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REVIEW

ADDICTION SSA

Reducing craving and consumption in individuals with drug addiction, obesity or overeating through neuromodulation intervention: a systematic review and meta-analysis of its follow-up effects

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Abstract

Background and aims: Non-invasive brain stimulation has shown potential in clinical applications aiming at reducing craving and consumption levels in individuals with drug addiction or overeating behaviour. However, it is unclear whether these intervention effects are maintained over time. This study aimed to measure the immediate, short- and long-term effects of excitatory transcranial direct current stimulation (tDCS) and high-frequency repetitive transcranial magnetic stimulation (rTMS) targeting at dorsolateral prefrontal cortex (dlPFC) in people with drug addiction or overeating.

Methods: A systematic review and random effects meta-analysis. We included 20 articles (total of 22 studies using randomized controlled trials: 3 alcohol dependence, 3 drug dependence, 12 smoking, 4 overeating; total: 720 participants) from January 2000 to June 2020, which reported at least one follow-up assessment of craving, consumption or abstinence levels after the intervention. We compared effects of active versus sham stimulation immediately after the intervention and at the last follow-up assessment, as compared with baseline.

Results: Excitatory neuromodulation of dlPFC activity reduced craving and consumption immediately after the intervention (craving: g = 0.734, CI = 0.447–1.021, P < 0.001; consumption: g = 0.527, CI = 0.309–0.745; P < 0.001), as well as during short-, mid- and long-term abstinence (craving: g = 0.677, CI = 0.440–0.914, P < 0.001; consumption: g = 0.445, CI = 0.245–0.645, P < 0.001; abstinence levels: g = 0.698, CI = 0.433–0.963, P < 0.001; average time of follow-up: 84 ± 83 days after last stimulation). Additional analysis demonstrated that the intervention effects were sustained in all populations studied (food, nicotine, alcohol or drug abuse) and with both stimulation techniques used (rTMS, tDCS). Interventions targeting at the left (vs right) hemisphere may be more effective.

Conclusions: Excitatory neuromodulation targeting the dorsolateral prefrontal cortex appears to lead to a sustained reduction of craving and consumption in individuals with addiction or overeating behaviour.

Sensen Song and Anna Zilverstand contributed equally to this article.

KEYWORDS
Addiction, brain stimulation, dlPFC, eating disorders, neuromodulation, rTMS, tDCS

INTRODUCTION

Drug addiction (e.g. illegal drugs, nicotine or alcohol) and obesity cause serious long-term harms to people's health. According to the United Nations Office on Drugs and Crime (UNODC) and World Health Organization (WHO) reports, there were 269 million illegal drug users [1] and 1.3 billion nicotine users around the world in 2018 [2]. Moreover, 3 million deaths every year resulted from harmful use of alcohol [3] and nearly 2 billion adults worldwide were overweight in 2016 [4]. In recent years, there is a growing interest in using non-invasive brain stimulation as a novel treatment option for drug addiction and overeating behaviour. The primary goal of these therapeutic interventions is to reduce consumption to less harmful levels or even stop consumption (i.e. achieving abstinence) of a specific substance [5] or overeating of palatable food [6].

Neuromodulation interventions in individuals with drug addiction and overeating behaviour have most often targeted dorsolateral prefrontal cortex (dlPFC) [7], because alterations in dlPFC function in these populations have been linked to a failure to exert cognitive control over drug/food intake [6,8–15]. At the core of this impairment seems to be a failure to inhibit cravings (i.e. intensive desire or urge to consume) and to self-regulate consumption in the presence of the substances/food or when facing associated cues [6,9–12,16,17]. The two types of non-invasive brain stimulation techniques that have been most widely used for neuromodulation interventions in these populations are repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) [5,18]. Conventional rTMS uses a figure of eight formed coil to generate brief focal electromagnetic pulses that penetrate the skull to stimulate specific brain regions (up to 1.5 cm below the skull). In contrast, a newer form of rTMS, deep rTMS [19], uses an H-coil to stimulate both surface cortical and deeper subcortical brain tissue (up to 4.5–5.5 cm from the skull). For both types of rTMS, high frequency (no less than 5 HZ) provides excitatory stimulation that increases neuronal excitability of the targeted brain area, whereas low frequency (no more than 1 HZ) reduces neuronal excitability [20]. Finally, intermittent theta burst stimulation (iTBS) is a new form of high frequency rTMS that also induces excitatory effects [21,22]. Unlike rTMS, tDCS delivers weak, but long-lasting low-intensity electric currents (most often used: 1 mA or 2 mA, 10–20 minutes continuous stimulation) through electrodes targeted at surface brain areas to enhance (anode) or reduce (cathode) cortical excitability [23]. Because of its position immediately under the cortical surface, dlPFC can be more easily stimulated with either rTMS or tDCS than other brain areas (such as mPFC [24]). Because of this and because of the important role of dlPFC in cognitive control, it is the most widely targeted brain area in neuromodulation interventions for people with drug addiction or overeating [7].

Previous systematic review and meta-analytical studies on the immediate effects of neuromodulation targeting at dlPFC, have found that these interventions led to a reduction of craving and consumption levels in individuals with drug addiction and overeating when the effects were assessed immediately after the intervention (e.g. [7,25,26]). Moreover, one meta-analysis found that the effect sizes of these improvements increased linearly with longer stimulation protocols, indicating a dose–response effect of the intervention [7]. However, no meta-analytical study has yet been conducted to systematically investigate the long-term effects of neuromodulation interventions in addiction, although they are of great importance for the clinical applicability of these stimulation protocols. Individual studies that investigated the long-term effects of these neuromodulation protocols have reported mixed results. For craving measures, some of these studies reported a significant relief at a 25-day [27], 1-month [28,29], or 12-month [30] follow-up, but others did not show such effects at a 2-week [31], 3-month [32] follow-up. For consumption or abstinence rate, some studies showed a significant improvement at a 1-month [28], or 6-month [33,34] follow-up, whereas other studies did not demonstrate such an improvement effect at a 2-month [35] or 4-month [36] follow-up.

