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Transcranial magnetic stimulation (TMS) in the treatment of substance addiction

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Abstract

Transcranial magnetic stimulation (TMS) is a non-invasive method of brain stimulation used to treat a variety of neuropsychiatric disorders, but is still in the early stages of study as addiction treatment. We identified 19 human studies using repetitive TMS (rTMS) to manipulate drug craving or use, which exposed a total of 316 adults to active rTMS. Nine studies involved tobacco, six alcohol, three cocaine, and one methamphetamine. The majority of studies targeted high-frequency (5–20 Hz; expected to stimulate neuronal activity) rTMS pulses to the dorsolateral prefrontal cortex. Only five studies were controlled clinical trials: two of four nicotine trials found decreased cigarette smoking; the cocaine trial found decreased cocaine use. Many aspects of optimal treatment remain unknown, including rTMS parameters, duration of treatment, relationship to cue-induced craving, and concomitant treatment. The mechanisms of rTMS potential therapeutic action in treating addictions are poorly understood, but may involve increased dopamine and glutamate function in corticomesolimbic brain circuits and modulation of neural activity in brain circuits that mediate cognitive processes relevant to addiction, such as response inhibition, selective attention, and reactivity to drug-associated cues. rTMS treatment of addiction must be considered experimental at this time, but appears to have a promising future.

Keywords

addiction; substance use disorder; TMS; transcranial magnetic stimulation; treatment

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Conflicts of interest

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Introduction

Transcranial magnetic stimulation (TMS) is a non-invasive, physical approach to psychiatric treatment which involves projecting a fluctuating magnetic field (magnetic pulses) through the skull into the brain.^{1,2} This generates electrical currents in brain tissue (via electromagnetic induction), and these currents then modulate neuronal firing. Multiple TMS pulses given consecutively are referred to as repetitive or rTMS (Fig. 1). In general, low frequency (< 1 Hz) rTMS reduces neuronal activity and cortical excitability, while higher frequency rTMS increases neuronal activity and cortical excitability^{3,4} and increases relative regional cerebral blood flow,⁵ although there are numerous exceptions, especially in the hemisphere contralateral to the site of rTMS application. Thus, low-frequency and high-frequency rTMS applied to the same brain site can have very different effects on brain circuits.⁶

rTMS neuronal effects persist for at least several minutes after the rTMS pulses, at least in the motor cortex.⁴ Because of synaptic connections, there are distal effects (both cortical and subcortical, ipsilateral and contralateral) on neural activity,^{7–10} regional cerebral blood flow,¹¹ and neurotransmitter activity,¹² which may differ from proximal effects.^{4, 5} TMS can be thought of as targeting brain circuits, rather than specific brain chemicals (e.g., neurotransmitters), although TMS behavioral effects often depend on the neurotransmitter systems within the brain circuit being manipulated.¹³ Because it is applied directly to the brain, TMS may be better tolerated than systemic medications by some patients (e.g., pregnant women, the elderly, or those with severe medical conditions such as heart disease). TMS technology can be used as an investigational research tool to study brain excitability or brain circuitry. This review focuses only on studies that have used rTMS either to temporarily modify a behavior related to the addictions or as a potential treatment.

Therapeutic studies generally use rTMS, which is being studied as treatment for a wide variety of psychiatric disorders,^{14,15} including depression, schizophrenia, bipolar disorder, obsessive-compulsive disorder, post-traumatic stress disorder, and autism. The U.S. Food and Drug Administration (FDA) has cleared two rTMS devices (Neuronetics, Malverne, PA, USA (October 2008); Brainsway, Jerusalem, Israel (February 2013)) for the treatment of major depressive disorder in adults.

Efficacy of rTMS treatment of addiction

The study of rTMS as an addiction treatment is at an early stage.¹⁶ We identified 16 human studies in the published literature, in which a total of 238 adults were exposed to active rTMS. These studies dealt with nicotine (tobacco) (Table 1), stimulants (cocaine or methamphetamine) (Table 2), or alcohol (Table 3). A majority (nine) are one- or two-session experimental laboratory studies using single- or double-blind sham rTMS, with drug craving as the major outcome measure. We also identified three unpublished studies (two with nicotine, one with cocaine) that exposed 78 adults to active rTMS. A recent meta-analysis of 17 sham-controlled studies on the effects of rTMS (nine studies: three cigarettes, three alcohol, three food) or transcranial direct current stimulation (tDCS) (eight studies: two cigarettes, two alcohol, three food, one marijuana) targeted at the dorsolateral prefrontal

cortex (DLPFC) found a significant reduction in substance craving, with a small-to-medium pooled standardized effect size (Hedge's g) of 0.476 (95% CI 0.316–0.636, $z = 5.832$, $P < 0.001$).¹⁷ There was no significant difference in effectiveness across the various substances ($Q(2) = 1.03$, $P = 0.60$), nor between rTMS and tDCS studies ($Q(1) = 0.27$, $P = 0.59$). Formal evaluation (using both Rosenthal's and Orwin's methods) revealed little likelihood that publication bias influenced the findings.

