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Advances in Repetitive Transcranial Magnetic Stimulation in the Treatment of Intracranial Atherosclerosis

He Xia[1,a,*]

[1]*Dingxi People's Hospital, Dingxi, Gansu, 743099, China*
[a]*370976174@qq.com*
[*]*Corresponding author*

Abstract: *Repetitive transcranial magnetic stimulation is widely used in stroke rehabilitation, and there is a large amount of clinical evidence showing its efficacy in improving functional impairments after intracranial atherosclerotic ischemic stroke, however, its molecular mechanism has not been fully elucidated. This article reviews the recent literature on the mechanism of repetitive transcranial magnetic stimulation in intracranial atherosclerotic ischemic stroke, motor dysfunction, cognitive dysfunction, pain, swallowing, and psychological dysfunction, with a view to providing a basis for clinical treatment.*

Keywords: *Repetitive intracranial magnetic stimulation; intracranial atherosclerosis; stroke; progress in application*

1. Introduction

Intracranial atherosclerosis is the leading cause of ischemic stroke, accounting for 30% to 50% of all strokes in Asian populations, with a high risk of recurrent infarction [1]. According to TOAST typing, there are various stroke mechanisms associated with intracranial atherosclerosis, and in addition to hemodynamic impairments caused by severe vascular stenosis, arterio-arterial embolism due to occlusion of perforating arteries and plaque rupture caused by large arterial atherosclerotic lesions are the main mechanisms by which ischemic stroke occurs [2]. Moreover, patients with arterial remodeling due to severe atherosclerosis may not have luminal stenosis but have formed atherosclerosis-prone plaques in the vessel wall [2]. According to the TOAST typing, the etiological typing of ischemic stroke by foreign scholars includes atherosclerosis of large arteries, cardiogenic embolism, small artery occlusion, other definite etiologies and unknown causes, in which atherosclerosis of intracranial arteries is further classified into carrier arteries (plaques or thrombus) blocking perforating arteries, perforating arterial occlusion and arterial embolism due to plaque rupture, hypoperfusion/decrease in embolus removal, and coexistence of the above mentioned multiple mechanisms [2]. In contrast, domestic scholars have proposed Chinese ischemic stroke typing criteria based on the etiology and pathogenesis of ischemic stroke and its manifestation on high-resolution magnetic resonance vascular wall imaging, which classify ischemic stroke into four types: arterio-arterial embolism, involvement of perforating arteries, decreased embolus clearance due to hypoperfusion, and perforating arteries' own lesions [2]. Of these, penetrating artery involvement is an intracranial atherosclerotic stroke, whereas penetrating artery disease is a small-vessel lesion, both of which can lead to acute occlusion of the penetrating artery, whereas atherosclerosis of the large arteries is the main etiologic factor for infarctions in most of the penetrating artery-supplied areas.

Repetitive transcranial magnetic stimulation, as a new neuromodulation technique, can specifically regulate the neural excitability of stimulated brain areas and is non-invasive and easy to administer.

As a new type of neuromodulation technology, repetitive transcranial magnetic stimulation can specifically regulate the excitability of stimulated brain areas, and is non-invasive and easy to operate, thus helping to provide a more accurate means of brain area regulation and prognosis assessment for stroke rehabilitation therapy. It is a neuromodulation technique that utilizes pulsed magnetic fields to act on the brain, changing the membrane potential of cortical nerve cells, affecting metabolism and neuroelectric activity in the brain, and thus causing a series of physiological and biochemical responses. Depending on the frequency of stimulation, repetitive transcranial magnetic stimulation can produce

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excitatory or inhibitory effects on cortical neurons in the stimulated brain area [3]. Common repetitive transcranial magnetic stimulation modes include high-frequency stimulation (>5 Hz) that increases cortical excitability and low-frequency stimulation (≤1 Hz) that decreases cortical excitability [4]. After more than 30 years of development, repetitive transcranial magnetic stimulation has been widely used in stroke, depression, Alzheimer's disease, Parkinson's disease and other central nervous system diseases [5]. The mechanism of action of repetitive transcranial magnetic stimulation has been preliminarily explained by existing studies. In addition to the classical interhemispheric competition model, the uninjured hemisphere compensation model, and the biphasic balance recovery model, which are macroscopic brain recovery models, we should also focus on the protein- and gene-level changes in the processes related to neuroprotection, ontogeny, remodeling, and inhibition of glial scar formation induced by repetitive transcranial magnetic stimulation [6].

