Author's response to reviews

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

Authors:

Erik Pålsson (erik.palsson@neuro.gu.se)
Clara Figueras (clarafiguerasdiaz@gmail.com)
Anette GM Johansson (Anette.Johansson.2@ki.se)
Carl-Johan Ekman (carl-johan.ekman@sll.se)
Björn Hultman (bjorn.hultman@sll.se)
Josefin Östlind (josefin.ostlind@vgregion.se)
Mikael Landén (mikael.landén@neuro.gu.se)

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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.

Reviewer 1

First, it is confusing on page 12 when current symptoms of mania are found to correlate with cognitive functioning when the authors stress in the abstract, method and discussion that the patients assessed are euthymic. It would be useful to clarify this. Some discussion of this issue is found on page 16.

The sample is now described as clinically stable and not euthymic. Criteria for defining this are included in the methods section.

Second, the conclusions are very strong suggesting that there are no differences in the bipolar I and II patient's cognitive performance. While I agree with the general conclusions, one could argue that because in almost all cases patient's with bipolar II disorder have intermediate performance (between the bipolar I and control participants) that it may be premature to rule out the hypothesis regarding a continuum. I wonder if factor derived summary scores of neurocognitive performance was obtained if the bipolar I and II patients might not have shown significant differences. As noted in the discussion the sample is sufficiently large to detect type II errors but that is based on a strategy in which all neurocognitive skills are assessed individually.

It is true that the performance of bipolar II patients appears intermediate in the neuropsychological tests, although no significant differences were found. A likely explanation is that this group was less exposed to antipsychotic medication. The use of a factor score might clarify whether this is true. In fact we are analyzing the same data set (but with more neuropsychological test data added) using PCA and discriminant function methods. This work will be published separately as the scope is different from the current study. However, the PCA method has only confirmed what is presented here. Performance is not associated with subdiagnosis in our patients sample but with the use of antipsychotic medication.

Finally, while diagnostic procedures are well articulated and well conceived. It may be overstating the accuracy of the procedures in that no estimates of reliability were assessed within the context of the diagnostic procedures and the diagnosis relied on consensus. I do believe that the approached used was adequate but perhaps some discussion of this limitation is warranted.

This limitation regarding certainty of the diagnostic procedure has been added to the discussion section of the manuscript.
Reviewer 2

1. Regarding comorbidity, the authors indicate in the response letter that “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.” These data analyses showing that these comorbidities do not influence the test results (which were apparently conducted) should be included in the manuscript. If these analyses do not support the idea that effects of comorbidity can be ruled out, then this limitation should be stated in the discussion.

ADHD and anxiety disorder co-morbidity are now included in the analysis. No of the previously reported associations were affected by this. ADHD was not associated with neuropsychological test performance whereas anxiety disorder was associated with worse performance on the phonetic part of the Verbal fluency test. Data on ADHD diagnosis is now only missing for 2 patients.

2. Were the regression analyses “stepwise” and if so, more details about the procedure are needed (e.g. forward selection, backward elimination, etc.). Alternatively, it appears that the regression techniques may have been standard multiple regression with simultaneous entry of independent variables. Please clarify.

Regression analyses were stepwise forward selection. This is more clearly noted in the statistics section and in table 3.

Minor Essential:
1. The strengths and unique aspects of the study are now well described in the author’s response letter, but these points were not all integrated into the introduction in the manuscript, and they should be included:
   - Relatively large sample size - Validated diagnosis - Population based control group - Control for medication effects and residual symptoms - Relatively large cognitive test battery

The aim section in the introduction has been changed to include all of the above points.

2. With exclusion criteria of MADRS > 14 and YMRS > 14, it is still possible that some patients with mild but significant mood symptoms were allowed in the study. Thus, the sample should be described as “clinically stable” rather than euthymic.

The sample is now described as clinically stable instead of euthymic in the text.

3. The units of all the neuropsychological measures in Table 2 have not been fully clarified. Specifically, are the Claeson-Dahl measures demographics-corrected or...
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raw scores? Are the various Rey Complex Figure Test scores in the table t-scores, raw scores, or a combination of these? The DKEFS scores appear to be scaled scores (mean 10, SD 3), and if so, this should be stated.

This has been further clarified in table 2.

4. English proofreading is needed in some portions of the manuscript to make it more readable.

The manuscript has now been proof read also by an external consultant.

Best wishes
Erik Pålsson