Only five studies (four with nicotine addiction (two unpublished), one with cocaine addiction (unpublished)) are phase II outpatient controlled clinical trials (i.e., randomized assignment, double blind, sham controlled) of the type that generate the rigorous scientific data required for regulatory approval. The largest trial sample size (including placebo group and noncompleters) is 115 subjects¹⁸ and the longest duration 4 weeks.¹⁹ We are not aware of any phase III clinical trial with rTMS in addiction. Given this absence of substantial clinical data, TMS is not approved for the treatment of addiction by any national regulatory agency, and should be considered an experimental treatment for this indication.

Nicotine (tobacco) addiction

Three of four experimental laboratory studies (Table 1) found that rTMS targeted to the DLPFC significantly reduced spontaneous or cue-induced nicotine craving.^{20–22} The fourth study, which found no change in craving, did find reduced cigarette smoking.²³ Two of four double-blind, sham-controlled outpatient clinical trials with nicotine-addicted outpatients found significantly reduced cigarette smoking.^{18,24} Changes in craving were not always consistent with changes in smoking. One trial found decreased cue-induced craving along with decreased smoking,²⁴ while another trial found no change in spontaneous craving associated with decreased smoking.¹⁸ A third trial (using single-pulse TMS) found a modest but significant decrease in spontaneous craving over 10 daily sessions (2 weeks), with no effect on smoking.²⁵ A fourth trial, involving participants with comorbid schizophrenia, found reduced spontaneous craving only during the first (of 4) week of treatment, with no effect on cigarette smoking.²⁶ Overall, these findings provide some evidence for the effectiveness of rTMS for smoking cessation, but little support for craving as a useful surrogate marker for changes in smoking.

Stimulant addiction

Two experimental laboratory studies targeting rTMS to the DLPFC gave differing results in stimulant addiction (Table 2). Low-frequency (1 Hz) rTMS targeted to the left DLPFC increased cue-induced methamphetamine craving,²⁷ while high-frequency (10 Hz) rTMS had no effect on spontaneous cocaine craving.²⁸ In contrast, high-frequency rTMS reduced spontaneous cocaine craving when targeted to the right DLPFC.²⁸ It remains unclear to what extent these differences are due to the frequency or laterality of rTMS or the type of drug craving assessed.

One 2-week, open-label inpatient study²⁹ and one 4-week, double-blind, sham-controlled outpatient clinical trial¹⁹ both found that high-frequency rTMS (10 or 20 Hz, respectively) targeted to the left DLPFC significantly decreased spontaneous cocaine craving. The controlled clinical trial also reported significantly decreased cocaine use, verified by urine

drug testing. Thus, there is promising clinical trial evidence that at least one week of high-frequency rTMS targeted to the left DLPFC reduces cocaine craving and use.

Alcohol addiction

Two experimental laboratory studies found no effect of high-frequency (20 Hz) rTMS targeted to the right DLPFC on spontaneous alcohol craving (Table 3).^{30,31} Two studies targeting high-frequency (10 or 20 Hz) rTMS to the DLPFC for 2 weeks (10 sessions) in inpatients who had completed acute detoxification found different effects: right-sided treatment reduced spontaneous alcohol craving,³² while left-sided treatment had no effect.³³ In contrast, a single outpatient case targeting low-frequency (1 Hz) rTMS to the dorsal anterior cingulate cortex³⁴ and three outpatient cases targeting high-frequency (20 Hz) rTMS to the DLPFC bilaterally (using a deep coil)³⁵ all reported decreased spontaneous alcohol craving after several sessions. Overall, there is limited evidence for the efficacy of rTMS in the treatment of alcohol addiction.

Safety of rTMS treatment of addiction

rTMS appears to be well tolerated by people with addiction, as it is by patients with depression,³⁶ although only seven (44%) of the 16 published studies we identified explicitly report on adverse events or tolerability. The only explicitly described adverse events are transient headache and scalp discomfort, which are also common in rTMS trials of depression. All studies followed international consensus TMS safety guidelines.³⁷ Active and sham rTMS groups have comparable drop-out rates in those studies that report them, and no study reported serious or unexpected adverse events. One study³² reported a seizure, the most clinically significant side-effect associated with TMS treatment. However, this self-limited seizure occurred in the sham rTMS group, in an alcohol-dependent inpatient within six days of discontinuation of benzodiazepine treatment for alcohol withdrawal. Thus, the seizure appears unrelated to rTMS itself.

