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## Mechanisms of repetitive transcranial magnetic stimulation for anti-depression: Evidence from preclinical studies

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### Abstract

This review summarizes the anti-depressant mechanisms of repetitive transcranial magnetic stimulation in preclinical studies, including anti-inflammatory effects mediated by activation of nuclear factor-E2-related factor 2 signaling pathway, anti-oxidative stress effects, enhancement of synaptic plasticity and neurogenesis *via* activation of the endocannabinoid system and brain derived neurotrophic factor signaling pathway, increasing the content of monoamine neurotransmitters *via* inhibition of Sirtuin 1/monoamine oxidase A signaling pathway, and reducing the activity of the hypothalamic-pituitary-adrenocortical axis. We also discuss the shortcomings of transcranial magnetic stimulation 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 stimulation target brain region.

**Key Words:** Repetitive transcranial magnetic stimulation; Anti-depressant mechanisms; Nuclear factor-e2-related factor 2; Endocannabinoid system; Monoamine oxidase; Hypothalamic-pituitary-adrenocortical axis; Brain derived neurotrophic factor

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**Core Tip:** Repetitive transcranial magnetic stimulation (rTMS) is an effective treatment for major depressive disorder. 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.

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## INTRODUCTION

Repetitive transcranial magnetic stimulation (rTMS), electroconvulsive therapy (ECT), and vagus nerve stimulation are three physical strategies that have been approved by the United States Food and Drug Administration for the treatment of major depressive disorder (MDD)<sup>[1]</sup>. Compared with ECT and vagus nerve stimulation, rTMS is more readily accepted by patients with MDD because it does not require anesthesia and minimally invasive surgery with fewer side effects.

Since rTMS is an effective treatment for MDD<sup>[2-6]</sup>, understanding its anti-depressant mechanisms may help to deepen the understanding of depression. This paper focuses on preclinical studies, reviews the underlying mechanisms of rTMS in animal models of depressive-like behavior, and discusses the shortcomings and deficiencies of rTMS in preclinical studies. Preclinical studies have shown that rTMS plays an anti-depressant role through a variety of mechanisms with diverse signaling pathways (Table 1).

## REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION ACTIVATES THE ANTI-INFLAMMATORY EFFECTS MEDIATED VIA THE NUCLEAR FACTOR-E2-RELATED FACTOR 2 SIGNALING PATHWAY

Inflammation is strongly associated with depression<sup>[7-10]</sup>. Patients with autoimmune and infectious diseases are more likely to develop depression<sup>[11]</sup>. Patients with aseptic inflammation in the brain (such as stroke) are more likely to be accompanied by depression<sup>[12]</sup>. There are few clinical studies on the effects of rTMS on immune inflammation in MDD patients. Langguth *et al*<sup>[13]</sup> reported the recurrence of rheumatoid arthritis in an elderly female patient with treatment-resistant depression (TRD) comorbid with rheumatoid arthritis after receiving 20 Hz (intensity, 90% motor threshold) rTMS. After the patient received rTMS, the peripheral C-reactive protein and interleukin-6 (IL-6) contents increased (from 6.7 mg/L to 25 mg/L and from 3.4 ng/L to 15 ng/L, respectively), indicating that rTMS enhanced the inflammatory response of the patient. In contrast, Zhao *et al*<sup>[14]</sup> recruited 58 elderly patients with TRD and 30 healthy controls. The levels of peripheral IL-1 $\beta$  and tumor necrosis factor  $\alpha$  (TNF $\alpha$ ) in the patients were higher than those in healthy controls. Compared with the non-rTMS treated group, peripheral IL-1 $\beta$  and TNF $\alpha$  levels were markedly reduced in patients who were continuously treated with 10 Hz (intensity, 80 % motor threshold) rTMS for 4 wk. In addition, the levels of peripheral pro-inflammatory cytokines had no observable change in healthy controls after treatment by rTMS, which was consistent with the results of animal studies<sup>[15]</sup>.