The current systematic review evaluated the long-term effects of the most widely used stimulation protocols (excitatory tDCS and rTMS targeting at dlPFC) that have been tested in controlled clinical trials. We investigated the following questions: (i) are the improvements seen immediately after the intervention stable, such that they are maintained over periods of days or months? (ii) If such stable improvements exist, are there differences in the effects between different types of populations (e.g. illegal drugs, alcohol, nicotine or food abuse), between stimulation techniques, or between stimulated hemispheres? (iii) If such stable improvements exist, are they maintained during short-, versus mid- or long-term abstinence?

METHODS

Literature search

We reported this study in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [37]. We followed the patient/population, intervention, comparison and outcomes study design (PICOS) framework to define our research question: we want to investigate the 'P' (patient/population) of individuals with addiction or overeating; the 'I' (intervention) tDCS or rTMS neuromodulation; 'C' (comparisons) with sham interventions; the 'O' (outcomes) craving or consumption or abstinence level at a follow-up evaluation; as assessed by the 'S' (study design) randomized controlled trials. Based on this framework, we first performed an online literature search (see Supplementary A for specific search terms) to identify studies published from January 2000 to June 2020 in PubMed, Web of Science, EMBASE, PsycINFO, Medline databases

and CNKI. Two authors (S.S. and W.G.) independently screened titles, abstracts or full texts, and excluded any irrelevant articles. We also carefully read previous meta-analysis studies [7,25,26,38–46] and recent review articles [5,6,18,47–49] to find additional potential studies that met inclusion criteria.

Inclusion and exclusion criteria

Only peer-reviewed studies satisfying the following criteria were included: (i) used excitatory tDCS or high-frequency rTMS (including conventional rTMS, deep rTMS and iTBS) stimulating the dlPFC in participants with (a) eating disorders (binge eating type/bulimia nervosa) or obesity or individuals with frequent food craving or (b) substance use disorder (e.g. nicotine, alcohol or illicit drugs) or frequent smoking; (ii) randomized controlled trials that used sham brain stimulation; (iii) reported at least one follow-up visit (>2 days after the last neuromodulation session [50]) during which craving or consumption or abstinence were assessed; and (iv) provided means, standard deviations, *t*, *F* or *P* statistics or other data that could be used to calculate the effect size. The inclusion criteria did not limit the tools used to assess clinical outcomes or the settings of the neuromodulation intervention parameters.

Studies meeting any of the following criteria were excluded: (i) included other types of patients (e.g. depression, schizophrenia or chronic pain); (ii) used techniques other than high frequency rTMS (e.g. low frequency rTMS or continuous theta burst stimulation) or excitatory tDCS; (iii) assessed the neuromodulation effects targeted at dlPFC using outcome measures other than craving or consumption or abstinence; (iv) combined neuromodulation with other intervention methods (e.g. cognitive-behavioural therapy or pharmacological therapy); and (v) not published in English, Chinese or German.

Risk of bias assessment and data extraction

The Cochrane Collaboration's risk of bias tool was used to evaluate the risk of bias for each study [51]. High, low or unclear risk ratings were assigned for (i) selection bias (including random sequence generation and allocation concealment); (ii) performance bias (including blinding of participants and personnel); (iii) detection bias (including blinding of each outcome assessment); (iv) attrition bias (including incomplete outcome data); (v) reporting bias (including selective reporting); (vi) other bias [51]. Additionally, the sham condition and blinding procedures used within studies were evaluated.

The extracted data included the study name, type of population, number of participants, stimulation technique, anodal/rTMS stimulation target, total number of stimulation sessions (per condition), intensity (% resting motor threshold) / frequency (Hz), current density / current duration, duration between the last stimulation session and follow-up evaluation, the measures used to assess craving or consumption or abstinence during follow-up. For studies without means and standard deviations, we used *P* values to calculate the effect size with Wilson's practical meta-analysis effect size calculator [52]. For studies that reported more than one outcome measures, we calculated each measure's effect size and merged them to obtain a pooled effect size by Comprehensive Meta-Analysis (CMA) software (e.g. one study used the Food Cravings Questionnaire-Trait, Food Craving Questionnaire-State and Food Craving Inventory [27]). We only evaluated the follow-up effect if the time interval between the last stimulation and the last follow-up evaluation was >2 days [50]. For studies with multiple follow-ups (multiple visits >2 days after the last neuromodulation session [50]) (Table 1), we only included data from the last follow-up in the respective analyses to avoid over-representation of these studies. If a study did not report sufficient data for calculating the effect size, we contacted the authors. If a study only used figures to report data, we used Engauge Digitizer [53] to extract the data from the figures.

Risk of bias assessment, blinding procedures valuation and data extraction were conducted by two authors (S.S. and W.G.) independently. Any disagreements were resolved through discussion.

Data analysis

The statistical analysis plan was not pre-registered. The analysis was done using CMA (version 2.0). A synthesized effect size Hedge's *g* was calculated to represent the effect across studies, with a 95% CI. Compared to Cohen's *d*, Hedge's *g* can be corrected for a possible bias of studies with small sample sizes [54]. A random-effects model was used for all meta-analyses, which provides a more conservative estimate and is more appropriate for generalization beyond the included studies than a fixed-effects model [54,55]. For each meta-analysis with at least 10 studies, a revised funnel plot after trim and fill technique [56] and Egger's regression intercept test was adopted to assess publication bias [57]. Higgins' I^2 statistic was used to evaluate between-study heterogeneity [58].