Despite this excellent safety record, caution is indicated when applying rTMS to individuals whose psychoactive substance use might be associated with increased cortical excitability, lowered seizure threshold, and increased seizure risk, e.g., during acute stimulant intoxication or acute alcohol withdrawal (especially in the first few days after cessation of intake).^{38,39} rTMS may be contraindicated for patients in these contexts. We are aware of one unpublished case of a patient with major depression (and alcohol use disorder) participating in a clinical trial of rTMS using an experimental deep coil (see below) who experienced a seizure during her 17th treatment following a weekend of heavy drinking (at least one-half bottle of wine) (SEC 510(k) Number K122288, dated July 10, 2012). The investigators attributed this seizure to the influence of acute alcohol withdrawal. Three small studies of cocaine-dependent subjects studied after at least three weeks of abstinence from cocaine and alcohol found an increased resting motor threshold but few significant differences from controls in specific measures of intracortical inhibition and facilitation.^{40–42} A recent, larger study of 52 abstinent cocaine-dependent inpatients found increased intracortical facilitation, suggestive of enhanced glutamatergic neurotransmission.⁴³ These findings leave open the possibility that cocaine users have some increased cortical excitability after early abstinence. Therefore, the excellent safety record to

date of TMS studies in alcohol- and cocaine-dependent subjects may be attributable, in part, to most studies being conducted in inpatients who had completed acute detoxification and had no access to substances at the time of treatment.^{29,32,33}

Optimal treatment parameters

Many, but not all, studies found significantly reduced drug craving in the active rTMS group versus the sham group. However, the relatively small number of studies, substantial inter-study heterogeneity in many study characteristics, and lack of head-to-head comparison studies make it difficult to definitively identify common factors associated with a beneficial treatment response. For example, the optimal TMS characteristics (e.g., type of magnetic coil, pulse frequency, number of pulses, laterality of treatment), duration of treatment, and combination with other treatments (pharmacological and psychosocial) remain unknown. We review in more detail below some of the major treatment parameters.

Target of rTMS pulses

All but four addiction studies targeted TMS pulses to the DLPFC, a brain region considered important in mediating addiction and which is also commonly targeted in depression treatment.^{44,45} Two studies that targeted other single cortical regions—the superior frontal gyrus⁴⁶ and the dorsal anterior cingulate cortex³⁴—also found significant TMS effects on drug craving. A third study, which targeted the lateral prefrontal cortex and insula bilaterally, found significantly decreased cigarette smoking, but no change in craving.¹⁸ A fourth study, which used individualized fMRI guidance to target the cortical region showing maximal blood oxygen level-dependent (BOLD) response to nicotine-associated visual cues, found a decrease in drug craving.²⁵ We are not aware of any head-to-head studies comparing different brain regions that would allow determination of the optimal target region.

Among the 15 addiction studies that targeted away from the midline, nine (60%) targeted only the left (presumably dominant) cortex and three (20%) the right (non-dominant) cortex. Three studies targeted both hemispheres, either sequentially²⁶ or concurrently,^{18,35} the latter two by means of experimental coils that generate a bilateral magnetic field (see below). There is no obvious pattern of laterality influence on TMS effects. A recent meta-analysis including nine rTMS studies and eight tDCS studies (all sham controlled and targeting the DLPFC) of substance craving (10 drugs, 6 food) found no significant difference in craving reduction between those targeting the left or right hemisphere ($Q(1) = 2.10$, $P = 0.15$); both left-sided ($g = 0.375$, $Z = 4.138$, $P < 0.001$) and right-sided ($g = 0.710$, $Z = 3.847$, $P < 0.001$) targeting were significantly effective.¹⁷ One (open-label) study directly compared left versus right DLPFC targeting:²⁸ the former had no effect, while the latter significantly reduced spontaneous cocaine craving. This finding is not consistent with the significant drug-craving reduction associated with left DLPFC targeting in other studies. Future, more rigorously designed head-to-head comparison studies are needed to resolve this issue.

Two factors complicate interpretation of optimal TMS targeting. First, location of the intended target region may vary across individuals. Two recent studies demonstrated substantial individual heterogeneity in cortical brain regions involved in cue-induced

tobacco craving.^{47,48} About one-third of these right-handed (left-hemisphere dominant) individuals showed their maximum regional cortical activation to tobacco-associated visual cues (assessed as fMRI BOLD response) in the right (non-dominant) hemisphere, opposite the side that would typically be targeted for TMS. This phenomenon is not unique to addiction processes. Brain regions mediating other cognitive functions also show substantial individual anatomic variability in TMS studies (e.g., auditory-visual multisensory integration,⁴⁹ short-term verbal memory,⁵⁰ and visual magnitude processing⁵¹).

Second, most standard (figure-eight) TMS coils rarely produce truly localized or unilateral effects. When a TMS coil excites one cortical region, other ipsilateral regions are almost always affected as well because of transynaptic connections. The opposite hemisphere may also be affected, assuming the individual has an intact corpus callosum. Numerous brain imaging studies find that rTMS produces larger effects on the side opposite the coil.^{8,52–54} Thus, although the coil is positioned on one side of the brain, effects are often bilateral.