Nuclear factor-E2-related factor 2 (Nrf2) is a transcription factor that binds to antioxidant response elements and has anti-inflammatory effects in addition to anti-oxidative stress<sup>[16-18]</sup>. There was significantly reduced expression of Nrf2 both in the hippocampus and prefrontal cortex (PFC) of depressive-like mice induced by chronic social defeat stress or stress susceptible rats induced by learned helplessness<sup>[18,19]</sup>. Moreover, autopsy revealed that Nrf2 expression was decreased in the PFC region of MDD patients<sup>[19,20]</sup>. Tian *et al*<sup>[21]</sup> found that depressive-like behavior induced by chronic unpredictable mild stress (CUMS) in rats were improved by rTMS (15 Hz/1.26 T) via increasing Nrf2 translocation into the nucleus and decreasing the expression of TNF $\alpha$ , inducible nitric oxide synthase, IL-1 $\beta$ , and IL-6 in the hippocampus. When the Nrf2



**Table 1 Main preclinical findings on antidepressant mechanisms of repetitive transcranial magnetic stimulation**

Ref.	Model	rTMS				Main findings
		Frequency (Hz)	Intensity (T)	Duration (d)	Coil size	
Tian <i>et al</i> <sup>[21]</sup> , 2020	CUMS	15	1.26	7	Inner diameter 2.5 cm; outer diameter 5 cm (SD rats)	Regulation of Nrf2-induced anti-inflammatory effect in the hippocampus
Yang <i>et al</i> <sup>[42]</sup> , 2019	CUS	1	20 mT	14	Not mentioned	Enhancement of synaptic plasticity in the hippocampus
Xue <i>et al</i> <sup>[45]</sup> , 2019	CUS	5	1.26	7	Inner diameter 2.5 cm; outer diameter 5 cm (SD rats)	Activation of the ECS in the hippocampus
Zhao <i>et al</i> <sup>[49]</sup> , 2018	CUMS	10	50% of the resting motor threshold	15	5 cm in diameter (SD rats)	Decreasing the activity of the HPA axis
Heath <i>et al</i> <sup>[48]</sup> , 2018	OB	10	50 mT	20	8 mm in diameter (C57BL/6J mice)	Activation of the BDNF signaling pathway and pro-proliferative in the hippocampus
Fang <i>et al</i> <sup>[43]</sup> , 2018	CUMS	15	rTMS device maximum power	7	Not mentioned	Activation of the ECS in the hippocampus
Peng <i>et al</i> <sup>[68]</sup> , 2017	CUS	5/10	0.84/1.26	7	Inner diameter 2.5 cm; outer diameter 5 cm (SD rats)	Suppression of Sirt1/MAO-A signaling in the PFC
Chen <i>et al</i> <sup>[47]</sup> , 2015	CUS	15	1.26	7	Inner diameter 2.5 cm; outer diameter 5 cm (SD rats)	Activation of the BDNF signaling pathway and pro-proliferative in the hippocampus
Wang <i>et al</i> <sup>[44]</sup> , 2014	CUMS	15	rTMS device maximum power	7	Inner diameter 2.5 cm; outer diameter 5 cm (SD rats)	Activation of the ECS and BDNF signaling pathway in the hippocampus
Kim <i>et al</i> <sup>[78]</sup> , 2014	CUMS	10	1.4	14	7 cm in diameter (SD rats)	Changing metabolic patterns in the brain
Feng <i>et al</i> <sup>[46]</sup> , 2012	CUMS	15	rTMS device maximum power	21	Inner diameter 5 cm; outer diameter 7 cm (SD rats)	Decreasing the activity of the HPA axis, and activation of BDNF signaling pathway in the hippocampus
Tasset <i>et al</i> <sup>[29]</sup> , 2010	OB	60	0.7 mT	14	Not mentioned	Anti-oxidative stress effects

BDNF: Brain derived neurotrophic factor; CUS: Chronic unpredictable stress; CUMS: Chronic unpredictable mild stress; ECS: Endocannabinoid system; HPA axis: Hypothalamic-pituitary-adrenocortical axis; MAO-A: Monoamine oxidase A; Nrf2: Nuclear factor-E2-related factor 2; OB: Olfactory bulbectomy; PFC: Prefrontal cortex; rTMS: Repetitive transcranial magnetic stimulation; SD rats: Sprague Dawley rats; Sirt1: Sirtuin 1.

gene was silenced, the anti-depressant effect of rTMS disappeared simultaneously with a decrease of inflammatory factors. The results suggested that rTMS plays an anti-depressant role *via* enhancement of an anti-inflammatory action mediated by the Nrf2 signaling pathway. However, the mechanism by which rTMS exerts its anti-depressant effect through an anti-inflammatory effect has not been fully elucidated. Therefore, more preclinical studies are needed in this respect.

