

Mechanism of Repetitive Transcranial Magnetic Stimulation for Depression

Zhengwu PENG, Cuihong ZHOU, Shanshan XUE, Jie BAI, Shoufen YU, Xiaosa LI, Huaning WANG, Qingrong TAN*

Summary: Depressive disorder is one of the most common mental health problems currently. However, the mechanism-based treatments for this disorder remain elusive. Repetitive transcranial magnetic stimulation (rTMS), a non-invasive procedure that could stimulate electrical activity by a pulsed magnetic field in the brain, is considered to be an effective treatment for depression. Here, we review the main findings from both clinical and basic research on rTMS for depression, including its antidepressant efficacy, basic principles, as well as its ability to regulate neural circuits, neurotransmitters and brain networks, neurogenesis in hippocampus, and synaptic, and molecular pathways.

Key words: Repetitive Transcranial Magnetic Stimulation; Depression; Neurophysiology

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1. Introduction

Depression with an annual prevalence of 5 to 15% has become one of the most common mental diseases. Although the typical treatment strategy is to administer antidepressant medications, unfortunately, not all patients respond to the available pharmacological treatments.^[1] Therefore, neurobiological interventions that directly target brain activity, including rTMS and transcranial direct current stimulation (tDCS) (Table 1), have emerged as promising tools in the psychiatric treatment arsenal.^[2] Of these, rTMS in particular has been identified as an effective antidepressant treatment for adolescents with drug-resistant depression. The purpose of the present review is to discuss the major aspects of rTMS as a treatment for depression to foster a better understanding of its therapeutic mechanisms.

2. Basic principles of rTMS

Transcranial magnetic stimulation (TMS) is a versatile method that non-invasively modulates neural processing

in the brain by inducing a short capacitor discharge of electric current into a stimulated coil, and subsequently generates a magnetic field, which then induces neural cell membrane potentials depolarizing in cortical tissue under the coil and affect the related nerve loop activity. The context-dependent including total pulses, the stimulation frequency and intensity of the magnetic stimulation, time duration between each strings, and target regions on the cortex are related to the bio-effects of TMS. Different types and combinations of the stimulation and the target brain region could induce different biological effects, and many certain stimulus models can induce prolonged effects on neural activity and may even exist after the period of treatment itself.^[3]

rTMS is one type of TMS that can be utilized as a potential treatment strategy for psychosocial diseases and nerve rehabilitation. Research found that high-frequency (HF) stimulation (>5 Hz) induces excitatory effects, whereas low-frequency (LF) stimulation (<1 Hz) makes for inhibitory effects in the brain. The most widely accepted mechanism for the long-term neural

Department of Psychiatry, Xijing Hospital, Fourth Military Medical University, Xi'an, China

*correspondence: Professor Qingrong Tan. Mailing address: 169 West Changle RD, Xi'an, China. Postcode: 710032. E-mail address: tanqingr@fmmu.edu.cn

Table 1. Merits and demerits. of rTMS and tDCS^[2]

| | rTMS | tDCS |
|-------------------------------------|---|--|
| Technology | heavy (several kilograms), large | light (1 kg), small (less than a shoe box) |
| Cost | 20,000 to 100,000 dollars | 20,000 to 100,000 dollars |
| Sham stimulation | Stimulate at an inactive site or use a "sham" coil that does not administer stimulation but does produce the same click sound | Entirely unaware of the difference between real and sham stimulation |
| Focality of stimulation | Without direct precise measurements, stimulation is limited to an area of ~25 mm ² | Two electrodes at two sites, stimulation occurs in an area of ~2500 mm ² |
| Neurophysiologic specificity | Axonal excitability, GABA _A and GABA _B synapse excitability | Unknown |
| Stimulus intensity | Grade stimulus intensity in terms of this active biologic marker | Stimulus intensities across individuals in terms of biologic effectiveness is not possible |
| Safety | Adverse effect: seizures | Few published studies of safety |

rTMS, repetitive transcranial magnetic stimulation; tDCS, transcranial direct current stimulation; GABA, gamma-aminobutyric acid.

