Current Addiction Reports (2019) 6:165–174
https://doi.org/10.1007/s40429-019-00266-y

GAMBLING (L CLARK, SECTION EDITOR)

Non-invasive Neuromodulation in Problem Gambling: What Are the Odds?

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Published online: 20 July 2019

Abstract

Purpose of Review Non-invasive neuromodulation as a potential therapeutic target in addiction treatment is a fast-growing, but nascent research field. With gambling disorder as the first behavioral addiction, the goal of this review is to provide an overview of the current state-of-the-art of neuromodulation in substance use disorders and gambling disorder.

Recent Findings Only a few neuromodulation studies in gambling disorder are present, most of these are single-session studies. Effects of rTMS on craving have been described, but large placebo effects are also present, indicating a need for larger, blinded, multiple-session neuromodulation trials.

Summary The field of neuromodulation in gambling is in its infancy, given the limited number of studies, with small sample sizes. The effects that neuromodulation can have on diminishing craving and improving cognitive functions in substance use disorders are promising. As these factors also play a role in relapse in gambling disorder, these findings in SUDs indicate that investment in larger studies in gambling disorder, focusing on both clinically relevant outcome measures and on intermediate working mechanisms like craving and cognitive functions, is warranted.

Keywords Non-invasive neuromodulation · Neurostimulation · Pathological gambling · Cognition · Craving · rTMS · tDCS

Introduction

Neuromodulation as an add-on treatment in addictive disorders is gaining momentum in clinical addiction research. In recent years, more and more small-scale trials, including clinical trials with surrogate clinical outcome measures like craving, and trials without an adequate control condition, have been performed. On the other hand, the number of large-scale sham-controlled trials with outcome measures focused on treatment success (e.g., reduced substance use; relapse) still is limited. With the introduction of gambling disorder into the category of substance-related and addictive disorders in the DSM-5, the question arises what these findings on neuromodulation in substance-related disorders imply for gambling disorder. In gambling disorder, studies of neurocognitive functioning have revealed similar impairments as in substance-related disorders [1•, 2–7], most consistently in the areas of executive functioning like behavioral impulsivity—response inhibition, planning, cognitive flexibility, and more motivational cognitive functions related to reward processing or reward sensitivity, like decision-making and delay discounting. These cognitive functions are malleable by neuromodulation techniques [8••], leading to the question whether neuromodulation may also be a technique which could improve neurocognitive functions in gambling disorders, and in this way, diminish relapse—by influencing some of the working mechanisms that lead to relapse [9–11]. This short review focuses on how neuromodulation studies in gambling disorders can benefit from the current state-of-the-art in neuromodulation in substance-related disorders, and what areas are most promising for future studies employing neuromodulation in gambling disorder.

This article is part of the Topical Collection on *Gambling*

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Non-invasive Neuromodulation in Addiction: Methods

Two main types of non-invasive neuromodulation are currently employed in addictive disorders: transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS). For these two types of neuromodulation, a variety of stimulation settings can be used, and different neural targets can be addressed. For TMS, repeated TMS (rTMS) induces brief electrical currents in the cortical tissue, due to brief magnetic pulses generated by the TMS coil. TMS can be applied at high frequency (usually 10–20 Hz), leading to an increase in excitability of the targeted cortical area, or at low frequency (e.g., 1 Hz), leading to a decrease in excitability of the targeted area in the brain [12]. High-frequency rTMS is an FDA-approved treatment method for treatment-resistant depression [13], and recently has also been approved by the FDA for obsessive compulsive disorder, as indicated on their website [14]. Besides high- and low-frequency stimulation, theta burst stimulation (TBS) is used as a distinct TMS protocol, in which patterned stimulation is applied, by bursts of very short trains of stimulation—with three pulses delivered with a frequency of 50 Hz and an inter-burst interval of 200 ms [15]. When applied as an intermittent protocol (iTBS), the effect is excitatory while with continuous TBS (cTBS) is inhibitory [15]. In rTMS studies in substance use disorders (SUD), the most frequent placement of the TMS coil is over the dorsolateral prefrontal cortex (DLPFC), either applied at the left or right side of the skull—although bilateral stimulation and other cortical sites are possible as well.

