

# World Journal of *Psychiatry*

*World J Psychiatr* 2020 October 19; 10(10): 223-244



**REVIEW**

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

*Luan D, Zhao MG, Shi YC, Li L, Cao YJ, Feng HX, Zhang ZJ*

**ORIGINAL ARTICLE**

**Observational Study**

- 234 Development of a depression in Parkinson's disease prediction model using machine learning

*Byeon H*

**ABOUT COVER**

Associate editor of *World Journal of Psychiatry*, Dr. Giuseppe Lanza is Senior Academic Researcher and Assistant Professor at the University of Catania (Italy). After graduation with honors in Medicine, he trained in the School of Neurology and was awarded the international PhD from the same University. From 2013 to 2018, he worked as Consultant Neurologist at the Oasi Research Institute-IRCCS in Troina (Italy), a World Health Organization (WHO) collaborating center. He has co-authored more than 130 publications in peer-reviewed journals and conferences and reviewed for several international journals. More recently, he obtained a Master of Science in Clinical Research and the National Scientific Qualification as Full Professor. His ongoing research interests involve the translational neurosciences, particularly the application of non-invasive brain stimulation techniques in the diagnosis and treatment of neurological and neuropsychiatric disorders. (L-Editor: Filipodia)

**AIMS AND SCOPE**

The primary aim of *World Journal of Psychiatry* (*WJP*, *World J Psychiatr*) is to provide scholars and readers from various fields of psychiatry with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

*WJP* mainly publishes articles reporting research results and findings obtained in the field of psychiatry and covering a wide range of topics including adolescent psychiatry, biological psychiatry, child psychiatry, community psychiatry, ethnopsychology, psychoanalysis, psychosomatic medicine, etc.

**INDEXING/ABSTRACTING**

The *WJP* is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Current Contents/Clinical Medicine, Journal Citation Reports/Science Edition, PubMed, and PubMed Central. The 2020 edition of Journal Citation Reports® cites the 2019 impact factor (IF) for *WJP* as 3.545; IF without journal self cites: 3.545; Ranking: 46 among 155 journals in psychiatry; and Quartile category: Q2.

**RESPONSIBLE EDITORS FOR THIS ISSUE**

Production Editor: Jia-Hui Li; Production Department Director: Yun-Xiaojuan Wu; Editorial Office Director: Jia-Ping Yan.

**NAME OF JOURNAL**

*World Journal of Psychiatry*

**ISSN**

ISSN 2220-3206 (online)

**LAUNCH DATE**

December 31, 2011

**FREQUENCY**

Monthly

**EDITORS-IN-CHIEF**

Rajesh R Tampi

**EDITORIAL BOARD MEMBERS**

<https://www.wjgnet.com/2220-3206/editorialboard.htm>

**PUBLICATION DATE**

October 19, 2020

**COPYRIGHT**

© 2020 Baishideng Publishing Group Inc

**INSTRUCTIONS TO AUTHORS**

<https://www.wjgnet.com/bpg/gerinfo/204>

**GUIDELINES FOR ETHICS DOCUMENTS**

<https://www.wjgnet.com/bpg/GerInfo/287>

**GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH**

<https://www.wjgnet.com/bpg/gerinfo/240>

**PUBLICATION ETHICS**

<https://www.wjgnet.com/bpg/GerInfo/288>

**PUBLICATION MISCONDUCT**

<https://www.wjgnet.com/bpg/gerinfo/208>

**ARTICLE PROCESSING CHARGE**

<https://www.wjgnet.com/bpg/gerinfo/242>

**STEPS FOR SUBMITTING MANUSCRIPTS**

<https://www.wjgnet.com/bpg/GerInfo/239>

**ONLINE SUBMISSION**

<https://www.f6publishing.com>

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

Di Luan, Ming-Ge Zhao, Ya-Chen Shi, Ling Li, Yu-Jia Cao, Hai-Xia Feng, Zhi-Jun Zhang

**ORCID number:** Di Luan 0000-0002-8832-7555; Ming-Ge Zhao 0000-0001-7885-5250; Ya-Chen Shi 0000-0003-2241-9227; Ling Li 0000-0003-2073-2105; Yu-Jia Cao 0000-0003-0837-9214; Hai-Xia Feng 0000-0002-1718-0971; Zhi-Jun Zhang 0000-0001-5480-0888.

**Author contributions:** Luan D and Zhang ZJ developed the framework of the paper; Luan D wrote the first draft; all authors worked in subsequent drafts, confirmed the last version before submission, and approved the final manuscript.

**Supported by** the National Key R and D Program of China, No. 2016YFC1306700; The Key Projects of National Natural Science Foundation of China, No. 81830040; Science and Technology Program of Guangdong, China, No. 2018B030334001; and Program of Excellent Talents in Medical Science of Jiangsu Province, China, No. JCRCA2016006.

