

Systematic Review

Transcranial Magnetic Stimulation for the Treatment of Gambling Disorder: A Systematic Review

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Abstract

Background: Gambling Disorder (GD) is a behavioral addiction listed within the diagnostic category of substance-related and addictive disorders. Recently, transcranial magnetic stimulation (TMS), which non-invasively stimulates the brain and has neuromodulatory properties, has emerged as an innovative treatment tool for GD, thus offering a new option for the management of this complex disorder. The present review explored the efficacy of TMS as a possible non-pharmacological treatment for GD. **Methods:** An exhaustive search was performed across the MEDLINE, Web of Science, and EMBASE databases using a specific search string related to GD and TMS. A total of 20 papers were selected for full-text examination, out of which eight fulfilled the inclusion criteria and were therefore systematically analyzed in the present review. **Results:** This review included eight studies: three randomized-controlled trials (RCTs), three non-controlled studies, one case series, and one case report. Two cross-over RCTs described a decrease in craving after high-frequency (excitatory), repetitive transcranial magnetic stimulation (rTMS) over the left dorsolateral prefrontal cortex (DLPFC) and the medial prefrontal cortex (PFC), respectively; another study applying low-frequency (inhibitory) rTMS on the right DLPFC did not find any positive effect on craving. Among uncontrolled studies, one demonstrated the beneficial effect of high-frequency rTMS over the left DLPFC, while another showed the efficacy of a continuous theta burst stimulation protocol directed over the pre-supplementary motor area, bilaterally. **Conclusion:** The included studies showed the promising effect of excitatory stimulation over the left PFC. However, further investigation is needed, particularly in terms of standardizing stimulation protocols and psychometric assessments.

Keywords: gambling disorder 1; craving 2; repetitive transcranial magnetic stimulation 3; theta burst stimulation 4

1. Introduction

Gambling disorder (GD) is a well-recognized psychiatric condition prevalent worldwide, with a prevalence in the general population of approximately 0.1–5.8% [1]. It is listed in the Diagnostic and Statistical Manual of Mental Disorders-Fifth Edition (DSM-5) under the classification of “Substance-Related and Addictive Disorders” [2], thus marking a shift from the earlier categorization as an “Impulse-Control Disorder” (DSM-IV). This reclassification underscores the recognition of behavioral addictions, alongside substance use disorders, highlighting their shared characteristics, including loss of control, craving, and significant impairment or distress [3]. GD is featured by a recurrent and persistent maladaptive gambling behavior which significantly affects personal, familial, or vocational pursuits. Core symptoms include persistent thoughts about gambling, a compulsion to gamble with escalating sums of

money to achieve the excitement desired, recurrent unsuccessful endeavors to manage or cease gambling, restlessness or irritability when trying to stop gambling, and gambling as a mean of evading challenges or alleviating feelings of guilt, helplessness, depression, or anxiety [4].

Theories and ongoing investigations propose that addictive behaviors exhibit shared neurobiological modifications in certain brain areas. It is suggested that impaired activity of the dopaminergic system is associated with the experience of craving within the reward system [5]. Craving refers to a strong and insistent desire to encounter behaviors and is recognized as a significant pathomechanism in the development of the addiction disorder [6,7]. Indeed, addiction is characterized by a state of compromised decision-making and diminished responsiveness to innate rewards, which can be attributed to the modified operation of the prefrontal cortex (PFC) and basal ganglia. Additionally, there



is an observed escalation in stress-conditioned reactions influenced by the limbic system [8]. Dopamine functions play a crucial role in different stages of drug addiction, also holding therapeutic potentials. The dopamine transporter (DAT) is responsible for controlling dopamine's activity at the synaptic level. Accordingly, in the study by Pettorruso *et al.* [9] in 2019, the authors found a decreased availability of striatal DAT in individuals with GD compared with healthy controls. They also discovered that the availability of striatal DAT exhibited an opposite relationship with the number of days devoted to gambling and the process of reward-based decision-making among individuals with GD. In this context, the discovery of decreased DAT availability in GD provides further confirmation of the significant involvement of dopamine dysregulation in this condition. Similarly, human imaging research has revealed a decline in dopamine receptors and reduced release of endogenous dopamine in the ventral striatum of individuals addicted to cocaine, heroin, and alcohol. Collectively, this evidence provides insights on the "dopamine-impooverished" state in the addicted human brain [10].

Regarding therapeutic options, although GD is considered an addictive disorder, there is currently no designated pharmacotherapy officially recommended for addressing GD. Opioid antagonists such as naltrexone and nalmefene have been suggested as potential substances for the treatment of GD. Other interventions that have shown potential benefits and have been examined as promising options include agents affecting the glutamatergic system, glutamatergic agents, and a combination of pharmacological and psychological interventions. Studies on the effectiveness of serotonergic antidepressants, opioid antagonists, and mood stabilizers showed inconclusive results; regarding psychotherapies Cognitive Behavioral therapy (CBT), family therapy and motivational interviewing are considered the most effective therapeutic strategies for treating GD [11,12]. Although further research is needed in this area, combining pharmacotherapy with psychotherapy may potentially result in improved positive outcomes rates compared with pharmacology-based treatments only [13].

Non-invasive brain stimulation techniques (NIBS) have been recently explored as potential diagnostic probe and treatment options for behavioral addictions and other psychiatric or neuropsychiatric disorders [14–18]. These techniques have been developed to study brain functions, to diagnose neurological and psychiatric disorders, and to provide treatments for various psychiatric and neurological conditions [15,16,19–21]. Among the commonly employed stimulation techniques for addiction treatment, theta burst stimulation (TBS) and repetitive transcranial magnetic stimulation (rTMS) have emerged as the most frequently adopted methods [22].