tDCS is a neuromodulation technique in which a small electrical current (1–2 mA) is induced through placement of a pair of saline-soaked sponge electrodes, which are again usually placed over the DLPFC. Unlike rTMS, which leads to action potentials in neuronal axons, tDCS only leads to modulation of neuronal excitability by this weak electrical current, through depolarization or hyperpolarization of the resting membrane potential [16]. In-depth review of all possible settings of rTMS and tDCS is beyond the scope of this article. For gambling disorder, a relevant question is whether neuromodulation techniques can add to the current arsenal in treatment methods. For this purpose, disease markers that have been related to the course of SUDs, or gambling disorder, and that have been studied in neuromodulation studies in SUDs, are summarized and discussed below. The current neuromodulation literature in SUDs can be divided into studies that have focused on the effects of neuromodulation on (1) craving, (2) cognitive functions, including executive functions and reward processing, and (3) treatment success related factors like relapse or treatment retention [for reviews, see 8••, 17, 18]. Neuromodulation studies in gambling disorder are discussed where such studies exist, or else implications of findings in SUDs for GD are presented.

Effects of Neuromodulation on Craving

Studies using non-invasive neuromodulation in SUDs mainly focus on craving as an outcome measure. An extensive body of literature indicates that both TMS and tDCS reduce craving, as indicated in numerous literature reviews [18–25, 26•]. However, caution is needed since these reviews point towards substantial variability among study results, and identify sources of heterogeneity between studies in many study characteristics including stimulation parameters, target area, method of craving assessment, and clinical patient characteristics. So far, three meta-analyses have been conducted on this topic. The first included studies using either tDCS or TMS, and included studies focusing on craving for substances but also food [17]. In this meta-analysis, a medium effect size was reported (Hedge's $g = 0.476$) in favor of active stimulation compared with sham stimulation in reducing craving. The other two, more recent meta-analyses narrowed down their inclusion criteria by including only randomized controlled trials using rTMS as the neuromodulation method. One found no overall difference between active and sham rTMS (Hedge's $g = 0.043$), but further analyses based on type, site, and substance found that active stimulation was superior to sham stimulation in studies that stimulated the right DLPFC [27••]. The other meta-analysis found a medium effect size (Hedge's $g = 0.75$) favoring active stimulation over placebo; when distinguishing nicotine use disorder and alcohol use disorder, the effect size was large for nicotine (Hedge's $g = 1.00$) and no favorable effect was present for alcohol (Hedge's $g = -0.06$) [28]. The contradictory conclusions of these meta-analyses further highlight the variability in the effects of neuromodulation on craving in SUDs.

In gambling disorder, craving and its neural equivalent, cue reactivity, resemble the findings on the role of craving and cue reactivity in SUDs. Cue reactivity is the reactivity in the brain to addiction-relevant cues, compared with neutral, non-addiction-related cues [29, 30]. For instance, increased neural cue reactivity in the striatum, putamen, orbitofrontal cortex, and insular cortex has been reported. I.e., when disordered gamblers are confronted with relevant gambling related cues, subcortical and fronto-striatal circuitry is increased in activity, and this is linked to higher self-reported craving [3, 31]. Only very recently, the first pilot studies on neuromodulation and its effects on craving in gambling disorder are emerging. Gay and colleagues [32••] studied 22 disordered gamblers who were in treatment, finding that a single-session high-frequency rTMS (10 Hz, 94 trains of 3.2 s) over the left DLPFC reduced cue-induced craving more than placebo (sham) stimulation. This study had a cross-over design and used a commercial sham coil in combination with local electrical stimulation with electromyography electrodes using a transcutaneous electrical nerve stimulation (TENS) stimulator to optimize blinding. This advanced form of placebo stimulation prevents that

participants in a cross-over study can discern active from sham stimulation by the differences in sensation on the skin. The findings for the active condition in this study thus cannot be attributed to placebo effects or unblinding; indeed, only 23% of participants guessed their stimulation allocation correctly. A further strength of this study was that neuronavigation was used to locate the DLPFC, thus optimizing the targeting of the stimulation site. A limitation of this study is the clinical validity of the outcome measure: the effects on cue-induced craving were measured directly after stimulation, but no changes in gambling behavior were found between active and sham rTMS in the seven days after stimulation.