**Conflict-of-interest statement:** The authors deny any conflict of interest.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative

**Di Luan, Ya-Chen Shi, Ling Li, Yu-Jia Cao, Zhi-Jun Zhang,** Department of Neurology, Affiliated Zhongda Hospital, Research Institution of Neuropsychiatry, School of Medicine, Southeast University, Nanjing 210009, Jiangsu Province, China

**Ming-Ge Zhao, Hai-Xia Feng,** Department of Nursing, School of Medicine, Southeast University, Nanjing 210009, Jiangsu Province, China

**Zhi-Jun Zhang,** Department of Psychology, Xinxiang Medical University, Xinxiang 453003, Henan Province, China

**Zhi-Jun Zhang,** Mental Health Center, Zhejiang University School of Medicine, Hangzhou 310013, Zhejiang province, China

**Corresponding author:** Zhi-Jun Zhang, MD, PhD, Doctor, Full Professor, Department of Neurology, Affiliated Zhongda Hospital, Research Institution of Neuropsychiatry, School of Medicine, Southeast University, No. 87 Dingjiaqiao, Nanjing 210009, Jiangsu Province, China. [janemengzhang@vip.163.com](mailto:janemengzhang@vip.163.com)

### 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

©The Author(s) 2020. Published by Baishideng Publishing Group Inc. All rights reserved.

Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

**Manuscript source:** Unsolicited manuscript

**Received:** June 16, 2020

**Peer-review started:** June 16, 2020

**First decision:** July 30, 2020

**Revised:** August 11, 2020

**Accepted:** September 2, 2020

**Article in press:** September 2, 2020

**Published online:** October 19, 2020

**P-Reviewer:** Kotzalidis GD

**S-Editor:** Zhang L

**L-Editor:** Wang TQ

**P-Editor:** Li JH



**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.

**Citation:** Luan D, Zhao MG, Shi YC, Li L, Cao YJ, Feng HX, Zhang ZJ. Mechanisms of repetitive transcranial magnetic stimulation for anti-depression: Evidence from preclinical studies. *World J Psychiatr* 2020; 10(10): 223-233

**URL:** <https://www.wjgnet.com/2220-3206/full/v10/i10/223.htm>

**DOI:** <https://dx.doi.org/10.5498/wjp.v10.i10.223>

## 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>[4]</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.

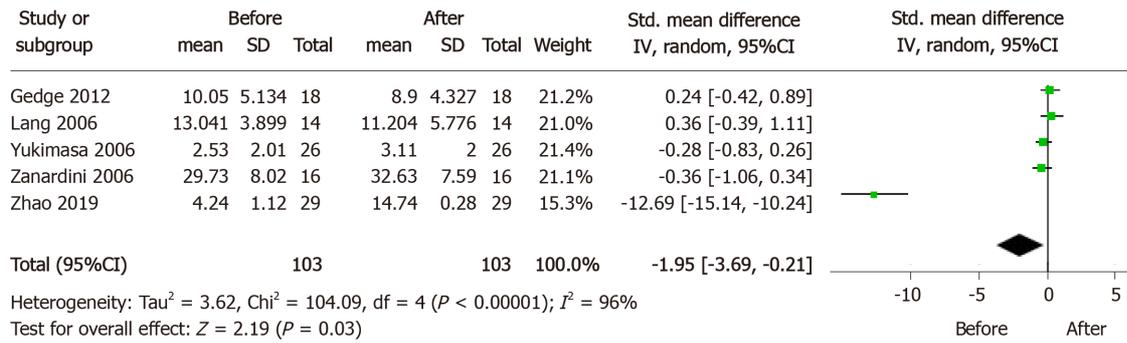
## SUPPRESSION OF SIRTUIN 1/MONOAMINE OXIDASE A SIGNALING PATHWAY

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.

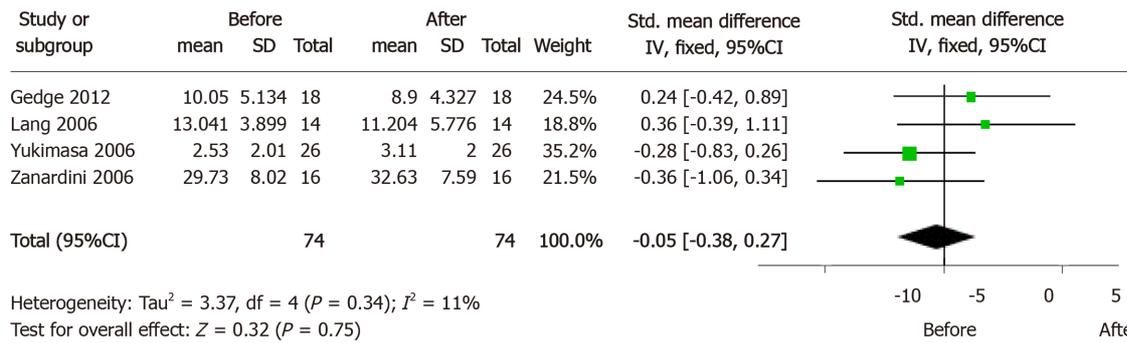
## DECREASING THE ACTIVITY OF THE HYPOTHALAMIC-PITUITARY-ADRENOCORTICAL AXIS

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.

