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REVIEW ARTICLE

Research progress on repetitive transcranial magnetic stimulation in the treatment of alcohol addiction: A narrative review

Raxida Umar[1,2], Shanshan Dong[2], Enli Luo[2]*, and Hao Lyu[3]*

[1]Department of Clinical Medicine, School of Medicine, Shenzhen University, Shenzhen, Guangdong, China

[2]Department of Traditional Chinese Medicine, South China Hospital, Medical School, Shenzhen University, Shenzhen, Guangdong, China

[3]Department of Neurosurgery, Shenzhen Second People's Hospital, Shenzhen, Guangdong, China

Abstract

Alcohol addiction is a complex psycho-physiological disorder affecting neurotransmitter release and nerve impulses in multiple central nervous system regions, causing severe physical and mental harm and societal burden. Existing treatments (medication, psychotherapy, traditional Chinese medicine) have limitations, including poor control of alcohol craving, high re-drinking rates, inadequate improvement of comorbid symptoms (anxiety, depression, cognitive decline), and issues such as non-specific drug targeting and subjective bias in psychotherapy. Repetitive transcranial magnetic stimulation (rTMS), a non-invasive physical therapy with advantages of painlessness, safety, and minimal side effects, has shown efficacy in neuropsychiatric disorders such as depression and cognitive decline. Although its application in alcohol addiction is in the early stage, clinical trials indicate that it can reduce alcohol craving and re-drinking rates. This review summarizes the pathogenesis of alcohol addiction and the clinical efficacy of rTMS, aiming to provide a reference for its promotion in substance addiction treatment.

Keywords: Repetitive transcranial magnetic stimulation; Alcohol; Substance addiction; Dopaminergic reward system

***Corresponding authors:**
Hao Lyu
(louielyu@link.cuhk.edu.hk)
Enli Luo
(lelzx19731965@163.com)

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1. Concept of alcohol addiction and epidemiological investigation

Alcohol use disorder includes alcohol dependence and alcohol abuse. Alcohol dependence refers to a progressive increase in a person's dependence on alcohol, accompanied by an increase in alcohol tolerance. On a reduction in alcohol consumption or termination of alcohol consumption, withdrawal reactions such as anxiety, palpitations, tremors, and sleep disorders will occur.[1] Alcohol addiction can affect the functions of important systems such as the nervous system, cardiovascular system and digestive system, causing serious harm to human health. Studies have shown that excessive alcohol consumption can lead to alcohol-related liver disease, which is mainly characterized by steatohepatitis and progressive liver fibrosis, and can cause a series of symptoms such as abnormal liver function, jaundice and coagulation dysfunction. The mortality rate of alcohol-related

liver disease can account for 40% of the mortality rate of liver diseases. In addition, the mortality rate of patients with severe alcoholic hepatitis can reach 30–40%.[2,3] A 30-year follow-up clinical trial in the UK has shown that both excessive and moderate alcohol consumption can lead to hippocampal atrophy, and the greater the amount of alcohol consumed, the more severe the degree of atrophy.[4] A retrospective study conducted in the United States from 2007 to 2020 shows that patients with alcohol use disorder have a higher risk of developing Alzheimer's disease and Parkinson's disease compared to the control group.[5] Some literature has pointed out that the incidence of cardiovascular accidents in patients with alcohol addiction after 1 year is 19.23%. In addition, researchers have pointed out that long-term alcohol consumption can not only reduce the left ventricular ejection fraction but also damage vascular endothelial cells.[6] In the field of mental disorders, the comorbidity rate of alcohol addiction with anxiety and depression is as high as 30%–50%.[7] Alcohol addiction not only causes damage to multiple systems but also has a high incidence rate. Globally, more than 40% of the population aged over 15 have a history of alcohol consumption; about 2.3 billion people consume around 35 billion liters of alcohol each year.[8] Researchers have statistically analyzed the drinking data of 189 countries from 1990 to 2017 and found that from 1990 to 2017, the global adult drinking rate increased from 45% to 47%, the per capita alcohol consumption increased from 5.9 L to 6.5 L, and the lifetime abstinence rate decreased from 46% to 43%. In addition, the researchers predicted the drinking data for 2030 and pointed out that the drinking rate will reach 50% in 2030, the per capita alcohol consumption will increase to 7.6L, while the abstinence rate will drop to 40%.[9] Meanwhile, adolescent alcohol addiction is also a problem that cannot be ignored. Adolescent alcohol exposure is associated with persistent deficits in prefrontal cortex function and increases the risk of alcohol use disorders in adulthood, as synaptic pruning and myelination during this period are particularly susceptible to ethanol-induced disruption.[10] Thus, alcohol addiction, characterized by a high incidence rate, poses a substantial health threat to the body and places a huge burden on society. At the same time, the success rate of alcohol abstinence among alcohol addicts is low. Therefore, clarifying the mechanism of alcohol addiction and researching treatment methods are of great social and scientific significance.