In a study in 30 disordered gamblers, using a cross-over design with sham and active right DLPFC rTMS (1 Hz, 6 min), reductions in craving were present in both the active and sham conditions [33••]. The large placebo effect in this study indicates that blinding in neuromodulation trials is of special importance. Such placebo effects have also been observed in pharmacological trials in gambling disorder, leading to speculation that gambling disorder is a condition that may be especially prone to placebo effects. This could be related to cognitive misperceptions present in gambling disorder, which for instance refer to thinking that one has control over random events present in gambling. As the allocation to placebo or active condition is also dependent on chance, specifically disordered gamblers may more frequently have a strong belief that they "are lucky," and are receiving the active medication or active neuromodulation. One other study investigated the effects of different forms of TMS on a construct related to craving, "desire to gamble," and on gambling behavior itself [34•]. In this study in nine disordered gamblers using a cross-over design, high-frequency rTMS (10 Hz, three times 15 trains of 1 s) over right medial prefrontal cortex (mPFC) was compared with continuous theta burst TMS (cTBS: three times 50 Hz triplets repeated at 5 Hz, 20 s) over right DLPFC as well as sham stimulation (vertex stimulation with an 8-shaped coil, perpendicular to the target area). The right DLPFC stimulation led to a decrease in desire to gamble scores after a session of slot machine play, whereas cTBS diminished diastolic blood pressure after slot machine play. We consider this study further in the sections on cognition and relapse.

Neuromodulation and Effects on Cognition

The dorsolateral prefrontal cortex (DLPFC) has a crucial role in higher cognitive functions like executive functions [35]. Executive functions have been shown to be impaired in SUDs [36], and further related to relapse in SUDs [9]. Enhancing DLPFC activity could result in increased cognitive functioning, which may be beneficial for treatment outcome in SUDs. Indeed, positive effects of non-invasive neuromodulation in SUD have been reported [37–49], as well as no effect [38, 41, 42, 44, 47, 50–54] and even in some rare cases negative effects [38, 43, 55].

Systematic reviews [8••, 26•, 56] discussing these studies in more depth highlight mostly promising effects on executive or cognitive functioning, but also point to methodological variability between studies such as duration of sessions, number of sessions, target areas, and neuromodulation as add-on treatment or as a standalone intervention, all impairing comparability. In addition, most studies have small sample sizes, there is a lack of double-blind sham-controlled studies, and different neurocognitive tasks are implemented to measure constructs like decision-making and response inhibition. Even in instances when similar tasks are used, the outcome measures employed can differ between the studies. Differences in population characteristics such as treatment seeking status, duration of abstinence, and type and severity of substance use may influence the effect of neuromodulation on cognitive functions. To shed light on these questions, standardized neuromodulation protocols are recommended. In general, the field needs larger sham-controlled clinical trials in order to firmly establish the effects of neuromodulation on executive functions; however, most studies that are currently present do indicate a positive effect of neuromodulation on cognitive functions in SUDs.

