Reviewer's report

Title: Serotonin transporter gene polymorphisms and brain function during emotional distraction from cognitive processing in posttraumatic stress disorder

Version: 1 Date: 20 January 2011

Reviewer: Tanja Jovanovic

Reviewer's report:

Review of Morey et al, BMC Psychiatry

The present study examined the relationship between serotonin transporter gene polymorphisms and cognitive processing of emotional stimuli using fMRI BOLD imaging in traumatized participants with and without PTSD. The authors found that SLC6A4 SNPs were associated with increased neural activation during processing of combat-related distractors in the prefrontal cortical areas of PTSD subjects; furthermore, the same stimuli produced a genotype X diagnosis trend for increased amygdala activation.

This study combines behavioral data (working memory task), neuroimaging, and genetic information in a clinical population. Studies of this nature are of tremendous importance to the discovery of neurobiological biomarkers associated with genotype and mental illness that can serve as intermediate phenotypes of the disorder. As the authors state, neural activation related to gene expression may function as such a phenotype for anxiety disorders.

The manuscript is very well written and the data are appropriately analyzed; the significant SLC6A4 SNP (rs16965628) has not yet been described in PTSD and thus has the potential to significantly contribute to the literature. As the authors themselves note, the sample size is small, and the significant findings are small relative to the number of comparisons examined; thus introducing concern for Type I error. Although this reduces enthusiasm for the study, I nevertheless recommend considering a revision, given that the brain activation observed is in areas already previously implicated in PTSD.

I have several minor essential revisions:

1. The discussion should include a stronger description of the effects of the gene variants. Although the authors note that the SNP that was significant “made the greatest contribution to the variation in serotonin transporter gene expression” in a study by Martin et al 2007, this is still somewhat vague as to the mechanism of action between serotonin and the observed neural activation.

2. The discussion includes a paragraph (pg 13-14) on the rs16965628 haplotype association with OCD. Given that the current study did not perform haplotype analyses, and the OCD results seem to be related to a different allele, this paragraph does not seem to contribute to the manuscript.

3. The authors hypothesize decreased vlPFC activation on pg 6 (which would be consistent with the neuroimaging literature in PTSD), yet the results find
increased activation in this area in PTSD subjects who are homozygous for the G allele of the rs1696528 SNP. Is this due to greater allocation of resources/effort in order to maintain working memory in the face of combat distractions? How is this particular intermediate phenotype related to PTSD?

4. There are several typos:
   • Pg 5, last paragraph, line 9, extra bracket
   • Pg 11, last paragraph, last 2 lines seem to be missing some words
   • Pg 15, 1st paragraph, Jancovic & Ressler, 2010 is misspelled and not included in the references list
   • Pg 15, 2nd paragraph, line 6, “involved” should be changed to “involving”, or restructure sentence
   • Pg 17, 2nd paragraph, line 6, quotation mark is missing

In summary, the paper looks at several very important variables and makes a significant contribution to the literature; however, it can be improved by focusing on the mechanisms of the gene expression with respect to the observed neural activation. I recommend publication with minor revision.

**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