

PEER-REVIEW REPORT

Name of journal: World Journal of Psychiatry

Manuscript NO: 57599

Title: The mechanism of repetitive transcranial magnetic stimulation for anti-depression:
Evidence from preclinical studies

Reviewer's code: 02548382

Position: Peer Reviewer

Academic degree: PhD

Professional title: Professor

Reviewer's Country/Territory: Italy

Author's Country/Territory: China

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Scientific quality	<input checked="" type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input checked="" type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input checked="" type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

Generally well-written review that a bit downplays dTMS towards the end of the paper. It is not supported by any evidence that dTMS does not provide well-focused stimulation to superficial structures. There follow my specific comments: The mechanism of repetitive transcranial magnetic stimulation for anti-depression: Evidence from preclinical studies The Abstract is too short and says nothing. You should expand by citing a literature search strategy and the databases where you conducted your inquiry, provide results and give the gist of what you found. Then you should conclude with a mechanism that you hold is the most likely to explain how rTMS works. There you should introduce the shortcomings of preclinical studies and state which they are. "Repetitive transcranial magnetic stimulation (rTMS) is an effective treatment for major depressive disorder (MDD). This paper reviews the anti-depressant mechanisms of rTMS that have been found in preclinical studies in recent years and discusses the shortcomings of TMS in preclinical studies." Introduction In the first paragraph, add also deep transcranial magnetic stimulation (dTMS) and direct transcranial current stimulation (dTCS). Add to title rTMS (rTMS activates the anti-inflammatory effects mediated via the nuclear factor-E2-related factor 2 (Nrf2) signaling pathway) "When Nrf2 gene was silenced, the antidepressant effect of rTMS disappeared simultaneously with counteracted of the reduction of inflammatory factors. The results suggest that rTMS plays an anti-depressive role via enhancing anti-inflammatory effect mediated by Nrf2 signaling pathway. However, the mechanism by which rTMS exerts its anti-depressant effect through anti-inflammatory has not been fully elucidated, there are few preclinical studies and more research is needed." It would be better to put it as follows: "When Nrf2 gene was silenced, the antidepressant effect of rTMS disappeared simultaneously with a decrement of inflammatory factors. Results suggest that rTMS plays an anti-depressant role via an

enhancement of an anti-inflammatory action mediated by Nrf2 signaling pathway. However, the mechanism by which rTMS exerts its anti-depressant effect through an anti-inflammatory effect has not been fully elucidated. In fact, there is a dearth of preclinical studies and more research is needed at this respect.” Anti-oxidative stress effects “one is the enzyme anti-oxidative stress system” correct to “one is the enzymatic anti-oxidative stress system”. Activation of endocannabinoid system (ECS) and brain derived neurotrophic factor (BDNF) signaling pathway enhances synaptic plasticity and neurogenesis “that ECS is involed in depression” change to “that ECS is involved in depression”. “2-arachidionylglycerol (2-AG)” change to “2-arachidonylglycerol (2-AG)” “N-arachidoneilodopamine” change to “N-arachidonoyldopamine” “depression-like Wista rats induced by chronic unpredictable stress (CUS)” change to “Wistar rats with a depression-like condition induced by chronic unpredictable stress (CUS)” Decrease the activity of the HPA axis “There are few preclinical and clinical studies that rTMS exerts an anti-depressant effect by reducing the activity of the HPA axis, and it may not yet provide sufficient evidence.” Change to “There are few preclinical and clinical studies supporting that rTMS exerts an anti-depressant effect by reducing the activity of the HPA axis, and the yet provided evidence is still insufficient.” Future perspectives “In addition, because deep brain stimulation (DBS) can treat depression [81-84], it suggests that neural circuit dysfunction may be one of the pathophysiological mechanisms of depression [85], but the specific mechanism of neural circuit dysfunction is poorly understood.” Change to “In addition, the fact that deep brain stimulation (DBS) may treat depression [81-84], suggests that neural circuit dysfunction may be one of the pathophysiological mechanisms of depression [85]; however, the specific mechanism of neural circuit dysfunction remains poorly understood.”

RE-REVIEW REPORT OF REVISED MANUSCRIPT

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Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input checked="" type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
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SPECIFIC COMMENTS TO AUTHORS



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Just two recommendations. Change the Abstract as follows: This review summarizes anti-depressant mechanisms of repetitive transcranial magnetic stimulation (rTMS) in preclinical studies, including anti-inflammatory effects mediated by activation of the Nrf2 signaling pathway, anti-oxidative stress effects, enhancement of synaptic plasticity and neurogenesis via activation of endocannabinoid and BDNF signaling pathways, increase of monoamine neurotransmitter content via inhibition of the Sirt1/MAO-A signaling pathway, and reduced HPA axis activity. It also discusses shortcomings of TMS in preclinical studies such as inaccurate positioning, shallow depth of stimulation, and difficulty in elucidating the neural circuit mechanism up- and down-stream of the stimulated target brain regions. Change the corresponding heading as follows: DECREASED ACTIVITY OF THE HPA AXIS