



Review article

Applications of TMS in individuals with methamphetamine use disorder: A review

Mingming Zhang^{a,b}, Lei Chen^{a,b}, Ziwei Ren^{a,b}, Zhiyan Wang^{a,b}, Wenbo Luo^{a,b,*}^a Research Center of Brain and Cognitive Neuroscience, Liaoning Normal University, Dalian, 116029, China^b Key Laboratory of Brain and Cognitive Neuroscience, Liaoning Province, Dalian, 116029, China

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ABSTRACT

Methamphetamine abuse results in a host of social and medical issues. Methamphetamine use disorder (MUD) can hinder the brain and impair cognitive functions and mental health. Transcranial magnetic stimulation (TMS) is a non-invasive approach in the treatment of MUD. Recent studies have demonstrated encouraging and positive effects of TMS on the craving, affective symptoms, sleep quality, and cognitive functions in individuals with MUD. The regulation of specific brain activities through TMS has also been found to be a contributing factor to these positive outcomes. It is essential to employ more techniques, participants, and stimulation parameters and targets in the future.

1. Introduction

Methamphetamine is one of the most prevalent synthetic drugs in the world and imposes heavy economic, social, and health burdens on the society. In 2020, approximately 284 million people aged 15–64 years used drugs globally, which was a 26 % increase from 2010; furthermore, 525 tons of amphetamine-type stimulants, including 375 tons of methamphetamine, were seized worldwide, which was an increase of 16 % from the previous year [1]. Although the number of drug abusers in China has decreased in 2022, approximately 588,000 people continue to use methamphetamine [2]. Methamphetamine use disorder (MUD) is a chronic disorder characterized by impulsivity, compulsion, and high relapse rates and is related to various physical and psychological problems [3]. MUD poses a significant public health threat as well [4,5].

Long-term methamphetamine use can cause severe brain damage. Patients with MUD develop cerebral atrophy in some regions, such as the insula [6], temporal lobe [7,8], dorsolateral prefrontal and orbitofrontal lobes [8], ventromedial prefrontal lobe, and hippocampus [9]. For example, compared with healthy controls, participants with MUD have thicker bilateral superior frontal cortex as well as reduced gray matter volume in the right hippocampus and bilateral nucleus accumbens and periinsular cortex [10]. Additionally, these patients experience imbalances in neurotransmitter systems [11] and cerebral functional connectivity [12]. Specifically, compared with healthy people, long-term methamphetamine use can alter dopamine release, reduce the activity of dopamine transporters and D2/D3 receptors, and ultimately lead to increased extracellular dopamine concentrations [13,14]. Furthermore, while at rest, the MUD group of participants in withdrawal demonstrated heightened functional connectivity in the brain and regions such as the hippocampus, striatum, amygdala, insula, and prefrontal cortex in contrast with healthy individuals [12].

* Corresponding author. Research Center of Brain and Cognitive Neuroscience, Liaoning Normal University, No. 850, Huanghe Road, Shahekou District, Dalian, 116029, China.

E-mail address: luowb@lnnu.edu.cn (W. Luo).

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The brain irregularities mentioned above are responsible for hindering cognitive and behavioral performances, which include but are not limited to attention, executive function, working memory, risk decision-making, and delay discounting [12,15]. For example, a decrease in the dopamine concentration in the caudate nucleus of individuals with MUD in abstinence is associated with poor behavioral performance of memory and executive functions [16]. Furthermore, studies have consistently demonstrated that extended consumption of methamphetamine results in a negative mood [17]. A Chinese study of 613 male patients with MUD found a higher incidence of depressive symptoms in them [18]. Patients with MUD have a weakened ability to cope with negative emotions, which makes it hard for them to successfully employ emotion regulation strategies [19]. Abnormal cerebral activities in the orbitofrontal lobe, dorsolateral prefrontal lobe, amygdala, and hypothalamus are also associated with increased anxiety and stress responses in individuals with MUD during the withdrawal phase [20]. These findings suggest a potential link between mood-related brain activity and withdrawal symptoms in this population.

