International Journal of Engineering Inventions
e-ISSN: 2278-7461, p-ISSN: 2319-6491
Volume 12, Issue 6 [June. 2023] PP: 125-132

Research Progress in the Treatment of Primary Insomnia with Repetitive Transcranial Magnetic Stimulation

Hou Yongmei
Department of Psychology, School of Humanity and Administration, Guangdong Medical University, Dongguan, Guangdong Province, China

[Abstract] *Primary insomnia is a worldwide mental health problem, which will not only cause heart disease, hypertension, diabetes and mental illness, but also cause work-related injuries, car accidents, suicide and other malignant events. Repetitive transcranial magnetic stimulation (rTMS) has become a new trend in the treatment of primary insomnia due to its effectiveness, safety, and non addiction. This article provides a review of research on the treatment of primary insomnia with repetitive transcranial magnetic stimulation, in order to provide reference for future clinical research.*

Key word: *Primary insomnia (PI); transcranial magnetic stimulation (TMS); epetitive transcranial magnetic stimulation (rTMS); Pittsburgh Sleep Quality Index (PSQI); Polysomnography (PSG)*

Date of Submission: 03-06-2023 Date of acceptance: 13-06-2023

I. Introduction

Primary insomnia (PI) belongs to sleep disorders, which refers to a subjective experience of dissatisfaction with sleep time and/or quality despite appropriate sleep opportunities and environments, without clear physical reasons, and affecting daytime social function. Its main clinical manifestations include repeated difficulty in falling asleep, easy of waking up after falling asleep, difficulty in falling asleep again after waking up, reduced sleep time, and decreased sleep quality. PI is a global mental health problem and the second most prevalent mental illness in neurology clinics [1]. Approximately 30% of adults worldwide experience insomnia symptoms [2]. Currently, the incidence of primary insomnia in China is 15%, and this incidence rate is on the rise year by year [3]. Although insomnia is not a critical disease, chronic insomnia will not only seriously affect the quality of life and work efficiency of patients, but also lead to a decline in cognitive function [4], causing anxiety and depression, inducing or aggravating physical diseases, increasing the risk of aging, dementia, diabetes, cardiovascular disease, cancer and suicide [5-10], and increasing the social medical burden.

There are two types of hypotheses about the pathogenesis of primary insomnia [11]: 1) excessive arousal. The main manifestation is an increase in the proportion of awakening time or degree of awakening in the central nervous system, and persistent excessive awakening, insufficient night sleep, difficulty falling asleep, and enhanced sympathetic nerve excitability. 2) The 3P hypothesis. It is believed that insomnia has three factors: maintenance, promotion, and susceptibility. Susceptibility factors are significantly related to personality development and the development of sleep regulatory centers; Triggering factors refer to the troubling events that may be encountered in work and life; Maintenance factors refer to factors that promote the occurrence of insomnia.

At present, there is no specific method for treating primary insomnia, and mostly use sedative and hypnotic drugs [12] or traditional Chinese medicine [13], psychological therapy [2], physical therapy [12], etc. Sedative and hypnotic drugs have strict indications and contraindications, which can easily lead to dependence, rebounding after drug reduction and withdrawal, and adverse reactions [14]. Traditional Chinese medicine can regulate body functions and fundamentally improve sleep quality, but its "syndrome and treatment differentiation" requires extremely high skills, and the mechanism of treatment also needs to be clarified [14]. Cognitive behavioral therapy and other psychotherapy have definite therapeutic effects, but their clinical application is limited due to their complex operation, high cost, slow onset, poor patient acceptance and compliance [11].

Transcranial magnetic stimulation (TMS), initiated by Barker et al. [15], is an effective, non-invasive and painless neurophysiological (physical) technology to change the membrane potential activity of brain nerve cells [16]. It has the characteristics of high safety, good tolerance, no addiction, easy operation, etc. Its mechanism can be simply described as follows: the time-varying current pulse generated by the magnetic field generator is introduced into the insulation coil on the scalp surface, so that the time-varying high flux magnetic field passes through the skull without attenuation, induces the induced electric field in the cerebral cortex and acts on the nerve cell membrane, changes the excitability of neurons, produces depolarization or

hyperpolarization, and regulates the metabolism and electrophysiological activities of neurotransmitters. Repetitive transcranial magnetic stimulation (rTMS) is to repeatedly stimulate specific areas of the cerebral cortex at a fixed frequency and intensity, enhance the influence of local and decentralized single pulse transcranial magnetic stimulation, and change the neurophysiology of brain nerve cells [17].

RTMS was originally used for the evaluation of cortical evoked potentials and the study of human brain function. It has now been widely used to treat various mental disorders such as insomnia and depression, and has good clinical application value [16]. In recent years, domestic and international studies [10] have shown that rTMS intervention can effectively improve the sleep structure and quality of PI patients, and has good safety and maintenance effects [12, 18].

