

Dear Dr. Ma and WJP Editors:

Thank you for reviewing our manuscript "Brain Reward Circuitry and the Neurobiology of Trauma." We appreciate the thoughtful comments by the reviewer and editor and are grateful for the opportunity to respond to each comment in further detail.

In addition to addressing the reviewer and science editor's comments point-by-point, we have reviewed the entire manuscript to ensure that all citations and references are in the proper format. We have also reviewed the journal's guidelines for the use of figures and have provided the figures in a separate PowerPoint file with the appropriate copyright information.

Please find below our point-by-point response to the reviewers' comments. We appreciate the opportunity to submit this manuscript. Please do not hesitate to contact us with any questions or concerns regarding the revisions.

Sincerely,
Timothy I Michaels, Ph.D.
Emily Stone, B.S.
Sonali Singal, B.S.
Vladan Novakovic, M.D.

Reviewer # 1:

- 1) Starting with the title 'brain reward... and neurobiology of trauma' is a weak connection to the substance use disorder, that has been detailed thereafter.

Response: Thank you for your comment. We agree with the reviewer and therefore have changed the title to "Brain Reward Circuitry: Overlapping Neurobiology of Trauma and Substance Use Disorders." This change has been made in all relevant locations in the revised manuscript.

- 2) Trauma (psychotrauma) obviously lead to increased risk of abusing with substances (BZD above all); but I did not found any word on ethanol... it is as important as maybe all psychotropics together in this field. Please systematize your ideas.

Response: Thank you for this comment. While we agree with the reviewer, we specifically chose not to highlight specific substances of abuse, as they all share a similar neurobiological pathway, in discussing the overlapping neurobiology. There have also been reviewed extensively elsewhere, which is why our manuscript does not specifically discuss alcohol or benzodiazepines in extensive detail.

- 3) Use one or more tables to showcase contributions of different authors. It is important to quote relevant sources. Kindly explain in details the methodology of choosing the authors that you are quoting. The bulk of studies is enormous. Focus on pioneering studies on PTSD.

Response: Thank you for this feedback. In the revised manuscript (please see title page of the revised document) we have provided a narrative of the contribution of different authors.

- 4) Several studies have suggested intrinsic role of locus coeruleus and adrenergic responses. Maybe it is not only amygdala and hippocampus, otherwise said...

Response: Thank you for this comment. We agree with the reviewer and have added a sentence in our conclusion (please see the revised manuscript) that addresses this point.

- 5) References are not formatted conformingly with journal guidelines: quote in numbers [1]...[2] and consult the journal website.

Response: Thank you for this comment. We have revised the entire manuscript to ensure that the references are now in the appropriate format consistent with the standards and practices of the World Journal of Psychiatry.

Science editor #1:

- 1) References: A total of 65 references are cited, including no references published in the last 3 years

Response: Thank you for this comment. We have replaced older references with more recent publications in the last three years (please see the revised manuscript) including the following:

María-Ríos CE, Morrow JD. Mechanisms of shared vulnerability to post-traumatic stress disorder and substance use disorders. *Front Behav Neurosci*. 2020 Jan 31;14:6. [DOI: 10.3389/fnbeh.2020.00006. PMID: 32082127; PMCID: PMC7006033]

Millman, ZB, Gallagher K, Demro C, Schiffman J, Reeves GM, Gold JM, Rakhshan Rouhakhtar PJ, Fitzgerald J, Andorko ND, Redman S, Buchanan RW, Rowland LM, Waltz JA. Evidence of reward system dysfunction in youth at clinical high-risk for psychosis from

two event-related fMRI paradigms. *Schizophr Res*, 2020; **226**: 111-119. [PMID: 30995969
DOI: 10.1016/j.schres.2019.03.017]

2) The "Author Contributions" section is missing. Please provide the author contributions

Response: Thank you for this feedback. In the revised manuscript (please see title page of the revised document) we have provided a narrative of the contribution of different authors.

3) The authors did not provide original pictures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor;

Response: Thank you for your comment. In the revised submission we have included the original file documents in a Powerpoint document (entitled "64549-Figures").

4) PMID and DOI numbers are missing in the reference list. Please provide the PubMed numbers and DOI citation numbers to the reference list and list all authors of the references. Please revise throughout

Response: Thank you for this comment. We have revised the entire manuscript to ensure that the references are now in the appropriate format consistent with the standards and practices of the World Journal of Psychiatry.

6) Please obtain permission for the use of picture(s). If an author of a submission is re-using a figure or figures published elsewhere, or that is copyrighted, the author must provide documentation that the previous publisher or copyright holder has given permission for the figure to be re-published; and correctly indicating the reference source and copyrights. And please cite the reference source in the references list.

Response: Thank you for this comment. For Figure 1, we have removed the previous image and replaced it one created by copyrighted by our authors. For Figure 2 and 3, we are awaiting a response from the publisher (Cold Spring Harbor Laboratory Press) and have attached documentation to that effect. The references for all figures are included in the references section of the revised manuscript.