## ANTI-OXIDATIVE STRESS EFFECTS

Humans produce reactive oxygen species (ROS) in the process of using O<sub>2</sub> to oxidize glucose to generate adenosine triphosphate. Excessive ROS act on lipids, proteins, and deoxyribonucleic acid, and produce a large number of peroxidation products such as lipid peroxidation products malondialdehyde and 4-hydroxyalkenals, resulting in oxidative stress, which is considered an important factor for disease development. There are two types of anti-oxidative stress systems in the body: One is the enzymatic anti-oxidative stress system including glutathione peroxidase (GSH-Px) and superoxide dismutase; The other is the non-enzymatic anti-oxidative stress system including glutathione (GSH). Several meta-studies have shown increased peroxidation products and decreased anti-oxidative stress agents in MDD patients<sup>[22-25]</sup>. Durmaz *et al*<sup>[26]</sup> found that, compared with the value before treatment, the serum content of

thiol, an anti-oxidant organic sulfur, was reduced in TRD patients after treatment with 20 Hz (intensity, 110 % motor threshold) rTMS. However, there are different views on the anti-depressant effect of rTMS through anti-oxidative stress. Aydın *et al*<sup>[27]</sup> found that there was no difference in serum thioredoxin, a protein with anti-oxidant function, between healthy and TRD patients, or between TRD patients before and after rTMS treatment.

The review of Medina-Fernández *et al*<sup>[28]</sup> detailed the anti-oxidative stress effects of rTMS in a variety of diseases. In preclinical studies of depression, the mechanism of anti-oxidative stress in rTMS has been poorly studied. Compared with sham rTMS group, rTMS at 60 Hz/0.7 mT increased the decreased contents of GSH, GSH-Px, and superoxide dismutase, and decreased the contents of malondialdehyde, 4-hydroxyalkenals, and caspase-3, a key terminal shear enzyme in apoptosis, in brain tissue homogenate in a rat depression model induced by olfactory bulbectomy<sup>[29]</sup>. The idea that oxidative stress is one of the causes or characteristics of MDD has not been widely accepted by the academic community. In addition, the anti-depressive role of rTMS through the mechanism of anti-oxidative stress has been controversial in clinical studies, in which the measurement of oxidative stress markers in peripheral blood may not reflect the real situation in the brain truthfully and completely. Unfortunately, only one preclinical study was found to clarify the mechanism of anti-oxidative stress in the anti-depressive effect of rTMS.

## ACTIVATION OF ENDOCANNABINOID SYSTEM AND BRAIN DERIVED NEUROTROPHIC FACTOR SIGNALING PATHWAY ENHANCES SYNAPTIC PLASTICITY AND NEUROGENESIS

Cumulative evidence suggests that the endocannabinoid system (ECS) is involved in the physiopathologic mechanism of depression<sup>[30-32]</sup>. ECS receptors include cannabinoid type 1 receptor (CB1R) and CB2R. ECS ligands include arachidonoyl ethanolamide (AEA), 2-arachidonylglycerol (2-AG), noladine ether, virodhamine, and N-arachidonoyldopamine. Other endogenous compounds such as palmitoylethanolamide and oleylethanolamide also have affinity for the ECS receptors. AEA and 2-AG are the most important ligands in the ECS. The key proteins in AEA biosynthesis and decomposition are N-acyl phosphatidyl ethanolamine-phospholipase D and fatty acid amide hydrolase, respectively. The key proteins in 2-AG biosynthesis and decomposition are diacylglycerol lipase  $\alpha$  (DAGL $\alpha$ ) and monoacylglycerol lipase (MAGL), respectively. Endocannabinoids produced in the postsynaptic element activate endocannabinoid receptors located in the presynaptic membrane and perform a number of anti-depressant biological functions including: (1) Reducing the activity of the hypothalamic-pituitary-adrenocortical (HPA) axis; (2) Enhancing hippocampal synaptic plasticity; (3) Promoting the neurogenesis of the hippocampus; and (4) Increasing the expression of brain derived neurotrophic factor (BDNF) in hippocampal tissue<sup>[33-36]</sup>. BDNF, a key factor affecting multiple signaling pathways in the brain, binds to the receptor TrkB on the membrane and activates the Ras/MAPK, PI3K/Akt, PLC $\gamma$ , and GTPase signaling pathways to promote neurogenesis and enhance synaptic plasticity<sup>[37-41]</sup>.