## REFERENCES

- 1 **Trapp NT**, Xiong W, Conway CR. Neurostimulation Therapies. *Handb Exp Pharmacol* 2019; **250**: 181-224 [PMID: 30294765 DOI: 10.1007/164\_2018\_157]
- 2 **Iglesias AH**. Transcranial Magnetic Stimulation as Treatment in Multiple Neurologic Conditions. *Curr Neurol Neurosci Rep* 2020; **20**: 1 [PMID: 32020300 DOI: 10.1007/s11910-020-1021-0]
- 3 **Lefaucheur JP**, Aleman A, Baeken C, Benninger DH, Brunelin J, Di Lazzaro V, Filipović SR, Grefkes C, Hasan A, Hummel FC, Jääskeläinen SK, Langguth B, Leocani L, Londero A, Nardone R, Nguyen JP, Nyffeler T, Oliveira-Maia AJ, Oliviero A, Padberg F, Palm U, Paulus W, Poulet E, Quartarone A, Rachid F, Rektorová I, Rossi S, Sahlsten H, Schecklmann M, Szekeley D, Ziemann U. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS): An update (2014-2018). *Clin Neurophysiol* 2020; **131**: 474-528 [PMID: 31901449 DOI: 10.1016/j.clinph.2019.11.002]
- 4 **Somani A**, Kar SK. Efficacy of repetitive transcranial magnetic stimulation in treatment-resistant depression: the evidence thus far. *Gen Psychiatr* 2019; **32**: e100074 [PMID: 31552384 DOI: 10.1136/gpsych-2019-100074]
- 5 **Trevizol AP**, Blumberger DM. An Update on Repetitive Transcranial Magnetic Stimulation for the Treatment of Major Depressive Disorder. *Clin Pharmacol Ther* 2019; **106**: 747-762 [PMID: 31206624 DOI: 10.1002/cpt.1550]
- 6 **Rizvi S**, Khan AM. Use of Transcranial Magnetic Stimulation for Depression. *Cureus* 2019; **11**: e4736 [PMID: 31355095 DOI: 10.7759/cureus.4736]
- 7 **Roman M**, Irwin MR. Novel neuroimmunologic therapeutics in depression: A clinical perspective on what we know so far. *Brain Behav Immun* 2020; **83**: 7-21 [PMID: 31550500 DOI: 10.1016/j.bbi.2019.09.016]
- 8 **Su WJ**, Cao ZY, Jiang CL. Blocking the trigger: An integrative view on the anti-inflammatory therapy of

