Received: 19 January 2021 | Accepted: 1 September 2021

DOI: 10.1111/add.15686

REVIEW

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

Sensen Song[1] | Anna Zilverstand[2] | Wenjun Gui[3,4] | Xuefei Pan[5] | Xiaolin Zhou[1,5,6,7]

[1]Department of Psychology, School of Humanities, Tongji University, Shanghai, China

[2]Department of Psychiatry & Behavioral Sciences, University of Minnesota, Minneapolis, MN, USA

[3]Key Laboratory of Mental Health, Institute of Psychology, Chinese Academy of Sciences, Beijing, China

[4]Department of Psychology, University of Chinese Academy of Sciences, Beijing, China

[5]School of Psychological and Cognitive Sciences, Peking University, Beijing, China

[6]PKU-IDG/McGovern Institute for Brain Research, Peking University, Beijing, China

[7]School of Psychology and Cognitive Science, East China Normal University, Shanghai, China

Correspondence
Xiaolin Zhou, School of Psychological and Cognitive Sciences, Peking University, Beijing 100871, China.
Email: xz104@pku.edu.cn

Funding information
National Natural Science Foundation of China, Grant/Award Numbers: 71942001, 31630034

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 pre-

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), inten-

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

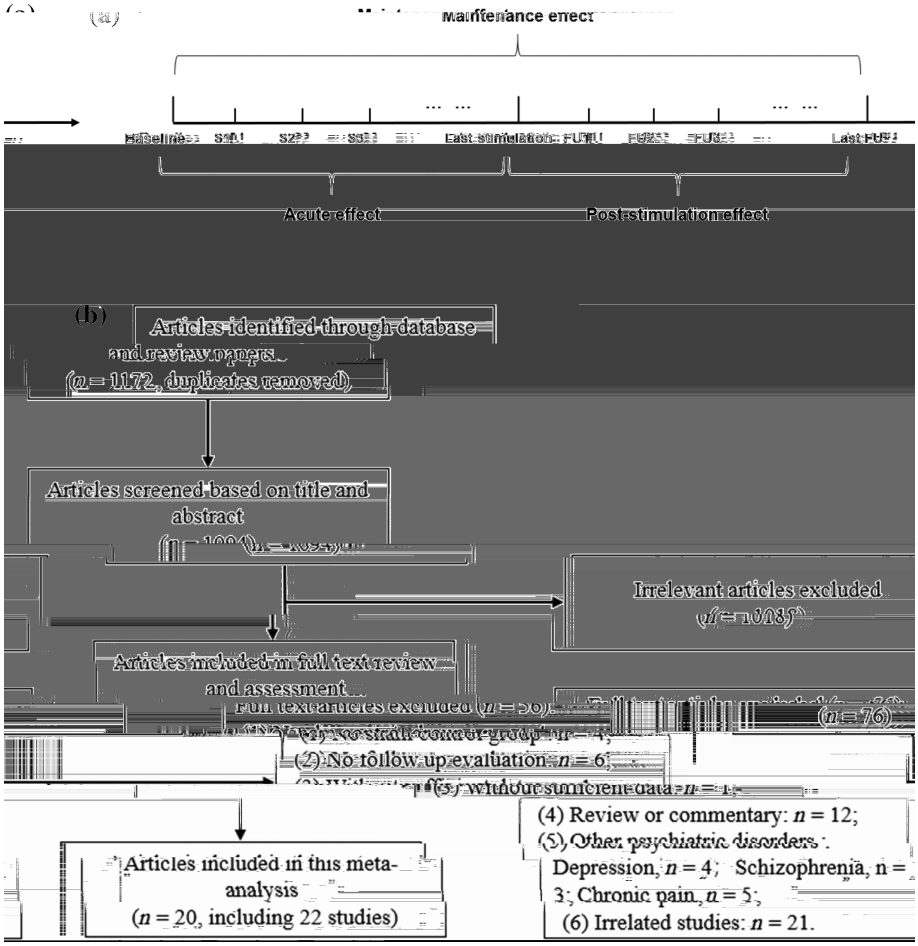

FIGURE 1 **(a)** The definition of the assessed effects (FU: follow-up) and **(b)** flow chart of the study selection process. S: stimulation session

