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Effects of repetitive transcranial magnetic stimulation (rTMS) on craving and substance consumption in patients with substance dependence: A systematic review and meta-analysis

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Abstract

Background and Aims: Repetitive transcranial magnetic stimulation (rTMS) is increasingly used as an intervention for treating substance dependence. We aimed to assess evidence of the anti-craving and consumption-reducing effects of rTMS in patients with alcohol, nicotine, and illicit drug dependence.

Methods: A systematic review and meta-analysis of 26 randomized controlled trials (RCTs) published from January 2000 to October 2018 that investigated the effects of rTMS on craving and substance consumption in patients with nicotine, alcohol and illicit drug dependence (n = 748). Craving, measured using self-reported questionnaires or visual analogue scale, and substance consumption, measured using self-report substance intake or number of addiction relapse cases, were considered as primary and secondary outcomes, respectively. Substance type, study design, and rTMS parameters were used as the independent factors in the meta-regression.

Results: Results showed that excitatory rTMS of the left dorsolateral prefrontal cortex (DLPFC) significantly reduced craving (Hedges' g = -0.62; 95% CI, -0.89 to -0.35; $P < 0.0001$),

compared with sham stimulation. Moreover, meta-regression revealed a significant positive association between the total number of stimulation pulses and effect size among studies using excitatory left DLPFC stimulation ($P = 0.01$). Effects of other rTMS protocols on craving were not significant. However, when examining substance consumption, excitatory rTMS of the left DLPFC and excitatory deep TMS (dTMS) of the bilateral DLPFC and insula revealed significant consumption-reducing effects, compared with sham stimulation.

Conclusion: Excitatory repetitive transcranial magnetic stimulation of the dorsolateral prefrontal cortex appears to have an acute effect on reducing craving and substance consumption in patients with substance dependence. The anti-craving effect may be associated with stimulation dose.

Keywords: Transcranial magnetic stimulation; Substance dependence; Addiction; Craving; Systematic review; Meta-analysis

Introduction

Substance dependence is a chronic psychiatric disorder consisting of three primary categories, including alcohol, nicotine and illicit drug addiction [1]. According to a global statistics report in 2017, the prevalence among the adult population was 18.4% for heavy alcohol consumption, 15.2% for daily tobacco smoking, and from 0.35% to 3.8% for different types of illicit drug use [2]. Craving, defined as an intense and uncontrollable desire to use a substance [3], is one of the key characteristics of substance dependence, which has been shown to be one of the most important contributors to relapse [4]. Several kinds of evidence indicate that substance dependence is a disorder of the dopaminergic system, as manifested in a hypodopaminergic state of the mesolimbic dopamine pathway [5]. Indeed, studies using positron emission tomography (PET) reported reduced ventral striatal D_2 receptors and diminished dopamine release in patients with substance dependence (e.g., [6]).

Besides the dopamine deficiency hypothesis, substance dependence has also been described as a disorder of the prefrontal cortex (PFC). The dorsal PFC network, including the dorsolateral prefrontal cortex (DLPFC) and the dorsal anterior cingulate cortex (dACC), governs executive functioning, including decision making and self-control, while the ventral PFC network, including the medial prefrontal cortex (MPFC), orbitofrontal cortex (OFC) and ventral anterior

cingulate cortex (vACC), are involved in limbic arousal and emotion processing [7]. Hence, an imbalance of these two systems, specifically a hyperactive emotional processing and hypoactive executive functioning system, has been hypothesized the cause of substance dependence [8]. Indeed, hyperactivation of the ventral PFC network has been associated with craving [9], resulting in substance use [10], whereas hypoactivity of the left [11] as well as the right DLPFC [12] has been observed in substance dependent individuals while performing cognitive tasks, indicating impairments of executive functions processed by the DLPFC network. However, it has also been assumed that the left DLPFC processes reward-based motivation whereas the right DLPFC is more involved in withdrawal-related behaviors and self-inhibition [13]. Therefore, the left DLPFC should be hyperactive as a result of amplified incentive salience of substance use. Indeed, a hemispheric asymmetry between left and right DLPFC frequency power, as measured with electroencephalography, has been demonstrated in patients with substance dependence [14].

Repetitive transcranial magnetic stimulation (rTMS), including theta burst stimulation (TBS) and deep TMS (dTMS), has emerged as a promising treatment for substance dependence due to its potential to suppress craving [10]. rTMS uses a changing magnetic field, through a coil placing over the head, to elicit electric current at a certain target in the brain cortex through electromagnetic induction. The repetitive nature of applied pulses activates neural networks

and can result in either excitatory or inhibitory after-effects [15]. Most studies aim to facilitate DLPFC by means of excitatory stimulation in order to strengthen executive functions and cognitive control [1]. Facilitating the right DLPFC or inhibiting left DLPFC in order to counterbalance the presumed hemispheric imbalance of DLPFC [13, 14] may therefore contribute to the reduction of substance dependence. Furthermore, a few attempts have been made to suppress MPFC, a core structure of the ventral PFC network, in order to reduce the presumed hyperactivities of the emotional system driven by drug rewards [16]. In some cases, the therapeutic effects of excitatory DLPFC stimulation also support the dopaminergic deficiency hypothesis, since increased dopamine release in the caudate nucleus was found upon stimulation [17].

A substantial amount of studies in the last decade investigated the effects of rTMS on craving in substance dependence, leading to mixed results. We identified four meta-analyses [1, 18-20] regarding the effect of rTMS in substance dependence, of which, two meta-analyses have investigated the effect of non-invasive brain stimulation (NIBS), including rTMS and transcranial direct current stimulation (tDCS), in patients with food craving as well as substance dependence [18, 20] and a significant anti-craving effect of excitatory DLPFC stimulation was found. Other two meta-analyses were performed to explore the effect of rTMS on craving in patients with substance dependence [1, 19]. One meta-analysis published in 2016

included eight studies and concluded that excitatory rTMS of the right DLPFC has a significant anti-craving effect [19]. Another meta-analysis published in 2017 and based on 10 studies showed a significant anti-craving effect of excitatory rTMS of either left or right DLPFC in patients with substance dependence [1].