2. Mechanism of action of repetitive transcranial magnetic stimulation

2.1. Repeated transcranial magnetic stimulation can promote neuronal protection

2.1.1. Enhance local microcirculation of lesions and counteract neuronal apoptosis or necrosis

Due to the blockage of blood supply arteries, infarction often occurs in the affected brain area of ischemic stroke, and becomes irreversible with the prolongation of time. Caglayan et al. [5] found that after the intervention of high-frequency repetitive transcranial magnetic stimulation of 20Hz in transient ischemia model rats, a significant enhancement of microcirculation in the core area of the cerebral ischemia and the hemidiaphragmatic zone was detected, and the staining of the slices suggested that the size of infarction was reduced. Recent studies have also confirmed that repetitive transcranial magnetic stimulation plays a protective role by enhancing cerebral perfusion and improving blood-brain barrier damage [7]. Blood-brain barrier damage is one of the pathological features of ischemic stroke, which is followed by an imbalance of inflammatory, oxidative, and electrolyte factors that leads to extensive neurological damage [8,9]. In addition, Caglayan et al. [5] showed that high-frequency repetitive transcranial magnetic stimulation significantly reduced DNA fragmentation, increased capillary density and neuronal survival; further studies found that high-frequency repetitive transcranial magnetic stimulation up-regulated the vascular endothelial growth factor-A (VEGF-A) and VEGF-B genes, and markedly increased the expression of the anti-apoptotic Bcl-xl protein, and reduced the expression of the apoptosis-related proteins Bax, Bax, Bax, and Bax-XL, as well as reduced the expression of the apoptosis-related protein Bax-XL. The in vitro experiments of Baek et al. [10] also showed that high-frequency repetitive transcranial magnetic stimulation significantly reduced the expression of Bax and cleaved-caspase-3, while the expression of Bcl-2 and pro-caspase-3 was significantly increased. caspase-3, and its anti-apoptotic mechanism is related to the activation of ERK and AKT signaling pathways, and it is interesting to note that low-frequency stimulation has the opposite effect.

2.1.2. Reduce local inflammation and oxidative stress

Foreign studies have shown [10] that repetitive transcranial magnetic stimulation plays a role in anti-inflammation, and high-frequency repetitive transcranial magnetic stimulation significantly reduced the expression of inflammation-related genes, such as interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α), transforming growth factor-β (TGF-β) and matrix metalloproteinase-9 (MMP-9). Liu Chaomeng et al. [11] found that repetitive transcranial magnetic stimulation significantly down-regulated serum MMP-9 and ultrasensitive C-reactive protein expression after intervening in patients with cerebral ischemic stroke. The anti-inflammatory effect of repetitive transcranial magnetic stimulation involves glial cells, and the over-activation of microglia can lead to inflammation. Zong et al. [12] found that IBA1 immunoreactivity was decreased in rats with repetitive transcranial magnetic stimulation interventions, indicating that the proliferation of microglia was inhibited; at the same time, the activation of the M1/M2 phenotype of microglia was altered, and the inhibition of the pro-inflammatory M1 phenotype and the enhancement of the anti-inflammatory M2 phenotype were used to decrease the inflammation and the inflammation response. Response. After repeated transcranial magnetic stimulation, 11 cellular pro-inflammatory factors, including ciliary neurotrophic factor (CNTF), chemokine ligand 1, interferon-gamma, interleukin-1α, IL-1β, interleukin-2 (IL-2), and interleukin-3 (IL-3), were significantly inhibited. Another study showed that oxidative stress plays an important role in ischemic brain injury, and ischemia-reperfusion generates a large number of reactive oxygen clusters, which leads to brain tissue injury [13]. Repetitive transcranial magnetic stimulation can effectively reduce the level of NADPH oxidase, significantly inhibit the expression of 3-nitrotyrosine, a

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marker of peroxynitrite production, which in turn promotes the production of manganese superoxide dismutase, achieving the effect of reducing neurooxidative damage and maintaining cellular redox homeostasis [14].

