

# Transcranial magnetic stimulation for the treatment of cocaine addiction: evidence to date

Corinna Bolloni  
Paola Badas  
Giorgio Corona  
Marco Diana

Laboratory of Cognitive Neuroscience, G Minardi Department of Chemistry and Pharmacy, University of Sassari, Sassari, Italy

**Abstract:** There is a common consensus in considering substance-use disorders (SUDs) a devastating chronic illness with social and psychological impact. Despite significant progress in understanding the neurobiology of SUDs, therapeutic advances have proceeded at a slower pace, in particular for cocaine-use disorder (CUD). Transcranial magnetic stimulation (TMS) is gaining support as a safe and cost-effective tool in the treatment of SUDs. In this review, we consider human studies that have investigated the efficacy of TMS in achieving therapeutic benefits in treating CUD. All studies conducted to date that have evaluated the therapeutic effect of TMS in CUD are included. We focus on the protocol of stimulation applied, emphasizing the neurophysiological effects of coils employed related to outcomes. Moreover, we examine the subjective and objective measurements used to assess the therapeutic effects along the timeline considered. The revision of scientific literatures underscores the therapeutic potential of TMS in treating CUD. However, the variability in stimulation protocols applied and the lack of methodological control do not allow us to draw firm conclusions, and further studies are warranted to examine the interaction between TMS patterns of stimulation relative to clinical outcomes in depth.

**Keywords:** TMS, cocaine-use disorder, PfcX, craving, intake, dopamine

## Introduction

The annual overview of the European drug situation highlighted that substance-use disorders (SUDs; ie, cannabis, cocaine, MDMA, amphetamines, opioids) represent a major public health concern in the Western world, with about 24.3 million young adult users (aged 15–34 years) in 2017.<sup>1</sup> SUDs can be described as a chronic neuropathology characterized by a reduction in the ability to control compulsive drug-seeking behavior, regardless of negative consequences.<sup>2</sup> Preclinical studies in rodents and human imaging evidence have shown the role of repetitive drug use in aberrant forms of neural plasticity consisting, briefly, in a significant reduction in dopaminergic activity linked to the dysfunction of cortical and subcortical pathways.<sup>3–21</sup> These findings complement the fundamental building blocks of the dopamine (DA) hypothesis of drug addiction, which ascribes to the hypofunctioning DA system a key role in the genesis of drug abuse and leads to the theory that functional “boosting” of DA signaling may hold beneficial effects in reducing drug craving/intake.<sup>4,22,23</sup>

Drug addiction is now considered a whole-brain pathology, since brain-wide activity patterns are compromised.<sup>1,18,19,24,25</sup> These changes in brain function lead to the

Correspondence: Corinna Bolloni; Marco Diana  
Laboratory of Cognitive Neuroscience, G Minardi Department of Chemistry and Pharmacy, University of Sassari, 23A Via Muroni, Sassari 07100, Italy  
Tel +39 079 228 711  
Email corinnabolloni@gmail.com; dsfdiana@uniss.it

motivational and cognitive impairment that characterizes addictive disorders.<sup>10,13,26</sup> Indeed, alterations in mesocortical brain networks and related dysfunction in dopaminergic activity are accompanied by increased salience for the abused substance and increased cue reactivity for related stimuli, which in turn support the motivation/drive to use the substance and to relapse.<sup>27–30</sup> This mechanism seems to have a putative role in the development of addiction, amplified and supported by an uncontrollable urge to take the substance of abuse (ie, craving), which leads to searching for the substance and relapse. Indeed, higher craving rates are related to higher relapse rates.<sup>18,19,31,32</sup> Despite the fact that drug craving is considered an important risk factor for relapse, it can be counteracted and restricted by exerting cognitive and behavioral control.<sup>33,34</sup> However, the diminished functioning of the dorsolateral prefrontal cortex (DlPFC) and anterior cingulate cortex provides a reason for the impaired inhibitory behavioral control and higher tendency to relapse in alcohol and/or drug use.<sup>34–38</sup>