effects of rTMS is that rTMS can alter synaptic plasticity, mainly the long-term potentiation/depression (LTP/LTD) of excitatory synaptic transmission.^[4] Indeed, findings from pharmacological and animal studies have shown that rTMS affects the neural processes that are related to the initiation and maintenance of synaptic plasticity, including the gene and protein expression underlying N-methyl-D-aspartate (NMDA) receptor function.^[5, 6] Moreover, depending on the intrinsic properties and geometrical orientation of the fibers within the stimulated cortical region, the magnetic stimulus induced current not only regulates the activity of local interneuronal circuits, but also influences those fibers which project antidromically or orthodromically to its distant brain structures. Recent study proposed a complementary proposition that in addition to LTP/LTD-like synaptic plasticity changes in excitatory transmission (e.g., a summation of effects in excitatory neural transmission dependent on the amount and rate of postsynaptic calcium influx^[7]), modulations of inhibitory interneuron activity and membrane potentials co-occur with excitatory alterations, with the balance of these effects underlying the ultimate effect of rTMS.^[8] Notably, rTMS activates cortical circuits and interacts with the spontaneous oscillatory rhythms induced by stimulation. This may bring about an activity-dependent modulation according to the phase-locking synchrony between the pattern of stimulation and cortical oscillations.^[9] In addition, rTMS is much less potent in terms of the consequences of cumulative stimulation or the duration of the after-effects than the standard protocols used to induce LTP/LTD, and rTMS is applied at extremely different spatial scales (i.e., at the level of single neurons and the whole cortical areas in rTMS).

3. Antidepressant efficacy of rTMS

The Food and Drug Administration (FDA) agency of the United States approved rTMS as a treatment for medication-resistant patients with major depression in 2008. It was definite that rTMS exerted ant-depressive effects with well tolerated and only minor adverse effects have been reported. As shown in Table 2, the biological effects of rTMS in humans and animals have been revealed. However, the proposed antidepressive capacities of rTMS have not been confirmed in patients with treatment-resistant depression (TRD).^[10]

Recently, 3 rTMS protocols have been used in depression treatment in clinical trials: low frequency (LF-rTMS) stimulation of the left dorsolateral prefrontal cortex (DLPFC), high frequency (HF-rTMS) stimulation of the right DLPFC, or a combination of the above. The efficacy of HF-rTMS of the left DLPFC (l-DLPFC) in depression is definite, with a Level A recommendation in European guidelines. Actually, a meta-analysis comprising 29 randomized controlled trials, indicated that of patients receiving HF-rTMS, about 18.6% and 29.3% could be classified as remitters and responders, respectively (compared with 5% and 10.4% of subjects receiving sham-rTMS).^[11] In contrast, the efficacy of LF-rTMS of the right DLPFC can only be defined as probable (Level B recommendation). However, other studies have indicated that the therapeutic effects of each approach were similar.^[12]

Different stimulus parameters can result in various antidepressive effects of rTMS. Lots of studies found that better efficacy was achieved when using higher-intensity pulses, more numbers of stimulations, or longer courses of treatment. Based on a review, the

Table 2. Biological effects of rTMS

| Articles | rTMS | Source | Effect |
|---------------------|----------------------------|--|--|
| Luborzewski 2007 | Left DLPFC, 20 Hz | Major depression Patients (17) | Glutamate↑ |
| Baeken 2011 | Left DLPFC, 10 Hz | Patients with unipolar depression (21) | 5-HT _{2A} receptor binding indices↑ |
| Pogarell 2006, 2007 | Left DLPFC, 10 Hz | Patients with major depressive disorder (5) | Dopamine↑ |
| Cho 2009 | Bilateral DLPFC, 10 Hz | Right-handed young healthy subjects (7) | Left Dopamine↑ |
| Daskalakis 2006 | 1 Hz, 6 Hz, 10 Hz | Healthy subjects (12) | Cortical inhibition ↑ |
| Zheng 2015 | Left DLPFC, 15 Hz | Patients with TRD (32) | N-acetylaspartate ↑ |
| Kang 2016 | Left DLPFC, 10 Hz | Patients with major depressive disorder (24) | DLPFC-left caudate connectivity↓ |
| Richieri 2017 | Left DLPFC, high-frequency | TRD Patients (58) | DLPFC-medial temporal limbic connectivity↑ |
| Downar 2014 | DMPFC, 10 Hz | MDD Patients (47) | Connectivity between Dorsomedial and dorsolateral↑ |
| Taylor 2017 | Left DLPFC, 10 Hz | depressive episodes patients (62) | Clinical depressive phenotype↓ |
| Lenz 2014 | Hippocampal CA1, 10 Hz | Brain slices of mouse | Excitatory postsynaptic currents↑, miniature excitatory synaptic current ↑ |
| Trippe 2009 | 1Hz | Rats(24) | GAD67↓, GAD65↑, GAT-1↑ |

