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Research Progress on the Neural Mechanisms and Brain Network Plasticity of Repetitive Transcranial Magnetic Stimulation in the Treatment of Chronic Insomnia

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Abstract: Chronic insomnia is a common sleep disorder characterized by difficulty initiating sleep, difficulty maintaining sleep, or early morning awakening. Accumulating evidence suggests that chronic insomnia is not merely a consequence of sleep loss or psychological stress, but a neuropsychiatric disorder involving abnormal cortical excitability, neurotransmitter imbalance, hypothalamic–pituitary–adrenal axis hyperactivation, and disrupted large scale brain network connectivity. In recent years, repetitive transcranial magnetic stimulation, as a safe and noninvasive neuromodulation technique, has shown promising therapeutic potential in the treatment of chronic insomnia. By modulating cortical excitability, synaptic plasticity, neurotransmitter release, and functional connectivity among sleep related brain networks, repetitive transcranial magnetic stimulation may improve sleep initiation, sleep maintenance, and associated emotional symptoms. This review summarizes the neurophysiological basis of chronic insomnia, the mechanisms and stimulation parameters of repetitive transcranial magnetic stimulation, and recent advances in brain network plasticity research related to its therapeutic effects. Current evidence indicates that repetitive transcranial magnetic stimulation can suppress hyperactivity of the default mode network, enhance executive control network function, regulate salience network activity, and restore the integration of thalamocortical and limbic circuits. These network level changes provide objective neuroimaging support for the clinical benefits of repetitive transcranial magnetic stimulation in chronic insomnia. Future studies should combine individualized neuronavigated stimulation with multimodal neuroimaging and longitudinal follow up to clarify the spatiotemporal dynamics of brain network plasticity and optimize precision nonpharmacological interventions for chronic insomnia.

Keywords: Chronic Insomnia; Repetitive Transcranial Magnetic Stimulation; Neural Mechanisms; Brain Network Plasticity; Functional Connectivity; Neuromodulation

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1. Introduction

Chronic insomnia is one of the most common sleep disorders and is primarily characterized by difficulty initiating sleep, difficulty maintaining sleep, or early morning awakening [1]. Epidemiological studies indicate that nearly one third of adults experience insomnia symptoms, and approximately 10% to 15% suffer from chronic insomnia, with a higher prevalence among older adults, women, and individuals exposed to high levels of stress [2]. Long term insomnia not only impairs quality of life and social functioning, but may also lead to cognitive decline, emotional disturbances, immune dysregulation, and

an increased risk of cardiovascular disease [3]. Current guidelines emphasize that chronic insomnia is not simply a result of insufficient sleep duration or psychological stress, but rather a neuropsychiatric disorder involving dysfunction across multiple brain regions, neurotransmitter systems, and neural networks. Its core pathological mechanisms are thought to be closely related to dysregulated cortical excitability, impaired emotion regulation circuits, and overactivation of the hypothalamic–pituitary–adrenal axis [4].

At present, treatment strategies for chronic insomnia include both pharmacological and nonpharmacological approaches. In clinical practice, pharmacotherapy remains the dominant option; however, it may cause adverse effects such as drug dependence, rebound insomnia, anxiety, depression, and even cognitive impairment after long term use [3]. Consequently, nonpharmacological interventions for chronic insomnia have become a major focus in sleep medicine research. In recent years, with the rapid development of neuromodulation technologies, repetitive transcranial magnetic stimulation, abbreviated as rTMS, has attracted increasing attention as a safe and noninvasive brain stimulation technique for neuropsychiatric disorders. Based on the principle of electromagnetic induction, rTMS applies pulsed magnetic fields to specific regions of the central nervous system, induces electric currents by altering neuronal membrane potentials, and thereby modulates neuronal metabolism, synaptic connectivity, synaptic plasticity, and neural network organization. As an externally applied electric field across the cell membrane, rTMS can alter transmembrane potential differences, induce depolarization, and activate excitable tissues. Its regulatory effects on neural excitability depend strongly on stimulation parameters, especially frequency. Different frequencies, intensities, and stimulation patterns may produce excitatory or inhibitory effects, thereby promoting the remodeling of dysfunctional brain networks [5].

