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REVIEW

Transcranial Magnetic Stimulation in Alcohol Use Disorder Treatment: A Narrative Review

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Main Points

- High-frequency repetitive transcranial magnetic stimulation (rTMS) applied to the right or left dorsolateral prefrontal cortex has been found effective in reducing alcohol cravings and cognitive dysfunctions in some studies.
- Intermittent theta burst stimulation (iTBS) has shown positive results in reducing depressive symptoms and relapse risk in alcohol dependence treatment, while continuous TBS has provided more limited short-term effects.
- Deep rTMS applied to deep brain structures such as the medial prefrontal cortex and anterior cingulate cortex has the potential to reduce relapse and improve impulse control.
- Variations in frequency, session numbers, and targeted brain regions in rTMS and TBS protocols influence treatment outcomes, highlighting the importance of standardizing protocols.
- Overall, rTMS shows promise as a treatment method for alcohol dependence, but optimizing treatment protocols and conducting further clinical research is necessary.

Abstract

Alcohol use disorder is a mental health problem characterized by symptoms such as withdrawal, tolerance, and intense alcohol craving, affecting approximately 8.5% of the global adult population. Non-invasive neuromodulation techniques like repetitive transcranial magnetic stimulation are gaining interest in alcohol use disorder treatment. This review aimed to assess the efficacy of repetitive transcranial magnetic stimulation, deep transcranial magnetic stimulation, and theta burst stimulation protocols in treating alcohol use disorder, focusing on randomized controlled studies with sham. The studies reviewed predominantly target the dorsolateral prefrontal cortex. Some repetitive transcranial magnetic stimulation protocols have shown positive effects on reducing craving and improving cognitive functions, while others did not find significant clinical changes. The results of deep transcranial magnetic stimulation studies targeting the medial prefrontal cortex and anterior cingulate cortex also vary; some report reductions in alcohol consumption, while others do not demonstrate significant effects. Theta burst stimulation studies suggest that particularly intermittent theta burst stimulation protocols may be effective in reducing depressive symptoms and relapse risk, whereas continuous theta burst stimulation protocols tend to have shorter and more limited effects. In conclusion, the efficacy of repetitive transcranial magnetic stimulation in the treatment of alcohol use disorder varies according to the targeted brain region, stimulation parameters, and patient characteristics. There is a need for studies with larger sample sizes, homogeneous protocols, and long-term follow-ups to more clearly define the role of repetitive transcranial magnetic stimulation in alcohol use disorder treatment.

Keywords: Alcohol use disorder, craving, repetitive transcranial magnetic stimulation

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Introduction

Alcohol is one of the most widely consumed psychoactive substances worldwide. According to the World Health Organization, alcohol was responsible for 3 million deaths globally, accounting for 5.3% of all deaths in 2019 (WHO, 2019). Alcohol use disorder (AUD) is characterized by symptoms such as withdrawal, tolerance, and craving related to alcohol consumption. This disorder is

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more common in men than in women and is estimated to affect about 8.5% of the adult population over their lifetime (American Psychiatric Association, 2013). The data on global alcohol consumption in 2019 show that an estimated 400 million people aged 15 years and older live with AUD, and an estimated 209 million live with alcohol dependence (WHO, 2019). AUD is considered a chronic and recurrent brain disease with a high comorbidity with mental health conditions such as depression, anxiety disorders, and personality disorders. AUD is an important causal factor in over 200 diseases, including cirrhosis, cancer, and cardiovascular diseases (WHO, 2019). Additionally, delirium tremens is a severe complication of AUD that may occur during alcohol withdrawal and can be life-threatening. In severe cases, patients may require high-dose pharmacological treatment in an intensive care unit (Korkmaz et al., 2024). Cognitive-behavioral therapy and support groups are also considered effective treatment approaches alongside pharmacotherapy. Moreover, the development of non-invasive brain stimulation methods, such as transcranial magnetic stimulation (TMS), has opened new avenues for treating AUD and comorbid mental disorders that may trigger AUD relapse

Neural Circuits of Alcohol Dependence

In recent years, significant progress has been made in understanding the effects of alcohol dependence on the central nervous system. Individuals with a tendency for addiction often exhibit increased craving and substance-seeking behaviors in response to substance-related cues. These behaviors may result from impaired executive control and dysregulated functioning of the limbic system, linked to abnormal activities in specific regions of the prefrontal cortex and striatum circuits (Hanlon et al., 2015). Neuromodulation techniques can target specific brain regions and functions, contributing to clinical insights into the neurobiological mechanisms associated with addiction. Addiction is particularly thought to be associated with hypodopaminergic activity within the mesolimbic dopamine pathway. Researchers using positron emission tomography have found a link between addiction and a drop in the number of ventral striatal D2 receptors and the release of dopamine (Nutt et al., 2015). The process of addiction is characterized by an increased subcortical response to reward-related stimuli and diminished prefrontal control. Therefore, there is an increase in craving and substance use tendencies, accompanied by impaired executive functions. This imbalance between heightened impulsivity and weakened prefrontal control often leads to the relapses frequently observed in addiction. The dorsolateral prefrontal cortex (DLPFC) and dorsal anterior cingulate cortex (ACC) are associated with executive functions, decision-making, and self-control. The ventral prefrontal network, which includes the medial prefrontal cortex (MPFC), orbitofrontal cortex, and ventral ACC, is related to limbic stimulation and emotional processes. Activation of the ventral prefrontal cortex can trigger craving and substance use, while hypoactivity in the DLPFC may lead to impairments in executive functions (Goldstein & Volkow, 2011). This imbalance between the two systems is considered a fundamental underlying cause of addiction.