- depression. *Brain Behav Immun* 2019; **82**: 10-12 [PMID: 31493446 DOI: 10.1016/j.bbi.2019.09.002]
- 9 **Lee CH**, Giuliani F. The Role of Inflammation in Depression and Fatigue. *Front Immunol* 2019; **10**: 1696 [PMID: 31379879 DOI: 10.3389/fimmu.2019.01696]
  - 10 **Maydych V**. The Interplay Between Stress, Inflammation, and Emotional Attention: Relevance for Depression. *Front Neurosci* 2019; **13**: 384 [PMID: 31068783 DOI: 10.3389/fnins.2019.00384]
  - 11 **Benros ME**, Waltoft BL, Nordentoft M, Ostergaard SD, Eaton WW, Krogh J, Mortensen PB. Autoimmune diseases and severe infections as risk factors for mood disorders: a nationwide study. *JAMA Psychiatry* 2013; **70**: 812-820 [PMID: 23760347 DOI: 10.1001/jamapsychiatry.2013.1111]
  - 12 **Robinson RG**, Jorge RE. Post-Stroke Depression: A Review. *Am J Psychiatry* 2016; **173**: 221-231 [PMID: 26684921 DOI: 10.1176/appi.ajp.2015.15030363]
  - 13 **Langguth B**, Braun S, Aigner JM, Landgrebe M, Weinerth J, Hajak G, Eichhammer P. Repetitive transcranial magnetic stimulation in a patient suffering from depression and rheumatoid arthritis: evidence for immunomodulatory effects. *Neuro Endocrinol Lett* 2005; **26**: 314-316 [PMID: 16136019]
  - 14 **Zhao X**, Li Y, Tian Q, Zhu B, Zhao Z. Repetitive transcranial magnetic stimulation increases serum brain-derived neurotrophic factor and decreases interleukin-1 $\beta$  and tumor necrosis factor- $\alpha$  in elderly patients with refractory depression. *J Int Med Res* 2019; **47**: 1848-1855 [PMID: 30616482 DOI: 10.1177/0300060518817417]
  - 15 **Okada K**, Matsunaga K, Yuhi T, Kuroda E, Yamashita U, Tsuji S. The long-term high-frequency repetitive transcranial magnetic stimulation does not induce mRNA expression of inflammatory mediators in the rat central nervous system. *Brain Res* 2002; **957**: 37-41 [PMID: 12443977 DOI: 10.1016/s0006-8993(02)03582-5]
  - 16 **Hashimoto K**. Essential Role of Keap1-Nrf2 Signaling in Mood Disorders: Overview and Future Perspective. *Front Pharmacol* 2018; **9**: 1182 [PMID: 30386243 DOI: 10.3389/fphar.2018.01182]
  - 17 **Kensler TW**, Wakabayashi N, Biswal S. Cell survival responses to environmental stresses via the Keap1-Nrf2-ARE pathway. *Annu Rev Pharmacol Toxicol* 2007; **47**: 89-116 [PMID: 16968214 DOI: 10.1146/annurev.pharmtox.46.120604.141046]
  - 18 **Yao W**, Zhang JC, Ishima T, Dong C, Yang C, Ren Q, Ma M, Han M, Wu J, Sukanuma H, Ushida Y, Yamamoto M, Hashimoto K. Role of Keap1-Nrf2 signaling in depression and dietary intake of glucoraphanin confers stress resilience in mice. *Sci Rep* 2016; **6**: 30659 [PMID: 27470577 DOI: 10.1038/srep30659]
  - 19 **Zhang JC**, Yao W, Dong C, Han M, Shirayama Y, Hashimoto K. Keap1-Nrf2 signaling pathway confers resilience versus susceptibility to inescapable electric stress. *Eur Arch Psychiatry Clin Neurosci* 2018; **268**: 865-870 [PMID: 29119264 DOI: 10.1007/s00406-017-0848-0]
  - 20 **Martín-Hernández D**, Caso JR, Javier Meana J, Callado LF, Madrigal JLM, García-Bueno B, Leza JC. Intracellular inflammatory and antioxidant pathways in postmortem frontal cortex of subjects with major depression: effect of antidepressants. *J Neuroinflammation* 2018; **15**: 251 [PMID: 30180869 DOI: 10.1186/s12974-018-1294-2]
  - 21 **Tian L**, Sun SS, Cui LB, Wang SQ, Peng ZW, Tan QR, Hou WG, Cai M. Repetitive Transcranial Magnetic Stimulation Elicits Antidepressant- and Anxiolytic-like Effect via Nuclear Factor-E2-related Factor 2-mediated Anti-inflammation Mechanism in Rats. *Neuroscience* 2020; **429**: 119-133 [PMID: 31918011 DOI: 10.1016/j.neuroscience.2019.12.025]
  - 22 **Black CN**, Bot M, Scheffer PG, Cuijpers P, Penninx BW. Is depression associated with increased oxidative stress? *Psychoneuroendocrinology* 2015; **51**: 164-175 [PMID: 25462890 DOI: 10.1016/j.psyneuen.2014.09.025]
  - 23 **Liu T**, Zhong S, Liao X, Chen J, He T, Lai S, Jia Y. A Meta-Analysis of Oxidative Stress Markers in Depression. *PLoS One* 2015; **10**: e0138904 [PMID: 26445247 DOI: 10.1371/journal.pone.0138904]
  - 24 **Mazereeuw G**, Herrmann N, Andreazza AC, Khan MM, Lanctôt KL. A meta-analysis of lipid peroxidation markers in major depression. *Neuropsychiatr Dis Treat* 2015; **11**: 2479-2491 [PMID: 26491326 DOI: 10.2147/NDT.S89922]
  - 25 **Palta P**, Samuel LJ, Miller ER 3rd, Szanton SL. Depression and oxidative stress: results from a meta-analysis of observational studies. *Psychosom Med* 2014; **76**: 12-19 [PMID: 24336428 DOI: 10.1097/PSY.000000000000009]
  - 26 **Durmaz O**, İspir E, Baykan H, Alişik M, Erel Ö. The Impact of Repetitive Transcranial Magnetic Stimulation on Oxidative Stress in Subjects With Medication-Resistant Depression. *J ECT* 2018; **34**: 127-131 [PMID: 29166316 DOI: 10.1097/YCT.0000000000000467]
  - 27 **Aydın EP**, Genç A, Dalkıran M, Uyar ET, Deniz İ, Özer ÖA, Karamustafalıoğlu KO. Thioredoxin is not a marker for treatment-resistance depression but associated with cognitive function: An rTMS study. *Prog Neuropsychopharmacol Biol Psychiatry* 2018; **80**: 322-328 [PMID: 28442424 DOI: 10.1016/j.pnpbp.2017.04.025]
  - 28 **Medina-Fernández FJ**, Escribano BM, Padilla-Del-Campo C, Drucker-Colín R, Pascual-Leone Á, Túnez I. Transcranial magnetic stimulation as an antioxidant. *Free Radic Res* 2018; **52**: 381-389 [PMID: 29385851 DOI: 10.1080/10715762.2018.1434313]
  - 29 **Tasset I**, Drucker-Colín R, Peña J, Jimena I, Montilla P, Medina FJ, Túnez I. Antioxidant-like effects and protective action of transcranial magnetic stimulation in depression caused by olfactory bulbectomy. *Neurochem Res* 2010; **35**: 1182-1187 [PMID: 20428940 DOI: 10.1007/s11064-010-0172-9]
  - 30 **Chadwick VL**, Rohleder C, Koethe D, Leweke FM. Cannabinoids and the endocannabinoid system in anxiety, depression, and dysregulation of emotion in humans. *Curr Opin Psychiatry* 2020; **33**: 20-42 [PMID: 31714262 DOI: 10.1097/YCO.0000000000000562]
  - 31 **Mechoulam R**, Parker LA. The endocannabinoid system and the brain. *Annu Rev Psychol* 2013; **64**: 21-47 [PMID: 22804774 DOI: 10.1146/annurev-psych-113011-143739]
  - 32 **Augustin SM**, Lovinger DM. Functional Relevance of Endocannabinoid-Dependent Synaptic Plasticity in the Central Nervous System. *ACS Chem Neurosci* 2018; **9**: 2146-2161 [PMID: 29400439 DOI: 10.1021/acchemneuro.7b00508]
  - 33 **Huang WJ**, Chen WW, Zhang X. Endocannabinoid system: Role in depression, reward and pain control

