Peer-review Comments and Author Responses

Reviewer 1

1. *The article provides a clear and concise summary of the studies reviewed, including details on the inclusion criteria, methods, and outcome measures. The use of references to specific texts throughout the article helps support the claims made and adds credibility to the review.*

Thank you very much for your positive general assessment of our manuscript.

2. *It would be helpful if the article provided more information on the limitations of the studies reviewed, such as the potential for bias and the varying inclusion criteria and methods used.*

We agree with the reviewer this is important information. We conducted the risk of bias assessment using the Cochrane RoB 2 risk of bias tool and also identified concerns regarding study inclusion criteria and methods, such as inappropriate use of statistical tests and lack of information on concealment randomization. Further, we provided some more information on the limitations of the discussion.

3. *Additionally, it would be beneficial to include a discussion on the potential implications of the findings for clinical practice and future research and the massive amount of patients excluded from the screening.*

We thank the reviewer for this comment. We agree that a slightly more detailed discussion of the possible implications of the findings we find for clinical practice and for conducting future research would be beneficial. We believe that further analysis of the implications of the findings and the reasons for excluding patients could provide valuable information for future research. Moreover, we added a paragraph on the potential implications of the discussion. Although there is a huge amount of patients excluded from screening, few drop-out patients were observed in the studies. Moreover, rTMS has been proven to be safe. Please have a lookout for it in our new attached column in Table 1 (column "side effects and drop-out").

4. *The article provides a valuable contribution to the literature on rTMS in treating treatment-resistant OCD and serves as a useful resource for clinicians and researchers interested in this area.*

We greatly appreciate your favorable overall evaluation of our manuscript.

Reviewer 2

5. *Reading your manuscript about such a relevant theme - the use of an alternative therapy for treatment-resistant Obsessive Compulsive Disorder - was very interesting. Although it seems that this therapy has already been studied in other patients, focusing on the treatment-resistant ones was a great approach and I believe that you were very successful in reviewing published RCTs about the theme. Results and description of studies were very well explained as well as the assessment of risk of bias. Studies included were very different in many aspects, including the technique of the therapy, time of follow-up, and blinding, and presented a high risk of bias, as you very well explained. Figures and tables were also very informative.*

Thank you for your effort and positive assessment of our manuscript as well as of the figures and tables.

6. *One piece of information that I missed reading was what was the definition of the included studies about patients who were considered treatment-resistant. Including definitions of each paper about this specific patient - and if they are comparable - would make your review even more complete and add this information about the patients that were included.*

We agree with the reviewer that this is important information. We included all papers with any kind of treatment resistance mentioned in the study population. Further, we elaborated the Levels for treatment resistance of the included paper in the text in addition to the previous already found assessment (according to Pallanti et al. 2002) in Table 1 under "population".

7. *Overall, your manuscript was very interesting to read and you addressed all topics that were proposed for the review. Also, you concluded that based on the studies no significant results were found and further investigation about the topic is needed to provide a solid and statistically significant conclusion about the use of this alternative therapy in the treatment of patients with treatment-resistant obsessive-compulsive disorder.*

Thank you very much. We appreciate this overall positive impression of our manuscript.

Reviewer 3

8. *The topic of the mini-review; „Transcranial Magnetic Stimulation of Dorsolateral Prefrontal Cortex in Treatment-Resistant Obsessive Compulsive Disorder" falls within the field of neuromodulation and its use in psychiatric disorders.*

This research area has been already explored and several studies (that investigate the use of rTMS for OCD and depression that are resistant to treatment) can be found. So even though the topic seems not entirely new, the focus on the rTMS of the dlPFC for treatment-resistant OCD patients might allow us to conclude on the potential novelty of the proposed mini-review.

Thank you for your effort and acknowledgment that our study is nevertheless timely.

9. *Maybe it would be worth considering exploring the topic wider for example on the role of advanced neuroimaging techniques for more precise localization of the dlPFC area during rTMS.*

Thank you for this kind suggestion. We understand the difficulty of using the not precise 5-cm rule for the localization of the dlPFC, like all our included studies used. However, while it is worth studying further, exploring this topic would be out of the scope of our review.

10. *The strengths of the proposed mini-review are for sure a clear structure and a concrete definition of the inclusion criteria. The mini-review nicely concludes the limitations of current knowledge and shows fields that should be explored further in the future.*

Thank you for the acknowledgment of our effort to make the manuscript comprehensible.

11. *The limitations of the mini-review are findings based on the small number of studies and their methodologies. The likely biases that could appear in the analyzed studies influence the results of the mini-review. You can suggest more about improvements in study design and methodology. Discuss the risk of bias in the included studies. Explain how potential biases, such as blinding issues or randomization problems, may have influenced the findings. Provide recommendations for improving the design of future studies.*

Thank you for your comment. We recognize the limitations of the mini-review, which is based on the small number of studies and their methodologies. We analyzed the risk of bias in the included studies, such as blinding and randomization issues, which may have influenced the findings and results of our mini-review, and added it to the text.

12. *Please also ensure that the language used in the mini-review is clear and precise.*

Thank you for this notification; we had a proper second look at it.
In conclusion, the mini-review gives a good overview of the state of research on rTMS applied to the dIPFC for treatment-resistant OCD. It highlights the need to conduct more and well standardized trials that could lead to conclusions on the efficacy of the examined intervention on the proposed population. This type of mini-review can be considered a starting point for broadening knowledge even further by conducting a meta-analysis or systematic review.