A growing number of studies have shown that rTMS has significant therapeutic effects in chronic insomnia, including shortening sleep latency, improving sleep efficiency, and alleviating accompanying symptoms such as anxiety and depression [6]. Neuroimaging evidence further suggests that rTMS may promote the reorganization of functional connectivity in the prefrontal cortex, thalamus, hippocampus, and other sleep related regions, while enhancing the dynamic balance between the default mode network and the executive control network, thus reflecting substantial brain network plasticity [7]. In addition, rTMS may regulate the gamma aminobutyric acid and glutamate balance [8], restore hypothalamic–pituitary–adrenal axis function, and reduce central hyperarousal [9], thereby providing a neurophysiological basis for its therapeutic effects. Therefore, this review systematically summarizes the neural mechanisms and brain network plasticity associated with rTMS in the treatment of chronic insomnia, with the aim of clarifying its multilevel mechanisms of action and network modulation patterns, and providing a theoretical basis and future directions for precision nonpharmacological interventions in chronic insomnia.

2. Neurophysiological Basis of Chronic Insomnia

The development and persistence of chronic insomnia involve a complex, multilevel interaction among central nervous system dysfunction, abnormal neurotransmitter regulation, and disrupted brain connectivity patterns. With the advancement of neuroimaging and electrophysiological techniques, the conceptual framework of chronic insomnia has gradually shifted from a traditional model of psychological and behavioral dysregulation to one of neural network abnormalities, providing new evidence for understanding its underlying neurobiology.

2.1 Functional Imbalance Between Cortical and Subcortical Structures

Studies using functional magnetic resonance imaging and functional near infrared spectroscopy have shown significant alterations in functional connectivity within the frontal lobe, parietal lobe, and limbic system in patients with chronic insomnia [10]. In particular, decreased activity in the dorsolateral prefrontal cortex, abbreviated as DLPFC, may weaken executive control and emotional inhibition, whereas hyperactivation of the amygdala and insula is closely associated with heightened emotional arousal and anxiety [11]. Dysfunction within the prefrontal–amygdala circuit is considered one of the key pathological features of chronic insomnia. In addition, the thalamus serves as a gating structure in the sleep wake transition [12]. Excessive thalamic excitability may disrupt the sleep wake cycle and impair both sleep initiation and sleep maintenance.

2.2 Abnormal Regulation of Neurotransmitter Systems

Neurotransmitters provide the essential chemical basis for maintaining the balance between sleep and wakefulness. Animal

studies have shown that mice with insomnia exhibit significantly reduced gamma aminobutyric acid, abbreviated as GABA, levels and elevated glutamate, abbreviated as Glu, levels, indicating an imbalance between cortical excitation and inhibition [13]. Magnetic resonance spectroscopy studies have further demonstrated that decreased GABA concentrations in the prefrontal cortex and thalamus are positively associated with prolonged sleep latency and increased nocturnal awakenings [14]. In addition, monoamine neurotransmitters such as serotonin, dopamine, and norepinephrine also participate in sleep regulation. Reduced serotonin levels may decrease the proportion of slow wave sleep, whereas excessive norepinephrine release may promote wakefulness. Recent evidence suggests that rTMS may help restore neurochemical homeostasis in insomnia by modulating the GABA to glutamate balance and monoamine neurotransmitter release [14].

2.3 Hyperactivation of the Hypothalamic–Pituitary–Adrenal Axis

The hypothalamic–pituitary–adrenal axis, abbreviated as the HPA axis, is not only a central component of the stress response but also plays an important role in the regulation of the neuroendocrine immune network. Studies have shown that HPA axis activity is closely related to the sleep wake cycle and serves as a reliable indicator of hyperarousal in patients with insomnia [15]. Elevated adrenocorticotropic hormone levels may increase sympathetic tone and substantially affect the alternation of the sleep wake cycle [16]. Long term HPA axis hyperactivity may suppress melatonin secretion through feedback mechanisms, disrupt circadian rhythms, and establish a vicious cycle of hyperarousal, insomnia, and stress [17]. Electrophysiological studies indicate that rTMS may improve sleep architecture and stress responses by suppressing excessive cortical excitability and reducing cortisol levels [18], thereby providing a physiological basis for further neuromodulation research.

2.4 Disrupted Brain Network Connectivity Patterns

Recent brain network studies have demonstrated that chronic insomnia is characterized by widespread functional connectivity imbalance [19]. Functional connectivity analyses suggest that patients with insomnia exhibit hyperactivity in the default mode network, abbreviated as DMN, together with reduced activity in the executive control network, abbreviated as ECN, and the salience network, abbreviated as SN, resulting in persistently elevated arousal . In particular, reduced connectivity between the prefrontal cortex and the hippocampus and thalamus may impair sleep related information integration and memory consolidation [20]. This network imbalance not only reflects the neurophysiological nature of insomnia, but also provides a rationale for targeting brain networks through neuromodulation techniques.