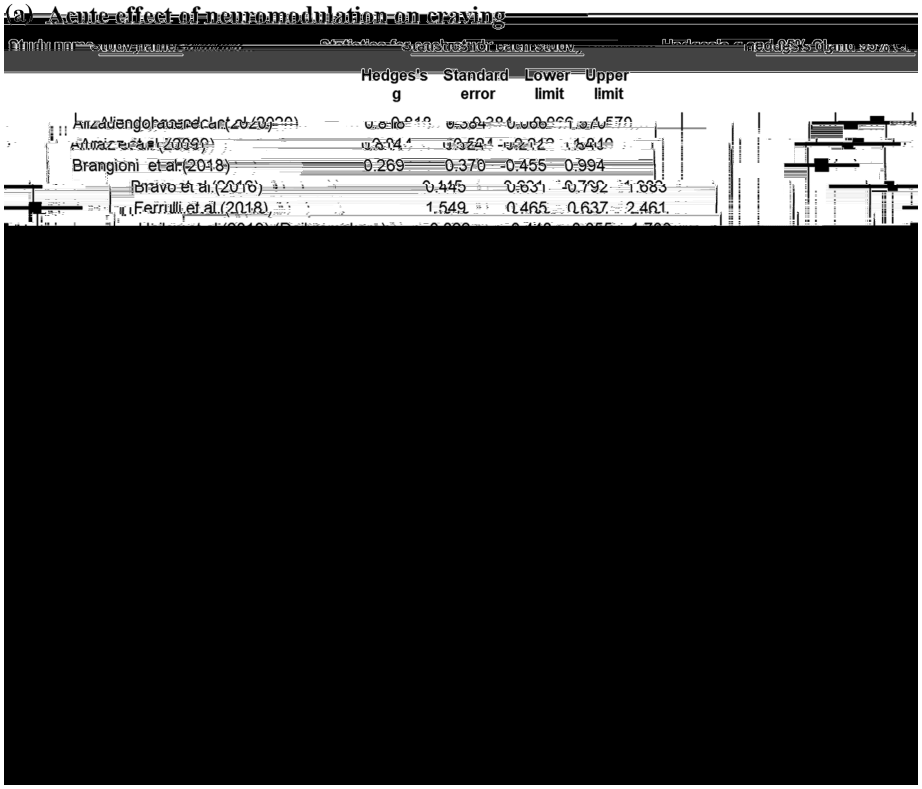

FIGURE 2 Acute effect of neuromodulation on craving **(a)** and consumption **(b)**

