Effects of single-session versus multi-session non-invasive brain stimulation on craving and consumption in individuals with drug addiction, eating disorders or obesity: A meta-analysis

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[a]

and over were defined as obese (Health United States Report 2016; [2]), with a cumulative lifetime risk of eating disorders characterized by excessive eating of 5.7% of the population (National Comorbidity Survey Replication 2001–2003; [3]). Novel treatment approaches, such as neuromodulation approaches, are urgently needed, as the efficacy of currently available therapeutic interventions in preventing relapse in drug addiction is only 40–60% [4], with similarly low success rates (~50%) in eating disorders [5].

The hallmark of drug addiction and excessive eating behavior is the lack of ability to refrain from consumption (e.g. smoking, drinking or eating); even when consumption is associated with potentially negative consequences. Compulsive consumption is generally preceded by craving, which has been defined as an "intensive desire or urge" to consume in drug addiction [6]. In drug addiction, craving predicts the maintenance of drug seeking behavior, as well as relapse after abstinence [7]. Reducing craving has hence been proposed to be a meaningful goal for clinical intervention studies [7]. Similar to drug craving, food craving is defined as an intense desire to consume a particular food that is difficult to resist [8]. Although still controversial, the existing evidence similarly points to food craving as a critical factor in the maintenance of eating disorders and obesity [9], with craving predicting body mass index and consumption of high caloric foods such as sweets and high-fat food [10]. Both drug addiction and disorders of excessive food intake are further characterized by a break-down of inhibitory self-control, which aggravates the intense urge to consume [11–13]. Because of these observed parallels between drug addiction and excessive eating behavior, the later has increasingly been conceptualized as eating addiction [14–16], which encompasses pathological binge eating as well as uncontrolled eating in individuals without a clinical diagnosis [16]. This comparison has been further substantiated by findings implicating common neural mechanisms between eating and drug addictions [12,13,16].

The intensified urge to consume in drug addiction is thought to have its neurobiological substrate both in an increased phasic (yet reduced tonic) response of the dopaminergic reward system in the presence of drugs or drug cues [17–21] and the decreased engagement of prefrontal systems underlying inhibitory self-control, such as the dorsolateral prefrontal cortex (dlPFC) [18,22]. Studies across different addicted populations have linked increased activation levels in the dopaminergic reward system during drug cue exposure to increased subjective craving [23,24]. In parallel, in eating addiction, the sensitization of the dopaminergic reward system has been linked to an increased drive for excessive intake of food [12,13,16]. Aggravating the problem, this observed hyper-reactivity of the reward system is potentiated by an reduced engagement of prefrontal systems (including the dlPFC) during attempts to self-regulate craving and inhibit consumption of drugs [22,25,26] or food [12,13,16]. The primary role of the dlPFC is thought to be the representation of contextual information when faced with conflicting outcomes [27], hence fulfilling a crucial role in the selection (and inhibition) of behavioral and cognitive responses in the face of different options [28–30]. Evidence further suggests that the dlPFC is the apex of the frontal control hierarchy, exerting influence on other frontal brain regions through its broad efferent connections [30]. As such its recruitment may be necessary for successful inhibition of a behavioral (consumption) or cognitive (craving) response. In drug addiction, the dlPFC has been shown to be hypo-active, specifically when attempting to inhibit behavioral responses [26,31] or to cognitively self-regulate craving [26,32,33], while it is hyperactivated when not attempting to self-regulate craving during drug cue exposure [26]. In analogy to its role in drug addiction, the dlPFC has also been implicated in the failure to inhibit excessive food intake in eating disorders and obesity [12,13]. Moreover, the attenuation of dlPFC activity by inhibitory forms of rTMS led to overconsumption of high-caloric foods in healthy weight individuals, providing evidence for its causal role in reducing consumption [34,35].