However, despite these recent advances in understanding the neurobiology of addiction, expectations of therapeutic treatments have fallen shorter than desired.<sup>39,40</sup> Transcranial magnetic stimulation (TMS) represents a nonpharmacological tool and a testable opportunity in the treatment of SUDs, owing to its capacity to target and modulate specific brain circuits that are involved in the neuropathology of addiction.<sup>41–44</sup>

Therefore, we searched among published studies that investigated the efficacy of TMS in the treatment of SUDs and focused on those applied to cocaine addicts. Papers were identified through NCBI PubMed research by using “TMS”, “addiction”, and “cocaine” as keywords. Among published studies, only six focused on the treatment of cocaine addiction. These are reviewed in the present paper, with particular reference to the stimulation protocol applied and outcome observed.

## TMS physiology

Since 1985, when TMS was implemented for the first time in the study of motor-cortex excitability, the potential therapeutic effect of brain stimulation is being investigated in different psychiatric disorders, such as major depression, obsessive-compulsive disorders, schizophrenia, and addictive disorders.<sup>41,43–50</sup> TMS can be described as a nonsurgical brain stimulation that is able to modulate cortical excitability through magnetic fields inducted over the scalp.<sup>51</sup> The passage of electric current in the coil induces a transient, high-intensity magnetic pulse that penetrates the scalp and

reaches the neurons of the targeted cortical area painlessly in the conscious subject. Generally, 1 Hz frequency (or below) of consecutive stimuli, ie, repetitive TMS (rTMS), inhibits cortical excitability, whereas high frequency (5–20 Hz) produces increased cortical excitability.<sup>43,44</sup> This change in cortical activity is able to produce both physiologic and behavioral effects, depending on the parameters of stimulation applied.<sup>52–54</sup> The total duration of the session, the frequency of stimulation employed, the intensity (relative to motor threshold [MT]), and pattern of stimulation are the key factors in determining long-lasting TMS effects, since physiological and behavioral effects are mediated by the traditional phenomena of Hebbian synaptic plasticity, consisting in long-term potentiation (LTP) and long-term depression (LTD) of neuronal activity.<sup>44,55,56</sup> Despite variability in the protocol of stimulation applied, a number of studies (Table S1) have shown efficacy of TMS in reducing craving and consumption in alcoholics and nicotine-dependent subjects. Additional recent work highlights the therapeutic potential of rTMS in cue-induced craving for methamphetamine, heroin-cue craving, and food craving.<sup>57–65</sup>

These findings suggest that rTMS modulates neural activity via two main mechanisms: through the frontostriatal glutamate-bearing afferents to medium spiny neurons of the ventral striatum, and projections from pyramidal neurons of the fifth layer of the PFC impinging upon DA-containing midbrain neurons, thereby inducing DA release in the nucleus accumbens.<sup>11,22,66,67</sup>

The effect of TMS to increase DA levels transiently in cortical areas and its ability to modulate reduced dopaminergic activity in the limbic system appears to be among the mechanisms in restoring predrug functionality at a system level.<sup>44</sup> On the other hand, by stimulating the PFC, functioning of the cortical network can be strengthened and hopefully improve executive-control circuits.<sup>7,9,35,68</sup>

## Key TMS factors

At present, the need to find the best stimulation parameters to optimize the clinical outcome is the main target. Recent studies have pointed out the importance of the characteristics of the magnetic E-field inducted in association with the clinical outcome, theorizing that a deeper stimulation may have more chance of reaching dysfunctional brain areas, and through this “direct way” better odds of obtaining long-lasting effects, such as reduction in craving and drug consumption.<sup>69–71</sup>