Methods of TMS targeting

In clinical practice for treatment of depression (including the U.S. FDA-approved Neuronetics NeuroStar TMS Therapy® system), rTMS pulses are targeted to the DLPFC by aiming at a scalp position 6 cm anterior (in the parasagittal plane) to the position over the cortical motor strip (M1) used to determine the resting motor threshold (i.e., the position that elicited maximum flexion of the *abductor pollicis longus* (thumb) muscle). This approach (5, 5.5, or 6 cm anterior to M1) is used by more than half (55%) of the addiction studies that targeted the DLPFC and report their targeting method (six (35%) studies did not report how they targeted). Another study used the international 10–20 system of scalp EEG electrode positioning (location F3); three used structural MRI scans of the brain to guide optically tracked frameless stereotactic positioning. Two rTMS addiction studies not targeting the DLPFC used either the international 10–20 EEG system (position FPz to target the superior frontal gyrus) or other scalp landmarks (to target the dorsal anterior cingulate cortex). A third study not targeting the DLPFC used fMRI scans of each participant's brain to identify the cortical region showing maximal BOLD response to drug-associated visual cues, then used optically tracked frameless stereotactic positioning to target TMS pulses to that region.²⁵

Experimental evidence suggests that these targeting methods vary in their accuracy and are inaccurate in many subjects, perhaps not surprising in view of the substantial inter-individual variability in the neuroanatomy of the human prefrontal cortex,^{55,56} including age- and gender-dependent variability in the DLPFC.⁵⁷ Four studies (involving 60 subjects) that directly compared the accuracy of the standard scalp landmark (5 cm anterior to M1) approach to structural MRI (Brodmann areas 46/9) for identifying the DLPFC found that the standard approach was at least 1 cm off in 73–100% of cases and at least 2 cm off in 41–100% of cases.^{58–61} Inaccurate targeting of the DLPFC could contribute to the modest effect sizes (or absence of significant effect) observed in rTMS addiction studies, as has been suggested for rTMS depression studies.⁶² Use of structural MRI or functional MRI (in conjunction with optically guided frameless stereotactic techniques) for individual targeting of the intended brain region, when compared to standard methods involving scalp

landmarks, appears to improve the efficacy of rTMS for treatment of depression (DLPFC),⁶² tinnitus (temporal cortex),⁶³ and motor tics (supplementary motor area)⁶⁴ and for experimental manipulation of motor function (primary motor cortex),⁶⁵ auditory–visual multisensory integration,⁴⁹ short-term verbal memory,⁵⁰ and visual magnitude processing,⁵¹ although the only direct head-to-head comparison involved depression treatment.⁶² This improved rTMS efficacy was observed even though it is clear that acute effects of TMS are not limited to the immediate area around the pulse target. There is no reason to believe that individualized MRI-guided targeting would not also improve the efficacy of TMS treatment for addiction.

Type of magnetic coil

All but three addiction studies used a standard 70-mm figure-eight TMS coil, as is commonly used in depression treatment. One study used a double-cone coil³⁴ and two studies^{18,35} used versions of a deep (H) coil developed by Brainsway, Ltd (Jerusalem, Israel) that delivers pulses deeper into the cortex than does the standard figure-eight coil.^{66–68} We are not aware of any study that directly compared different types of TMS coil.

Coil type may have substantial influence on the use of rTMS as treatment, and may obviate some issues related to optimal targeting. If the relevant cortical circuits vary greatly across individuals, then one either has to do brain imaging and within-individual guidance to determine each person's correct coil placement, or one could use a coil with a large pulse area (and/or bilateral coverage) that would be likely to stimulate the proper location for most individuals. A potential limitation of this approach is that such a coil might also stimulate regions and circuits that interfere with the therapeutic response or contribute to adverse effects. In addition, high-frequency rTMS of a larger brain volume might theoretically increase the risk of seizure, although this is unlikely given that inhibitory as well as excitatory circuits and interneurons would be stimulated by the rTMS. Hybrid approaches might also work, e.g., initially target rTMS at a region that would stimulate the relevant circuit in a majority of individuals, and then proceed to image-guided stimulation or a broader coil in those patients who do not respond.

Pulse frequency

Three-quarters of addiction studies (74%) used high-frequency (> 1 Hz) rTMS pulses, which are generally considered to stimulate neuronal activity.^{3,69} Three studies (18%) used low-frequency (< 1 Hz) pulses, which are considered to inhibit neuronal activity.^{3,69} We are aware of only two studies that directly compared high versus low frequency rTMS pulses. A single-session laboratory study found that 1 Hz treatment produced opposite effects on nicotine craving from those produced by 10 Hz treatment (see Table 1).⁴⁶ A 3-week outpatient controlled clinical trial found 10 Hz rTMS significantly more effective than 1 Hz.¹⁸ Cross-study comparisons yield inconsistent findings. Two low-frequency (1 Hz) experimental laboratory studies targeting the superior frontal gyrus or left DLPFC found increased spontaneous nicotine craving (but no change in cue-induced craving)⁴⁶ and cue-induced methamphetamine craving,²⁷ respectively. In contrast, two other low-frequency (1 Hz) studies targeting the left DLPFC or dorsal anterior cingulate cortex found decreased cue-induced nicotine craving²⁰ and spontaneous alcohol craving,³⁴ respectively.