Recent reviews of the neurobiological effects of the available cognitive-behavioral and pharmacological treatments in drug addiction have proposed that the dlPFC is an important neural target of treatment, showing the potential for a (partial) normalization of its functions after treatment [26,32]. While the dlPFC is by no means the only target for treatment and inhibitory control is not the only mechanism impaired in drug and eating addictions (for in depth reviews see Refs. [12,13,16–18,20,26]), the dlPFC is particularly suited as a target for non-invasive neuromodulation approaches with currently widely used non-invasive neuromodulation techniques, such as repetitive Transcranial Magnetic Stimulation (rTMS) and transcranial Direct Current Stimulation (tDCS), both because of its involvement in inhibitory control and its closeness to the scalp [36]. Repetitive TMS with standard figure-eight electromagnetic coils exerts its neuromodulatory influence by generating (repetitive) magnetic pulses which induce small electrical currents within a focal area in the superficial brain tissue below the scalp [36]. In rTMS, trains of pulses are used to achieve a sustained alteration of neural excitability in the targeted region [37]. Excitatory rTMs, which has a frequency of more than 5 Hz ("high frequency rTMS") lowers the threshold for (self-) engaging the targeted brain region, whereas low frequency stimulation ($\leq$1 Hz) would have inhibitory effects [38]. Similarly, tDCS can either increase or decrease neuronal excitability. tDCS generates a low intensity electric field (0.5–2 mA) between two electrodes, increasing neuronal excitability under the anodal, but decreasing it under the cathodal electrode [39], allowing for a targeted approach. When applied for a sufficient duration, increases in cortical excitability are sustained [39] and linked to changes in synaptic plasticity [40]. The hypothesized neuro-behavioral mechanism of the reviewed excitatory rTMS/tDCS interventions is thus to upregulate neuronal excitability of the dlPFC, such that the threshold for engaging this region during (self-)regulation of craving and consumption is lowered. In this meta-analysis, we focused on quantifying the effects of excitatory neuromodulation targeted at dlPFC, because we hypothesized that such interventions are of particular clinical benefit in a population characterized by hypoactivation of the dlPFC during attempted self-regulation.

There are a number of reasons for us to perform the current meta-analysis. First, no meta-analysis has been carried out to quantify the effects of neuromodulation approaches to reduce both craving and consumption in populations with drug addiction and excessive eating behavior. Previous meta-analyses on this topic only focused on craving measures of these disorders [41], or only concerned the regulation of eating behavior [42,43] or two types of drug users (alcohol and nicotine) [44]. These previous analyses included a much smaller number of studies (17 studies [41], 11 studies [42], or 10 studies [44], as compared to 48 studies in the current analysis), providing a less reliable estimate of the effect sizes. Second, none of the previous meta-analyses investigated the impact of the number of sessions or administered pulses, which could be important when evaluating a potential dose-response effect. However, previous findings from individual studies that directly compared single-to multiple-session protocols found that single-session interventions yielded smaller improvements as compared to interventions with five [45,46] or eight sessions [47]. Third, previous meta-analyses on drug addiction only used craving as an outcome measure [41,44], even though reducing consumption is the most important goal of these interventions. Fourth, previous meta-analyses on the effects in drug addiction only

included individuals with alcohol and nicotine addictions [41,44], but not illicit drug users. Fifth, the current meta-analysis addressed potential influences by differences in methodological approach (stimulated hemisphere, study design) on both craving and consumption, in addition to the re-evaluation of the effect of the stimulation technique employed (rTMS vs tDCS) [41].

Methods

To identify pertinent studies, a two-staged literature search was carried out. First, an online search was conducted in PubMed, Web of Science, PsycINFO and Embase database covering peer-reviewed articles from January 1990 to July 2018. This search was performed following the PICO-method (Patient/Population, Intervention, Comparison, Outcome). Key elements were the 'P' (substance or eating addiction), the 'I' (tDCS or rTMS stimulation), the 'C' (Active and Sham stimulation) and the 'O' (craving or consumption levels). See Supplementary A for full search terms. Second, an additional literature search was performed using the reference lists of the identified studies, of other meta-analytical studies [41–44] and a number of relevant review articles [36,48–53]; the goal was to search for as many potential studies as possible.