3. Mechanisms and Parameter Characteristics of Repetitive Transcranial Magnetic Stimulation

Repetitive transcranial magnetic stimulation is a noninvasive neuromodulation technique based on the principle of electromagnetic induction. By placing a stimulation coil over the scalp and delivering rapidly changing magnetic fields, rTMS induces electric currents in the cortex and modulates neuronal membrane potentials and synaptic transmission. rTMS can produce sustained neuroplastic changes in both local and remote brain regions and has been widely investigated in the treatment of depression, anxiety, chronic pain, and sleep disorders [21]. Its core therapeutic value lies in the bidirectional regulation of cortical excitability and network activity through specific parameter settings.

3.1 Basic Principles of rTMS

rTMS applies pulsed magnetic fields to specific areas of the central nervous system, induces electric currents by altering cortical neuronal membrane potentials, and thereby influences neuronal metabolism, synaptic connectivity, synaptic plasticity, and neural network optimization. As an externally superimposed electric field across the cell membrane, rTMS can change transmembrane potential differences, induce membrane depolarization, and activate excitable tissues. Repeated magnetic stimulation may produce long term potentiation like or long term depression like effects at the synaptic level, thereby enabling plastic regulation of neural circuits [22].

The therapeutic effects of rTMS are closely associated with stimulation frequency, intensity, number of pulses, target site, and treatment duration. Different combinations of frequency and intensity can induce specific physiological responses in different brain regions and generate either facilitatory or inhibitory effects on cortical activity. High frequency stimulation, defined as 5 Hz or higher, is generally considered excitatory and may enhance neural excitability, whereas low frequency stimulation,

defined as 1 Hz or lower, is usually inhibitory and may reduce cortical activity. Theta burst stimulation, abbreviated as TBS, delivers short bursts of high frequency pulses nested within a low frequency rhythm and can induce long term potentiation like or long term depression like synaptic plasticity [23].

In clinical practice, stimulation intensity is usually expressed as a percentage of the individual motor threshold, abbreviated as MT, typically ranging from 80% to 120% of MT. Intensities that are too low may fail to induce significant effects, whereas intensities that are too high may increase the risk of adverse events. With regard to stimulation targets, the left DLPFC is one of the most frequently used sites in insomnia treatment because of its close involvement in emotion regulation, attentional control, and sleep initiation. Some studies have also applied stimulation over the right DLPFC to improve sleep quality and anxiety symptoms. Recent expert consensus suggests that bilateral DLPFC stimulation may be more effective than unilateral stimulation for insomnia [24]. Regarding treatment duration, most clinical studies adopt a protocol of one session per day for two to four weeks, and cumulative stimulation dose appears to be positively associated with therapeutic efficacy.

3.2 Neural Regulatory Mechanisms of rTMS

The mechanisms by which transcranial magnetic stimulation improves chronic insomnia are related to reduced cortical excitability, shortened sleep latency, and increased slow wave sleep [5]. The therapeutic effects of rTMS on insomnia severity may involve neurotransmitter release, synaptic plasticity, and neural network optimization. Through cumulative stimulation effects, rTMS excites neurons in multiple directions and at multiple levels, thereby facilitating not only regional reconstruction of cortical function but also long lasting biological effects through long term potentiation like mechanisms, ultimately enhancing synaptic plasticity.

Studies have shown that patients with chronic insomnia exhibit abnormal cortical activity, including disturbances in sleep wake rhythm regulation and neurotransmitter control [18]. By acting on the cerebral cortex, rTMS may improve sleep quality through normalization of these abnormal cortical activities. rTMS can modulate postsynaptic receptor density and neurotransmitter release and induce long term potentiation like and long term depression like plasticity, thereby providing a basis for brain plasticity [25]. The dorsolateral prefrontal cortex has direct fiber projections to the hypothalamus and direct or indirect connections with the basal forebrain. By strengthening communication between the prefrontal cortex, hypothalamus, and basal forebrain, rTMS may optimize neural network organization and trigger chain like changes in interregional functional connectivity, thereby restoring the dynamic balance of sleep wake related networks in patients with chronic insomnia.

3.3 Parameter Applications in Chronic Insomnia

In studies on chronic insomnia, most protocols have used low frequency 1 Hz rTMS over the left DLPFC to inhibit excessive cortical excitability, reduce arousal, and improve sleep architecture. Some studies have applied high frequency stimulation over the right DLPFC to enhance prefrontal regulation of the limbic system and thereby alleviate anxiety and emotional hyperarousal [26]. More recent research has combined functional neuroimaging with neuronavigated rTMS to individualize target localization according to eachpatient’ss functional connectivity profile, thereby improving treatment precision and reproducibility [26].