The activation of targeted brain areas depends on the shape of the magnetic E-field, spatial accuracy, and

penetration depth of stimulation.<sup>72</sup> These factors are dictated by coil geometry, which then defines the capability of stimulation to activate the brain areas of interest aimed at restoring the dysfunctional neuronal network, eventually. Considering that the intensity of the E-field is maximal closest to the coil, stimulation intensity is strongest over the brain surface and rapidly attenuates with distance.<sup>73</sup> The most widely used coil implemented in the study of TMS effects is the figure-of-eight coil, which owing to its geometry (figure of eight), is able to project focal fields over the brain surface with high spatial resolution (2.5–3 cm<sup>2</sup>).<sup>74</sup> However, the E-fields remain quite superficial and tend to dissipate in intensity rapidly, with little chance of reaching deeper brain areas disrupted by the neuropathology of addiction.<sup>73</sup> Moreover, discrepancies in the geometry of magnetic fields generated by the figure-of-eight coil and thus in the localization of the area targeted may account for the variability in effects observed.

In 2002, Roth et al designed a new coil called a Heschl-coil (H-coil) able to stimulate the PFC bilaterally and through the stimulation of frontostriatal projections activate midbrain DA neurons and other subcortical areas involved in dopaminergic activity, at least in theory.<sup>69,75</sup> Recently, Malik et al tested the capacity of the H-coil to modulate DA release in eight healthy subjects, finding that low-frequency rTMS (1 Hz) significantly decreased DA levels in the substantia nigra and sensorimotor and associative striata.<sup>76</sup> This novel coil seems to have more chance of obtaining consistent and prolonged effects, presumably due to its ability to stimulate subcortical brain regions that are involved in the development of addiction's neuropathology. However, since cortical thickness is contained within 2 cm from the skin surface,

targeting fifth-layer cortical pyramidal neurons (efferent) may suffice to modulate subcortical circuitries involved in taking and relapse.<sup>22,44,77</sup>

If the coil geometry is among the key factors in the efficacy of stimulation to activate the targeted brain areas, anatomical pathways also play an important role in the final effect of stimulation.<sup>53,72</sup> For this reason, the TMS navigator device integrated with a magnetic resonance imaging guide was developed, which is able to identify the targeted area to stimulate and to estimate the orientation, intensity, and gradients of the E-fields based on the subject's brain anatomy.<sup>78</sup> This innovative integrated approach of TMS plus neuronavigation will be useful in future to optimize the TMS effect and by that to ameliorate clinical benefits.

## TMS for treatment of cocaine addiction: evidence to date

The six studies that investigated the effect of TMS in cocaine addiction are discussed herein and summarized in Table 1. In 2007, Camprodon et al investigated the effect of rTMS on cocaine craving. Secondary end points were changes in anxiety, happiness, sadness, and discomfort.<sup>79</sup> In this randomized crossover study, six patients fulfilling *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM)-IV criteria for cocaine dependence underwent two sessions of rTMS – one to the left and one to the right DIPFC – with a week's break between sessions. Patients were asked to complete a visual analog scale (VAS) ranging from “not at all” to “more than ever” before, immediately after, and 4 hours after TMS. Notably, during the whole study, patients remained hospitalized. The protocol of stimulation

**Table 1** Studies that have implemented TMS in the treatment of cocaine addicts

	n	TMS device and parameters	Target area	Control group	Assessment	Results
Terraneo et al <sup>85</sup>	32	rTMS (8-coil), 8 sessions, 40 trains, 15 Hz, 100% MT, 2,400 pulses	DIPFCx, left	Pharm	Urine, craving	More cocaine-free urine samples in rTMS group, reduction in craving in rTMS group
Rapinesi et al <sup>86</sup>	7	rTMS (H coil), 12 sessions, 20 trains, 20 Hz, 100% MT, 720 pulses	DIPFCx, bilateral	No	Craving (VAS)	Reduction in craving
Bolloni et al <sup>87</sup>	10	rTMS (H1 coil), 12 sessions, 20 trains, 10 Hz, 100% MT, 1,000 pulses	DIPFCx, bilateral	Sham TMS	Hair analysis	Reduction in Intake in 10 Hz rTMS group, no difference among subjects
Politi et al <sup>81</sup>	36	rTMS (8-coil), 10 sessions, 20 trains, 15 Hz, 100% MT, 600 pulses	DIPFCx, left	No	Craving (VAS)	Reduction in craving
Camprodon et al <sup>79</sup>	6	rTMS, 2 sessions, 20 trains, 10 Hz, 90% MT, 2,000 pulses	DIPFCx, right/left	No	Craving (VAS)	Reduction in craving with right rTMS
Hanlon et al <sup>92</sup>	11	cTBS + fMRI, 1 session, 110% MT, 1,800 pulses	MPFCx, left	Sham TMS	Craving	Reduction in craving