As illustrated in Fig. 1a, three different effects of neuromodulation on craving, consumption and abstinence were calculated: (i) the acute (or immediate) effect of neuromodulation during ongoing stimulation sessions (i.e. active [last-stimulation minus baseline] vs sham [last-stimulation minus baseline]); (ii) the maintenance effect (i.e. the follow-up effects we hypothesized to find in the current meta-analysis) of the neuromodulation intervention until the last follow-up assessment as compared to the baseline (i.e. active [last follow-up minus baseline] vs sham [last follow-up minus baseline]); and (iii) a potential post-stimulation effect between the last stimulation and the last follow-up evaluation (i.e. active [last follow-up minus last-stimulation] vs sham [last follow-up minus last-stimulation]). If there was a larger effect in the active neuromodulation condition as compared to the sham condition, then the effect size was defined as a positive value. Furthermore, to investigate if there were differences between drug and 'food' addiction [12,59], drug-specific effects [10], or differences by neuromodulation protocol [49], we performed subgroup analyses using Q test [52] to explore whether maintenance effects differed by (i) the type of populations, stimulation technique

TABLE 1 Study and sample characteristics for included studies

Study name	*Type of population*	*No. of participants*	*Stimulation technique*	*Anodal/rTMS stimulation target*	*Total no. of sessions*	*Intensity (%RMT)/ frequency (Hz)*	*Current density/ current duration*	*Duration between the last stimulation session and follow-up*	*Craving measure (follow-up)*	*Consumption measure (follow-up)*	*Abstinence measure (follow-up)*
Alcohol (3 studies)											
Klauss *et al*. [34]	Alcohol dependence	33	tDCS	Right dlPFC	5	NA	2 mA/26 min	1,2,3 and 4 weeks, 2,3,4,5 and 6 months	NA	NA	Self-report abstinence
Klauss *et al*. [69]	Alcohol dependence	45	tDCS	Right dlPFC	10	NA	2 mA/20 min	3 months	NA	NA	Self-report abstinence
Mishra *et al*. [64]	Alcohol dependence	45	rTMS	Right dlPFC	10	110/10	NA	1 month	ACQ	NA	NA
Food (4 studies)											
Bravo *et al*. [63]	Obesity	10	tDCS	Right dlPFC	5	NA	2 mA/30 min	10 days and 25 days	VAS	NA	NA
Ferrulli *et al*. [30]	Obesity	23	dTMS	Bilaterally PFC and insula	15	120/18	NA	1,6 and 12 months	FCQ-T	NA	NA
Kim *et al*. [31]	Obesity	57	rTMS	Left dlPFC	4	110/10	NA	2 weeks	VAS	Calories consumed	NA
Ljubisavljevic *et al*. [27]	Healthy individuals with frequent food cravings	27	tDCS	Right dlPFC	5	NA	2 mA/20 min	25 days	FCQ-T, FCQ-S and FCI	NA	NA
Nicotine (12 studies)											
Alghamdi *et al*. [36]	At least 10 cigarettes per day for at least 1 year	18	tDCS	Left dlPFC	3	NA	1.5 mA/20 min	1,2,3,4,5,6,7,8 days and 4 months	NA	Self-report cigarettes consumed	NA
Amiaz *et al*. [65]	Nicotine dependence	14	rTMS	Left dlPFC	10	100/10	NA	6 months	VAS	Self-report cigarettes consumed	NA
Behnam *et al*. [66] (study 1)[a]	Addicted to cigarette nicotine	68	tDCS	Left dlPFC	20	NA	2 mA/20 min	5 months	NA	Self-report cigarettes consumed	NA
Behnam *et al*. [66] (study 2)[b]		67	tDCS	Left dlPFC	20	NA	2 mA/20 min	3 months	NA		NA

(Continues)

TABLE 1 (Continued)

Study name	*Type of population*	*No. of participants*	*Stimulation technique*	*Anodal/rTMS stimulation target*	*Total no. of sessions*	*Intensity (%RMT)/ frequency (Hz)*	*Current density/ current duration*	*Duration between the last stimulation session and follow-up*	*Craving measure (follow-up)*	*Consumption measure (follow-up)*	*Abstinence measure (follow-up)*
	Addicted to cigarette nicotine									Self-report cigarettes consumed	
Brangioni *et al.* [62]	At least 10 cigarettes per day for at least 1 year	28	tDCS	Left dlPFC	5	NA	1 mA/20 min	2 days and 4 weeks	VAS	Self-report cigarettes consumed	NA
Dinur-Klein *et al.* [33]	Daily intake of at least 20 cigarettes	52	dTMS	Bilaterally PFC and insula	13	120/10	NA	6 months	NA	Self-report cigarettes consumed	Self-report abstinence
Fecteau *et al.* [68]	Average daily intake of at least 15 cigarettes	12	tDCS	Right dlPFC	5	NA	2 mA/30 min	1, 2, 3 and 4 days	NA	Self-report cigarettes consumed	NA
Hajloo *et al.* [60] (Daily smokers)	More than 10 cigarettes per day	20	tDCS	Left dlPFC	10	NA	2 mA/20 min	1 month	DDQ	NA	NA
Hajloo *et al.* [60] (Social smokers)	No more than 20 cigarettes per week	20	tDCS	Left dlPFC	10	NA	2 mA/20 min	1 month	DDQ	NA	NA
Li *et al.* [28]	Smoking 10 or more cigarettes per day	30	rTMS	Left dlPFC	10	100/10	NA	1 month and 3 months [c]	QSU-B	Self-report cigarettes consumed	Self-report abstinence
Mondino *et al.* [67]	Smoked between 10 and 25 cigarettes per day	28	tDCS	Right dlPFC	10	NA	2 mA/20 min	1–23 days	NA	Self-report cigarettes consumed	NA
Sheffer *et al.* [70]	Smoke 5–20 cigarettes daily	20	rTMS	Left dlPFC	8	110/20	NA	2, 6 and 10 weeks	NA	NA	Exhaled carbon monoxide
Drugs (3 studies)											
Alizadehgoradel *et al.* [29]	Methamphetamine dependence	28	tDCS	Left dlPFC	10	NA	2 mA/20 min	1 month	DDQ (desire and intention)	NA	NA

(Continues)

TABLE 1 (Continued)

Study name	Type of population	No. of participants	Stimulation technique	Anodal/rTMS stimulation target	Total no. of sessions	Intensity (%RMT)/ frequency (Hz)	Current density/ current duration	Duration between the last stimulation session and follow-up	Craving measure (follow-up)	Consumption measure (follow-up)	Abstinence measure (follow-up)
Klauss *et al.* [35]	Crack-cocaine dependence	29	tDCS	Right dlPFC	10	NA	2 mA/20 min	30 days and 60 days	NA	NA	Self-report abstinence
Liang *et al.* [61]	Methamphetamine dependence	46	rTMS	Left dlPFC	10	100/10	NA	3 months	VAS	NA	NA