Individuals predisposed to addiction exhibit heightened craving responses to substance-related cues and engage in substance-seeking behaviors. These behaviors are associated with hypodopaminergic activity in the mesolimbic dopamine system and dysfunctions in D2 receptors. The ventral striatum plays a central role in reward-related decision-making processes, and a decrease in dopamine release may lead to a reduced reward sensitivity associated with addiction (Hanlon et al., 2015). Hypoactivity of the prefrontal cortex can lead to impaired executive control and impulsive behaviors. This condition particularly complicates the regulation of alcohol consumption during the early stages of the addiction cycle and increases the individual's risk of relapse (Goldstein & Volkow, 2011). Neuroimaging studies have shown that these changes in the reward system associated with addiction are linked to disruptions in the connections between the ventral striatum and the prefrontal cortex (Goldstein & Volkow, 2011). Dysregulations between the limbic system and prefrontal network are a critical factor that triggers addictive behaviors. The limbic system, particularly the amygdala, regulates emotional arousal associated with addiction and activation of the reward system. A reduction in the prefrontal cortex's capacity to modulate this activation makes it more difficult for individuals to control substance-seeking behaviors (Goldstein & Volkow, 2011). Understanding these mechanisms may provide important guidance in selecting target regions for crTMS (Hanlon et al., 2015). The effects of TMS on dopamine pathways may induce positive changes in circuits associated with addiction. High-frequency rTMS has been shown to strengthen the connectivity between the ventral striatum and the prefrontal cortex, while also increasing dopamine release in reward circuits (Cho & Strafella, 2009; Goldstein & Volkow, 2011). These effects may contribute to the improvement of executive functions and the reduction of alcohol cravings (Hanlon et al., 2015).

Transcranial Magnetic Stimulation

TMS is a non-invasive brain stimulation technique that modulates neuronal activity by delivering magnetic pulses to the cerebral cortex. It is used to treat various neuropsychiatric diseases, particularly major depressive disorder and obsessive – compulsive disorder. Compared to other non-pharmacological treatment options, TMS is preferred in clinical applications due to its fewer side effects and repeatability (Lefaucheur et al., 2020). When magnetic pulses are applied to the scalp during TMS, electromagnetic induction happens. This can have long-lasting effects on the target cortical area, making it more active (long-term potentiation [LTP]-like) or less active (long-term depression [LTD]-like). High-frequency rTMS (e.g., 10 Hz) applied to the frontal cortex can alter dopaminergic activity by changing dopamine release in monosynaptic striatal targets (Cho & Strafella, 2009). High-frequency TMS (>10 Hz) or intermittent theta burst stimulation (iTBS) can change the activity of the cortex in a way that is similar to LTP. On the other hand, low-frequency TMS (1 – 5 Hz) or continuous theta burst stimulation (cTBS) can change the activity in a way that is similar to LTD (Mueller et al., 2014). Simple rTMS protocols are delivered through individual stimulation pulses at fixed intervals. Low-frequency protocols are usually administered at 1 Hz, with stimulation intensity and pulse numbers varying across studies. It is believed that low-frequency rTMS at 1 Hz has an inhibitory effect, although the impact may not be evident at intensities below the motor threshold. High-frequency protocols (5 – 25 Hz) tend to increase cortical excitability, with the duration of effects varying according to stimulation intensity and the number of pulses. This stimulation has been effective for up to 90

minutes post-stimulation in some studies (Cho & Strafella, 2009; Hanlon et al., 2015).

Another protocol of rTMS is theta burst stimulation (TBS), which is based on a pattern used in animal studies to induce synaptic plasticity. TBS is administered through short bursts of high-frequency stimulation, typically at 80% of the motor threshold. The iTBS (iTBS) protocol increases the excitability of the motor cortex through short-duration stimulations, while the cTBS protocol induces depression in motor-evoked potentials through continuous stimulation (Huang et al., 2005). TBS protocols may provide more consistent results than rTMS protocols, which is attributed to the consistency in the applied stimulation intensity and pulse numbers.

High-frequency rTMS (e.g., 10 Hz), particularly when applied to the frontal cortex, can influence dopaminergic activity by altering dopamine release in monosynaptic striatal targets (Cho & Strafella, 2009). Low-frequency TMS protocols (1 Hz) regulate hyperactive limbic regions, enhancing impulse control, while high-frequency TMS protocols (10 Hz and above) support executive functions in the DLPFC. These mechanisms hold the potential for reducing impulsivity in the addiction cycle and improving motivational processes (Cho & Strafella, 2009; Hanlon et al., 2015). High-frequency (>10 Hz) TMS or iTBS can improve executive functions and impulse control by inducing long-lasting potentiation-like effects on cortical activity, potentially reducing anhedonia and relapse risk (Padula et al., 2024). Conversely, low-frequency TMS (1 – 5 Hz) or cTBS inhibits neural circuits by inducing long-term depression-like effects on activity, reducing sensitivity to cues in the MPFC, and decreasing craving (McCalley et al., 2023). Paired associative stimulation (PAS) combines repeated stimulation of somatosensory afferents with cortical stimulation. This protocol is based on the Hebbian concept, where the sequential order of presynaptic and postsynaptic stimulation can induce LTP or LTD (Klomjai et al., 2015). In human studies, the effect of PAS may vary depending on the interstimulus interval, and pharmacologically, N-methyl-D-aspartate and gamma-aminobutyric acid receptors, as well as neurotransmitters like dopamine, may play a role in its effects.