As outlined in the introduction, disordered gambling has been associated with diminished cognitive-motivational functioning, as most consistently shown in executive functions and decision-making [1•, 2–5]. These functions in turn have been linked to relapse in SUDs [9], and in disordered gambling [10, 11]. Thus, improving cognitive-motivational functioning in disordered gambling may improve treatment effects. The number of studies investigating neuromodulation in disordered gambling is very limited as of yet, and for effects on cognitive functions, only three published studies are present: A study performed by Soyata and colleagues focused on the effects of tDCS on decision-making and flexibility in 20 disordered gamblers, using a cross-over design. Compared with sham, tDCS (anode right DLPFC, 2 mA, 35 cm^2, 20 min) over the right DLPFC resulted in improvement in decision-making as measured with the Iowa gambling task, and in improvement of cognitive flexibility as measured with the Wisconsin Card Sorting Test [57••]. However, no long-term cognitive outcomes or clinical measures were included in this study, which can be viewed more as a neuroscientific study into working mechanisms of tDCS in gambling disorder. The study by Zack and colleagues, discussed in detail in the section on craving and neuromodulation above, indicated no changes of either mPFC high-frequency rTMS or cTBS on impulsive choice as measured with the delay discounting task, whereas interference effects on the Stroop became larger, contrary to expectations [34•]. Finally, Dickler et al. [58] describe the effect of one anodal tDCS session (1 mA, 35 mm^2, 30 min) over the right DLPFC on gamma-aminobutyric acid (GABA), glutamate, and

N-acetyl aspartate (NAA) levels in the right DLPFC and right striatum. Active stimulation increased GABA concentrations in the right DLPFC; however, no significant changes in glutamate and NAA concentrations were observed. Also, no changes in metabolite concentrations were observed in the right striatum. Furthermore, correlations were performed between behavior (risk taking as assessed with the BART and impulsivity as assessed with the BIS-11) and metabolite levels during active stimulation. Positive correlations were found between risk taking and prefrontal glutamate, risk taking and striatal GABA, and impulsivity and striatal NAA. Authors suggest this implicates that when gambling disordered patients are more impulsive or more risk taking, they were more likely to respond to tDCS; however, no direct comparison was made for correlations between metabolite concentrations and sham stimulation.

Effects of Non-invasive Neuromodulation on Relapse

Substance use outcome measures have been reported in only a minority of neuromodulation trials in SUD populations [for reviews, see 26•, 59••]. We will here elaborate on a few clinical trials with substantial (1–12 months) follow-up periods. For tDCS, one study applied five sessions of standalone tDCS treatment to participants that smoked at least ten cigarettes per day. Active stimulation significantly decreased cigarettes smoked per day and was modified by the level of motivation to quit smoking at baseline [60]. Of the four studies that applied tDCS in alcohol-dependent patients as add-on treatment with clinically relevant follow-up periods, two reported positive results on relapse [54, 61] and two reported no effect of tDCS compared with placebo on relapse [47, 52]. For an overview of these studies and their stimulation protocol, see Table 1. Altogether, based on the mixed results of the limited available studies using tDCS to reduce substance use, it is currently premature to draw firm conclusions on efficacy.

Next to tDCS, several clinical trials in SUDs with rTMS are present. Three larger rTMS studies in heavy smokers were conducted. The first showed significantly less relapse during treatment, although at follow-up, no significant differences between groups were found [62]. Another study found evidence for HF compared with LF and sham regarding nicotine intake, response rate, and reduction in cigarettes consumed at six months follow-up [63]. The third study did not find differences in cigarette consumption at six-month follow-up [64]. Regarding alcohol as substance of use, two clinical trials are available. The first study showed a positive effect on several outcomes related to alcohol use or relapse during the four-week treatment, but no longer follow-up period was conducted in this study [65]. The other study found decreased number of drinks consumed daily up to three months in the active group, while this pattern was not found in the sham group

Table 1 Overview of studies using tDCS

Study	Substance	Stimulation protocol	Treatment type	Number of sessions	Outcome measure	Follow-up period	Effect
Brangioni et al., 2018 [51]	Nicotine	Anodal left DLPFC, 1 mA, 35 cm^2, 20 min	Stand alone	5	Cigarettes smoked per day	1 month	Sham > active
Klauss et al., 2014 [40]	Alcohol	Anode right DLPFC, cathode left DLPFC, 2 mA, 35 cm^2, 13 min on: 20 min off: 13 min on	Add-on	5	Relapse (not further specified)	6 months	Sham > active
Klauss et al., 2018 [52]	Alcohol	Anode right DLPFC, cathode left DLPFC, 2 mA, 35 cm^2, 20 min	Add-on	10	Relapses (first episode of return to the previous uncontrolled pattern of alcohol use) Time to relapse	3 months	Sham > active
Den Uyl et al., 2017 [38]	Alcohol	Anode left DLPFC, 2 mA, 35 cm^2, 20 min	Add-on	4		3 months	Active = sham
Da Silva et al., 2013 [34•]	Alcohol	Anode left DLPFC, 2 mA, 35 cm^2, 20 min	Add-on	5	Relapse (not further specified)	4 weeks	Active = sham