2.2. Repeat transcranial magnetic stimulation and neuroplasticity mechanism

Neuroplasticity is the modifiability of the nervous system in terms of structure and function, mainly includes the pathways of synaptic regeneration, synaptic plasticity, neurogenesis, and reorganization of the neural network. Structural plasticity is manifested in changes in synapse length, branching, dendritic spine density, synaptic morphology and number, etc. Functional plasticity is manifested in repeated synaptic activity and changes in synaptic transmission efficiency, such as long-duration enhancement and inhibition of synaptic efficiency.

2.2.1. Upregulation of brain-derived neurotrophic factors

Brain-derived neurotrophic factor (BDNF) plays an important role in neuronal survival, nerve repair and neuroplasticity. The mechanism by which repetitive transcranial magnetic stimulation promotes neuroplasticity is related to the enhanced expression of BDNF after intervention [5]. Baek et al. [10] showed that high-frequency repetitive transcranial magnetic stimulation activated the Ca2+-CaMKII-CREB signaling pathway to increase the expression of BDNF proteins in the cells after glycoxidative deprivation/reentry injury. In this pathway, Ca2+ forms a complex with calmodulin and binds to the calmodulin kinase II (CaMKII) binding domain, which subsequently leads to phosphorylation of the cyclic adenylate response binding element to bind to the CRE element of DNA to initiate transcription of BDNF, which also protects neurons by regulating cytoskeletal and synaptic proteins [5]. BDNF binds to the cell-surface receptor TrkB, which upon activation increases NDNF expression. TrkB increases the probability of NMDA receptor opening and promotes postsynaptic dense protein-95 recruitment, thereby enhancing synaptic function to promote LTP [15].

2.2.2. Remodeling synaptic structure

The synaptic structure is closely related to the efficiency of nerve conduction, and its alterations mainly include the morphology, distribution and structure of axons and dendritic spines, and the expression of membrane proteins before and after the synapse. The dense band of the postsynaptic membrane contains AMPARs, which are gated ion channels composed of 1-4 subunits of glutamate receptors, and mediate most of the rapid excitatory synaptic transmission in the brain, and synaptic plasticity is partly determined by the AMPARs in the posterior membrane. Repetitive transcranial magnetic stimulation at 60 Hz combined with peripheral neuromuscular stimulation significantly increased ipsilateral cortical GluR2/3 content protein levels, thereby enhancing synaptic strength. Studies have shown that astrocytes subjected to repetitive transcranial magnetic stimulation promote synapse formation [16]. OGD/R neurons co-cultured with astrocytes subjected to repetitive transcranial magnetic stimulation attenuated the loss of axon density and synapse length, and the expression of postsynaptic dense band protein, synaptophysin-I and synaptophysin were up-regulated, which represent the remodeling of synapses. Assessment of neuroplasticity-related genes showed that high-frequency repetitive transcranial magnetic stimulation significantly enhanced the gene expression of synaptic growth-associated protein-43 and decreased the gene expression of neural cell adhesion molecule 1, neuromucin, proteoglycans, EphrinA5, and EphrinB1, which inhibit axon growth [10]. High-frequency repetitive transcranial magnetic stimulation at 15 Hz modulated dendritic spiking in the motor cortex of adult mice that resulted in apical and basal dendritic, the molecular mechanism of which may be related to neurotransmitters, BDNF and calcium-dependent signaling pathways.