Interpretation of these findings is complicated by differences in targeted brain region and the confounding of pulse frequency with total number of pulses (as number and duration of rTMS sessions were equivalent across groups).

Number of rTMS pulses

The evidence from depression treatment indicates that total number of rTMS pulses delivered to the patient is positively associated with treatment efficacy.^{70–72} We are not aware of any addiction studies that directly address this question. There is circumstantial evidence from two multi-session studies of cocaine addiction that this relationship holds for addiction treatment. A 2-week, 10-session open-label trial found a gradual reduction in craving over time, which was statistically significant by the seventh session.²⁹ A (unpublished) 4-week, 20-session controlled clinical trial found no significant reduction in cocaine use until the fourth week of treatment (the time course of craving reduction was not reported).¹⁹ Three case reports of people with alcohol addiction (and comorbid dysthymia) suggest a similar pattern, in that alcohol craving was not significantly decreased until 5–10 sessions.³⁵ In contrast, a controlled clinical trial in outpatients with nicotine addiction (and comorbid schizophrenia) found that TMS significantly reduced craving only during the first of the four treatment weeks,²⁶ suggesting possible dissipation of or tolerance to beneficial effects with continued TMS treatment.

Sham treatment and blinding

The primary outcome measure in the majority of rTMS addiction studies conducted to date is substance craving. This is a subjective response that is influenced not only by the intended experimental intervention, but also by environmental context, the individual's psychological state (including mood, focus of attention, and expectancy of short-term substance use⁷³), withdrawal or abstinence status, and treatment-seeking status.⁷⁴ The cortical (fMRI BOLD) response to craving is also influenced by these factors.^{74,75} In addition, there is evidence that medical devices in general⁷⁶ and rTMS in particular⁷⁷ may generate a strong placebo response. These characteristics make adequate blinding of treatment and use of sham TMS procedures especially important. For example, active TMS produces muscle twitching and scalp discomfort/pain, which could dampen craving via nonspecific cognitive or affective processes, independently of any direct TMS influence on brain circuits mediating craving. The ideal sham TMS procedure would control for these effects.

Three-quarters (74%) of the identified rTMS addiction studies were single- or double-blind. All of the published studies provided some information about blinding methods; none reported information on the success of blinding, consistent with the low rates of such reporting found in other rTMS clinical trials.^{78,79} The commonest blinding methods were tilting the active coil 45° or 90° away from the scalp surface (four studies) and use of a separate sham coil (three studies). The adequacy of these blinding methods remains unclear, although two recent systematic reviews of blinding success in randomized, sham-controlled clinical trials of rTMS treatment for other disorders found no significant treatment-group difference in proportion of participants who correctly identified their treatment assignment.^{78,79} However, participants receiving active rTMS were significantly more likely to think they had received active rTMS than were those who received sham rTMS.⁷⁹

Two of the identified TMS addiction studies^{22, 27} used as their sham TMS procedure transcutaneous electrical nerve stimulation (TENS) combined with either a sham TMS coil or tilting of the active coil by 45°. Intensity of the TENS was individually adjusted for each participant at baseline to match their subjective experience (primarily scalp discomfort) during open-label active TMS.⁸⁰ This sham procedure is potentially the most effective of those used to date, although it is also the most complicated and time-consuming. However, even matching active and sham TMS at baseline may not be sufficient to ensure complete blinding. A recent controlled clinical trial of rTMS treatment for depression that used such a sham procedure found that ratings of scalp pain declined significantly over the first three weeks of the trial in participants receiving active rTMS, but remained steady in those receiving sham rTMS.⁸¹

Unanswered clinical questions

In light of the paucity of clinical trial data, it is not surprising that many clinically important questions about TMS treatment of addiction remain unanswered. These include the optimal duration of treatment, combining TMS with other pharmacological and psychosocial treatments, the persistence of treatment effects, and the safety and efficacy of TMS in patients with comorbid psychiatric disorders and of various ages.

Because the duration of rTMS treatment covaries with the number of administered TMS pulses in all studies to date, it is impossible to identify the relative contributions of these two parameters. Experience with rTMS treatment of depression suggests that longer treatment duration and/or higher number of TMS pulses are associated with better outcome.^{71,72} We are not aware of any study that directly compared different durations of rTMS treatment for addiction.