Abbreviation: DLPFC, dorsolateral prefrontal cortex

(note however that no comparison between the active and sham group was conducted) [66]. Besides nicotine and alcohol, two pilot studies in cocaine use disorder are present. In the first study, outpatient cocaine-dependent individuals showed decreased cocaine intake in the active group and not in the placebo group (note: direct comparison between groups was not significant) [67]. In the second, open-label pilot study, decreased cocaine use after rTMS treatment compared with medical treatment only was found [68]. For an overview of these studies and their stimulation protocol, see Table 2. Summarizing these results, the effect of neuromodulation on substance use is scarcely studied and results are not at all conclusive. Therefore, further studies are needed before any conclusions can be drawn. The field is in need of studies that are sham controlled; at least single blind and conducted in larger clinical samples where tDCS or rTMS is added to conventional evidence-based therapies for SUD, as indicated in reviews [8••, 26•, 59••]. As reducing or abstaining from substances is the main goal of SUD treatment, it is highly relevant for future studies to include clinically relevant follow-up periods assessing substance use.

Of the three studies in gambling disorder that used neuromodulation and studied effects on actual gambling behavior or clinical gambling scales, two studies are single-session studies: one assessed acute gambling behavior (on a lab-based slot machine) directly after single-session rTMS, cTBS, or sham stimulation [34•], and no effects on acute gambling behavior were present. In another study, no effects of a single session of left DLPFC stimulation vs sham stimulation on gambling behavior in the week after stimulation were present [32••]. Finally, in a case series study in five disordered gamblers, effects of 15 daily sessions with deep rTMS, using an H1 coil, with a 1-Hz inhibitory DLPFC protocol were investigated. This case series in four participants (the fifth patient dropped out) did result in improvement on clinical scales, ranging from the Hamilton Depression Rating Scale to the Yale-Brown Obsessive Compulsive Scale, a non-specified visual analogue scale, and the South Oaks Gambling Screen after the last rTMS session [69]. Although the authors report diminished scores after 15 sessions (in three patients) and after two session (one patient), information from colaterals indicated no improvement in problem gambling. This led the authors to conclude that the 1-Hz stimulation was not effective, and that an excitatory stimulation (e.g., 10 Hz) may have differential effects. See Table 3 for an overview of the studies conducted in gambling disorder.

Clearly, from the first two studies, it is evident that these studies were not clinical trials, designed to investigate long-term effects of neuromodulation on diminishing problematic gambling. The third case series study actually was the first one to employ TMS in gambling disorder, but only concerns four disordered gamblers. Thus, the first clinical trial studies are still needed addressing the clinical potential of neuromo dulation in gambling disorder.

Table 2 Overview of studies using rTMS

Study	Substance	Stimulation protocol	Treatment type	Number of sessions	Outcome measure	Follow-up period	Effect
Trojak et al., 2015 [53]	Nicotine	1 Hz, 6 trains of 60 s over the right DLPFC	Combined with nicotine replacement therapy	10	Abstinence	1 month	Active = sham
Dinur-Klein et al., 2014 [63]	Nicotine	HF: 10 Hz, 33 trains of 3 s or LF: 1 Hz, 10 min over the lateral PFC and insula with an H-coil	Stand alone	13	Cigarettes consumed	6 months	Sham > active
Amiaz et al., 2009 [64]	Nicotine	10 Hz, 20 trains of 5 s over the left DLPFC	Stand alone	10 (followed by a maintenance phase of 4 sessions in 1 month)	Cigarette consumption	6 months	Active = sham
Addolorato et al., 2017 [65]	Alcohol	Deep high-frequency rTMS (10 Hz, 20 trains of 5 s, bilateral DLPFC with H-coil)	Add-on	12	Abstinence	1 month	Sham < active
Ceccanti et al., 2015 [66]	Alcohol	20 Hz, 30 trains of 2.5 s over the medial PFC	Add-on	10	Number of drinks consumed	3 months	Sham > active
Bolloni et al., 2016 [67]	Cocaine	10 Hz, 20 5-s trains over the bilateral PFC	Add-on	12	Cocaine intake	6 months	Sham > active
Terraneo et al., 2016 [68]	Cocaine	15 Hz, 40 trains of 4 s over the left DLPFC	Add-on	10	Cocaine intake	2 months	Treatment as usual > active