Types of Transcranial Magnetic Stimulation Coils

The most commonly used coil type is the figure-of-eight coil, where two loops of wire converge at the center to form an "8" shape. This design creates a focused magnetic field, allowing for more localized stimulation. This characteristic makes it easier to target specific brain areas, particularly the motor cortex near the surface (Rossi et al., 2009). The circular coil has a circular structure and offers a broad stimulation area, making it suitable for cases that require widespread stimulation. However, it is more limited than the figure-of-eight coil in terms of depth and precision in targeting. It is generally used for stimulating brain regions near the surface. Moreover, stimulation with circular coils may reach deeper areas compared to figure-of-eight coils. The H1 coil has a circular design developed for deep TMS (dTMS) applications to reach deeper brain structures. Each type of H-coil is designed to target specific brain regions (e.g., the H1 coil is used for the prefrontal cortex). This coil is notable for its broader stimulation area and increased depth of stimulation (Levkovitz et al., 2015).

Alcohol Dependence and Transcranial Magnetic Stimulation

The dorsal and ventral fronto-striatal circuits involved in the addiction cycle play an important role in regulating executive control and limbic stimulation. Targeting these circuits in TMS is thought to improve symptoms such as relapse and impulse control in AUD (Mahoney et al., 2020). In particular, the ACC and MPFC have been evaluated as potential targets for TMS in AUD treatment. These regions have important connections to cortical and subcortical areas that regulate craving, reward-based decision-making, and substance-seeking behaviors (Camchong et al., 2013). Notably, neural responses of the ACC to alcohol-related cues have been observed to correlate with individual alcohol craving, addiction severity, and relapse (Durazzo & Meyerhoff, 2020). In addiction-related studies, TMS applied to the DLPFC has been frequently used to modulate executive functions and cognitive control (Feil & Zangen, 2010). This practice is supported by findings suggesting that stimulation of the DLPFC can reduce activity in the MPFC (Hanlon et al., 2016). Additionally, TMS applied to the DLPFC can increase dopamine release in the caudate nucleus, and this effect may reduce craving by stimulating dopamine release in mesolimbic dopaminergic structures such as the tegmental area and nucleus accumbens (Hauer et al., 2019). Furthermore, DLPFC stimulation may help control substance use-related impulses, aiding in the maintenance of abstinence periods (Hauer et al., 2019). Although most TMS studies on addiction apply excitatory protocols to the left DLPFC, some studies targeting the right DLPFC in AUD have also reported efficacy (Ekhtiari et al., 2019). There are meta-analyses indicating that high-frequency TMS applied to the right DLPFC is effective in reducing craving (Enokibara et al., 2016; Maiti et al., 2017). However, a comprehensive meta-analysis by Zhang et al. (2019) has shown that TMS applied to the left DLPFC also reduces craving.

The differences between these meta-analyses may be explained by variations in the content of the evaluated studies and the stimulation parameters. For instance, some meta-analyses include not only studies related to AUD but also those on food cravings or other types of addiction (Enokibara et al., 2016; Maiti et al., 2017). This suggests that the effect of rTMS on craving may vary depending on the target brain region, stimulation dose, and protocol (Ekhtiari et al., 2019). Recent reviews investigating the effects of rTMS on cognitive functions have reported positive outcomes for both right and left DLPFC applications (Naish et al., 2018). It is recommended that in the treatment of addiction, not only the brain region to be stimulated but also the targeted neural networks and the functional effects of stimulation be taken into consideration (Ekhtiari et al., 2019).

Material and Methods

Search Strategy

This review examined studies evaluating the efficacy of rTMS treatment in patients diagnosed with AUD. The search process covered studies published up until September 2024 and was conducted using the PubMed database. The keywords used were "alcohol use disorder," "alcohol dependence," "TMS," "transcranial magnetic stimulation," "theta burst stimulation," and "craving." Searches using these terms yielded the following number of results:

1. Using "alcohol use disorder" and "alcohol dependence" with "TMS" and "transcranial magnetic stimulation," 34 results were found.
2. Using "alcohol use disorder" and "theta burst stimulation," 18 results were found.
3. Using "craving" and "alcohol" with "transcranial magnetic stimulation," 95 results were found.
4. Combinations of "TMS," "transcranial magnetic stimulation," "alcohol use," and "alcoholic" produced 30 results.

Duplicate publications were removed from the search results, and the remaining studies were assessed according to the inclusion and exclusion criteria. Following this process, a total of 24 articles were selected for review.

Inclusion and Exclusion Criteria

Inclusion criteria: For this review, studies must be sham-controlled randomized controlled trials (RCTs). Exclusion criteria: Studies that meta-analyze, review, and case series or were published in languages other than English were excluded.

Results

The types of TMS used in the 24 studies are presented in (Figure 1). Table 1 summarizes the details of the studies included in this review, covering parameters such as sample size, stimulation protocol, targeted brain regions, and treatment outcomes. This table provides a comprehensive overview of the TMS applications and their efficacy in the context of AUD treatment.

Transcranial Magnetic Stimulation in Alcohol Use Disorder

Our review included a total of 13 studies applying rTMS for alcohol dependence. These studies featured sample sizes ranging from 20 to 75 and incorporated various assessment parameters and application protocols. Most of the studies targeted the right DLPFC, with only four focusing on the left DLPFC (Del Felice et al., 2016; Höppner et al., 2011; Raikwar et al., 2020; Zhang et al., 2022). The rTMS protocols applied were generally high-frequency, mostly at 10 Hz or 20 Hz. The treatment durations and the number of sessions varied, with an average of 10 sessions over 2 weeks being a common protocol. Mishra et al. (2010) reported that rTMS applied to the right DLPFC at a 10 Hz frequency, with 4.9-second trains repeated 20 times per session for a total of 10 sessions (one per day), significantly reduced alcohol craving and had a moderate effect. In contrast, Höppner et al. (2011), using 20 Hz stimulation, and Raikwar et al. (2020), using 10 Hz to the left DLPFC for 10 days, found no significant difference between rTMS and sham stimulation regarding alcohol craving or mood state. Höppner et al. (2011) also demonstrated that patients receiving active rTMS exhibited an increased rate of incorrect perceptions of alcohol-related images in an attentional blink paradigm, suggesting that rTMS might influence attentional processing.