Transcranial magnetic stimulation (TMS) has demonstrated therapeutic promise in addressing substance and behavioral addictions by targeting specific regions of the

brain, either focal or wide bilateral areas. Mostly based on the frequency of stimulation (with high frequencies being excitatory and low frequencies being inhibitory), TMS can improve the reduced functionality of the prefrontal areas using excitatory protocols or it can decrease the abnormally increased functionality of the limbic system through inhibitory protocols. The application of this technique might potentially help in regulating activity in certain brain areas that have been implicated in the development of the disorders [23]. The persistent decrease in the physiological activity of the dopamine system suggests that increasing its activity to reestablish pre-drug levels might result in substantial clinical benefits, including reducing cravings, relapse, and drug-seeking/taking behaviors [24]. Moreover, previous research indicates that the mesolimbic dopamine system is "hypofunctional" in the addicted brain [25], thus suggesting that diminished dopamine functionality results in reduced engagement with stimuli unrelated to drugs and an increased susceptibility to the drug that is most frequently consumed. Consequently, it has been hypothesized that restoring dopamine function might offer therapeutic advantages in treating addiction. The PFC has a crucial role in controlling the release of dopamine in subcortical regions. Functional brain imaging, such as positron emission tomography (PET), can be applied to evaluate alterations in cerebral blood flow and glucose metabolism induced by TMS [23]. As such, TMS can be employed to enhance the endogenous activity of dopamine-containing neurons. Of note, Strafella *et al.* [26] in their study discovered that rTMS targeted to the left mid-dorsolateral prefrontal cortex was able to induce the release of dopamine in the striatal region of the human brain, thus opening a window into a potential wide range of clinical applications. From this pioneering discovery, novel targets for rTMS are under evaluation to increase its effectiveness in treating addiction, and research is ongoing to find the optimal protocol to boost dopaminergic transmission in the addicted brain. TMS can thus be considered a useful tool to test the dopamine hypothesis of drug addiction and instrumental in the search for addiction therapeutics [27].

However, although recent studies have shown evidence supporting the effectiveness of TMS in addiction, it has not yet been established as a standard treatment. Among the available publications, in 2020 Zucchella *et al.* [28] systematically reviewed studies applying rTMS or transcranial direct current stimulation (tDCS) in GD and problem gambling, identified using the PubMed, Web of Science, and Science Direct databases, from database inception to December 19, 2019. Eleven studies were analyzed, of which six were controlled and five were uncontrolled; however, the clinical and methodological heterogeneity of the included studies prevented the authors from drawing any conclusion on the efficacy of NIBS interventions for GD. Therefore, the current study aimed to provide an updated and comprehensive systematic review based on multiple

databases and not limited to clinical trials, focusing on the assessment of the efficacy of TMS protocols, specifically rTMS and TBS, for the treatment of GD.

2. Materials and Methods

2.1 Protocol

A systematic search was carried out following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) Statement [29]. The protocol was registered prior to the start of the search process. We registered our protocol on INPLASY with the following registration number: INPLASY 202310054. PRISMA checklist is shown in **Supplementary Material**.

2.2 Information Sources and Search Strategy

On May 16, 2023, we carried out a comprehensive search across the MEDLINE (via PubMed), EMBASE, and Web of Science databases. In our original protocol, we intended to incorporate PsycInfo as one of our primary databases for the literature search. However, due to the subsequent constraints on resources, we had to prioritize our database selection. To carry out our comprehensive research on the various databases, we employed the following search string: (“gambling disorder” OR “problem gambling” OR “pathological gambling” OR “compulsive gambling” OR “gambling addiction” OR “gambling addictions” OR “problematic gambling” OR “pathological gamblers” OR “problem gamblers” OR “pathological gamblers” OR “gamblers anonymous” OR “gambling addicts” OR gambling) AND (“transcranial magnetic stimulation” OR TMS OR rTMS OR “repetitive TMS” OR “theta burst stimulation” OR “theta burst” OR TBS OR cTBS OR iTBS).

The string was modified, when necessary, to accommodate the specific formatting and search parameters of each individual database. Both the process of selecting studies and extracting data were conducted by two pairs of authors (AC/CCh and ADF/GT) in a blinded manner. All discrepancies were resolved by a third expert author (CCo).

2.3 Inclusion and Exclusion Criteria

2.3.1 Design

Both randomized controlled trials (RCTs) and non-randomized controlled trials written in English were initially sought based on our protocol. Upon further screening and for a more comprehensive search, we also included case series and case studies, whereas conference abstracts, letters, commentaries, books, and chapters were excluded.

2.3.2 Population

In the initial protocol, we aimed to focus on adult patients diagnosed solely with GD or clinically significant gambling. However, during the review process, we recognized the relevance of studies that included participants also with some coexisting psychiatric conditions, given the

frequent comorbidity observed in this patient population. Therefore, as a deviation from the original protocol for the sake of completeness, we also included studies that involved adult patients with GD or clinically significant gambling, regardless of the presence of other psychiatric disorders, setting, or ongoing therapy. Pediatric or adolescent populations remained excluded, thus ensuring our focus on adult-based interventions and outcomes only.

2.3.3 Intervention

Studies that used rTMS and TBS were included. There was no restriction on the number of sessions; therefore, every study evaluating both single sessions and multiple sessions was included.

2.3.4 Comparator

No restriction on the comparator was applied. Therefore, all types of comparators were included, such as sham-stimulation, treatment as usual, waiting list, or no treatment.

2.3.5 Outcomes

The primary outcome was the efficacy of TMS in reducing gambling symptoms, which were evaluated by using self-rated and clinician-rated psychometric scales. As secondary outcomes, we assessed changes in anxiety and depressive symptoms, sleep quality, and safety outcomes, including both serious and non-serious adverse events.

2.4 Data Extraction and Analysis

Information was collected using a data extraction form located on Airtable, encompassing the following details: author, publication year, country, study design, patient characteristics, stimulation protocol (including the total number of sessions and session frequency), stimulation frequency and intensity, stimulation area, comparator, primary outcomes, and follow-up information. Data extraction was performed independently by two pairs of authors (AC/CCh and ADF/GT) and conflicts were resolved with the involvement of a third, experienced author (CCo).

2.5 Quality Assessment for Included Studies

The evaluation of risk bias was carried out utilizing the Cochrane risk-of-bias tool 2 for RCTs, while for non-controlled studies, the National Institutes of Health Quality Assessment Tool was employed [30]. The assessment of bias was carried out independently by two authors (ADF and AR), and any discrepancies were resolved through the intervention of a third experienced author (CCo).