Although an anti-craving effect of rTMS intervention has been indicated by previous literature, the effect of different rTMS protocols on craving and substance consumption and the association between stimulation parameters and effect sizes has not been systematically investigated. Therefore, we aimed to examine assess existing evidence of the anti-craving and consumption-reducing effects of rTMS in patients with alcohol, nicotine, and illicit drug dependence by conducting a meta-analytic review to evaluate the effects of different published rTMS protocols. Our research questions were: (1) Is there any significant effect of the published rTMS protocols on craving, assessed using meta-analysis? (2) Is there any association among study designs, various rTMS parameters, substance types and effect sizes, assessed using meta-regression? (3) What is the methodological quality of published results, i.e. is there any evidence for publication bias? Does the methodological quality affect the robustness of significant findings? and (4) Does the reduced craving after rTMS intervention relate to a reduction in substance consumption?

Methods

Literature search

This study followed the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) [21]. A literature search was conducted for studies published from January 1st, 2000 to October 5th, 2018 that were indexed in four electronic databases including PubMed, EMBASE, Web of Science and Medline. The exact search terms can be found in the supplementary section. Two authors (JJQZ and RGO) independently read and identified all titles and excluded any irrelevant papers. In addition, reference lists of previously published reviews were manually screened for relevant articles [1, 16, 18-20, 22, 23].

Inclusion and exclusion criteria

We followed the PICOS framework (http://www.webcitation.org/77dvNDz2q) for inclusion of studies; therefore, studies were considered for this review if they satisfied the following criteria. Population (P): studies recruiting adult participants with substance dependence, including nicotine, alcohol and illicit drug dependence (i.e. heroin, cocaine, methamphetamine [MA] and cannabis); Intervention (I): intervention using rTMS; Comparison (C): studies with sham rTMS or no intervention control; Outcomes (O): studies providing any outcome assessing the craving level to the addictive substance, with or without the presence of addictive substance cues, as the primary outcome; studies including any outcome related substance consumption, assessed

by self-report substance intake or number of addiction relapse cases, was also included as the secondary outcome. Study design (S): studies using randomized controlled trials (RCTs), with either parallel (between-subject) or cross-over (within-subject) design.

Studies meeting any of the following criteria were excluded: (1) study recruited subjects with other neuropsychiatric disorders except substance dependence; (2) study were published as conferences abstracts, dissertations or in books; (3) study without sufficient reported data to calculate the effect size; and (4) study was not published in English or German.

Quality assessment and data extraction

Two independent authors (JJQZ and GSK) rated each study and extracted study information. Any discrepancies were resolved via discussion with the third author (KNKF). The quality of the included RCTs was assessed using Physiotherapy Evidence Database (PEDro) scale [24]. The following information from each article was extracted from each article: (1) study design; (2) the sample number of participants; (3) the stimulation protocol, including type of active stimulation, brain target, intensity, frequency, total sessions, total number of applied pulses and type of sham stimulation; (4) assessment time points; (5) main outcomes assessing craving and substance consumption.

Data analysis

Statistical analyses were performed using the Comprehensive Meta-analysis (CMA version 3.0). Authors were contacted by email in case of missing data. Reported standard errors of the mean (SEM) were converted to standard deviations (SD) using the formula $SD = SEM \times \sqrt{n}$ (n = sample size). For graphically reported data, we used a graph digitizer (http://www.webcitation.org/77dui8IFb) to extract the data from the figures. Absolute change scores (i.e., post minus pre-stimulation scores) were used as estimation of individual effect sizes in order to correct for baseline differences between groups. Hence, a negative value indicates a decrease in craving or substance consumption. Hedges' g and its 95% confidence interval (CI) were computed in all meta-analyses since craving and substance consumption were assessed via different methods across trials. Hedges' g is a variation of Cohen's d which corrects for a possible bias of small sample sizes. [25] Between-study heterogeneity was examined using Higgins' I^2 statistic. Studies with an I^2 of 25% to 50% were considered to have low heterogeneity, I^2 of values of 50% to 75%, and > 75% were considered indicative of moderate and high level of heterogeneity, respectively [25]. Random-effects meta-analysis was performed given the clinical and methodological diversity among included trials [26]. Durability of rTMS effects was evaluated by using the change scores between the post-intervention and the follow-up data, if they were available.

Given previous evidence that study design (cross-over versus parallel design) [27] and addicted substance type [1] may mediate stimulation effects, univariate meta-regression was performed first to identify the potential influence of these two independent variables on effect sizes (dependent variables). As both factors were not significant, the main analysis was carried out including all studies. However, post-hoc subgroup analyses for each addicted substance was performed separately in an explicitly exploratory analysis.

For rTMS protocols on stimulation targets that revealed significant effects, we further assessed the influence of different rTMS parameters (i.e., the number of sessions, total pulses of stimulation, stimulation pulse per session, frequency, or intensity) using meta-regression. Sensitivity analysis was performed using the leave-one-out method in case of significant results. Publication bias was investigated by inspecting funnel plots and calculating Egger's test in case of more than 10 articles per subgroup [28]. The statistical threshold was set at $P < 0.05$ (two-tailed), except that a threshold of $P < 0.1$ (two-tailed) was used for Egger's test [29].

Results

Study selection

Figure 1 shows the detailed selection process of included studies. A total of 26 articles comprising 748 patients were included in our meta-analysis [30-55]. See Table 1 for the details

of included studies.

Methodological quality of included studies

The results of the methodological quality assessment by PEDro are summarized in supplementary Table S1. The mean score was 7.54, ranging from 5 to 9, which indicates a moderate to high quality of included studies.

Excitatory rTMS of DLPFC on craving

Seventeen studies investigated the effects of excitatory stimulation of left [30, 32-35, 38-40, 45, 48, 54, 55] and right [34, 42, 50, 51, 53] DLPFC using HF rTMS, except for one study [47] that employed iTBS, a potent form of excitatory rTMS. Univariate meta-regression to investigate the potential influence of substance type and study design indicated neither a significant effect of substance (Q = 2.26, P = 0.32 for studies stimulating left DLPFC and Q = 1.97, P = 0.37 for studies stimulating right DLPFC) nor of study design (Q = 1.26 , P = 0.26 for studies stimulating left DLPFC and Q = 0.50, P = 0.48 for studies stimulating right DLPFC). Thus, meta-analysis was carried out by including all substances and study designs.

