MEDS Public Health and Preventive Medicine (2023)
Clausius Scientific Press, Canada

DOI: 10.23977/phpm.2023.030504
ISSN 2616-1915 Vol. 3 Num. 5

Advances in the Antidepressant Effects of iTBS

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Keywords: Repetitive transcranial magnetic stimulation; intermittent burst magnetic stimulation; depression

Abstract: Repetitive transcranial magnetic stimulation (rTMS), as a safe, effective, and noninvasive physical therapy technique, can reduce the risk of recurrence of depression, and intermittent bursting magnetic stimulation (iTBS), as a new form of transcranial magnetic stimulation, can improve the symptoms of depression faster and increase the efficacy of antidepressant treatments. iTBS, compared with conventional rTMS, has the advantages of longer duration and higher efficiency, and the specific mechanism of action of iTBS remains to be investigated. This review will discuss the basic information of iTBS, its antidepressant effects and its specific mechanism of action.

1. Introduction

Transcranial Magnetic Stimulation (TMS) has various modes, such as Repetitive Transcranial Magnetic Stimulation (rTMS), Theta Burst Stimulation (TBS) and so on, among which iTBS is a new magnetic stimulation treatment mode proposed in 2005 [1], which is a special stimulation mode of rTMS. iTBS as a new form of transcranial magnetic stimulation modality [2], its plexiform stimulation mode more accurately simulates the treatment mode of rTMS [1] , which is aspecial stimulation mode of rTMS. iTBS as a new form of transcranial magnetic stimulation [2], has a plexiform stimulation mode that more accurately mimics the natural rhythms of the brain, thus obtaining a more efficient effect, and it is gradually becoming the new clinical antidepressant treatment choice. iTBS stimulation is performed by stimulating for 2 seconds each time, followed by an interval of 8 seconds, and the cycle is repeated 20 times, releasing a total of 600 pulses[3]. iTBS, a new transcranial magnetic stimulation mode, has been approved by the FDA in 2018 as an option for the treatment of refractory depression. Currently, iTBS is widely used in the treatment of neurological disorders [4]. When performing motor function therapy, stimulation by iTBS can effectively activate the neural information transmission in the motor cortex and cerebellum, and the cerebellum is treated by iTBS, and for the cerebellum treated by iTBS, it improves the motor imbalance symptom through the enhancement of functional connectivity [1]. Currently, iTBS is currently available in an increasing number of ways to interact with putative synaptic plasticity in the human brain, due to its inherent advantages of short duration and the use of low-intensity stimulation pulses, making it more acceptable to participants than some other non-invasive brain stimulation protocols [5].

2. The antidepressant effects of iTBS

Depression is a disease with a very high prevalence, common target, jeopardizing public health, causing serious functional impairment and a huge social burden, and the onset of depression is relatively insidious, the causative factors are complex, and the pathogenesis is not clear [6]. It is predicted that by 2030, depression will become the first disease with the highest global burden [7]. At present, the main clinical program for the treatment of depression is drug therapy, but because drug therapy is sometimes very easy to cause other aspects of the adverse symptoms, it is difficult to achieve the ideal effect of depression treatment through a single drug therapy. iTBS, as a kind of non-invasive magnetic stimulation of nerve cells, has become an effective means of antidepressant treatment. It has been demonstrated [8] that iTBS, as a tolerated form of repetitive transcranial magnetic stimulation, has excellent antidepressant effects in the treatment of patients with refractory depression. The Centre for Addiction and Mental Health in Toronto, Canada, published a study in Lancent on the efficacy of iTBS in patients with refractory depression [9], in which it was mentioned that the statistical response rate to iTBS for the treatment of refractory depression was 49%, and the remission rate reached 32%. In a study of patients with first-episode depression, it was found that multiple daily iTBS treatments produced clinically meaningful antidepressant effects in less time [10]. Unlike the selection of patients with refractory depression, early and rapid antidepressant treatment of patients with first-episode depression and the production of clinical symptomatic improvement will greatly improve patient compliance, reduce the patient's resistance and will greatly reduce the risk of suicide, reduce the number of relapses, and contribute to the recovery of patients' social functioning. Some studies have demonstrated through neuroimaging [11] that iTBS can actively stimulate the improvement of patients' social functioning and have an improvement in patients' depressive symptoms. It has been demonstrated that left cortical sexual activity decreases when depression occurs [12], while iTBS acts as an excitatory agent [13], which is capable of inducing stable, long-lasting excitation in a short period of time, and improves patients' depressive state in a short period of time. Related studies have demonstrated that iTBS also has a significant role in improving patients' cognitive function [14]. iTBS will improve patients' cognitive function by modulating frontal lobe plasticity.The Chinese Version Perceived Stress Scale (CPSS) developed by Cohen, Kamarch, and Mermelstein in 1983 was used, which consists of 14 entries and uses a 5-point Likert scale with the subjects' feelings, reactions, and level of agreement as the rating indicators. Seven of the entries are reverse scored. Scores range from 1 "never" to 5 "always", with higher scores indicating greater stress. The scale not only measures the perceived stress of individuals, but also their ability to cope with stress and related coping characteristics. The internal consistency coefficient α of the scale in this study was 0.886, and the scale has good reliability and validity among Chinese adults [14].