3. Results

The search yielded an initial total of 207 results. After removing duplicates, 100 studies were screened based on their title and abstract, leading to the inclusion of 20 papers for thorough examination of their full texts. After the full-text examination, 12 studies were excluded, whereas

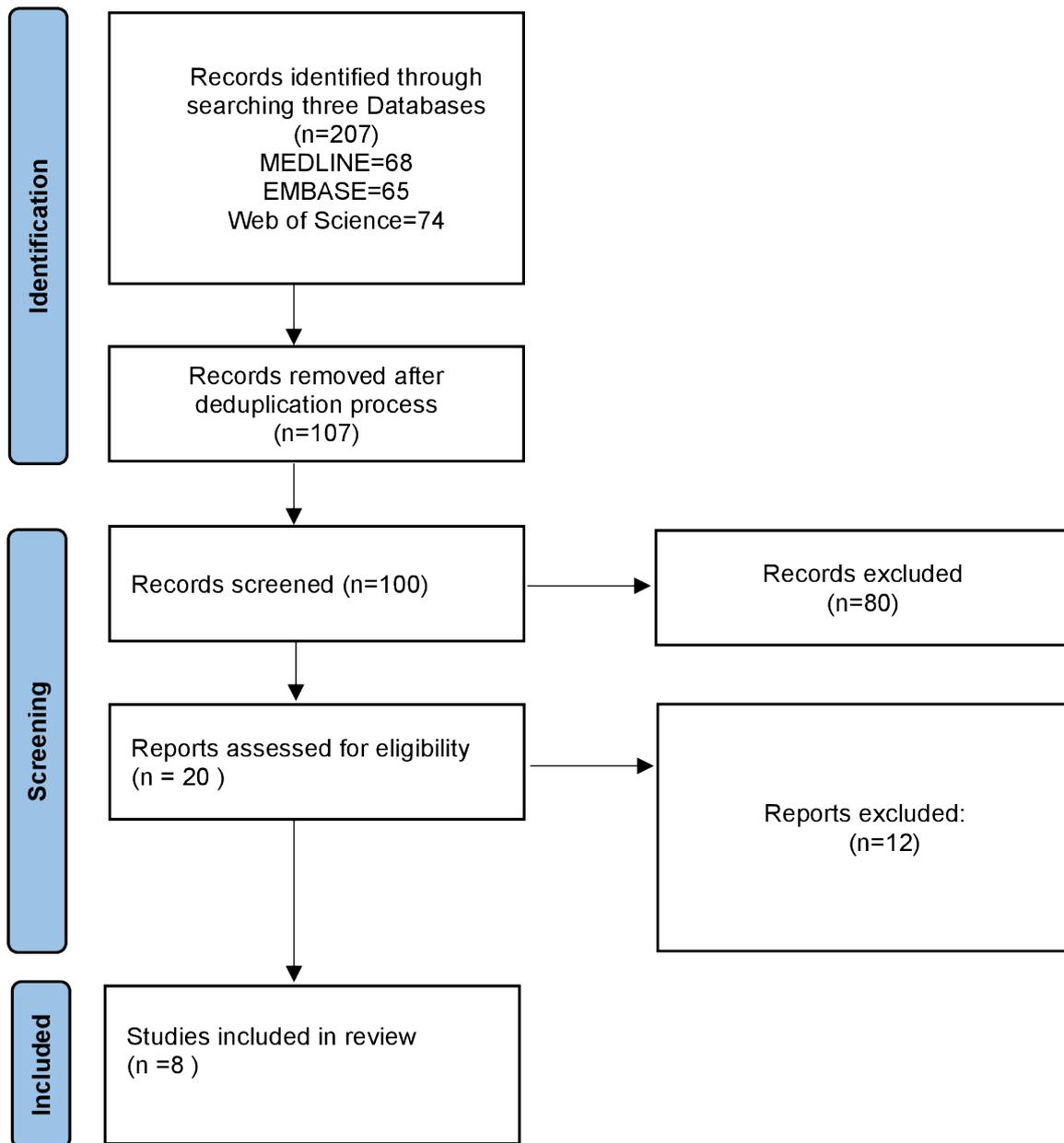


Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flowchart outlining the study selection process.

eight studies fulfilled the inclusion criteria and were consequently included in the systematic review.

Fig. 1 shows the PRISMA flowchart illustrating the search, screening, and selection process.

3.1 Study Characteristics

Three of the included studies were RCT [31–33], three were open label [34–36], one was a case series [37], and one was a case study [38]. The earliest publication date was 2013 and the most recent was 2022. In our systematic re-

view, we analyzed and synthesized studies published from 2013 to 2022. Specifically, two articles were published in 2013–2016 [33,36] one in 2017 [31], one in 2018 [32], two in 2019 [9,37], one in 2020 [34], and one in 2022 [35].

The therapeutic protocols identified were high-frequency (HF)-rTMS and cTBS. The areas of stimulation were the dorsolateral prefrontal cortex (DLPFC), the medial prefrontal cortex (mPFC), and the pre-supplementary motor area (pre-SMA). Treatment duration ranged from one day (one single session) to several weeks. Two studies used

Table 1. Description of the included studies.

Author (year)	Country	Study Design	Setting	Population	Intervention	Stimulation protocol	Comparator	Gambling-Related outcomes	Other outcomes	Timeframe for follow-up	Results
Cardullo <i>et al.</i> [37] 2019	Italy	Case series	Not specified	N = 7 (7 males)	rTMS	Sessions: twice a day for the first 5 days, then two sessions daily once a week over 8 weeks.	NA	- Gambling-Symptom Assessment Scale (G-SAS)	- Cocaine Craving Questionnaire (CCQ) - 19-item Pittsburgh Sleep Quality Index (PSQI) - Beck Depression Inventory-II (BDI-II) - Self-rating Anxiety Scale (SAS) - Symptoms checklist-90 (SCL-90) - Global Severity Index (GSI)	- Baseline - 5 days - 30 days - 60 days	- G-SAS: Improvement at each time point - CCQ: Improvement at each time point - PSQI: Improvement at each time point - SAS: Improvement at each time point - GSI: Improvement at each time point - BDI-II: improvement at each time point
				Mean Age (Standard deviation - SD): 42.14 years (5.74)	High frequency	Stimulation parameters: 100% of motor threshold, 15 Hz, 60 impulses per stimulation train.					
				Diagnosis: South Oaks Gambling Screen (SOGS) score ≥ 5	Area: left DLPFC	Inter-train interval: 15 s; 40 total trains for a session duration of 13 min.					

Table 1. Continued.