2.2.3. Enhancement of neurogenesis

Peng et al. [17] found that 10Hz high-frequency repetitive transcranial magnetic stimulation could enhance neurogenesis in the ipsilateral subventricular region, which was consistent with the results of 20Hz high-frequency repetitive transcranial magnetic stimulation by Luo et al. [18], and the possible mechanism was related to the activation of BNDF/TrkB pathway. Cui et al. [19] showed that high-frequency repetitive transcranial magnetic stimulation increased Ki69-positive cells in the basal ganglia region and bicortin was expressed in the repetitive transcranial magnetic stimulation group, indicating that transcranial magnetic stimulation induced the proliferation and differentiation of neural stem cells and in vitro experiments proved that the direction of neural stem cell differentiation was obviously shifted to neurons under the treatment of repetitive transcranial magnetic stimulation; Bioinformatic analysis found that the mechanism of action of transcranial magnetic stimulation was related to the activation of MAPK pathway. Bioinformatic analysis revealed that the mechanism of

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transcranial magnetic stimulation is closely related to the MAPK pathway, and the intervention promotes Ca2+ inward flow and activates the calcium signaling pathway - the MAPK signaling pathway may be an intermediate bridge between calcium ions and CREB phosphorylation. In vitro studies have found that repetitive transcranial magnetic stimulation may promote the proliferation of NSCs by upregulating the expression of the neuronal miR-106b gene and suppressing the expression of its downstream gene p21.

2.3. Repeated transcranial magnetic stimulation inhibits glial scar production

After stroke, glial cells such as astrocytes, microglia and oligodendrocyte group cells are activated, which cooperate with extracellular matrix components to promote the formation of glial scar in the area around the infarct core. The glial scar and its secreted inhibitory molecules such as chondroitin sulfate and chondroitin sulfate proteoglycans constitute a physicochemical barrier that affects axonal growth and neuronal migration, impeding the recovery of neurological function [20]. Repetitive transcranial magnetic stimulation treatment of stroke rats significantly reduced the thickness of glial scar in the peri-infarct cortex and the thickness of reactive astrocytes, and reactive astrocyte hyperplasia is the most important feature of glial scar after stroke [21]. In addition, high-frequency repetitive transcranial magnetic stimulation significantly reduces the number of microglia in the ischemic striatum and shrinks the area of glial scarring [10]. Astrocytes, microglia, and oligodendrocyte group cells in ischemia enhance the potential to differentiate into reactive astrocytes and together with them promote scar formation, whereas repetitive transcranial magnetic stimulation leads to the differentiation of astrocytes, microglia, and oligodendrocyte group cells into neoplastic oligodendrocytes to enhance myelin repair. It is hypothesized that repetitive transcranial magnetic stimulation may inhibit glial scar formation by decreasing the number of astrocytes and astrocytes, microglia and oligodendrocyte group cells. The mechanism is related to the down-regulation of pro-inflammatory or growth factors such as CNTF, IL-1α, IL-6, TNF-α, TGF-β, and MMP-9 by repetitive transcranial magnetic stimulation, which reduces the activation of reactive astrocytes and decreases the proliferation and migration of cells of the astrocyte, microglia, and oligodendrocyte groups to the site of injury.