Abbreviations: *DLPFC*, dorsolateral prefrontal cortex; *HF*, high frequency; *LF*, low frequency; *PFC*, prefrontal cortex

Table 3 Overview of studies performing NIBS with gambling disorder

Study	Stimulation technique	Target area	Stimulation protocol	Treatment type	Number of sessions	Outcome measure	Effect
Gay et al., 2017 [32••]	HF-rTMS	Left DLPFC	10 Hz, 110% MT, 94 trains of 3.2 s	Add-on	1	Cue-induced craving	Sham > active
						Gambling behavior in week after stimulation	Sham = active
Sauvaget et al., 2018 [33••]	LF-rTMS	Right DLPFC	1 Hz, 120% MT, 6 min	Add-on	1	Craving	Sham = active
Zack et al., 2016 [34•]	HF-rTMS	Right MPFC	10 Hz, 80% MT, 15 trains of 1 s	Stand alone	1	Desire to gamble	Sham > active
						Impulsive choice behavior assessed by the delay discounting task	Sham = active
						interference effect assessed by the Stroop task	Sham < active
						Acute gambling behavior	Sham = active
	cTBS	Right DLPFC	50 Hz triplets, repeated at 5 Hz, 80% MT, 900 pulses	Stand alone	1	Diastolic blood pressure	Sham > active
						Impulsive choice behavior assessed by the delay discounting task	Sham = active
						Interference effect assessed by the Stroop task	Sham < active
						Acute gambling behavior	Sham = active
Soyata et al., 2018 [57]	Anodal tDCS	Right DLPFC	2 mA, 35 cm^2, 20 min	Add-on	3	Net score on the Iowa gambling task	Sham > active
						Number of perseverative errors on the Wisconsin Card Sorting task	Sham > active
Dickler et al., 2018 [58]	Anodal tDCS	Right DLPFC	1 mA, 35 mm^2, 30 min	Add-on	1	Levels of N-acetyl aspartate, GABA, and glutamate in the right DLPFC and right striatum	Sham = active
Rosenberg et al., 2013 [69]	Deep TMS	Left DLPFC	1 Hz, 10 min, 110% of motor threshold, 15 daily sessions	Stand alone		Hamilton Depression Rating Scale, Hamilton Anxiety Scale, Yale-Brown Obsessive Compulsive Scale, South Oaks Gambling Screen, Dannon and Ainhold Gambling Scale Clinical Global Impression-Improvement Scale, Social Adjustment Scale, Visual Analogue Scale	Clinical scales improved, collateral information: no change in problem gambling

Abbreviations: *DLPFC*, dorsolateral prefrontal cortex; *MPFC*, medial prefrontal cortex; *rTMS*, repetitive transcranial magnetic stimulation; *HF*, high frequency; *LF*, low frequency; *cTBS*, continuous theta burst stimulation; *GABA*, gamma-aminobutyric acid

Conclusion and Discussion

In reviewing the current evidence for neuromodulation as a treatment target in addiction, and its specific implications for gambling disorder, it can be concluded that neuromodulation targets relevant working mechanisms related to development, course, and relapse in SUDs. Several reviews and meta-analyses indicate that neuromodulation in SUDs has a beneficial effect on craving and cognitive functions [8••, 18]. At the same time, the evidence for effects of neuromodulation on clinical outcome measures in addiction is still limited. For gambling disorder, a mere six studies on neuromodulation are present that investigated outcome measures ranging from gambling urges, craving, cognitive flexibility, and decision-making to gambling behavior directly following neuromodulation. Clearly, the field is in need of larger studies.