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

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

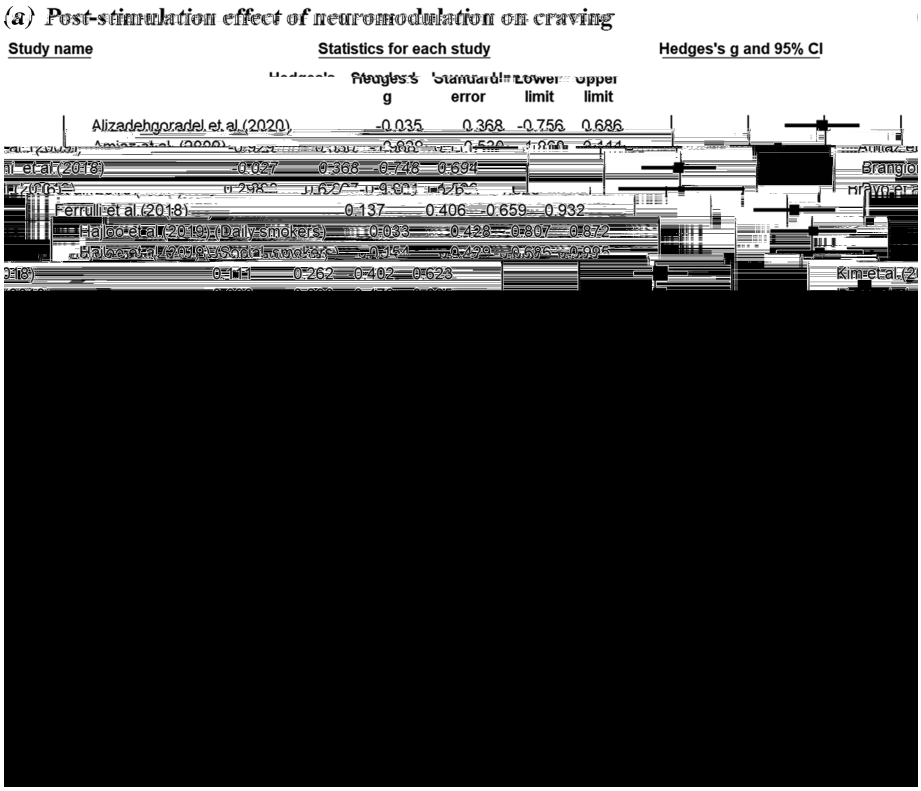

FIGURE 4 Post-stimulation effect of neuromodulation on craving **(a)** and consumption **(b)**

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 dem-

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.

ACKNOWLEDGEMENTS

We thank all authors of the original individual studies who kindly provided their data for current meta-analysis. This work was supported by the National Natural Science Foundation of China (31630034, 71942001).

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.

ORCID

Sensen Song https://orcid.org/0000-0003-1114-0116
Anna Zilverstand https://orcid.org/0000-0002-4889-9700

REFERENCES

substance consumption in patients with substance dependence: A systematic review and meta-analysis. Addiction. 2019;114(12): 2137–2149.
26. Jansen JM, Daams JG, Koeter MW, Veltman DJ, van den Brink W, Goudriaan AE. Effects of non-invasive neurostimulation on craving: A meta-analysis. Neurosci Biobehav Rev. 2013;37(10 Pt 2): 2472–2480.
27. Ljubisavljevic M, Maxood K, Bjekic J, Oommen J, Nagelkerke N. Long-term effects of repeated prefrontal cortex Transcranial direct current stimulation (tDCS) on food craving in Normal and overweight young adults. Brain Stimul. 2016;9(6):826–833.
28. Li X, Hartwell KJ, Henderson S, Badran BW, Brady KT, George MS. Two weeks of image-guided left dorsolateral prefrontal cortex repetitive Transcranial magnetic stimulation improves smoking cessation: A double-blind, sham-controlled, randomized clinical trial. Brain Stimul. 2020;13(5):1271–1279.
29. Alizadehgoradel J, Nejati V, Movahed FS, Imani S, Taherifard M, Mosayebi-Samani M, et al. Repeated stimulation of the dorsolateral-prefrontal cortex improves executive dysfunctions and craving in drug addiction: A randomized, double-blind, parallel-group study. Brain Stimul. 2020;13(3):582–593.
30. Ferrulli A, Macrì C, Terruzzi I, Massarini S, Ambrogi F, Adamo M, et al. Weight loss induced by deep transcranial magnetic stimulation in obesity: A randomized, double-blind, sham-controlled study. Diab Obes Metab. 2019;21(8):1849–1860.
31. Kim SH, Chung JH, Kim TH, Lim SH, Kim Y, Lee YA, et al. The effects of repetitive transcranial magnetic stimulation on eating behaviors and body weight in obesity: A randomized controlled study. Brain Stimul. 2018;11(3):528–535.
32. Verveer I, Remmerswaal D, Jongerling J, van der Veen FM, Franken IHA. No effect of repetitive tDCS on daily smoking behaviour in light smokers: A placebo controlled EMA study. PLoS One. 2020;15(5):e0233414.
33. Dinur-Klein L, Dannon P, Hadar A, Rosenberg O, Roth Y, Kotler M, et al. Smoking cessation induced by deep repetitive transcranial magnetic stimulation of the prefrontal and insular cortices: A prospective, randomized controlled trial. Biol Psychiatry. 2014;76(9):742–749.
34. Klauss J, Penido Pinheiro LC, Silva Merlo BL, Correia Santos GA, Fregni F, Nitsche MA, et al. A randomized controlled trial of targeted prefrontal cortex modulation with tDCS in patients with alcohol dependence. Int J Neuropsychopharmacol. 2014;17(11):1793–1803.
35. Klauss J, Anders QS, Felippe LV, Ferreira LVB, Cruz MA, Nitsche MA, et al. Lack of additional effects of extended sessions of transcranial direct current stimulation (tDCS) over dorsolateral prefrontal cortex on craving and relapses in crack-cocaine users. Front Pharmacol. 2018;9:1198.
36. Alghamdi F, Alhussien A, Alohali M, Alatawi A, Almusned T, Fecteau S, et al. Effect of transcranial direct current stimulation on the number of smoked cigarettes in tobacco smokers. PLoS One. 2019;14(2):e0212312.
37. Moher D, Liberati A, Tetzlaff J, Altman DG, The PG. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. PLoS Med. 2009;6(7):e1000097.
38. Mostafavi S-A, Khaleghi A, Mohammadi MR, Akhondzadeh S. Is transcranial direct current stimulation an effective modality in reducing food craving? A systematic review and meta-analysis. Nutr Neurosci. 2020;23(1):55–67.
39. Mostafavi SA, Khaleghi A, Mohammadi MR. Noninvasive brain stimulation in alcohol craving: A systematic review and meta-analysis. Prog Neuropsychopharmacol Biol Psychiatry. 2020;101: 109938.
40. Hall PA, Lowe CJ. Cravings, currents and cadavers: What is the magnitude of tDCS effects on food craving outcomes? Nutr Neurosci. 2020;23(6):490–493.
41. Chen J, Qin J, He Q, Zou Z. A meta-analysis of Transcranial direct current stimulation on substance and food craving: What effect do modulators have? Front Psychiatry. 2020;11:598.
42. Ma T, Sun Y, Ku Y. Effects of non-invasive brain stimulation on stimulant craving in users of cocaine, amphetamine, or methamphetamine: A systematic review and meta-analysis. Front Neurosci. 2019; 13:1095.
43. Kang N, Kim RK, Kim HJ. Effects of transcranial direct current stimu-

