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PEER-REVIEW REPORT

Name of journal: *World Journal of Psychiatry*

Manuscript NO: 76005

Title: Delayed improvements in visual memory task performance and negative symptoms among chronic schizophrenia patients after high-frequency repetitive transcranial magnetic stimulation

Provenance and peer review: Unsolicited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 05688164
Position: Peer Reviewer
Academic degree: BSc, MD, PhD
Professional title: Research Fellow
Reviewer's Country/Territory: Hungary
Author's Country/Territory: China

Manuscript submission date: 2022-02-28

Reviewer chosen by: AI Technique

Reviewer accepted review: 2022-02-28 08:12

Reviewer performed review: 2022-03-01 13:48

Review time: 1 Day and 5 Hours

Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [ ] Minor revision [Y] Major revision [ ] Rejection

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Re-review	[Y] Yes [ ] No
Peer-reviewer statements	Peer-Review: [ ] Anonymous [Y] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

1 March 2022 Review on the manuscript titled "Delayed improvement in visual memory task and negative symptoms in chronic schizophrenia patients after high-frequency repetitive transcranial magnetic stimulation" by Du X et al, submitted to World Journal of Psychiatry Manuscript ID: 74070 Dear Authors, Du and colleagues in the present study entitled 'Delayed improvement in visual memory task and negative symptoms in chronic schizophrenia patients after high-frequency repetitive transcranial magnetic stimulation', investigated the current status of knowledge of application of non-invasive brain stimulation (NIBS) in treatment of schizophrenia. For this purpose, 47 patients with chronic schizophrenia with marked negative symptoms on stable treatment were randomly assigned into two groups, active repetitive transcranial magnetic stimulation (rTMS) over left dorsolateral prefrontal cortex (DLPFC) or sham stimulation for 4 weeks and followed up for another 4 weeks. Cognitive functions and clinical symptoms were also assessed. Results showed that 4 weeks after the end of treatment, rTMS treatment significantly increased visual memory compared to the sham condition. Authors concluded by stating that high-frequency transcranial magnetic stimulation can improve visual memory function and reduce negative symptoms in patients with schizophrenia, but the effect is delayed. The main strength of this manuscript is that it addresses an interesting and timely question, providing a captivating interpretation and describing how transcranial magnetic stimulation over DLPFC could reduce negative symptoms and improve cognitive impairments in schizophrenia. In general, I think the idea of this article is really interesting and the

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authors' fascinating observations on this timely topic may be of interest to the readers of World Journal of Psychiatry. However, some comments, as well as some crucial evidence that should be included to support the author's argumentation, needed to be addressed to improve the quality of the manuscript, its adequacy, and its readability prior to the publication in the present form. I suggest reshaping some parts of the Introduction and Discussion sections by adding more evidence. Please consider the following comments: 1. Abstract: Please proportionally present background, aim, methods, results, and conclusion, as the aim and the conclusions are not sufficiently described. Also, I think that the lack of an explanation of what "improvement of cognitive impairments" means in this study makes the reader unable to grasp the key aspects of this paper by consulting the abstract. 2. Keywords: Please consider adding 'Non-invasive brain stimulation (NIBS)' as keyword. 3. In general, I recommend authors to use more references to back their claims, especially in the Introduction of the manuscript, which I believe is lacking. Thus, I recommend the authors to attempt to expand the topic of their article, as the bibliography is too concise. Nevertheless, I believe that less than 60/70 articles are highly inadequate for a research paper. Currently authors cite only 45 papers, and in my opinion they too low. Therefore, I suggest the authors to focus their efforts on researching relevant literature: in my opinion, adding more citations will help to provide better and more accurate background to this study. In this review, I will try to help the authors by suggesting relevant articles that suit their manuscript. 4. Introduction: I suggest the authors to reorganize this section, which seems too thin, and yet, dispersive. I think that more organized and detailed information about schizophrenia would provide suitable background here. I suggest the authors to make an effort to provide a brief overview of the pertinent published literature that offer a perspective on definition, causes and symptoms of schizophrenia, because as it stands, this information is not highlighted in the text. The background should be presented in

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the following order: schizophrenia in general including brief descriptions of epidemiology, pathogenesis, symptoms, current treatment, and challenge in treatment, and finally the authors' hypothesis. Thus, I suggest presenting a short description of schizophrenia in general, risk, pathogenesis, prognosis, comorbidity, treatment, and current challenge of management in the first paragraph, leading to the indication and background of NIBS and rTMS (https://doi.org/10.3390/brainsci11111544; https://doi.org/10.3390/biomedicines9040403; . https://doi.org/10.3390/biomedicines9030235; https://doi.org/10.3390/biomedicines8080243; doi: 10.3389/fpsyt.2022.845493. Furthermore, I would suggest adding more information on neural substrates of schizophrenia, specifically on frontal lobe dysfunction, and on related effects on patients' memory and learning impairments. Specifically, I would suggest exploring prefrontal cortex's key role and how its disrupted function may contribute to irregular behavioral responses and therefore to the development of many mood psychiatry disorders, including depression or anxiety, and those that are common in schizophrenia: evidence from a recent study conducted on patients with lesion in ventromedial portion of prefrontal cortex (https://doi.org/10.1523/JNEUROSCI.0304-20.2020) revealed that the ventromedial prefrontal cortex (vmPFC) is involved in the acquisition of emotional conditioning (i.e., learning), assessing how naturally occurring bilateral lesion centered on the vmPFC compromises the generation of a conditioned psychophysiological response during the acquisition of pavlovian threat conditioning (i.e., emotional learning). Also, in a recent theoretical review (https://doi.org/10.1038/s41380-021-01326-4) that focused on neurobiology of emotional conditioning, the role of ventromedial prefrontal cortex (vmPFC) was analyzed in the processing of safety-threat information and their relative value, and how this region is fundamental for the evaluation and representation of stimulus-outcome's

