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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 examine existing evidence of the anti-craving and consumption-reducing effects of rTMS in patients with nicotine, alcohol, and illicit drug dependence.

Design: Systematic review and meta-analysis.

Setting: Any published randomized controlled trial published from any setting that investigated the effects of rTMS on craving and substance consumption in substance dependent individuals.

Participants: Patients with nicotine, alcohol, and illicit drug dependence.

Measurements: 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.

Findings: Twenty-six studies were included. Results showed that excitatory rTMS of the left dorsolateral prefrontal cortex (DLPFC) significantly reduced craving (Hedges' g = -0.62; 95% CI, -0.84 to -0.41; $P < 0.0001$). However, subgroup analysis revealed that only patients with nicotine dependence (Hedges' g = -0.47; 95% CI, -0.79 to -0.14; $P = 0.005$) and illicit drug dependence (Hedges' g = -0.81; 95% CI, -1.11 to -0.50; $P < 0.0001$) benefited from this kind of 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 TMS protocols on craving were insignificant. 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.

Conclusion: Excitatory rTMS of the left DLPFC appears to have an immediate effect on reducing craving and substance consumption in patients with nicotine and illicit drug dependence. The anti-craving effect may be associated with stimulation dose.

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

Introduction

Substance dependence is a chronic psychiatric disorder consisting of three primary categories, including nicotine, alcohol and drug addiction [1]. Craving, defined as an intense and uncontrollable desire to use a substance [2], is one of the key characteristics of substance dependence, which has been shown to be one of the most important contributors to relapse [3]. 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 [4]. Indeed, studies using positron emission tomography (PET) reported reduced ventral striatal D2 receptors and diminished dopamine release in patients with substance dependence (e.g., [5]).

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 [6]. 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 [7]. Indeed, hyperactivation of the ventral PFC network has been associated with craving [8], resulting in substance use [9], whereas hypoactivity of the left [10] as well as the right DLPFC [11] 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 [12]. 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 [13].

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 [9]. 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 [12, 13] 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 [14]. 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 [15].

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, 16-18] 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 [16, 17] 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, 18]. One meta-analysis published in 2016 included only eight studies and concluded that excitatory rTMS of the right DLPFC has a significant anti-craving effect [18]. 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 nicotine but not alcohol dependence [1].

Although an anti-craving effect of rTMS stimulation has been indicated by previous literature, the effect of different rTMS protocols on craving and substance consumption has not been systematically investigated and no study has systematically explored the association between rTMS parameters and effect sizes. We therefore aimed to summarize these studies by conducting a systematic review and meta-analysis. First, we attempted to assess the clinical benefits of all published rTMS protocols for craving. We went on to examine potential associations between various rTMS parameters and their effect sizes through meta-regression analysis. Finally, we determined reduction in substance consumption to be an assumed outcome of the reduced craving, after rTMS intervention.

Methods

Literature search

This study followed the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) [19]. 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 keywords used for

identifying TMS were: transcranial magnetic stimulation and theta burst stimulation. The keywords used for identifying substance dependence included: substance dependence, substance-related disorder, substance use disorder, substance addiction, substance abuse, craving, alcohol, ethanol, tobacco, cigarette, smoking, nicotine, psychostimulant drug, psychoactive drug, cocaine, cannabis, marijuana, heroin, morphine, opioids and amphetamine. Two authors (JJQZ and RO) 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, 14, 16-18, 20, 21].

Inclusion and exclusion criteria

We followed the PICOS framework (https://linkeddata.cochrane.org/pico-ontology) 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 or cross-over 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 with insufficient reported data to calculate the effect size; and (4) study was not published in English or German.

Quality assessment and data extraction

The quality of the included RCTs was assessed using Physiotherapy Evidence Database (PEDro) scale [22]. PEDro scale consists of 10 items, including random allocation, concealment of allocation, baseline equivalence, blinding procedure, intention to treat analysis, adequate follow-up, between-group statistical analysis, measurement of data variability and point estimates.

Two independent authors (JJQZ and GSK) rated each study and extracted study

information. 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. Any discrepancies were resolved via discussion with the third author (KNKF).

Data analysis

Statistical analyses were performed using the Comprehensive Meta-analysis (CMA version 3.0). Change scores were used for the estimation of individual effect sizes in order to correct for baseline differences between groups. Authors were contacted by email in case of missing data. Reported standard errors 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://getdata-graph-digitizer.com/) to extract the data from the figures. Hedges' g and its 95% confidence interval (CI) were computed in all meta-analysis 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.[23] 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. If I^2 was below 50%, the fixed-effect model was used. Otherwise, the random-effects model was used. [22]. Durability of TMS effects was evaluated by using the change scores between the post-intervention and the follow-up data, if they were available. Meta-regression was performed to identify any association between effect sizes and TMS parameters in case of more than 10 articles per subgroup.

Publication bias was investigated by inspecting funnel plots and calculating Egger's test. Sensitivity analysis was performed using the leave-one-out method in case of significant results. 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 [24].

Results

Study selection

The initial search yielded 1502 results. After removing duplicates, a total of 1175 records were screened, of which, 1015 citations were regarded as the irrelevant studies and then removed. A total of 160 citations were subjected to full-text review, of which, 129 articles were excluded for the following reasons: the studies were irrelevant to our

topic (n = 24); participants with substance use disorders comorbid with other known psychiatric disorders (n = 4); participants with pathological gambling or food craving (n = 11) ; study without a control group (n = 8); RCT without a sham or no intervention control (n = 2), study without an outcome related to craving or substance intake (n = 5), study published as conference abstract or book chapter, review, editorial material, commentary or study protocol (n = 47), study not published in English or German (n = 2) and study using overlapping patients dataset (n = 4). Therefore, 31 articles satisfied our inclusion criteria. Five articles without sufficient data for meta-analysis were excluded. Finally, a total of 26 articles comprising 748 patients were included in our meta-analysis [25-50]. Figure 1 shows the selection process of included studies.

Characteristics of included studies

Among the 26 included articles, 9 studied nicotine craving, 7 alcohol, 4 MA, 3 cocaine, 1 heroin, 1 cannabis and 1 both cocaine and alcohol craving. Twelve studies applied a single session of stimulation whereas the number of sessions in the other studies varied from 4 to 16 (see Table 1 for more details of included studies). Most studies targeted the DLPFC, except for 4 studies that stimulated MPFC [26, 31, 38, 39] and one study that stimulated superior frontal gyrus (SFG) [47]. dTMS was used in 4 studies [26, 32, 39, 41] whereas intermittent TBS (iTBS) was used in one [42] and continuous TBS

(cTBS) was used in two articles [31, 38]. Other studies employed either high-frequency (HF) or low-frequency (LF) rTMS. 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 of included studies was 7.54, ranging from 5 to 9, which indicated the quality of the studies was from moderate to high.

Excitatory rTMS of DLPFC on craving

Seventeen studies investigated the effects of excitatory stimulation of left [25, 27-30, 33-35, 40, 43, 49, 50] and right [29, 37, 45, 46, 48] DLPFC using HF rTMS, except for one study [42] that employed iTBS, a potent form of excitatory rTMS. Meta-analysis for left DLPFC stimulation showed a significant anti-craving effect with medium effect size (Hedges' g = -0.62; 95% CI, -0.84 to -0.41; $P < 0.0001$). 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 -0.53). Conversely, right DLPFC stimulation had no significant anti-craving effect (Hedges' g = -0.60; 95% CI, -1.44 to 0.24; $P = 0.16$; see Figure 2).

When investigating each type of substance dependence separately, meta-analysis showed beneficial effects of excitatory left DLPFC stimulation for nicotine dependence (Hedges' g = -0.47; 95% CI, -0.79 to -0.14; P = 0.005) and illicit drug dependence (Hedges' g = -0.81; 95% CI, -1.14 to -0.50; $P < 0.0001$), but not for alcohol dependence (Hedges' g = -0.25; 95% CI -1.16, to 0.66; P = 0.66).

To determine the durability of effects of left DLPFC stimulation, meta-analysis was performed on three articles that reported follow-up data [27, 35, 49]. 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 (Hedges' g = 0.16; 95% CI, -0.23 to 0.56; P = 0.42).

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

Three articles [29, 36, 44] 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 [31, 38] exploring the anti-craving effect of continuous theta burst stimulation (cTBS) of left MPFC (10/20 coordinate: FP1) and one study [47] 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 [26, 32, 39, 41], 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 [51].

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] (Hedges' g = -0.78; 95% CI -1.53 to -0.03; $P = 0.042$) and excitatory dTMS of the bilateral DLPFC and insula [32, 41] (Hedges' g = -1.16; 95% CI -1.64 to -0.69; $P < 0.0001$) resulted in a significant reduction of substance consumption, compared with sham stimulation. However, applying excitatory dTMS of the MPFC [26, 39] or inhibitory dTMS of the bilateral DLPFC and insula [41] yielded no significant effects on substance consumption, compared with sham stimulation (see Figure 4).