Currently, MUD treatment focuses on pharmacotherapy and psychotherapy. Despite the lack of approval from the US Food and Drug Administration or European Medicines Agency, randomized controlled trials have tried several drugs, such as antidepressants, antipsychotics, psychostimulants, anticonvulsants, and opioid antagonists, for short- or long-term detoxification in the treatment of MUD [21]. However, patients with MUD may become drug-dependent following pharmacotherapy; therefore, it is necessary to choose the drugs and their doses carefully. Alternatively, several psychotherapy techniques are available for the treatment of MUD, such as motivational therapy, cognitive behavioral therapy, and contingency management [22]. For example, ²³ found that contingency management was effective in stimulant use disorders and may have additional effects when combined with drugs or other psychotherapies. Despite the potential benefits of psychotherapy, it is important to note that it is a prolonged process and is highly subjective.

With the widespread application of physical therapy in the field of mental illness, transcranial magnetic stimulation (TMS) has become a viable treatment option for MUD. TMS is a safe, painless, and non-invasive treatment. Furthermore, TMS can modulate neural circuits and neurotransmitter systems typically involved in psychiatric and neurological disorders [23,24]. This article provides an overview of the fundamental principles of TMS technology, the distinguishing features of various modes, and the therapeutic outcomes of TMS in managing MUD. Finally, the effects of TMS on brain activity are analyzed to explore treatment options for MUD and augment the existing body of knowledge on MUD treatment.

2. Transcranial magnetic stimulation

The basic principle of TMS is Faraday's law of electromagnetic induction. An electrical current is transmitted through a capacitor to a coil of copper wire loop embedded within a plastic enclosure. The consequent magnetic field is perpendicular to the coil's plane and can penetrate the skull without any loss of intensity and subsequently induce an electrical current. If the induced current is sufficiently strong, it alters the electrical potential of the conducting surface of the neuronal membrane, thus generating an action potential [25].

TMS devices commonly offer the option of administering monophasic or biphasic pulses, which can be customized with specific pulse widths. Additionally, the pulse parameters can be easily adjusted to meet individual needs. Different types of coils can be selected based on the depth of the stimulus target [26,27]. The two most prevalent types of coils utilized are figure-eight coils, which elicit targeted stimuli, and circular coils, which elicit non-targeted stimuli [28]. The spatial resolution and stimulation effects of TMS are influenced by various factors, such as the coil's shape, position, and orientation, as well as the pulse shape and stimulation intensity [29–32].

Repetitive TMS (rTMS) is characterized by the delivery of more than two bursts of pulses, which primarily target the primary motor areas to elicit long-lasting effects on corticospinal excitability that can persist for several minutes to hours [33,34]. The implementation of pre- and post-intervention motor evoked potential measures can yield comparable outcomes. In contrast, the effects of rTMS on non-motor regions are evaluated using more indirect measures, including electroencephalogram (EEG), magnetic resonance imaging (MRI), and behavioral assessments. Classical rTMS can be administered at either a low frequency (≤ 1 Hz) or a high frequency (≥ 5 Hz) [34–36]. Continuous and intermittent theta-burst stimulation (cTBS and iTBS, respectively) can be differentiated based on their modes of operation. Low-frequency rTMS and cTBS demonstrate inhibitory effects and elicit long-term depression, whereas high-frequency rTMS and iTBS demonstrate excitatory effects and induce long-term potentiation.

3. Effect of TMS on MUD treatment

3.1. Craving

Craving refers to the subjective urge of individuals, including those in withdrawal, to acquire and use an addictive substance in the face of stress, low dose, or drug-related environmental cues [37,38]. In laboratory settings, the absence of cues and the presence of cues are frequently used to measure the influence of drug-related stimuli on individuals, by inducing cravings. These stimuli include text, images, audio, video, and depiction of drug use. Cravings are primarily measured using subjective reporting methods, such as the Desires for Speed Questionnaire [39], and visual analog scores. Recent studies have used virtual reality technology to immerse participants in drug-related environments, thus greatly improving the ecological validity and authenticity of craving measurements [40–45]. People with elevated MUD scores tend to experience more intense cravings and a higher probability of relapse within a short period of withdrawal [43]. Similar to cocaine, opium, and alcohol, methamphetamine triggers a desire that involves various brain regions, including the prefrontal lobe, nucleus accumbens, and forebrain, which are commonly associated with addiction [46–49].