**Abbreviations:** rTMS, repetitive transcranial magnetic stimulation; MT, motor threshold; cTBS, continuous θ-burst stimulation; fMRI, functional magnetic resonance imaging; DIPFCx, dorsolateral prefrontal cortex; MPFCx, medial prefrontal cortex; VAS, visual analogue scale.

consisted in two sessions of stimulation (right/left) with 20 trains each of 10-second length and 1 second of interstimulus for a total of 2,000 pulses. The frequency of stimulation was 10 Hz, while the intensity was 90% of the individual's MT. The authors found a transient effect of one session of 10Hz rTMS over the right DIPfCx, but not the left, which consisted in a (statistically) significant reduction in craving for cocaine. A significant difference in "desire to consume cocaine" was found between baseline and post-TMS ratings craving and between post-TMS and 4 hours post-TMS, but no significant difference was found between pre-TMS and 4 hours later. Despite the TMS effect resolving in 4 hours after stimulation, this research provided the first evidence that one session of high-intensity rTMS over the right DIPfCx transiently reduce craving in chronic cocaine abusers.<sup>79,80</sup> Following this preliminary study, Politi et al explored the potential of rTMS in reducing cocaine craving by applying it over the left DIPfCx for ten daily sessions. High-frequency (15 Hz) rTMS was administered over the left DIPfCx of 36 cocaine addicts.<sup>81</sup> The stimulation consisted of 20 trains of rTMS at 100% subjective MT for a total of 600 pulses. No control group was considered in this experiment. As in the previous study, the researchers assessed the TMS effects through the VAS, and found a reduction in craving level. Although different in the paradigm applied, these two studies suggest that rTMS reduces cocaine craving. Moreover, they demonstrated the central role of DIPfCx in modulating craving, as suggested earlier by imaging studies.<sup>82-84</sup>

Terraneo et al studied the effects of rTMS on cocaine intake by applying it over the left DIPfCx.<sup>85</sup> The authors assessed the rTMS effect with an objective marker of cocaine consumption. The primary outcome of the study was the use of cocaine assessed by urine drug screen. Secondary outcomes were cocaine craving and depressive symptoms. Unlike previous studies, the authors described the stimulator device used and the procedure to obtain subjective MT. They employed a figure-of-eight coil (as per Camprodon et al and Politi et al) to deliver the treatment, which consisted of eight sessions of rTMS delivered at 15 Hz and 100% MT, 60 pulses per train, and 40 stimulation trains, with 15 seconds of interstimulus interval for a total of 2,400 pulses. They used a TMS Navigator. This approach allows the experimenter to have higher methodological control. The experiment was designed in two stages, and included a control group treated with a routine pharmacological protocol consisting in pramipexole 0.35 mg three times daily, bupropion 150 mg daily, oxazepam 15 mg three times daily, triazolam 0.25 mg daily, and  $\gamma$ -hydroxybutyrate 1.75 g daily.<sup>85</sup> A total of 32 cocaine addicts