Meta-regression

We performed univariate meta-regression analysis on the studies using excitatory rTMS of left DLPFC [25, 27-30, 33-35, 40, 43, 49, 50], using the total number of pulses, the

number of sessions, pulse per session and intensity (% RMT) as predictors. 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 and intensity were insignificant.

Publication bias

Publication bias was examined based on the studies using excitatory rTMS of the left DLPFC [25, 27-30, 33-35, 40, 43, 49, 50]. The Funnel plot showed no sign of publication bias (Figure 5) which was supported by a nonsignificant value from Egger's test (P = 0.75).

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. Furthermore, subgroup analysis revealed that the effect was only significant

for nicotine and illicit drug dependence but not for alcohol dependence. 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 [3]. Our results indicate an anti-craving effect of excitatory rTMS of the DLPFC, which is broadly in line with previous meta-analyses [1, 16-18]. Yet, several important differences underpinning the greater extent of the current analysis compared to previous ones must be noted. Jansen et al. [17] 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. [16] 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. [18] 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.[18] 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 for nicotine, but not for alcohol dependence. 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 [52]. 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 [53]. However, interpretations on the laterality of results must be made with great caution since 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. Hence, laterality effects are confounded by substance dependence type and disentangling these effects requires further systematic investigations.

Inhibitory rTMS protocols were not quantitatively evaluated by any previously published meta-analysis [1, 16-18]. Effects of inhibitory rTMS targeting DLPFC on craving are inconsistent according to 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. [12] However, Li et al. [44] 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. [8] 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. [29] 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, 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 [32, 41] while the other two studies targeted the MPFC [26, 39]. 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) [32, 41]. 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 [54]. A possible reason for this is that dTMS has been shown to elicit dopamine release and improve dopaminergic binding in the striatum [32, 55], 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 [31, 38]. 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 [56, 57]. Rose et al. [47] 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 [44, 47, 50] were designed without a wash-out period. However, all studies with a cross-over design that we included in this review only applied a single-session rTMS, which was unlikely to cause significant carry-over effects. 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 in the included studies. Although our meta-analysis showed some promising results in favor of left DLPFC and bilateral DLPFC excitatory stimulations, they were based on a limited amount of studies (n = 4) and therefore should be regarded as preliminary. Lastly, 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 [49]) at follow-up also may bias the estimation of effect size. Durability of effects is of utmost importance for a successful addiction treatment and future studies are encouraged to conduct follow-up measurements after the completion of rTMS treatment.

Conclusions

Excitatory rTMS of the left DLPFC has an immediate craving alleviating effect in patients with nicotine and illicit drug dependence. This anti-craving effect may be dose dependent. Our findings have important implications for the treatment of nicotine and illicit drug addiction and suggest that therapeutic brain stimulation should be focused on excitatory stimulation on the left DLPFC. Our results further highlight the need to optimize intervention parameters in order to increase the durability of the anti-craving and consumption-reducing effects.

Contributors

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

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Declaration of Conflicting Interests

The authors declare no conflicts of interest.

Figure legends

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 of DLPFC 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.

Figure 5. Funnel plot of standard error by Hedges' g.

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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) [50]	Cross-over	11	rTMS	lDLPFC	90	20	1/1000	Sham coil	Pre, post	VAS	NA
Amiaz R et al (2009) [49]	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) [47]	Cross-over	15	rTMS	SFG	90	10; 1	1/2700; 1/270	M1 stimulation	Pre, post	SJQ	NA
Li X et al (2013)a [43]	Cross-over	14	rTMS	lDLPFC	100	10	1/3000	Sham coil	Pre, post	QSU-B	NA
Pripfl J et al (2014) [40]	Cross-over	11	rTMS	lDLPFC	90	10	1/1200	Vertex stimulation	Pre, post	5-point rating	NA
Dieler A et al (2014) [42]	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) [41]	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	Parallel	V: 18; S: 18	rTMS	rDLPFC	120	1	10/3600	Sham coil	Pre, post, 6-w,	VAS	Percentage of

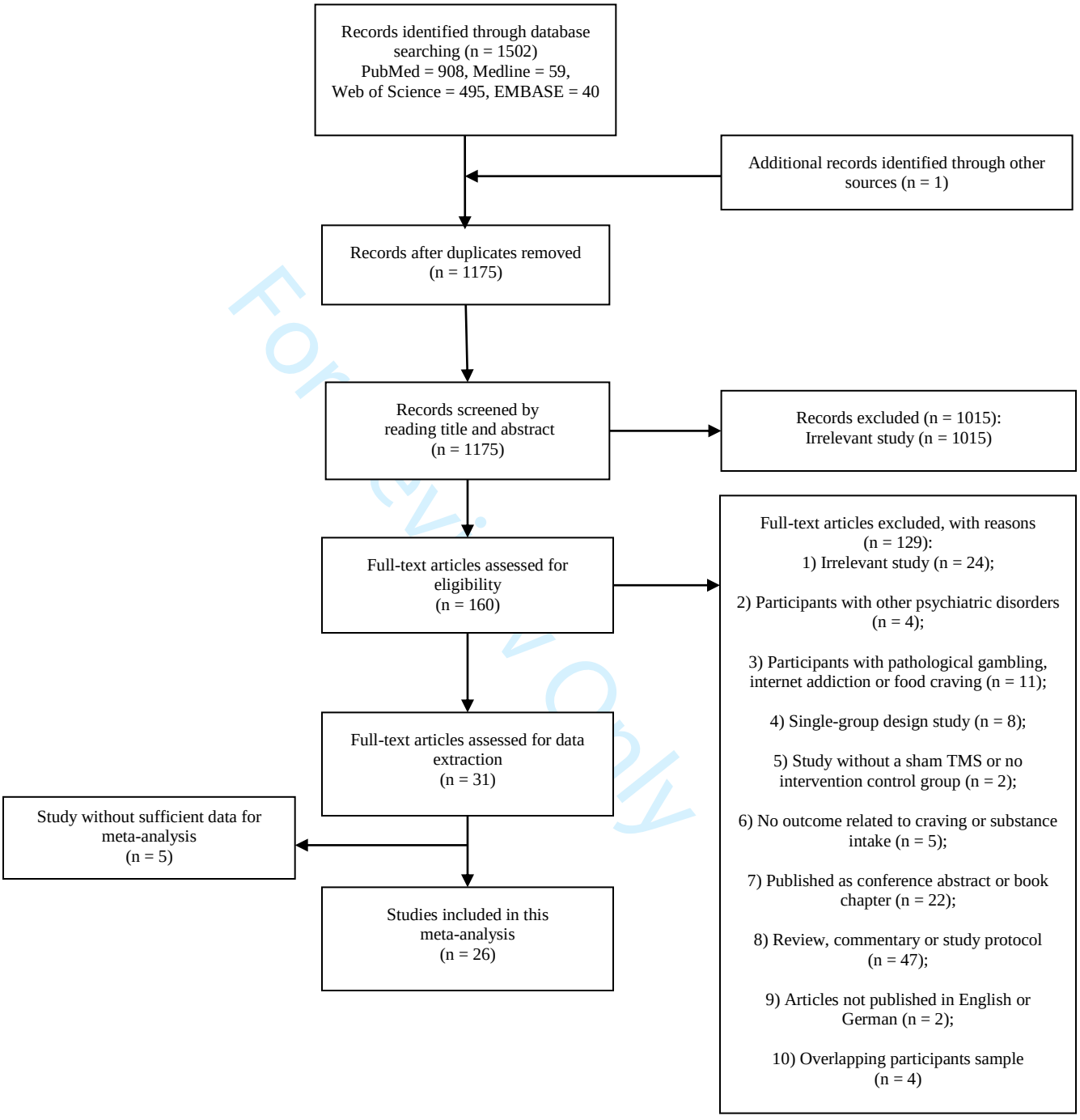
(2015) [36]									12-w FU		relapses
Li X et al (2017) [30]	Cross-over	11	rTMS	lDLPFC	100	10	1/3000	Sham coil	Pre, post	VAS	NA
Alcohol dependence											
Mishra B et al (2010) [48]	Parallel	V: 30; S: 15	rTMS	rDLPFC	110	10	10/10000	Sham coil	Pre, post, 1-m FU	ACQ	NA
Herremans S et al (2012) [46]	Parallel	V: 15; S: 16	rTMS	rDLPFC	110	20	1/1560	Titled coil	Pre, post	OCDS	NA
Herremans S et al (2013) [45]	Cross-over	29	rTMS	rDLPFC	110	20	1/1560	Titled coil	Pre, post	OCDS	NA
Herremans S et al (2015) [37]	Parallel	V: 11; S: 13	rTMS	rDLPFC	110	20	1/1560	Titled coil	Pre, post	OCDS	NA
Ceccanti M et al (2015) [39]	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) [35]	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) [31]	Cross-over	24	cTBS	lMPFC	80 - 110	50 (cTBS)	1/3600	Sham coil	Pre, post	VAS	NA