The current studies in gambling disorder all employed single-session (cross-over) designs and thus, the field is in need of studies that also focus on multiple-session neuromodulation protocols, as the potential to have longer-term effects on craving, cognition, and clinical outcome measures is higher for multiple-session neuromodulation trials. In this respect, clinical trials in depression could be used as a starting point, because rTMS is now approved in several countries as a treatment method for treatment-refractory depression. In gambling disorder, several evidence-based treatment strategies are present, with larger effect sizes for psychosocial interventions compared with pharmacological interventions [70, 71]. It is possible that the add-on of neuromodulation to psychosocial treatment methods, like cognitive behavioral therapy or motivational interviewing, may render the brain more flexible, thus enhancing treatment effects. An alternative working mechanism may be that DLPFC stimulation by rTMS or neuromodulation by tDCS may enhance cognitive control over craving, by improving DLPFC functioning. With regular rTMS targeted at the DLPFC, changes in striatal dopamine binding in depressed patients indicate that multiple sessions of high-frequency rTMS can induce an increase in striatal dopamine release [72]. Newer technological advances in neuromodulation may broaden possibilities for neuromodulation in addictive disorders as well. For example, deep rTMS has been shown to enable subcortical changes in dopamine functioning, by changing dopamine transporter availability in alcohol-dependent patients [65], and this may render larger clinical effects.

Besides the need for multiple-session rTMS studies, sample sizes need to be increased in order for the field to move beyond pilot studies, as currently, the studies are very small. In addition, rTMS seems to be associated with a high placebo response, which exists in pharmacological studies in disordered gambling as well [71]. Well-controlled trials employing sham stimulation protocols, including formal assessment of blinding in participants, are needed to overcome this problem. Cross-over designs may not be ideal for blinding, although recent studies employing commercially available sham coils in combination with local electrical stimulation with electromyography electrodes can optimize blinding [32••].

As current therapies for disordered gambling have a comparable treatment efficacy with those of SUDs and other psychiatric disorders, there is a clear possibility for the improvement of treatment effects. While neuromodulation still has a long way to go in terms of clinical evidence base in SUDs and gambling disorder, the available treatment options for addictive disorders are all cost-effective. Therefore, there is no reason why cost-effectiveness would not be possible for neuromodulation, as the availability of neuromodulation equipment, like more costly TMS machines, will increase, now that it is approved for other psychiatric disorders, like treatment-refractory depression and obsessive compulsive disorder recently.

In conclusion, although the number of studies employing neuromodulation in gambling disorder is limited, and there is no evidence yet from formal RCTs in gambling disorder, there are indications that neuromodulation can diminish craving and improve cognitive functions in gambling disorder. As evidence from SUDs regarding the effects of neuromodulation on craving and cognitive functions is promising, disordered gambling may benefit from neuromodulation, not only through a direct effect on reducing gambling problems but also through enhancing executive functions, thus improving control over craving, or through diminishing craving, potentially through subcortical changes induced by neuromodulation.

Compliance with Ethical Standards

Conflict of Interest Dr. Goudriaan reports grants from ZonMw, Health Research The Netherlands, outside the submitted work. R. S. Schluter has nothing to disclose.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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8.•• Schluter RS, Daams JG, van Holst RJ, Goudriaan AE. Effects of non-invasive neuromodulation on executive and other cognitive functions in addictive disorders: a systematic review. Front Neurosci. 2018;12:642. https://doi.org/10.3389/fnins.2018.00642 **In this systematic review (PRISMA), effects of neuromodulation on executive and related cognitive functions in substance use disorders are reviewed. In the majority of studies, either improvement or no effects are reported, whereas negative effects of neuromodulation are only present in a few studies. As gambling disorder also is associated with diminished executive functions, this review points to relevant potential working mechanisms of neuromodulation for gambling disorder.**
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