2. Pathogenesis of alcohol addiction

A growing body of studies indicates that alcohol addiction is mainly caused by the mesolimbic dopamine reward pathway. The reward pathway is mainly composed of the ventral tegmental (VTA), nucleus accumbens, amygdala, hippocampus, prefrontal cortex, etc. Some researchers have pointed out that PKCδ-positive neurons in the central amygdala can lead to compulsive drinking in mice. In the initial stage of the experiment, mice obtained alcohol by pressing a controlled lever. To identify alcohol-susceptible mice, researchers added an electric shock on this basis, i.e., each time a mouse pressed the lever, it would receive an electric shock while getting alcohol. One-third of the mice still pressed the lever while receiving an electric shock, which were regarded as alcohol-susceptible. Researchers found PKCδ-positive neurons in the central amygdala of these alcohol-susceptible mice. Through molecular methods, it was found that these neurons led to the compulsive behavior of mice. When the PKCδ-positive neurons were inhibited, the mice regained their ability to self-control alcohol consumption.[11] In a study, researchers placed two water bottles, one filled with pure water and the other with alcohol, in the mouse cages. The alcohol concentration in the alcohol-filled bottle was increased every 4 days. The mice were divided into a low-alcohol-drinking group (LAD) and a high-alcohol-drinking group (HAD) according to their alcohol consumption status. When the researchers compared the VTA activities in the brains of the two groups of mice, they found that the indices, such as the VTA neuron firing rate and the burst potential frequency in the HAD group, decreased significantly compared with those in the LAD group. When optogenetic methods were used to excite the VTA and increase neuron activity, the alcohol consumption of the mice decreased compared with that before, and this situation could last for 48 h.[12] Single-dose administration of 50 mM ethanol was given to the juvenile group (30 days after birth) and the adult group (210 days after birth) of mice respectively to simulate acute alcohol intoxication. It was found that expression of a total of 72 proteins in the mouse hippocampus underwent significant alterations. Among them, 32 proteins showed differential changes in expression in both juveniles and adults, indicating that alcohol can cause changes in the synaptic proteins of the brain hippocampus, with more pronounced changes detected in juvenile mice.[13]

Alcohol acts on the brain mainly through pathways such as influencing the release of central neurotransmitters, altering the activity of central nervous system receptors, and changing the genes encoding the expression of neural receptors.[14] Some researchers have found that in the brains of long-term drinkers and rats, the average diffusion rate of the extracellular space in gray matter increases over time. However, these changes can occur shortly after alcohol consumption. The increase in the extracellular space diffusion rate will lead to an increase in the concentration of neurotransmitters such as dopamine, thus resulting in