A single TMS has been observed to affect the cravings of individuals with MUD. For instance, ⁵¹ stimulated the left dorsolateral prefrontal cortex (IDLDFC) in 10 patients with MUD and eight healthy controls at hourly intervals using parameters of 1 Hz, 15 min,

900 pulses, 100 % resting motor threshold (RMT), and a figure-eight coil. Methamphetamine-related and neutral images were utilized for the assessment of pre- and post-intervention cravings. The results revealed an increased craving in the stimulation group compared with the control group.

Researchers have also explored the effects of multiple TMS interventions. ⁵² used a double-blind design and randomly assigned 30 men with MUD to the stimulation group (10 Hz, 80 % RMT, 5 s on, 15 s off, 8 min, 1200 pulses, once a day for five consecutive days, IDLPFC) and control group (same parameters as those in the stimulation group with the coil at 90° to the scalp). The results revealed that the decrease in craving after the first intervention was not significant. After five interventions, cravings were significantly reduced in the stimulation group but not in the control group. ⁵³ randomly assigned 50 men with MUD to five groups (10 Hz-P3, 10 Hz-IDLPFC, 10 Hz-rDLPC, 1 Hz-IDLPFC, and 1 Hz-rDLPC) and conducted interventions for five consecutive days. The results revealed that 10 Hz/1 Hz and IDLPFC/rDLPC significantly reduced the cravings after the first and fifth days, whereas there were no significant changes in the P3 group. ⁵⁴ used high-frequency rTMS to evaluate drug craving in patients with MUD (34 patients in the treatment group and 30 in the control group) by stimulating the IDLPFC. The parameters for the true stimulation group were 10 Hz, IDLPFC, 11 min, 400 pulses, and 100 % RMT. The results revealed that high-frequency rTMS reduced drug cravings after 4 weeks of intervention.

Additionally, studies have examined the sustained effects of TMS interventions. ⁵⁵ recruited 195 patients with MUD and randomly divided them into three groups: 10 Hz-IDLPFC, 1 Hz-IDLPFC, and a control group. The intervention program lasted 4 weeks and was tracked for 2 months. The treatment groups demonstrated significantly reduced cravings, and the effect was maintained at 2 months after the intervention. Similarly, ⁵⁶ applied the same stimulus as did ⁵³ in 48 males with MUD with an acute withdrawal response; the control group was treated with a coil at 90° to the scalp. The intervention lasted 10 days, with 2 days of rest after the first 5 days. The results demonstrated that the cravings of the participants in the treatment group decreased and persisted for 3 months following the intervention.

The advantages of cTBS and iTBS include short duration, safety, and tolerability [50]. These two protocols are instrumental for patients with MUD. ⁵⁸ randomly assigned 83 patients with MUD to iTBS-IDLPFC, cTBS-IDLPFC, and cTBS-rDLPC groups with 600 pulses for 4 min in iTBS and 600 pulses for 40 s in cTBS. The participants received two interventions per day, approximately 4 h apart, for five consecutive days, and baseline and post-experiment cravings were assessed. The cravings significantly decreased in the iTBS-IDLPFC and cTBS-rDLPC groups but not in the cTBS-IDLPFC group. Su et al. prolonged the treatment with iTBS-IDLPFC to 4 weeks and found significantly decreased cravings compared with the control group (rotating the coil 180° away from the scalp) [51–53]. Furthermore, they demonstrated that at 1 year of follow-up, only one person in the iTBS-IDLPFC group (n = 32) and three people in the control group (n = 31) had relapsed. ⁶² conducted a craving assessment after weekly interventions and found decreased cravings in the first week in the iTBS-IDLPFC group; however, the effect weakened subsequently. ⁶³ examined novel targets and combined effects of cTBS and iTBS; they randomly assigned participants to iTBS-IDLPFC, cTBS-left ventromedial prefrontal cortex (lvmPFC), superimposed stimulation, and control groups. They found that the real stimulation significantly reduced cravings with no significant differences between the three experimental groups.