Author (year)	Country	Study Design	Setting	Population	Intervention	Stimulation protocol	Comparator	Gambling-Related outcomes	Other outcomes	Timeframe for follow-up	Results
Gay <i>et al.</i> [31] 2017	France	RCT	Not specified	N = 22 (14 males - 8 female)	rTMS	Sessions: single session	TMS-Sham	- Yale-Brown Obsessive-Compulsive Scale adapted for Pathological Gambling (PG-YBOCS) - 100-mm visual analogue scale	None	- Baseline - 7 days	- Cue-induced craving (VAS): Improvement - PG-YBOCS: No improvement - Numeric scale for desire to gamble: No improvement - Numeric scale for control to gamble: No improvement
				Mean Age (SD): 51.0 years (13.7)	High frequency	Stimulation parameters: 110 of RMT; 10 Hz; 94 trains of 3.2-s duration at 10-s intervals, for a total of 3008 pulses per session and total treatment duration of 20 min 30 ss					
				Diagnosis: DSM-IV Criteria	Area: left						

Table 1. Continued.

Author (year)	Country	Study Design	Setting	Population	Intervention	Stimulation protocol	Comparator	Gambling-Related outcomes	Other outcomes	Timeframe for follow-up	Results
Pettorruso <i>et al.</i> [9] 2019	Italy	Case study	Out-patients	N = 1 (male)	rTMS	Session: 20 sessions (twice a day, 5 days/week), then a weekly maintenance protocol (two applications/week) for 12 weeks.	None	- G-SAS (Gambling Symptom Assessment Scale)	- BDI (Beck Depression Inventory)	- T0: baseline	- No episodes of gambling relapse over six months
				Age 40 years	High frequency	Duration of each individual session: NR.		- PG-YBOCS (Pathological Gambling Adaptation of the Yale-Brown Obsessive-Compulsive Scale)	- ISI (Insomnia Severity Index)	- T1: 1 week	- Patient-reported significant decrease in gambling craving
				Diagnosis: patient with 12-year history of GD, according to DSM-5	Area: left DLPFC	Stimulation parameters: 100% of the RMT; 15 Hz; 60 pulses per train, inter train pause of 15 s, 40 stimulation trains, 2400 pulses/session.			- YMRS (Young Mania Rating Scale)	- T2: 2 weeks	- Reduced in DAT presence in striatal regions
									- DAT-SPECT (Only at T0 and T2)	- T3: 1 months - T4: 2 months - T5: 3 months - T6: 6 months	

Table 1. Continued.

Author (year)	Country	Study Design	Setting	Population	Intervention	Stimulation protocol	Comparator	Gambling-Related outcomes	Other outcomes	Timeframe for follow-up	Results
Pettorruso <i>et al.</i> [34] 2020	Italy	Open label study	Out-patients	N = 8 (1 female)	rTMS	Sessions: 20 sessions (twice a day, 5 days/week) + 24 session (two daily, once a week) in 12 weeks. Each session lasting 13 min	None	- Gambling Symptom assessment (G-SAS)	- Beck Depression Inventory	- T0: baseline	- G-SAS: Improvement at each time points;
				Mean Age (SD): 40.6 (11.2)	High frequency	Stimulation parameters: 100% of the RMT; 15 Hz; 60 pulses per train, inter-train interval of 15 s, 40 trains/session, 2400 pulses/session)		- Pathological Adaptation of the Yale-Brown Obsessive-Compulsive Scale	- Zung Self-Rating Anxiety Scale	- T1: after 2 weeks of intensive treatment phase	- Days of gambling (Timeline Back): Improvement at each time points
				Diagnosis: 5 Criteria for GD	Area: DLPFC	left		- Gambling behaviors Timeline Follow Back		- T2: after 4 weeks of rTMS maintenance treatment	- PG-YBOCS: No improvement
										- T3: after 8 weeks of rTMS maintenance treatment	- BDI: No improvement
										- T4: after 12 weeks of rTMS maintenance treatment	- SAS: No improvement

Table 1. Continued.

Author (year)	Country	Study Design	Setting	Population	Intervention	Stimulation protocol	Comparator	Gambling-Related outcomes	Other outcomes	Timeframe for follow-up	Results
Sauvaget <i>et al.</i> [32] 2018	France	RCT	Out-patients	N = 30	rTMS	Sessions: single session	TMS-Sham	- Visual Analog Scale (VAS) for craving - Gambling Craving Scale (GACS) (only 3 first questions)	- Heart rate (bpm) - Systolic blood pressure - Diastolic blood pressure	- At baseline - Before the rTMS session - Immediately after the rTMS session - Every 5 min until the craving intensity returned to the baseline level.	- VAS - cue induced craving: No differences between active and sham rTMS - GACS (gambling-related craving) - 3 items used to measure the desire to gamble: No differences between active and sham rTMS - Heart rate: No differences between active and sham rTMS - Systolic blood pressure: No differences between active and sham rTMS - Diastolic blood pressure: No differences between active and sham rTMS
				Mean Age (age interval): 33 (28–42)	Low frequency	Stimulation parameters: 120% of the RMT, 1 Hz with one train producing 360 pulses in a single 6-min session.					
				Sham arm: 39 (34.5–56)	Area: right DLPFC						
				Diagnosis: 5 or more of the DSM-IV diagnostic criteria for GD							

Table 1. Continued.

Author (year)	Country	Study Design	Setting	Population	Intervention	Stimulation protocol	Comparator	Gambling-Related outcomes	Other outcomes	Timeframe for follow-up	Results
Rosenberg <i>et al.</i> [36] 2013	Israel	Open label study	Out-patients	N = 5 (5 males)	Deep TMS	H-coil Deep H-coil stimulation/day for 15 days	None	- Yale-Brown Obsessive-Compulsive Scale (Y-BOCS)	- 24-item Hamilton Depression Rating Scale (HDRS)	- T0: baseline	SAS, Y-BOCS, VAS, DAGS, CGI-I, HDRS significantly decreased 24 h after 15 stimulation treatments but from co-lateral analysis, as opposed to improvement of scores, all patients continued gambling
				Mean Age (SD): 39 (NR)	Low frequency	Stimulation parameters: 110% of the motor threshold; 1 Hz; session duration 10 min.		- South Oaks Gambling Screen (SOGS)	- Hamilton Anxiety Scale (HARS)	- T1: 24 h after the last session	
				Diagnosis: Pathological gambling according to DSM-IV-TR criteria	Area: left			- Dannon and Ainhold Gambling Scale (DAGS)	- Clinical Impressions—Improvement Scale (CGI-I)		
								- Visual Analogue Scale (VAS)	- Social Adjustment Scale (SAS)		

Table 1. Continued.