alcohol addiction.[15] In the brain, the dopamine-producing neurons encoding reward and those encoding punishment are in an antagonistic state. However, when substance addiction occurs, the brain will still seek rewards even when exposed to harmful stimuli. The optogenetic self-stimulation method was used to simulate the substance-addicted state in mice. After weeks of withdrawal, addiction was induced again. At the same time, electric shock stimulation was applied, and some mice were still able to persevere.[16,17] Some research has found that in the amygdala of alcohol-addicted rats, the expression of the protein GAT-3, which maintains the inhibitory neurotransmitter gamma-aminobutyric acid (GABA), decreases. When this gene was knocked out in non-alcohol-addicted rats, the rats started to show a preference for alcohol.[18] In addition, in alcohol-addicted mice, there is a decrease in GABAB receptors, accompanied by a decline in the downstream G-protein-coupled inwardly rectifying potassium channels (GIRK) and a reduction in the amplitude of GABAB-mediated inhibitory postsynaptic currents.[19] In addition, some researchers have pointed out that long-term heavy drinking can lead to an increase in the level of cortisol in the brain, thus inhibiting the hypothalamic–pituitary–adrenal axis in the brain and weakening its ability to participate in the stress response. By conducting positron emission tomography (PET) scans on moderate to severe alcohol-addicted individuals, researchers found that, compared with the healthy control group, the activity of 11β-hydroxysteroid dehydrogenase 1 (11β-HSD1) in the prefrontal-limbic circuit of alcohol-addicted individuals is 41.7% higher. Elevated levels of 11β-HSD1 in the brain reduce the reactivity of alcohol-addicted patients to stimuli, thereby enhancing addictive behavior.[20] The N-methyl-D-aspartic acid receptor (NMDA receptor) is a subtype of the ionotropic glutamate receptor, with a complex molecular structure. It plays a crucial role in various aspects, including the regulation of neuronal survival, the development of dendritic and axonal structures of neurons, and the formation of synaptic plasticity. Alcohol can inhibit the function of NMDA receptors, and during withdrawal, the overactivation of these receptors leads to withdrawal symptoms.[21] All of the above research findings can provide new targets for the treatment of alcohol addiction.

3. Working principle and clinical applications of repetitive transcranial magnetic stimulation (rTMS)

rTMS is a non-invasive neurostimulation technique. Its working principle is to generate continuous magnetic pulses through an electromagnetic coil placed on the head, thereby stimulating the motor area of the cerebral cortex, spinal nerve roots, and peripheral nerves. This causes neurons in the corresponding areas to generate induced currents due to depolarization, regulating their excitability. It has the advantages of being painless, non-invasive, highly safe, and minimal side effects. Clinically, by adjusting parameters such as the intensity, frequency, duration, and number of pulses of rTMS, good results have been achieved in the treatment of various neurological and psychiatric diseases. The changes in brain activity caused by different stimulation types also vary. Among them, low-frequency rTMS and continuous transcranial magnetic stimulation modes can induce cerebral cortex inhibition; high-frequency rTMS and intermittent transcranial magnetic stimulation modes, on the other hand, cause cerebral cortex excitation.[22]

At present, rTMS is being applied more and more widely in clinical practice. In patients with major depressive disorder, changes occur in the cortex-striatum-thalamus-cortex circuit with the thalamus as the core. Specifically, there is a reduction in the gray matter volume (GMV) and gray matter density (GMD) in the thalamus, striatum, superior temporal gyrus, and cingulate gyrus regions; while an increase in GMV and GMD is observed in the occipital cortex.[23] In a clinical trial, when researchers used LF-rTMS to stimulate the right dorsolateral prefrontal cortex (DLPFC) of patients with major depressive disorder, they found an increase in brain activity in the striatum, thalamus, and regions of the default mode network, and corresponding clinical symptoms were alleviated. However, when stimulating the left DLPFC, no significant changes were observed.[24] Apart from common mental illnesses, such as depression, rTMS is also used in the treatment of substance addiction and stroke. Researchers administered rTMS treatment to 14 long-term smokers for 10 days. The stimulation sites were the left DLPFC and the superior medial frontal cortex, with a stimulation intensity of 20 Hz. After the treatment, when observing the patients' cerebral blood flow and brain entropy, a reduction in the patients' resting-state brain activity was found. Subsequently, a 25-day follow-up was carried out on the patients, and 90% of them did not smoke during this period.[25] In addition, other clinical studies have also obtained the same experimental results by stimulating the same sites with rTMS.[26] Due to its ability to improve the body's speech, swallowing, and motor functions, rTMS also plays an important role in post-stroke rehabilitation. A review indicates that rTMS enhances neural plasticity through mechanisms such as anti-neuronal apoptosis, promotion of synaptic plasticity in related nerve cells, and facilitation of stem cell proliferation and migration.[27] In a clinical study, 36 patients with acute stroke were evenly and randomly divided into four groups: rTMS/pseudo-sensory stimulation (sham SS), sham rTMS/SS, rTMS/SS, and

