Transcranial Magnetic Stimulation for Substance Use Disorders

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BACKGROUND & INTRODUCTION

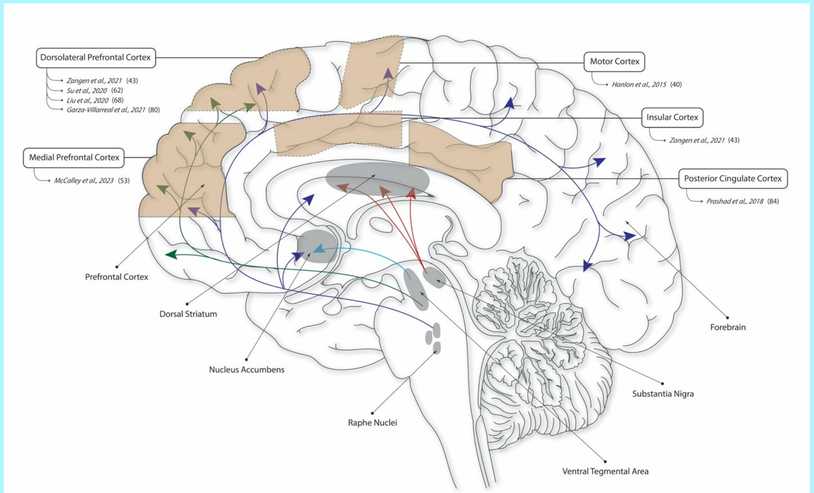
Substance use disorders (SUDs) represent a significant public health challenge, with recent data revealing an alarming increase in prevalence. In 2020, approximately 40.3 million individuals aged 12 and older in the United States experienced a SUD, a figure that rose to 48.7 million by 2022. Approximately eight million of these individuals had concurrent alcohol and drug use disorders. SUDs frequently coexist with mental health disorders such as anxiety and depression, which affect approximately 20% of patients with SUDs. However, the complications associated with SUDs extend beyond psychological issues, impacting various aspects of life including work and relationships, and leading to severe health problems.

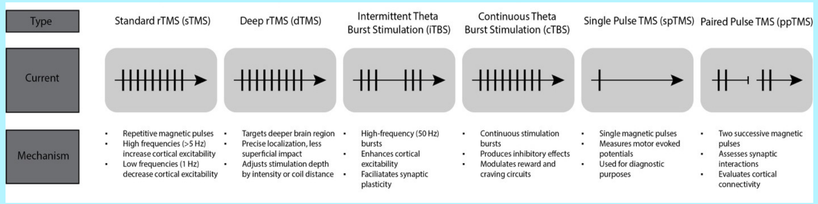
Current treatment modalities for SUDs encompass detoxification, cognitive and behavioral therapies, and pharmaceutical interventions. Despite these options, several challenges hinder effective treatment, including high relapse rates, high cost of medication and therapy, and an insufficient number of healthcare facilities and professionals across the United States (U.S.). In addition, the stigma associated with SUDs and mental health challenges often prevents individuals from seeking professional help, with many attempting to self-manage their conditions. Although stigmatizing attitudes have been slow to dissolve, these retributive viewpoints have been giving way to a cultural and medical consensus that addiction is a treatable chronic disorder of the brain.

A multi-dimensional approach to treating SUDs involves a combination of pharmacological, behavioral, psychosocial, and neuromodulation interventions; however, the aim of the present review is to provide an update on TMS as a therapeutic intervention for SUDs. This review provides evidence of TMS interventions targeting specific brain regions and delves into how this approach modulates the underlying neurobiological mechanisms and circuitry implicated in addiction and SUDs. We further analyze and review randomized clinical trials (RCTs) that show efficacy for various protocols such as repetitive, single-pulse, and paired-pulse TMS as wells as theta burst stimulation in SUDs. Finally, we discuss the integration of neuroimaging to uncover functional connectivity changes in the brain and identify potential biomarkers that predict TMS treatment response.

