

Dear Editor and Reviewers:

Thank you for giving us the opportunity to revise our manuscript entitled, “The mechanism of repetitive transcranial magnetic stimulation for anti-depression: Evidence from preclinical studies” (Manuscript ID: 57599). Those comments are all valuable and very helpful for revising and improving our paper. We have studied reviewer’s comments carefully and have revised the manuscript accordingly. We hope that you will find our revised manuscript satisfactory. We would like to express our great appreciations to your work on our paper. Please do not hesitate to contact me if you need any further information.

Kind regards,

Di Luan

### **Responses to the reviewers:**

#### **-Reviewer 1**

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 involved in depression” change to “that ECS is involved in depression”. “2-arachidonylglycerol (2-AG)” change to “2-arachidonylglycerol (2-AG)” “N-arachidonyldopamine” change to “N-arachidonyldopamine” “depression-like Wistar 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.”

Response: Thank you for your comments.

Regarding the discussion of dTMS at the end of the article, we changed it into " Deep TMS can stimulate relatively deep brain regions compared to other TMS, but it may cause the superficial regions to be strongly stimulated." strictly and objectively.

We have rewritten the Abstract as required. The part of the Abstract briefly introduces the possible anti-depressant mechanisms of rTMS derived from preclinical evidence, and briefly describes the drawbacks of rTMS in preclinical studies.

We have also corrected the spelling and grammar mistakes and the expression of some sentence patterns mentioned in your review comments.

Before uploading the revised manuscript, the corresponding author carefully reviewed the manuscript and made many changes to the grammar and narrative style. I hope you'll find it satisfactory.

Thank you for your patience, care and professionalism. In this difficult time when the epidemic is raging, please take special care of your body.