Author (year)	Country	Study Design	Setting	Population	Intervention	Stimulation protocol	Comparator	Gambling-Related outcomes	Other outcomes	Timeframe for follow-up	Results
Salerno <i>et al.</i> [35] 2022	USA	Open label study	Out-patients	N = 6 (5 males, 1 female)	cTBS	cTBS, 10 sessions	None	- Pathological Gambling version of the Yale-Brown Obsessive-Compulsive Scale (PG-YBOCS) - Gambling Urges Questionnaire (GUQ)	- Hamilton Anxiety Scale (HAM-A) - Hamilton Depression Scale (HAM-D) - Sheehan Disability Scale (SDS) - Clinical Global Impression Scale (CGI) - Fagerström Test for Nicotine Dependence (FTND)	- T0: baseline - T1: after 10 cTBS stimulations - T2: 30 days after the end of treatment	- PG-YBOCS (evaluating severity of GD): Improvement at each time-point - CGI: Improvement between baseline and mid- and post-treatment but not mid- and post-treatment. - SDS: No improvement at each time-point - FTND: No improvement at each time-point - GUQ: No improvement at each time-point - BIS-11: No improvement at each time-point - HAM-A (anxiety): No improvement at each time-point - HAM-D (depression): No improvement at each time-point
				Mean Age (SD): 45.7 (NR)	Area: SMA bilaterally	pre- Stimulation parameters: 80% of RMT; bursts of three pulses separated by 20 ms (i.e., 50 Hz), with each triplet being repeated every 200 ms (i.e., 5 Hz). Two trains of 600 pulses each separated by 1 min (a total of 1200 pulses).					
				Diagnosis: GD according to DSM-5 criteria A history of illness of at least 1 year PG-YBOCS score of 16							

Table 1. Continued.

Author (year)	Country	Study Design	Setting	Population	Intervention	Stimulation protocol	Comparator	Gambling-Related outcomes	Other outcomes	Timeframe for follow-up	Results
Zack <i>et al.</i> [33] 2016	USA	RCT	Others (community recruited)	N = 9 (9 males)	rTMS	rTMS, single session	TMS-Sham	- Desire to gamble (VAS)	- Stroop task - Delayed discontinuing task	- Before and after each stimulation	- Desire to gamble (VAS) - rTMS: Improvement in comparison to sham
				Mean Age (SD) 43.2 (13.2)	High frequency	Stimulation parameters: 80% of the AMT; 10 Hz; Three separate epochs of rTMS were administered with a 5-min break between epochs. For each epoch, 15 sets of 10 pulses were delivered with a frequency of 10 Hz, and a 10-s break was given between sets. Total pulses 450.					
				Diagnosis: PD	Area: mPFC	cTBS, single session			- Blood pressure - Profile of Mood State (POMS)		- cTBS: No differences in comparison to sham ARCI:
					cTBS Area: right DLPFC	Stimulation parameters: 80% of AMT, Each TBS burst consisted of three pulses at 50 Hz, with each train being repeated every 200 ms (5 Hz). cTBS consisted of continuous repetition of trains for 20 s (300 pulses).			- Addiction Research Center Inventory (ARCI)		- rTMS: No differences in comparison to sham - cTBS: Improvement in comparison to sham POMS: - rTMS and cTBS: No differences in comparison to sham

DLPFC, dorsolateral prefrontal cortex; rTMS, repetitive transcranial magnetic stimulation; NA, not applicable; RCT, randomized-controlled trial; DSM-5, Disorders-Fifth Edition; GD, Gambling Disorder; RMT, resting motor threshold; cTBS, continuous theta burst stimulation; pre-SMA, pre-supplementary motor area; mPFC, medial prefrontal cortex; PD, Parkinson's disease; AMT, active motor threshold; DAT-SPECT, Dopamine transporter availability - Single-photon emission computerized tomography; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders-IV; TBS, continuous theta burst stimulation; DAT, Dopamine transporter availability; SD, standard deviations; NR, Not reported.

Table 2. Risk of bias assessment of the randomized controlled trials (RCTs), evaluated with the Cochrane Risk of Bias Tool 2.

Cochrane Risk of Bias Tool 2						
Study	Randomization process	Deviation from intended interventions	Missing outcome data	Outcome measures	Reported results selection	Overall
Gay <i>et al.</i> [31], 2017	Some concerns	Some concerns	Low	Low	Some concerns	Some concerns
Sauvaget <i>et al.</i> [32], 2018	Some concerns	Low	Low	Low	Some concerns	Some concerns
Zack <i>et al.</i> [33], 2016	Some concerns	Some concerns	Low	Low	Some concerns	Some concerns

rTMS in augmentation to pharmacological therapy [34,37], while there was one article assessing the deep ‘H coil’ TMS [36].

The following gambling-related outcome assessment scales were used: Gambling-Symptom Assessment Scale (G-SAS), Yale-Brown Obsessive-Compulsive Scale adapted for Pathological Gambling (PG-YBOCS), 100-mm Visual Analogue Scale (VAS) for cue-induced craving, Numeric scale for desire, Numeric scale for control, Gambling Craving Scale (GACS) (only the first three questions), the Yale-Brown Obsessive-Compulsive Scale (YBOCS), Gambling Urges Questionnaire (GUQ), and the Dannon and Ainhold Gambling Scale (DAGS).

A detailed description of the included studies is summarized in Table 1 (Ref. [9,31–37]).

3.2 Quality Assessment of the Included Studies

The evaluation of the potential bias in RCTs was conducted employing the Cochrane Risk of Bias assessment tool 2. [39]. All studies [31–33] were rated as having “some concerns” in domain 1 (bias arising from the randomization process). Indeed, although all the studies had implemented a randomization process, none guaranteed allocation concealment through the involvement of an external entity. Moreover, both Gay *et al.* [31] and Zack *et al.* [33] lack information regarding the applied randomization method, stating exclusively that this process had been carried out. Regarding domain 2 (risk of bias due to deviations from the intended interventions), Gay *et al.* [31] and Zack *et al.* [33], were categorized as having some concerns risk of bias, whereas Sauvaget *et al.* [32] was considered as having low risk in the same domain. All studies [31–33] showed low risk of bias in domain 3 (bias due to missing outcome data), and 4 (bias in measurement of the outcome). However, for domain 5, all studies were categorized as having “some concerns” because they did not specifically report planning the data analysis methods before the availability of the data.