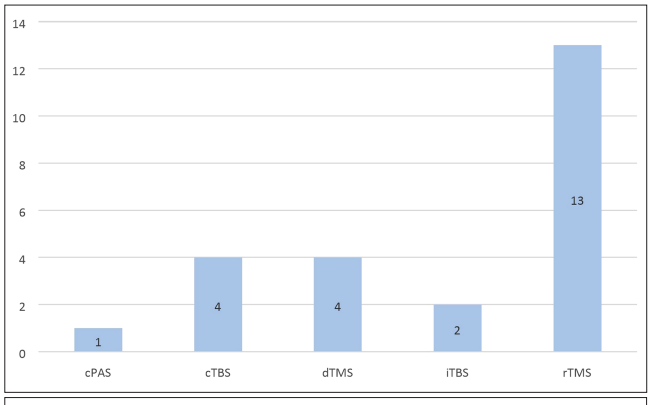

Figure 1. Types of TMS Used in All Studies.

Herremans et al. (2012, 2013) applied single-session rTMS to the right DLPFC (20 Hz, 40 trains, each lasting 19 seconds, with 12-second intervals, totaling 1560 pulses). While no immediate or delayed effect on alcohol craving was observed, the 2012 study reported improvements in attentional processes. Jansen et al. (2015) found that a single session of active rTMS (10 Hz frequency, 60 trains of 5 seconds each) applied to the right DLPFC positively influenced brain connectivity in alcohol-dependent individuals, leading to increased reward/motivation network activity. Qiao et al. (2016) applied rTMS to the right DLPFC at 10 Hz, 80% motor threshold, with eight trains of 10 seconds each, separated by 5-second intervals, for a total of 20 sessions. They observed improvements in memory functions and hippocampal metabolite ratios post-TMS. Del Felice et al. (2016) applied high-frequency rTMS (10 Hz at 100% motor threshold) to the left DLPFC twice a week for four sessions, noting improvements in attention and inhibitory control without significant effects on alcohol craving. Mishra et al. (2016) delivered 10 daily sessions of rTMS to the right DLPFC at 10 Hz, reaching a total of 1000 pulses per session, finding that rTMS increased cerebral blood flow and reduced vascular resistance. Jansen et al. (2019) administered a single session of rTMS to the right DLPFC (10 Hz frequency, 60 trains of 5 seconds), reporting its impact on emotional processing, though without a significant effect on reducing alcohol craving. Zhang et al. (2022) applied high-frequency rTMS to the left DLPFC at 20 Hz for 10 daily sessions (5-second trains with 15-second intervals), resulting in a reduction in heavy drinking behaviors and improvement in mental health indicators. In another study, patients with AUD received high-frequency rTMS to the right DLPFC (10 Hz at 110% motor threshold, 60 trains of 5 seconds) for 10 consecutive days. However, there was no significant difference between the active rTMS and sham groups in terms of alcohol consumption and craving reduction (Hoven et al., 2023) (Table 1).

Deep Transcranial Magnetic Stimulation in Alcohol Use Disorder

In studies using dTMS, the areas of application were primarily the bilateral insular cortex (Perini et al., 2020), the MPFC (Ceccanti et al., 2015), and the MPFC, including the ACC (Harel et al., 2022; Selim et al., 2024). A total of five dTMS studies showed that dTMS had some positive outcomes in AUD; however, the efficacy varied according to the protocol and the targeted region. In the study by Ceccanti et al. (2015), dTMS was applied to the MPFC at a frequency of 20 Hz in daily sessions for 10 consecutive days. Similarly, in the study by Harel et al. (2022), a protocol was implemented targeting the MPFC and ACC with the H7 coil, using 10 Hz stimulation, over 3 weeks with five sessions per week, followed by five maintenance sessions over a 3-month follow-up period. Both studies reported that dTMS reduced alcohol consumption, heavy drinking behaviors, and alcohol craving. However, Perini et al. (2020) targeted

Table 1.
The Details of All Studies

Author, Year	Article Type	Sample Size	Assessment Parameters (Scales)	TMS Type	Protocol	Application Area (Brain Region)	Coil Type	Sessions	Treatment Duration	Detoxification Duration	Effects	Efficacy
(Mishra et al., 2010)	Randomized controlled trial	45	Alcohol Craving Questionnaire, CIWA-Ar	rTMS	High-frequency rTMS (10 Hz)	Right DLPFC	Figure-8 coil	10	10 days	10 days	Significant reduction in craving scores post-rTMS, moderate effect size ($\eta^2 = 0.401$)	Demonstrated efficacy in reducing craving and preventing relapse
(Höppner et al., 2011)	Randomized sham-controlled study	19	OCDS, HDRS, BDI	rTMS	High-frequency rTMS (20 Hz)	Left DLPFC	Figure-8 coil	10	10 days	N/A	No significant differences in craving or mood between real and sham stimulation groups, but differences in attention to alcohol-related pictures in the AB paradigm	No significant effect on clinical parameters such as craving or mood, but an attentional bias effect found
(Herremans et al., 2013)	Naturalistic study	31	OCDS	rTMS	HF-rTMS 20 Hz, 1560 pulses per session	Right DLPFC	Figure-8 coil	1	Single session	12.03 days	No immediate or delayed changes in craving measurements	One session is too short to affect craving in alcohol dependence
(Herremans et al., 2012)	Randomized, sham-controlled study	29	OCDS, Go-NoGo task (RT and IIRTV)	rTMS	HF-rTMS 20 Hz, 1560 pulses per session	Right DLPFC	Figure-8 coil	1	Single session	14.24 days	Reduced intra-individual reaction time variability (IIRTV), no effect on craving measurements	Improvement in attentional lapses, no impact on craving
(Jansen et al., 2015)	Randomized controlled trial	75	CIDI (DSM-IV), AUDIT, BDI, BAI	rTMS	HF-rTMS 10 Hz, 60 5-second trains	Right DLPFC	Figure-8 coil	2	21.7 days (average)	≥3 weeks	Increased connectivity within left FPn; a trend towards increased reward/motivation network connectivity	Positive impact on network connectivity in ADPs, suggesting cognitive control improvements
(Herremans et al., 2015)	Research article	26	AUQ, OCDS, Likert scale	rTMS	Accelerated HF-rTMS (20 Hz, 15 sessions)	Right DLPFC	Figure-8 coil	15	4 days	1 week	Decrease in general craving but no significant change in cue-induced craving	Positive impact on general craving, no effect on cue-induced craving