II. The mechanism of rTMS in the treatment of PI

2.1 Regulating cortical metabolism levels

Neuroimaging shows that the excitability of bilateral DLPFC in patients with insomnia is higher than that in healthy people. TMS measurement also shows that the cortex is overexcited among healthy people with restless legs syndrome, obstructive sleep apnea syndrome, chronic insomnia and sleep deprivation [19-22]. RTMS can regulate the excitability/plasticity of the stimulated and connected regions, so cortical excitability can be regulated, promoted, or suppressed based on stimulation parameters, especially stimulation frequency.

Transcranial magnetic stimulation is mainly divided into three stimulation modes: single stimulation, paired stimulation and repetitive stimulation. The single stimulation mode is mainly used for nerve detection, paired stimulation is mainly used to study the inhibition and facilitation of cerebral cortex, and repetitive stimulation mode is used for clinical treatment. The repetitive stimulation mode includes conventional rTMS and Theta burst stimulation (TBS). Compared with single pulse and paired TMS, rTMS can induce sustained changes in neural activity, affect cortical metabolism by regulating stimulation frequency, and regulate brain excitatory and inhibitory functions. High frequency rTMS (>5Hz) can cause an increase in the excitatory and metabolic levels of local brain tissue, while low frequency rTMS (1-5Hz) can reduce the excitatory and metabolic levels of local brain tissue [15]. A study found that rTMS can increase the amplitude of brain waves in slow-wave sleep, ensure the quality of deep sleep, improve memory, and help the body recover; and rTMS can also be used as a non drug means to induce the appearance of slow waves in cerebral cortex [23]. Therefore, rTMS can reverse the disordered pattern of brain excitability, similar to the response after drug treatment. High frequency rTMS can improve the metabolism and excitability of brain neurons, improve the secretion and release of sleep related neurotransmitters, induce hyperpolarization of cortical neurons, reduce the metabolism and excitability of corresponding cortex, and reduce the amplitude of action evoked potential (MEP) that reflects the excitability of motor cortex, thus playing a role in improving sleep. LANZA G et al. [20] also showed that low-frequency (1Hz) rTMS can reduce the amplitude of MEPs in healthy control groups and patients with restless leg syndrome (RLS).

Abnormal brain network connectivity is one of the important causes of primary insomnia, and TMS combined with electroencephalography (EEG) can detect and improve excitability and dynamic connectivity in different regions of the brain. Song et al. [24] treated 20 patients with primary insomnia with low frequency (1 Hz) rTMS by directly acting on the right posterior parietal cortex nerve cells through pulsed magnetic fields. And then, transcranial Doppler ultrasound electroencephalography (TMSEEG) was performed before and after treatment. It was found that before treatment, there was too much information outflow in the left occipital area, midline frontal area and right posterior temporal area, and insufficient information outflow in the right central, parietal and temporal areas. After treatment, the information outflow from the left temporal area increased, while the information outflow from the midline frontal area decreased. It is suggests that rTMS can improve sleep quality by reversing abnormal connections in the brain network. Through a systematic review of relevant literature, Jiang et al. [25] found that rTMS is effective in treating primary insomnia, but the placebo effect of fake rTMS is very significant. It is speculated that the psychological expectation brought about by the placebo effect generates endogenous substances by acting on the sleep wake-up network, and then visualizes the psychological expectation through the neuroendocrine system. Further research is needed to confirm the mechanism of the placebo effect in the treatment of primary insomnia with rTMS.

2.2 Deepening sleep depth and adjusting sleep cycle

A complete sleep process includes two parts: non rapid eye movement (NREM) and rapid eye movement (REM) sleep. NREM sleep is divided into four sleep stages: the first (N1) and second (N2) stages are called light sleep, and the third (N3) and fourth (N4) stages are called deep sleep or slow-wave sleep. Each NREM sleep stage and its subsequent REM sleep form a sleep cycle, with 4-5 such sleep cycles typically occurring throughout the entire night. The waking phase can also occur between the two sleep cycles. As nighttime sleep progresses, the REM sleep duration gradually prolongs in various sleep cycle. Compared to healthy individuals, short term insomnia patients with increased arousal index, BMI index, and N1 phase

proportion, as well as decreased N3 duration and proportion, are more likely to cause chronic insomnia [26]. RTMS can deepen sleep depth and prolong sleep time by inhibiting the excessive arousal of cerebral cortex. Jiang et al. [27] randomly assigned 120 patients with chronic PI to three study groups, respectively receiving medication, cognitive behavioral intervention, and rTMS treatment on DLPFC. Compared with the drug therapy and cognitive behavioral intervention, rTMS treatment significantly improved the sleep cycle of phase 3 and REM, optimized sleep structure, improved sleep quality, and maintained treatment effectiveness.