3. Clinical application of repetitive transcranial magnetic stimulation for stroke rehabilitation

3.1. Upper limb motor dysfunction

3.1.1. Mechanism of action

In improving upper limb motor function in hemiplegia after stroke, low-frequency repetitive transcranial magnetic stimulation applied to the healthy hemisphere seems to be more effective than high-frequency repetitive transcranial magnetic stimulation applied to the affected hemisphere, but both of them have a positive effect on the recovery of upper limb motor function at different periods of time after stroke. For repetitive transcranial magnetic stimulation treatment of motor dysfunction after stroke, the 2019 updated guidelines of the International Federation of Clinical Neurophysiology recommend [22] that low-frequency stimulation of the primary motor cortex on the healthy side in the acute and subacute phases is effective in improving motor dysfunction of the hand (grade A recommendation with definite efficacy), high-frequency stimulation of the M1 area on the affected side in the acute and subacute phases is a grade B recommendation, and low-frequency stimulation of the healthy side M1 in the chronic phase is a grade C recommendation. Area in the chronic stage is recommended as grade C. In addition, foreign scholars [4] found that the efficacy of repetitive transcranial magnetic stimulation on upper limb motor dysfunction is time-dependent, i.e., from the acute stage to the subacute stage and then to the chronic stage, the therapeutic effect of each period decreases sequentially, and this result is also consistent with the change of the recommendation level of the IFCN guideline relative to each period after stroke. In contrast, walking ability and balance are often impaired in stroke patients and significantly affect quality of life; therefore, the study of repetitive transcranial magnetic stimulation for lower limb motor function is also of greater clinical relevance. Two meta-analyses found that repetitive transcranial magnetic stimulation combined with other rehabilitation therapies effectively improved walking speed, step frequency, and Fugl-Meye lower limb motor scores in stroke patients, and both excitatory/inhibitory stimulation improved walking speed in stroke patients at different times [23]. The results of a recent meta-analysis suggested that low-frequency repetitive transcranial magnetic stimulation was superior to sham stimulation in promoting the recovery of lower limb motor function [24].

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3.1.2. Time of intervention

Staging after stroke is often divided as follows [25]: the hyperacute phase is within 6 h after onset, the acute phase is 6 to 24 h after onset, and the subacute phase is 24 h to 6 weeks after onset. The chronic phase was more than 6 weeks after onset. Subacute phase (24 h to 6 weeks after stroke): upper limb motor dysfunction is related to the suppression of excitability of the motor cortex on the affected side, and its excitability increases with the passage of time and the improvement of upper limb function, and this phenomenon is most prominent in the first 6 weeks after stroke and reaches stabilization at about 12 weeks, and the application of repetitive transcranial magnetic stimulation in the first few weeks after stroke promotes, directly or indirectly, the excitability of the affected motor cortex on the neuroplasticity and recovery of motor function. Relevant clinical trials and basic experiments [25] have shown that repetitive transcranial magnetic stimulation applied in the subacute period after stroke promotes the balance of the two cerebral hemispheres by regulating cortical excitability on the one hand, and on the other hand improves neuronal survival by reducing neuronal death on the affected side and stimulating the peripheral surviving neurons to promote the recovery of patients' functions. Chronic phase (>6 weeks after stroke): the abnormal reduction of primary motor cortex output of the affected hemisphere and transcallosal inhibition of the affected hemisphere by the healthy hemisphere in the chronic phase are correlated with the degree of recovery of upper limb and hand dysfunction in patients [25]. For patients in the chronic phase, a treatment strategy that eases the excitability of the affected motor cortex and inhibits the excitability of the healthy motor cortex is often chosen. Hirakawa et al. [26] performed 1 Hz repetitive transcranial magnetic stimulation of the healthy hemisphere in 26 chronic stroke patients with severe upper limb dysfunction more than 6 months after the onset of stroke and strengthened the upper limb motor training at the same time, and the upper limbs of the patients were treated with Fugl-Meyer score and transcallosal inhibition of the affected hemisphere for 24 times after the treatment. Fugl-Meyer score and Wolf motor function test score were significantly improved after 24 sessions.

3.1.3. Targets of repetitive transcranial magnetic stimulation

The most commonly used stimulation target of repetitive transcranial magnetic stimulation is the primary motor cortex (M1 area). Clinical studies have found that the premotor cortex, supplementary motor area, dorsal premotor cortex, parietal sulcus and other brain areas can also be used as the target of repetitive transcranial magnetic stimulation to promote the recovery of upper limb function. In addition, for patients with upper limb motor dysfunction accompanied by cognitive impairment or depression, the left dorsolateral frontal lobe area can be selected as the stimulation target to improve the cognitive and depressive state of the patients, and then promote the recovery of their motor function.