3. Possible potential mechanisms of action of iTBS

3.1. Neurotransmitters and their receptors

Neurotransmitters have an important role in maintaining homeostasis in the brain, and some studies have shown that neurotransmitters have a close relationship with the onset and treatment of depression.In some early clinical studies, it was found that the monoamine function in the brain of patients with depression was decreased [15], and insufficient monoamine neurotransmitter function is one of the main factors in the development of depression, and intracerebral serotonin (5 a hydroxytryptamine (5HT) and norepinephrine (NE), as clinically common monoamine neurotransmitters, are considered to be one of the main causative factors of depression [16]. In several previous studies, it has also been found [17] that TMS can increase serum 5-HT levels in patients. On

the other hand, NE is a key neurotransmitter in the central nervous system that has a strong positive correlation with patients' attention, interest in life, energy and anxiety [18]. It has also been suggested that NE may have a major impact on midbrain pathogenesis and disease progression[19]. Compared with normal people, the NE expression level of depressed patients was higher than that of normal people, and after antidepressant treatment, the NE level decreased significantly, which proved that the occurrence of depression was closely related to the NE level. iTBS is a method to stimulate the basic activity processes of the brain by means of a fast-changing magnetic field, which can depolarize the neurons in the brain to achieve the purpose of activating or inhibiting the neuronal activity, and the results of the previous studies have proved [20]. Previous studies have demonstrated [20] that iTBS stimulates the cerebral cortex with a pulsed magnetic field and promotes the formation of induced currents, which improves brain metabolism and neurological activity and promotes the secretion of neurotransmitters, such as 5-HT and NE, which excites the cerebral cortex, and inhibits depression and reduces the symptoms of depression in patients through neuromodulation.

3.2. Brain-derived neurotrophic factor (BDNF)

As brain-derived neurotrophic factor (BDNF) is closely related to depression, it can promote the proliferation and differentiation of various types of neurons, and it has a trophic effect on neurons. BDNF also plays a crucial role in the synthesis of neurotransmitters and neurotrophic factors. It is associated with long-term potentiation (LTP) and the functioning of learning and memory [21]. Abnormalities in the regulation and expression of BDNF can lead to cognitive and behavioral deficits [22], as mentioned in the hypothesis of neural influences on depressive disorders [22]. The hypothesis also suggests that decreased BDNF expression contributes to the development of depressive disorders [24]. Furthermore, antidepressant treatment promotes neuronal survival by increasing BDNF expression in the brain [25]. Therefore, it is suggested that elevated BDNF levels may improve depression in patients [26]. A clinical trial has pointed out that [27].The expression of serum BDNF levels was significantly lower in depressed patients compared to normal controls. However, after effective antidepressant treatment, the expression of serum BDNF levels was normalized in the patients. This finding confirms that BDNF is a key indicator of the effectiveness of antidepressant treatment. Additionally, studies have shown that increased neurogenesis is accompanied by a significant increase in the protein expression level of BDNF [28]. Animal experiments have also demonstrated that TMS improves depressive-like behavior, promotes hippocampal cell neurogenesis, and increases BDNF expression in rats [29]. Furthermore, it has been observed that TMS induces an increase in 5-HT receptor autoreceptor activity in the brain [30]. It has also been proposed that repetitive magnetic stimulation lowers the threshold of synaptic transmission, leading to the activation of previously inactive synapses and the creation of new conduction pathways [31].And all these proved to us that BDNF receptor level is a possible potential mechanism for the antidepressant effect of iTBS.