rTMS, repetitive transcranial magnetic stimulation; DLPFC, dorsolateral prefrontal cortex; DMPFC, dorsomedial prefrontal cortex; ↑, increased; 5-HT, serotonin; ↓, decreased; GAD, glutamic acid decarboxylase; GAT-1, gamma-aminobutyric acid transporter 1.

parameters that are associated with the effectiveness of rTMS are combinations including delivery of >1000 pulses per session, stimulation intensity >100% of the motor threshold, and >10 rTMS sessions.^[13] However, further research is needed to determine the most effective parameters.

Although rTMS might be a possible alternative to electroconvulsive therapy (ECT) in the treatment of depression, several studies estimating efficacies and acceptabilities of them have yielded conflicting findings. As mentioned above, a meta-analysis indicated that the efficacy of rTMS is tied to the stimulus parameters. Other studies within the meta-analysis over the last decade reported that ECT is more effective than rTMS for the treatment of major depression. rTMS was as effective as ECT for non-psychotic depression, but ECT was more efficient for patients with psychotic features. However, evidence about the long-term or medium-term efficacy of rTMS is still not sufficient.^[14]

4. Neurotransmitters involved in rTMS stimulation

Research indicates that the number of elements, such as reductions in motor slowness in bodily speech and movement, improved facial expressivity, and increased

voice volume are associated with the antidepressive effects of rTMS and the clinical outcome as well.^[15, 16] Although the main mechanisms underlying these changes are poorly understood, some studies have proposed the activation of neurotransmitter systems as a working mechanistic model. Below, we review the roles that important neurotransmitters play in depression and discuss how they are affected by rTMS.

4.1 Serotonin

Serotonin (5-HT) is an important excitatory transmitter that is involved in hypothalamic-pituitary-adrenal system regulation. Extensive study has found that the serotonergic system also plays a critical role in depression. Indeed, the expression of 5-HT_{1A} receptor mRNA was found to be decreased in the hippocampus and prefrontal cortex of patients with major depressive disorder (MDD), as well as in the hippocampus of animal models exhibiting signs of depression. Accordingly, an increase in serotonergic neurotransmission has been proposed to underlie the antidepressant effects of drugs, as well as rTMS. Several evidences have demonstrated that state-dependent changes and metabolic in the left DLPFC of MDD can be reversed by rTMS.^[17] From an

electrophysiological point of view, 5-HT_{2A} receptors in the hippocampus might be influenced via pyramidal neurons by the stimulation of the DLPFC. Another research reported that the serotonergic system changes induced by HF-rTMS treatment is correlated positively with 5-HT_{2A} receptor binding indices in the bilateral DLPFC and negatively with right hippocampal 5-HT_{2A} receptor uptake values.^[18] Patients exposed to chronic rTMS, the sensitivity of 5-HT_{1A} and 5-HT_{1B} auto-receptors were reduced, which control the level of 5-HT in the frontal cortex.

4.2 Dopamine

Preclinical studies and clinical trials, including several meta-analyses, indicate the role of dopamine in the pathophysiology of MDD and other forms of depression. In fact, the alterations in the expression of transporters and peripheral receptors in the dopaminergic system might be potential predictors of treatment responses and biomarkers for the diagnosis of depression. Regarding the antidepressive effects of rTMS, studies in animals and humans have found that prefrontal rTMS can induce dopamine release in the mesostriatal, mesolimbic, and striatal regions. Acute rTMS challenge showed similar striatal dopaminergic effects to those associated with the administration of d-amphetamine, a substance known to increase synaptic dopamine.^[19, 20] These findings, together with those from similar earlier reports, support the hypothesis that rTMS could affect the level of dopamine, and thus improves MDD. In the future, experiments that combine positron emission tomography (PET) with dopaminergic high-affinity ligands and rTMS may provide more important information about the specific cortical neural networks and their functional connectivity involved in depression.^[21]