61. Liang Y, Wang L, Yuan T-F. Targeting withdrawal symptoms in men addicted to methamphetamine with Transcranial magnetic stimulation: A randomized clinical trial. JAMA Psychiat. 2018;75(11): 1199–1201.
62. Brangioni M, Pereira DA, Thibaut A, Fregni F, Brasil-Neto JP, Boechat-Barros R. Effects of prefrontal Transcranial direct current stimulation and motivation to quit in tobacco smokers: A randomized, sham controlled, double-blind trial. Front Pharmacol. 2018; 9:14.
63. Bravo GL, Poje AB, Perissinotti I, Marcondes BF, Villamar MF, Manzardo AM, et al. Transcranial direct current stimulation reduces food-craving and measures of hyperphagia behavior in participants with Prader-Willi syndrome. Am J Med Genet B Neuropsychiatr Genet. 2016;171B(2):266–275.
64. Mishra BR, Nizamie SH, Das B, Praharaj SK. Efficacy of repetitive transcranial magnetic stimulation in alcohol dependence: A sham-controlled study. Addiction. 2010;105(1):49–55.
65. Amiaz R, Levy D, Vainiger D, Grunhaus L, Zangen A. Repeated high-frequency transcranial magnetic stimulation over the dorsolateral prefrontal cortex reduces cigarette craving and consumption. Addiction. 2009;104(4):653–660.
66. Behnam SG, Mousavi SA, Emamian MH. The effects of transcranial direct current stimulation compared to standard bupropion for the treatment of tobacco dependence: A randomized sham-controlled trial. Eur Psychiat. 2019;60:41–48.
67. Mondino M, Luck D, Grot S, Januel D, Suaud-Chagny MF, Poulet E, et al. Effects of repeated transcranial direct current stimulation on smoking, craving and brain reactivity to smoking cues. Sci Rep. 2018; 8:8724.
68. Fecteau S, Agosta S, Hone-Blanchet A, Fregni F, Boggio P, Ciraulo D, et al. Modulation of smoking and decision-making behaviors with transcranial direct current stimulation in tobacco smokers: A preliminary study. Drug Alcohol Depen. 2014;140:78–84.
69. Klauss J, Anders QS, Felippe LV, Nitsche MA, Nakamura-Palacios EM. Multiple sessions of Transcranial direct current stimulation (tDCS) reduced craving and relapses for alcohol use: A randomized placebo-controlled trial in alcohol use disorder. Front Pharmacol. 2018;9:716.
70. Sheffer CE, Bickel WK, Brandon TH, Franck CT, Deen D, Panissidi L, et al. Preventing relapse to smoking with transcranial magnetic stim-