2.3 Regulating the release of sleep related neurotransmitters

The neurotransmitters related to sleep are mainly cortisol, adrenocortical hormone, thyroid hormone, free T3 and T4, 5-hydroxytryptamine (5-HT), dopamine, melatonin, γ-Gamma aminobutyric acid (GABA), etc. [28]. The secretion of most neurotransmitters is related to different brain regions, in which 5-HT neurons are concentrated in the raphe nuclei, and the dorsal lateral prefrontal cortex (DLPFC) can induce the release of dopamine and melatonin, which provides a reference target for rTMS to treat primary insomnia. Previous studies found that the brain of PI patients is mostly in the state of excessive arousal. The more serious insomnia is, the more active the hypothalamic-pituitary-adrenal axis (HPA) and hypothalamic-pituitary-thyroid axis (HPT) are, which leads to the increase of serum cortisol, adrenocortical hormone, thyroid hormone, free T3 and T4 [29]. In addition, 5-HT, as an important component of the upstream activation system, plays an important role in maintaining arousal and alertness, and its increase in content is also an important mechanism for promoting sleep [30]. GABA is an inhibitory neurotransmitter closely related to the excitability of the cerebral cortex [31]. The increase of GABA can cause the inhibition of sympathetic preganglionic neurons, reduce the activity of neurons , slow down the nerve conduction velocity [32], which weakens the synaptic connections of the brainstem reticular structure. The brainstem reticular structure is the common uplink channel of the non-specific projection system, and the weakening of its synaptic connections will inhibit the function of the brainstem uplink reticular excitation system, which is beneficial for increasing non rapid eye movement sleep (NREMS). Low frequency rTMS can reduce local brain tissue metabolite levels, downregulate HPA and HPT activities, promote the release of 5-HT and melatonin [33], increase GABA [34], and lower content dopamine in the brain [35], thus regulate the sleep-wake cycle, increase NREMS, and promote sleep. Animal experiments show that rats deprived of REM sleep increase the content of GABA in the brain, which is considered as a self-regulation mechanism of sleep deprived animals [36]. Zhang et al. [37] conducted rTMS treatment on insomnia officers and soldiers who rushed to high altitude and found that their serum GABA levels significantly increased, PSQI scores significantly decreased, and sleep quality significantly improved. It is suggested that rTMS can improve high-altitude insomnia by increasing serum GABA, exerting its neuroinhibitory effect. Brain derived neurotrophic factor (BDNF) is a kind of active peptide hormone that can nourish nerves. It belongs to one of the four major neurotrophin that have been found, and plays a role in physiological regulation of neuron development, survival, apoptosis, etc., mainly through receptor tyrosine kinase B (TrkB) [38]. In sleep deprivation rats, it is found that the increase of REM phase frequency in the sleep cycle is closely related to the increase of BDNF in the body, which may be a rebound phenomenon caused by brain self-regulation [39]. In addition, studies on sleep disorders associated with depression, stress, and cognitive impairment have shown that BDNF can improve insomnia symptoms [40-41]. Based on the above analysis, we have evidence that both BDNF and GABA are involved in sleep regulation, and BDNF can promote GABA's inhibitory function on neurons. A study investigated the impact of low-frequency rTMS treatment on primary insomnia patients with bilateral DLPFC. After rTMS treatment, the PSQI scores significantly decreased, the serum BDNF and GABA concentrations significantly increased, and the amplitude of MEPs significantly decreased; the changes in PSQI scores are positively correlated with changes in the amplitude of MEPs, and negatively correlated with changes in serum BDNF and GABA levels; and the amplitude of MEPs is negatively correlated with changes in serum BDNF and GABA levels. Therefore, rTMS may reduce cortical excitability by regulating the levels of BDNF and GABA in the brain [31].

2.4 Promoting cognitive function recovery

PI patients often suffer from cognitive impairment, which seriously affects their quality of life. The hippocampus is one of functional areas of the brain, which is related to human cognition and is particularly important for spatial learning and memory. More and more evidence shows that neurogenesis in the hippocampus plays an important role in cognitive function [42]. Guo et al. [43] performed rTMS stimulation on rats with middle cerebral artery occlusion (MCAO) for 3 seconds, resting for 50 seconds, and repeating 10 times at a frequency of 10 Hz (300 times per day) with a stimulation intensity of 120% MT. The results showed that rTMS promoted the neurogenesis of ipsilateral hippocampus after focal cerebral ischemia, inhibited neuronal apoptosis, increased the expression level of BDNF signal components in ischemic hippocampus, and changed the expression level of apoptosis related proteins. It can be seen that rTMS promotes cognitive recovery by regulating extracellular factors related to neurotrophin such as BDNF in the hippocampus. On the other hand,

the Wisconsin Card Test (WCST) was used to evaluate cognitive impairment of the patients. The results also showed that the rTMS group had significantly higher therapeutic effects on abstract generalization, work, and cognitive transfer than the control group, indicating that rTMS had a certain improvement in cognitive function [42].

2.5 Regulating neuroendocrine levels

The dysfunction of the hypothalamic-pituitary-adrenal axis (HPA axis) is one of the neurobiological factors of insomnia. Under normal circumstances, the activity of HPA axis follows the circadian rhythm. Specifically, glucocorticoids rapidly increase in the second half of the night and reach their peak shortly after waking up (i.e. cortisol arousal response), gradually decreasing during the day and reaching their lowest level (lowest point) in the first half of the night, typically 1-2 hours after sleep begins [44-45]. The increase in cortisol is believed to be related to staying awake during the day, and their relative loss at night may consolidate sleep and/or shorten nocturnal awakening time [46]. The application of low-frequency rTMS on the right DLPFC of PI patients has advantages in improving the function of HPA axis, which can reduce the contents of serum thyroid hormone (TSH), adrenocorticotropic hormone (ATCH), serum free triiodothyronine (FT3), and serum free thyroxine (FT4) [27]. Another study [47] pointed out that applying rTMS treatment to PI patients significantly reduced their sleep quality scores, T3, T4, and TSH. It can be seen that rTMS effectively inhibits high levels of arousal in the cortex of PI patients and improves parameters such as sleep efficiency and quality. Its mechanism is mediated by inhibiting excessive stimulation of the HPA axis in the body and reducing the serum concentration of these hormones.