4. Research Progress on Brain Network Plasticity Induced by rTMS in Chronic Insomnia

With the rapid development of neuroimaging techniques, research on sleep disorders has shifted from focusing on dysfunction within isolated brain regions to examining abnormal coordination across distributed brain networks. Chronic insomnia is increasingly regarded as a typical disorder of large scale brain network dysconnectivity, characterized by an imbalance between persistently hyperactive arousal networks and suppressed sleep initiation networks. By modulating specific cortical targets and their remote connectivity pathways, rTMS can induce plastic reorganization of brain networks and thereby improve the neural circuitry underlying insomnia. Recent studies using functional magnetic resonance imaging, functional near infrared spectroscopy, and electroencephalography imaging fusion techniques have highlighted the important role of rTMS in promoting network level integration and remodeling.

4.1 Remodeling of the Default Mode Network

The default mode network mainly includes the medial prefrontal cortex, posterior cingulate cortex, precuneus, and hippocampus, and is closely associated with self referential thinking and resting state arousal. Patients with chronic insomnia often exhibit excessive activation of the DMN, especially increased functional connectivity between the medial prefrontal cortex and posterior cingulate cortex, which may contribute to heightened presleep arousal and excessive cognitive activity. By suppressing frontal hyperactivity, rTMS may reduce overall DMN coupling strength [27]. Studies have shown that after low frequency rTMS over the left DLPFC, functional connectivity between the medial prefrontal cortex and posterior cingulate cortex is significantly reduced in patients with insomnia, DMN resting state activity tends to normalize, and subjective sleep latency and nocturnal awakenings are significantly decreased [28]. Functional near infrared spectroscopy studies have also found that rTMS can reduce fluctuations in oxygenated hemoglobin concentration in the frontal cortex, indicating a suppressive effect on cortical metabolic activity [29], which supports restoration of the DMN from an energy metabolism perspective.

4.2 Enhancement of the Executive Control Network

The executive control network mainly includes the dorsolateral prefrontal cortex and posterior parietal regions and is responsible for higher order functions such as attentional control, emotional regulation, and cognitive inhibition. Patients with chronic insomnia often show impaired ECN function and are less able to suppress internal thoughts and negative emotions effectively [30]. By targeting the left DLPFC, rTMS may restore functional connectivity within the ECN and enhance its integration efficiency [31]. rTMS intervention has been reported to increase prefrontal activation and task related response speed, suggesting long term plastic improvements in cognitive control and sustained attention. Functional magnetic resonance imaging studies have shown that after rTMS treatment, functional connectivity between the DLPFC and parietal regions is significantly increased, while negative coupling between the DLPFC and the amygdala and hippocampus is enhanced, suggesting that rTMS may strengthen the top down inhibitory influence of the executive control network over emotional and arousal systems [32].

4.3 Regulation of the Salience Network

The salience network, composed primarily of the anterior cingulate cortex and insula, is responsible for switching attention between internal and external stimuli and regulating emotional arousal. Chronic insomnia is often associated with excessive SN activity, especially increased insular activation, which may lead to sustained activation of the arousal system [33]. After stimulation of the DLPFC, rTMS may reduce the hypersensitivity of the salience network through cross network regulation, thereby restoring normal response thresholds to internal and external stimuli. Studies have shown that the functional connectivity between the anterior cingulate cortex and insula decreases after rTMS treatment and is significantly negatively correlated with subjective anxiety scores and arousal levels [34]. These findings suggest that rTMS may help restore the dynamic balance between arousal and sleep initiation by downregulating salience network activity.

4.4 Integration of Thalamocortical Circuits and Limbic System Networks

The thalamus is a key relay structure in sleep wake regulation. Thalamocortical circuits involving the cortex, hippocampus, and limbic system play essential roles in sleep regulation. Functional connectivity of the thalamus is generally increased in patients with chronic insomnia, suggesting impairment of its gating function. rTMS may restore synchronous rhythms within cortical thalamic circuits by modulating remote connectivity between the DLPFC and thalamus. Studies have reported that following rTMS, functional connectivity between the thalamus and frontal and parietal cortices is significantly reduced, alpha power increases, and the number of sleep spindles rises, suggesting facilitation of slow wave sleep generation and suppression of wakefulness. At the same time, rTMS may improve connectivity within limbic circuits involving the hippocampus, amygdala, and prefrontal cortex, thereby enhancing the stability of emotional and memory processing and providing a neural basis for sleep consolidation [35].