sham rTMS/sham SS. Ten sessions of rTMS stimulation were applied to the primary somatosensory cortex of the affected hemisphere in each patient, followed by SS stimulation. The excitability of the primary motor cortex and the primary somatosensory cortex was evaluated using motor evoked potentials and somatosensory evoked potentials. The results showed that, except for the sham rTMS/sham SS group, the interhemispheric asymmetry of the excitability of the primary somatosensory cortex increased in all other somatosensory stimulation groups. In addition, the excitability of the primary motor cortex increased only in the rTMS/SS group.[28] The researchers randomly divided 42 patients into three groups: Bilateral cerebellar rTMS (biCRB-rTMS), unilateral cerebellar rTMS (uniCRB-rTMS), and sham-rTMS group, and adjusted the rTMS stimulation frequency to a high frequency of 10 Hz. A comprehensive assessment of the swallowing function of the patients was conducted at the baseline level, on the day of the intervention, and on the 14th day after the intervention. It was found that the swallowing function of all three groups had improved compared to before. However, the swallowing function of the biCRB-rTMS group was significantly improved in all aspects compared to the other two groups. In addition, the biCRB-rTMS and uniCRB-rTMS groups were accompanied by an increase in corticobulbar excitability.[29] In addition, the U.S. Food and Drug Administration has approved the use of 10 Hz deep transcranial magnetic stimulation (DTMS, which is a type of rTMS) to stimulate the dorsomedial prefrontal cortex and the anterior cingulate gyrus for the treatment of obsessive–compulsive disorder.[30] Overall, rTMS is one of the most promising methods in the clinical treatment of neuropsychiatric diseases. Moreover, rTMS treatment has relatively few side effects. In alcohol addiction trials, the adverse reactions to rTMS are mild, including headache (15–20%) and transient dizziness (5–8%), with no reports of seizures. This is consistent with the overall safety profile of neurostimulation in the treatment of neuropsychiatric disorders.[31] However, more data and clinical experience are still needed to verify and support its efficacy and safety.

4. Neural mechanisms of rTMS in alcohol addiction treatment

4.1. Regulating neurotransmitter levels

Alcohol addiction is associated with multiple neurotransmitters such as dopamine, glutamate, and GABA. These neurotransmitters play an important role in the pathophysiological process of alcohol addiction, and rTMS may help alleviate addiction symptoms by regulating their levels. First, the dopamine system is at the core of the reward pathway in alcohol addiction.[32] Alcohol intake stimulates the mesolimbic dopamine system, leading to an increase in dopamine release, which in turn produces a sense of pleasure and reinforcement. Long-term alcohol consumption can lead to a dysfunction of the dopamine system, promoting a strong craving for alcohol. In addition, studies have shown that chronic alcohol intake regulates the synchrony between gene transcription in the midbrain and the regulation of dopamine terminals.[33] Studies have shown that rTMS, by stimulating the prefrontal cortex (such as DLPFC), can indirectly regulate the activity of dopaminergic neurons, thereby reducing the craving for alcohol and dependent behaviors.[34] Second, the balance between glutamate and GABA is also crucial in alcohol addiction. Glutamate is the main excitatory neurotransmitter, while GABA is the main inhibitory neurotransmitter. Long-term alcohol consumption can lead to overactivity of the glutamate system and hypofunction of the GABA system, which in turn triggers withdrawal symptoms, anxiety, and impulsive behaviors. rTMS can restore the balance between glutamate and GABA by regulating the excitability of the prefrontal cortex. For example, low-frequency rTMS has been proven to be able to reduce glutamatergic activity while enhancing GABAergic inhibition, thus alleviating withdrawal symptoms and problems with impulse control.[35] In addition, rTMS may also exert its therapeutic effects by regulating other neurotransmitters and molecules related to neural plasticity, such as brain-derived neurotrophic factor (BDNF), which plays an important role in neural plasticity and cognitive function. Individuals with alcohol addiction usually show a decrease in BDNF levels. rTMS may improve the cognitive function and emotional regulation ability of addicts by increasing BDNF expression.[36]