III. Clinical efficacy and side effects of rTMS in the treatment of PI

3.1 Clinical efficacy

There are many related studies both domestically and internationally, including pre-and post test and inter group control studies of rTMS treatment, comparison between rTMS treatment and drug or non-drug treatment, and comparison between rTMS treatment combined with other therapies and rTMS treatment alone or other therapies alone. Various research ideas and protocols have confirmed the effectiveness of rTMS treatment on PI, which can improve the subjective experience (scale evaluation results), objective detection indicators (EEG test results), and neuroendocrine of patients' sleep quality. The effect of rTMS treatment combined with other therapies is better than that of rTMS alone or other therapies alone.

3.1.1 Clinical efficacy of rTMS alone on PI

Some studies [47] have found that rTMS can reduce scores of PSQI and serum T3, T4, and TSH in patients with PI. There have also been studies on the EEG network of rTMS in treating PI, indirectly demonstrating the clinical efficacy. For example, Song et al. [24] located low-frequency (1Hz) rTMS in the right posterior parietal cortex to treat PI patients. EEG showed insufficient information outflow in the left posterior temporal area, midfrontal area, and middle right area of PI patients. Low frequency (1Hz) rTMS stimulation of the right parietal region reversed these changes and improved clinical symptoms, resulting in a decrease in total PSQI score. The Insomnia Severity Index (ISI) and Epworth Sleepiness Scale (ESS) scores both decreased, and the patient's sleep quality significantly improved. Nardone et al. [48] found that applying low-frequency (1Hz) rTMS to the primary motor area (M1) can effectively reduce cortical overexcitement in PI patients, improve abnormal changes in motor evoked potential (MEP) amplitude, and thus improve sleep quality. In summary, whether from the comparison of clinical scales or EEG studies of patients, although the stimulation of brain regions is different, the efficacy of rTMS in treating PI is still significant. The shortcomings are that the research tools are relatively single and there is a lack of long-term efficacy tracking.

3.1.2 Comparison of clinical efficacy between rTMS and other therapies for PI

Research in this area includes rTMS and drug therapy, as well as comparisons between rTMS and non drug therapy. There are different opinions on the superiority and inferiority of rTMS compared to other therapies. Some studies suggest that drugs have faster onset and better short-term effects, while rTMS has slower onset and better long-term effects; and the therapeutic effect of rTMS is superior to other non drug therapies: easy to operate, safe and economical, faster onset, and better efficacy.

⑴ Comparison of clinical efficacy between rTMS and drug therapy on PI

Wang et al. [49] divided 189 PI patients into an experimental group (n=101), and a control group (n=88). The experimental group received rTMS, while the control group received conventional medication (estazolam). There was no statistically significant difference in PSQI scores between the two groups before treatment. During treatment, PSQI scores inboth groups decreased, with the lowest at the 5th to 10th day of

treatment. The decrease in the drug group was greater than that in rTMS group; After treatment, PSQI scores of rTMS group slightly increased, while those of the drug group increased more significantly.

Wu et al. [12] divided 80 PI patients into a control group and an observation group with a random number table, with 40 patients in each group. The control group received alprazolam treatment, while the observation group received rTMS. There was no statistically significant difference in the scores of PSQI between the two groups before treatment. After treatment, the PSQI scores and PSG monitoring indicators in the observation group were significantly lower than those in the control group, while sleep efficiency, REM duration, awakening frequency, and sleep latency were significantly better than those in the control group.

⑵ Comparison of clinical efficacy between rTMS and non drug therapy on PI

Ni et al. [50] used a random number table to divide 100 PI patients into an ob-servation group (50 cases) and a control group (50 cases). The control group received alt-ernating magnetic field therapy, while the observation group received rTMS therapy. The PSQI scores, serum glycine, glutamate, and GABA before and after treatment were compared. The results showed that there was an intergroup effect in the PSQI scores of the two

groups, and the treatment effect of observation group was better than that of the control group, and the total effective rate of treatment (96.0%) was higher than that of the control group (74.0%); there was an intergroup effect (both $P<0.05$) on the levels of various neurotransmitters, and the therapeutic effect of the observation group was better than that of the control group; both groups had a time effect ($P<0.05$), and there was an interaction effect between grouping and time ($P<0.05$). It was shown that the levels of various neurotransmitters in the two groups showed a trend of change over time, and the effect of time factor in the observation group was more significant.

