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: Scott Stoltenberg

Reviewer's report:

In this revised manuscript, the authors report the results of two studies. The main finding is that in a very small sample (for contemporary genetic association studies) with either depression or anxiety disorders (N=55), there is an association with serotonin transporter genotype, such that those genotypes with reduced transcriptional efficiency report higher mean harm avoidance scores. No association is observed between serotonin transporter genotype and HA scores in a modest sized sample of healthy individuals screened for Axis I disorders. The pattern of findings in the meta-analysis support the interpretation that associations between serotonin transporter genotypes and harm avoidance or neuroticism are not observed in healthy populations that are screened for mental illness. The authors make the point that psychiatric screening is necessary in behavior genetic analyses of so-called healthy populations to be sure that overlooked mental illness does not confound the results. Clearly, this is only an issue when the traits under analyses are associated with the mental illness for which one would screen. So, in an important sense, this study confirms the association with lower transcriptionally efficient genotypes of the serotonin transporter and either depression or anxiety and Harm Avoidance. If the mental illness was wholly unrelated to the genes in question or the phenotype under analysis, screening for hidden mental illness would not be necessary. Such a result begs the question, for what other phenotypes should the "healthy" population be screened before testing for relevant associations? Obesity, impulsivity, perhaps or maybe aggression?

The manuscript is generally improved and the results are interesting and add to our understanding of the associations among serotonin transporter genotypes, HA and depression/anxiety spectrum disorders.

By the standards of contemporary psychiatric genetic studies, this study has a modest sample size and examines few genetic variants. No mention is made for controlling for the false discovery rate and none of the p-values would survive correction for multiple comparisons. That said, the pattern of results is consistent with earlier findings and the novel finding is the explicit control for diagnosis in the "healthy" control group. Little mention is made in the discussion of the study's limitations. The meta-analysis supports the finding in Study I,
which is quite important for this study. It shows that the pattern in Study I may not be uncommon. The reader is left to speculate about the mechanism of such a finding. The authors make a few comments in the discussion that are difficult to understand such as "In light of these data, we can speculate that also the genotyping of the both functional polymorphisms (5-HTTLPR and rs25531) and the haplotypes analysis could be taken into account in relation to anxiety-related personality traits." and "The symptomatology of depressive and anxiety disorders could interfere with anxiety-related traits in the possible associations with the serotonin transporter and also the higher frequency of the S allele observed in depressed and anxiety disorder patients;". As a minor note, although the quality of written English was improved, it could benefit from additional editing.

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Needs some language corrections before being published

**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