A detailed description of the risk of bias assessment for the RCTs is summarized in Table 2 (Ref. [31–33]).

The evaluation of the quality of non-randomized, uncontrolled studies was conducted using the National Institutes of Health (NIH) tool [30]. Rosenberg *et al.* [36] did

not provide clear details regarding the inclusion and exclusion criteria. None of the studies, except for Rosenberg *et al.*’s, reported establishing the inclusion/exclusion criteria before enrolling patients. Regarding sample size, except for Cardullo *et al.*’s study [37], no other study conducted a calculation to estimate the number of patients needed for inclusion. In all the studies where this calculation was not made, the sample size was deemed insufficient. None of the studies mentioned any heterogeneity in the implemented interventions, except for Rosenberg *et al.*’s study, where one patient included in the analysis had twice as many sessions (30) compared with the other included patients. Furthermore, only Rosenberg *et al.*’s study had a loss of follow-up rate of at least 20%, as one out of the five analyzed patients was lost to follow-up.

All studies [35–38] conducted a statistical analysis to examine changes in various outcomes before and after treatment, providing a *p*-value. The exception was Rosenberg *et al.*’s study [36], which only reported mean values and standard deviations before and after treatment. Finally, all studies evaluated the outcomes at multiple time points, except for Rosenberg *et al.*’s study.

A detailed description of the quality assessment for the non-controlled studies is summarized in Table 3 (Ref. [34–37]).

Table 3. Quality assessment for the non-controlled studies, evaluated using the National Institutes of Health Quality Assessment Tool.

National Institutes of Health Quality Assessment Tool	
Study Name	Overall Judgment
Cardullo <i>et al.</i> [37], 2019	Good
Pettoruso <i>et al.</i> [34], 2020	Good
Rosenberg <i>et al.</i> [36], 2013	Poor
Salerno <i>et al.</i> [35], 2022	Fair

3.3 Repetitive Transcranial Magnetic Stimulation

3.3.1 RCTs

Three RCTs with a cross-over design evaluated the effectiveness of a single session of rTMS in GD [31–33].

Zack *et al.* [33] investigated the impact of high frequency-repetitive transcranial magnetic stimulation (HF-rTMS) (10 Hz) targeting the mPFC in nine patients [40]. The stimulation intensity was established at 80% of the active motor threshold (AMT), which denotes the minimum TMS intensity required to induce motor evoked potentials in the designated muscle during muscle contraction, by employing single-pulse stimuli on the motor cortex. The study reported a significant reduction in the desire to gamble, as measured by a VAS, during the post-game assessment. However, no significant difference was observed in the other outcomes measured by the Addiction Research Center Inventory (ARCI) and the Profile of Mood States (POMS), as well as in heart rate and systolic/diastolic blood pressure.

Similarly, Gay *et al.* [31] evaluated the impact of a solitary session of HF-rTMS (10 Hz) directed at the left DLPFC in 22 patients with GD. The stimulation was administered at an intensity of 110% of the resting motor threshold (RMT), which is defined as the AMT but measured during muscle relaxation [40].

The outcomes indicated noteworthy statistical differences between the experimental and control groups for cue-induced craving, as measured through a VAS. However, no differences were observed in gambling behavior, including the severity of the disease evaluated through the PG-YBOCS, and the desire and control to gamble assessed through the respective scales.

In contrast, Sauvaget *et al.* [32] conducted a study in which they administered a solitary session of inhibitory (low frequency) rTMS (LF-rTMS) (1 Hz) to the right DLPFC in 30 patients with GD. The stimulation was administered at an intensity level equivalent to 120% of the RMT. The results did not show a significant difference between rTMS and sham (fictitious) stimulation in the cue-induced craving levels, as measured through a VAS, and the desire to gamble, assessed through the three items of the GACS. No statistical difference was also reported in the heart rate, systolic blood pressure, and diastolic blood pressure.

3.3.2 Open Label Studies

Rosenberg *et al.* [36] conducted the first open-label trial, treating five patients with GD, with 15 daily sessions of deep H-coil LF-rTMS (1 Hz) targeting the left DLPFC. The stimulation intensity was established at 110% of the Motor Threshold (MT), and each session lasted for a duration of 10 minutes. Although there was a statistically significant improvement across different psychometric scales, 24 hours after the fifteenth stimulation, all patients continued to gamble, thus challenging the improvement achieved. As a result, the authors deemed the results as negative.

In 2020, Pettorruso *et al.* [34] performed research involving a group of eight individuals diagnosed with GD, following a similar methodology to their group study in 2019. The treatment consisted of 44 sessions of HF-rTMS (15 Hz), targeting the left DLPFC. The outcomes revealed

a statistically significant improvement in the G-SAS and Days of Gambling (assessed through the Timeline Follow Back method) scales at all study time points. However, no improvement was observed in other psychometric scales, such as the PG-YBOCS, the Beck Depression Inventory (BDI-II), and the self-rate State Anxiety Scale (SAS).

3.3.3 Case Series and Case Study

The case series published by Cardullo *et al.* [37] evaluated the effectiveness of 21 sessions of HF-rTMS (15 Hz) targeting the left DLPFC in seven men with GD and cocaine use disorder. The intervention resulted in a statistically significant improvement in gambling severity, as reflected in the G-SAS scores, as well as a reduction in cocaine craving, as indicated by the Cocaine Craving Questionnaire scores. Furthermore, the secondary outcomes, including sleep disturbance, depression, anxiety, and other negative affect symptoms, showed improvement at 5 days, 1 month, and 2 months compared with the baseline, as assessed through the Pittsburgh Sleep Quality Index (PSQI), BDI-II, SAS, and the Global Severity Index of the Symptoms Checklist 90–Revised.

In 2019, Pettorruso *et al.* [38] released a case study featuring a 40-year-old patient who had a 12-year history of GD. The study aimed to assess the effectiveness of 44 sessions of HF-rTMS at a frequency of 15 Hz, directed towards the left DLPFC. The treatment was divided into two phases: an initial phase of 20 sessions, twice a day for 2 weeks, followed by a maintenance protocol of two sessions daily, once a week, for a duration of 3 months. The stimulation intensity was set at 100% of the RMT. The study reported no relapse in gambling episodes during the 6 months following the treatment. Additionally, the authors used the single-photon emission computed tomography (SPECT) 2 weeks after the end of the treatment and observed a reduction in the DAT availability within the striatal regions 2 weeks after concluding the treatment. They noted a decrease in the availability of DAT within the striatal regions.