- (Review). *Mol Med Rep* 2016; **14**: 2899-2903 [PMID: 27484193 DOI: 10.3892/mmr.2016.5585]
- 34 **Poleszak E**, Wośko S, Sławińska K, Szopa A, Wróbel A, Serefko A. Cannabinoids in depressive disorders. *Life Sci* 2018; **213**: 18-24 [PMID: 30290188 DOI: 10.1016/j.lfs.2018.09.058]
- 35 **Zhou D**, Li Y, Tian T, Quan W, Wang L, Shao Q, Fu LQ, Zhang XH, Wang XY, Zhang H, Ma YM. Role of the endocannabinoid system in the formation and development of depression. *Pharmazie* 2017; **72**: 435-439 [PMID: 29441900 DOI: 10.1691/ph.2017.7474]
- 36 **Estrada JA**, Contreras I. Endocannabinoid receptors in the CNS: potential drug targets for the prevention and treatment of neurologic and psychiatric disorders. *Curr Neuroparmacol* 2020 [PMID: 32065105 DOI: 10.2174/1570159X18666200217140255]
- 37 **Björkholm C**, Monteggia LM. BDNF - a key transducer of antidepressant effects. *Neuropharmacology* 2016; **102**: 72-79 [PMID: 26519901 DOI: 10.1016/j.neuropharm.2015.10.034]
- 38 **Caviedes A**, Lafourcade C, Soto C, Wynken U. BDNF/NF- $\kappa$ B Signaling in the Neurobiology of Depression. *Curr Pharm Des* 2017; **23**: 3154-3163 [PMID: 28078988 DOI: 10.2174/1381612823666170111141915]
- 39 **Hing B**, Sathyaputri L, Potash JB. A comprehensive review of genetic and epigenetic mechanisms that regulate BDNF expression and function with relevance to major depressive disorder. *Am J Med Genet B Neuropsychiatr Genet* 2018; **177**: 143-167 [PMID: 29243873 DOI: 10.1002/ajmg.b.32616]
- 40 **Kowiński P**, Lietzau G, Czuba E, Waśkow M, Steliga A, Moryś J. BDNF: A Key Factor with Multipotent Impact on Brain Signaling and Synaptic Plasticity. *Cell Mol Neurobiol* 2018; **38**: 579-593 [PMID: 28623429 DOI: 10.1007/s10571-017-0510-4]
- 41 **Leal G**, Bramham CR, Duarte CB. BDNF and Hippocampal Synaptic Plasticity. *Vitam Horm* 2017; **104**: 153-195 [PMID: 28215294 DOI: 10.1016/bs.vh.2016.10.004]
- 42 **Yang J**, Wang L, Wang F, Tang X, Zhou P, Liang R, Zheng C, Ming D. Low-Frequency Pulsed Magnetic Field Improves Depression-Like Behaviors and Cognitive Impairments in Depressive Rats Mainly via Modulating Synaptic Function. *Front Neurosci* 2019; **13**: 820 [PMID: 31481866 DOI: 10.3389/fnins.2019.00820]
- 43 **Fang G**, Wang Y. Effects of rTMS on Hippocampal Endocannabinoids and Depressive-like Behaviors in Adolescent Rats. *Neurochem Res* 2018; **43**: 1756-1765 [PMID: 29987693 DOI: 10.1007/s11064-018-2591-y]
- 44 **Wang HN**, Wang L, Zhang RG, Chen YC, Liu L, Gao F, Nie H, Hou WG, Peng ZW, Tan Q. Anti-depressive mechanism of repetitive transcranial magnetic stimulation in rat: the role of the endocannabinoid system. *J Psychiatr Res* 2014; **51**: 79-87 [PMID: 24479995 DOI: 10.1016/j.jpsychires.2014.01.004]
- 45 **Xue SS**, Xue F, Ma QR, Wang SQ, Wang Y, Tan QR, Wang HN, Zhou CH, Peng ZW. Repetitive high-frequency transcranial magnetic stimulation reverses depressive-like behaviors and protein expression at hippocampal synapses in chronic unpredictable stress-treated rats by enhancing endocannabinoid signaling. *Pharmacol Biochem Behav* 2019; **184**: 172738 [PMID: 31229467 DOI: 10.1016/j.pbb.2019.172738]
- 46 **Feng SF**, Shi TY, Fan-Yang, Wang WN, Chen YC, Tan QR. Long-lasting effects of chronic rTMS to treat chronic rodent model of depression. *Behav Brain Res* 2012; **232**: 245-251 [PMID: 22537774 DOI: 10.1016/j.bbr.2012.04.019]
- 47 **Chen YH**, Zhang RG, Xue F, Wang HN, Chen YC, Hu GT, Peng Y, Peng ZW, Tan QR. Quetiapine and repetitive transcranial magnetic stimulation ameliorate depression-like behaviors and up-regulate the proliferation of hippocampal-derived neural stem cells in a rat model of depression: The involvement of the BDNF/ERK signal pathway. *Pharmacol Biochem Behav* 2015; **136**: 39-46 [PMID: 26176197 DOI: 10.1016/j.pbb.2015.07.005]
- 48 **Heath A**, Lindberg DR, Makowiecki K, Gray A, Asp AJ, Rodger J, Choi DS, Croarkin PE. Medium- and high-intensity rTMS reduces psychomotor agitation with distinct neurobiologic mechanisms. *Transl Psychiatry* 2018; **8**: 126 [PMID: 29976924 DOI: 10.1038/s41398-018-0129-3]
- 49 **Zhao L**, Ren H, Gu S, Li X, Jiang C, Li J, Zhang M, Mu J, Li W, Wang W, Zhang Z, Song J. rTMS ameliorated depressive-like behaviors by restoring HPA axis balance and prohibiting hippocampal neuron apoptosis in a rat model of depression. *Psychiatry Res* 2018; **269**: 126-133 [PMID: 30145293 DOI: 10.1016/j.psychres.2018.08.017]
- 50 **Beuzon G**, Timour Q, Saoud M. Predictors of response to repetitive transcranial magnetic stimulation (rTMS) in the treatment of major depressive disorder. *Encephale* 2017; **43**: 3-9 [PMID: 28034451 DOI: 10.1016/j.encep.2016.11.002]
- 51 **Silverstein WK**, Noda Y, Barr MS, Vila-Rodriguez F, Rajji TK, Fitzgerald PB, Downar J, Mulsant BH, Vigod S, Daskalakis ZJ, Blumberger DM. NEUROBIOLOGICAL PREDICTORS OF RESPONSE TO DORSOLATERAL PREFRONTAL CORTEX REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION IN DEPRESSION: A SYSTEMATIC REVIEW. *Depress Anxiety* 2015; **32**: 871-891 [PMID: 26382227 DOI: 10.1002/da.22424]
- 52 **Gedge L**, Beaudoin A, Lazowski L, du Toit R, Jokic R, Milev R. Effects of electroconvulsive therapy and repetitive transcranial magnetic stimulation on serum brain-derived neurotrophic factor levels in patients with depression. *Front Psychiatry* 2012; **3**: 12 [PMID: 22375129 DOI: 10.3389/fpsy.2012.00012]
- 53 **Lang UE**, Bajbouj M, Gallinat J, Hellweg R. Brain-derived neurotrophic factor serum concentrations in depressive patients during vagus nerve stimulation and repetitive transcranial magnetic stimulation. *Psychopharmacology (Berl)* 2006; **187**: 56-59 [PMID: 16767416 DOI: 10.1007/s00213-006-0399-y]
- 54 **Yukimasa T**, Yoshimura R, Tamagawa A, Uozumi T, Shinkai K, Ueda N, Tsuji S, Nakamura J. High-frequency repetitive transcranial magnetic stimulation improves refractory depression by influencing catecholamine and brain-derived neurotrophic factors. *Pharmacopsychiatry* 2006; **39**: 52-59 [PMID: 16555165 DOI: 10.1055/s-2006-931542]
- 55 **Zanardini R**, Gazzoli A, Ventriglia M, Perez J, Bignotti S, Rossini PM, Gennarelli M, Bocchio-Chiavetto L. Effect of repetitive transcranial magnetic stimulation on serum brain derived neurotrophic factor in drug resistant depressed patients. *J Affect Disord* 2006; **91**: 83-86 [PMID: 16448701 DOI: 10.1016/j.jad.2005.12.029]
- 56 **Luan D**, Zhang Y, Yang Q, Zhou Z, Huang X, Zhao S, Yuan L. Efficacy and Safety of Intravenous Thrombolysis in Patients with Unknown Onset Stroke: A Meta-Analysis. *Behav Neurol* 2019; **2019**: 5406923