Addolorato G et al (2017) [32]	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 [44]	Cross-over	10	rTMS	lDLPFC	100	1	1/900	Tilted coil	Pre, post	VAS	NA
Su H et al (2017) [28]	Parallel	V: 15; S: 15	rTMS	lDLPFC	80	10	5/6000	Tilted coil	Pre, post	VAS	NA
Liu Q et al (2017) [29]	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) [27]	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) [38]	Cross-over	11	cTBS	lMPFC	80 - 110	50 (cTBS)	1/1800	Inactive surface	Pre, post	VAS	NA
Terraneo A et al (2016) [33]	Parallel	V: 16; C: 13	rTMS	lDLPFC	100	15	8/19200	NA	Pre, post	VAS	NA
Hanlon C et al (2017) [31]	Cross-over	25	cTBS	lMPFC	80 - 110	50 (cTBS)	1/3600	Sham coil	Pre, post	VAS	NA

Martinez D et al (2018) [26]	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) [34]	Parallel	V: 10; S: 10	rTMS	lDLPFC	100	10	5/10000	Titled coil	Pre, post	VAS	NA
Cannabis dependence											
Sahlem G et al (2018) [25]	Cross-over	14	rTMS	lDLPFC	110	10	1/4000	Sham coil	Pre, post	MCQ	NA

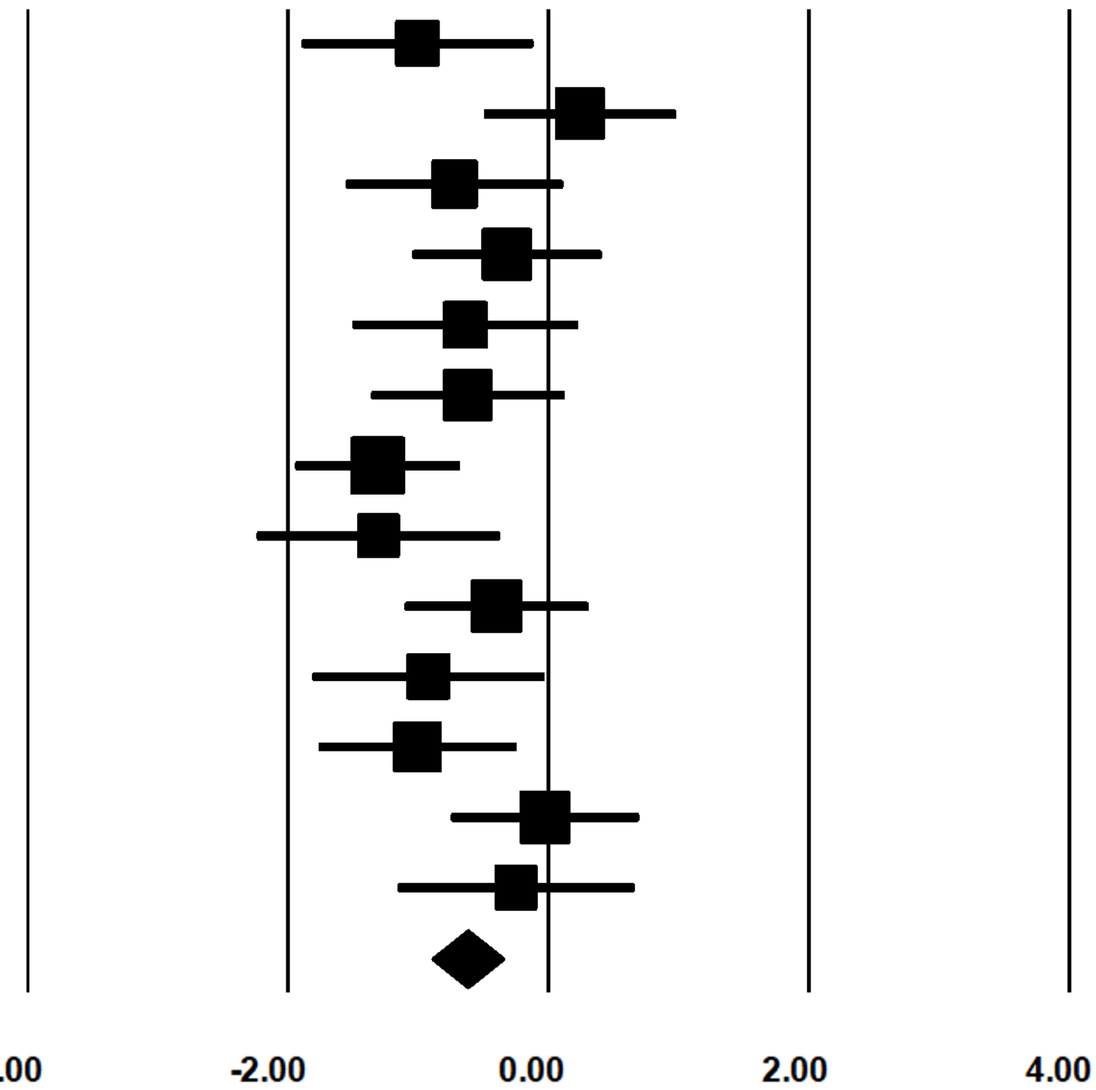
Abbreviations: V: Verum; S: Sham; d: day; w: week; m: month; C: Control; FU: Follow-up; NA: Not available; RMT: Resting motor threshold; rTMS: Repetitive Transcranial magnetic stimulation; lDLPFC: left dorsal lateral prefrontal cortex; VAS: Visual analogue scale; RS: Real stimulation with smoking cues 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.

Figure 1. Flowchart of literature search.



(A) Excitatory rTMS of the left DLPFC

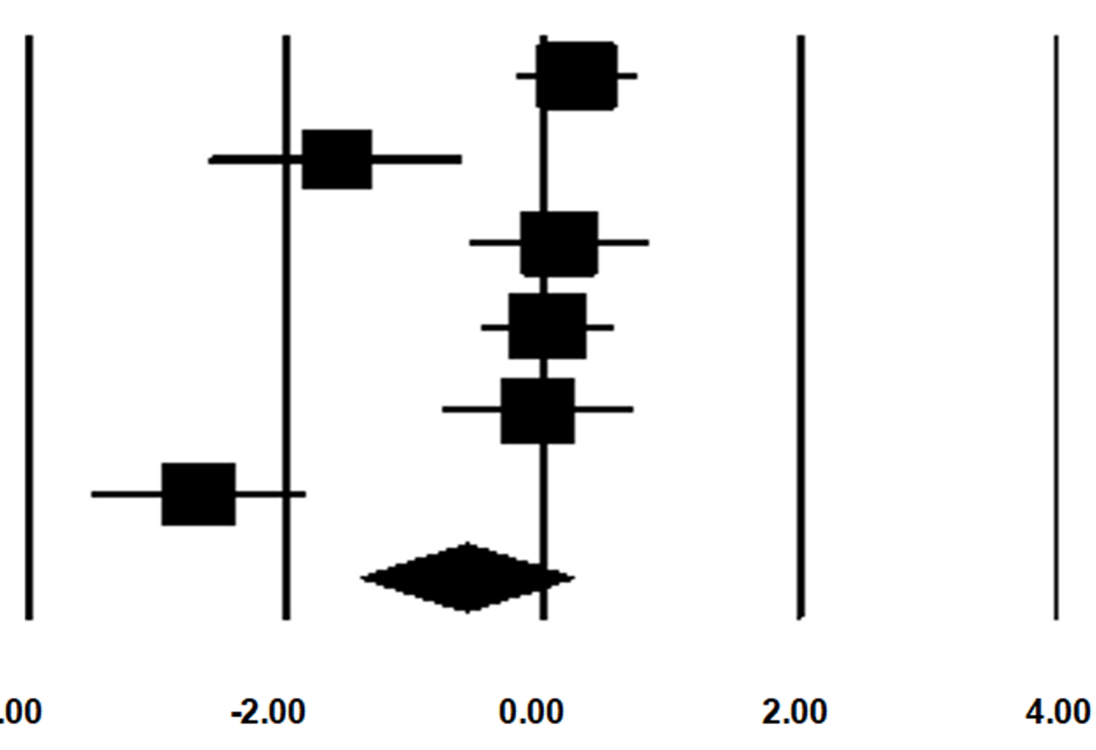
		Hedges' g	Lower limit	Higher limit
Amiaz R et al (2009)a	Nicotine	-1.008	-1.891	0.124
Amiaz R et al (2009)b	Nicotine	0.242	-0.492	0.977
Johann M et al (2003)	Nicotine	-0.721	-1.553	0.111
Li X et al (2013)a	Nicotine	-0.319	-1.043	0.405
Li X et al (2017)	Nicotine	-0.640	-1.502	0.223
Pripfl J et al (2014)	Nicotine	-0.620	-1.358	0.117
Liang Y et al (2018)	MA	-1.312	-1.940	-0.683
Liu Q et al (2017)a	MA	-1.305	-2.237	-0.373
Su H et al (2017)	MA	-0.398	-1.102	0.305
Shen Y et al (2016)	Heroin	-0.922	-1.809	-0.035
Terraneo A et al (2016)	Cocaine	-1.006	-1.763	-0.249
Sahlem G et al (2018)	Cannabis	-0.026	-0.746	0.693
Del Felice A et al (2016)	Alcohol	-0.249	-1.157	0.659
		-0.622	-0.838	-0.407