There is limited evidence on the persistence of rTMS addiction treatment effects, as few studies include follow-up visits after the end of treatment or report time-course data. A single-session (2000 pulses), open-label experimental laboratory study found that high-frequency (10 Hz) rTMS targeted to the right DLPFC reduced spontaneous cocaine craving for less than 4 hours.²⁸ A 2-week outpatient controlled clinical trial of high-frequency (10 Hz) rTMS targeted to the left DLPFC found that the reductions in nicotine craving and cigarette smoking observed during treatment tended to dissipate over the first 2 weeks of follow-up, but could not be formally analyzed because of the high drop-out rate.²⁴ At a 6-month telephone follow-up, there were no significant group differences. In contrast, a 3-week outpatient controlled clinical trial of high-frequency (10 Hz) rTMS targeted to the left prefrontal cortex and insula bilaterally found some persistence of treatment effect at 6-month follow-up.¹⁸ A 4-week outpatient controlled clinical trial of high-frequency (5 Hz) TMS targeted to the left DLPFC found that the reduced cocaine use observed during the fourth week of treatment persisted over the subsequent 8 weeks of follow-up.¹⁹

rTMS is well tolerated when used together with antidepressant medication in the treatment of depression,^{82,83} but experience with rTMS and concomitant medications in addiction treatment is extremely limited. One controlled clinical trial in nicotine addiction added medication (transdermal nicotine) and weekly group therapy at the third week of rTMS

treatment (quit date), but still found no significant decrease in cigarette smoking.²⁶ The combined treatment was well tolerated.

In theory, some concomitant medications might raise safety concerns if they increased cortical excitability or lowered the seizure threshold, thereby increasing the risk of rTMS-induced seizures. This caution might apply to agonist substitution treatment of stimulant dependence, as several such oral medications (e.g., amphetamine, methylphenidate) induce seizures at high doses and increase cortical excitability at therapeutic doses.^{84,85} Conversely, several medications being evaluated for treatment of cocaine or cannabis addiction reduce cortical excitability and increase cortical inhibition, either by blocking voltage-gated sodium or calcium ion channels (e.g., topiramate) or enhancing γ -amino-butyric acid (GABA) neurotransmitter function (e.g., vigabatrin, baclofen).⁸⁶ These actions could potentially hinder the therapeutic effect of rTMS.

Although TMS is being studied as treatment for a variety of other psychiatric disorders,^{14,87} we are aware of only two studies involving rTMS treatment of addiction in patients with a comorbid psychiatric disorder. A small controlled clinical trial of high-frequency rTMS targeted to the bilateral DLPFC in patients with nicotine addiction and comorbid schizophrenia found no significant effect on cigarette smoking, although the treatment was well tolerated.²⁶ An outpatient case series of three patients with alcohol addiction and comorbid dysthymia found that high-frequency rTMS targeted to the bilateral DLPFC significantly reduced spontaneous alcohol craving and depressive symptoms by the second week of treatment, and was well tolerated.³⁵

We are not aware of any studies of rTMS treatment for addiction conducted in children or the elderly, so the safety and efficacy for this indication outside the adult age range remain unknown.

Mechanism of action

The mechanism of rTMS therapeutic action in addiction is not well established, but may be understood in terms of both modulation of neurotransmitter activity (especially dopamine and glutamate) in brain regions mediating addiction and modulation of brain circuits mediating psychological processes important to addiction, such as drug craving, salience and reactivity to drug-associated cues, risk–reward decision making, or inhibition of prepotent responses.

Drug addiction is associated with decreased dopamine function (e.g., dopamine D₂ receptor binding potential, presynaptic dopamine release) in brain regions such as the orbitofrontal cortex (considered to mediate salience attribution), the DLPFC (mediating executive functions such as regulation of intentional behavior), the anterior cingulate gyrus (mediating inhibitory control of behavior), and the ventral striatum (including the nucleus accumbens, mediating reward).^{88,89} Increasing dopamine function in these brain regions could have therapeutic benefit.

Both animal and human studies suggest that high-frequency rTMS increases dopamine activity in cortical, striatal, and limbic brain regions.⁹⁰ High-frequency rTMS targeted at the

left DLPFC induces dopamine release in the ipsilateral anterior cingulate cortex, orbitofrontal cortex, and striatum.^{12,91} In rat studies, high-frequency (20 or 25 Hz) rTMS over the frontal cortex releases dopamine throughout the mesolimbic and mesostriatal circuits,^{92–94} and this effect is enhanced in animals undergoing drug withdrawal.⁹⁵ Thus, the therapeutic benefit observed in clinical trials of high-frequency rTMS targeted at the DLPFC could be related to enhanced dopamine activity in these brain regions.

The excitatory neurotransmitter glutamate also plays a key role in addiction.^{96,97} Chronic drug use is associated with dysregulation of glutamate homeostasis in the brain (maintained by the cysteine–glutamate exchanger and glutamate transporter 1) and increased activity of several types of glutamate receptors (especially AMPA and metabotropic glutamate receptors 2 and 3). These neurotransmitter changes are associated with altered synaptic plasticity in the frontal cortex and the nucleus accumbens that, in animal studies, mediates increased reactivity to drug-associated cues and drug-seeking behavior after extinction of drug self-administration (i.e., relapse). Ameliorating or reversing these glutamatergic changes could have therapeutic benefit.

