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# The Treatment of Addiction by Repetitive Transcranial Magnetic Stimulation (rTMS): Current Data and Future Recommendations

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## Abstract

Addiction is a major public health problem for which more effective treatment options are needed. Repetitive transcranial magnetic stimulation (rTMS) is a noninvasive brain stimulation technique that has been investigated as a potential treatment for addiction. This review includes 40 studies published between the years 1985 and 2019 that evaluated the use of rTMS in substance use and gambling disorders. Evidence demonstrates that rTMS may be effective for nicotine, cocaine, methamphetamine and gambling addiction. Further studies are needed to identify optimal rTMS stimulation parameters.

***Keywords:*** *Repetitive Transcranial Magnetic Stimulation; rTMS; Addiction; Drug; Illicit Substance; Gambling*

## Abbreviations

rTMS: Repetitive Transcranial Magnetic Stimulation; DSM-V: Diagnostic and Statistical Manual of Mental Disorders Fifth Edition; DLPFC: Dorsolateral Prefrontal Cortex; Hz: Hertz; MT: Motor Threshold; FP: Frontal Parietal; SFG: Superior Frontal Gyrus; MCx: Motor Cortex; ICx: Inferior Colliculus; MPFCx: Medial Prefrontal Cortex; ACC: Anterior Cingulate Cortex; OCD: Obsessive-Compulsive Disorder; FDA: Food and Drug Administration; cTBS: Continuous Theta Burst Stimulation; SPECT: Single-Photon Emission Computerized Tomography; DAT: Dopamine Transporter; MRI: Magnetic Resonance Imaging; fMRI: Functional Magnetic Resonance Imaging; VAS: Visual Analogue Scale; BOLD: Blood Oxygenation Level-Dependent

## Introduction

Addiction is a chronic brain disease characterized by continued compulsive behaviors despite harmful consequences [1]. Although there have been significant advancements in the pharmacological, behavioral and psychosocial approaches to treating addiction, long-term treatment efficacy is lacking [2]. For substance use disorders 40 - 60% of patients relapse within one year after acute treatment [3]. There is a need for improved therapeutic interventions, especially for the maintenance of sobriety. Research suggests repetitive transcranial magnetic stimulation (rTMS) may be an effective neuromodulatory therapy for the treatment of addiction [5].

rTMS is a noninvasive, non-systemic brain stimulation technique that is indicated by the Food and Drug Administration (FDA) for the treatment of depression and obsessive-compulsive disorder (OCD) [6]. rTMS uses a magnetic resonance imaging (MRI)-strength magnetic coil to produce magnetic pulses that pass through the skull and induce a small electric current in underlying cortical neurons, thereby modulating neurotransmission and neurocircuitry [7].

rTMS treatment parameters include the coil design, scalp placement, magnetic pulse type, pattern, duration and frequency and stimulation intensity. In general, high frequency, intermittent rTMS facilitates cortical excitability and low frequency, continuous rTMS inhibits excitability [8,9].

rTMS is a safe, well-tolerated, outpatient procedure [10,11]. Mild headache and scalp discomfort are reported side effects. rTMS is contraindicated in patients with implanted ferromagnetic devices in or around the head and must be used with caution in patients with implanted physiologic devices.

Research has demonstrated that alterations in dopamine neurotransmission and changes in mesocortical and mesolimbic brain pathways play a central role in addictive disorders [12-15]. rTMS results in immediate neuronal excitation or inhibition as well as produces long-lasting neuroplastic changes that persist after the period of stimulation [16-18]. Using rTMS to specifically target and modulate the neurocircuitry involved in addiction has the potential for acute and maintenance addiction treatment. rTMS could improve executive function, aid response inhibition, decrease impulsivity, inhibit cravings and promote abstinence. This paper provides an overview of research of rTMS in treating addiction in humans.