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value needed to produce sustained physiological responses. Secondary, authors also might to consider some studies that have focused on this topic (https://doi.org/10.1162/NECO_a_00779; https://doi.org/10.1111/cns.12835; https://doi.org/10.1038/s41386-021-01101-7). 5. Introduction: In according with the previous suggested literature, I would also recommend adding information from a very recent perspective manuscript that has focused on providing a deeper understanding of human learning neural networks, showed the crucial role of human PFC, giving interesting insights on the involvement of this important brain region in the advancement of alternative, more precise and individualized treatments for a variety of neurologic and psychiatric disorders (https://doi.org/10.17219/acem/146756). 6. The aims of this study are generally clear and to the point; however, I believe that there are some ambiguous points that require clarification or refining. I think that authors here need to be explicit regarding how they operationally determined the association between improvement in memory after rTMS treatment and improvement in negatives symptoms of schizophrenia, as it is the variable that is manipulated in the study. 7.

Design: I suggest Authors to reorganize/rewrite this paragraph because, as it stands, this section is way too much inhomogeneous and dispersive, and describes the research procedures in an excessively broad way. Also, I would ask the authors to provide an explanatory figure that clearly shows experiment design process. 8. Active and sham rTMS: Could the authors indicate proper reference for the number of trains, the stimulation intensity, the frequency, the stimulation site and the number of sessions utilized? May provide evidence for the parameters that they considered that could have represented the best protocol for schizophrenia treatment? 9. Discussion: In my opinion, this paragraph would benefit from some thoughtful as well as in-depth considerations by the authors, because as it stands, it is very descriptive but not enough theoretical as a discussion should be. Also, I believe that this study would be more

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compelling and useful to a broad readership if the authors could expand their examination of the efficacy of non-invasive brain stimulation (NIBS) for negative symptoms in schizophrenia, and investigate the effects of non-invasive brain stimulation (NIBS) on two forms of insight, clinical and cognitive, in patients with mood disorders. On this subject, I recommend citing recent evidence that revealed that the application of NIBS induces long-lasting effects, noninvasively modulating the abnormal activity of neural circuits (i.e., amygdala-PFC-hippocampus) involved in mood psychiatry disorders, and modulates a variety of cognitive functions: results from a crucial study (https://doi.org/10.1016/j.cub.2020.06.091) showed causal evidence for the application of NIBS over DLPFC after memory reactivation in reducing responding to learned fear. Furthermore, a recent review acknowledged the implementation of NIBS to modulate in general emotional memories (https://doi.org/10.1016/j.neubiorev.2021.04.036). Similarly, another recent study illustrated the therapeutic potential of NIBS as a valid alternative in the treatment of abnormally persistent fear memories that characterized those patients with anxiety disorders that do not respond to psychotherapy and/or drug treatments (https://doi.org/10.1016/j.jad.2021.02.076). I may also recommend additional studies that have focused on this issue (https://doi.org/10.3390/biomedicines10010076; https://doi.org/10.3390/biomedicines9050517). These findings highlight how NIBS and are a valuable tool in research and have potential diagnostic and therapeutic applications for many mood psychiatry disorders, including depression or anxiety, and those that are common in schizophrenia. 10. I believe that the 'Conclusions' section would be useful to adequately indicate convey what the authors believe is the take-home message of their study, and therefore provide a synthesis of the data presented in the paper as well as possible keys to advancing research and understanding of the prevalence of depression in post-stroke patients. 11. In according to the previous

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comment, I would ask the authors to better define a proper 'Limitations and future directions' section before the end of the manuscript, in which authors can describe in detail and report all the technical issues brought to the surface. 12. Figures: Please insert Figure 1 and Figure 2 into the main text close to their first citation, in this case in page 6, and provide a comprehensive explanatory title and caption. Overall, the manuscript contains 3 figures, 2 tables and 45 references. In my opinion, the number of references it is too low for an original research article, and this prevents the possibility of publishing it in this form. References should be more than 60/70 for original research articles. However, the manuscript might carry important value presenting effect of rTMS on visual memory in patients with schizophrenia. I hope that, after these careful revisions, the manuscript can meet the Journal's high standards for publication. I am available for a new round of revision of this article. I declare no conflict of interest regarding this manuscript. Best regards, Reviewer

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Provenance and peer review: Unsolicited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 03940498
Position: Editorial Board
Academic degree: PsyD

Professional title: Academic Fellow, Professor

Reviewer's Country/Territory: Poland

Author's Country/Territory: China

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Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [Y] Minor revision [ ] Major revision [ ] Rejection

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Re-review	[ ] Yes [Y] No
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

"Second-generation antipsychotics have limited effect on negative symptoms"? In the contrary: the impact on negative symptoms is one factor which differentiates second-generation antipsychotics from classic neuroleptics ! No information whether antipsychotic drugs have been changed before the study started and what was the effect of such a change? How the athors are able to exclude that those Pts who did not improve after the rTMS showed previously no satisfectory response to previous drugs treatment?

What was the explanation of the finding that there was no correlation between PRN and SANS score? The suggestion is that the correlation between Delta SANSS and Delta rTSM might be helpful. Authors suggestion on the need of the follow-ups tudy should be underlined.