3.1.4. Repetitive Transcranial Magnetic Stimulation Treatment Options

(1) High-frequency repetitive transcranial magnetic stimulation: Animal experiments have shown [27] that high-frequency repetitive transcranial magnetic stimulation can reduce infarct volume and promote functional recovery by inhibiting the neurotoxic effects of astrocytes in rats after ischemia/reperfusion injury and reversing them to neuroprotective effects. Guan et al. [28] found that 5Hz repetitive transcranial magnetic stimulation of the affected side of the M1 area of the patients within 1 week of stroke significantly improved the upper limbs of the patients. transcranial magnetic stimulation can significantly improve patients' upper limb. A study by Guo et al [29] found that 10Hz repetitive transcranial magnetic stimulation of the M1 area of the affected side and 1Hz repetitive transcranial magnetic stimulation of the M1 area of the healthy side both had a positive effect on the recovery of motor function in patients with subcortical strokes when compared with the sham stimulation group. And that the 10Hz group was more conducive to reorganisation of the functional connectivity of the motor network of the brain on the affected side, which resulted in a greater benefit for the recovery of motor deficits in the upper limbs.

(2) Low-frequency repetitive transcranial magnetic stimulation: It has been found [25] that 3 Hz repetitive transcranial magnetic stimulation of the affected hemisphere and 1 Hz repetitive transcranial magnetic stimulation of the healthy hemisphere can improve the motor function by regulating the excitability of the motor cortex in patients with subacute stage of stroke, and the effect of this can be sustained for at least 3 months after the intervention, and the effect of this can be more far-reaching than that of the 3 Hz repetitive transcranial magnetic stimulation of the affected hemisphere in improving the functional disorders of the upper limb. In terms of improving upper limb dysfunction, 1 Hz repetitive transcranial magnetic stimulation in the healthy hemisphere had a more profound effect than 3 Hz repetitive transcranial magnetic stimulation in the affected hemisphere. It has also been

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shown [25] that rTMS stimulation of the M1 region of the healthy cerebral hemisphere at 1 Hz in patients with dominant hemisphere stroke improves the dexterity of the patient's hand after stroke, with a nonsignificant short-term (3-week) effect and a significant long-term (6-month) effect.

(3) Combination of high-frequency and low-frequency: Long et al. [30] demonstrated that the combined application of high-frequency repetitive transcranial magnetic stimulation and low-frequency repetitive transcranial magnetic stimulation can effectively promote the recovery of upper limb motor function in patients with acute stroke, and that this treatment plan is more easily tolerated by patients. A study by Chen et al. [31] also found that in the subacute phase of stroke, the combined application of low-frequency and high-frequency repetitive transcranial magnetic stimulation had a synergistic effect on the improvement of motor function and cortical excitability in patients.

(4) Peripheral magnetic stimulation: Experiments have proved [25] that magnetic stimulation of muscles or peripheral nerves can help the recovery of upper limb motor function in stroke patients by promoting plasticity changes in the M1 area and providing sensory inputs.Chen et al. [32] proved that peripheral magnetic stimulation can improve the upper limb Fugl-Meyer scores and Barthel indices of patients with stroke, and the therapeutic efficacy is better than low-frequency repetitive transcranial magnetic stimulation. transcranial magnetic stimulation. It was also found that repetitive peripheral magnetic stimulation could reduce the upper limb flexor muscle spasm on the hemiplegic side of stroke patients, which could help to improve the upper limb motor function and the ability of daily life activities of the patients.