ACQ = Alcohol Craving Questionnaire; DDQ = Desires for Drug Questionnaire; dTMS = deep repetitive Transcranial Magnetic Stimulation; dlPFC = dorsolateral prefrontal cortex; FCI = Food Craving Inventory; FCQ-S = Food Craving Questionnaire-State; FCQ-T = Food Cravings Questionnaire-Trait; NA = not available; PFC = prefrontal cortex; QSU-B = Questionnaire of Smoking Urges-Brief; RMT = resting motor threshold; rTMS = repetitive transcranial magnetic stimulation; tDCS = transcranial direct current stimulation; VAS = Visual Analogue Scale. Note that: we only reported the outcome measures collected during the last follow-up evaluation. [a]Behnam et al. [66] (study 1) used a protocol of 20 sessions during 4 continuous weeks. [b]Behnam et al. [66] (study 2) used a protocol of 20 sessions for 12 continuous weeks. [c]We reported the 1-month instead of the 3-month follow-up, to keep the follow-up time points consistent across all three outcome measures reported.

and anodal stimulation hemisphere; or (ii) by duration between the last stimulation and the last follow-up assessment (short-term: 3–30 days; mid-term: 1–6 months; long-term: > 6 months [50]).

RESULTS

The flow chart of the study selection process is shown in Fig. 1b. A total of 20 articles (including 22 studies) [27–31,33–36,60–70] were included in the final analysis and 10 of them were registered as clinical trials. The detailed information for all included 22 studies was summarized in Table 1. The data extracted from each individual study was summarized in Supporting information Table S1. The mean duration between the last stimulation session and the last follow-up evaluation was 84 ± 83 days, ranging from 4 days to 12 months. Not all studies reported all three outcome measures (craving, consumption and abstinence). Specifically, there were 12 studies, 10 studies and 6 studies assessing the follow-up effect on craving, consumption and abstinence, respectively.

Methodological quality of included studies

Supporting information Figure S1 summarizes the evaluation of the risk of bias for all included studies and indicates that almost all studies were of high quality (i.e. at relatively low risk of bias) except for one study [67], which showed high risk for 'other bias'. Furthermore, Supporting information Table S2 summarizes the evaluation of the sham condition and blinding procedures used. Both assessments showed that all included studies used effective blinding procedures to avoid bias.

Acute effect of neuromodulation on craving and consumption

We, first, evaluated the acute effect of neuromodulation interventions targeted at dlPFC for all studies that conducted an assessment of clinical outcomes immediately after the last intervention. We found a significant acute effect of active neuromodulation (vs sham neuromodulation) on craving (g = 0.734, CI = 0.447–1.021, P < 0.001, [Fig. 2a]; I^2 = 41.74%, P = 0.071) as compared to the baseline, with a medium effect size. A small amount of potential publication bias was found by funnel plot (Supporting information Fig. S2A), which was consistent with a non-significant result from Egger's test ($t_{[9]}$ = 1.738, P = 0.116).

We also found a significant acute effect of active neuromodulation (vs sham neuromodulation) on consumption (g = 0.527, CI = 0.309–0.745; P < 0.001, [Fig. 2b]; I^2 = 0.00%, P = 0.529) as compared to the baseline, with a medium effect size. The acute effect on consumption was retained after the exclusion of the study that used deep rTMS [33] (g = 0.470, CI = 0.233–0.706, P < 0.001; I^2 = 0.00%, P = 0.588) or the study with high risk bias [67] (g = 0.563, CI = 0.335–0.791, P < 0.001; I^2 = 0.00%, P = 0.545) or

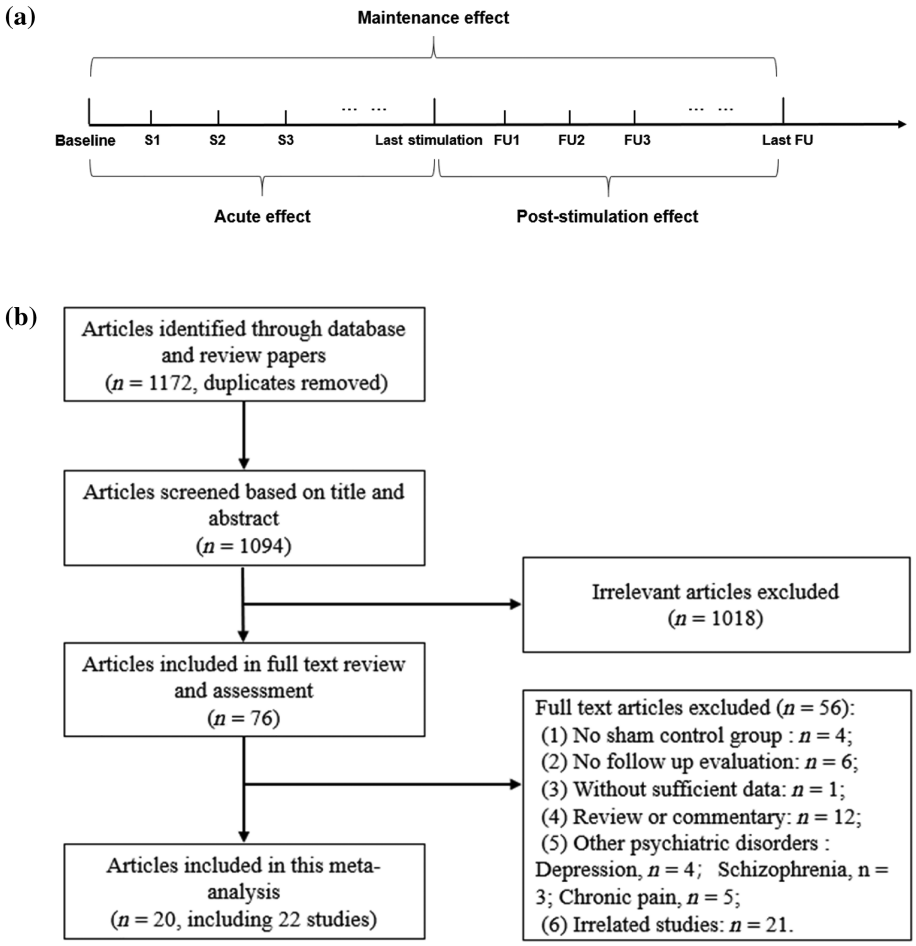

FIGURE 1 **(a)** The definition of the assessed effects (FU: follow-up) and **(b)** flow chart of the study selection process. S: stimulation session