were randomly assigned to the experimental group (rTMS over left DIPfCx) or the control group during 29 days. The rTMS treatment was applied with daily sessions for the first 5 days, and once a week for the following 3 weeks. At the end of stage 1, a 63-day follow-up took place, during which the participants could choose to continue in the same group or switch to the other. During stage 2, participants belonging to control group in stage 1 received the same protocol of stimulation applied in the rTMS experimental group. At the end of stage 1, 16 patients (100%) concluded the treatment in the rTMS group, while 13 patients (81%) concluded the pharmacological treatment in the control group. The authors analyzed the urine drug tests in the two groups at the end of stage 1, finding a higher number of cocaine-free urine samples in the rTMS group. Similar observations were found in the craving VAS, which resulted in significantly lower scores in the experimental group. The ten subjects that switched to the rTMS group in stage 2 displayed significant improvement with favorable outcomes comparable to those of the rTMS group. No differences were found in secondary outcomes. In spite of the open-label design and the use of a variety of pharmacological treatments as a control group, this study provided significant progress in methodological control, since an objective marker of cocaine consumption was used. Another important aspect of the Terraneo et al study is the direct comparison between rTMS-treated patients and pharmacological treatment (as usual) patients.<sup>85</sup> Rapinesi et al administered 12 sessions of rTMS through the H-coil to seven cocaine addicts.<sup>86</sup> The 12 sessions were applied three times a week alternately during 4 weeks. Bilateral rTMS was delivered at high frequency (15 Hz) and 100% MT in 20 trains with 2 seconds of interstimulus interval for a total of 8,640 pulses (720 pulses/session). They used cocaine craving measured with VAS as an outcome assessed the week before, each week during the treatment and 1 month after rTMS. At the end of the study, the authors found a significant craving reduction from baseline to 2 weeks and 4 weeks and from baseline to 1 month later. Despite there being a significant increase of craving from week 4 to 8, this study provided the first evidence of medium-term effect (baseline to 1 month after treatment) of bilateral rTMS of the Pfcx as a whole in cocaine craving. However, the small sample, absence of a control group, and subjective outcome did not allow the authors to make any definitive conclusion. In 2016, we designed a double-blind randomized pilot study to test the efficacy of bilateral deep rTMS in cocaine intake.<sup>87</sup> A total of 18 treatment-seeking patients with current CUD according to DSM-IV criteria were recruited and randomly assigned to

active 10 Hz stimulation or sham stimulation. A total of 12 sessions of rTMS were administered three times/week (every other day) for 4 weeks at 100% MT over the bilateral PFC. Each session comprised 20 trains of 50 pulses with 15 seconds of interstimulus interval between trains, for a total of 1,000 pulses per session.<sup>88,89</sup> The activation of the sham protocol by a magnetic card reader mimicked the acoustic sounds of the active one without inducing magnetic fields. We considered as outcome the cocaine intake assessed by hair analysis before treatment and at 1, 3, and 6 months later. We decided to use the hair test as a measure of drug intake, because it provides long-term information on drug consumption with higher sensitivity and specificity than urine analysis.<sup>90,91</sup> We also monitored the subjects who abandoned the study before the end of treatment (dropouts) and relapses among those patients who completed the protocol. Three subjects from the sham group (37%) and one from the active group (10%) abandoned the study before ending the 12 sessions of stimulation. Two subjects of four (50%) from the sham group relapsed three times after the treatment, while two subjects of six (33%) from the active group reported one relapse after 6 months from onset of treatment. At the end of the study we analyzed the effect of deep rTMS on cocaine intake on ten cocaine addicts over a 6-month period. Between-group analysis indicated no difference on cocaine intake along time; however, the exploratory within-group analysis showed a significant reduction in the amount of cocaine detected from baseline to 3 and 6 months later in the active group and not in the sham one. Notably a lower rate of dropout was observed in the active group compared to the sham. In contrast to previous studies, we tested the effect of TMS in both active and sham groups, finding a profound reduction in cocaine intake in both but no difference in cocaine intake between the two experimental condition, thereby highlighting a strong placebo effect.<sup>79,81,85,86</sup> However, the paucity of the sample may have played a role in these results. Moreover, we used as outcome an objective measure of cocaine intake (hair analysis) over 6 months. Cocaine craving was not measured. In 2015, Hanlon et al, starting from a new theoretical model to choose the target area to be stimulated, applied continuous  $\theta$ -burst stimulation (cTBS) over the medial prefrontal cortex (MPFC).<sup>92</sup> Unlike classic rTMS, which delivers several trains of consecutive stimuli, cTBS delivers bursts of three pulses at 50 Hz applied at 5 Hz at an amplitude determined by subjective MT. cTBS is expected to induce LTD (whereas intermittent TBS should produce LTP) in a given brain area, and similar effects have been observed in humans by using continuous or intermittent TBS, respec-