3.2. Repeat the effect of transcranial magnetic stimulation on cognitive dysfunction

Post-stroke cognitive dysfunction refers to a series of syndromes of cognitive impairment within 6 months after stroke, which not only leads to cognitive dysfunction, but also accelerates the cognitive dysfunction of the patients and eventually progresses to dementia. Early cognitive rehabilitation training not only improves cognitive dysfunction of post-stroke patients, but also promotes the recovery of daily life activities of the patients. A large number of studies have been conducted at home and abroad on the effects of repetitive transcranial magnetic stimulation on cognitive function, showing that repetitive transcranial magnetic stimulation can improve aphasia, unilateral spatial neglect or other cognitive dysfunctions in patients with stroke [25]. Moser et al. performed repetitive transcranial magnetic stimulation on 19 patients with executive dysfunction, and found that the TMT and SCWT scores of patients in the repetitive transcranial magnetic stimulation group were significantly higher than those of the pseudo-stimulation group, thus significantly increasing the TMT, SCWT scores of patients with stroke. The results showed that the TMT, SCWT and other test scores of patients in the repeated transcranial magnetic stimulation group were significantly higher than those of the pseudo-stimulation group, thus indicating that the executive function of patients in the repeated transcranial magnetic stimulation group improved significantly compared with that of the pseudo-stimulation group, and facilitated the reconstruction of the cortical network. Chinese scholars [33] randomly divided 40 patients with post-stroke cognitive dysfunction into magnetic stimulation group and pseudostimulation group, and received 1Hz transcranial magnetic stimulation to stimulate the dorsolateral cortex of the right prefrontal cortex. After 4 weeks of treatment and 2 months after the end of treatment, the patients' cognitive assessment and behavioral memory scale scores were significantly improved and significantly better than those of the sham-stimulation group, which was considered to be a possible result of activation of the structure of the cortico-subcortical neural network and changes in synaptic plasticity. Overseas scholars and others [33] selected seven cases of cerebrovascular patients with mild executive dysfunction as research subjects. They set the frequency of repetitive transcranial magnetic stimulation to 10Hz, and set the pulse count to 450. They selected the stimulation site as DLPFC and conducted neuropsychological tests before and after treatment. The results of the study showed that high-frequency repetitive transcranial magnetic stimulation of the DLPFC improved patients' problem-solving abilities. The repetitive transcranial magnetic stimulation may modulate activity in specific neural circuits involved in information processing in a given cognitive domain. And its long-lasting effects may be due to indirect activation of the DLPFC, located in the midbrain (dopamine) and/or the brainstem (norepinephrine and serotonin), as well as its cortical and subcortical targets.

3.3. Repeat the effect of transcranial magnetic stimulation on pain dysfunction

After systematic and comprehensive rehabilitation treatment, most stroke patients' motor and sensory functions have recovered to different degrees, but some of them still have persistent pain in the

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affected limbs. The pain related to the injured area after stroke and excluding other causes is called post-stroke central pain. The pain can occur within a few days after stroke and can last for months or even years, which has a serious impact on the patient's psychological and other functional recovery, and is not conducive to the patient's recovery progress. At present, the clinical mechanism of the pain is still unclear, and neuropathic medication is the mainstay of the treatment, but because the effect of medication is unclear, and prolonged use of the medication may lead to drug dependence, the clinical guideline recommendation level is not high. Some foreign researchers have also reported that repetitive transcranial magnetic stimulation is used to treat central pain after stroke, and the primary motor area (M1) may be a more effective site of action for pain relief [33]. Kobayashi et al. [34] selected 18 cases of patients with central pain after stroke to be included in the study, and selected 10 columns and 10s of 5Hz-repetitive transcranial magnetic stimulation trains to stimulate the affected side of the M1 area, and the repetitive transcranial magnetic stimulation was delivered through the primary motor cortex on the affected side. The repetitive transcranial magnetic stimulation sessions were repeated once a week for 12 weeks and intervened for one year in six of the patients. Repetitive transcranial magnetic stimulation was effective in 61.1% of patients at week 12. The findings suggest that repetitive transcranial magnetic stimulation of the primary motor cortex once a week to maintain the primary motor cortex helps to relieve post-stroke pain.