3.1.3 Clinical efficacy of rTMS combined with other therapies on PI

⑴ Clinical efficacy of rTMS combined with drug therapy

The combination of rTMS and hypnotic sedative drugs is the most common and has been proven to improve drug efficacy. Zhang et al. [51] divided 114 PI patients into a study group (n=57) and a control group (n=57) with a random number table. The control group received estazolam combined with pseudo stimulation of ILF-TMS, while the study group received estazolam combined with real stimulation of ILF-TMS. After one month of treatment, the total effective rate of the study group was higher than that of the control group, the total sleep time and sleep efficiency were higher than those of the control group, the time to fall asleep and wake up were shorter than those of the control group, the stage II and III of NREM were longer than those of the control group, while the stage I of sleep was shorter than that of the control group; the PSQI, ISI, SAS, SDS scores were lower than those of the control group, and the serum GDNF, BDNF were higher than those of the control group.

The combination of rTMS with traditional Chinese medicine therapy is a trend in the treatment of PI in China. Among them, acupuncture and moxibustion combined with rTMS has a gratifying effect. After treatment, patients' various sleep parameters and insomnia severity index significantly reduced. Polysomnography (PSG) also showed that compared to before treatment, the sleep latency was significantly shortened, the number of awakenings was significantly reduced, the REM time was increased, and sleep efficiency was significantly improved. Two months of follow-up after treatment showed that sleep parameters of the study group were still significantly better than those of the control group [52]. Hou [53] divided 86 PI patients into two groups: the control group (n=43) received oral Modified Jieyu Ningxin Tang, while the study group (n=43) received transcranial magnetic stimulation treatment in addition to Modified Jieyu Ningxin Tang. Both groups were treated continuously for 14 days. The total effective rate of treatment in the study group (93.02%) was significantly higher than that in the control group (76.74%). After treatment, the PSQI scores of both groups significantly decreased, and the PSQI scores of study group were significantly lower than those of control group. The serum 5-HT in both groups were significantly higher than before treatment, while DA were significantly lower than before treatment. The serum 5-HT in the study group was significantly higher than that in the control group, while DA was significantly lower than that in the control group.

⑵ Clinical efficacy of rTMS combined with other non drug treatments on PI

Guo [54] divided 133 PI patients into a control group and an observation group with a random number table: the control group received five tone therapy, while the observation group received rTMS on the basis of five tone therapy. After 2 weeks of treatment,the total effective rate of the observation group (96.97%) was higher than that of the control group (86.57%); The total score of PSQI and scores of 7 dimensions in the observation group were lower than those in the control group, while the HAMA and HAMD scoreswere lower than those in the control group; There was no statistically significant difference in the incidence of adverse reactions between the observation group (6.06%) and the control group (8.96%).

Zhang et al. [55] divided 98 PI patients into a study group (n=51) and a control group (n=47). The

control group received LF-TMS treatment, while the study group received CBT combined with LF-TMS treatment. The treatment effects, sleep quality, and adverse emotions of the two groups were compared. The results showed that the total effective rate of the study group was 94.12%, significantly higher than 78.72% in the control group ($P<0.05$). After treatment, the PSQI scores, HAMD and HAMA scores of the study group were significantly lower than those of the control group ($P<0.05$).

3.1.4 Clinical efficacy of rTMS at different sites

Lu et al. [56] divided 160 PI patients into sham stimulation group, left group, right group, and Cz group, with 40 patients in each group. The sham stimulation group received rTMS sham stimulation treatment, while the left group, right group, and Cz group received rTMS treatment at three different locations respectively: left dorsolateral prefrontal cortex (DLPFC), right DLPFC, and 1cm after Cz point. After treatment, the total score and subscale scores of DBAS, SDMT and MoCA scores of the Cz group, left group, and right group increased; the PSQI scores of the Cz group, left group, and right group were all lower than those of the sham stimulation group, while the total score and subscale scores of DBAS, SDMT, and MoCA scores were higher than those of the sham stimulation group ($P<0.05$); The scores of PSQI and DBAS consequence subscale score in the left and right groups were lower than those in the Cz group; DBAS total score and scores on subscales except for the consequence subscale, SDMT and MoCA scores of the Cz group, left group, and right group increased; the scores of expectation, control, and prediction subscales of DBAS in the right group were higher than those in the left group; the P3 peak latencies of ERPs in the Cz group, left group, and right group were shorter than before treatment, and the P3 amplitudes were higher than before treatment; compared with the sham stimulation group, the P3 peak latencies of ERPs in the Cz group, left group, and right group were shortened, and the P3 amplitudes were increased; compared with the Cz group, the P3 peak latencies of ERPs in both the left and right groups shortened, and the P3 amplitudes increased. The total effective rates of the Cz group, left group, and right group were higher than that of the sham stimulation group. The total effective rates of the left and right groups were higher than those of the Cz group. There was no statistically significant difference in total effective rate between the left and right group. It can be seen that rTMS treatment for left DLPFC or right DLPFC can significantly improve the sleep quality, sleep beliefs and attitudes, and cognitive function of PI patients, and the efficacy is superior to other treatment areas.