TMS is generally used for cravings in patients with MUD because reducing cravings may help in preventing relapses. Excitation of the IDLPFC and inhibition of the rDLPC have been found to reduce cravings with the effects lasting for some time. It must be noted that iTBS may reduce cravings better than 10 Hz rTMS [54]. However, future research should examine more participants, compare different TMS parameters, seek more effective stimulation targets, and adopt various technical methods, such as virtual reality, physiological indicators, and brain signals, to comprehensively evaluate cravings. Differences between the sexes in the effects of TMS on craving reduction should also be analyzed.

3.2. Affective symptoms

Methamphetamine consumption in those with MUD has been found to aggravate affective symptoms, specifically depression and anxiety [55]. Men with MUD (16.6 %) had a significantly higher prevalence of depression than healthy individuals (3.99 %) in China [56]. ¹⁸ conducted an observational study and found that individuals with MUD who abstained for 1–7 days experienced widespread anxiety symptoms.

TMS is effective in treating emotional problems in individuals with MUD. ⁶⁸ presented MUD patients with a disgusting, fearful, sad, or neutral picture of a situation and asked them to judge the orientation of a yellow arrow in the picture to examine their emotional attention. They found that individuals with MUD did not have a negative preference compared with the healthy group (the response was shorter in the negative condition than neutral condition). Furthermore, they found that, compared with the control group, the use of 10-Hz high-frequency intervention to the IDLPFC could improve the response speed to negative pictures in the MUD group. Therefore, TMS improved the emotional attention function of individuals with MUD, and the effect lasted for 2 weeks. ⁵⁶ used the Self-Rating Depression Scale and the Self-Rating Anxiety Scale and found that depression in men with MUD was effectively reduced following a 10-Hz intervention on the rDLPC with no significant effects on the anxiety symptoms. Therefore, high-frequency rTMS targeting the rDLPC could help with depression in patients with MUD.

Furthermore, studies have found that iTBS-IDLPFC, cTBS-IDLPFC, and cTBS-rDLPC groups in MUD demonstrated varying degrees of improvements in depression and anxiety with no effects on impulsivity [57]. Combined cTBS targeting the left vmPFC and iTBS targeting the IDLPFC were effective in ameliorating depression and withdrawal symptoms in patients with MUD [58]. Therefore, TMS in different modes is an effective treatment for individuals with MUD since it may be preventative against potential relapses.

Affective symptoms are known to be potent triggers for cravings, which can result in relapse in patients with MUD in withdrawal. Patients with MUD with depressive symptoms demonstrated stronger drug cravings and individual aggression than those without depressive symptoms [18]. Although previous studies have focused on depression and anxiety, the effects of TMS on other affective

symptoms (e.g., boredom and guilt) in patients with MUD remain unclear. Changes in the emotional state of the participants should also be evaluated across multiple dimensions, such as physiological and cerebral. The cerebral mechanisms of emotional problems generally involve subcortical tissues and regions, such as the insula and amygdala; therefore, functional MRI (fMRI) technology, combined with functional connections, should be used to evaluate its effects.

3.3. Sleep quality

Sleep and circadian rhythm disorders are significant contributors to addiction, particularly in instances of relapse [59].⁷⁰ found that recreational users of methamphetamine experienced acute sleep disruption, which was significantly dose-dependent. Disruption of sleep is associated with neurodegenerative diseases that affect brain health [60].