Fixed-effect model
Heterogeneity: I^2 = 35.36 %
Test for overall effect: Z = -5.66 (*P* < 0.0001)

(B) Excitatory rTMS of the right DLPFC

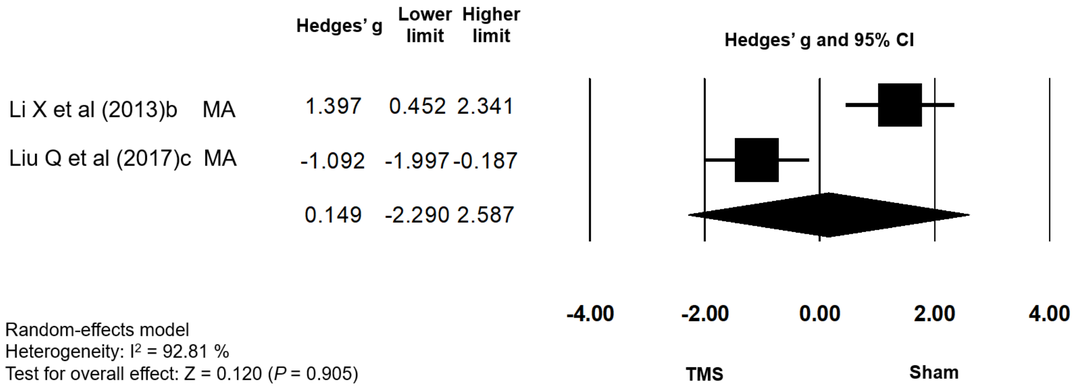
		Hedges' g	Lower limit	Higher limit
Dieler A et al (2014)	Nicotine	0.262	-0.191	0.715
Liu Q et al (2017)b	MA	-1.611	-2.587	-0.634
Herreman S et al (2012)	Alcohol	0.129	-0.558	0.816
Herreman S et al (2013)	Alcohol	0.046	-0.461	0.554
Herreman S et al (2015)	Alcohol	-0.037	-0.782	0.707
Mishra B et al (2010)	Alcohol	-2.676	-3.498	-1.853
		-0.600	-1.432	0.233



Random-effects model
Heterogeneity: I^2 = 89.70 %
Test for overall effect: Z = -1.412 (*P* = 0.158)

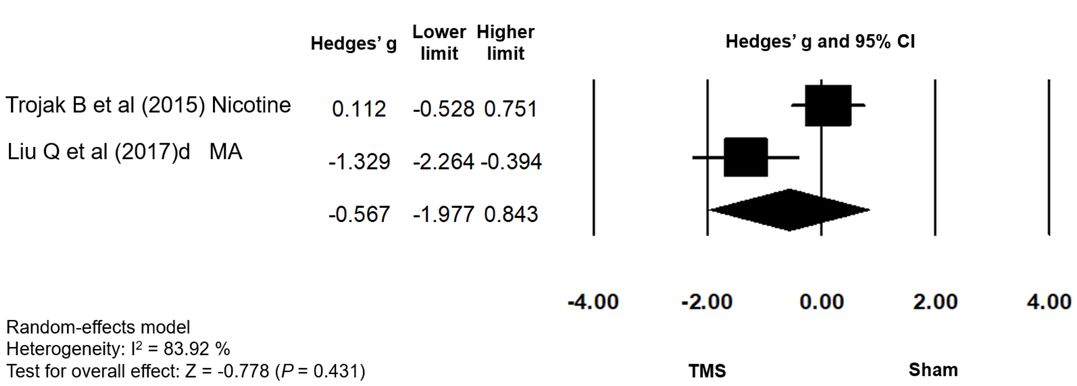
Figure 3 Meta-analysis of the immediate effects of other rTMS protocols over DLPFC on craving

(A) Inhibitory rTMS of the left DLPFC



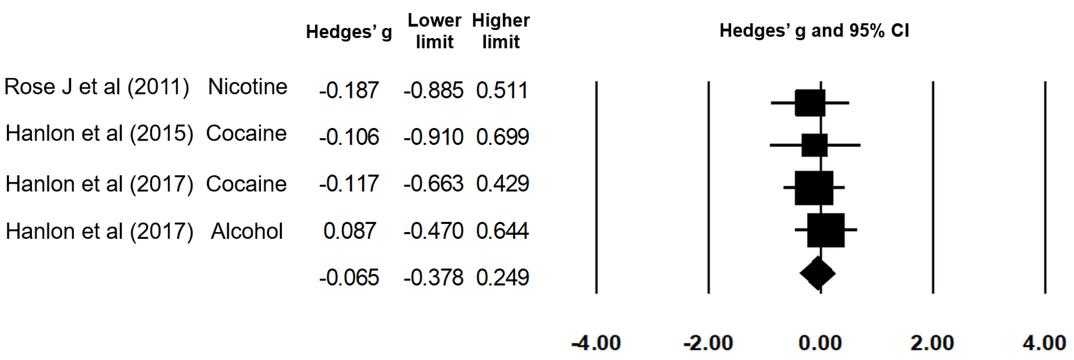
Random-effects model
Heterogeneity: I^2 = 92.81 %
Test for overall effect: Z = 0.120 (*P* = 0.905)

(B) Inhibitory rTMS of the right DLPFC



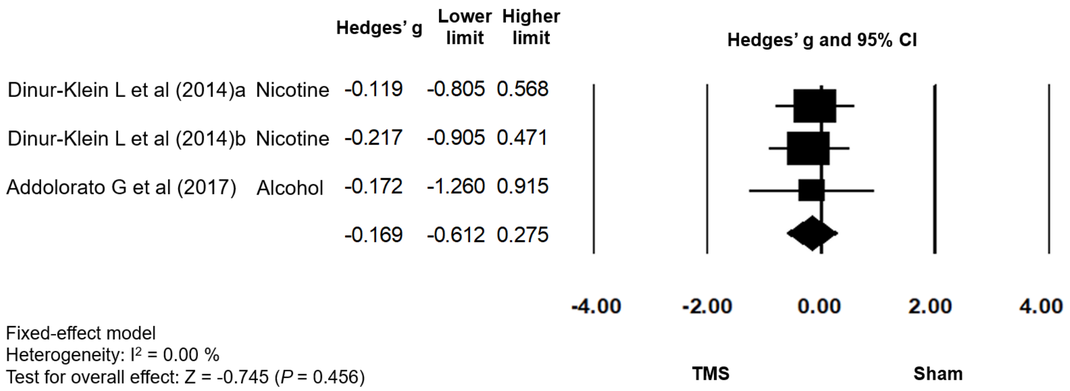
Random-effects model
Heterogeneity: I^2 = 83.92 %
Test for overall effect: Z = -0.778 (*P* = 0.431)

(C) Inhibitory rTMS of the MPFC



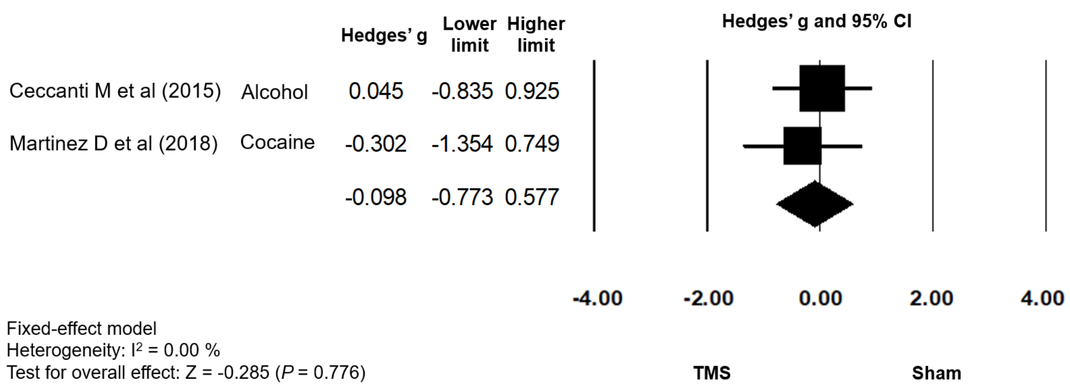
Fixed-effect model
Heterogeneity: I^2 = 0.00 %
Test for overall effect: Z = -0.404 (*P* = 0.686)