Reviewer 4

13. *Abstract: It already included both (treatment-resistant and those who had not failed first-line treatment). Novelty could raise concerns. Maybe it would be worth considering exploring the topic wider; for example, on the role of advanced neuroimaging techniques for more precise localization of the dlPFC area during rTMS.*

Thank you for your thoughtful suggestion. We acknowledge the challenges associated with using the somewhat imprecise 5-cm rule for dlPFC localization, as employed in all the studies we included. However, although a topic worth further investigation, delving into this issue would be beyond the scope of our review.

14. *Introduction: This citation in the mini-review is crucial and adds credibility to the review and demonstrates that it builds upon existing knowledge. It is good to base the introduction on papers like a meta-analysis by Fitzsimmons et al. (2022). You should consider if the niche you are highlighting below is enough.*

Thank you for your raising concern about the novelty of our study. While the meta-analysis of Fitzsimmons et al. (2022) focused on all possible targets and frequencies to compare them in a general OCD population, we focused on the dlPFC with a low frequency only in patients who are resistant to other standard-of-care treatments. It enables a more comprehensive interpretation of this protocol for our targeted population. Moreover, the meta-analysis has the disadvantage, that all papers have to supply the same kind of variable to analyze it. Therefore, they have other exclusion criteria as a review. This can also be seen in this situation. While we included 5 RCTs within the above-mentioned specifics, Fitzsimmons et al. (2022) displayed just 2 taking into account that one of our included papers was published later, it is still 100% more. Thus, we are still confident that our study is timely and sufficient.

15. *Methods (study criteria): Always remember to clearly define your inclusion and exclusion criteria. You can consider specifying what "treatment-resistant" OCD is, as this is a critical factor in your analysis.*

Thank you for noticing this issue. We have not elaborated on this inclusion criteria since we wanted it to be broad for not missing substantial papers. Moreover, there is an existing definition by Pallanti et al. 2002 that classified the level of non-response, which we addressed for our included papers in Table 1.

16. *Methods (search criteria): Maybe you could consider expanding the list of databases or resources for the search. Think about mentioning if gray literature, conference proceedings, or other sources were included in the search.*

Thank you for this input. We acknowledge that the current version of the Cochrane Handbook for Systematic Reviews of Interventions (version 6.4) strongly suggests the search in grey literature, like dissertations and conference presentations. We excluded this option due to our focus on randomized clinical trials (RCTs) and observational studies only, which we expected to find all in our used databases.

17. *Methods (Data extraction): If the quality of the included studies were assessed you could provide details of the criteria or tools used for quality assessment.*

Please allow us to omit a detailed description of the tool we used for the risk-of-bias assessment. However, we added some more information on the used RoB 2 Cochrane risk-of-bias tool for randomized trials (Higgins et al., 2011) available online with detailed information on the tool and its use (https://methods.cochrane.org/bias/resources/rob-2-revised-cochrane-risk-bias-tool-randomized-trials).

18. *Results (overall): Overall, the discussion in your mini-review reflects the cautious and evidence-based stance that the existing literature does not provide a definitive answer regarding the efficacy of rTMS in the dlPFC for treatment-resistant OCD. Isn't it? Maybe worth considering would be re-writing a bit in this section focusing on the need for larger, high-quality trials, optimized protocols, and precise localization techniques to better understand and refine the potential therapeutic role of rTMS.*

Thank you for your comment. The discussion in our mini-review reflects a cautious approach based on the current evidence regarding the efficacy of rTMS on the dlPFC for treatment-resistant OCD. It would be possible to provide additional information in this section, such as the need for larger, high-quality trials, treatment protocols that are tailored to individual patients, and imaging techniques to identify the target brain regions accurately. This would highlight the importance of conducting more research in this area, which could provide valuable information that can be used to design and conduct more effective trials in the future. Therefore, we will take your comment into account in our mini-review.

19. Results (second paragraph): You could discuss the heterogeneity among the included studies, including variations in rTMS parameters, study durations, and follow-up periods. Try to explain how this heterogeneity might impact the ability to draw consistent conclusions.

Thank you for your input here. While we appreciate the suggestion, we wanted to focus on the findings in this part of the review and discuss some of the aspects in the following section.

19. *Discussion (overall): What types of studies are needed to address the existing gaps and inconsistencies? Explanation of how potential biases, such as blinding issues or randomization problems, may have influenced the findings could be wider. You could suggest improvements in study design and methodology. Maybe conclude the discussion section by summarizing the key takeaways and emphasizing the need for further research to establish the efficacy of rTMS in treating treatment-resistant OCD.*

Thank you for your comment here. We agree with you the potential biases should be discussed, and thus, we have added the implications of the blinding and randomization issues in the fourth paragraph of the discussion. Moreover, we have added a final paragraph with the main takeaway points and the type of future studies needed to establish the efficacy of rTMS as an adjunctive treatment option for OCD patients.

20. *Discussion (fourth paragraph): Very high risk for bias. And maybe consider "As 4 on 5 included papers…".*
21.

Thank you for this suggestion. We implemented it in the revised manuscript.

22. Conclusion (overall): Please consider highlighting your results in this part and potential bias. The inconsistency in outcomes is attributed also to factors such as different rTMS protocols, small sample sizes, short-term study durations, and variations in blinding strategies.

We highlighted the previous limitations a bit more in this section according to your suggestions, thank you.