Table 2 summarized the pooled results from all meta-analysis. Meta-analysis for left DLPFC stimulation showed a significant anti-craving effect with medium effect size (Figure 2A)

compared with sham stimulation. Individual effect estimates showed low heterogeneity (I^2 = 35.36%) and the overall anti-craving effect was robust to leave-one-out sensitivity analysis (Hedges' g from -0.70 to -0.54; see Figure S1). To explore the effect of various rTMS parameters and effect sizes, univariate meta-regression analysis was performed using the total number of pulses, the number of sessions, pulse per session, frequency and intensity (% RMT) as the independent factors. The analysis showed that the total number of pulses was a significant predictor of the effect size (P = 0.01), whereas the number of sessions, pulse per session, frequency and intensity were insignificant. The funnel plot showed no sign of publication bias (Figure S2) which was supported by a nonsignificant value from Egger's test (P = 0.75). Despite a non-significant meta-regression on the effect of addicted substance type (see above), *post-hoc* meta-analysis was conducted for each substance separately in an exploratory approach, given previous evidence that stimulation effects may differ between substance type [1]. This analysis yielded a large effect size for illicit drug dependence, followed by a medium effect size for nicotine dependence and a small effect size for alcohol dependence (Figure S3).

Conversely, meta-analysis including all studies for right DLPFC stimulation showed no significant anti-craving effect (Figure 2B), compared to sham stimulation.

To determine the durability of effects of left DLPFC stimulation, meta-analysis was performed on three articles that reported follow-up data [32, 40, 54]. The mean time delay between the last TMS session and follow-up was 4 ± 2.5 months, ranging from 1 to 6 months. However, the summary effect estimate indicated no significant durability of anti-craving effects (Figure S4).

Inhibitory stimulation of DLPFC and MPFC and effects of deep TMS on craving

Three articles [34, 41, 49] applied LF rTMS of either left or right DLPFC. Effect estimates were highly heterogeneous ($I^2 > 75\%$) and neither left nor right DLPFC stimulation showed a significant anti-craving effect. Furthermore, two studies [36, 43] exploring the anti-craving effect of continuous theta burst stimulation (cTBS) of left MPFC (10/20 coordinate: FP1) and one study [52] investigating LF stimulation of the SFG (10/20 coordinate: FPz) indicated no significant anti-craving effects. Finally, four studies using dTMS were subjected to meta-analysis [10, 31, 44, 46], indicating no significant effect for any region stimulated (see Figure 3). dTMS uses a so-called H coil and is presumably able to reach deeper (5 to 7 cm) brain regions but elicits a more diffused stimulation [56]. Given the limited number of studies using inhibitory stimulation and dTMS, we refrained from performing meta-regression analysis.

Effects of rTMS and dTMS on substance consumption

Meta-analysis was performed to explore the effects of various rTMS protocols on substance

consumption of patients with substance dependence. The analysis revealed that both excitatory rTMS of the left DLPFC [33, 49] and excitatory dTMS of the bilateral DLPFC and insula [37, 46] resulted in a significant reduction of substance consumption, compared with sham stimulation. However, applying excitatory dTMS of the MPFC [31, 44] or inhibitory dTMS of the bilateral DLPFC and insula [46] yielded no significant effects on substance consumption, compared with sham stimulation (Figure 4).

Discussion

Our review was based on 26 published articles and included data from 748 patients with substance dependence. We systematically investigated the effect of different published rTMS protocols on craving and substance consumption. Our meta-analysis revealed a significant anti-craving effect of excitatory rTMS of the left DLPFC in patients with substance dependence, which was robust in leave-one-out analysis. However, this effect was limited in duration, as indicated by a non-significant treatment effect at follow-up. Meta-regression indicated an association between stimulation dosage (i.e. total number of stimulation pulses) and anti-craving effect. Inhibitory stimulation protocols as well as dTMS had no significant effects on craving in our meta-analysis. Regarding substance consumption, meta-analysis showed an immediate consumption-reducing effect in studies using excitatory left DLPFC rTMS and dTMS of the bilateral DLPFC and insula.

Craving is a common target for intervention in studies, as it is considered the main reason for relapse in substance addiction [4]. Our results indicate an anti-craving effect of excitatory rTMS of the DLPFC, which is broadly in line with previous meta-analyses [1, 18-20]. Yet, several important differences underpinning the greater extent of the current analysis compared to previous ones must be noted. Jansen et al. [20] found no significant difference between left and right DLPFC stimulation, but right DLPFC stimulation yielded a numerically larger effect size than left stimulation (Hedges' g = 0.71 *vs.* 0.38). Similarly, Song et al. [18] also concluded that no differential effect of left and right DLPFC could be found, based on the results of their meta-analysis. However, both of their reviews analyzed both rTMS and tDCS studies, and a substantial amount of their included studies focused on food craving, which was excluded in our analysis. Enokibara et al. [19] showed that right but not left DLPFC stimulation is superior to sham stimulation with a large effect size (Hedges' g = 1.48); however, only three studies were pooled in their meta-analysis. Likewise, only a limited number of ten studies were included in a recent meta-analysis by Maiti et al.,[1] in which authors observed significant anti-craving effects of HF rTMS. Our analysis was based on more studies and revealed that the left but not right DLPFC stimulation is superior to sham stimulation. Yet, the majority of included studies in our analysis investigated the effects of left DLPFC stimulation whereas Maiti et al. did not systematically assess laterality of DLPFC stimulation [1].

Excitatory rTMS targeting left DLPFC shows promise in reducing both craving and substance consumption, which may be a result of dopamine release and/or activation of the dorsal PFC executive functioning system. Cho et al. investigated the effects of 10 Hz rTMS of either left or right DLPFC on dopamine release in young healthy individuals [57]. Their results indicated that only left but not right stimulation significantly increased dopamine release. Moreover, Ko et al. reported that cTBS of the left but not right DLPFC, reduced dopamine release and interfered with participant' performance in an executive function task [58].

Although our meta-regression analysis indicated no significant substance heterogeneity for stimulation effects, exploratory analyses revealed that excitatory rTMS of the left DLPFC seems to be more effective in reducing craving for patients with illicit drug abuse, than for those with nicotine or alcohol dependence. Among our included studies, many studies targeting the right DLPFC focused on alcohol dependence (four out of six studies) while left DLPFC stimulation was usually applied in either illicit drugs abuse or nicotine dependence. Therefore, our conclusion that left but not right DLPFC stimulation has anti-craving effects must be interpreted with caution since the laterality effects may be confounded by substance type and disentangling these effects requires further systematic investigations.

