

## 76582-Responses to the Reviewers and Editor

First, we would like to sincerely thank the editor and the reviewers for their time invested to improve the quality of our paper titled **Depressive disorder and antidepressants from an epigenetic point of view**. We addressed all the concerns raised by the reviewers and tried to follow all their suggestions as much as possible.

Detailed responses to comments are given below. Our revision now also includes the revised manuscript in which all the modifications are marked (track changes). We would like to confirm that the revised manuscript was sent to a native English-speaking expert to polish the manuscript.

### Answers to the Reviewers

#### Reviewer #1:

Specific Comments to Authors: In this review manuscript, the authors discussed depressive disorder and antidepressants from an epigenetic point of view. The topic is interesting. Some concerns and suggestions are listed as below:

1. Microglia can be pre-conditioned through epigenetic-driven innate immune memory that persists for several months. Epigenetic alterations of microglia during early life may re-program the communication between microglia and other cells in the CNS and have significant later consequences for behavior and disease. This point should be discussed. Ref: Innate immune memory in the brain shapes neurological disease hallmarks, Nature, 2018.

**Our response:** Thank you for your comment. We checked articles in relation to microglia and its role in depressive disorder and early life stress. This part is included in the Introduction: Cytokine Theory of Depressive Disorder.

2. From a sex viewpoint, females have been reported to have higher levels of DNA methyltransferase enzyme activity, DNA methylation, and methylated CpG sites than do males in the neonatal POA. Inhibiting DNA methyltransferase causes masculinized neuronal markers and male sexual behavior in female rats, suggesting that DNA methylation serves as the basis for the sex-specific transcriptomes in selective brain regions. This point should be discussed. Ref: Uncovering sex differences of rodent microglia, Journal of Neuroinflammation, 2021.

**Our response:** We included this in the Introduction: Depressive Disorder, where we discuss how epigenetic changes between women and men cause differences in susceptibility to develop a depressive disorder.

#### Reviewer #2:

Specific Comments to Authors: Overall: Good topic, important conversation, general interest. The authors do a good job of performing a review of the available studies on epigenetic changes in depressive disorder and the effects on antidepressants. This work can be published in WJP after revision.

1. Authors need to add relevant diagrams with reference to the literature, thus increasing the readability of the article. For example: Epigenetic Modifications of Major Depressive Disorder.

**Our response:** Thank you for your helpful suggestion. We have added the diagrams / figures which we hope will further contribute to readers' understanding of the content of our review paper.

2. The article needs to add a prospective section after the conclusion. Give some inspiring points for future research.

**Our response:** Thank you for your suggestion. However, as the mini review format of the World Journal of Psychiatry does not include a future perspective as stand-alone section we included it in the Conclusion, more specifically, we extended current future outlook in the Conclusion section.