(D) Excitatory dTMS of the bilateral DLPFC and insula



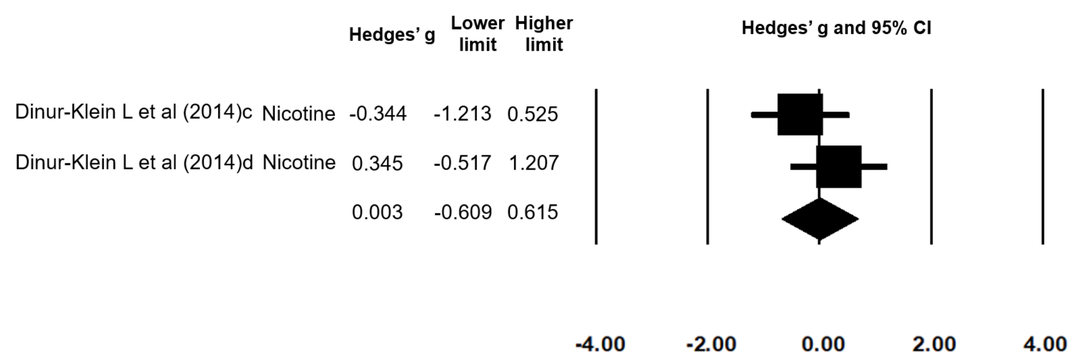
Fixed-effect model
Heterogeneity: I^2 = 0.00 %
Test for overall effect: Z = -0.745 (*P* = 0.456)

(E) Excitatory dTMS of the MPFC



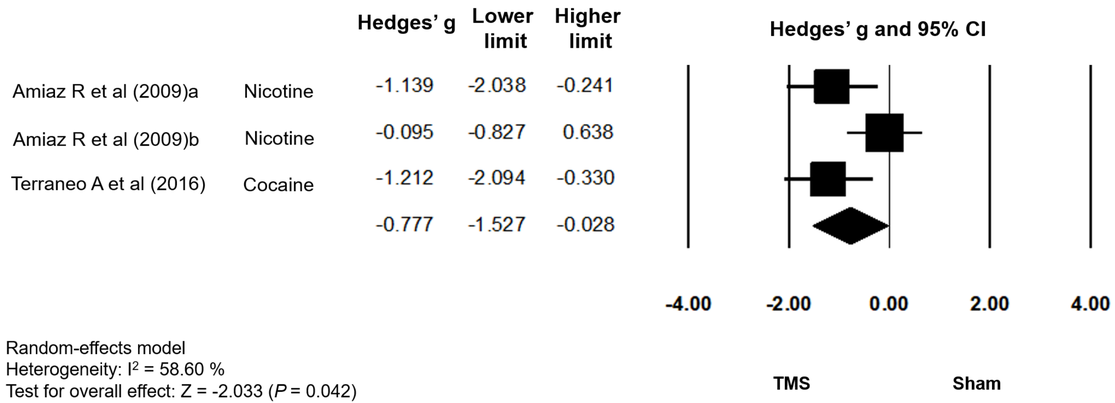
Fixed-effect model
Heterogeneity: I^2 = 0.00 %
Test for overall effect: Z = -0.285 (*P* = 0.776)

(F) Inhibitory dTMS of the bilateral DLPFC and insula



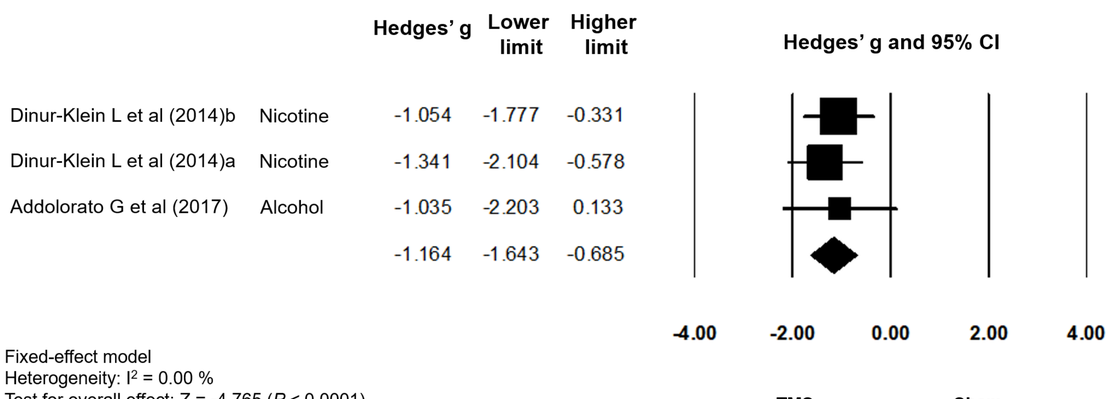
Fixed-effect model
Heterogeneity: I^2 = 17.80 %
Test for overall effect: Z = 0.010 (*P* = 0.992)

(A) Excitatory rTMS of the left DLPFC



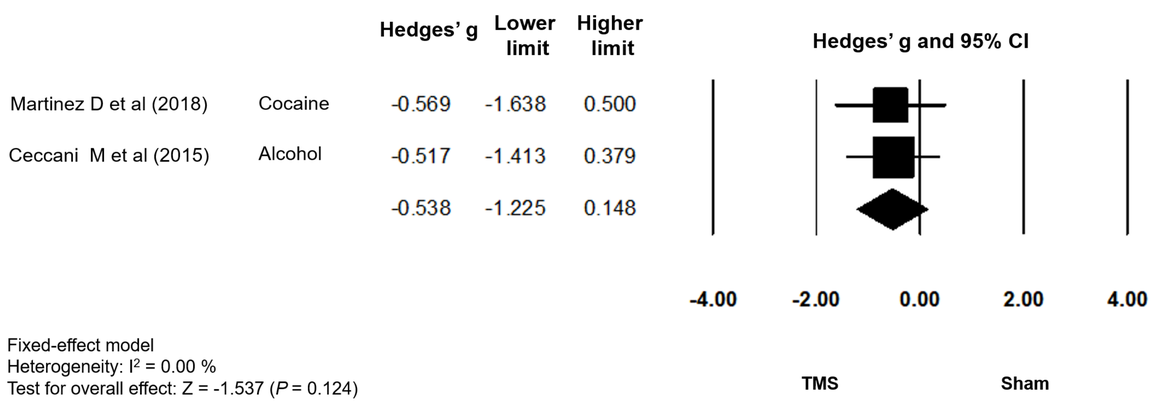
Random-effects model
Heterogeneity: I^2 = 58.60 %
Test for overall effect: Z = -2.033 (*P* = 0.042)

(B) Excitatory dTMS of the bilateral DLPFC and insula



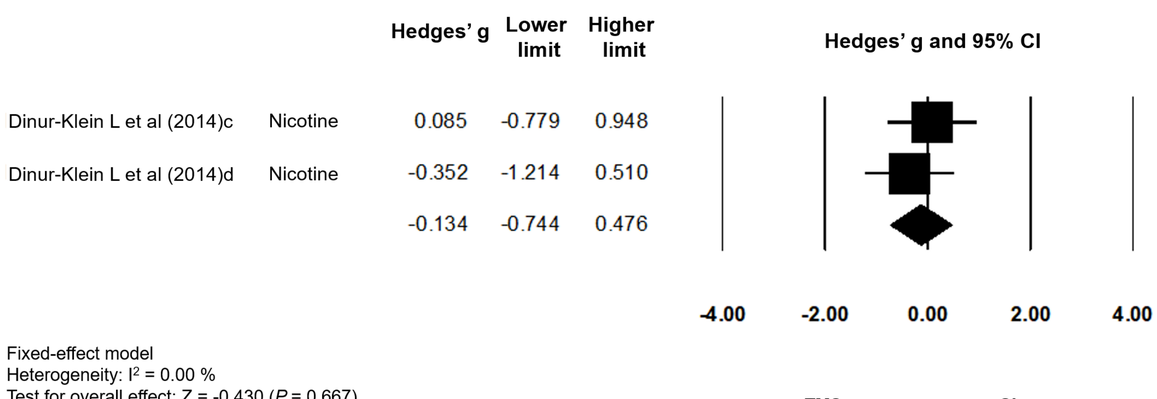
Fixed-effect model
Heterogeneity: I^2 = 0.00 %
Test for overall effect: Z = -4.765 (*P* < 0.0001)