Inhibitory rTMS protocols were not quantitatively evaluated by any previously published meta-analysis [1, 18-20]. Effects of inhibitory rTMS targeting DLPFC on craving are inconsistent based on the studies included in our meta-analysis. According to the hemispheric imbalance hypothesis of DLPFC in substance dependence, left DLPFC should be inhibited in order to reduce the abnormal salience towards addictive drugs. [13] However, Li et al. [49] demonstrated an elevated level of craving immediately after a single-session 1 Hz rTMS of the left DLPFC, compared with sham stimulation. Hayashi et al. [9] reported that a single-session 1 Hz rTMS of the left DLPFC suppressed craving and associated activity of the medial OFC in patients with nicotine dependence, particularly when cigarettes were available immediately after intervention. Moreover, Liu et al. [34] reported an anti-craving effect of 5-session 1 Hz rTMS of the left DLPFC in MA users. Given the limited number of studies (four out of 26 studies) and significant methodological heterogeneities of studies, we were unable to systematically evaluate the potential confounds of inhibitory protocols and conclusions must be made with great caution. In any case, the available evidence highlights the importance of patients' features and timing of stimulation when considering inhibitory DLPFC stimulation.

Four articles included in our meta-analysis investigated the effects of dTMS, of which two studies targeted the bilateral DLPFC and insula [37, 46] while the other two studies targeted the MPFC [31, 44]. Although the anti-craving effect of dTMS remained insignificant according

to our meta-analysis, we found that excitatory dTMS of the bilateral DLPFC and insula significantly reduced substance consumption immediately after intervention (12 to 13 sessions) [37, 46]. This is in line with another recent RCT by Bolloni et al. which was, however, not included in our meta-analysis because of methodological issues; the authors applied 12 sessions of daily dTMS of the bilateral DLPFC and insula and observed a trend in reduction of cocaine consumption [59]. A possible reason for this is that dTMS has been shown to elicit dopamine release and improve dopaminergic binding in the striatum [37, 60], which may compensate presumed dopaminergic deficiency in addiction. However, research on dTMS as an intervention in addiction is still at its early stage, with relatively limited clinical evidence, and effects induced by dTMS beyond the dopamine system have not been thoroughly investigated.

An attempt to attenuate MPFC activity, which is related to limbic arousal, and automatic and impulsive behavior using cTBS, was done by Hanlon et al. in three separate groups of patients with substance dependence [36, 43]. However, results were not supportive of an anti-craving effect using this protocol. Still, cue-induced brain activations in caudate, nucleus accumbens, ACC and OFC were shown to be reduced after applying cTBS, indicating a suppressive effect of the ventral PFC network [61, 62]. Rose et al. [52] found that a single-session of 10 Hz rTMS to SFG (10/20 coordinate FPz) increased levels of craving in patients with nicotine dependence, a finding that further underpins the role of MPFC in craving modulation. Thus, targeting the

impulsive system may be another promising strategy to control craving in patients with substance dependence, but further studies are necessary.

There are several limitations in our review. Firstly, as the craving level is assessed by self-reported questionnaires or visual analogue scale, blinding is necessary in order to avoid biases in treatment effect and evaluation. However, the number of studies with a double-blind design was found to be limited (eight of 26 studies). Secondly, several included studies had a cross-over design while three of them [49, 52, 55] were designed without a wash-out period. However, all included studies with a cross-over design only applied single-session rTMS, which makes carry-over effects rather unlikely. Thirdly, our systematic review primarily focused on craving, as it is the most popular outcome employed by rTMS studies regarding addiction; however, substance use is also an important outcome reflecting the severity of substance dependence which is surprisingly seldom investigated. Although our meta-analysis showed some promising results in favor of excitatory left and bilateral DLPFC stimulations, they were based on a limited amount of studies (n = 4) and therefore should be regarded as preliminary. Fourthly, highly heterogeneous rTMS parameters were applied among included studies. Although we performed meta-regression, which indicated a relationship between stimulation dose and anti-craving effects, the optimal TMS parameters for treating substance dependence is still awaiting to be determined. Lastly, we only observed a significant immediate effect of excitatory rTMS

of the left DLPFC which seemed to wear off at follow-up. This might be due to inadequate power, since only a limited number of studies (n = 4) provided follow-up data. Significant number of drop-out (up to around 30% of participants in one of the analyzed studies [54]) at follow-up also may bias the estimation of effect size. Durability of effects are of utmost importance for a successful addiction treatment and future studies are encouraged to conduct follow-up measurements after the completion of rTMS intervention.

Conclusions

Excitatory rTMS of the left DLPFC has an immediate craving alleviating effect in patients with substance dependence. This anti-craving effect may be dose dependent. Our results further highlight the need to optimize intervention parameters and to increase the durability of the anti-craving and consumption-reducing effects.

Contributors

RGO and KNKF designed the study. JJQZ and RGO performed the literature search. JJQZ, RGO and GSK screened and extracted information from the articles. JJQZ extracted the data and performed the meta-analysis. GSK cross-checked the data for meta-analysis. All authors wrote the first manuscript. JJQZ, KNKF, AMHS and GSK revised the manuscript. All authors approved the final manuscript.

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Declaration of Conflicting Interests

The authors declare no conflicts of interest.

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Figure 1. Flowchart of literature search.