3.4 Continuous Theta Burst Stimulation

3.4.1 RCTs

Zack *et al.* [33] evaluated the effectiveness of cTBS in individuals with GD. The study involved one session of cTBS on the right DLPFC. The stimulation parameters encompassed an intensity set at 80% of the AMT. The results did not exhibit a difference compared with sham stimulation in terms of the urge to gamble as evaluated through a VAS. However, the same type of stimulation showed an improvement in the ARCI amphetamine scale, which assesses psychostimulant-like sensations. Additionally, a significant reduction in diastolic blood pressure was observed.

3.4.2 Open Label Studies

Salerno *et al.* [35] conducted a study to assess the efficacy of 10 sessions of cTBS towards the pre-SMA, bi-

laterally, in a sample of six patients with GD. Each session was administered at an intensity of 80% of the RMT by using bursts of three pulses at a frequency of 50 Hz, repeated every 200 ms (5 Hz). The study reported a statistically significant improvement in the severity of GD symptoms, as assessed by the PG-YBOCS and the Clinical Global Impression (CGI) scores. Of note, these improvements were observed up to the 30-day follow-up, although no significant difference was found in the other outcome measures, including the Zung Self-Rating Depression Scale, the Fagerström Test for Nicotine Dependence, the Gambling Urge Questionnaire, the Barratt Impulsiveness Scale-11, the Hamilton Anxiety Rating Scale, and the Hamilton Depression Rating Scale.

4. Discussion

This systematic review examined the effect of rTMS on individuals with GD. Among the studies included, three used multiple sessions at 15 Hz, two followed a single-session protocol at 10 Hz, and one study applied LF-rTMS. Additionally, two studies employed cTBS and one study employed the deep “H Coil” stimulation.

4.1 Studies Delivering HF-rTMS to the Left DLPFC

Overall, among the studies that applied excitatory protocols of rTMS to the left DLPFC, an improvement in gambling symptomatology was observed as assessed through G-SAS or by clinical observation [31,34,37,38]. However, the same studies did not show a corresponding improvement in this outcome when measured using PG-YBOCS. These conflicting findings might stem from differences in the characteristics of the two assessment scales. Specifically, a study by Kim *et al.* [41] demonstrated discrepancies in terms of reliability, internal consistency, and agreement with both physician and patient ratings between the two instruments. Among these domains, the PG-YBOCS exhibited superior performance.

Zack and colleagues [33] stated that a single active HF-rTMS session (10 Hz) targeting the left DLPFC was linked to a decreased post-game “desire to gamble” when compared with the sham stimulation. They hypothesized that this would have decreased cravings and delay discounting in a similar manner to the effects observed in non-treatment-seeking smokers [42]. This reduction in impulsive decision-making, as evidenced by a shift towards delayed options, has also been observed in healthy volunteers undergoing HF-rTMS over the mPFC [43]. Additionally, the administration of a single session of high-frequency rTMS has shown to reduce acute cravings in several groups of addicted individuals [44–48], including those cravings for food [49]. Gay *et al.* [31] reached a similar conclusion: the authors stated that a single session of HF-rTMS targeting the left DLPFC decreased cravings triggered by cues, although it did not affect the overall PG-YBOCS scale score. The choice to use a single session was supported

by previous evidence from studies reporting a reduction in binge eating within 24 hours following active rTMS compared with sham stimulation [50], thus assuming a similar mechanism in behavioral addictions.

Among non-controlled studies, three of them employed several sessions of HF-rTMS [34,37,38]. In all these studies, patients underwent rTMS targeting the left DLPFC. This choice was centered on the concept that reduced activity in the prefrontal pathways may be associated with a progressive loss of control over gambling urges and behaviors, as highlighted by Moccia *et al.* [51] and Schluter *et al.* [52]. Pettorruso and colleagues [38] conducted SPECT examinations based on the hypothesis of dopamine dysregulation in addictive disorders [53]. As such, they aimed to investigate the role of rTMS in restoring dopaminergic activity by increasing DAT levels, as demonstrated in cocaine users [54]. To the best of our knowledge, this is the first study to combine rTMS with SPECT, thus opening future directions in the application of neuromodulatory techniques in the treatment of patients with GD, as previously suggested [55]. However, in one patient with GD, a bilateral reduction in the tracer uptake within the striatum was observed, indicating a decrease in DAT availability following rTMS. The authors suggested that rTMS may enhance dopaminergic transmission through a down-regulation of DAT, potentially mediated by gene expression modulation induced by rTMS over the left DLPFC. Comparable results have been documented among individuals diagnosed with alcohol use disorder [56]. In the case series conducted by Cardullo *et al.* [37], the included population consisted not only of individuals with gambling addiction, but also those with cocaine use disorder, given the high prevalence of comorbidity between these two conditions. It is known that there are common alterations in the mesolimbic reward system between substance-related disorders and GD [57]. Notably, the study found a decrease in cocaine craving and a reduction in Gambling-Symptom Assessment Scale (GSAS) score. In this context, much evidence has been reported regarding the reduction of cocaine craving after rTMS treatment, particularly after multiple sessions of HF stimulation targeting the left DLPFC. It has been suggested that the same neuromodulatory property could potentially have a role in the treatment of GD as well [58].

One non-randomized controlled trial only supported the positive impact of multiple sessions of HF-rTMS directed at the left DLPFC as a treatment for gambling-related symptoms, although noteworthy differences were not detected in the PG-YBOCS scores [34]. Previous studies [59] have demonstrated that HF-rTMS targeting the left DLPFC leads to the release of dopamine in the striatum, affecting both the mesolimbic and mesostriatal circuits.

This finding indicates that the positive outcomes detected in the context of rTMS treatment may be associated with dopamine regulation/plasticity, as observed in individuals with cocaine use disorder [58]. The choice to use mul-

multiple sessions of HF-rTMS was based on the inconclusive results of previous studies employing single-session HF-rTMS targeting the same area. The authors proposed that multiple sessions would play a more crucial role in maintenance treatment and be able to sustain positive outcomes on general symptoms.