## Materials and Methods

For this review, the search strategy included online search engines such as PubMed, PsycINFO, PsychiatryOnline and Cochrane Library. All studies reporting on the use of rTMS in addiction published between the years 1985 and 2019, excluding case reports, were included. Based on the diagnostic changes made in the Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-V), both substance-use and gambling disorders were included. One study was excluded due to its evaluation of dual diagnoses cocaine and gambling addiction. Search terms used in various combinations included "rTMS" with "addiction", "alcohol", "tobacco", "nicotine", "heroin", "cocaine", "opioids", "cannabis", "marijuana", "MDMA", "ecstasy", "drug", and "gambling".

## Results and Discussion

### rTMS and nicotine

Table 1 summarizes 12 papers that examined rTMS in nicotine use disorder. One study investigating high frequency rTMS to the SFG reported mixed results [19]. One study investigating low frequency rTMS to the right DLPFC reported no effect on craving [20]. However, a majority of studies reported that high frequency rTMS applied to the left DLPFC reduces nicotine craving [21-27] and consumption [22,27-30].

| Study | N | TMS Parameters | Target Area | Control Group | Assessment | Results |
|---|---|---|---|---|---|---|
| Johann., *et al*. (2003) [21] | n=11, all received both active and sham | rTMS, 20 Hz, 90% MT, 1 session | DLPFC, left | Sham | Craving | Reduction in craving |
| Eichhammer., *et al*. (2003) [28] | n=14, all received both active and sham | rTMS, 20 Hz, 90% MT, 2 active and 2 sham sessions | DLPFC, left | Sham | Craving, Smoking | No effect on craving, significant reduction in smoking |
| Amiaz., *et al*. (2009) [22] | n=48:<br>22 active, 26 sham | rTMS, 10 Hz,100% MT, 10 sessions | DLPFC, left | Sham | Cue-induced craving, cigarette consumption | Reduction in cue-induced craving and cigarette consumption |

| | | | | | | |
|---|---|---|---|---|---|---|
| Rose., *et al*. (2011) [19] | n=15; all received active | rTMS, 1 Hz, 10 Hz, 90% MT, 3 sessions (1 active 1 Hz, 1 active 10 Hz, 1 MOC) | SFG, MCx | No | Cue-induced craving | Craving after smoking-cue presentations was elevated in the 10 Hz SFG and reduced after neutral-cue presentations; upon smoking, craving reduction in 10 Hz rTMS over SFG |
| Wing., *et al*. (2012) [23] | n=15; 6 active, 9 sham | rTMS, 20 Hz, 90% MT, 20 sessions | DLPFC, left/right | Sham | Craving, smoking | Reduction in craving, no effect on smoking |
| Li., *et al*. (2013) [24] | n=16, all received both active and sham | rTMS, 10 Hz, 100% MT, 2 sessions (1 active, 1 sham) | DLPFC, left | Sham | Cue-induced craving | Reduction in craving |
| Hayashi., *et al*. (2013) [25] | n=10, all received both active and sham | rTMS, 1 Hz, 110% MT | DLPFC, left | Sham | Cue-induced craving + fMRI | Reduction in cue-induced craving and reduction in fMRI signal in OfCx |
| Pripfl., *et al*. (2014) [26] | n=14, all received both active and sham | rTMS, 10 Hz, 90% MT. 1 session | DLPFC, left | Sham | Cue-induced craving | Reduction in cue-induced craving |
| Prikryl., *et al*. (2014) [29] | n=35:<br>18 active, 17 sham | rTMS, 10 Hz, 110% MT, 21 sessions | DLPFC, left | Sham | Smoking | Reduction in smoking |
| Dinur-Klein., *et al*. (2014) [27] | n=77, all received both active and sham | H-coil, 1 and 10 Hz, 110% MT, 13 sessions | DLPFC, bilateral, ICx | Sham | Cigarette consumption, craving | Reduction in craving and cigarette consumption after 10 Hz rTMS |
| Trojak., *et al*. (2015) [20] | n=37, 18 active, 19 sham | rTMS, 1Hz, 120% MT, 10 sessions | DLPFC, right | Sham | Craving | No effect on craving |
| Sheffer., *et al*. (2018) [30] | 29; 16 active, 13 sham | rTMS, 110% MT, 20Hz, 8 sessions | DLPFC, left | Sham | Relative relapse risk, abstinence rates, uptake self-help intervention | Reduced the relative risk of relapse, increased abstinence rates and increased uptake of the self-help intervention |

