Reviewer's report

Title: Interaction between stress and the BDNF Val66Met polymorphism in depression: a systematic review and meta-analysis

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Reviewer: Charles CB Nemeroff

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Review BMC Medicine:

Hussang et al. have conducted a review and meta-analysis concerning the relationship of early-life stress, more recent life stressors, and the BDNF val/met polymorphism in vulnerability to depression. This is a topic of considerable interest and in the space below, a number of issues are raised which the authors should address:

1. An important issue is whether there is sufficient power to draw conclusions from the extant literature. The author should make clear how many subjects are contained within this meta-analysis in terms of total number of subjects and then in terms of subjects related to childhood adversity versus more recent life stressors. The authors should explicitly state whether they believe, from a statistical genetic point of view, whether the sample is adequate in order to draw the conclusions drawn in the current analysis.

2. There is a discussion of the neurotrophic hypothesis of depression and antidepressant action, which is inexorably linked to neurogenesis. However, many investigators have been unable to confirm antidepressant-induced increases in hypocampal neurogenesis and similarly, the link between BDNF antidepressants and neurogenesis seems more tenuous than ever. The author should comment on this current controversy.

3. There is reference to studies showing differences in serum concentrations of BDNF in depression. What is the source of serum BDNF and is there any reason to believe that this reflects in any way CNS availability of BDNF?

4. The authors’ focus on the val/met polymorphism--they should explicitly state whether other polymorphisms in the BDNF gene exist and whether they believe that these may be relevant as well.

5. There is frequent reference to the seminal studies of Caspi and colleagues on the serotonin transporter. However, a number of other genes have been shown to interact with early adversity to increase vulnerability to depression and post-traumatic stress disorder. These include the CRF1 receptor gene, as well as FKBP5, PAC1, and others. Reference to these findings should be made as well.

6. It would be of considerable interest to determine whether the authors using this dataset would be able to determine whether there is a child adversity X more recent life stressor X BDNF polymorphism effect in vulnerability to depression and other disorders. This should be discussed at least as a potential future
direction.

Quality of written English: Acceptable

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:

I declare that I have no competing interests