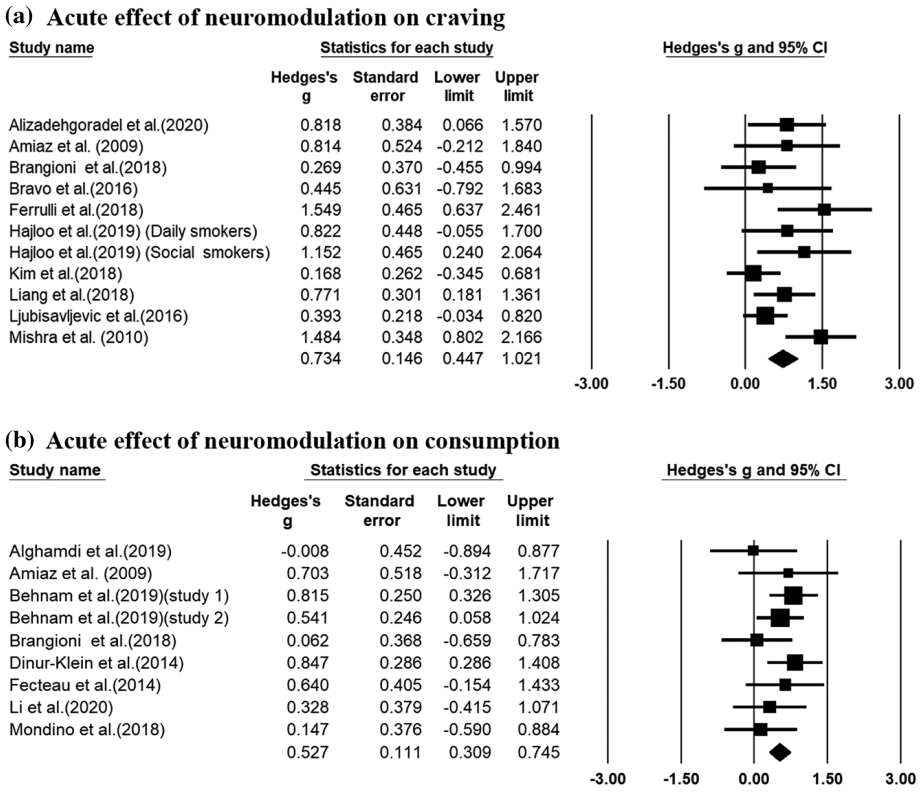

FIGURE 2 Acute effect of neuromodulation on craving **(a)** and consumption **(b)**

both of the two studies [33,67] (g = 0.507, CI = 0.257–0.757, P < 0.001; I^2 = 0.00%, P = 0.573). We did not assess the publication bias for the acute effect of neuromodulation on consumption because of the low number of studies (n = 9).

Maintenance effect of neuromodulation on craving, consumption and abstinence

To see if neuromodulation intervention effects were sustained over a longer time period, we then tested for a significant effect at the last follow-up assessment (84 ± 83 days) as compared to the baseline. Active stimulation targeted at dlPFC (vs sham stimulation) led to a reduction of craving at follow-up, with a medium effect size (g = 0.677, CI = 0.440–0.914, P < 0.001, [Fig. 3a]; I^2 = 23.60%, P = 0.212). The maintenance effect on craving was retained after excluding the study that used deep rTMS [30] (g = 0.625, CI = 0.413–0.838, P < 0.001; I^2 = 5.31%, P = 0.393). A relatively small amount of potential publication bias was found for the maintenance effect of neuromodulation on craving by funnel plot (Supporting information Fig. S2B), consistent with a non-significant result from Egger's test ($t_{[10]}$ = 0.434, P = 0.673).

Second, active neuromodulation interventions also led to a significant reduction of consumption at the last follow-up evaluation, with a small effect size (g = 0.445, CI = 0.245–0.645, P < 0.001, [Fig. 3b]; I^2 = 0.00%, P = 0.770). The maintenance effect on consumption was retained after the exclusion of the study that used deep rTMS [33] (g = 0.384, CI = 0.170–0.598, P < 0.001; I^2 = 0.00%, P = 0.921) or the study with high risk bias [67] (g = 0.479, CI = 0.271–0.687, P < 0.001; I^2 = 0.00%, P = 0.827) or both of the two studies [33,67] (g = 0.417, CI = 0.194–0.641, P < 0.001; I^2 = 0.00%, P = 0.949). No sign of publication bias was found for the maintenance effect of neuromodulation on