4.3 Gamma-aminobutyric acid

Gamma-aminobutyric acid (GABA) is the main inhibitory neurotransmitter in the brain, and increasing evidence suggests that GABA contributes to the pathophysiology of depression. Notably, reduced markers of GABA function and low levels of brain-derived neurotrophic factor (BDNF) have been reported in MDD.^[22] As such, GABA may be a potential target for antidepressant therapies. Reduced GABA-mediated inhibition of incoming information in pyramidal dendrites may represent a putative microcircuitry-level phenotype underlying the increased activation of the subgenual anterior cingulate cortex (sACC) and amygdala that is frequently reported in studies of patients with MDD.^[23] Research on the chronic effects of rTMS on hippocampal evoked potentials demonstrates that rTMS is accompanied by changes in local hippocampal inhibitory circuits. Although a deficiency of the glutaminergic/GABA ratio in MDD has been proposed, the influence of rTMS on the glutaminergic/GABA system has only been

demonstrated in healthy people.^[24] Another research showed that different rTMS stimulations, including LF and intermittent stimulation and continuous theta-bursts might affect the expression of activity-dependent proteins in cortical inhibitory interneurons, such as GABA transporter 1, glutamic acid decarboxylase (GAD) 65 and 67.

Although the common effects on protein expression, different frequency of rTMS produces different influence in distinct neuronal subsystems due to different time course and quantity. Glutamate/glutamine levels in the prefrontal cortices (PFC) can be increased by a single HF-rTMS session, implying that this application may act by stimulating glutaminergic prefrontal neurons.^[25] Regarding inhibitory effects, active rTMS resulted in increases in cortical inhibition^[26]; however, in that study, only the left motor cortex was stimulated. Other neurotransmitters are known to be influenced by rTMS in MDD. For example, the N-acetylaspartate concentration was increased in the left ACC after rTMS treatment, and this increase is associated with an improvement in cognitive function in patients with TRD. In addition, norepinephrine and acetylcholine are also affected in MDD, and these neurotransmitters are modulated by rTMS as well.^[27]

5. rTMS modifies neural circuits and brain networks

To date, few studies deciphering how antidepressant rTMS mediates and is mediated by neural circuits and brain networks have been published. Several reports have indicated that applying HF-rTMS over the left DLPFC exerts therapeutic effects in patients with MDD. One such report demonstrated that the therapeutic effects of rTMS were likely induced via modulation of the functional connectivity in the frontostriatal network.^[28] In addition, rTMS of the DLPFC in patients with TRD was found to produce remote temporal hypoperfusion that corresponded with changes in functional connectivity between the DLPFC and the default mode network (DMN), especially within the medial temporal limbic areas.^[29] Another study suggested that the response to rTMS may depend on the distinct depression subtype, whereby the subtype with preserved hedonic function is responsive to dorsomedial rTMS while the subtype with disrupted hedonic function and abnormally lateralized connectivity to the ventromedial prefrontal cortex is unresponsive to dorsomedial rTMS.^[30] The connectivity from the right dorsal lateral prefrontal cortex to the left precuneus and left inferior parietal lobule is also associated with individual' early life stress status negatively. These results demonstrate that the dissociation between executive and default mode networks is more in patients with early life stress than in individuals without stress in early life, and may reveal neuroimaging assessments in future rTMS studies of early life stress-related conditions.^[31] Finally, research has informed that the changes in connectivity occurring after antidepressant treatment might be

partly associated with the mechanisms of treatment administration. A previous review proposed a series of recommendations that might guide future research to explore the effects of antidepressant treatments on brain connectivity.^[32]

6. rTMS promotes hippocampal neurogenesis and synaptic plasticity

The therapeutic mechanisms of rTMS have been suggested to include hippocampal neurogenesis and plasticity paradigms.^[33] rTMS-induced plasticity, including the induction of LTP and LTD, has been confirmed in animal rTMS studies. It is generally believed that the rTMS-induced LTP/LTD is related to pulse frequency. For instance, it was found that applying 1-Hz rTMS for >10 min produces LTD-reminiscent outcomes, while 5-Hz rTMS produced an effect similar to LTP. Determinants of whether LTP or LTD is induced may be related to the intracellular Ca^{2+} level and the strength of the Ca^{2+} internal flow in the postsynaptic membrane.^[34]