3.4. Repeated effects of transcranial magnetic stimulation on swallowing dysfunction

The need for improvement of swallowing dysfunction after stroke was demonstrated in a study that followed 570 patients with post-stroke swallowing dysfunction for a period of 3 months with the same number of patients without swallowing dysfunction after stroke and found that dysphagia still affects the majority of stroke patients and may have a significant impact on clinical outcomes, mortality and hospitalization [33]. Simons et al. [35] found that that RTMS can painlessly stimulate the brain through the intact skull and was used to study the physiological phenomena of swallowing and the effects of dysphagia, finding positive efficacy of RTMS in the recovery of neurogenic dysphagia. And related studies found [33] using RTMS with dysphagia related muscle groups are mostly innervated by bilateral motor hemispheres and premotor cortex, in which the dominant hemisphere is in a guiding position for swallowing, and the enhancement of non-dominant hemisphere premotor cortex related areas facilitates the recovery of swallowing function. In another study [33], the posterior cranial fossa stimulated the cerebellum and elicited a direct motor response in the pharynx by administering paired pulse paradigms with active or sham RTMS conditioning pulses to cerebellar and control sites followed by suprathreshold RTMS training in the cortical pharyngeal region, with the paired pulses being delivered at different stimulation intervals and assessing the magnitude of the cortical response. When used in conjunction with repetitive transcranial magnetic stimulation, the cerebellum was able to strongly facilitate motor pathways in the swallowing cortex. This finding suggests that repetitive transcranial magnetic stimulation is useful in the treatment of nerve damage by increasing excitatory neurostimulation of the cerebellum for recovery from dysphagia after injury may have a therapeutic role.

3.5. Repeated effects of transcranial magnetic stimulation on depression

Post-stroke depressive state is one of the common complications of cerebrovascular disease. Repetitive transcranial magnetic stimulation has been increasingly studied as a non-invasive treatment in various psychiatric disorders, including depression, and it has been approved by the US Food and Drug Administration for the rehabilitation of major depression. Currently there is no clear statement for the mechanism of post-stroke depression, but Yulug et al. [36] showed that repetitive transcranial magnetic stimulation may act on oxidative damage, stress hormones, dopamine and 5-hydroxytryptamine levels, expression of brain-derived neurotrophic factors, neuroinflammation, and hippocampal cell proliferation, and play an important neuroprotective role, so repetitive transcranial magnetic stimulation has a clinical depression therapeutic and neurorestorative effects in clinical depression. It has therapeutic and neurorestorative effects in clinical depression. Gu et al. [37] randomized chronic stroke patients into two groups: the repetitive transcranial magnetic stimulation group, in which patients received ten high-frequency (10Hz) stimulations, and the sham-operated group, in which patients received ten sham-operated stimulations. The results of the functional assessment using the Beck Depression Scale, and the 17 items of the Hamilton Depression at two time points before and after the intervention showed that the Beck Depression Score and the 17 items of the Hamilton Depression Score of the Repetitive Transcranial Magnetic Stimulation Group were significantly lower than those of the Sham Surgery Group. The results suggest that repetitive

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transcranial magnetic stimulation is a beneficial treatment for post-stroke depression. The results suggest that rRTMS is a beneficial treatment for post-stroke depression.

4. Summary

In summary, evidence from both clinical and basic research has demonstrated that repetitive transcranial magnetic stimulation is a feasible nonpharmacological intervention modality to promote recovery from multiple dysfunctions and complications of stroke after intracranial atherosclerosis. However, the large number of stimulation parameters and the complexity of the mechanism of action of repetitive transcranial magnetic stimulation may be the main reason for the heterogeneity of the current clinical outcomes and the results of basic research. Significant differences in terms of different intervention protocols and clinical outcome indicators have made the study of optimal stimulation parameters very difficult. Therefore, for more effective stimulation protocols, multicenter studies with larger sample sizes should be conducted after detailed evaluation, which will help clinicians to translate them into clinical practice protocols as early as possible, and help more patients to achieve precise treatment.

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