(*Continued*)

Table 1.
The Details of All Studies (Continued)

Author, Year	Article Type	Sample Size	Assessment Parameters (Scales)	TMS Type	Protocol	Application Area (Brain Region)	Coil Type	Sessions	Treatment Duration	Detoxification Duration	Effects	Efficacy
(Ceccanti et al., 2015)	Randomized double-blind controlled trial	18	Cortisol, prolactin levels, VAS for craving, alcohol intake	dTMS	High-frequency deep rTMS (20 Hz)	MPFC	H-coil	10	N/A	N/A	Significant reduction in cortisol levels, prolactin, alcohol intake, and craving in the real stimulation group	Deep rTMS showed potential efficacy in reducing alcohol-related biomarkers and behavior
(Qiao et al., 2016)	Original research	38	HVLT-R, BVMT-R, 1H-MRS (NAA/Cr, Cho/Cr)	rTMS	High-frequency rTMS (10 Hz) on right DLPFC	Right DLPFC	Figure-8 coil	20	4 sessions per week, each lasting 5 days, with 2-day intervals	2 weeks	Improved memory function, increased NAA/Cr, Cho/Cr levels in the hippocampus	Significant improvement in memory and brain metabolite levels
(Mishra, 2016)	Original research	75	Transcranial Doppler sonography (CBFV, PI, RI)	rTMS	High-frequency rTMS (10 Hz)	Right DLPFC	Figure-8 coil	10	5 sessions per week for 2 weeks	14 – 18 days	Increased cerebral blood flow velocity (CBFV), decreased pulsatility index (PI), and resistance index (RI)	Significant increase in CBFV and decrease in PI/RI compared to sham
(Del Felice et al., 2016)	Sham-controlled study	17	EEG, VAS, SCL-90-R, Stroop Test, Go/No-Go Task	rTMS	High-frequency rTMS (10 Hz)	Left DLPFC	Figure-8 coil	4	2 sessions per week over 2 weeks	6+ days	Improved inhibitory control, selective attention, and decreased depressive symptoms	Reduced fast EEG frequencies, no significant effect on alcohol craving
(Hanlon et al., 2017)	Single-blind, sham-controlled pilot study	49	BOLD signal, self-reported craving	cTBS	Continuous TBS, 6 trains, 110% rMT	FP1	Figure-8 coil	2	2 visits (within 7 – 14 days)	48 hours (cocaine users)	Decreased BOLD signal in the orbitofrontal cortex, insula, anterior cingulate, and other salience network areas	Short-term effect on brain activity, no significant change in self-reported craving
(Kearney-Ramos et al., 2018)	Single-blinded, sham-controlled experiment	49	Self-reported craving, fMRI	cTBS	Continuous TBS (cTBS), 3600 pulses	Left VMPFC	Figure-8 coil	6	7 – 14 days	2.5 days	Attenuated frontostriatal connectivity to drug/alcohol cues, no significant effect on self-reported craving	Neural effects are seen, behavioral effects not significant

Table 1.
The Details of All Studies (Continued)

Author, Year	Article Type	Sample Size	Assessment Parameters (Scales)	TMS Type	Protocol	Application Area (Brain Region)	Coil Type	Sessions	Treatment Duration	Detoxification Duration	Effects	Efficacy
(McNeill et al., 2018)	Randomized, sham-controlled study	20	SST, ad libitum alcohol consumption	cTBS	cTBS, 600 pulses	Right DLPFC	Figure-8 coil	1	Single session	N/A	Impaired inhibitory control, increased alcohol consumption after stimulation	Increased alcohol consumption, not mediated by inhibitory control
(Jansen et al., 2019)	Randomized controlled trial	75	Emotion reappraisal task, AUQ, fMRI	rTMS	High-frequency rTMS (10 Hz, 110% MT)	Right DLPFC	Figure-8 coil	1	N/A	3 weeks	Reduced emotional impact of images in AUD patients, no significant effect on alcohol-related cravings	Significant effects on emotion processing but no effect on craving reduction
(Perini et al., 2020)	Randomized controlled trial	56	AUDIT, ADS, ASI, PACS, TLFB, AUQ, MRI	dTMS	High-frequency deep TMS (10 Hz)	Bilateral insular cortex	H-Coil	15	3 weeks	N/A	No significant difference in alcohol craving and consumption between active and sham groups	No significant effect on alcohol-related behaviors
(Raikwar et al., 2020)	Randomized controlled trial	60	ACQ-NOW	rTMS	High-frequency rTMS (10 Hz)	Left DLPFC	Figure-8 coil	10	10 days	N/A	No significant reduction in craving scores between active and sham groups	No significant effect on craving reduction
(Harel et al., 2022)	Randomized controlled trial	51	AUDIT, ADS, TLFB, PACS, fMRI	dTMS	High-frequency deep TMS (10 Hz)	MPFC, ACC	H-coil	15	3 weeks	5 days	Significant reduction in heavy drinking days decreased craving levels	Demonstrated efficacy in reducing heavy drinking and craving
(Bozzay et al., 2021)	Randomized controlled trial	50	PCL-5, IDS-SR, alcohol use (SCID-5)	iTBS	iTBS, 80% motor threshold, 1800 pulses	Right DLPFC	Figure-8 coil	10	~2 weeks for each phase	N/A	Improved depression symptoms in AUD patients, safe in comorbid AUD	Effective in reducing depressive symptoms, safe in mild AUD
(Zhang et al., 2022)	Randomized controlled trial	45	VAS, serum NfL levels, SF-36 (Mental health component)	rTMS	High-frequency rTMS (20 Hz), 3000 pulses/ session	Left DLPFC	Figure-8 coil	10	2 weeks	N/A	Significant reduction in heavy drinking, craving, and serum NfL levels, improvement in mental health	rTMS significantly reduced drinking and improved mental health indicators