5. Conclusion

The neurophysiological basis of chronic insomnia is mainly characterized by increased cortical excitability, reduced

inhibitory neurotransmission, and impaired integration of large scale brain networks. These abnormal mechanisms interact with one another and jointly maintain the pathological state of insomnia. A deeper understanding of these neural mechanisms not only helps clarify the biological nature of insomnia but also provides a theoretical foundation for neuromodulation techniques such as rTMS.

By applying an external magnetic field to cortical neurons, rTMS can regulate neuroplasticity at the cortical and subcortical circuit level, restore brain network balance, and promote reconstruction of sleep related function in patients with chronic insomnia. The brain network plasticity induced by rTMS is mainly reflected in suppression of default mode network hyperactivity, reduction of resting state hyperarousal, enhancement of executive control network function, improvement of emotional and attentional regulation, modulation of salience network activity, restoration of the balance between arousal and sleep initiation, and reconstruction of thalamocortical and limbic circuits, thereby synchronously optimizing sleep rhythms and cognitive function. These network level changes provide objective neuroimaging evidence for the therapeutic effects of rTMS in chronic insomnia and offer new directions for future precision brain modulation interventions. Future studies should combine individualized neuronavigated rTMS with multimodal imaging techniques to further clarify the spatiotemporal evolution of brain network plasticity from the perspective of dynamic connectivity and directional causal interactions.

6. Future Perspectives

Current research on the mechanisms by which rTMS improves insomnia remains largely focused on the regulation of cortical excitability and neurotransmitter balance, whereas its effects on multiregional circuits and dynamic interactions across brain networks have not yet been fully elucidated. Future studies should integrate multimodal neuroimaging and molecular biomarker monitoring to establish multiscale mechanistic models spanning molecular, cellular, circuit, and systems levels. High temporal resolution electroencephalography combined with high spatial resolution functional imaging may help reveal the dynamic evolution of rTMS induced neuroplasticity across different time windows and provide spatiotemporal evidence for its long term regulatory effects.

The efficacy of rTMS is highly dependent on precise parameter settings and appropriate target selection. At present, most studies still rely on empirical stimulation protocols and lack precision targeting strategies based on individual brain functional characteristics. Future research should develop individualized target localization methods based on neuroimaging navigation systems combined with resting state functional connectivity maps, cortical thickness, and metabolic indicators. Machine learning models may also be used to identify optimal combinations of stimulation frequency, intensity, pulse number, and treatment duration, thereby improving personalization and reproducibility. In addition, the development of closed loop neuromodulation systems that monitor brain activity in real time and adaptively adjust stimulation parameters may substantially improve therapeutic efficiency and the induction of neuroplasticity.

Although rTMS alone can improve sleep quality and emotional status, its effects may be limited in magnitude and duration. Future studies should explore multimodal intervention strategies that combine rTMS with cognitive behavioral therapy, exercise interventions, mindfulness based approaches, and pharmacotherapy to promote coordinated recovery of sleep and emotional systems from multiple dimensions. Investigation of the synergistic mechanisms underlying these combined treatments may provide new theoretical foundations and clinical pathways for comprehensive insomnia management.

Most existing studies have focused on short term therapeutic effects and lack follow up data or long term plasticity indicators. Future longitudinal studies should include follow up assessments at six to twelve months after treatment to evaluate the durability and reversibility of neural network remodeling. In addition, structural plasticity changes induced by rTMS, such as alterations in gray matter volume, white matter integrity, and synaptic density, should be examined. By integrating diffusion tensor imaging and morphometric analysis, researchers may better elucidate the structural mechanisms by which rTMS promotes neural network reconstruction and thereby provide empirical support for its long term efficacy.

Clinical translation of rTMS in insomnia treatment still faces several challenges, including insufficient standardization, large interindividual variability, and a lack of objective evaluation systems. Future work should establish multidimensional evaluation frameworks based on neuroimaging and physiological signals by integrating subjective sleep questionnaires, objective polysomnography, and brain network functional indices to generate quantitative efficacy criteria. At the same time,

multicenter randomized controlled trials are needed to develop unified parameter protocols and safety assessment systems, thereby strengthening the evidence base for the clinical application of rTMS in chronic insomnia. Ethical and safety issues should also be given close attention, and risk warning and patient suitability screening mechanisms should be established to ensure the scientific rigor and controllability of rTMS interventions.

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Conflict of Interests

The authors declare that there is no conflict of interest regarding the publication of this paper.

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