One Hz/20 mT rTMS increased the expression of synaptic proteins PSD95 and NR2B in the hippocampus of Wistar rats with a depressive-like behavior induced by chronic unpredictable stress (CUS)<sup>[42]</sup>. rTMS at 15 Hz (intensity, device maximum power) reduced the expression of MAGL and Bax, increased the contents of 2-AG, CB1R, BDNF, and Bcl-2, and promoted neurogenesis in the hippocampus, improving depressive-like behavior induced by CUS. CB1R antagonist (AM251) counteracts the biological function of the above mentioned rTMS<sup>[43,44]</sup>. rTMS at 5 Hz/1.26 T improved depressive-like behavior induced by CUS in rats *via* increasing the expression of CB1R, DAGL $\alpha$ , N-acyl phosphatidyl ethanolamine-phospholipase D, PSD95, and synaptophysin, and decreasing the expression of MAGL and fatty acid amide hydrolase in the hippocampus. The anti-depressant effect of rTMS was offset by short hairpin RNA targeting DAGL or CB1R<sup>[45]</sup>. The above preclinical studies suggested that rTMS plays an anti-depressant role by activating the ECS, which may provide evidence for the development of new anti-depressants targeting ECS.

Moreover, several preclinical studies have observed that rTMS increased the content of BDNF in the hippocampus and PFC, and promoted hippocampal neurogenesis in rodent CUMS, CUS, and olfactory bulbectomy depression models<sup>[44,46-49]</sup>. However, there are inconsistencies between the results of preclinical and clinical studies. BDNF

may be involved in hippocampal neurogenesis and synaptic plasticity as a neurotrophic factor, but the existence of a neuro-regenerative disorder hypothesis for depression is controversial. As compared with normal controls, the serum BDNF level markedly decreased in MDD patients, and significantly negatively correlated with the severity of depressive symptoms. In addition, in TRD patients carrying a homozygous BDNF Val/Val allele, the BDNF levels increased after treatment by rTMS<sup>[50,51]</sup>. However, the results of treatment effect were controversial in TRD patients, and it can be confirmed to be a predictor of treatment response in TRD patients. We included five relevant articles and conducted a mini meta-analysis using Review Manager 5.3 software<sup>[14,52-55]</sup>. It was found that serum BDNF levels in TRD patients increased after rTMS treatment (Figure 1A). Considering the issue of high heterogeneity, we applied the leave-one-out method to analyze the results<sup>[56]</sup>, and found that after removing the study of Zhao *et al*<sup>[14]</sup>, the heterogeneity decreased from 96% to 11%, and the conclusion that rTMS treatment had no effect on serum BDNF content in TRD patients was reached, which was consistent with the study results of Brunoni *et al*<sup>[57]</sup> (Figure 1B). BDNF is a macromolecular protein that does not easily cross the blood-brain barrier, which may be responsible for the inconsistency between the results of the above preclinical and clinical studies.

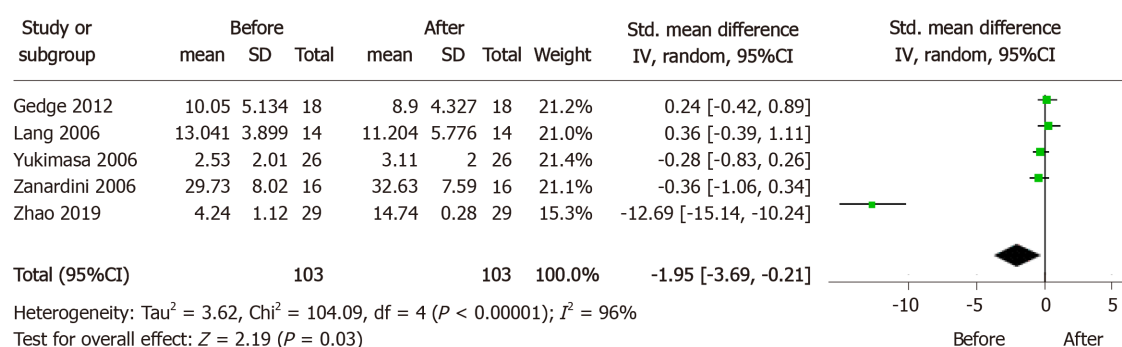
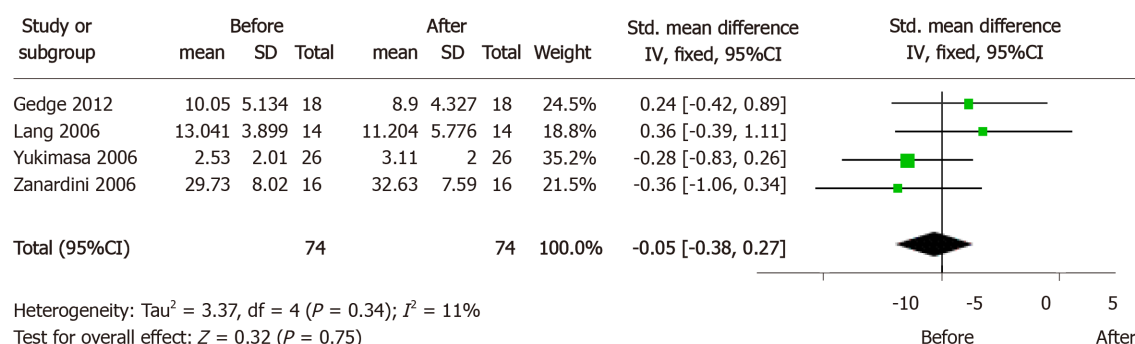
## SUPPRESSION OF SIRTUIN 1/MONOAMINE OXIDASE A SIGNALING PATHWAY