In rats, high-frequency (20 Hz), but not low-frequency (1 Hz), rTMS to the brain produced a long-lasting increase in AMPA-type glutamate receptors in the hippocampus, but not in the prelimbic cortex or striatum,⁹⁸ while high-frequency (20 Hz) intracranial electrical stimulation to the prefrontal cortex, in a pattern mimicking rTMS, increased AMPA-type glutamate receptors in the nucleus accumbens and reduced cocaine-seeking behavior.⁹⁹ These findings suggest that the therapeutic benefits of high-frequency rTMS could be related to its effects on brain glutamate.

In cognitive terms, high-frequency rTMS targeted at the DLPFC of healthy volunteers or patients with mood disorders or schizophrenia improves executive function, response inhibition, and selective attention,¹⁰⁰ all cognitive functions that tend to be impaired in individuals with addiction.^{101–103} High-frequency rTMS targeted at the DLPFC might also reduce drug craving by activating prefrontal brain circuits that mediate response inhibition and control of impulsive behavior, and/or by activating subcortical regions that inhibit craving, analogous to the mechanism by which prefrontal rTMS decreases pain or increases pain tolerance.^{13,104,105} Low-frequency rTMS targeted at the DLPFC might also reduce craving by minimizing the enhanced DLPFC activity associated with drug-cue reactivity and cue-induced craving.¹⁰⁶

We are aware of only two studies that used brain imaging (fMRI in both cases) to directly investigate the neural mechanism of rTMS. Both studies used low-frequency (1 Hz), presumably inhibitory, rTMS, so their findings may not generalize to the vast majority of studies that use high-frequency, presumably excitatory, TMS. A study that targeted the left DLPFC in cigarette smokers found that rTMS inactivation of the DLPFC reduced cue-induced craving and the temporally associated BOLD activation in the DLPFC, anterior cingulate, and ventral striatum.²⁰ A study that targeted the dorsal anterior cingulate cortex in alcohol-dependent outpatients found that TMS reduced cue-induced craving (and subsequent alcohol intake) and the temporally associated BOLD activation in the left posterior cingulate cortex, anterior cingulate cortex, and nucleus accumbens.³⁴ These findings suggest that low-

frequency TMS reduces cue-induced substance craving by inhibiting neural activity in brain circuits known to mediate cue-induced craving. However, two other low-frequency TMS studies had different results. One targeting the superior frontal gyrus found no change in cue-induced nicotine craving (and increased spontaneous craving),⁴⁶ and one targeting low-frequency TMS to the left DLPFC found increased cue-induced methamphetamine craving.²⁷ The reason for these discrepant findings remains unclear.

Conclusions and future research

High-frequency (5–10 Hz) rTMS applied to the DLPFC is a non-invasive physical approach to addiction treatment that has seen limited evaluation in clinical trials for nicotine, cocaine, and alcohol addiction and is not approved for this indication by any national regulatory agency. Three of four outpatient controlled clinical trials in nicotine addiction (one using single-pulse TMS) gave positive results in terms of reduced craving or use or both, with the negative trial involving outpatients with comorbid schizophrenia. Two outpatient clinical trials (one open-label) in cocaine addiction both found decreased craving, with the controlled trial also reporting decreased cocaine use. One inpatient controlled clinical trial in alcohol addiction reported decreased craving. Other potentially effective TMS approaches remain largely unevaluated (e.g., low-frequency stimulation, targets other than the DLPFC, and individualized targeting (such as fMRI guidance)). In summary, the clinical trial evidence supporting rTMS as treatment for addiction is generally favorable, but limited. Therefore, while rTMS is well tolerated by individuals with addiction, it cannot be recommended at this time as a first-line treatment for addiction.

To fulfill the promise of TMS as an addiction treatment, the field needs controlled clinical trials, conducted under rigorous standards with respect to participant characterization, randomization, blinding (sham) procedures, outcome measures, and other design criteria, to identify optimum rTMS parameters for treatment (e.g., pulse parameters, coil type, brain target) and optimum treatment conditions (e.g., duration, concomitant treatments). In particular, we suggest that direct, head-to-head comparative studies evaluating key rTMS parameters and treatment conditions would advance the field, for example (1) low-frequency versus high-frequency rTMS; (2) systematic evaluation of cumulative number of pulses needed to see a treatment effect; (3) the standard figure-eight coil versus other coil designs with broader or bilateral field coverage and so-called deep coils that could target brain regions considered important to addiction (e.g., the insula¹⁰⁷ and deep prefrontal projections to the nucleus accumbens (ventral striatum)); (4) typical left DLPFC brain target versus right DLPFC, bilateral DLPFC, or other targets (e.g., the insula); and (5) rTMS with versus without specific concomitant psychosocial or pharmacological treatments .

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Figure 1. Transcranial magnetic stimulation. A fluctuating magnetic field penetrates the skull and induces electric current (Faraday's Law) within brain tissue. Reprinted by permission from Macmillan Publishers Ltd: *Nature Reviews Neuroscience* **8**: 559–567 (July 2007), doi: 10.1038/nrn2169.