(*Continued*)

Table 1.
The Details of All Studies (Continued)

Author, Year	Article Type	Sample Size	Assessment Parameters (Scales)	TMS Type	Protocol	Application Area (Brain Region)	Coil Type	Sessions	Treatment Duration	Detoxification Duration	Effects	Efficacy
(Hoven et al., 2023)	Randomized controlled trial	80	Alcohol use, AUQ, OCDS, TLFB	rTMS	High-frequency rTMS (10 Hz), 3000 pulses/ session	Right DLPFC	Figure-8 coil	10	2 weeks	N/A	No significant difference in abstinent days or cravings between active and sham groups	No evidence of long-term effects on alcohol use or craving reduction
(McCalley et al., 2023)	Double-blind, sham-controlled trial	50	OCDS, AUQ, BDI-II, STAI, fMRI	cTBS	cTBS, 3600 pulses/ session	MPFC	Figure-8 coil	10	2 – 3 weeks	N/A	Significant reduction in alcohol cue reactivity increased sobriety after 3 months	Increased retention and sobriety compared to sham group
(Selim et al., 2024)	Research article	37	Fractional anisotropy (FA), brain functional connectivity, PACS, and drinking	dTMS	High-frequency deep TMS (10 Hz)	MPFC, ACC	H-coil	15	3 weeks	5 days	Arrest progression of white matter changes, decreased craving, and relapse scores	Positive effect on white matter integrity and reduced craving
(Sallie et al., 2024)	Research article	55	SST, UPPS-P, MCQ	cPAS	Paired associative stimulation (cPAS) (0.2 Hz),100 pulses/ session	rIFC, pre-SMA	Figure-8 coil	2	1 week	N/A	Impaired plasticity in AUD group, improvements in response inhibition in healthy controls	AUD group showed impaired cortical excitability and reduced plasticity
(Padula et al., 2024)	Randomized, double-blind, sham-controlled trial	17	Craving, mood, alcohol cue-reactivity (fMRI), relapse	iTBS	iTBS, 600 pulses/ session, 2 – 3 sessions/ day	Left DLPFC	Figure-8 coil	20	7-10 days	N/A	Reduced relapse rates, anhedonia, and alcohol cue-reactivity	Effective for reducing relapse, anhedonia, and alcohol cue-reactivity

Note: ACC = anterior cingulate cortex; ACQ-NOW = alcohol craving questionnaire – now; ADS = alcohol dependence scale; AInsC = anterior insular cortex; ASI = addiction severity index; AUDIT = alcohol use disorders identification test; AUQ = alcohol urge questionnaire; BOLD= blood oxygen level dependent; BDI = Beck depression inventory; BDI-II = Beck depression inventory-II; BVMT-R = brief visuospatial memory test-revised; CBFV = cerebral blood flow velocity; Cho/Cr = choline/creatine ratio; CIDI = composite international diagnostic interview; CIWA-Ar = clinical institute withdrawal assessment for alcohol – revised; cPAS = continuous paired associative stimulation; cTBS = continuous theta burst stimulation; DLPFC = dorsolateral prefrontal cortex; DSM-IV = diagnostic and statistical manual of mental disorders, fourth edition; dTMS = deep transcranial magnetic stimulation; EEG = electroencephalogram; FA = fractional anisotropy; FPn = fronto-parietal network; fMRI = functional magnetic resonance imaging; HDRS = Hamilton depression rating scale; HF-rTMS = high-frequency repetitive transcranial magnetic stimulation; HVLT-R = Hopkins verbal learning test-revised; IDS-SR = inventory of depressive symptomatology-self report; IIRTV = intra-individual reaction time variability; iTBS = intermittent theta burst stimulation; MCQ = monetary choice questionnaire; MPFC = medial prefrontal cortex; MT = motor threshold; NAA/Cr = N-acetylaspartate/creatine ratio; NfL = neurofilament light chain; OCDS = obsessive compulsive drinking scale; PAC = Penn alcohol craving scale; PACS = Penn alcohol craving scale; PCL-5 = PTSD checklist for DSM-5; PI = pulsatility index; PTSD = post-traumatic stress disorder; rIFC pre-SMA = right inferior frontal cortex and supplementary motor area; RI = resistance index; rTMS = repetitive transcranial magnetic stimulation; SCL-90-R = symptom checklist-90-revised; SCID-5 = structured clinical interview for DSM-5; SMA = supplementary motor area; SST = stop signal task; STAI = state-trait anxiety inventory; TLFB = timeline follow back; TMS = transcranial magnetic stimulation; UPPS-P = UPPS-P impulsive behavior scale; VAS = visual analoge scale; VMPFC = ventromedial prefrontal cortex.
Go/No-Go Task: A test of impulse control where participants respond to "go" stimuli and inhibit responses to "no-go" stimuli. H-coil: A type of coil used in deep TMS for stimulating deeper brain areas.