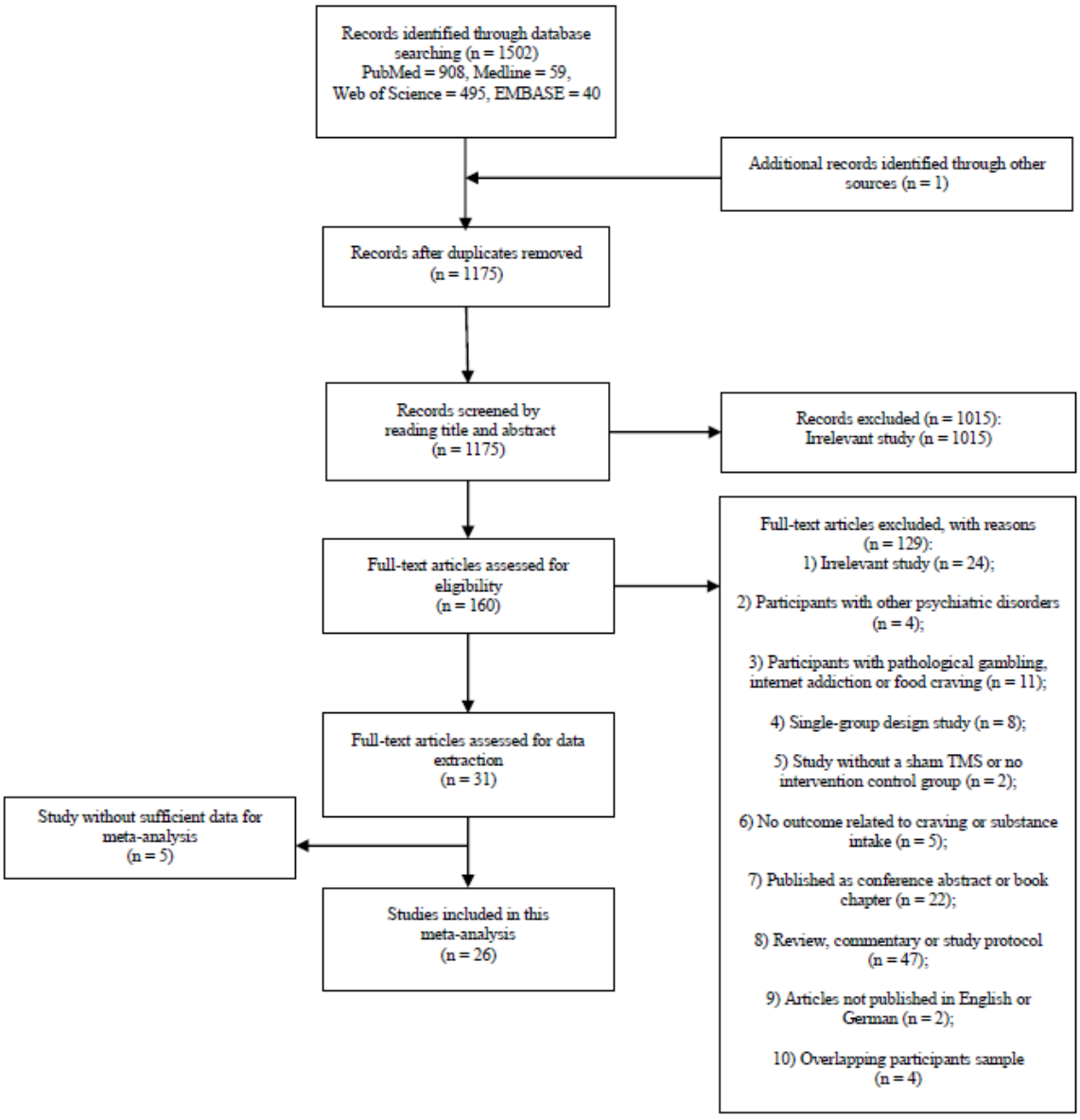

Figure 1. Flowchart of literature search.