tively.<sup>93–96</sup> On these bases, Hanlon et al performed a single-blind, sham-controlled, crossover study to test the efficacy of cTBS over MPFC to modulate craving in cocaine-dependent subjects.<sup>92</sup> Craving was evaluated through self-report (score 0–10) three times before and three times after cTBS sessions. They recruited eleven chronic cocaine users, who underwent behavioral assessment and urine drug screens before treatment with TMS–blood-oxygen-level dependent (BOLD) scanning. Then, each subject underwent both real and sham rTMS administered over FP1 (landmark based on an EEG 10–20 system). Subsequently, another TMS/BOLD scan was acquired. To obtain an estimate of LTD induced by cTBS, the researchers compared the evoked BOLD signal after real/sham stimulation to the evoked BOLD signal pre-real/sham cTBS, and the same procedure was applied for craving. The results showed lower TMS-evoked activity in the cortical area near the coil (MPFC), as well as in projections to arginine vasotocin after real cTBS and a greater reduction than sham cTBS in the Insula, middle temporal gyrus, thalamus, and caudate. Moreover, they found an increase in craving after sham stimulation, but no significant difference in mean scores was found between the two groups.

Despite the small sample, this study offered a new contribution and perspective to the stimulation models implemented, since instead of stimulating the DIPFC network and amplifying executive cortical control through LTP plasticity, they targeted the MPFC, in order to attenuate limbic drive circuits through LTD-like plasticity. Further, Hanlon et al reported similar encouraging results on the MPFC.<sup>97</sup>

## Discussion

In this paper, we reviewed studies that investigated the potential of rTMS in the treatment of cocaine addiction. We reviewed protocols of stimulation delivered, outcomes used, and results observed. Despite CUD representing a world health emergency associated with high relapse rates (short-term relapse rates can reach 75%) significant disability, and substantial mortality, only six studies had explored the effects of TMS in CUD.<sup>98</sup> Moreover, there has been no US Food and Drug Administration-approved pharmacotherapy to date, and behavioral approaches to chronic cocaine use have had limited success.

Studies that investigated the therapeutic potential of TMS had generally small samples, were variable in the protocol of stimulation applied, and different in the measurement of outcomes considered. An important issue concerns the study design applied. From this revision of the literature, it emerged that only two studies provided a sham control group,



an element that maximizes methodological control, allowing evaluation of the placebo effect so as to derive the real effect of treatment implemented (ie, TMS). In terms of stimulation paradigms, studies differed in both coil employed and parameters adopted. The majority of rTMS studies in CUD have used the figure-of-8 coil to target the DIPfCx (left side), a central node in the frontostriatal network whose functionality is inhibited in addiction disorders.<sup>8,9</sup> Cortical dysfunction may account at least in part for the impaired executive control that is required to resist drug-related stimuli and cease drug-seeking behavior. For this reason, papers reviewed here aimed at prefrontal brain regions, in order to enhance cortical activity, improve behavioral control, and through this inhibit drug intake. From a neurobiological perspective, the clinical beneficial effects of TMS over DIPfCx are supported by the evidence, which demonstrated the enhancement of dopaminergic activity in the midbrain (nucleus accumbens), which is depressed in addiction.<sup>64,65–99</sup> Two studies implemented the H-coil in the treatment of cocaine addiction, finding a significant reduction in craving and intake.<sup>86,87</sup> However, only one study considered the sham group, reporting a lasting reduction in cocaine intake, but no difference between the real and the control groups.<sup>87</sup> The small sample, however, does not permit any firm conclusion on the efficacy of rTMS in the treatment of cocaine addiction, but results are nevertheless encouraging and foster future investigations. Another study changed the theoretical model by using bursts of pulses (cTBS) over the MPfCx.<sup>92</sup> This new model started from the hypothesis that the MPfCx is the primary cortical input to the ventral striatum, a central node in elaborating the salience of drug-related stimuli and the motivation/drive for drug seeking. This hypothesis is supported by a previous study, which demonstrated that LTP-like (10 Hz) rTMS to the MPfCx in a group of eleven healthy non-drug-using subjects was associated with a significant reduction in DA-binding potential in the dorsal striatum, reflecting a release of DA in these areas.<sup>98</sup> Despite the small sample, this new approach could provide a novel efficacious strategy to target the areas involved in craving for cocaine, and reiterates the key role played by impoverished DA transmission in these effects.<sup>22</sup>