***Table 1:*** *Summary of studies on rTMS in the treatment of nicotine use disorder.*

## rTMS and alcohol

Table 2 summarizes 11 papers that examined rTMS in alcohol use disorder. Two papers investigating high frequency rTMS to the left DLPFC reported no effect on craving [31,32]. Several studies using high frequency stimulation to the right DLPFC yielded mixed results [33-39]. Two studies with highly varied rTMS parameters reported decreases in consumption [40,41].

| Study | N | TMS Parameters | Target Area | Control Group | Assessment | Results |
|---|---|---|---|---|---|---|
| Mishra., *et al*. (2010) [33] | n = 45: 30 active, 15 sham | rTMS, 10 Hz, 110% MT, 10 sessions | DLPFC, right | Sham | Craving | Reduction in craving |
| Höppner., *et al.* (2011) [31] | n = 19, 10 active, 9 sham | rTMS, 20Hz, 90% MT, 10 sessions | DLPFC, left | Sham | Craving | No effect on craving |
| Herremans., *et al*. (2012) [34] | n = 31, all received both active and sham | rTMS, 20 Hz, 110% MT, 1 session | DLPFC, right | Sham | Craving | No effect on craving |
| Herremans., *et al*. (2013) [35] | n = 29; all received both active and sham | rTMS, 20 Hz, 110% MT, 1 session | DLPFC, right | Sham | Craving | No effect on craving |
| Mishra., *et al*. (2015) [36] | n = 20; 10 rTMS to right DLPfCx, 10 rTMS to left DLPfCx | rTMS, 10 Hz, 110% MT, 10 sessions | DLPFC, right/ left | No | Craving | Reduction in craving after rTMS in both conditions |
| Herremans., *et al*. (2015) [37] | n = 26; 13 active, 13 sham | rTMS, 20 Hz, 110% MT, 15 sessions | DLPFC, right | Sham | Cue-induced craving | No effect on craving |
| Ceccanti., *et al*. (2015) [40] | n = 18: 9 active, 9 sham | rTMS, 20Hz, 120% MT, 10 sessions | MPfCx | Sham | Craving | Reduction in craving and drinking days |
| Herremans., *et al*. (2016) [38] | n = 19; all received both active and sham | rTMS, 20Hz, 110%MT, 14 sessions | DLPFC, right | Sham | Relapse within 4 weeks of stimulation | After 4 weeks, 13 of 19 patients had relapsed |
| del Felice., *et al*. (2016) [32] | n = 17; 8 active, 9 sham | rTMS, 10Hz, 100% MT, 4 sessions | DLPFC, left | Sham | Craving, consumption | No effect on craving |
| Addolorato., *et al*. (2017) [41] | 11; 5 active, 6 sham | Deep rTMS, 10 Hz, 100% MT, 12 sessions | DLPFC, bilateral | Sham | Intake, SPECT (DAT) | Decrease in alcohol intake and DAT availability |
| Jansen *et al*. (2019) [39] | 39 alcohol use disorder, 36 healthy controls; all received active and sham | rTMS, 10Hz, 110% MT, 1 session | DLPFC, right | Sham | Craving, emotion reappraisal | No effect on craving, reduced emotion reappraisal |

***Table 2:*** *Summary of studies on rTMS in the treatment of alcohol use disorder.*

## rTMS and Cocaine

Table 3 summarizes 8 papers that examined rTMS in cocaine use disorder. One study of continuous theta burst stimulation (cTBS) yielded positive results [42]. Seven studies reported a reduction in cocaine craving [43-46] and consumption [47] using excitatory rTMS over the left or bilateral DLPFC as well as using inhibitory rTBS over the MPFCx [48,49].