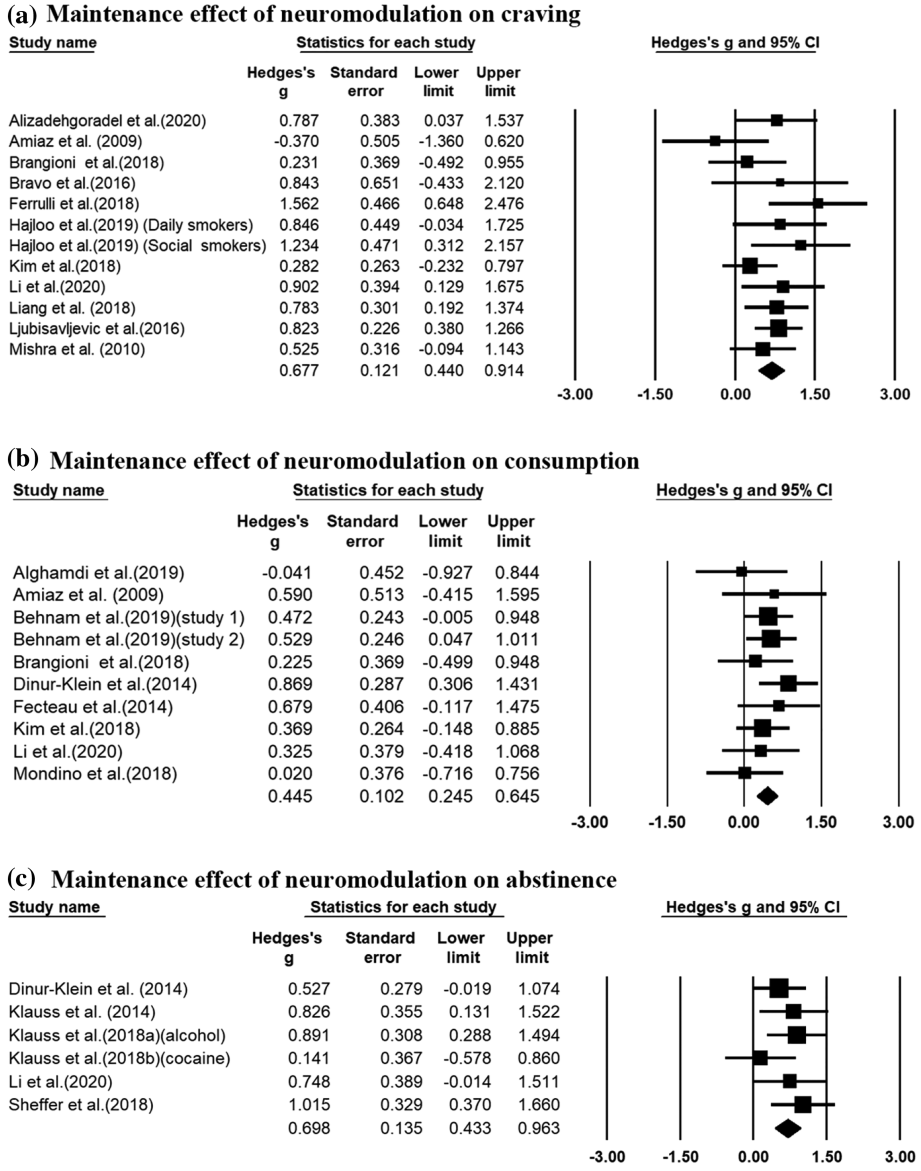

FIGURE 3 Maintenance effect of neuromodulation on craving **(a)**, consumption **(b)** and abstinence **(c)**

consumption by funnel plot (Supporting information Fig. S2C), consistent with a non-significant result from Egger's test ($t_{[8]}$ = 1.041, P = 0.328).

Third, we found that active neuromodulation interventions significantly increased abstinence rates at the last follow-up assessment, with a medium effect size (g = 0.698, CI = 0.433–0.963, P < 0.0001, [Fig. 3c]; I^2 = 0.00%, P = 0.529). The maintenance effect on abstinence rates was retained after exclusion of the study that used deep TMS [33] (g = 0.750, CI = 0.447–1.053, P < 0.0001; I^2 = 0.00%, P = 0.454). We did not assess the publication bias for maintenance effect of neuromodulation on abstinence because of the small number of studies (n = 6).

Maintenance effects by population type, stimulation technique and stimulated hemisphere

As presented in Table 2, additional analysis demonstrated a maintenance effect on craving regardless of the population studied (food, nicotine, or drug abuse), the stimulation technique used (rTMS vs

TABLE 2 Maintenance effects by population type, stimulation techniques and stimulated hemispheres

			Effect size			*Heterogeneity*	
Measure	*Moderator*	*Number of studies*	*Hedge's g*	*95% CI*	*P value*	I^2	*P value*
Craving	Type of population						
	Alcohol	1	NA	NA	NA	NA	NA
	Food	4	0.786	[0.287, 1.284]	0.002	52.24%	0.099
	Nicotine	5	0.581	[0.065, 1.096]	0.027	45.76%	0.117
	Drug	2	0.785	[0.321, 1.249]	0.001	0.00%	0.994
	Stimulation techniques						
	rTMS	6	0.610	[0.197, 1.022]	0.004	51.95%	0.065
	tDCS	6	0.767	[0.476, 1.057]	<0.001	0.00%	0.669
	Anodal stimulation hemisphere						
	Right dlPFC	3	0.731	[0.384, 1.077]	<0.001	0.00%	0.732
	Left dlPFC	8	0.581	[0.280, 0.882]	<0.001	25.53%	0.225
Consumption	Type of population						
	Alcohol	NA	NA	NA	NA	NA	NA
	Food	1	NA	NA	NA	NA	NA
	Nicotine	9	0.459	[0.242, 0.675]	<0.001	0.00%	0.692
	Drug	NA	NA	NA	NA	NA	NA
	Stimulation techniques						
	rTMS	4	0.546	[0.225, 0.867]	0.001	0.00%	0.559
	tDCS	6	0.381	[0.126, 0.637]	0.003	0.00%	0.697
	Anodal stimulation hemisphere						
	Right dlPFC	2	0.332	[−0.313, 0.977]	0.314	29.55%	0.234
	Left dlPFC	7	0.395	[0.162, 0.628]	<0.001	0.00%	0.943
Abstinence	Type of population						
	Alcohol	2	0.863	[0.408, 1.319]	<0.001	0.00%	0.890
	Food	NA	NA	NA	NA	NA	NA
	Nicotine	3	0.735	[0.369, 1.101]	<0.001	0.00%	0.527
	Drug	1	NA	NA	NA	NA	NA
	Stimulation techniques						
	rTMS	3	0.735	[0.369, 1.101]	<0.001	0.00%	0.527
	tDCS	3	0.646	[0.190, 1.102]	0.005	28.13%	0.249
	Anodal stimulation hemisphere						
	Right dlPFC	3	0.646	[0.190, 1.102]	0.005	28.13%	0.249
	Left dlPFC	2	0.904	[0.411, 1.396]	<0.001	0.00%	0.600

dlPFC = dorsolateral prefrontal cortex; NA = not available; rTMS = repetitive transcranial magnetic stimulation; tDCS = transcranial direct current stimulation. Note that we did not perform a meta-analysis if less than two studies were available.

tDCS) or the stimulated hemisphere (left vs right dlPFC). Similarly, the maintenance effect on consumption was significant independently of the stimulation technique used (rTMS vs tDCS). However, the maintenance effect on consumption was only significant when stimulation was targeted at the left dlPFC, but not when it was targeted at the right dlPFC (7 left dlPFC studies; 2 right dlPFC studies) (Table 2). Effects on consumption by population could not be compared, because most consumption was only assessed in smokers (9 studies) and only one study on food consumption. Finally, the maintenance effect on abstinence was significant for both populations assessed (alcohol and nicotine abuse), both stimulation techniques used (rTMS vs tDCS) and protocols that stimulated either hemisphere (right vs left dlPFC) (Table 2).