4.2. Altering cortical excitability

One of the mechanisms of action of rTMS in the treatment of alcohol addiction is through regulating the excitability of the cerebral cortex. Individuals with alcohol addiction usually exhibit abnormal functions in the prefrontal cortex (such as the DLPFC), including reduced cortical excitability and impaired neural plasticity. Meanwhile, the strength of the effective connectivity between the cortical and subcortical regions mediates the severity of addiction. rTMS can directly or indirectly regulate the excitability of the target brain regions by inducing electric currents through a magnetic field, thus improving the neurological dysfunctions associated with addiction.[37] High-frequency rTMS (usually at 10 Hz) can increase cortical excitability, while low-frequency rTMS (usually at 1 Hz) reduces cortical excitability.[38] In the case of alcohol addiction, high-frequency rTMS is often used to stimulate the DLPFC

to enhance its excitability and functional connectivity, thereby improving cognitive control, decision-making ability, and emotional regulation. Studies have shown that high-frequency rTMS can reverse the cortical inhibitory state caused by alcohol, restore neural plasticity, and reduce the craving for alcohol.[34] In addition, low-frequency rTMS may relieve withdrawal symptoms and impulsive behaviors by reducing the excitability of overactive brain regions (such as the limbic system). Hence, by regulating cortical excitability, rTMS may provide a new method of neural regulation for the treatment of alcohol addiction.[35]

4.3. Influencing brain plasticity

rTMS also plays a role in the treatment of alcohol addiction by regulating brain plasticity. Individuals with substance addiction usually exhibit impaired neural plasticity, including abnormal synaptic function and altered connections between brain regions.[39] rTMS can regulate the excitability and neural plasticity of the target brain regions by inducing electric currents through a magnetic field, thereby improving the neurological dysfunctions associated with addiction.[40]

4.4. Regulating the hypothalamic-pituitary-adrenal (HPA) axis

As the core pathway of the stress response, the HPA axis often shows dysfunction in alcohol addiction, which is closely related to craving, withdrawal, and relapse. Long-term alcohol exposure can lead to overactivation of the HPA axis and an increase in cortisol levels, while after withdrawal, it may trigger blunted responses of the HPA axis, exacerbating emotional and cognitive impairments.[41] In addition, abnormal HPA function can also lead to alcohol addiction.[19] At the same time, serotonin (5-HT) can have an impact on the function of the HPA axis.[42] However, the mechanism has not been fully clarified, and further research is needed on the specific effects of rTMS parameters (such as frequency and target points) on the HPA axis. Overall, rTMS provides a potential intervention for regulating the dysregulation of the HPA axis in patients with alcohol use disorder, but validation of its long-term efficacy and exploration of biomarkers are still warranted.

5. Clinical research progress of rTMS in the treatment of alcohol addiction

In this study, we included six articles (Table 1) reporting clinical trials on the treatment of alcohol addiction with rTMS by searching PubMed. These studies primarily utilized high-frequency rTMS, targeting brain regions including the left DLPFC, right DLPFC, and insular cortex, with treatment courses typically spanning 10–20 sessions. Four of the following six studies yielded positive

Table 1. Basic characteristics of the included literature and rTMS treatment parameters

Author	Sample size (observation group, control group)	Stimulation type in observation group	Stimulation type in control group	Stimulation site	Stimulation intensity	Stimulation frequency	Total number of pulses per stimulation	Treatment course	Primary outcome	Medication use	Research results
Del Felice *et al.*[43]	20 (10, 10)	rTMS	Sham rTMS	Left DLPFC	100% MT	10 Hz	1,000 pulses	3 weeks	Craving and number of drinks	Alprazolam or diazepam, disulfiram	Ineffective
Mishra *et al.*[34]	*45 (15, 30)*	rTMS	Sham rTMS	Right DLPFC	110%MT	10 Hz	1,000 pulses	1 month	Alcohol consumption, frequency of alcohol consumption	/	Effective
Mishra *et al.*[44]	*20 (10,10)*	rTMS	rTMS (left DLPFC)	Right DLPFC	110%MT	10 Hz	1,000 pulses	1 month	Visual Analogue Scale	/	Effective
Harel *et al.*[35]	51 (24, 27)	dTMS	Sham rTMS	Medial PFC, ACC	100%MT	10 Hz	3,000 pulses	3 weeks	Percentage of days with heavy drinking	/	Effective
Hoven *et al.*[45]	80 (40, 40)	rTMS	ShamrTMS	Right DLPFC	110% MT	10 Hz	/	10consecutive work-days	Number of abstinent days	/	Ineffective
Perini *et al.*[46]	56 (29, 27)	rTMS	ShamrTMS	Insular cortex	120%MT	10 Hz	1,500 pulses	3 weeks	Heavy drinking days	/	Effective