(C) Excitatory dTMS of the MPFC



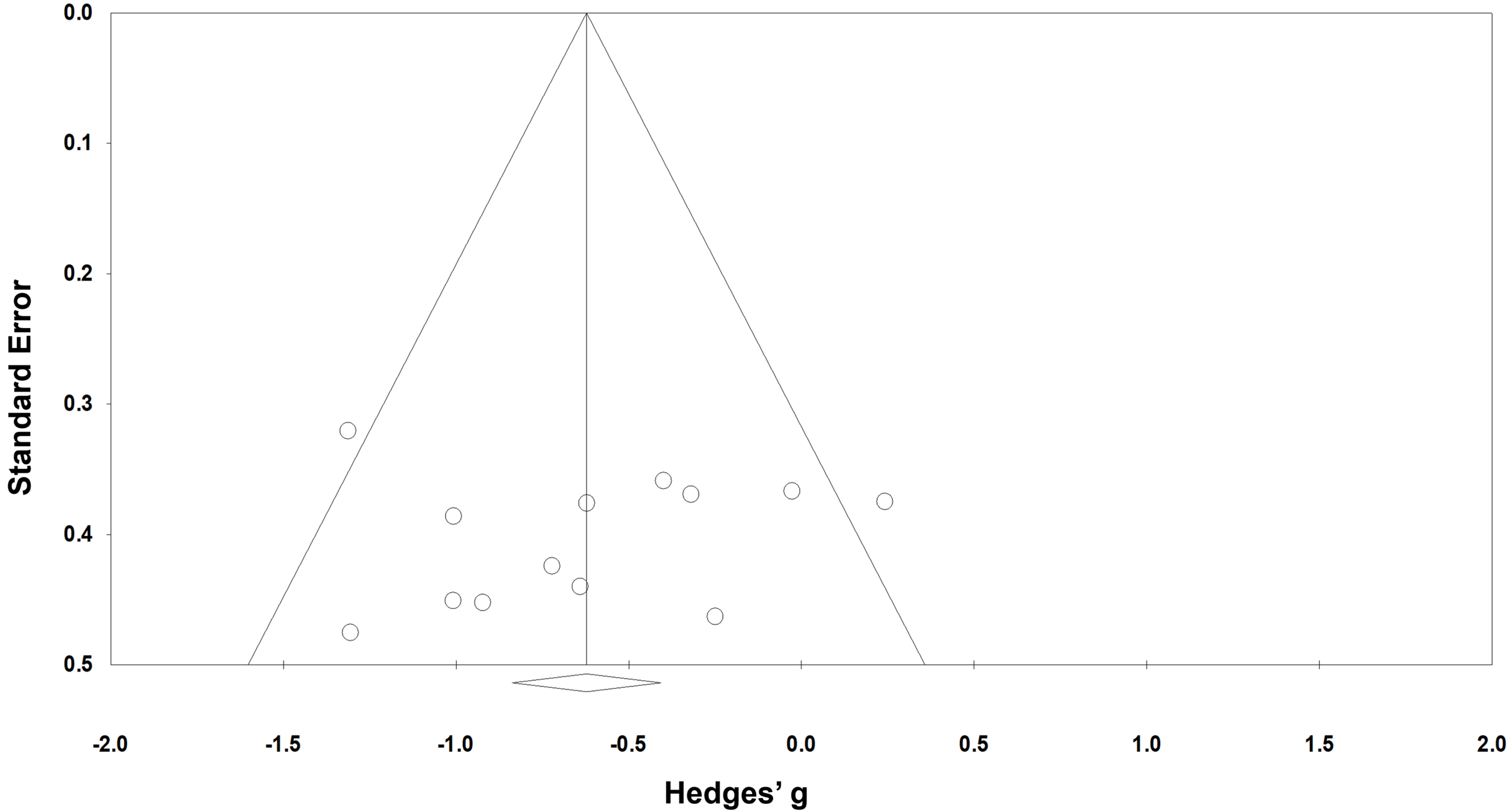
Fixed-effect model
Heterogeneity: I^2 = 0.00 %
Test for overall effect: Z = -1.537 (*P* = 0.124)

(D) Inhibitory dTMS of the bilateral DLPFC and insula



Fixed-effect model
Heterogeneity: I^2 = 0.00 %
Test for overall effect: Z = -0.430 (*P* = 0.667)

Figure 5 Tunnel plot of standard error by Hedges' g



Supplemental section

Table S1: Methodological quality assessment of included studies

Study	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Total scores
Nicotine dependence											
Johann M et al (2003)	1	0	1	1	0	1	1	1	1	1	8
Amiaz R et al (2009)	1	0	1	1	1	1	0	1	1	1	8
Rose J et al (2011)	1	0	1	1	0	1	1	1	1	1	8
Li X et al (2013)a	1	0	1	1	0	1	0	1	1	1	7
Pripfl J et al (2014)	1	0	0	0	0	0	1	1	1	1	5
Dieler A et al (2014)	1	0	1	1	0	1	1	1	1	1	8
Dinur-Klein L et al (2014)	1	0	1	1	1	1	1	0	1	1	8
Trojak B et al (2015)	1	0	1	1	0	1	0	1	1	1	7
Li X et al (2017)	1	0	1	1	0	1	1	1	1	1	8
Alcohol dependence											
Mishra B et al (2010)	1	0	1	1	0	1	1	1	1	1	8
Herremans S et al	1	0	1	1	0	1	0	1	1	1	7

(2012)											
Herremans S et al (2013)	1	0	1	1	0	1	0	0	1	1	6
Herremans S et al (2015)	1	0	1	1	1	1	0	1	1	1	8
Ceccanti M et al (2015)	1	0	1	1	1	1	0	1	1	1	8
Del Felice A et al (2016)	1	0	1	1	0	1	0	1	1	1	8
Hanlon C et al (2017)	1	0	1	1	0	1	1	1	1	1	8
Addolorato G et al (2017)	1	0	0	1	1	1	0	0	1	1	6
Drug dependence											
Li X et al (2013)b	1	0	1	1	0	1	1	1	1	1	8
Hanlon C et al (2015)	1	0	1	1	0	1	1	1	1	1	8
Shen Y et al (2016)	1	0	0	1	0	1	1	1	1	1	7
Terraneo A et al (2016)	1	0	1	0	0	0	1	1	1	1	6
Su H et al (2017)	1	0	1	1	1	1	1	1	1	1	9
Liu Q et al (2017)	1	0	1	1	0	1	1	1	1	1	8

Sahlem G et al (2018)	1	0	1	1	1	1	0	1	1	1	8
Liang Y et al (2018)	1	0	1	1	1	1	0	1	1	1	8
Martinez D et al (2018)	1	0	1	1	0	1	1	1	1	1	8

Notes: item 1: random allocation; item 2: concealment of allocation; item 3: baseline equivalence; item 4: blinding procedure (subjects); item 5: blinding procedure (therapists); item 6: blinding procedure (assessors); item 7: intention to treat analysis; item 8: adequate follow-up; item 9: between-group statistical analysis item 10: measurement of data variability and point estimates.

Table S2. Data extracted from individual study for Meta-analysis

Study	Outcome assessing craving	Craving			Outcome assessing consumption	Substance consumption		
		Pre	Post	FU		Pre	Post	FU
Johann M et al (2003)	VAS	Change scores (post/pre %): V: 48.0 (20.3); S: 68.4 (32.1);		/	NA	/	/	/
Amiaz R et al (2009)	VAS	RS: 4.3 (3.1); RN: 3.6 (2.9); SS: 4.4 (2.9); SN: 4.3 (2.3);	**10-d TMS**: RS: 2.5 (1.8); RN: 3.5 (2.5); SS: 5.1 (3.0); SN: 3.6 (2.5);	**6-m FU**: RS: 6.3 (3.4); RN: 5.2 (2.9); SS: 4.6 (4.6); SN: 6.1 (4.1);	Self-report cigarettes/d	RS: 29.2 (13.3); RN: 28.7 (9.9); SS: 27.4 (13.0); SN: 30.5 (15.1);	**10-d TMS**: RS: 10.7 (7.6); RN: 13.8 (7.8); SS: 18.1 (7.8); SN: 16.6 (11.6);	**6-m FU**: RS: 14.1 (7.4); RN: 21.7 (12.6); SS: 23.6 (19.8); SN: 22.1 (16.3);
Rose J et al (2011)	SJQ	Change scores (post-pre) **HF**: 1.0 (0.9); **LF**: 0.2 (1.1); **S**: 0.4 (1.1);		/	NA	/	/	/
Li X et al (2013)a	QSU-B	**V**: 64.1 (22.1); **S**: 63.0 (18.0);	**V**: 45.7 (24.0); **S**: 52.4 (23.6);	/	NA	/	/	/
Pripfl J et al (2014)	5-point rating	Change scores (post-pre): **V**: -0.7 (0.7); **S**: -0.3 (0.6);		/	NA	/	/	/