The frequency of stimulation observed in the studies revised was 10–20 Hz, with one to 12 sessions. The intensity of stimulation, varied from 90% to 120% of MT. In all studies, the targeted area was identified through scalp landmarks, and only one study used neuronavigation to enhance accuracy in targeting the selected brain region to be stimulated.<sup>85,99</sup> The total number of pulses, a key factor in stimulation efficacy, varied and comprised between 600 and 2,400 pulses/session.<sup>100–102</sup> For these reasons, all studies

reviewed implemented a repetitive-stimulation protocol for several sessions, and this is one of the areas that should be investigated further in future studies to achieve long-lasting effects.<sup>39</sup> However, none of these studies has been replicated so far and the variability of the stimulation protocol implemented does not allow firm conclusions. Another important factor concerns the measurements of outcome and the follow-up assessment along the timeline. Half the studies used a self-report scale (VAS) as a measurement for craving. This is a construct developed to define and evaluate the desire/drive to take the substance of abuse reported by the addicts, and thereby it is a subjective measure that correlates with clinical effects and relapse rates.<sup>31,33</sup> Only two studies of six were objective markers of intake consisting in urine drug tests and hair analysis used. Finally, the timeline of the experimental procedure must be considered.<sup>85,87</sup> Most of the studies revised evaluated the TMS effects after treatment, and only one study performed 3- and 6-month follow-up.<sup>87</sup> This aspect must be evaluated carefully for short- and long-term effects so as to modulate the protocol and maximize the stimulation effects.

## Conclusion

We observed encouraging but preliminary evidence of efficacy of rTMS in treating behavioral and psychological symptoms of cocaine addiction. However, the very small samples and lack of methodological control do not permit identification of a specific protocol of stimulation as superior vs others, although the Pfcx appears to be the brain area targeted and with solid neurobiological rationale promises to yield more favorable outcomes in terms of reduction of cocaine intake in future.<sup>22,44,92</sup> Further studies are needed, and should employ standard methodological procedures to find the exact location of targeted areas to improve effectiveness of stimulation, consider subjective (craving) and objective (intake) measurements in relation to neurophysiologic substrates to have a comprehensive understanding of the neuropathology, and consider timeline follow-up to evaluate the lasting nature of neural changes induced by rTMS carefully. Overall, rTMS appears ready to be scrutinized with scientific rigor in a condition (ie, CUD) presently bereft of specific pharmacological and efficacious treatment.

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## Disclosure

The authors report no conflicts of interest in this work.