Certain monoamine oxidase (MAO) inhibitors are used to treat patients with MDD, which include phenelzine, brofaromine, toloxatone, isocarboxazide, tranylcypromine, and moclobemide. MAO includes MAO-A and MAO-B subtypes in the brain, where MAO-A is involved in the metabolism of 5-hydroxytryptamine, norepinephrine, and dopamine, and MAO-B metabolizes dopamine, benzylamine, and phenethylamine<sup>[58-60]</sup>. Moreover, MAO-A produces ROS during the process of metabolizing monoamine neurotransmitters, which promotes neuronal apoptosis<sup>[61,62]</sup>. The expression of MAO-A is regulated by the transcription factors NHLH2, KLF11, R1, and FOXO1. Among them, NHLH2 and FOXO1 need to be deacetylated by Sirtuin 1 (Sirt1) to play the role of transcription factors<sup>[63-67]</sup>. Injection of Sirt1 inhibitor EX527 into the PFC of CUS rats improved depressive-like behavior. Further, the 5-hydroxytryptamine concentration in the PFC was increased by reducing the expression of Sirt1 and MAO-A and the activity of MAO, and the depressive-like behavior in CUS rats was improved after treatment by rTMS at 5 Hz/0.84 T, 5 Hz/1.26 T, 10 Hz/0.84 T, and 10 Hz/1.26 T<sup>[68]</sup>. MAO inhibitors take several weeks to demonstrate anti-depressant efficacy<sup>[69,70]</sup>, whereas rTMS is not only effective in patients with TRD but also works faster than anti-depressants. Therefore, the Sirt1/MAO-A signaling pathway may not be a key mechanism for anti-depressant therapy in rTMS, especially for patients with TRD.

## DECREASING THE ACTIVITY OF THE HYPOTHALAMIC-PITUITARY-ADRENOCORTICAL AXIS

Hyperactivity of the HPA axis may be one of the pathophysiological mechanisms of depression<sup>[71-73]</sup>. Both preclinical and clinical studies have found increased activity of the HPA axis either in depressive-like animal models or in MDD patients. However, the results were contradictory, especially in clinical studies. There are many interfering factors for hormone levels, such as changes in circadian rhythm<sup>[74]</sup>. Drugs targeting the HPA axis have not been successful in clinical trials<sup>[70]</sup>. As a result, it has not been possible to use HPA related measurements in the diagnosis of MDD, and there may be many mechanisms that have not been clarified. rTMS at 10 Hz (intensity, 50 % of the resting motor threshold) and 15 Hz (intensity, device maximum power) reduced the levels of adrenocorticotrophic hormone and cortisol in peripheral blood of depressive-like rats induced by CUMS<sup>[46,49]</sup>. 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 current evidence is still insufficient.



**A****B**

**Figure 1** Forest plots of serum brain derived neurotrophic factor levels in treatment-resistant depression patients before and after repetitive transcranial magnetic stimulation treatment.

## FUTURE PERSPECTIVES

This review summarizes several newly discovered anti-depressant mechanisms of rTMS in preclinical studies, including: (1) Anti-inflammatory effects mediated by activation of the Nrf2 signaling pathway; (2) Anti-oxidative stress effects; (3) Enhancement of synaptic plasticity and neurogenesis *via* activation of the ECS and BDNF signaling pathway; (4) Increasing the content of monoamine neurotransmitters *via* inhibition of the Sirt1/MAO-A signaling pathway; and (5) reducing the activity of the HPA axis.