Table 1
Published studies of repetitive transcranial magnetic stimulation (rTMS) and nicotine craving

Site of pulses	Targeting method	n	TMS Parameters			Blinding (sham)	Safety	outcome	Reference
			Pulse frequency (Hz)	Pulse intensity (% RMT)	Sessions	Total # pulses			
Superior frontal gyrus	FPz (10-20)	15	10	90%	1	4500	No	? ↑ cue-induced craving ↓ spontaneous craving	46
Superior frontal gyrus	FPz (10-20)	15	1	90%	1	450	No	? no cue-induced craving, → spontaneous craving	46
L DLPFC	5 cm anterior MI	14	20	90%	2	2000	DB (shamcoil)	Mild HA ↓ smoking no spontaneous craving	23
L DLPFC	?	11	20	90%	1	1000	SB (sham coil)	? ↓ spontaneous craving	21
L DLPFC	5 cm anterior MI	26	10	100%	10	10,000	DB (metal plate under coil)	? ↓ smoking ↓ cue- induced craving	24
L & R DLPFC		6*	20	90%	20	15,000 per side	SB (coil tilted)	No group AEs ↓ spontaneous craving 1st week only No smoking	26
L DLPFC	6 cm ant MI	16	10	100%	1	3000	DB (matched TENS + sham coil)	"mild discomfort" with simulation ↓ cue included craving	22
L DLPFC	MRI-based MNI coordinates	10		110%	1	1800	SB (coil tilted)	? ↓ cue included craving	20

NOTE: Site of pulses: DLPFC, dorsolateral prefrontal cortex; L, left; R, right; 10-20, 10-20 EEG localization scheme; M1, motor cortex spot eliciting contraction of abductor pollicis longus muscle; MRI, magnetic resonance imaging; MNI, Montreal Neurological Institute; n, number receiving active rTMS (total = 98)

comorbid schizophrenia receiving nicotine replacement therapy and weekly counseling RMT, resting motor threshold; DB, double-blind; SB, single-blind; matched TENS, transcutaneous electrical nerve stimulation matched for pain intensity to active TMS; HA, headache; AEs, adverse events.

* methamphetamine-deptenden

Table 2

Published studies of rTMS and cocaine/methamphetamine craving

Site of pulses	Targeting Method	n	TMS Parameters			linding (sham)	Safety	Outcome	References
			Pulse frequency (Hz)	Pulse intensity (% RMT)	# sessions	Total # pulses			
R DLPFC	?	6	10	90%	1	2000	No	?	↓ spontaneous craving
L DLPFC	?	6	10	90%	1	2000	No	?	No spontaneous craving
L DLPFC	?	36	15	100%	10	6000	No	?	↓ spontaneous craving
LDLPFC	6 cm anterior M1	10 *	1	100%	1	900	S (matched TENS with tilted coil)	Transient scalp discomfort, no group	↑ cue-induced craving

Note: DLPFC, dorsolateral prefrontal cortex; L, left; R, right; M1, motor cortex spot eliciting contraction of *abductorpollicis longus* muscle; n, number receiving active rTMS (total 69)

RMT = resting motor threshold; D, double-blind; S, single-blind; HA, headache; SE, side-effects D, double-blind; S, single-blind; matched TENS, transcutaneous electrical nerve stimulation matched for pain intensity to active TMS.

* methamphetamine-deptenden

Table 3

Published studies of rTMS and alcohol craving

Site of pulses	Targeting method	n	TMS Parameters				Blinding	Safety	Outcome	References
			Pulse frequency (Hz)	Pulse intensity (% RMT)	# sessions	Total # pulses				
R DLPFC	?	30	10	110%	10	9800	SB (sham coil)	Active: transient HA, scalp pain Sham: 1 seizure	↓ spontaneous craving	32
Dorsal ACC	1.5 cm anterior to 1/3 N-I	1	1	(50% machine output)	21	37,800	No	?	↓ spontaneous craving	34
L DLPFC	F3 (10-20)	10	20	90%	10	10,000	SB (coil position, 60% RMT)	Well tolerated, no SE	No spontaneous craving ↓ attention to alcohol cues	33
R DLPFC	MRI	15	20	110%	1	1560	SB (tilt coil, blindfolded)	?	No spontaneous craving	30
R DLPFC	MRI	29	20	110%	1	1560	SB (tilt coil, blindfolded)	?	No spontaneous craving	31
Bilateral [#] DLPFC	5.5 cm anterior M1	3 [*]	20	120%	20	?	No	Well tolerated	↓ spontaneous craving ↓ depression	35

Note: DLPFC, dorsolateral prefrontal cortex; ACC, anterior cingulate cortex; L, left; R, right; #, deep (H) coil generating bilateral TMS pulses; N-I, line connecting nasion andinion; 10-20, 10-20 EEG localization scheme; MRI, magnetic resonance imaging; M1, motor cortex spot eliciting contraction of abductor pollicis longus muscle; n, number receiving active rTMS (total = 88); treated with anti-depressants and anxiolytics; RMT = resting motor threshold, D, double-blind; S, single-blind; HA, headache; SE, side-effects

^{*} comorbid dysthymic disorder