American Journal of Psychiatry – Review of manuscript “Characteristics of bipolar I patients grouped by externalizing disorders” by Dr Swaminathan

Outcome: Major revision

The rationale and aim of the study are interesting and deserve to be explored further. However, there are quite a few issues with the paper structure, literature background, development of the rationale, and formulation conclusions that we think should be addressed before this paper can be published.

Rationale backing up the authors’ hypotheses and work approach requires additional content in the introduction and more detailed formulation of the authors’ hypotheses. For example the last sentence of the introduction refers to the heritability of the BP disease, but the authors did not talk about this topic in the body of the introduction, and did not even report which genes or behaviors have been shown to be heritable, what has already been done etc. It is recommended that the author adds a definition of the terms “Discover/Validation sample”.

Page 5: In the “Clinical parameters” section of the methods, the authors could have presented all the information regarding the testing “Waves” in a flowchart showing Ns for each variable.

Page 8 and 9: the authors has 2 headers called “hypotheses”, it is once again confusing and unclear why they haven’t simply had two subsections for “Statistics” called “behavioral” and “genetic”.

Page 9: The author use the title “subject distribution” but it’s unclear what distribution refers to: “Age? Frequency of behavior?” To maximize the readability the author could also refer to the % of frequencies listed on this page (for example when he refers to Ns of participants suffering from alcohol abuse).

Methodology: why didn’t the author use a MANOVA to compare the three groups?

Page 14: The authors didn’t explain or suggest any link between specific genes and externalizing behaviors. They mentioned in the introduction that there are “4 variants of genetic variants that may place subjects at Bipolar risk” but doesn’t discuss this further. A genetic variant discussed in the conclusions is Diversin. Are there any studies in humans? Or only in zebra fish? Can they discuss further if there could be an association between glucose metabolism and bipolar disorder for example?

The discussion should be restructured. The first paragraph f page 14 appears could be a more logic way of starting a discussion. One could then continue with some of the paragraphs at page 13 and conclude with the paragraphs at page 15. It is unclear why the paragraph at page 13 starting with “To determine whether the differences….” is included in the discussion and not in the results section. I would also suggest that the authors provide additional discussion on their current findings and discuss further possible biological mechanisms and implications for the clinical practice.

Overall: There are a few grammar mistakes, prose is awkward, and some sentences have no real meaning. Thorough proofreading is needed. To maximize readability, the authors should add a glossary and write out the following in full throughout the article -- including in tables and figures -- rephrasing as needed to avoid any awkward prose: specifically for ASPD, ADHD etc. Please modify Tables 3 and 4 in order to keep each table on the same page.

Rationale backing up the authors’ hypotheses and work approach requires additional explanation in the introduction. For example the last sentence of the introduction refers to the heritability of the BP disease, but the authors did not talk about this topic in the body of the introduction, and did not explicitly explain which genes they expect to be related to externalizing disorders or what work has already been done etc. The authors mentioned in the introduction that there are “4 variants of genetic variants that may place subjects at Bipolar risk” but do not discuss this important topic this further in terms of which genetic variants they expect to play an important role in these disorders. The genetic variant discussed in the conclusions is Diversin, it is however unclear whether there are other studies on Diversin in humans? Or only in zebra fish? Also could the authors discuss further if there could be an association between glucose metabolism (influenced by Diversin possibly?) and psychiatric disorders for example? In terms of methodology: why didn’t the author use a MANOVA to compare the three groups?

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