The short-, mid- and long-term maintenance effect

To assess if the intervention effects were stable over time, we separated studies into three subgroups that conducted the last follow-up evaluation during short-, mid- or long-term duration relative to the end of the intervention. We found that effects were overall stable and had similar effect sizes over time. Craving was significantly reduced during short-term (3–30 days: 3 studies, $g = 0.603$, CI = 0.211–0.995, $P = 0.003$; $I^2 = 22.26\%$, $P = 0.276$), mid-term (1–6 months: 8 studies, $g = 0.636$, CI = 0.352–0.920, $P < 0.001$; $I^2 = 12.18\%$, $P = 0.335$) or long-term abstinence (> 6 months: 1 study, $g = 1.562$, CI = 0.648–2.476, $P = 0.001$). Effects on consumption had smaller effect sizes than effects on craving. There was a marginally significant reduction of consumption during short-term (3–30 days: 3 studies, $g = 0.347$, CI = −0.026-0.721, $P = 0.068$; $I^2 = 0.00\%$, $P = 0.488$) and a significant reduction during mid-term abstinence (1–6 months after the last intervention: 7 studies, $g = 0.484$, CI = 0.248–0.721, $P < 0.001$; $I^2 = 0.00\%$, $P = 0.691$). No study assessed consumption during long-term abstinence. All studies that assessed abstinence did this during mid-term abstinence (see Fig. 3c).

Post-stimulation effect of neuromodulation on craving and consumption

Finally, as a control analysis, we evaluated if the effects of neuromodulation interventions were stable after the last stimulation session, to investigate if there was a delayed post-stimulation effect. We found no further change in the level of craving ($g = 0.106$, CI = −0.095–0.306, $P = 0.301$, [Fig. 4a]; $I^2 = 0.00\%$, $P = 0.814$) or consumption ($g = -0.015$, CI = −0.247–0.217; $P = 0.899$, [Fig. 4b]; $I^2 = 0.00\%$, $P = 0.984$) after the last stimulation session, indicating the stability of effects after the intervention was concluded. The post-stimulation effect on consumption remained non-significant after the exclusion of the study with high risk bias [67] ($g = -0.034$, CI = −0.279–0.211, $P = 0.786$; $I^2 = 0.00\%$, $P = 0.975$). No sign of publication bias was found for the post-stimulation effect of neuromodulation on craving by funnel plot (Supporting information

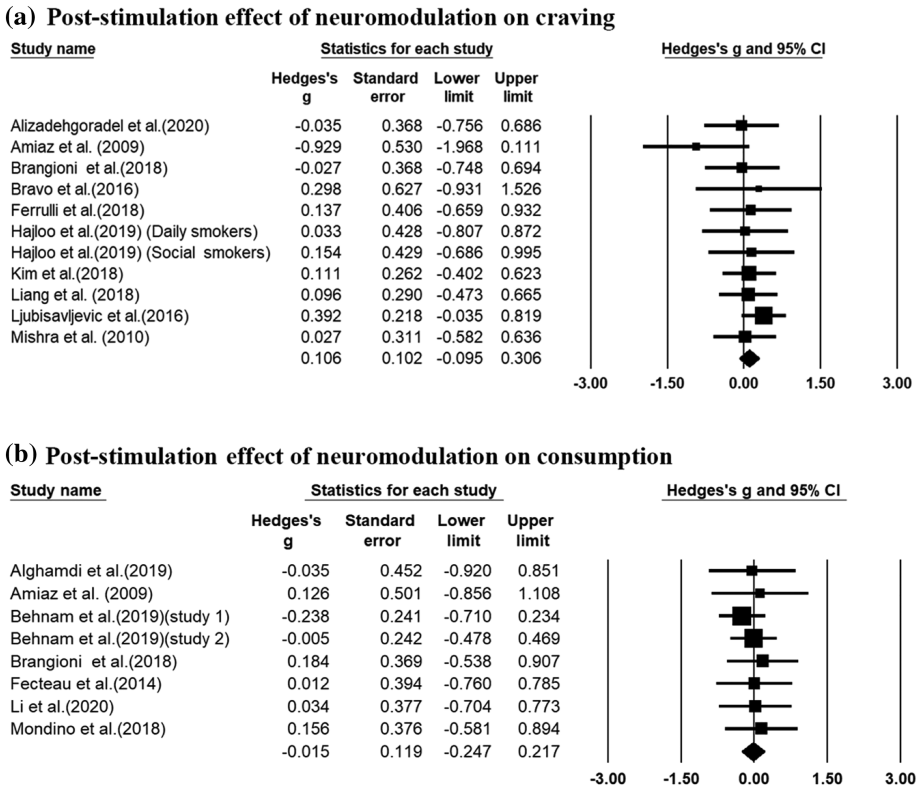

FIGURE 4 Post-stimulation effect of neuromodulation on craving **(a)** and consumption **(b)**

Fig. S2D) or by Egger's test ($t_{[9]}$ = 2.113, P = 0.064). We did not assess the publication bias for the post-stimulation effect of intervention on consumption because of the small number of studies (n = 8).

