**Ms. Ref. No.: JPR5764**

**Title: Connectome Signatures of Neurocognitive Abnormalities in Euthymic Bipolar I Disorder**

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By Ajilore et al.

Background: the authors investigate the structural and functional correlates of neuropsychological deficits in BD by using cutting edge neuroimaging techniques such as MRI, DTI and fMRI, and use sophisticated analyses e.g. connectome to link neuropsychological, structural and functional brain estimates. The sample includes BD I patients aged approx. 40 years, with a traditional illness onset (approx. 20 years). Functional activity during an inhibition task (go/no go) and a thorough neuropsychological testing are included. The authors focus on functional activation in BA 47 as it has been associated with BD in previous studies. Alongside deficits in working memory and processing speed the authors report a link between FA values in the CC, interhemispheric integration and processing speed. Reduced functional activation in the BA47 during the go/no go was also found. The authors mention that their findings corroborate findings from their previous paper (FYI subset of the sample used in this paper) (Leow et al. 2013), which was the first published study to find “connectome abnormalities” in BD.

Comments: Overall I commend the authors for work and their novel and original idea to merge a range of neurocognitive measures to better understand the neural signature of BD. However, I have a few comments on their paper and think that major revisions are needed.

Overall:

-Abstract: What is the “take home message of this paper? What is the relevance of the current findings and future directions?

-Overall: the authors should describe their DTI data collection and measurements to a greater extent than done in this paper. Also in the abstract they should mention DTI in their methodology and explain acronyms such as FA before using it in the results section. Similarly, parameters of data collection are needed in the methodology. Also could the authors explain why they used FA? What about other parameters? In the discussion they are encouraged to discuss what a reduced FA would mean based on their theoretical model.

-Introduction: the authors should provide a summary of their previous findings “Leow et al. 2013” and provide some context in terms of relevance of the findings and why is it important merging these measures.

-Connectome analyses and words such as “hemispherical integration” or “nodal integration” should be described or at least explained in the introduction to help the unfamiliar reader understand why such analyses are important. In the discussion the authors should also provide a better interpretation of what reduced nodal length or hemispherical integration really means in terms of neural, cognitive and global functioning.

-The authors state that working memory and FA in the genou were mediated by processing speed…since the working memory tasks included in this paper were time based isn’t this result almost intuitive? Would this result remain the same if working memory tasks had not been time-based?

-Also how do the current findings differ from those observed in older populations? Could the authors comment on the model of accelerated aging in relation to BD. I am mentioning this given that processing speed is bound to be increased over time. Could the authors be observing a pattern of results similar to that observed in early dementia.

-ROI: could the authors explain the selection of the brain region. Why only BA47? Why not ACC too for instance (given the choice of the task)? This region has a special role in monitoring and is involved in both reward and mood regulation, which are also impaired in BD.

Results: I would recommend that the authors present their findings based on the following structure: cognitive performance overall, structural findings, functional findings (subsection “functional activation” and “behavioral findings”) and connectome analyses. Further RTs and/or accuracy levels for all neuropsychological tasks and the fmri task should be shown in a table, including p-values.

Page 12: the authors refer to a conditional process model. Could they please describe this approach in the methods and explain why they selected it.

fMRI analyses: were reaction times during the go/no go task during the fMRI investigation included as a covariate in the fMRI analyses?

Page 14: I would recommend that the authors clarify/rewrite what they mean by “consistent with known….speed”. It is a vague and somewhat confusing statement.

Additional comments could be made in the discussion in terms of: 1. Will the reported abnormalities change over time? In particular, do the authors think that neuropsychological impairment worsen over time and why?

2. How/can these findings be generalized to BD II or other mood disorder populations. 3.The authors use heterogeneous techniques to measure asuring neurocognitive functioning. While cognitive testing is a direct observation of brain function one could say that fMRI and DTI measures are indirect measure of neural functioning. For instance fMRI measures could be affected by hemodynamic changes associated with medical comorbidities (highly common in BD) and DTI may be affected by differing levels of water in the brain. Could the authors comment on these potential confounding effects?

4.Could the authors explain how changes in BA 47 would affect the cortico-limbic functioning? How would the current findings explain mood and behavioral abnormalities observed in BD?

Illustrations: Table 1:the authors report results for the NP and BD sample and HC. Are the HC samples reported here age/gender matched counterparts? Please clarify