Reviewer's report

Title: Neurocognitive profiles in treatment-resistant bipolar I and bipolar II disorder depression

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Reviewer: George Konstantakopoulos

Reviewer's report:

The authors present a study on cognitive impairment in bipolar disorder (BD) depression. They examined cognitive performance in patients with bipolar depression and its association with demographic and clinical characteristics. They assessed 19 BD I and 32 BD II patients with treatment-resistant depression with the MATRICS Consensus Cognitive Battery (MCCB) and found that a high proportion of the patients had clinically significant impairment. BD I patients had higher rates of global deficits, lower processing speed and greater IQ decline than BD II patients. Moreover, age and education but not illness characteristics (other than BD subtype) were associated with the severity of impairment in many cognitive domains. The authors concluded that there is clinically important cognitive dysfunction in this group of BD patients, especially in BD I. The manuscript is interesting and of scientific importance. However, it would be strengthened by attention to the following issues:

Major Compulsory Revisions

1. A major concern is that the sample size is relative small for the detection of other differences between the two BD patient-groups (type II error); therefore, the negative findings of this study should be confirmed by larger studies. This should be stated clearly in the limitation section of the paper.

2. Other recent studies that compared cognitive functioning between different acute phases of BD (e.g. Gruber et al. Journal of Affective Disorders 2007, Ioannidi et al. Bipolar Disorders 2010) or between bipolar and unipolar depression (Xu et al. Journal of Affective Disorders 2012) should also be mentioned. Moreover, the main findings of all the previous studies should be briefly presented in the Background.

3. I think that a short sentence about the usefulness of further research on illness phases and other factors potentially affecting the cognitive functioning of patients with BD should be added at the end of the first paragraph.

4. The paper would be strengthened by presenting a rationale for using a treatment-resistant BD-depression sample in this study.

5. The normality of all continuous variables should be tested and non-parametric tests should be used for the non-normally distributed variables.

6. Duration of illness and previous history of psychotic symptoms (as a categorical variable) might be associated with worse neurocognitive performance
in BD (see Depp et al. Journal of Affective Disorders 2007, and Bora et al. Journal of Affective Disorders 2010). Thus, correlations between these factors and neurocognitive scores should be computed and the strength of possible significant associations should be further examined through multiple regression analysis.

7. It would be useful for the readers if the authors briefly comment on similarities and differences between their findings in treatment-resistant BD depression and the findings of previous studies in (a) BD-euthymic phase, (b) BD-depression, and (c) acute phases of recurrent unipolar depression. For this purpose, they could use relevant reviews and meta-analyses.

8. The no significant correlation between severity of symptoms (especially depressive symptoms) and cognitive impairment in this study might be due to small variance, since all the participants were severely affected. The authors could consider this notion when discussing about the relationship between symptom-severity and cognition in BD.

9. The authors should clarify that the influence of the mood state on cognitive functions in BD was not examined by the present study and that perspective studies examining cognitive performance during illness episodes and in remission are warranted to address this issue.

10. The part of the discussion about the influence of age on cognitive functioning should be shorter. Moreover, the authors should briefly comment on previous findings about the effect of age on cognition (e.g. Schouws et al. Bipolar Disorders 2012).

Discretionary Revisions

1. Information on the MCCB and its use in BD research should be included in the Methods, not in the Background.

2. Could the authors provide a justification for the use ANOVA – and not t-test – for the comparisons in neurocognitive scores?

3. I cannot understand the exact meaning of this sentence: “The stronger influence of age compared to illness characteristics on cognitive functioning might reflect patients’ difficulties in recalling their illness history.”

Level of interest: An article of importance in its field

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

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:

I declare that I have no competing interests.