3.2 Side effects of rTMS treatment for PI

The most common side effect is localized pain in the head and neck, which may be related to forced posture and head fixation during treatment. Additionally, some patients have a slight increase in their auditory threshold during treatment, and after treatment, their auditory threshold can gradually return to baseline levels. RTMS may also cause transient psychiatric symptoms, such as anxiety, syncope, but the probability of occurrence is extremely low [29]. The most serious side effect is seizure during treatment. The mechanism may be that pyramidal cells are overactivated and the excitement spreads to adjacent neurons. Epilepsy is most likely to occur in the first few days of treatment, or when pulses are applied at high frequencies and short intervals between stimulus sequences. If rTMS is implemented according to the guidelines, the incidence of epilepsy is less than 60/1000 [57].

IV. Limitations of previous research

Although existing research has made beneficial explorations into the mechanism and clinical efficacy of rTMS in treating PI, with high academic value, these studies still have many shortcomings. First, the frequency of stimulation given ranges from low frequency (1Hz) to high frequency (10Hz), but further research has not been conducted on the mechanisms of sleep improvement under these two types of frequencies, nor has defined the relationship between treatment effectiveness and stimulation frequency. Second, the treatment plan is not unified. The parameter settings used vary in terms of coil type, stimulation site, stimulation frequency, stimulation intensity, and stimulation quantity. The stimulation sites used in the literature included in the review include the dorsolateral prefrontal cortex, parietal lobe, frontal lobe, etc. The stimulation frequencies include ultra-low frequency, low frequency, and high frequency, and the stimulation intensity covers a resting motion threshold of 80% to 110%, with a total stimulation count of 700-5000. These different parameter settings result in a decrease in the comparability of clinical efficacy among various studies. Third, the treatment course and evaluation tools vary, reducing the comparability of efficacy between different studies. Final, the sample size is mostly small, which reduces the research efficiency and its generalizable value.

V. Research Prospects

First, uture research should increase research on brain imaging and cognitive function in the treatment of PI patients with rTMS, in order to further explore its therapeutic mechanism. Second, attempt to treat PI patients with multifrequency stimulation, and further clarify the therapeutic effects and related mechanisms

between different frequencies. Third, further standardize the brain area for treatment, stimulation time, and stimulation frequency to improve the effectiveness of stimulation. Final, expand the sample size and conduct a rigorous double blind randomized controlled study.

