meta-analysis on a psychiatrically healthy population.

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Reviewer: Luis F Garcia

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The present paper raises two different studies about the relationship between two polymorphisms of the serotonin transporter gene and anxiety personality traits. In general, the paper has good quality and adds useful information to the literature, however, I think that some aspects of the organization and discussion may be improved.

First of all, the title is not right. Note that some analysis with the new sample and meta-analysis are conducted on diagnosed samples. Secondly, organization of the paper is confused. I think it will be easier to understand the paper if new study and meta-analysis were named as Study 1 and study 2, respectively, and, therefore, Method and results sections for each study were separated. With the present format, it is difficult to follow both studies. Besides, the study 1 may be used to support the meta-analysis.

On the other hand, I have some comments about other aspects of the paper. The introduction is brief but adequate. I have one comment only. Authors speak in the entire section about healthy and psychiatric samples, however, they change the names for controls and screened samples in the last paragraph. They should retain the nomenclature of the entire section.

In the method section of the first study, authors state that “only healthy volunteers.........were enrolled in the study” (p. 6). But this statement is false since subjects with diagnosis of axis I were also analysed. The next sentence is “The personality traits were assessed by the Italian version of M.I.N.I.” (p.6). I guess this is a mistake since, as far as I understand, personality traits were assessed by the Italian version of the TCI. Besides, the reference 27 should be associated to the publication of the Italian version of the TCI, not the American one.

Analyses were well conducted and presented, but I do not understand why group variable is introduced as a covariate since analyses were further conducted separately for both samples. Also, figure 1 could be deleted since all relevant
information is reported on table 1.

In regard to the discussion section, the mixture of both studies make hard to understand this section. With respect to the first study, authors suggest the relevance of employing more stringent inclusion/exclusion criteria. But, it is not clear if they advise for not including psychiatric patients or they call for including them in this kind of genetic studies. In fact, this is the most serious concern I have about the paper. Authors do not explain the reason for reported differences between healthy and psychiatric samples. Note that the pattern of HA means for healthy subjects is the opposite of that found for the psychiatric subsample. This is strange since the expected pattern will be the same for both samples. Authors should discuss the reason for such result.

Let me to advance a tentative explanation. In the meta-analysis by Munafo et al., (2003), they suggest that extreme groups analysis may give more chances of finding significant associations. They are theoretical and statistical reasons to expect that. I think that including psychiatric samples implies to work with the entire distribution of the trait. On the contrary, the sample distribution may be truncated and, therefore, reducing the statistical effects. This bias may be stronger on volunteer and elder samples as the one analysed in the new study. So, psychiatric sample would be the right side of the phenotype distribution. If you look at the means of the groups, you should note that the averages are quite larger in the psychiatric sample than in the healthy one.

Considering the meta-analysis, I was not be able of understand if authors conclude that there is an association between 5-HTTLPR and NEO or TCI. Please, clarify the redaction of the discussion about the meta-analysis.

Finally, it is somewhat contradictory that 5-HTTLPR was not involvement in anxiety related traits variability but it was confirmed (supported?) to be a risk factor for depression/anxiety spectrum disorders. This contradiction is difficult to sustain since it is well known that anxiety traits are strongly linked to the depression/anxiety disorders. If authors retain both conclusions, they should raise some explanation for such contradiction.

References:


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