- [PMID: 31565095 DOI: 10.1155/2019/5406923]
- 57 **Brunoni AR**, Baeken C, Machado-Vieira R, Gattaz WF, Vanderhasselt MA. BDNF blood levels after non-invasive brain stimulation interventions in major depressive disorder: a systematic review and meta-analysis. *World J Biol Psychiatry* 2015; **16**: 114-122 [PMID: 25264290 DOI: 10.3109/15622975.2014.958101]
  - 58 **Higuchi Y**, Soga T, Parhar IS. Regulatory Pathways of Monoamine Oxidase A during Social Stress. *Front Neurosci* 2017; **11**: 604 [PMID: 29163009 DOI: 10.3389/fnins.2017.00604]
  - 59 **Higuchi Y**, Soga T, Parhar IS. Potential Roles of microRNAs in the Regulation of Monoamine Oxidase A in the Brain. *Front Mol Neurosci* 2018; **11**: 339 [PMID: 30271325 DOI: 10.3389/fnmol.2018.00339]
  - 60 **Naoi M**, Riederer P, Maruyama W. Modulation of monoamine oxidase (MAO) expression in neuropsychiatric disorders: genetic and environmental factors involved in type A MAO expression. *J Neural Transm (Vienna)* 2016; **123**: 91-106 [PMID: 25604428 DOI: 10.1007/s00702-014-1362-4]
  - 61 **Ou XM**, Stockmeier CA, Meltzer HY, Overholser JC, Jurjus GJ, Dieter L, Chen K, Lu D, Johnson C, Youdim MB, Austin MC, Luo J, Sawa A, May W, Shih JC. A novel role for glyceraldehyde-3-phosphate dehydrogenase and monoamine oxidase B cascade in ethanol-induced cellular damage. *Biol Psychiatry* 2010; **67**: 855-863 [PMID: 20022592 DOI: 10.1016/j.biopsych.2009.10.032]
  - 62 **Youdim MB**, Bakhle YS. Monoamine oxidase: isoforms and inhibitors in Parkinson's disease and depressive illness. *Br J Pharmacol* 2006; **147** Suppl 1: S287-S296 [PMID: 16402116 DOI: 10.1038/sj.bjp.0706464]
  - 63 **Grunewald M**, Johnson S, Lu D, Wang Z, Lomber G, Albert PR, Stockmeier CA, Meyer JH, Urrutia R, Miczek KA, Austin MC, Wang J, Paul IA, Woolverton WL, Seo S, Sittman DB, Ou XM. Mechanistic role for a novel glucocorticoid-KLF11 (TIEG2) protein pathway in stress-induced monoamine oxidase A expression. *J Biol Chem* 2012; **287**: 24195-24206 [PMID: 22628545 DOI: 10.1074/jbc.M112.373936]
  - 64 **Harris S**, Johnson S, Duncan JW, Udemgba C, Meyer JH, Albert PR, Lomber G, Urrutia R, Ou XM, Stockmeier CA, Wang JM. Evidence revealing deregulation of the KLF11-MAO A pathway in association with chronic stress and depressive disorders. *Neuropsychopharmacology* 2015; **40**: 1373-1382 [PMID: 25502632 DOI: 10.1038/npp.2014.321]
  - 65 **Johnson S**, Stockmeier CA, Meyer JH, Austin MC, Albert PR, Wang J, May WL, Rajkowska G, Overholser JC, Jurjus G, Dieter L, Johnson C, Sittman DB, Ou XM. The reduction of R1, a novel repressor protein for monoamine oxidase A, in major depressive disorder. *Neuropsychopharmacology* 2011; **36**: 2139-2148 [PMID: 21654740 DOI: 10.1038/npp.2011.105]
  - 66 **Libert S**, Pointer K, Bell EL, Das A, Cohen DE, Asara JM, Kapur K, Bergmann S, Preisig M, Otowa T, Kendler KS, Chen X, Hetta JM, van den Oord EJ, Rubio JP, Guarente L. SIRT1 activates MAO-A in the brain to mediate anxiety and exploratory drive. *Cell* 2011; **147**: 1459-1472 [PMID: 22169038 DOI: 10.1016/j.cell.2011.10.054]
  - 67 **Wu JB**, Shih JC. Valproic acid induces monoamine oxidase A via Akt/forkhead box O1 activation. *Mol Pharmacol* 2011; **80**: 714-723 [PMID: 21775495 DOI: 10.1124/mol.111.072744]