Metaplasticity is a high-order form of synaptic plasticity, in which the induction or expression of long-term potentiation (LTP) or long-term depression (LTD) is modulated by the pre-stimulatory activity. Metaplasticity in the human motor cortex can also be studied using rTMS. Studies have shown that metaplasticity involves regulating the activation of NMDA receptors (through G-protein-coupled receptors) and the processes involved in the rise of postsynaptic intracellular Ca^{2+} .^[35] Generally, the excitability of the motor cortex was decreased by LF-rTMS administration but increased by HF-rTMS administration.^[36] Recent research found that long term (20-40s) continuous theta-burst rTMS (50 Hz) stimulation decreases the excitability of the motor cortex significantly, and short continuous (200ms) theta bursts can induce lasting reductions of excitability in motor cortical, and this approach seems to be more effective than LF-rTMS. Furthermore, rTMS can affect neuronal activity processes including excitatory threshold changes, synaptic efficacy and spontaneous activity without inducing a significant neuron discharge phenomenon.^[37] Except the regulation on LTP/LTD of excitatory synapses, rTMS can also simultaneously regulate the membrane potential and neuronal excitability of inhibitory neurons. Importantly, the electric field induced by rTMS affects not only the excitability of the cortex, but also the excitability of white matter structures. Recent progress has demonstrated that astrocytes regulate neural circuits^[38] and respond to neuronal activity.^[39] Additionally, calcium signals are known to be associated with astrocyte-neuron communication in the synapse.^[40] Currently, rTMS is the main candidate for regulating astrocytes to control nerve connections and potential astrocytes in response to damage.^[41] Lots of studies have reported that high frequency rTMS (3 mT, 50 Hz) can not only induce interleukin-6 release but also increase cell proliferation and intracellular Ca^{2+} level in

astrocytoma cell line. In addition, 1-Hz rTMS stimulation can also raise the intracellular calcium in astrocytes cytoplasm and nucleus significantly, while the increased calcium did not affect the migration and proliferation of astrocytes in the scratch test.^[42] Other studies have suggested that hippocampal neurogenesis might be involved in the antidepressant effects of rTMS. For instance, Ueyama et al. found that treatment with 25-Hz rTMS for 2 weeks increased hippocampal dentate gyrus cell proliferation in rats.^[43] Nevertheless, additional research is needed to determine whether these newly derived cells play an antidepressant role.

7. rTMS affects various molecular pathways

Several cell-signaling pathways have been shown to be affected by rTMS. Here, we focus on BDNF, which acts upstream of extracellular signal-regulated kinase (ERK) 1/2, and on the endocannabinoid system. BDNF is involved in the survival and differentiation of specific regions of the central nervous system (CNS) and may modulate synaptic plasticity and neuronal connectivity.^[44] Evidences indicate that BDNF can rescue cell death of neurons that caused by ischemic injury, hypoglycemia or excitotoxicity. In addition, BDNF in particular has garnered tremendous interest due to its neuroprotective, anti-inflammatory, and antidepressant effects.^[45] The administration of BDNF in CNS is associated with increased expression of the 5HT1A receptor gene, and induces antidepressant effects in animal models. Furthermore, BDNF knockout mice exhibit neurological deficits and depressive-like behavior, which indicates that BDNF might play an important role in the pathogenesis of depression.

Previous study showed that rTMS can lead to LTP- and LTD-like changes in the auditory cortex.^[46] Clinical studies have revealed that rTMS administration on frontal lobe can also produce the expression of neurotrophic factors in patients with depression. And increased plasma levels of BDNF in patients with drug-resistant severe depression after 10 sessions of HF-rTMS and identified a trend for an association between improvement in the patients' depression scores and the increased plasma BDNF levels after rTMS treatment.^[47] In contrast, Lang et al.^[48] reported that the BDNF serum concentration did not change upon HF-rTMS in patients with MDD and indicated that none of the peripheral nerve neurotrophic factor changes were associated with clinical parameters. Similarly, Gedge et al.^[49] identified no changes of peripheral BDNF level in patients with drug-resistant MDD after HF-rTMS treatment. However, in a study by our laboratory examining the mechanisms of rTMS in the treatment of depression, we found that rTMS improved chronic unpredictable stress, improved cell proliferation in the hippocampus, and increased BDNF and p-ERK1/2 protein level in a rat model of depression.^[50] Another study also showed that rTMS promoted the proliferation of hippocampal neural stem cells (NSCs), and increased

the expression of phosphorylated ERK1/2 and BDNF in the hippocampus and in hippocampal NSCs of a rat model of depression.^[51]