Several studies have evaluated the use of TMS to improve sleep quality in patients with MUD.⁵⁶ tested the effects of rTMS on sleep quality. The intervention lasted for 10 days, with 2 days of rest after the first 5 days. They found that targeting the IDLPFC with 10 Hz rTMS effectively improved sleep quality in patients with MUD. In another study, patients with MUD received twice-daily TBS over five consecutive days for a total of 10 sessions.⁵⁸ found that sleep quality significantly improved in the cTBS-IDLPFC and iTBS-IDLPFC groups after the intervention with no significant changes in the cTBS-rDLPFC groups.⁵⁹ randomly divided patients with MUD into the iTBS group and control group and targeted the IDLPFC. Improvements in sleep quality were assessed using the Pittsburgh Sleep Quality Index before and after treatment (4 weeks). The results revealed that iTBS-IDLPFC significantly improved sleep quality [51–53] following 10 sessions were conducted over 2 weeks (one session per day, 5 days per week) [58].⁶³ found that combined cTBS-lvmPFC and iTBS-IDLPFC significantly improved sleep quality over iTBS-IDLPFC alone.

Previous studies have demonstrated the potential of TMS in improving sleep quality in patients with MUD. Further studies should integrate technical approaches to reveal the mechanism of improved sleep following TMS, scrutinize its efficacy across all sleep stages, and ascertain alterations in sleep-related EEG indices (e.g., beta frequency spectrum). It is also essential to investigate the relationship between sleep and the formation of addictive memories.

3.4. Cognitive functions

Compared with healthy controls, patients with MUD exhibit varying levels of cognitive dysfunction [15,61,62–64]. TMS has been employed to address cognitive impairments in MUD patients.

⁵² adopted a high-frequency rTMS protocol (10 Hz-IDLPFC, 5 days of intervention), and the participants completed the Chinese version of the Cognitive State Test Set before and after the intervention, including international shopping order tasks (language learning and memory), Groton maze learning tasks (problem solving/error monitoring), 2-back tasks (working memory), continuous paired associative learning tasks (spatial working memory), and social-emotional cognitive tasks (social cognition). The results revealed that, compared with the control group, the treatment group demonstrated significantly improved language learning, memory, and social cognitive abilities. Su et al. administered a 4-week iTBS protocol that targeted the IDLPFC, and the results revealed that the treatment group experienced a significant increase in correct scores on the international shopping list task, while the control group (coils rotated 180°) did not demonstrate any significant changes. Additionally, the treatment group demonstrated a significant decrease in error scores on the Groton maze learning task, further highlighting the positive effects of the iTBS protocol [51,52,65]. Therefore, TMS effectively improved cognitive functions, such as speech, memory, and problem solving in patients with MUD.⁶³ employed 2-weeks of cTBS targeting the lvmPFC and iTBS targeting the IDLPFC, which did not affect the results of cognitive tests. However, the baseline levels of depression and spatial working memory performance were significantly positive in predicting the therapeutic effect of craving, and individuals with MUD with better baseline levels were able to respond better to TMS treatment.⁷⁵ asked patients with MUD to perform free-recall tasks before and after iTBS. Participants who received multiple iTBS on IDLPFC had improved working memory performance, increased working memory capacity, and enhanced therapeutic efficacy compared with the control group.

rTMS also affects impulse and inhibitory controls in individuals with MUD.⁷⁶ used 10 Hz high-frequency rTMS to stimulate the IDLPFC and found that, compared with the control group (coils rotated 90°), the treatment group demonstrated a significant decrease in response time in the two-item choice oddball task. These results revealed that this intervention could regulate the attentional control function of individuals with MUD.⁷⁷ observed that receiving 10 days of 1 Hz rTMS on the IDLPFC improved the impulse inhibition of patients with MUD, which was measured using a two-choice oddball paradigm. This effect was maintained for 3 weeks following the intervention. Changes in impulse inhibition were positively correlated with craving reduction.⁵⁴ examined the decision-making abilities of patients with MUD. Following high-frequency rTMS over the IDLPFC, patients with MUD had a lower level of impulsive decision-making than those in the control group.