3.3. Synaptic plasticity

Synaptic plasticity is a property or phenomenon in which synapses undergo longer-lasting changes in form and function. The ability of synapses to perceive, evaluate, and store complex information is one of the most basic and important functions of the brain, and synaptic plasticity, with its ability to respond adaptively to subsequent relevant stimuli and activity-dependent changes in the strength of neuronal connectivity, has long been considered to be an important component of learning and memory, and the onset of depression is closely related to synaptic dysfunction.[32], Thus, synaptic plasticity has been recognized as one of the possible etiological factors contributing to the development of depression, and synaptic plasticity also describes the modifiability of the strength of

synaptic connections, i.e., alterations in synaptic structure and efficiency of transmission, during neural activity, which includes long-term potentiation and long-term depression (LTD) [33], it has been shown [34] that TMS can effectively promote the formation of LTP and enhance the spatial cognitive ability of rats, and clinical studies have also proved [35] that the severity of depression is closely related to alterations in the structure and function of synaptic plasticity in these key areas of the brain. The antidepressant drugs we usually use exert their antidepressant effects by improving synaptic plasticity and reversing chronic stress-induced defects in the connectivity of key neural circuits. In a related study [36], TMS will significantly improve the spatial learning and memory ability of experimental mice through the principle of synaptic plasticity and can repair their memory deficits. All these show us that TMS can enhance synaptic functional plasticity and thus prevent or ameliorate the damage to synaptic function that may be caused by depression. Thus synaptic plasticity is a key factor in the current mechanism of antidepressant action of iTBS.

4. Comparison of antidepressant efficacy of itbs with other modalities of other rTMS

In recent years, it has been found that the efficacy of TMS varies depending on the parameter settings: stimulation site, magnetic field direction, [37]number of stimuli delivered, as well as the frequency, intensity and duration of stimulation [38]. iTBS differs from the stimulation sequence of conventional rTMS by the addition of bursting clusters or plexus stimulation modes, whereby each cluster is equivalent to one pulse of conventional rTMS, and the combination of multiple plexus stimuli is equivalent to one string stimulation of conventional rTMS. Each cluster is equivalent to one pulse of conventional rTMS, and the combination of multiple clusters is equivalent to a single stimulus of conventional rTMS. iTBS mimics the physiological burst firing of action potentials in the CNS through cluster stimulation, which better mimics the natural rhythms of the brain and the normal neurophysiology of human beings, and excites the cerebral cortex by modulating synaptic plasticity to produce plastic changes in LTP. iTBS stimulation also mimics hippocampal pyramidal neurons by modulating synaptic plasticity to produce plastic changes in LTP. It induces LTP in the hippocampus by mimicking the common pattern of neuronal firing in the hippocampal pyramids. This only occurs when the stimulation is performed at intervals of less than 2 seconds. iTBS often exerts a faster and more stable effect than traditional rTMS protocols and is extremely well tolerated [39]. While high-frequency rTMS is often time-consuming[40], iTBS, as a new type of, has nearly the same antidepressant efficacy as high-frequency rTMS [10] and is more consistent with neuronal firing patterns [41], which is a great advantage of iTBS. iTBS is shorter in duration, smaller in intensity, and closer to the central nervous system. The shorter stimulation time, smaller stimulation intensity and closer to the physiological rhythms of the central nervous system [42] ,can induce more lasting excitatory changes in the brain in a shorter time and regulate neuroplasticity more effectively. In some clinical studies, iTBS was compared with rTMS [8], compared with rTMS, iTBS mode has another great advantage that it is characterized by plexiform stimulation, the amount of stimulation only needs 80% of motor evoked potentials, the stimulation time duration is reduced, and the stimulation modulation effect on the nerve is obvious, and there are some studies proving that [8], the intensity of the effective stimulation in the mode of iTBS is only as high as the motor threshold (motor threshold). What's more, some studies have proved [41] that the intensity of effective stimulation in iTBS mode is only 60% of the motor threshold (MT), while the stimulation intensity of rTMS mode is 100%-200% of the MT. The advantages of the iTBS treatment mode are more obvious in terms of saving therapeutic resources and improving the therapeutic efficiency, etc. Moreover, the side effects of iTBS are less compared with that of the conventional rTMS, which can satisfy the clinical needs of a large number of patients treated in the daily life and improve the efficiency of the use of iTBS. Even under the premise of the same effect as conventional rTMS, iTBS has the advantages of shorter

treatment time and less stimulation, which makes the patient's compliance stronger.

5. Conclusions

The etiology of depression, including its general disorder, treatment options, relapse prevention, and other related issues, remains to be comprehensively addressed. Thus far, the pathogenesis underlying depression has remained elusive. However, existing literature and research provide evidence supporting the therapeutic efficacy of intermittent theta burst stimulation (iTBS) and shed light on its mechanism of action in treating depression. Consequently, iTBS holds great promise as an antidepressant intervention; nevertheless, further research is required to validate its effectiveness in clinical practice.

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