The endocannabinoid system has also been suggested to be involved in the pathophysiology by recent genetic and pharmacological studies. For instance, research using the chronic unpredictable stress model of depression found that the density of endocannabinoids and CB1 receptor binding sites is decreased in a number of brain areas that are often related to affective disorders.^[52] Further, the antidepressant-like effects induced by antidepressant drugs in animal models, the administration of inhibitors of anandamide uptake or metabolism, and CB1 receptor agonists all up-regulated the expression of endocannabinoids and the CB1 receptor. Research from our laboratory showed reduced hippocampal expression levels of the CB1 receptor, BDNF and B-cell lymphoma 2 (Bcl-2)/Bax proteins, as well as cell proliferation in chronic unpredictable mild stress depression-model rats. However, applying rTMS to these rats increased cell proliferation and up-regulated CB1 receptors, and BDNF and Bcl-2/Bax expression in the hippocampus, and these findings were correlated with reductions in depression-like behavior.^[53]

Finally, rTMS may also affect other factors. For instance, applying chronic rTMS promoted BK channels, increase Homer1a expression and reduced the number of cingulate pyramidal cells exhibiting excitability in depressive-like mice models, thus led to an improvement in the depressive-like phenotype.^[54]

8. Conclusions

At present, there is no conclusive evidence to support using rTMS as a substitutive therapy for depression. While positive results have been reported frequently in both open and randomized controlled studies, the optimal treatment parameters for individual therapy, such as the location, intensity, frequency and duration of stimulation, remain unclear. Meanwhile, sham-controlled research has occasionally demonstrated symptom improvement in participants, with some studies reporting similar responses to rTMS and sham-rTMS treatment. Therefore, research addressing these

issues is needed before a proper clinical trial can be designed. Finally, we must realize that despite the exciting achievements regarding our understanding of the neurobiological mechanisms underlying rTMS, the clinical utility of rTMS can only be determined by assessing its safety, long-lasting, and improvements in quality of life for patients.

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Conflict of interest statement

All authors declare that they have no any conflict of interest in this study.

Authors' contributions

Zhengwu Peng: introduction, basic principles of rTMS, and conclusions, as well as the integration of the full text.

Cuihong Zhou: rTMS promotes neurogenesis in hippocampus and synaptic plasticity, the formatting of the full text.

Shanshan Xue: rTMS regulates neurotransmitter.

Jie Bai: rTMS regulates neural circuit and brain network.

Shoufen Yu: rTMS improves depression by adjusting various molecular pathways.

Xiaosa Li: the antidepressant efficacy of transcranial magnetic stimulation.

Huaning Wang: draft revision and formatting.

Qingrong Tan: providing the outline, guidance, and revisions of the article.

重复经颅磁刺激治疗抑郁症的机制研究进展

Peng Z, Zhou C, Xue S, Bai J, Yu S, Li X, Wang H, Tan Q

概述: 抑郁障碍是目前最常见的心理健康问题之一。然而, 对于该疾病的基于机制的治疗方法仍然是难以捉摸的。重复经颅磁刺激 (rTMS) 是一种非侵入性的程序, 它可以以一种脉冲磁场来刺激大脑中的电活动, 被认为是一种有效的抑郁症治疗方式。在这里, 我们

回顾了关于 rTMS 治疗抑郁症的临床和基础研究的主要发现, 包括它的抗抑郁疗效, 基本原理, 调节神经回路、神经递质和脑网络、海马神经发生、和突出的功效, 以及分子通路。

关键词: 重复经颅磁刺激; 抑郁症; 神经生理

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Zhengwu Peng obtained a masters degree from the Institute of Animal Science and Technology of Northwest Agriculture and Forestry University in 2009, and a PhD degree from the department of preventive medicine of the Fourth Military Medical University, Xi'an, China in 2016. Since 2009, he has been working in the department of Psychiatry, Xijing Hospital, Fourth Military Medical University, Xi'an, China. Now he is working as an associated researcher and laboratory supervisor and interested in researching the mechanism of antidepressant and antipsychotic drugs.