## rTMS and methamphetamine

Table 4 summarizes 3 papers that examined rTMS in methamphetamine use disorder. One study using low frequency rTMS reported an increase in craving [50]. Two studies using high frequency rTMS over the left DLPFC reported reductions in cue-induced craving [51,52].

| Study | N | TMS Parameters | Target Area | Control Group | Assessment | Results |
|---|---|---|---|---|---|---|
| Camprodon., *et al*. (2007) [43] | n = 6, 6 active no controls | rTMS, 2 sessions, 20 trains, 10 Hz, 90% MT, 2,000 pulses, 1 session | DLPFC, right/left | No | Craving (VAS) | Reduction in craving with right rTMS |
| Politi., *et al*. (2008) [44] | n = 36: 36 active, no controls | rTMS (8-coil), 10 sessions, 20 trains, 15 Hz, 100% MT, 600 pulses, 10 sessions | DLPFC, left | No | Craving (VAS) | Reduction in craving |
| Hanlon., *et al*. (2016) [48] | n = 11; 6 received active, 5 received sham | cTBS + fMRI, 1 session, 110% MT, 1,800 pulses, 6 sessions | MPfCx, left | Sham TMS | Craving | Reduction in craving |
| Terraneo., *et al*. (2016) [45] | n = 25; 10 active, 15 sham | rTMS (8-coil), 8 sessions, 40 trains, 15 Hz, 100% MT, 2,400 pulses, >8 sessions | DLPFC, left | Pharm | Urine, craving | More cocaine-free urine samples in rTMS group, reduction in craving in rTMS group |
| Rapinesi., *et al*. (2016) [46] | n = 24, 7 active, 7 sham | rTMS (H coil), 12 sessions, 20 trains, 20 Hz, 100% MT, 720 pulses, 12 sessions | DLPFC, bilateral | No | Craving (VAS) | Reduction in craving |
| Bolloni., *et al*. (2016) [47] | n = 18; 10 active, 8 sham | rTMS (H1 coil), 12 sessions, 20 trains, 10 Hz, 100% MT, 1,000 pulses, 12 sessions | DLPFC, bilateral | Sham | Hair analysis | Reduction in Intake in 10 Hz rTMS group, no difference among subjects |
| Hanlon., *et al*. (2017) [42] | n = 49; all received both active and sham | cTBS, 1 sham session and 1 active session, 6 trains, 5 Hz, 110%rMT, 60 second interval | FP, left | Sham | Evoked BOLD signal | Decreased TMS-evoked BOLD signal in the OFC and several cortical nodes |
| Martinez *et al*. (2019) [49] | n = 18; 6 1Hz, 6 10Hz, 6 sham) | rTMS (H coil), 1Hz or 10 Hz, 13 sessions | MPFCx, ACC | Sham | Choice: money vs. smoked cocaine | Choices for cocaine decreased in high frequency group (10Hz) |

***Table 3:*** *Summary of studies on rTMS in the treatment of cocaine use disorder.*

| Study | N | TMS Parameters | Target Area | Control Group | Assessment | Results |
|---|---|---|---|---|---|---|
| Li., *et al*. (2013) [50] | n = 18, all received both active and sham | rTMS, 1Hz, 100% MT, 2 sessions (1 active, 1 sham) separated by 1 hour | DLPFC, left | Sham | Craving | Increase in craving |
| Su., *et al*. (2017) [51] | n = 30: 15 active, 15 control | rTMS, 10 Hz, 80% MT, 5 sessions | DLPFC, left | Sham | Cue-induced craving | Reduction in cue-induced craving |
| Liu., *et al*. (2019) [52] | n = 90; 45 active, 45 sham | rTMS, 10 Hz, 20 sessions | DLPFC | Control (routine addiction treatment), active (routine addiction treatment with rTMS add on) | Cue-induced craving | Reduced craving that lasted at least 30 days after rTMS treatment |