  - 68 **Peng ZW**, Xue F, Zhou CH, Zhang RG, Wang Y, Liu L, Sang HF, Wang HN, Tan QR. Repetitive transcranial magnetic stimulation inhibits Sirt1/MAO-A signaling in the prefrontal cortex in a rat model of depression and cortex-derived astrocytes. *Mol Cell Biochem* 2018; **442**: 59-72 [PMID: 28948423 DOI: 10.1007/s11010-017-3193-8]
  - 69 **Willner P**, Scheel-Kröger J, Belzung C. The neurobiology of depression and antidepressant action. *Neurosci Biobehav Rev* 2013; **37**: 2331-2371 [PMID: 23261405 DOI: 10.1016/j.neubiorev.2012.12.007]
  - 70 **Malhi GS**, Mann JJ. Depression. *Lancet* 2018; **392**: 2299-2312 [PMID: 30396512 DOI: 10.1016/S0140-6736(18)31948-2]
  - 71 **Juruena MF**, Bocharova M, Agustini B, Young AH. Atypical depression and non-atypical depression: Is HPA axis function a biomarker? *J Affect Disord* 2018; **233**: 45-67 [PMID: 29150144 DOI: 10.1016/j.jad.2017.09.052]
  - 72 **Menke A**. Is the HPA Axis as Target for Depression Outdated, or Is There a New Hope? *Front Psychiatry* 2019; **10**: 101 [PMID: 30890970 DOI: 10.3389/fpsy.2019.00101]
  - 73 **Pariante CM**, Lightman SL. The HPA axis in major depression: classical theories and new developments. *Trends Neurosci* 2008; **31**: 464-468 [PMID: 18675469 DOI: 10.1016/j.tins.2008.06.006]
  - 74 **Liyanarachchi K**, Ross R, Debono M. Human studies on hypothalamo-pituitary-adrenal (HPA) axis. *Best Pract Res Clin Endocrinol Metab* 2017; **31**: 459-473 [PMID: 29223281 DOI: 10.1016/j.beem.2017.10.011]
  - 75 **Galletly C**, Gill S, Clarke P, Burton C, Fitzgerald PB. A randomized trial comparing repetitive transcranial magnetic stimulation given 3 days/week and 5 days/week for the treatment of major depression: is efficacy related to the duration of treatment or the number of treatments? *Psychol Med* 2012; **42**: 981-988 [PMID: 21910937 DOI: 10.1017/S0033291711001760]
  - 76 **Herrmann LL**, Ebmeier KP. Factors modifying the efficacy of transcranial magnetic stimulation in the treatment of depression: a review. *J Clin Psychiatry* 2006; **67**: 1870-1876 [PMID: 17194264 DOI: 10.4088/jcp.v67n1206]
  - 77 **Kessler RC**, Bromet EJ. The epidemiology of depression across cultures. *Annu Rev Public Health* 2013; **34**: 119-138 [PMID: 23514317 DOI: 10.1146/annurev-publhealth-031912-114409]
  - 78 **Kim SY**, Lee DW, Kim H, Bang E, Chae JH, Choe BY. Chronic repetitive transcranial magnetic stimulation enhances GABAergic and cholinergic metabolism in chronic unpredictable mild stress rat model: <sup>1</sup>H-NMR spectroscopy study at 11. *Neurosci Lett* 2014; **572**: 32-37 [PMID: 24796814 DOI: 10.1016/j.neulet.2014.04.033]
  - 79 **Koenigs M**, Grafman J. The functional neuroanatomy of depression: distinct roles for ventromedial and dorsolateral prefrontal cortex. *Behav Brain Res* 2009; **201**: 239-243 [PMID: 19428640 DOI: 10.1016/j.bbr.2009.03.004]
  - 80 **Williams LM**. Amygdala-Guided Neurofeedback for Major Depression. *Am J Psychiatry* 2017; **174**: 717-718 [PMID: 28760026 DOI: 10.1176/appi.ajp.2017.17050561]
  - 81 **Zhang Z**, Zhang H, Xie CM, Zhang M, Shi Y, Song R, Lu X, Zhang H, Li K, Wang B, Yang Y, Li X, Zhu J, Zhao Y, Yuan TF, Northoff G. Task-related functional magnetic resonance imaging-based neuronavigation for the treatment of depression by individualized repetitive transcranial magnetic stimulation of the visual