DISCUSSION

We investigated three main questions in this systematic review. Our results demonstrated that neuromodulation interventions decrease craving and consumption levels in people with drug addiction (or overeating) immediately after the intervention and that these effects remain stable over time, from short-term to mid-term to long-term abstinence. Our control analysis further demonstrated that effect sizes were stable after the end of the intervention. Data quality checks indicated high quality of the included studies. There was no evidence for differences between participant populations or between stimulation techniques, although neuromodulation targeting the left hemisphere may be more efficacious than targeting the right hemisphere.

We replicated previous recent meta-analysis demonstrating the reduction of craving and consumption levels in people with drug addiction (or overeating) immediately after the neuromodulation intervention [7,25,41]. Importantly, we extended these previous results by demonstrating that such intervention effects were sustained over time. Our findings converged with a previous study that conducted multiple follow-up assessments; Ferrulli *et al*. [30] demonstrated significantly reduced craving levels at 1-month (g = 2.363, CI = 1.315–3.410; P < 0.001), 6-month (g = 2.510, CI = 1.434–3.586; P < 0.001) and 12-month (g = 1.562, CI = 0.648–2.476; P = 0.001) follow-up evaluation. Because studies with multiple follow-up assessments are challenging to conduct and, therefore rare, our meta-analytical approach provides the first systematic investigation of sustained intervention effects by looking at a large number of existing studies (N = 720 participants included). Moreover, we were able to compare studies that followed participants for different durations of time, demonstrating similar effect sizes during short-, mid- and long-term abstinence and suggesting that intervention effects remain stable for several months. However, we would like to note that although we found that effects were stable over time after the last neuromodulation session, longer (or multiple) interventions have been shown to enhance the initial intervention effect [7].

Our results further demonstrate that neuromodulation interventions effects were equally stable over time for different populations (e.g. in individuals with alcohol, nicotine, drug or overeating behaviour). This extends previous findings from recent meta-analyses that compared the acute effects of neuromodulation on different populations with drug addiction (or overeating) and found that neuromodulation protocols targeted at dlPFC are equally effective in individuals with alcohol [7,41], nicotine [7,41,43], drug [7,41,42] addiction or overeating behaviour [7,38,40,41,44,45]. We also demonstrated that stimulation effects were maintained independently of the used stimulation techniques (rTMS or tDCS). This finding also converges with results from previous meta-analysis showing that the immediate effects of neuromodulation interventions did not differ by stimulation technique [7,26]. Moreover, we demonstrated that excluding the two deep rTMS studies [30, 33] from our analysis—because these protocols may potentially have different, more powerful effects—did not change any of our results.

Finally, we investigated if there were differences in sustained effects between the stimulated hemispheres. Our results demonstrated a significant sustained effect of both left and right hemisphere stimulation on craving levels and abstinence rates, consistent with the effects reported in some of the previous meta-analyses focused on acute effects [7,26,41]. Meanwhile, we found an effect of left, but not right dlPFC stimulation on consumption levels, consistent with other meta-analysis that found that left, but not right dlPFC stimulation reduced craving in people with drug addiction (or overeating) [25,45]. However, because of the lower number of studies with right dlPFC stimulation that measured consumption levels in the current meta-analysis, these results remain inconclusive. Only two studies fall in this category, both of which used tDCS and were conducted on smokers. The first study showed a trend of significant consumption reduction (12 participants, 5 sessions: g = 0.679, CI = −0.117–1.475; P = 0.094) [68], whereas the second found no such effect (29 participants, 10 sessions: g = 0.02, CI = −0.313–0.977; P = 0.957) [67]. The combined effect of these two studies is non-significant. Future research—preferably direct comparisons between right and left dlPFC stimulation in the same study—is therefore, needed to determine if these studies were outliers, or if stimulation protocols targeting right dlPFC may indeed be less effective as suggested by the current results and previous meta-analyses [25,45].

Despite its strengths, the current meta-analysis has several limitations. First, the analysis investigating differences by population, stimulation technique and target site often only included a limited number of studies and should, therefore, be repeated as more studies become available. Second, there was a considerable lack of studies with a long-term follow-up (>6 months follow-up) and the effects beyond 6 months need to be interpreted with caution. Ideally, future studies should conduct at least two follow-ups, one during mid- (1–6 months) and one during long-term (>6 months) abstinence or follow participants longitudinally in regular intervals. The current results strongly support the use of such future studies. Third, our meta-analysis did not include studies targeting other brain sites, such as inferior frontal cortex [71] or medial prefrontal cortex [72], studies that have adopted inhibiting protocols (e.g. 1 HZ rTMS [73]); or studies that used neuromodulation in combination with drug therapy (e.g. nicotine replacement therapy [74]) or cognitive-behavioural therapy (CBT) [75], because of the low number of studies with such experimental designs. The efficacy of such novel protocols in comparison to 'standard' excitatory dlPFC protocols remains to be evaluated. Fourth, although iTBS is the fastest growing stimulation type in clinical applications, none of the studies conducted so far met our screening criteria (e.g. [75–80]). Fifth, we used P values to assess the maintenance effect of neuromodulation on abstinence. Among the six included studies, one reported corrected [33] whereas five reported

uncorrected [28,34,35,69,70] *P* values. These differences in approach may have affected the results of this analysis. Finally, the inclusion of only published data in this systematic review might have inadvertently increased the risk of bias.

CONCLUSIONS

Excitatory neuromodulation targeting dlPFC led to a sustained reduction of craving and consumption levels in individuals with addiction or overeating behaviour. These effects did not differ by the investigated population (e.g. individuals with alcohol, nicotine, drug or overeating behaviour) or stimulation protocol used (rTMS or tDCS). The current results provide initial evidence for the efficacy of neuromodulation interventions as a potential clinical treatment for individuals with drug addiction or overeating behaviour.

DECLARATION OF INTERESTS

None.

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AUTHOR CONTRIBUTIONS

Sensen Song: Conceptualization; data curation; formal analysis; methodology; visualization. **Anna Zilverstand:** Conceptualization; formal analysis; methodology; visualization. **Wenjun Gui:** Conceptualization; data curation; methodology; visualization. **Xuefei Pan:** Formal analysis; methodology. **Xiaolin Zhou:** Conceptualization; funding acquisition; methodology; supervision.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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