Abbreviations: ACC: Anterior cingulate cortex; DLPFC: Dorsolateral prefrontal cortex; PFC: Prefrontal cortex; rTMS: Repetitive transcranial magnetic stimulation.

results, while two studies yielded negative results. Results indicated that active rTMS significantly outperformed sham stimulation in reducing alcohol consumption, alleviating craving, and improving abstinence rates. Right-sided prefrontal stimulation appeared more effective than left-sided stimulation in suppressing craving, while insula-targeted protocols significantly reduced heavy drinking. The intervention was well-tolerated, with no severe adverse effects reported. These findings suggest that rTMS may modulate reward circuitry and inhibitory control pathways, positioning it as a promising adjunctive therapy for alcohol dependence. However, further research is needed to optimize stimulation parameters and validate long-term outcomes.

6. Future research directions

Although rTMS has made certain progress in the treatment of alcohol addiction, there are still many issues that need exploration through in-depth research. First of all, the standardization of stimulation parameters urgently needs to be addressed. There are significant differences in stimulation modes, stimulation targets, stimulation frequencies, stimulation intensities, and other parameters in different studies, which makes it difficult to compare and generalize the research results. In the future, large-scale, multicenter clinical trials are needed to determine the optimal combination of stimulation parameters.

Secondly, the mechanism of the impact of rTMS on brain function remains unclear, and fundamental research on the treatment of alcohol addiction with rTMS should be strengthened. It is necessary to explore its mechanism of action in depth and further clarify the specific molecular and cellular mechanisms of rTMS in regulating neurotransmitters, altering cortical excitability, influencing brain plasticity, and regulating the HPA axis. At the same time, combined with neuroimaging techniques such as functional magnetic resonance imaging and PET, in-depth research on the changes in brain function before and after rTMS treatment should be carried out to provide a more solid theoretical basis for clinical treatment.

In addition, combination therapy is also one of the future research directions. Combining rTMS with drug therapy, psychotherapy, *etc.* may produce better therapeutic effects. This may include using rTMS in combination with alcohol-abstinence drugs such as naltrexone and acamprosate, or combining it with psychotherapy methods such as cognitive behavioral therapy and motivational enhancement therapy, followed by observation of their synergistic effects.

Finally, it is also important to study the differences in the responses of different individuals to rTMS treatment. There are large individual differences among patients with alcohol addiction, including genetic factors, the degree of addiction, comorbid conditions, etc. These factors may affect the therapeutic effect of rTMS. By studying individual differences and achieving personalized treatment, it will help improve the efficacy of rTMS in the treatment of alcohol addiction.

7. Conclusion

As a non-invasive neural modulation technique, rTMS demonstrates potential for the treatment of alcohol addiction. Current research shows that rTMS can, to a certain extent, reduce patients' craving for alcohol, decrease the relapse rate of drinking, and improve cognitive function and emotional state. However, due to the lack of standardization of stimulation parameters, the unclear mechanism of its impact on brain function, and the influence of individual differences and other factors, the application of rTMS in the treatment of alcohol addiction still needs further validation through in-depth research. Addressing the above issues may lead to the formulation of a range of more effective and safe treatment options for patients with alcohol addiction, improving their quality of life and thereby reducing the social burden.

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Conflict of interest

The authors declare that they have no competing interests.

Author contributions

Conceptualization: Raxida Umar, Shanshan Dong, Enli Luo
Writing–original draft: Raxida Umar
Writing–review & editing: Raxida Umar, Hao Lyu

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