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## Supplementary material

**Table S1** Studies that have used TMS in the treatment of other addiction disorders

	Study	n	TMS device and parameters	Target area	Control group	Assessment	Results
Nicotine	Johann et al <sup>103</sup>	11	rTMS, 20 Hz, 90% MT	DIPfCx, left	Sham	Craving	Reduction in craving
	Li et al <sup>104</sup>	16	rTMS, 10 Hz, 100% MT	DIPfCx, left	Sham	Cue-induced craving	Reduction in craving
	Eichhammer et al <sup>105</sup>	14	rTMS, 20 Hz, 90% MT	DIPfCx, left	Sham	Craving, smoking	No effect on craving, significant reduction in smoking
	Pripfl et al <sup>106</sup>	14	rTMS, 10 Hz, 90% MT	DIPfCx, left	Sham	Cue-induced craving	Reduction in cue-induced craving
	Hayashi et al <sup>107</sup>	10	rTMS, 1 Hz, 110% MT	DIPfCx, left	Sham	Cue-induced craving + fMRI	Reduction in cue-induced craving and reduction in fMRI signal in OfCx
	Rose et al <sup>108</sup>	15	rTMS, 1 Hz, 10 Hz, 90% MT	SFG, MCx	Randomized open-label crossover	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
	Amiaz et al <sup>160</sup>	48	rTMS, 10 Hz, 100% MT,	DIPfCx, left	Sham	Cue-induced craving, cigarette consumption	Reduction in cue-induced craving and cigarette consumption
	Wing et al <sup>109</sup>	15	rTMS, 20 Hz, 90% MT	DIPfCx, left/right	Sham	Craving, smoking	Reduction in craving, no effect on smoking
	Prikryl et al <sup>110</sup>	35	rTMS, 10 Hz, 110% MT	DIPfCx, left	Sham	Smoking	Reduction in smoking
	Dinur-Klein et al <sup>61</sup>	115	H-coil, 1/10 Hz, 110% MT	DIPfCx, bilateral, ICx	Sham	Cigarette consumption, craving	Reduction in craving and cigarette consumption after 10 Hz rTMS
Alcohol	Trojak et al <sup>111</sup>	37	rTMS, 1 Hz, 120% MT	DIPfCx, right	Sham	Craving	No effect on craving
	Addolorato et al <sup>112</sup>	11	Deep rTMS, 10 Hz, 100% MT	DIPfCx, bilateral	Sham	Intake, SPECT (DAT)	Decrease in alcohol intake and DAT availability
	Mishra et al <sup>58</sup>	45	rTMS, 10 Hz, 110% MT	DIPfCx, right	Sham	Craving	Reduction in craving
	Mishra et al <sup>113</sup>	20	rTMS, 10 Hz, 110% MT	DIPfCx, right/left	Randomized double-blind	Craving	Reduction in craving after rTMS in both conditions
	Herremans et al <sup>114</sup>	36	rTMS, 20 Hz, 110% MT	DIPfCx, right	Sham	Craving	No effect on craving
	Herremans et al <sup>115</sup>	29	rTMS, 20 Hz, 110% MT	DIPfCx, right	Sham	Craving	No effect on craving
	Herremans et al <sup>116</sup>	26	rTMS, 20 Hz, 110% MT	DIPfCx, right	Sham	Cue-induced craving	No effect on craving
	Höppner et al <sup>117</sup>	19	rTMS, 20 Hz, 90% MT	DIPfCx, left	Sham	Craving	No effect on craving
	Ceccanti et al <sup>57</sup>	18	rTMS, 20 Hz, 120% MT	MPfCx	Sham	Craving	Reduction in craving and drinking days
	del Felice et al <sup>118</sup>	17	rTMS, 10 Hz, 100% MT	DIPfCx, left	Sham	Craving, consumption	No effect on craving
Heroin	Shen et al <sup>63</sup>	20	rTMS, 10 Hz, 100% MT	DIPfCx, left	Sham	Cue-induced craving	Reduction in cue-induced craving
Methamphetamine	Li et al <sup>62</sup>	10	rTMS, 1 Hz, 100% MT	DIPfCx, left	Sham	Craving	Increase in craving
	Su et al <sup>119</sup>	30	rTMS, 10 Hz, 80% MT	DIPfCx, left	Sham	Cue-induced craving	Reduction in cue-induced craving

**Abbreviations:** rTMS, repetitive transcranial magnetic stimulation; MT, motor threshold; DIPfCx, dorsolateral prefrontal cortex; ICx, insular cortex; SFG, superior frontal gyrus; MCx, motor cortex; MPfCx, medial prefrontal cortex; fMRI, functional magnetic resonance imaging; SPECT, single-photon-emission computed tomography; OfCx, orbitofrontal cortex.

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