

Dear Reviewers and Editors,

Thank you and the anonymous referees for your valuable time and efforts dedicated to reviewing our manuscript titled " Resting-State Functional Magnetic Resonance Imaging Study of Vulnerable Brain Regions in Adolescents with Major Depressive Disorder: An Activation Likelihood Estimation Meta-analysis". We appreciate your thoughtful feedback and the potential consideration for publication in the World Journal of Psychiatry.

Given the constructive criticism, we have updated the document and would like to resubmit it for your consideration. The reviewers' comments have been taken into consideration, and the updated manuscript highlights the changes. Below this letter are detailed responses to the reviewers' comments.

We sincerely hope that this revised manuscript has addressed all your comments and suggestions. We appreciated for reviewers' warm work earnestly, and hope that the correction will meet with approval. Thank you once again for the valuable feedback, which has significantly contributed to the enhancement of our manuscript."

Yours sincerely,

YONGZHE

We would like to express our sincere thanks to the reviewers and editors for the constructive comments. We believe that the comments have been very useful to improve the quality of the manuscript.

Replies to Editors and Reviewers

Reviewer 1

Specific Comments to Authors

1. Dear colleagues, I have a few comments on your manuscript: - The English is relatively good, but I found several minor mistakes, like "We aims" (Abstract), "a ALE meta-analysis" (Abstract). At the end of Abstract, there are several words which do not form a sentence at all - "Enhancing our grasp... adolescents". No verb is present. The English should still be improved.

Answer:

Thank you for your valuable feedback. We appreciate your careful review of our manuscript. We acknowledge the noted language errors, such as "We aims" and "a ALE meta-analysis" in the Abstract, as well as the incomplete sentence at the end of the Abstract. We have taken your suggestions seriously and have engaged a professional English editing service to conduct a thorough polishing of the manuscript. In the revised version of the document, we have also included a new language certificate to attest to the improvements made. We hope these enhancements contribute to the overall quality and readability of our manuscript.

2. Literature Search: In which languages did you look up the relevant articles and why did you choose these languages?

Answer:

Thank you very much for your suggestion. We conducted a comprehensive search in English, utilizing databases such as PubMed, Google Scholar, Embase, and Web of Science to identify articles meeting our inclusion criteria. English, being the predominant language for scientific communication, ensures accessibility to a broader audience and comprehensive coverage of relevant research. Meanwhile, we explored the Chinese Language Database (CNKI) to capture studies conducted in Chinese-speaking regions, aiming to provide a more comprehensive overview of the existing literature on adolescent major depressive disorder (MDD) and resting-state functional magnetic resonance imaging (rs-fMRI), particularly in Asian populations. This dual-language approach enhances the comprehensiveness of our literature review, capturing a broader spectrum of findings.

3. Study Selection: You write about "adolescent participants" but you should state their age.

Answer:

Thanks for your constructive suggestion. We appreciate the importance of clarity in defining this demographic group. As there is currently no universally agreed-upon definition of the adolescent age range, and definitions vary among countries, we followed the criteria set forth by each respective author in our review. As there is currently no universally agreed-upon definition of the adolescent age range, and definitions vary among countries, we followed the criteria set forth by each respective author in our review. In the studies collected for this meta-analysis, there were no statistically significant age differences between the case and control groups. Therefore, the results of our study are

relatively reliable. Additionally, we acknowledge the World Health Organization's (WHO) general definition, which typically considers individuals aged 10 to 19 as adolescents [Reference: https://www.who.int/zh/health-topics/adolescent-health#tab=tab_1]. It is essential to note that regional variations in defining the adolescent age range may exist. We have incorporated this consideration into our study to ensure a comprehensive representation of the adolescent population.

4. Discussion - the first paragraph: You write that "these results provided a potential therapeutic target for the treatment of brain injury...". Which kind of therapies do you mean?

Answer:

Thank you very much for your suggestion. In the initial discussion paragraph, we alluded to potential therapeutic targets for the treatment of brain injury in the context of adolescent MDD. These targets may encompass diverse therapeutic modalities, such as neuroregulation techniques^[1], repetitive transcranial magnetic stimulation^[2], etc. However, our aim is to underscore the significance of comprehending these vulnerable brain regions as a groundwork for future research delving into targeted therapeutic interventions.

Reference

[1] Lindsay, Dickey., Samantha, Pegg., Emilia, Cardenas., Haley, Green., Anh, Dao., James, G., Waxmonsky., Koraly, Pérez-Edgar., Autumn, Kujawa. (2023). Neural Predictors of Improvement With Cognitive Behavioral Therapy for Adolescents With Depression: An Examination of Reward Responsiveness and Emotion Regulation. *Research on Child and Adolescent Psychopathology*. doi: 10.1007/s10802-023-01054-z

[2] A., V., Nikiforov. (2022). Association between mild traumatic brain injury, brain structure, and mental health outcomes in the Adolescent Brain Cognitive Development Study. doi: 10.1101/2022.06.02.22275940

5. Conclusion: You write about "more targeted interventions". You should specify them more.

Answer:

Thank you for the comment. Future research could delve into interventions precisely tailored to modulate activity in the vulnerable brain regions identified. These interventions target the activity of the right cuneus and left precuneus, both implicated in MDD ^[1]. Precision medicine approaches and innovative therapeutic modalities are under exploration to address the observed neural alterations in adolescent MDD ^[2]. Continuous theta burst stimulation over the precuneus influences functional connectivity in the left temporal pole and modulates the modular structure of the precuneus network ^[3]. These findings underscore the potential of targeted interventions in addressing neural alterations in adolescent MDD. Further research is essential to develop precise strategies for these interventions.

Reference

- [1] Matteo, Mancini., Chiara, Mastropasqua., Sonia, Bonni., Viviana, Ponzo., Mara, Cercignani., Silvia, Conforto., Giacomo, Koch., Marco, Bozzali. (2017). Theta Burst Stimulation of the Precuneus Modulates Resting State Connectivity in the Left Temporal Pole. Brain Topography. doi: 10.1007/S10548-017-0559-X
- [2] Bo, Zhang., Shouliang, Qi., Shuang, Liu., Xiaoya, Liu., Xinhua, Wei., Dong, Ming. (2021). Altered spontaneous neural activity in the precuneus, middle and superior frontal gyri, and

hippocampus in college students with subclinical depression.. BMC Psychiatry. doi:

10.1186/S12888-021-03292-1

[3] Abraham, Zangen., Samuel, Zibman., Aron, Tendler., Noam, Barnea-Ygael., Uri, Alyagon., Daniel, M., Blumberger., Geoffrey, Grammer., Hadar, Shalev., Tatiana, Gulevsky., Tanya, Vapnik., Alexander, Bystritsky., Igor, Filipčić., David, Feifel., Ahava, Stein., Frederic, Deutsch., Yiftach, Roth., Mark, S., George. (2023). Pursuing personalized medicine for depression by targeting the lateral or medial prefrontal cortex with Deep TMS. JCI insight. doi:

10.1172/jci.insight.165271

6. References: The numbers are missing in References 1 and 2 at the beginning of the Reference.

Answer:

Thank you for pointing that out. We apologize for the oversight. We have revised the references to include the missing numbers. (Page 23, Line 5)