the bilateral insular cortex with the H8 coil, applying dTMS at 120% of the motor threshold and 10 Hz frequency in 15 sessions over 3 weeks (five sessions per week). The study found no significant difference between sham and active stimulation in terms of craving and alcohol consumption. Similarly, another study targeted the right anterior insula, administering dTMS at 120% of the individual motor threshold and 1 Hz frequency in a single 10-minute session per treatment (with a minimum of 72 hours between the active and sham sessions). This study concluded that low-frequency dTMS was ineffective in modulating insula activity and did not produce significant changes in alcohol-related risk-taking or impulse control parameters. The study by Selim et al. (2024) targeted the MPFC and ACC in patients with AUD, using the H7 coil for 15 sessions over 3 weeks at a frequency of 10 Hz (one session per day) and with subsequent maintenance sessions during the follow-up period. The study reported positive effects of dTMS on white matter integrity and alcohol craving, though the sustainability of these effects was noted to be uncertain (Table 1).

Theta Burst Stimulation in Alcohol Use Disorder

TBS studies comprised four cTBS and two iTBS studies. The cTBS studies targeted the left frontal pole (Hanlon et al., 2017), midline frontocortical region (Kearney-Ramos et al., 2018), MPFC (McCalley et al., 2023), and right DLPFC (McNeill et al., 2018). Most cTBS studies noted some short-term effects on alcohol craving, brain activity, and connectivity; however, these effects did not translate into significant clinical improvements. One study applied cTBS to the left ventro MPFC in a single session of 3600 pulses at 110% resting motor threshold, with each participant receiving two sessions (active and sham). The treatment was found to significantly reduce cue reactivity related to substances, which was associated with decreased functional brain connectivity (Kearney-Ramos et al., 2018). In McCalley et al.'s (2023) study, cTBS was applied to the MPFC's left frontal pole (FP1) at 110% of the resting motor threshold with a total of 3600 pulses per session. Ten sessions were administered over approximately 14.8 days, with one session each working day. The study found that individuals receiving real cTBS showed increased odds of maintaining abstinence for 3 months and demonstrated a reduced brain response to alcohol-related cues, particularly in MPFC-striatum and MPFC-insula connections. Hanlon et al. (2017) targeted the FP1 with cTBS at 5 Hz in six trains, each containing 600 pulses, totaling 3600 pulses in a single day, comparing real versus sham cTBS. Post-treatment evaluation revealed no significant change in craving. McNeill et al. (2018) administered a single session of cTBS to the right DLPFC at 80% resting motor threshold with bursts of three pulses at 50 Hz, totaling 600 pulses. They found that cTBS impaired inhibition control and increased alcohol consumption. Of the two iTBS studies, one applied iTBS to the right DLPFC at 80% active motor threshold for 10 consecutive days, with sessions lasting 9.5 minutes each and containing 1800 pulses per session. The sham group could also choose to receive an additional 10 open-label iTBS sessions. The results showed that iTBS significantly improved depressive symptoms, but no effect on post-traumatic stress disorder (PTSD) symptoms related to the presence of AUD was observed (Bozzay et al., 2021). In the study by Padula et al. (2024), iTBS was administered to the left DLPFC over 20 sessions across 7 – 10 days, with 2 – 3 sessions per day and 600 pulses per session, demonstrating effectiveness in reducing relapse risk for up to 3 months and decreasing anhedonia and brain reactivity to alcohol cues (Table 1).

Accelerated Transcranial Magnetic Stimulat in Alcohol Use Disorder

Regarding the application of accelerated rTMS, Herremans et al. (2015) implemented an accelerated protocol with a total of 15 sessions over 4 days and found a significant reduction in overall craving; however, no specific effect on cue-induced craving was detected. Considering the general outcomes of the studies, the most frequently targeted brain regions were the right and left DLPFC. The role of the DLPFC in AUD is associated with its sensitivity to treatment. Some studies targeting the right DLPFC yielded positive results, while others did not find a significant effect. Studies focusing on the left DLPFC also reported some positive outcomes; however, the clinical impact remains uncertain. The MPFC was targeted with dTMS, which led to some favorable results, although the consistency of its effectiveness varied. Due to the limited number of studies targeting deep brain regions such as the ACC and ventromedial prefrontal cortex (VMPFC), further research is required to establish the efficacy of TMS treatment in these areas (Table 1).

Cortical Paired Associative Stimulation in Alcohol Use Disorder

In the study by Sallie et al. (2024), cortical PAS targeted the right inferior frontal cortex and the presupplementary motor area, delivering 100 pairs of stimuli at 0.2 Hz over a period of 8.3 minutes to investigate the effects on response inhibition. While cortical PAS was found to enhance response inhibition and improve the plasticity of the fronto-striatal network in healthy individuals, this effect was not observed in individuals with AUD. This finding suggests that these individuals may have impaired cortical plasticity capacity (Table 1).