References

[1]. Motomura Y, Katsunuma R, Ayabe N, et al. Decreased activity in the reward network of chronic insomnia patients [J]. Sci Rep, 2021, 11(1): 3600.
[2]. Haynes J, Talbert M, Fox S, et al. Cognitive Behavioral Therapy in the Treatment of Insomnia [J]. South Med J, 2018, 111(2): 75-80.
[3]. Song LM, Lu SS, Wang DW, et al The correlation between sleep structure, attention, and memory in patients with chronic insomnia [J]. Journal of Shandong University (Medical Edition), 2019, 57(4): 52-58
[4]. Shekleton JA, Roger SNL, Rajaratnam SMW. Searching for the daytime impairments of primary insomnia [J]. Sleep Med Rev, 2010, 14(1): 47-60.
[5]. Pan XL, Su ZF. Research progress on the correlation between insomnia and telomere length and aging [J]. Chinese General Practice Medicine, 2023, 21(3): 481-484.
[6]. Hung CM, Li YC, Chen HJ, et al. Risk of dementia in patients with primary insomnia: A nationwide population-based case –control study [J]. BMC Psychiatry, 2018, 18(1): 38.
[7]. Shi T, Min M, Sun C, et al. Does insomnia predict a high risk of cancer? A systematic review and meta-analysis of cohort studies[J]. J Sleep Res, 2020, 29(1): e12876.
[8]. Benca RM, Buysse DJ. Reconsidering insomnia as a disorder rather than just a symptom in psychiatric practice [J]. J Clin Psychiatry, 2018, 79(1): 49-54.
[9]. Gel F, Guyatt G, Tian J, et al. Insomnia and risk of mortality from all-cause, cardiovascular disease, and cancer: Systematic review and meta-analysis of prospective cohort studies [J]. Sleep Med Rev, 2019, 48: 101215.
[10]. Jessica D, Ribeiro, James L Pease, Peter M Gutierrez, et al．Sleep problems outperform depression and hopelessness as cross-sectional and longitudinal predictors of suicidal ideation and behavior in young adults in the military [J]. J Affect Disord, 2012, 136(3): 743-750.
[11]. Krystal AD, Prather AA, Ashb Rook LH. The assessment and management of insomnia: An update [J]. World Psychiatry, 2019, 18: 337-352.
[12]. Wu DY, Zhuang XL. Clinical observation of repeated transcranial magnetic stimulation in the treatment of insomnia [J]. World Journal of Sleep Medicine, 2022, 9 (11): 2031-2033.
[13]. Yu YH, Min CY, Zhan F, et al. Clinical observation on the treatment of liver depression type insomnia with compound Tiaogan Yangxin Formula and its regulating effect on the structure of intestinal microflora [J]. Journal of Chinese Medical Materials, 2021, 44(9): 2210-2213.
[14]. Sleep Disorder Group, Neurology Branch, Chinese Medical Association. Guidelines for the diagnosis and treatment of insomnia in Chinese adults (2012)[J]. Chinese Journal of Neurology, 2012, 45(7): 534-540.
[15]. Barker AT, Shields K. Transcranial magnetic stimulation：Basic principles and clinical applications in migraine [J]. Headache, 2017, 57(3): 517-524.
[16]. Latorre A, Rocchi L, Berardelli A, et al. The use of transcranial magnetic stimulation as a treatment for movement disorders: A critical review [J]. Mov Disord, 2019, 34(6): 769-782.
[17]. Lefaucheur JP, Nathalie Andre-Obadia, Antal A, et al. Evidence-based guidelines on the therapeuticus of repetitive transcranial magnetic stimulation (rTMS) [J]. Clinical Nearo Physiology, 2014, 125(111): 2150-2206.
[18]. He Y, Sun N, Wang Z, et al. Effect of repetitive transcranial magnetic stimulation (rTMS) for insomnia: A protocol for a systematic review [J]. BMJ Open, 2019, 9(7): e29206.
[19]. LANZA G, BACHMANN CG, GHORAYEB I, et al. Central and peripheral nervous system excitability in restless legs syndrome [J]. Sleep Medicine, 2017, 31: 49-60.
[20]. LANZA G, LANUZZA B, ARICÒ D, et al. Impaired short-term plasticity in restless legs syndrome：a pilot rTMS study [J]. Sleep Medicine, 2018, 46: 1- 4.
[21]. LANZA G, CANTONE M, ARICÒ D, et al. Clinical and electrophysiological impact of repetitive low-frequency transcranial magnetic stimulation on the sensory-motor network in patients with restless legs syndrome[J]. Therapeutic Advances in Neurological Disorders, 2018, 11: 1276981541.
[22]. Salas Rem, Kalloo A, Earley CJ, et al. Connecting clinical aspects to corticomotor excitability in restless legs syndrome: A TMS study [J]. Sleep Medicine, 2018, 49:105-112.
[23]. Nardone R, Sebastianelli L, Versace V, et al. Effects of repetitive transcranial magnetic stimulation in subjects with sleep disorders[J]. Sleep Medicine, 2020, 71: 113-121.
[24]. Song P, Lin H, Li S, et al. Reprtitive transcranial magnetic stimulation (rTMS) modulates time-varying electroencepha-lography (EEG) network in primary insomnia patients: A TMS-EEG study [J]. Sleep, 2019, 56:157-163.
[25]. Jiang B, He D, Guo Z, et al. Efficacy and placebo response of repetitive transcranial magnetic stimulation for primary insomnia [J]. Sleep Medicine, 2019, 63: 9-13.
[26]. Wu DJ, Ruan LM, Ji Y, et al. The effect of sleep structural characteristics on the chronicity of insomnia in patients with short-term insomnia disorder [J]. Modern Practical Medicine, 2023, 35(2): 194-197.
[27]. Jiang CG, Zhang T, Yue FG, et al. Efficacy of repetitive transcranial magnetic stimulation in the treatment of patients with chronic primary insomnia [J]. Cell Biochemistry and Biophysics, 2013, 67(1): 169-173.
[28]. Peter LH, Holst Sebastian C, Amandine V. Clinical and experimental human sleep-wake pharmacogenetics [J]. Handb Exp Pharmacol, 2019, 253: 207-241.
[29]. Xia L, Chen GH, Li ZH, et al. Alterations in hypothalamus- pituitary- adrenal/thyroid axes and gonadotropin-relreasing hormone in the patients with primary insomnia: A clinical research [J]. PLoS ONE, 2017, 8(8):1-6.
[30]. Yang C, Ran MZ, Ouyang PR, et al. The role of serotonin in sleep awakening [J]. Progress in Modern Biomedical Sciences, 2015, 15(11): 2191-2194.
[31]. Feng J, Zhang Q, Zhang c, et al. The effect of sequential bilateral low frequency rTMS over dorsolateral prefrontal cortext on serum level of BDNF and GABA in patients with primary insomnia [J]. Brain Behav, 2019, 9(2): e1206.
[32]. Carlijn P, Wierenga Corette J. The postnatal GABA shift: A developmental perspective [J]. Neurosci Biobehav R, 2021, (124): 179-192.
[33]. Lu RL, Zhang CL, Liu YY, et al. The effect of bilateral low frequency rTMS over dorsolateral prefrontal cortext on serum brain-derived neurotropic factor and serotonin in patients with generalied anxiety disorder [J]. Neurosci Lett, 2018, 684:67-71.