Preclinical research has an incomparable huge advantage in obtaining brain specimens compared to clinical research. In the future preclinical research on rTMS mechanism, the following issues can be appropriately considered:

(1) The efficacy of rTMS is closely related to parameters, treatment time, and experimental protocol<sup>[75,76]</sup>, and there is no unified treatment protocol in preclinical studies although it is available in clinical practice;

(2) Epidemiological studies show that the morbidity of females is higher than that of males for MDD<sup>[70,77]</sup>. However, all the studies in Table 1 used male rodents, which may be inappropriate or incomplete to elucidate the anti-depressant mechanisms of rTMS in animals;

(3) Different intensity of 10 Hz rTMS affects the metabolic patterns in the brain and periphery of the depression models<sup>[48,78]</sup>. rTMS at 1.4 T reduced the level of  $\gamma$ -amino butyric acid in the hippocampus and PFC regions of CUMS rats<sup>[78]</sup>. rTMS at 1 T increased the content of  $\alpha$ -amino butyric acid and reduced the content of 3-methylhistidine in peripheral blood of mice suffering from olfactory bulbectomy<sup>[48]</sup>. Recently, proteomics and metabolomics techniques are gradually used to explore the anti-depressant mechanism of rTMS to focus on screening candidate biomolecule or biomarkers, which may provide a clue for further elucidating the relevant mechanisms;

(4) Preclinical studies have mostly focused on the hippocampus in animal models of depressive-like behavior. However, an increasing amount of evidence indicates that, other core brain regions are also closely associated with the development and progression of depression, such as the PFC, amygdala, cingulate gyrus, habenula, and

visual cortex<sup>[79-81]</sup>, which should be considered in future studies. In addition, deep brain stimulation plays an important anti-depressant role in patients with MDD<sup>[82-85]</sup>, suggesting that neural circuit dysfunction may be one of the mechanisms of depression<sup>[86]</sup>; however, there is no animal research to probe the regulation of neural circuits related to the anti-depressant effect of rTMS, which may be one of the future research directions;

(5) The shortcomings of TMS include inaccurate positioning and shallow depth of stimulation, which cause the difficulty to elucidate the neural circuit mechanism of up- and down-stream of the stimulation target region in animal models.

The left and right dorsolateral PFC of MDD patients have asymmetric low and high activity, respectively<sup>[87]</sup>. In clinical practice, high and/or low frequency rTMS are commonly used to stimulate the left and/or right side, respectively, to obtain anti-depressant effects. However, in preclinical studies, as shown in Table 1, due to the relatively large diameter of the coils of the rTMS device, it is not possible to accurately stimulate a specific brain region in rodents, and instead a large range of a hemisphere or even the whole brain is stimulated. This may be detrimental to the elucidation of the potential anti-depressant mechanism of rTMS. The development of rTMS devices for rats and mice with appropriate size and precise focus may be more conducive to exploring the mechanism of the anti-depressant effect of rTMS.

Another unavoidable defect of TMS is the problem of depth of stimulation, that is, TMS can only stimulate the superficial cerebral cortex, but has no stimulation effect on the subcortical brain regions<sup>[88]</sup>. Deep TMS can stimulate relatively deep brain regions compared to other TMS, but it may cause the superficial regions to be strongly stimulated<sup>[89]</sup>. In addition, TMS has energy consumption in non-target tissues such as the scalp, skull, and cerebrospinal fluid, which can reduce the energy occupancy rate of target tissues.

The application of a smaller size rTMS coil can achieve precise positioning, but the efficacy of the stimulation is insufficient and the therapeutic effect is affected. Excitingly, enhancing the therapeutic effect by using magnetic nanoparticles may be in a creative way. Kong *et al*<sup>[90]</sup> found that magnetic nanoparticles could pass through the blood-brain barrier in mice. Furthermore, Li *et al*<sup>[91]</sup> intravenously injected magnetic nanoparticles with a core of Fe<sub>3</sub>O<sub>4</sub> in rats, which can enhance the therapeutic effect of TMS. Our research team constructed a novel superparamagnetic Fe<sub>2</sub>O<sub>3</sub> nanoparticle, accurately injected it into the left prelimbic cortex of CUMS mice treated by rTMS at 10 Hz/0.1 T for 5 d, and significantly improving the depressive symptoms of these mice<sup>[92]</sup>.

## CONCLUSION

In conclusion, fully elucidating the anti-depressant mechanisms of rTMS will increase the chances of discovering new therapeutic strategies.

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