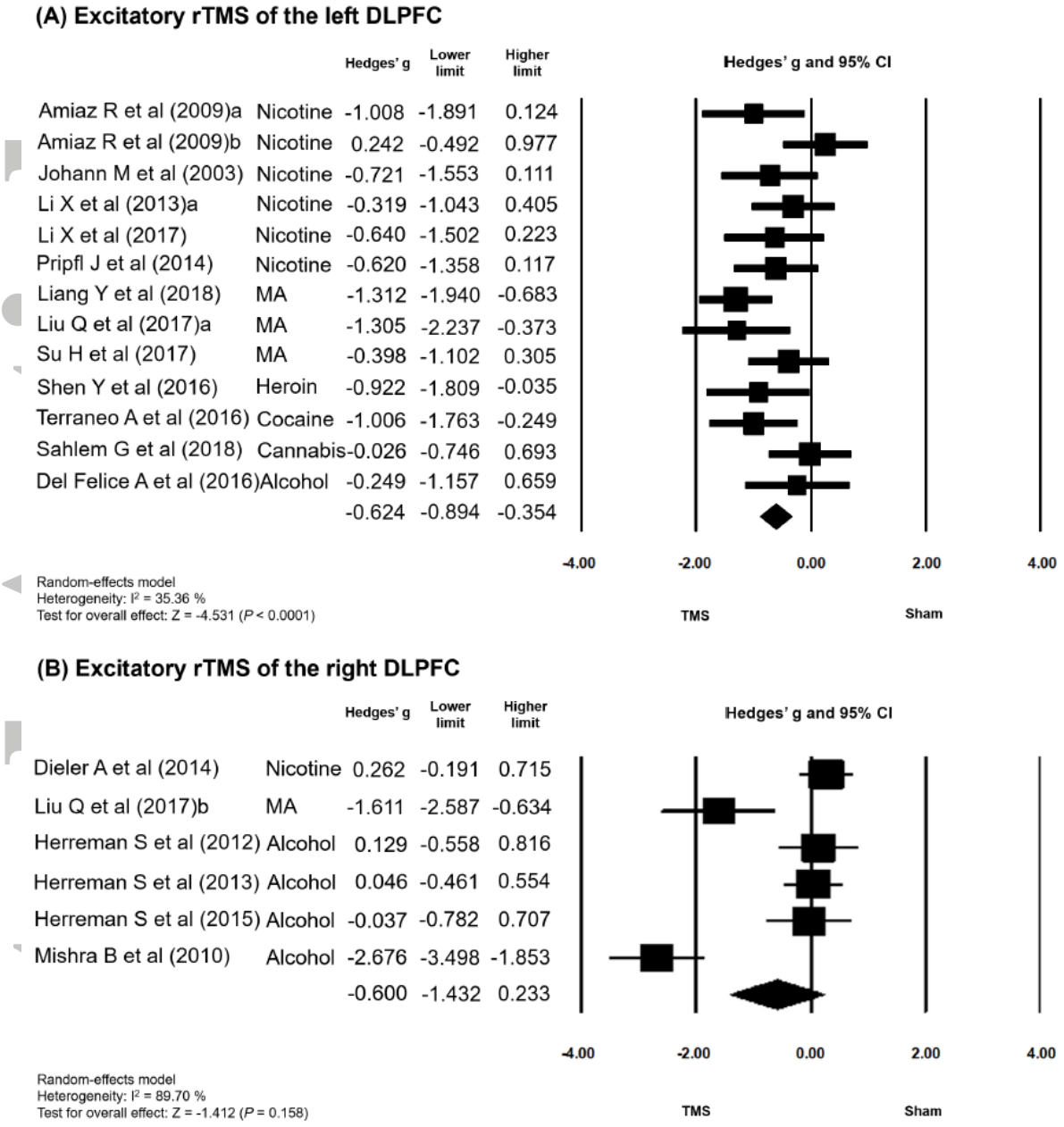

Figure 2. Meta-analysis of the immediate effects of excitatory rTMS of the DLPFC on craving: (A) Meta-analysis of studies using excitatory rTMS of the left DLPFC on craving, shows a significant anti-craving effect with an effect size of -0.62 and (B) Meta-analysis of studies using excitatory rTMS of the right DLPFC on craving, showing an insignificant effect on craving.

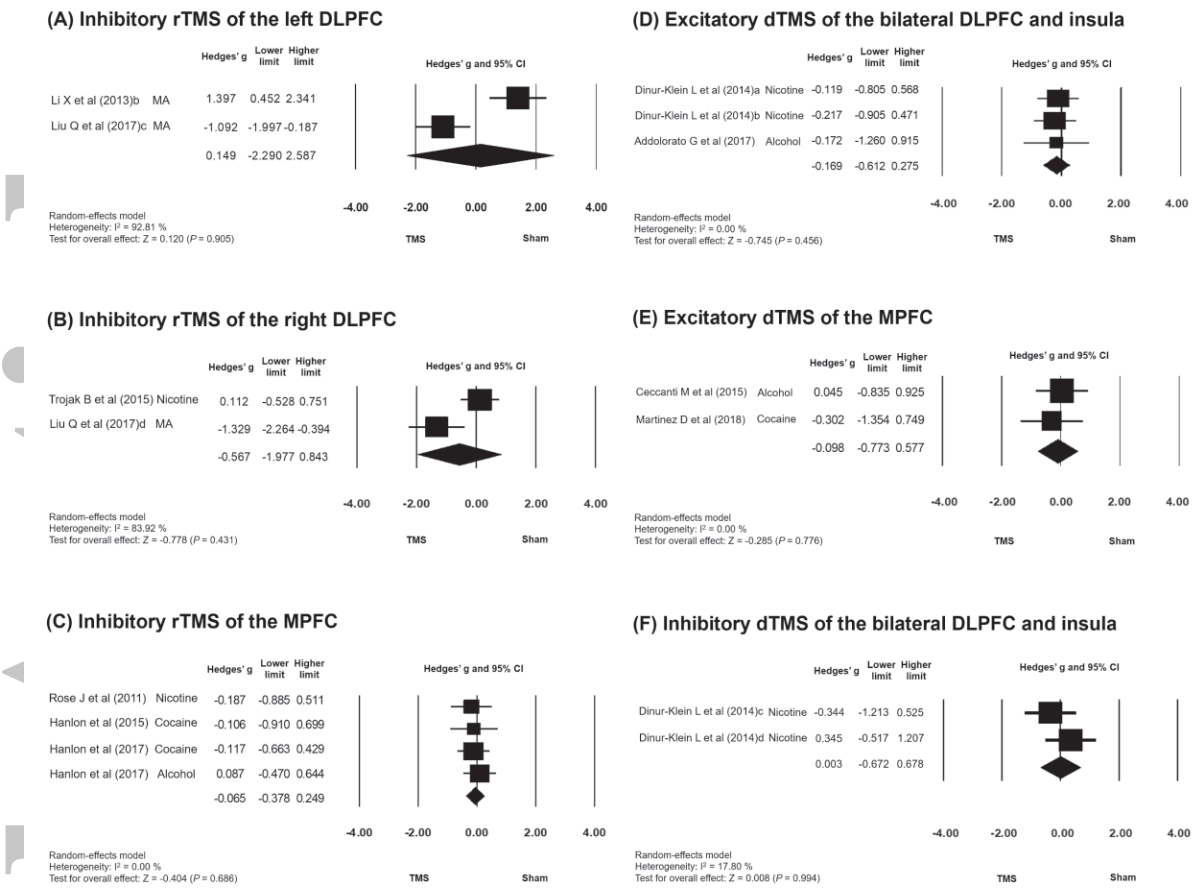

Figure 3. Meta-analysis of the immediate effects of other rTMS protocols of the DLPFC on craving: (A) Meta-analysis of studies using inhibitory rTMS of the left DLPFC; (B) Meta-analysis of studies using inhibitory rTMS of the right DLPFC; (C) Meta-analysis of studies using inhibitory rTMS of the MPFC; (D) Meta-analysis of studies using excitatory dTMS of the bilateral DLPFC and insula; (E) Meta-analysis of studies using excitatory dTMS of the MPFC; and (F) Meta-analysis of studies using inhibitory dTMS of the bilateral DLPFC and insula. All above TMS protocols show insignificant effects on craving.