[34]. Levitt JG, Kalender G, Joseph ON, et al. Dorsolateral prefrontalγ-aminobutyric acid in patients with treatment-resistant depression after transcranial magnetic stimulation measured with magnetic resonance spectroscopy [J]. J Psychiatr Neurosci: JPN, 2019, 44(6): 386-394.
[35]. Saima M, Mark J, Sang-Soo C, et al. Deep TMS of the insula using the H-coil modulates dopamine release: a crossover PHNO-PET pilot trial in healthy human [J]. Brain Imaging Behav, 2017, 12(5): 1306-1307.
[36]. Bao L, Si L, Wang Y, et al. Effect of two GABA-ergic drugs on the cognitive functions of rapid eye movement in sleep deprived and recovered rats [J]. Experimental and Therapeutic Medicine, 2016, 12(2): 1075-1084.
[37]. Zhang Y, Dong LP, Li JC, et al. The effect of repeated transcranial magnetic stimulation on serum GABA levels in soldiers with acute insomnia at high altitude [J]. Northwest Journal of National Defense Medicine, 2020, 41(9): 570-573.
[38]. BÉJOT Y, MOSSIAT C, GIROUD M, et al. Circulating and brain BDNF levels in stroke rats. Relevance to clinical studies [J]. PloS One, 2011, 6(12): e29405.
[39]. Datta S, Knapp CM, Koul-Tiwari R, et al. The homeostatic regulation of REM sleep: A role for localized [J]. Behavioural Brain Research, 2015, 292: 381-392.
[40]. BJÖRKHOLM C, MONTEGGIA LM. BDNF - a key transducer of antidepressant effects [J]. Neuropharmacology, 2016, 102: 72-79.
[41]. Giese M, Unternaehrer E, Brand S, et al. The interplay of stress and sleep impacts BDNF level [J]. PloS One, 2013, 8(10): e76050.
[42]. SUÁREZ-PEREIRA I, ÁM CARRIÓN. Updating stored memory requires adult hippocampal neurogenesis [J]. Scientific Reports, 2015, 5: 13993.
[43]. Guo F, Lou J, Han X, et al. Repetitive transcranial magnetic stimulation ameliorates cognitive impairment by enhancing neurogenesis and suppressing apoptosis in the hippocampus in rats with ischemic stroke [J]. Frontiers in Physiology, 2017, 8: 559.
[44]. Xi HQ, Wu WZ, Liu CY, et al. The acupuncture method of "Tongdu Tiaoshen" regulates the hypothalamic pituitary adrenal axis in the treatment of chronic insomnia [J]. Acupuncture Research, 2020, 45(7): 552-556.
[45]. Kong SL, Gao CY, Yang ZL, et al The effect of transcranial microcurrent stimulation on HPA, BDNF levels and clinical symptoms in patients with mild depression [J]. International Journal of Psychiatry, 2021, 48(1): 22-25.
[46]. Lv X, He H, Li XX, et al. Research progress on the correlation between HPA axis and insomnia disorder [J]. World Journal of Sleep Medicine, 2019, 6(7): 1009-1012.
[47]. Li J, Peng JL, Zhang G. The efficacy of repetitive transcranial magnetic stimulation combined with Tianma injection in the treatment of insomnia patients and its effect on hormone levels in the hypothalamic-pituitary-thyroid axis [J]. Journal of Shenyang Pharmaceutical University, 2021, 38 (S2): 42-43.
[48]. Nardone R, Golaszewski S, Frey V, et al. Altered response to repetitive transcranial magnetic stimulation patients with chronic primary insomnia [J]. Sleep Med, 2020, 72(prepublish): 126-129.
[49]. Wang YG, Li YL, Lin JY, et al. Comparative analysis of repeated transcranial magnetic stimulation (rTMS) and estazolam in the treatment of insomnia [J]. Journal of Rare Diseases, 2023, 30(3): 80-81.
[50]. Ni Z, Liu L. Clinical effects and neuroendocrine effects of low-frequency repetitive transcranial stimulation on patients with primary insomnia [J]. Chinese General Practice Medicine, 2022, 20(1): 62-64.
[51]. Zhang Y, Guo YP, Yang QC. Effects of ultra-low frequency transcranial magnetic stimulation combined with estazolam on sleep EEG parameters and serum neurotrophin expression in patients with insomnia [J]. Guangzhou Pharmaceutical, 2022, 53(3): 32-37.
[52]. Zhang YP, Liao WJ, Xia WG. Effect of acupuncture cooperated with low-frequency repetitive transcranial magnetic stimulation on chronic insomnia：A randomized clinical trial [J]. Current Medical Science, 2018, 38(3): 491-498.
[53]. Hou HC. Clinical study on the treatment of insomnia patients with liver depression and spleen deficiency syndrome by transcranial magnetic stimulation combined with Modified Jieyu Ningxin Tang [J]. Heilongjiang Medicine Journal, 2021, 34(2): 340-342.
[54]. Guo YT. Analysis of the therapeutic effect of repetitive transcranial magnetic stimulation therapy on insomnia [J]. Chinese Medical Device Information, 2022, 28(10): 153-155.
[55]. Zhang HF, Guo H, Jia JD, et al. The efficacy of cognitive behavioral therapy combined with low-frequency transcranial magnetic stimulation in the treatment of insomnia [J]. Clinical Medical Engineering, 2022, 29(4): 451-452.
[56]. Lu Y, Liu JT, Zheng C, et al. Observational study on the efficacy of repeated transcranial magnetic stimulation at different sites in the treatment of chronic insomnia and the improvement of cognitive function [J]. Journal of Psychiatry, 2021,34(5): 440-444.
[57]. Lerner AJ, Wassermann EM, Tamir DI. Seizures from transcrnial magnetic stimulation 2012-2016: results of a survey of active laboratories and clinics [J]. Clin Neurophysiol, 2019, 130(8): 1409-1416.