Discussion

Transcranial magnetic stimulation has attracted growing interest in recent years for the treatment of AUD. The findings from the studies reviewed in this article indicate that rTMS and TBS protocols can have varying degrees of effects on alcohol craving, cognitive functions, and mental health parameters. However, the variability in these results can be attributed to several factors, such as the targeted brain region, stimulation protocols, and treatment parameters used in TMS applications. Studies using rTMS most frequently targeted the DLPFC. High-frequency stimulation of the DLPFC showed positive effects in some studies, such as reducing alcohol craving and improving cognitive functions, supporting the role of this region in addiction-related neural circuits (Mishra et al., 2010; Zhang et al., 2022). However, in other studies, rTMS applied to the DLPFC did not produce significant effects on alcohol consumption, craving, or other clinical parameters (Höppner et al., 2011; Raikwar et al., 2020). Such discrepancies may arise from variations in the number of sessions, stimulation frequency, choice of target region, and sample size. Specifically, single-session applications may have limited effects, while protocols involving a higher number of sessions tend to yield more prominent results (Herremans et al., 2012, 2013). In TBS studies, the effects of cTBS and iTBS protocols were compared. While cTBS

demonstrated some short-term effects, it did not significantly improve alcohol craving or other clinical outcomes (Hanlon et al., 2017; Kearney-Ramos et al., 2018). In contrast, iTBS studies showed promising results, particularly in parameters such as depressive symptoms, anhedonia, and relapse (Bozzay et al., 2021; Padula et al., 2024). These findings suggest that iTBS, with its shorter and more intense protocols, may provide more distinct clinical benefits.

Studies on accelerated rTMS (intensive TMS) also showed that concentrated protocols effectively reduced general craving, but they were less impactful in altering sensitivity to alcohol-related cues (Herremans et al., 2015). This suggests that while accelerated rTMS may effectively reduce overall craving, it may be limited in modulating cue reactivity. Apart from the DLPFC, other brain regions targeted by TMS, such as the MPFC and ACC, also showed favorable results, particularly in deep TMS applications (Ceccanti et al., 2015; Harel et al., 2022). Given the roles of these structures in reward mechanisms and impulse control, dTMS holds significant potential for reducing alcohol consumption and preventing relapse (Ceccanti et al., 2015; Harel et al., 2022). Studies on how the connectivity of the MPFC with the limbic system can be modulated by TMS may open new avenues in the fight against addiction (Hanlon et al., 2016). Most of these studies used high-frequency stimulation, finding reductions in alcohol consumption, cortisol levels, and improvements in alcohol-related biological markers. However, these positive outcomes were not always consistent; some studies, such as Perini et al. (2020), found no significant difference between targeted regions and clinical results. Overall, the efficacy of TMS and TBS varies depending on individual patient characteristics, targeted brain regions, and stimulation parameters. Possible reasons for these conflicting results may include differences in patient populations, variations in the power of the devices used, and variability in the techniques employed. For example, the small sample sizes in some studies may have limited the generalizability of their findings (Perini et al., 2020). This variability highlights the need for more comprehensive and controlled studies to better understand the clinical application of TMS in the treatment of AUD. Further research is needed on the effects of TMS in patient subgroups with comorbidities such as anxiety and depression. Specifically, in AUD patients with comorbid depression, it has been reported that TMS improves depressive symptoms and reduces the risk of relapse (Bozzay et al., 2021). Such subgroup analyses are crucial for understanding which AUD patients may benefit most from TMS.

Limitations and Future Recomendations

Most of the studies included in this review employed varying stimulation protocols, target regions, and assessment criteria, which makes comparability across results challenging. To draw clearer conclusions on the efficacy of rTMS, TBS, and dTMS, further research with large sample sizes, standardized protocols, and long-term follow-up outcomes is needed. Long-term follow-up studies are necessary to understand how TMS affects relapse rates and to optimize treatment protocols. Specifically, the long-term sustainability of findings, such as the positive effects of dTMS on white matter integrity, should be investigated. The effects of different TMS protocols on AUD patients with comorbid anxiety or depression could also be explored. Furthermore, RCTs comparing the effects of different stimulation sites and treatment parameters, taking into account comorbid psychiatric diagnoses, will play a key role in determining the most effective application strategies for TMS in AUD treatment.

Conclusion

The studies reviewed in this article suggest that TMS has potential as a treatment option for AUD. By targeting specific neural circuits involved in executive functions and emotional processes, TMS may provide positive effects such as reducing alcohol craving, improving cognitive functions, and enhancing mental health parameters. However, these effects vary across studies, potentially due to differences in session numbers, targeted brain regions, stimulation protocols, and individual patient characteristics. High-frequency (>10 Hz) rTMS, particularly when applied to the right or left DLPFC, has been found to be effective in some studies for reducing alcohol craving and improving executive functions. However, variability in protocols and study designs limits the generalizability of these findings. Other TMS protocols, such as TBS, also appear promising for the treatment of alcohol dependence, but further research is necessary to clarify their efficacy. iTBS has been considered an effective treatment option for AUD due to its potential for short-term, intensive effects. Conversely, the efficacy of cTBS and accelerated rTMS is focused more on short-term impacts, and the long-term clinical benefits of these protocols remain uncertain. dTMS has shown some positive effects on alcohol consumption and related neurobiological functions, though the consistency of these effects has not yet been established.

Compared to traditional rTMS, modern TMS protocols (e.g., iTBS) appear to offer advantages in terms of speed and efficacy. Specifically, iTBS has been reported to be effective in conditions that require short but intense treatment sessions (Padula et al., 2024). A detailed explanation of the clinical applications of such technologies for therapists may help optimize treatment outcomes.

In conclusion, the efficacy of rTMS and dTMS in the treatment of alcohol use disorder varies depending on the targeted brain regions and patient groups. Therefore, while it is not possible to recommend standard protocols regarding the ideal frequency and number of sessions, high-frequency rTMS applied to the right DLPFC and dTMS targeted at the MPFC have shown promising results in certain patient groups (Mishra et al., 2010; Ceccanti et al., 2015). How these findings can be translated into clinical practice could be further clarified through the development of standardized treatment protocols.

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