- cortex. *Sci China Life Sci* 2020 [PMID: 32542515 DOI: 10.1007/s11427-020-1730-5]
- 82 **Kisely S**, Li A, Warren N, Siskind D. A systematic review and meta-analysis of deep brain stimulation for depression. *Depress Anxiety* 2018; **35**: 468-480 [PMID: 29697875 DOI: 10.1002/da.22746]
- 83 **Dandekar MP**, Fenoy AJ, Carvalho AF, Soares JC, Quevedo J. Deep brain stimulation for treatment-resistant depression: an integrative review of preclinical and clinical findings and translational implications. *Mol Psychiatry* 2018; **23**: 1094-1112 [PMID: 29483673 DOI: 10.1038/mp.2018.2]
- 84 **Zhou C**, Zhang H, Qin Y, Tian T, Xu B, Chen J, Zhou X, Zeng L, Fang L, Qi X, Lian B, Wang H, Hu Z, Xie P. A systematic review and meta-analysis of deep brain stimulation in treatment-resistant depression. *Prog Neuropsychopharmacol Biol Psychiatry* 2018; **82**: 224-232 [PMID: 29146474 DOI: 10.1016/j.pnpbp.2017.11.012]
- 85 **Drobisz D**, Damborská A. Deep brain stimulation targets for treating depression. *Behav Brain Res* 2019; **359**: 266-273 [PMID: 30414974 DOI: 10.1016/j.bbr.2018.11.004]
- 86 **Chaudhury D**, Liu H, Han MH. Neuronal correlates of depression. *Cell Mol Life Sci* 2015; **72**: 4825-4848 [PMID: 26542802 DOI: 10.1007/s00018-015-2044-6]
- 87 **Brunoni AR**, Chaimani A, Moffa AH, Razza LB, Gattaz WF, Daskalakis ZJ, Carvalho AF. Repetitive Transcranial Magnetic Stimulation for the Acute Treatment of Major Depressive Episodes: A Systematic Review With Network Meta-analysis. *JAMA Psychiatry* 2017; **74**: 143-152 [PMID: 28030740 DOI: 10.1001/jamapsychiatry.2016.3644]
- 88 **Wagner T**, Gangitano M, Romero R, Théoret H, Kobayashi M, Ansel D, Ives J, Cuffin N, Schomer D, Pascual-Leone A. Intracranial measurement of current densities induced by transcranial magnetic stimulation in the human brain. *Neurosci Lett* 2004; **354**: 91-94 [PMID: 14698446 DOI: 10.1016/s0304-3940(03)00861-9]
- 89 **Deng ZD**, Peterchev AV, Lisanby SH. Coil design considerations for deep-brain transcranial magnetic stimulation (dTMS). *Conf Proc IEEE Eng Med Biol Soc* 2008; **2008**: 5675-5679 [PMID: 19164005 DOI: 10.1109/IEMBS.2008.4650502]
- 90 **Kong SD**, Lee J, Ramachandran S, Eliceiri BP, Shubayev VI, Lal R, Jin S. Magnetic targeting of nanoparticles across the intact blood-brain barrier. *J Control Release* 2012; **164**: 49-57 [PMID: 23063548 DOI: 10.1016/j.jconrel.2012.09.021]
- 91 **Li R**, Wang J, Yu X, Xu P, Zhang S, Xu J, Bai Y, Dai Z, Sun Y, Ye R, Liu X, Ruan G, Xu G. Enhancing the effects of transcranial magnetic stimulation with intravenously injected magnetic nanoparticles. *Biomater Sci* 2019; **7**: 2297-2307 [PMID: 31050344 DOI: 10.1039/c9bm00178f]
- 92 **Lu QB**, Sun JF, Yang QY, Cai WW, Xia MQ, Wu FF, Gu N, Zhang ZJ. Magnetic brain stimulation using iron oxide nanoparticle-mediated selective treatment of the left prefrontal cortex as a novel strategy to rapidly improve depressive-like symptoms in mice. *Zool Res* 2020; **41**: 381-394 [PMID: 32400977 DOI: 10.24272/j.issn.2095-8137.2020.076]



Published by **Baishideng Publishing Group Inc**  
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

**Telephone:** +1-925-3991568

**E-mail:** [bpgoffice@wjgnet.com](mailto:bpgoffice@wjgnet.com)

**Help Desk:** <https://www.f6publishing.com/helpdesk>

<https://www.wjgnet.com>