Furthermore, TMS regulates the attentional bias of patients with MUD.⁷⁸ linked EEG with behavioral data to investigate the modulation of iTBS on methamphetamine-related attentional bias and the corresponding electrophysiological changes. Patients with MUD were randomly assigned to treatment (IDLPFC for 4 weeks) and control (coils rotated by 180°) groups. The participants completed the Addiction Stroop Task, and EEG was recorded before and after the treatment. The results revealed that iTBS significantly reduced not only the error rate of methamphetamine words but also the beta band power on the electrodes in the central frontal region. There was a significant time-by-group effect for N1 amplitude and P3 latency, which indicates that iTBS might regulate attention bias and beta oscillation in patients with MUD during the attention processing of methamphetamine-related words.

In summary, researchers have preliminarily investigated the effects of TMS on cravings, affective symptoms, sleep quality, and cognitive functions in patients with MUD. TMS can effectively reduce cravings and withdrawal symptoms and improve the emotional

status, sleep quality, attention preferences, learning ability, impulsivity, and emotional processing in individuals with MUD. These effects can be maintained for some time. Further research is warranted to determine if there are any differences in efficacy between conventional rTMS and iTBS or cTBS on MUD treatment.

4. Mechanisms underlying the effects of TMS on brain function

TMS can regulate cravings, withdrawal responses, and cognitive and emotional functions of individuals with MUD as it effectively modulates brain activity. Therefore, recent studies have attempted to unravel the underlying brain mechanisms.

In terms of brain metabolism, gamma aminobutyric acid (GABA, inhibitory) and glutamate (excitatory) neurotransmitter systems are critical in the pathological mechanisms involved in MUD and partially represent the underlying mechanism of the corresponding therapeutic effects of TMS. Studies using magnetic resonance spectroscopy have found differences in brain metabolism between individuals with MUD and controls [66–71].⁶⁰ found that a 4-week iTBS protocol significantly reduced GABA/N-acetyl-aspartate (NAA) concentrations in the treatment group and glutamate and glutamine/NAA concentrations in the control group. Changes in GABA in the treatment group were significantly negatively correlated with score changes on the Groton maze learning task (problem solving/error monitoring). This finding indicates that the effects of TMS on the cognitive function of individuals with MUD may be related to changes in the GABA levels in the prefrontal cortex.⁶¹ found that stimulation of the IDLPFC around the iTBS regimen significantly enhanced the functional connectivity with the inferior parietal lobule and was significantly negatively correlated with cravings.

In summary, several studies have revealed that TMS may have a therapeutic effect on the regulation of cortical pathways in patients with MUD. However, studies are limited and primarily focus on some neurotransmitters. In order to advance our understanding further, it is imperative to integrate various technologies, such as EEG, neurotransmitters level assessments (e.g., 5-hydroxytryptamine and dopamine), neuroimaging (e.g., functional near-infrared spectroscopy, fMRI, positron emission tomography, and single photon emission computed tomography), and artificial intelligence [72,73].

5. Conclusion

This study reviewed the effects of methamphetamine on brain function and the treatment of patients with MUD using TMS. TMS effectively reduces cravings and affective symptoms and improves the cognitive function of individuals with MUD. In the future, the persistence of the positive effects of TMS should be further evaluated. Furthermore, it is imperative that future studies should systematically explore additional permutations of stimulus parameters, targets, and specific interventions by employing neural navigation techniques. To maximize the efficacy of TMS interventions, reduce the risk of relapse, and enable successful reintegration into society of individuals with MUD, it may be beneficial to combine TMS treatments with other modalities. This approach has the potential to promote cognitive function recovery and yield superior outcomes.

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Data availability statement

No data was used for the research described in the article.

Additional information

No additional information is available for this paper.

CRedit authorship contribution statement

Mingming Zhang: Writing – review & editing, Writing – original draft, Funding acquisition, Conceptualization. **Lei Chen:** Writing – review & editing. **Ziwei Ren:** Writing – review & editing. **Zhiyan Wang:** Writing – review & editing. **Wenbo Luo:** Project administration, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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