Dieler A et al (2014)	QSU	**V**: 83.6 (36.8); **S**: 81.9 (35.9);	**V**: 56.5 (33.8); **S**: 47.7 (16.7);	/	Number of relapses	/	/	12-m FU: **V**: 28; **S**: 31;
Dinur-Klein L et al (2014)	sTCQ	**10+**: 47.1 (17.1); **1+**: 51.0 (12.3); **0+**: 50.1 (17.1); **10-**: 51.9 (13.5); **1-**: 44.2 (18.1); **0-**: 54.3 (13.7);	**10+**: 31.8 (14.5); **1+**: 43.2 (13.9); **0+**: 36.9 (15.1); **10-**: 36.3 (17.2); **1-**: 27.6 (10.9); **0-**: 42.8 (15.8);	/	Self-report cigarettes/d	**10+**: 27.9 (1.1); **1+**: 24.2 (6.5); **0+**: 27.2 (9.0); **10-**: 29.7 (8.8); **1-**: 26.9 (6.5); **0-**: 31.0 (7.7);	**10+**: 5.8 (8.2); **1+**: 18.3 (10.5); **0+**: 20.2 (13.3); **10-**: 10.3 (9.9); **1-**: 14.8 (9.5); **0-**: 22.7 (10.4);	/
Trojak B et al (2015)	VAS	Change scores (post-pre): **V**: -2.6 (3.5); **S**: -3.0 (3.5);		/	Percentage of relapses		**V**: 11.2 %; **S**: 50 %;	**12-w FU**: **V**: 72.3 %; **S**: 72.3 %;
Li X et al (2017)	VAS	**V**: 6.8 (2.3); **S**: 5.4 (2.4);	**V**: 6.4 (2.4); **S**: 6.5 (2.1);	/	NA	/	/	/
Mishra B et al (2010)	ACQ	**V**: 245.2 (23.5); **S**: 244.5 (28.7);	**V**: 43.4 (18.1); **S**: 86.7 (11.2);	**1-m FU**: **V**: 44.3 (73.8); **S**: 89.9 (103.8);	NA	/	/	/

Herremans S et al (2012)	OCDS	**V**: 4.7 (3.0); **S**: 5.8 (3.5);	**V**: 4.3 (3.7); **S**: 5.0 (3.4);	/	NA	/	/	/
Herremans S et al (2013)	OCDS	**V**: 9.5 (7.7); **S**: 12.8 (10.1);	**V**: 8.6 (7.9); **S**: 11.6 (9.4);	/	NA	/	/	/
Herremans S et al (2015)	TLS	**V**: 2.6 (2.8); **S**: 2.5 (3.1);	**V**: 2.2 (2.1); **S**: 2.2 (3.0);	/	NA	/	/	/
Ceccanti M et al (2015)	VAS	**V**: 26.7 (21.9); **S**: 43.9 (38.7);	**V**: 17.4 (21.0); **S**: 33.3 (33.0);	**2-m FU**: **V**: 15.5 (27.7); **S**: 49.5 (51.1);	Daily alcohol intake	**V**: 18.6 (14.7); **S**: 10.1 (8.4);	**V**: 0.0 (0.0); **S**: 2.3 (4.5);	**2-m FU**: **V**: 1.0 (2.2); **S**: 2.0 (1.7);
Del Felice A et al (2016)	VAS	**V**: 3.8 (5.4); **S**: 5.0 (7.7);	**V**: 1.0 (1.2); **S**: 4.3 (5.4);	**1-m FU**: **V**: 0.9 (1.3); **S**: 1.9 (1.8)	NA	/	/	/
Hanlon C et al (2017)	VAS	**V**: 1.5 (1.5); **S**: 1.4 (1.6);	**V**: 1.7 (1.5); **S**: 1.4 (1.6);	/	NA	/	/	/
Addolorato G et al (2017)	OCDS	**V**: 32.2 (13.7); **S**: 23.0 (10.3);	/	**1-m FU**: **V**: 22.4 (17.5); **S**: 15.9 (11.2);	TLFB - total drinks	**V**: 224.8 (151.2); **S**: 97.2 (11.0);	/	**1-m FU**: **V**: 75.0 (94.0); **S**: 58.0 (100.6);
Li X et al	VAS	**V**: 23.1	**V**: 24.9	/	NA	/	/	/

(2013)b		(10.4); **S**: 23.1 (10.4);	(5.0); **S**: 17.9 (4.6);					
Su H et al (2017)	VAS	**V**: 27.5 (27.2); **S**: 34.0 (35.4);	**V**: 5.7 (6.7); **S**: 22.3 (34.4);	/	NA	/	/	/
Liu Q et al (2017)	VAS	**HF** (left): 68.0 (19.3); **HF** (right): 76.0 (10.8); **LF** (left): 60.0 (0.0); **LF** (right): 69 (13.7); **S**: 74.0 (20.1);	**HF** (left): 27.0 (29.1); **HF** (right): 37.0 (17.7); **LF** (left): 31.0 (18.5); **LF** (right): 36 (17.1); S: 67.4 (20.8);	/	NA	/	/	/
Liang Y et al (2018)	VAS	**V**: 34.6 (21.9); **S**: 36.4 (21.9);	**V**: 6.7 (9.2); **S**: 29.5 (20.8);	**3-m FU**: **V**: 7.1 (13.7); **S**: 32.3 (24.3);	NA	/	/	/
Hanlon C et al (2015)	VAS	**V**: 3.6 (2.5); **S**: 3.3 (1.6);	**V**: 2.3 (2.5); **S**: 2.3 (2.3);	/	NA	/	/	/
Terraneo A et al (2016)	VAS	**V**: 3.5 (1.5); **C**: 3.8 (1.4);	**V**: 0.9 (1.6); **C**: 2.6 (0.8);	/				

Hanlon C et al (2017)	VAS	**V**: 3.7 (2.9); **S**: 3.3 (2.7);	**V**: 2.9 (2.8); **S**: 2.9 (2.3);	/	NA	/	/	/
Martinez D et al (2018)	VAS	**HF**: 61.0 (38.1); **LF**: 21.7 (28.8) **S**: 16.8 (25.0);	**HF**: 37.7 (48.2); **LF**: 4.5 (4.8); **S**: 2.8 (4.0);	/	Choice for cocaine in a self-administration session	**HF**: 3.8 (4.0); **LF**: 4.7 (3.3); **S**: 4.8 (3.8);	**HF**: 1.8 (1.9); **LF**: 5.5 (3.5); **S**: 4.7 (4.0);	
Shen Y et al (2016)	VAS	**V**: 60.4 (35.4); **S**: 62.0 (30.0);	**V**: 25.0 (29.1); **S**: 55.0 (29.1);	/	NA	/	/	/
Sahlem G et al (2018)	MCQ	**V**: 45.4 (7.4); **S**: 43.5 (7.3);	**V**: 40.9 (7.3); **S**: 39.2 (7.4);	/	NA	/	/	/

Values are represented as mean (SD), number or percentage.

Abbreviations: V: Verum; S: Sham; d: day; w: week; m: month; C: Control; FU: Follow-up; NA: Not available; 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; 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; sTCQ: Short version of the Tobacco Craving questionnaire; ACQ: Alcohol craving questionnaire; OCDS: Obsessive-compulsive drinking scale; TLS: Ten-point Likert scales; TLFB: Timeline followback; MCQ: Marijuana craving questionnaire.

Supplemental Figures Legends

Figure S1. Sensitivity analysis by the leave-one-out method;

Figure S2. Subgroup meta-analysis shows beneficial effects of excitatory left DLPFC stimulation for reducing nicotine and drug craving, but not for alcohol craving;

Figure S3. Meta-analysis investigating the durability of effects of excitatory rTMS of the left DLPFC shows a insignificant effect on craving;

Statistics with study removed

		Point	Lower limit	Upper limit
Amiaz R et al (2009)a	Nicotine	-0.598	-0.820	-0.376
Amiaz R et al (2009)b	Nicotine	-0.704	-0.929	-0.478
Del Felice A et al (2016)	Alcohol	-0.645	-0.866	-0.423
Johann M et al (2003)	Nicotine	-0.615	-0.838	-0.392
Li X et al (2013)a	Nicotine	-0.652	-0.878	-0.426
Li X et al (2017)	Nicotine	-0.621	-0.844	-0.399
Liang Y et al (2018)	MA	-0.530	-0.760	-0.301
Liu Q et al (2017)a	MA	-0.584	-0.805	-0.362
Pripfl J et al (2014)	Nicotine	-0.622	-0.848	-0.397
Sahlem G et al (2018)	Cannabis	-0.681	-0.907	-0.455
Shen Y et al (2016)	Heroin	-0.603	-0.826	-0.381
Su H et al (2017)	MA	-0.645	-0.872	-0.419
Terraneo A et al (2016)	Cocaine	-0.588	-0.813	-0.364
		-0.622	-0.838	-0.407