4.2 Studies Delivering LF-rTMS to the Right DLPFC

Only one study conducted by Sauvaget *et al.* [32] assessed the efficacy of LF-rTMS over the right DLPFC in reducing cue-induced craving. The authors addressed cue-induced craving in their study using LF-rTMS in a single session over the right DLPFC. They ascribed their lack of success to a robust placebo effect and the specific parameters chosen for rTMS. This was grounded in earlier evidence that highlighted a connection between craving and heightened activity in the right DLPFC [60]. The authors induced craving by presenting visual cues and then asked the patients to complete a VAS assessment immediately after. Since visual-induced craving may contribute to this overactivation in pathological gamblers [61,62], the authors indicated that the rTMS occurred during the peak level of craving, and it was anticipated that subsequent measurements would decrease at a later point in time.

4.3 Studies Delivering LF-rTMS to the Left DLPFC

Among the eight studies included, Rosenberg *et al.* [36] applied deep H-coil LF-rTMS over the left DLPFC. The rationale was substantiated by prior research that indicated heightened activation of the PFC in individuals when exposed to gambling-related stimuli in cue-exposure paradigms, as demonstrated by van Holst *et al.* in 2010 [63], and the possibility to reach dopaminergic subcortical areas with the use of an H-shaped coil [64]. The Deep H coil TMS was administered targeting the left DLPFC. Despite the patients reporting immediate improvement, this protocol showed ineffectiveness. Based on the initial effect, it was assumed that there might have been a transient positive, sham-like, effect, as it was unlikely a real effect of rTMS.

4.4 Studies Delivering cTBS to the Right DLPFC or Pre-SMA

Zack *et al.* [33] assessed the efficacy of a single cTBS session directed over the right DLPFC. Regarding TBS, specifically continuous stimulation protocols have demonstrated a positive effect on impulsivity, decision-making, and delayed discounting by targeting the right DLPFC, which is a brain area known for its inhibitory control [43]. Zack and colleagues [33] administered a cTBS session over the right DLPFC compared with a sham stimulation. They did not observe any difference in the “desire to gamble”, as measured by a post-session VAS. Considering previous research by Ngetich *et al.* [65], who found that cTBS over the right DLPFC had mixed effects (re-

sulting in impaired goal-directed behavior on one hand and reduced impulsivity on the other), the lack of significant findings in the desire to gamble could be explained by the interference caused by impaired goal-directed behavior on decision-making. Nevertheless, the study yielded significant findings in terms of secondary outcomes: these included a notable reduction in subjective psychostimulant-like arousal effects, in the Stroop interference test, and in diastolic blood pressure compared with the sham group. The authors attributed these outcomes to the enhancement of gamma-aminobutyric acid (GABA) levels, the involvement of which was demonstrated in studies involving cTBS over the primary motor cortex [66]. The mechanism behind this phenomenon suggests that cTBS may increase the inhibitory activities of interneurons, resulting in higher concentrations of GABA. Zack and colleagues explained the reduction in psychostimulant-like and arousing effects of the task, as well as the increase in the Stroop interference test, by proposing that stimulation of the prefrontal GABA neurons may impair the ability to shift attention away from a target stimulus [67].

Concerning cTBS, it has shown the ability to modulate cognitive control and motor inhibition in healthy participants by targeting the pre-SMA [68]. This modulation can be achieved either through the hyperactivation of pathways to the subthalamic nuclei or through its direct connections with the striatum. Building upon these promising findings, Salerno *et al.* [35] designed their study using cTBS as a “proof-of-concept” trial. Although cTBS over the pre-SMA was not originally part of the protocol, previous evidence highlighted it as a crucial region to target for ongoing response inhibition and conflict resolution, eventually resulting in a decrease in risky decisions and an enhancement in inhibitory control [69]. The study showed a progressive reduction in severity, measured by PG-YBOCS over the follow-up period, and an improvement in the CGI scores. Additionally, the study confirmed that cTBS was a safe treatment option, without any reported side effects.

4.5 Current Evidence and Study Limitations

The articles included in our systematic review have various limitations. Most of the included studies did not employ validated questionnaires to evaluate the sensation of craving, but different VASs, thus making it difficult to compare all these results. Additionally, not all articles mentioned the term ‘craving’, but rather defined symptoms such as ‘urge to gamble’ or ‘desire to gamble’. Craving, alongside the compromised capacity to manage impulses, stems from gradual alterations in synapses and circuits, brought about by prolonged exposure to addictive substances [24]. Interestingly, all these neural alterations may be targeted by TMS, although, to date, it remains challenging to implement. It would be advantageous to establish a common “craving network” that is consistent among individuals, regardless of whether they have substance use-related disor-

ders. This would enable the identification and tracking of a neural pattern associated with craving or the drive for motivated behaviors [70]. Furthermore, the included studies had short follow-up periods, often limited to the time of the procedure, which resulted in an inadequate evaluation of the long-term effects.

Our systematic review also had some intrinsic limitations. The inclusion of diverse clinical populations, as well as the inclusion of case reports and case series, the high risk of bias in multiple domains of the included studies, and the concurrent use of other treatments introduce limitations and confounding factors regarding treatment efficacy. In particular, the placebo effect may have influenced many of the results obtained, and randomized sham control trials are therefore needed in future.

5. Conclusions

The studies included in this systematic review focused on the modulation of different brain regions, particularly with respect to the right and left DLPFC. Although the evidence regarding inhibitory protocols over the left DLPFC did not support its efficacy, activating approaches over the left DLPFC may be considered useful to treat different clinical aspects of GD. Continuous TBS shows encouraging results, although two different areas, with different rationales and outcomes, were selected. Future research should place greater emphasis on characterizing study samples based on specific symptoms and further longitudinal RCTs should be carried out to monitor the long-term effects and safety of NIBS in GD and other addiction disorders.

Availability of Data and Materials

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Author Contributions

CCo, MSS, AP designed the research study. CChi, AC, ADF, GT performed the research. LM, AR, PC, MP, GL, provided help and advice on the research methodology. AD and AR analyzed the data. CCo, CChi, AC, ADF, GT, and GL wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest. Carmen Concerto is serving as one of the Guest editors of this journal. Giuseppe Lanza is serving as one of the Editorial Board member of this journal. We declare that Carmen Concerto and Giuseppe Lanza had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to Gernot Riedel.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at <https://doi.org/10.31083/j.jin2206164>.

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