RESULTS & DISCUSSION: PATHOPHYSIOLOGY, TMS PROTOCOLS, RANDOMIZED CONTROLLED TRIALS, & NEUROIMAGING

Study	SUD	TMS Type	Brain Region	Coil Placement	Main Findings
Hanlon et al., 2015	Cocaine	Single-pulse TMS (spTMS) & Paired-pulse TMS (ppTMS)	Primary Motor Cortex	Coil placed over the left motor cortex, tangential to the scalp, with the handle pointing backward and laterally at 45° from the midline.	• Cocaine users showed higher motor thresholds (p=0.033) and higher long interval cortical facilitation (p=0.006) than age- and gender-matched non-drug users. • Elevated long interval cortical facilitation (LICF) correlated with significant increased blood oxygen level dependent (BOLD) signaling in the right primary motor cortex of cocaine users (p<0.05).
Zangen et al., 2021	Tobacco	Repetitive TMS (rTMS)	Lateral Prefrontal Cortex and Insular Cortex	Coil placed to localize the optimal helmet position for activation of the right abductor pollicis brevis muscle, then aligned symmetrically and moved 6 cm anteriorly.	• Quit rate was higher for the active rTMS group at week 18 (63%) compared to sham (50%) (p=0.003). • Greater reduction in cigarette consumption and craving was seen in the active group compared to sham group by week 2 of treatment (p=0.022).
McCalley et al., 2023	Alcohol	Continuous Theta Burst Stimulation (cTBS)	Medial Prefrontal Cortex (MPFC)	Coil placed over FP1, a standard EEG site correlating to the left frontal pole.	• Participants receiving cTBS were 3.09 times more likely to remain sober after 3 months and 2.71 times more likely to remain enrolled in the study after 3 months. • cTBS led to a substantial reduction in MPFC-striatum and MPFC-insula connectivity from 2 to 3 months after treatment (p<0.05).
Su et al., 2020	Metham-phetamine	Intermittent Theta Burst Stimulation (iTBS)	Left Dorsolateral Prefrontal Cortex (DLPFC)	Coil placed over F3, a standard EEG site correlating to the left dorsolateral prefrontal cortex.	• iTBS reduced cue-induced craving over 4 weeks in methamphetamine users (p<0.001) while sham did not (p>0.5). • iTBS significantly improved cognitive function (p<0.001) and sleep quality (p=0.006).
Liu et al., 2020	Heroin	Repetitive TMS (rTMS)	Left Dorsolateral Prefrontal Cortex (DLPFC)	Coil placed over F3 using the 10–20 EEG system.	• Both 10 Hz and 1 Hz rTMS reduced cue-induced craving in heroin patients compared to controls (p<0.0001). • Effects lasted up to 60 days after the end of treatment.
Garza-Villarreal et al., 2021	Cocaine	Repetitive TMS (rTMS)	Left Dorsolateral Prefrontal Cortex (DLPFC)	Coil placed 5 cm along and 2 cm anterior to the interaural line, at a 45° angle with respect to the interhemispheric fissure; some participants received the F3 method.	• rTMS reduced cocaine craving (p=0.013) and impulsivity (p=0.011) in the active group compared to the sham group. • Functional connectivity between the DLPFC and ventromedial PFC increased, particularly in the active group, but was not significant over 3 months (p>0.5).
Prashad et al., 2018	Cannabis	Repetitive TMS (rTMS)	Posterior Cingulate Cortex (PCC)	Coil placed 4 cm behind the motor strip using a double-cone coil (DCC).	• Cannabis users exhibited increased responses to self-relevant stimuli, as compared to age- and sex- matched controls, which were normalized by high-frequency rTMS (10 Hz). • No significant effect of rTMS on cannabis-related stimuli (p>0.5).





Study	Imaging Modality	Population	Key Findings	Relevance
[11C]raclopride PET study (Strafella et al., 2001)	PET	Healthy individuals	7.3% reduction in [11C]raclopride binding in ipsilateral caudate nucleus, indicating increased dopamine release.	Highlights PET's utility in tracking dopamine release for TMS efficacy in SUDs.
Structural brain integrity study (Kearny-Ramos et al., 2018)	fMRI, DTI, VBM	Cocaine-dependent individuals	TMS-evoked BOLD responses in striatal regions (e.g., caudate, putamen) correlated with 15% higher fractional anisotropy in white matter tracts and 12% greater gray matter volume in the VMPFC.	Establishes white and gray matter integrity as biomarkers for optimizing TMS efficacy.
Sensorimotor excitability study (Hanlon et al., 2020)	fMRI	Chronic cocaine users	Resting motor thresholds were 10.8% higher in cocaine users, while intracortical facilitation was elevated by 15%, linked to increased BOLD signals in motor cortices.	Demonstrates TMS-fMRI integration to refine protocols for disrupted cortical facilitation in SUDs.
Drug cue-reactivity study (Hanlon et al., 2018)	fMRI	Individuals with cocaine, alcohol, or nicotine dependence	Drug-related cues increased MPFC activation in 40% of participants; MPFC 'hot spots' were within 2–5 cm of scalp landmarks for 49% of individuals.	Identifies individualized TMS targets for SUDs using cue-elicited brain activity.
Structural MRI in alcohol use disorder (Quoilin et al., 2021)	Structural MRI	Detoxified alcohol-dependent patients	Cortical thickness reductions of 20% in MPFC and 15% in SMA correlated with weaker preparatory suppression and poorer behavioral inhibition, respectively.	Links structural deficits to motor and cognitive dysfunctions, informing TMS biomarker selection.
HF-rTMS in alcohol-dependent patients (Herremans et al., 2015)	fMRI	Detoxified alcohol-dependent patients	15 HF-rTMS sessions reduced general craving scores by 25% but showed no significant change in cue-induced craving; left inferior parietal lobule activity decreased by 18%.	Reveals fMRI's role in tracking indirect TMS effects on attentional and reward networks.
cTBS effects in cocaine and alcohol dependence (Hanlon et al., 2017)	BOLD fMRI	Cocaine and alcohol-dependent individuals	cTBS decreased evoked BOLD responses by 22% in caudate, 18% in nucleus accumbens, and 20% in orbitofrontal cortex in cocaine users; alcohol-dependent individuals showed 25% reduction in anterior insula activity.	Supports fMRI in guiding TMS for modulating salience circuits in SUDs.

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