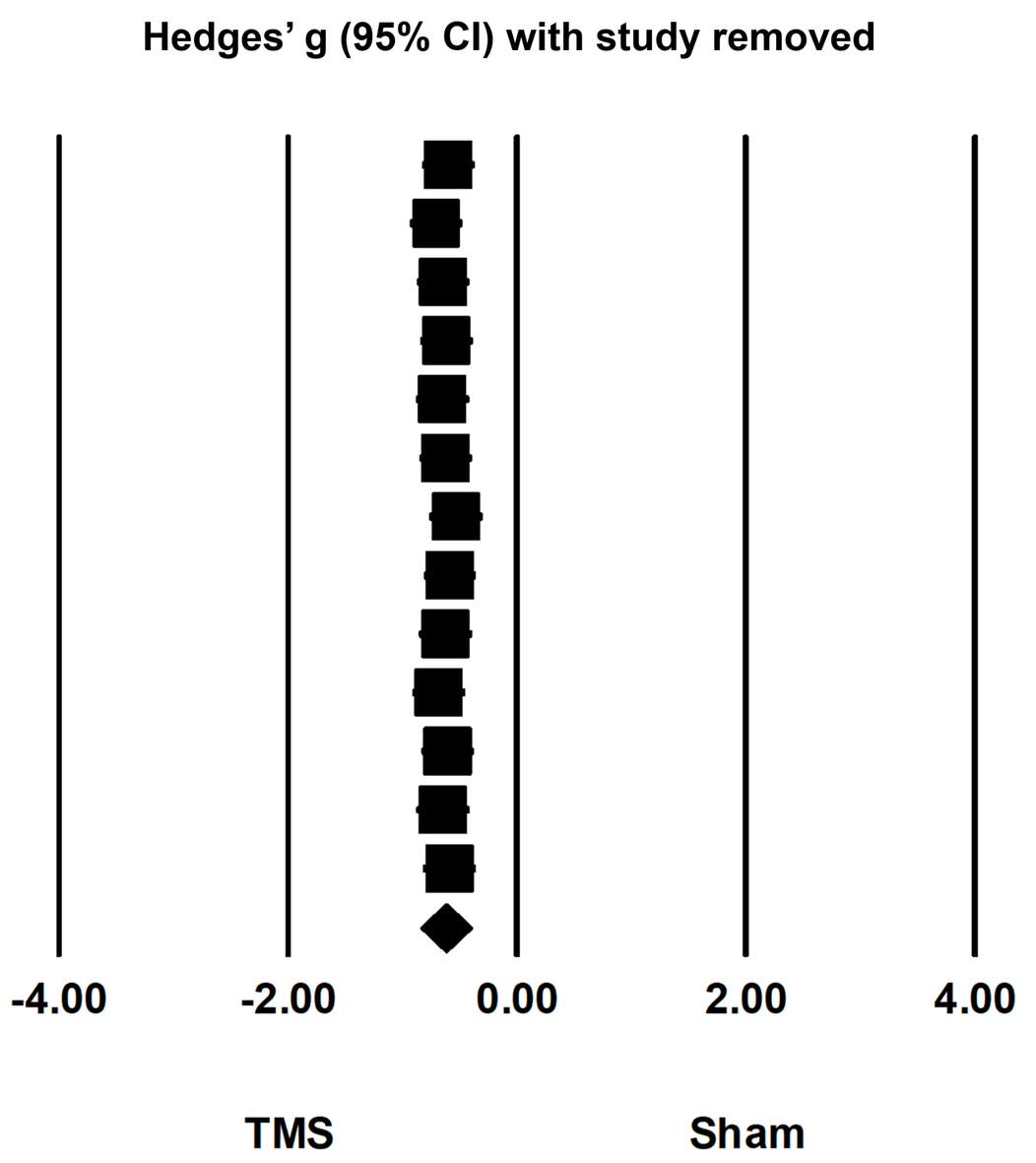


Figure S1 Sensitivity analysis by the leave-one-out method

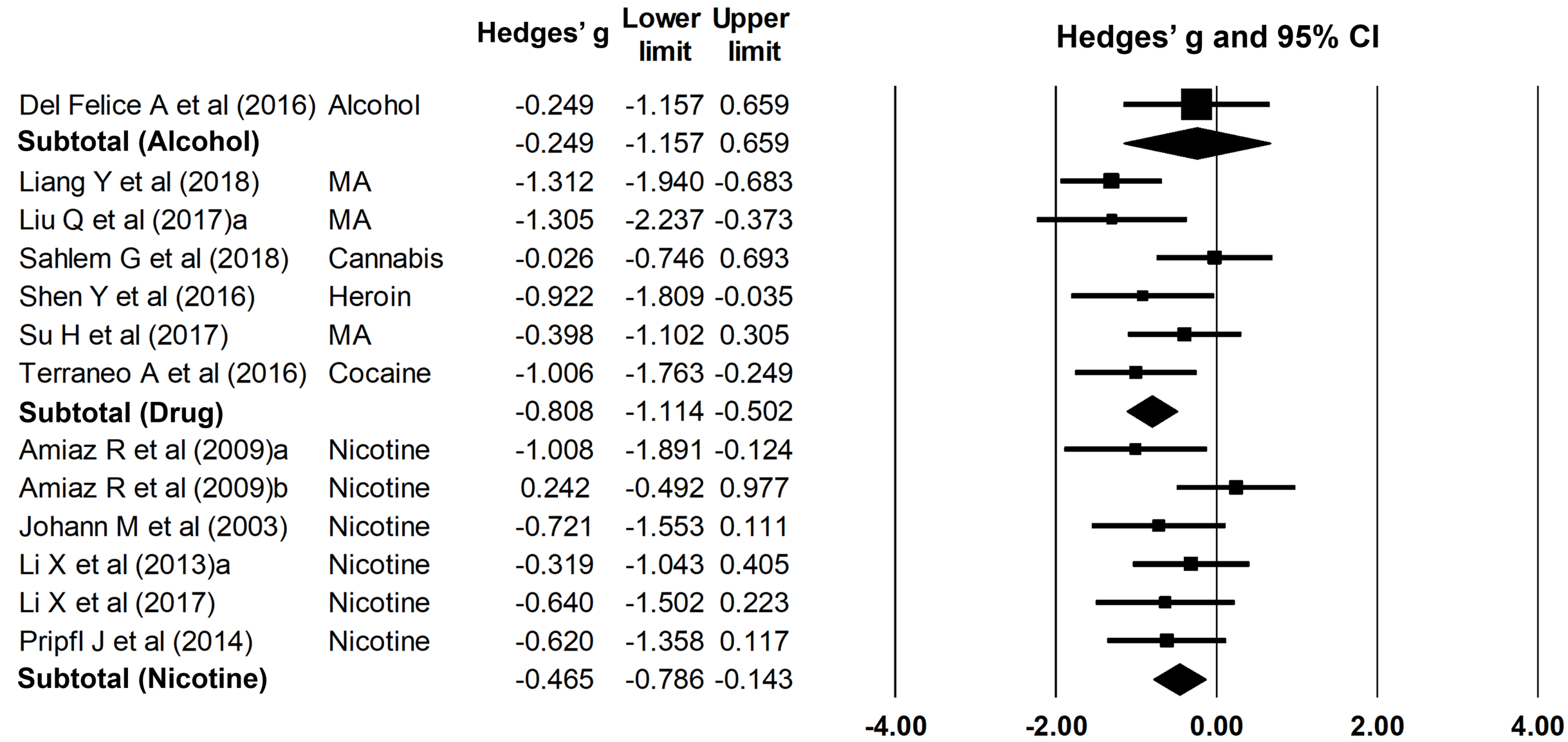
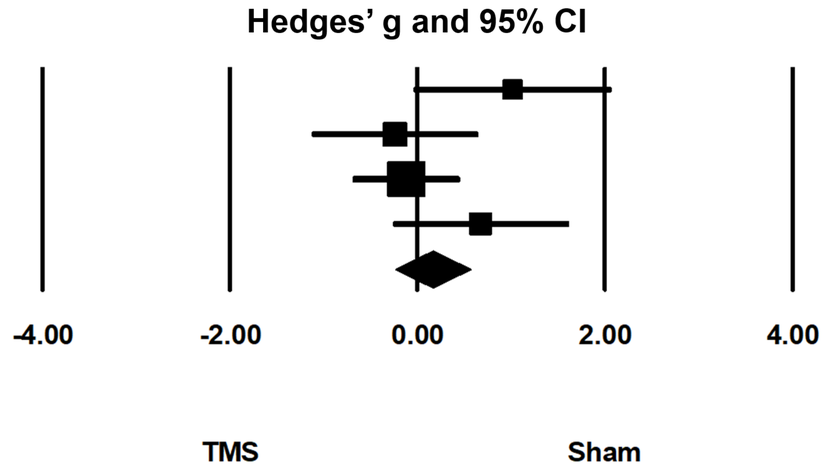


Figure S2 Subgroup meta-analysis shows beneficial effects of excitatory left DLPFC stimulation for reducing nicotine and drug craving, but not for alcohol craving

		Follow-up	Hedges' g	Lower limit	Higher limit
Amiaz R et al (2009)a	Nicotine	6-month	1.017	-0.034	2.068
Amiaz R et al (2009)b	Nicotine	6-month	-0.236	-1.119	0.647
Liang Y et al (2018)	MA	3-month	-0.117	-0.686	0.452
Del Felice A et al (2016)	Alcohol	1-month	0.678	-0.254	1.610
			0.161	-0.233	0.556



Fixed-effect model
Heterogeneity: I^2 = 44.71 %
Test for overall effect: Z = 0.855 (*P* = 0.393)

Figure S3 Meta-analysis investigating the durability of effects of excitatory rTMS of the left DLPFC shows a insignificant effect on craving