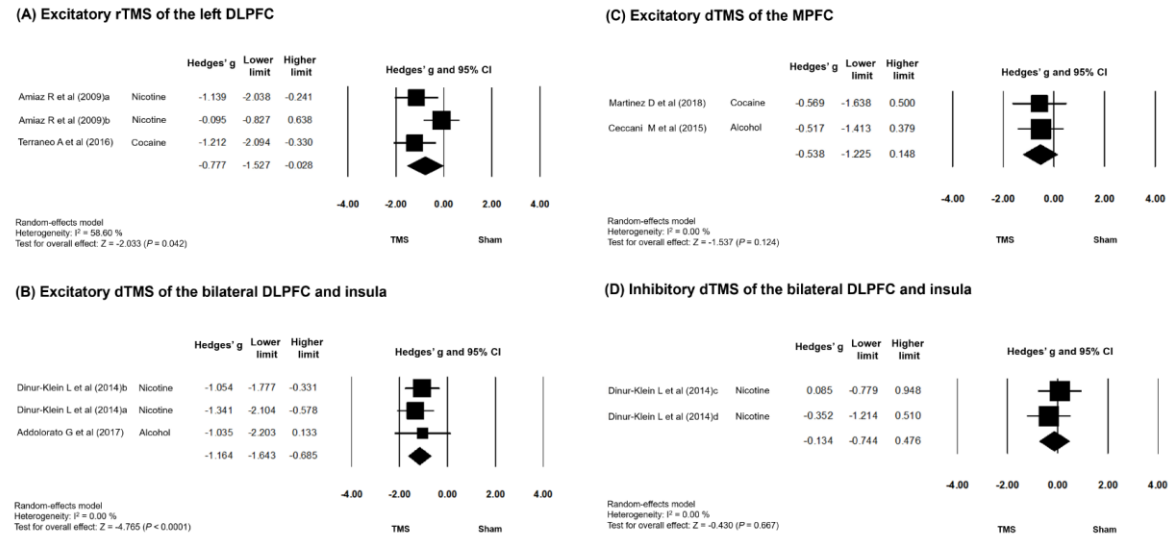

Figure 4. Meta-analysis of the immediate effects of rTMS on substance consumption: (A) Meta-analysis of studies using excitatory rTMS of the left DLPFC shows a significant effect on reducing substance consumption, with an effect size of -0.78; (B) Meta-analysis of studies using dTMS of the bilateral DLPFC shows a significant effect on reducing substance consumption, with an effect size of -1.16; (C) Meta-analysis of studies using excitatory dTMS of the MPFC, showing a suppressive but an insignificant effect on substance consumption, with an effect size of -0.54; and (D) Meta-analysis of studies using inhibitory dTMS of the MPFC shows an insignificant effect on substance consumption.

Table 1. Characteristics of Included Studies

Study	Study design	Sample number	Active stimulation	Brain target	Intensity (% RMT)	Frequency (Hz)	Total sessions/total pulses	Type of sham	Assessment time points	Main outcome (craving)	Main outcome (substance consumption)
Nicotine dependence											
Johann M et al (2003)	Cross-over	11	rTMS	lDLPFC	90	20	1/1000	Sham coil	Pre, post	VAS	NA
Amiaz R et al (2009)	Parallel	RS: 12; RN: 14; SS: 9; SN: 13	rTMS	lDLPFC	100	10	16/16000	Surface isolation	Pre, 10-d TMS, 6-m FU	VAS	Self-report cigarettes/d
Rose J et al (2011)	Cross-over	15	rTMS	SFG	90	10; 1	1/2700; 1/270	M1 stimulation	Pre, post	SJQ	NA
Li X et al (2013)a	Cross-over	14	rTMS	lDLPFC	100	10	1/3000	Sham coil	Pre, post	QSU-B	NA
Pripfl J et al (2014)	Cross-over	11	rTMS	lDLPFC	90	10	1/1200	Vertex stimulation	Pre, post	5-point rating	NA
Dieler A et al (2014)	Parallel	V: 38; S: 36	rTMS	rDLPFC	80	50 (iTBS)	4/2400	Intensity reduction	Pre, 10-d TMS, 3-m, 6-m, 12-m FU	QSU	Number of relapses
Dinur-Klein L et al (2014)	Parallel	10+: 16; 10-: 16; 1+: 7; 1-: 7; 0+: 15; 0-: 15	dTMS	Bilateral DLPFC and insula	120	10; 1	13/12870; 13/7800	Sham coil	Pre, post, 6-m FU	sTCQ	Self-report cigarettes/d
Trojak B et al (2015)	Parallel	V: 18; S: 18	rTMS	rDLPFC	120	1	10/3600	Sham coil	Pre, post, 6-w, 12-w FU	VAS	Percentage of relapses
Li X et al	Cross-over	11	rTMS	lDLPFC	100	10	1/3000	Sham coil	Pre, post	VAS	NA

(2017)											
Alcohol dependence											
Mishra B et al (2010)	Parallel	V: 30; S: 15	rTMS	rDLPFC	110	10	10/10000	Sham coil	Pre, post, 1-m FU	ACQ	NA
Herremans S et al (2012)	Parallel	V: 15; S: 16	rTMS	rDLPFC	110	20	1/1560	Titled coil	Pre, post	OCDS	NA
Herremans S et al (2013)	Cross-over	29	rTMS	rDLPFC	110	20	1/1560	Titled coil	Pre, post	OCDS	NA
Herremans S et al (2015)	Parallel	V: 11; S: 13	rTMS	rDLPFC	110	20	1/1560	Titled coil	Pre, post	OCDS	NA
Ceccanti M et al (2015)	Parallel	V: 9; S: 9	dTMS	MPFC	120	20	10/15000	Sham coil	Pre, post, 1-m, 2-m, 3-m FU	VAS	Daily alcohol intake
Del Felice A et al (2016)	Parallel	V: 8; S: 9	rTMS	lDLPFC	100	10	4/4000	Surface isolation	Pre, post, 1-m FU	VAS	NA
Hanlon C et al (2017)	Cross-over	24	cTBS	lMPFC	80 - 110	50 (cTBS)	1/3600	Sham coil	Pre, post	VAS	NA
Addolorato G et al (2017)	Parallel	V: 5; S: 6	dTMS	Bilateral DLPFC and insula	100	10	12/12000	Sham coil	Pre, post, 1-m FU	OCDS	TLFB - total drinks
MA dependence											
Li X et al (2013)b	Cross-over	10	rTMS	lDLPFC	100	1	1/900	Tilted coil	Pre, post	VAS	NA
Su H et al (2017)	Parallel	V: 15; S: 15	rTMS	lDLPFC	80	10	5/6000	Tilted coil	Pre, post	VAS	NA

