Author's response to reviews

Title: Neurocognitive function in bipolar disorder: a comparison between bipolar I and II disorder and matched controls

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Author's response to reviews: see over
To the editor of BMC Psychiatry,

The following changes have been made to the manuscript and tables in response to the reviewer’s comments.

Editor
1. Authors Contribution has been added to the manuscript.
2. Acknowledgment has been added to the manuscript.
3. Competing Interest has been added to the manuscript.

Reviewer 1
1. An additional proof-reading of the manuscript for language corrections has been performed.

Reviewer 2
The review of existing work in this area is incomplete, as there are several studies comparing neuropsychological functioning in bipolar I and II that are missing (e.g. Chang et al., 2011; Hsiao et al., 2009). In particular, there is a meta-analytic study that quantified cognitive deficits between bipolar I and II (Bora et al., 2011) that was omitted, and which seems highly relevant to the topic of discussion.

1. References to the relevant studies and their findings have been added to the introduction.

Related to point 1 above, there is not sufficient development of what this particular study attempts to add to the existing literature in light of existing work. What is special or unique about the present study that will provide a better or more valid comparison of cognitive deficits between these two subgroups of BD? How will this study resolve the unclear or conflicting cognitive findings in this area of research? The novel contribution from this study needs to be better developed in the introduction. Alternatively, should this study be viewed as a replication effort with no other novel contribution per se?

2. The aims section of the introduction has been changed to better present what the study will add to the existing work. Given the fact that question of whether different subgroups of bipolar disorder have different cognitive impairments remains unresolved, replication studies are extremely important. The strengths of the present study in this regard can be summarized as
   - Relatively large sample size
   - Validated diagnosis
   - Population based control group
   - Control for medication effects and residual symptoms
   - Relatively large cognitive test battery

The patient sample is described as euthymic, but in the methods section it is stated that “euthymia was determined by the physician’s overall diagnostic judgment.”
This is peculiar, especially since objective mood ratings (MADRS, YMRS) were obtained on the day of testing. It would be better to use these ratings (e.g. scoring below a certain point on each scale) as the basis for classifying patients as euthymic on the day of testing. Defining euthymia in this way would capitalize on one of the methodological strengths of this study-namely the fact that mood ratings were obtained on the day of testing.

3. MADRS and YMRS cut-offs for euthymia have been added to the methods section

Were there any comorbid conditions such as learning disorder/ADHD or anxiety disorders in the patient sample? More importantly, were there differences between the two patient groups on these comorbidities, and if so, how could this have influenced findings?

4. Frequencies for co-morbid ADHD and anxiety disorder have been added to table 1. A preliminary analysis does not suggest that either factor has significantly influenced the results, although co-morbid anxiety disorder and ADHD was more common in the bipolar type II group. For ADHD, several patients have missing information regarding diagnosis but it still appears unlikely that this factor has influenced the results. Neither factor was strongly correlated to any of the cognitive test variables analyzed in table 3.

Although the recruitment procedures for the control group are generally well described in the “control group” section, it is not clear how the final number of 86 controls was achieved. If 7 demographics matched persons were selected for each enrolled patient, this would create a very large pool of potential controls for inclusion (7 x 110 total patients = 770 controls). How were these 770 potential controls reduced to the final sample of 86?

5. The section describing the control sample has been clarified to better account for selection procedure.

For the various neuropsychological measures it was not clear whether raw scores were used or demographics corrected scores (e.g. z-scores, t-scores, standard scores, etc.). If the latter, where did these corrected scores come from (e.g. test manuals)?

6. This has been clarified in table 2.

There are a large number of comparisons in Table 3, and thus significant correlations could be occurring just by chance. There should be some type of correction for multiple comparisons for the data in this table.

7. The analysis has been revised. A stepwise linear regression model was applied for each test variable to identify the strongest correlations with test performance.
The conclusion that treatment with antipsychotic drugs could associate with or lead to cognitive deficits should be stated more tentatively based on the following points. First, the magnitude of the correlations between cognitive variables and antipsychotic use are rather small (most significant correlations are under .30). Secondly, these presented correlations do not control or partial out other potential influences that could be driving this relationship (such as diagnostic patient group, history of psychosis, residual symptoms, treatment with other medications).

8. The analysis has been revised. A stepwise linear regression model was applied for each test variable to control for other potential influences.

For the Claeson-Dahl Learning and Memory test, how many learning trials were involved? Moreover, as described this test sounds more like a typical test of episodic memory than a test of working memory.

9. This has been corrected, the description of the Claeson-Dahl Learning and Memory test now states that it is a test of episodic memory.

Other changes
1. Descriptors of the TMT trials in table 2 have been corrected. The descriptors have also been corrected in the manuscript.

Best wishes
Erik Pålsson