***Table 4:*** *Summary of studies on rTMS in the treatment of methamphetamine use disorder.*

## rTMS and Cannabis

Table 5 summarizes one paper that examined rTMS in cannabis use disorder. This study used one session of high frequency stimulation to the left DLPFC and reported no reduction in craving [53].

| Study | N | TMS Parameters | Target Area | Control Group | Assessment | Results |
|---|---|---|---|---|---|---|
| Sahlem., *et al*. (2018) [53] | N= 16; 7 active, 9 sham | rTMS, 10 Hz, 110% MT, 1 session | DLPFC, left | Sham | Craving | No reduction in craving |

***Table 5:*** *Summary of studies on rTMS in the treatment of cannabis use disorder.*

## rTMS and Heroin

Table 6 summarizes one paper that examined rTMS in heroin use disorder. This study reported a reduction in cue-induced craving with high frequency rTMS over the left DLPFC [54].

| Study | N | TMS Parameters | Target Area | Control Group | Assessment | Results |
|---|---|---|---|---|---|---|
| Shen., *et al*. (2016) [54] | n = 20: 10 active, 10 sham | rTMS, 10Hz, 100% MT, 5 sessions | DLPFC | Sham | Cue-induced | Reduction in cue-induced craving |

***Table 6****: Summary of studies on rTMS in the treatment of heroin use disorder.*

## rTMS and Gambling

Table 7 summarizes 4 papers that examined rTMS in gambling disorder. One study investigating high frequency stimulation over the medial and dorsolateral PFC reported reduced craving [55]. Studies using low frequency stimulation yielded mixed results [56-58].

| Study | N | TMS Parameters | Target Area | Control Group | Assessment | Results |
|---|---|---|---|---|---|---|
| Rosenberg., *et al*. (2013) [58] | 4, all received active treatment | dTMS (H coil), 1 Hz, 15 sessions, 110%MT | DLPFC, left | None | Craving | No effect on craving |
| Zack., *et al*. (2016) [55] | n = 9, all received both active and sham | rTMS (MPFCx) and cTBS (DLPFC, right), 10Hz, 80% MT, 1 session | MPFCx, DLPFC, right | Sham | Cue-induced craving | Reduced self-report desire to gamble |
| Gay., *et al*. (2017) [56] | n = 22, all received both active and sham | rTMS, 1Hz, 110% MT, 1 session | DLPFC, left | Sham | Cue-induced craving | Reduced cue induced craving |
| Sauvaget., *et al*. (2018) [57] | n = 30, all received both active and sham | rTMS, 1 Hz, 120% MT, 1 session, 1 Hz | DLPFC, right | Sham | Cue-induced craving | No effect |

***Table 7:*** *Summary of studies on rTMS in the treatment of gambling addiction.*

## Conclusion

The present review paper of 40 studies investigating rTMS for addiction in humans reveals a growing body of evidence suggesting that rTMS, specifically high frequency rTMS targeting the left DLPFC may be an effective intervention in nicotine [21-30], cocaine [43-47], methamphetamine [51,52] and gambling addiction [55]. Efficacy results are mixed for the treatment of alcohol use disorder [31-41]. There is insufficient data for cannabis and heroin use disorders. Although conclusions regarding the efficacy of rTMS in addiction are challenging due to small sample sizes and the tremendous variability of rTMS stimulus parameters, this review supports the need for further research.

rTMS pulse duration and stimulus interval are critical in modulating neuroplasticity while avoiding the homeostatic mechanisms that limit or counter-act plasticity [59-62]. Further studies with large sample sizes, randomization and blinding, consistent stimulus parameters and outcome measures are indicated. Moreover, further research is needed to establish the durability of rTMS effects and whether or not maintenance rTMS has a place in relapse prevention. Because addiction is a multifaceted illness that involves neurobiology, psychodynamics and environmental stressors, future studies should also consider the application of rTMS in combination with therapies such as replacement therapy, contingency management, 12 step support and contained environments.

## Conflict of Interest

Martha Koo and Emily Pedersen declare no conflicts of interest.

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