Liu Q et al (2017)	Parallel	HF (left): 10 HF (right): 10 LF (left): 10 LF (right): 10 S: 10	rTMS	l/rDLPFC	100	10; 1	5/10000; 5/3000	P3 stimulation	Pre, post	VAS	NA
Liang Y et al (2018)	Parallel	V: 24 S: 22	rTMS	lDLPFC	100	10	10/20000	Titled coil	Pre, post, 3-m FU	VAS	NA
Cocaine dependence											
Hanlon C et al (2015)	Cross-over	11	cTBS	lMPFC	80 - 110	50 (cTBS)	1/1800	Inactive surface	Pre, post	VAS	NA
Terraneo A et al (2016)	Parallel	V: 16; C: 13	rTMS	lDLPFC	100	15	8/19200	NA	Pre, post	VAS	NA
Hanlon C et al (2017)	Cross-over	25	cTBS	lMPFC	80 - 110	50 (cTBS)	1/3600	Sham coil	Pre, post	VAS	NA
Martinez D et al (2018)	Parallel	HF: 6; LF: 6 S: 6	dTMS	MPFC	90 - 120	10	13/15600; 13/11700	Sham coil	Pre, post	VAS	Choice for cocaine in a self-administration session
Heroin dependence											
Shen Y et al (2016)	Parallel	V: 10; S: 10	rTMS	lDLPFC	100	10	5/10000	Titled coil	Pre, post	VAS	NA
Cannabis dependence											
Sahlem G et al (2018)	Cross-over	14	rTMS	lDLPFC	110	10	1/4000	Sham coil	Pre, post	MCQ	NA

Abbreviations: V: Verum; S: Sham; d: day; w: week; m: month; C: Control; FU: Follow-up; NA: Not available; RMT: Resting motor threshold; rTMS: Repetitive Transcranial

magnetic stimulation; lDLPFC: left dorsal lateral prefrontal cortex; VAS: Visual analogue scale; RS: Real stimulation with smoking cues exposure; RN: Real stimulation with neutral cues exposure; SS: Sham stimulation with smoking cues exposure; SN: Sham stimulation with neutral cues exposure; HF: High-frequency; LF: Low-frequency; SFG: Superior frontal gyrus; SJQ: Shiffman-Jarvik questionnaire; M1: Primary motor cortex; 10+: 10 Hz rTMS with smoking cues exposure; 10-: 10 Hz rTMS without smoking cues exposure; 1+: 1 Hz rTMS with smoking cues exposure; 1-: 1 Hz rTMS without smoking cues exposure; 0+: sham rTMS with smoking cues exposure; 0-: sham rTMS without smoking cues exposure; QSU-B: Questionnaire of smoking urges-brief; iTBS: intermittent theta burst stimulation; rDLPFC: Right dorsal lateral prefrontal cortex; QSU: Questionnaire of smoking urges; dTMS: Deep transcranial magnetic stimulation; sTCQ: Short version of the Tobacco Craving questionnaire; ACQ: Alcohol craving questionnaire; OCDS: Obsessive-compulsive drinking scale; TLS: Ten-point Likert scales; cTBS: continuous theta burst stimulation; lMPFC: left medial prefrontal cortex; TLFB: Timeline followback; MA: methamphetamine; MPFC: Medial prefrontal cortex; MCQ: Marijuana craving questionnaire.

Table 2. Summary of effect sizes for each analysis shown fully in forest plots

rTMS Protocol	Outcome	Type of substance	Effect size			Heterogeneity		Figure
			g	95% CI	*P*	I^2	*P*	
Immediate effect								
Excitatory rTMS of the lDLPFC	Craving	All substances	-0.624	-0.894 to -0.354	*P* < 0.0001	35.36%	*P* = 0.100	Figure 2A
		Alcohol	-0.249	-1.157 to 0.659	*P* = 0.591	NA	NA	Figure S3
		Nicotine	-0.471	-0.820 to -0.122	*P* = 0.008	14.63%	*P* = 0.320	Figure S3
		Illicit drugs	-0.812	-1.244 to -0.379	*P* = 0.0002	48.58%	*P* = 0.083	Figure S3
Excitatory rTMS of the rDLPFC	Craving	All substances	-0.600	-1.432 to 0.233	*P* = 0.158	89.70%	*P* < 0.0001	Figure 2B
Inhibitory rTMS of the lDLPFC	Craving	MA	0.149	-2.290 to 2.587	*P* = 0.905	92.81%	*P* < 0.0001	Figure 3A
Inhibitory rTMS of the rDLPFC	Craving	Nicotine/MA	-0.567	-1.977 to 0.843	*P* = 0.431	83.92%	*P* = 0.013	Figure 3B
Inhibitory rTMS of the MPFC	Craving	All substances	-0.065	-0.378 to 0.249	*P* = 0.686	0.00%	*P* = 0.930	Figure 3C
Excitatory dTMS of the bilateral DLPFC and insula	Craving	Nicotine/Alcohol	-0.169	-0.612 to 0.275	*P* = 0.456	0.00%	*P* = 0.980	Figure 3D
Excitatory dTMS of the MPFC	Craving	Alcohol/Cocaine	-0.098	-0.773 to 0.577	*P* = 0.776	0.00%	*P* = 0.620	Figure 3E
Inhibitory dTMS of the bilateral DLPFC and insula	Craving	Nicotine	0.003	-0.672 to 0.678	*P* = 0.994	17.80%	*P* = 0.270	Figure 3F
Excitatory rTMS of the lDLPFC	Substance consumption	Nicotine/Cocaine	-0.777	-1.527 to -0.028	*P* = 0.042	58.60%	*P* = 0.089	Figure 4A
Excitatory dTMS of the	Substance	Nicotine/Alcohol	-1.164	-1.643 to -0.685	*P* < 0.0001	0.00%	*P* = 0.843	Figure 4B

bilateral DLPFC and insula	consumption							
Excitatory dTMS of the MPFC	Substance consumption	Cocaine/Alcohol	-0.538	-1.225 to 0.148	$P = 0.124$	0.00%	$P = 0.942$	Figure 4C
Inhibitory dTMS of the bilateral DLPFC and insula	Substance consumption	Nicotine	-0.134	-0.774 to 0.476	$P = 0.667$	0.00%	$P = 0.483$	Figure 4D
Durability of treatment effect								
Excitatory rTMS of the lDLPFC	Craving	All substances	0.244	-0.316 to 0.805	$P = 0.393$	44.71%	$P = 0.143$	Figure S4

Abbreviations: rTMS: Repetitive Transcranial magnetic stimulation; lDLPFC: left dorsal lateral prefrontal cortex; rDLPFC: Right dorsal lateral prefrontal cortex; dTMS: Deep transcranial magnetic stimulation; MPFC: Medial prefrontal cortex; MA: methamphetamine; NA: Not applicable.