Inclusion criteria

This work followed PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. Peer-reviewed studies published in all language journals and meeting the following criteria were included in the current meta-analysis: (1) randomized controlled trials (RCTs) and controlled clinical trials (CCTs), focusing on high-frequency rTMS or anodal tDCS targeting the dlPFC in patients with (a) substance use disorder (e.g. alcohol, cannabis, cocaine, heroin, methamphetamine and nicotine) or frequent smoking or (b) eating disorders (Bulimia Nervosa/Binge Eating type) or individuals with frequent food craving or obesity; (2) including at least one craving or consumption measure as an outcome; (3) comparing real to sham brain stimulation; (4) having provided means, standard deviations (SDs), t, F or p statistics and the number of participants in each intervention group, or other data that could be used to calculate effect size. The inclusion criteria did not consider the craving assessment tool, consumption assessment tool, number of stimulation sessions, stimulated hemisphere, or method of localization for the site of stimulation.

Exclusion criteria

We excluded studies from our meta-analysis if they: (1) focused on populations other than the ones mentioned above (e.g. schizophrenia, Prader-Willi syndrome, depression, posttraumatic stress disorder or chronic pain); (2) assessed the effects of stimulation using techniques other than tDCS or high frequency rTMS (e.g., deep TMS, continuous theta burst stimulation, electro convulsive therapy and low frequency rTMS); (3) assessed the effect of dlPFC stimulation using outcome measures other than craving or consumption; (4) lacked a sham stimulation condition in experiment design; (5) did not provide enough information to calculate effect size; (6) were case studies or review articles.

Data extraction

The extracted data included the study name, population, type of substance involved, number of stimulation sessions per condition, side of stimulation (right vs. left), stimulation technique (tDCS vs. rTMS), number of participants, study design, blinding method, blinding evaluation, total number of pulses, craving measures, consumption measures and standardized effect sizes for the effect of stimulation on craving and consumption levels. When means and standard deviations were not available, effect sizes were computed from t-values, F-values or p-values. When studies included more than one measures on craving or consumption, we averaged them to compute one pooled effect size. For example, if a study included two measures of craving [(Visual Analogue Scale (VAS) and Food Craving Questionnaire State (FCQ-S)], these two measurements were summarized by their pooled effect size [54]. If a study reported results of measures both during the stimulation and post-stimulation, only the data of the post-stimulation was included [55]. For the five studies [56–60], which included both left and right dlPFC stimulation data, a combined effect size for both sites was calculated. However, when evaluating left with right hemisphere stimulation, we computed separate effect sizes for each stimulation site for these studies. When the reported data was insufficient for the current data analysis, the authors were contacted. If the authors could not be reached or the data were only available in chart format, means and SDs were estimated using Engauge Digitizer [61]. Each study included in the meta-analysis was independently coded by two of the authors (S.S. and W.G.); discrepancies were addressed by discussion.

Data analysis

To assess the risk of bias within the individual studies, we used a standardized critical appraisal instrument named the Cochrane Collaboration's risk of bias tool [62]. Ratings (high, low, or unclear risk) were assigned to evaluate bias on the following domains: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias) and other bias (if any). In addition, we evaluated the used control condition and blinding procedures for all included studies. Blinding of the outcome assessment was assessed for craving and consumption independently. Two reviewers (S.S. and

potential influences of the population, stimulation technique and study design on such intervention effects. In particular, as five studies [56–60] included both left and right dlPFC stimulation data, in order to exclude the multiple effect sizes in individual studies, we used Z-test (instead of Q-test) to assess the potential influences of the stimulated hemisphere [63]. Furthermore, we used Egger's regression intercept test to measure for publication bias [68]. All suitable data were calculated with the software Comprehensive Meta-Analysis 2.0 (CMA) (http://www.meta-analysis 2.0.com).

Results

The results of the initial search are summarized in Fig. 1. We included a total of 48 studies focusing on non-invasive brain stimulation interventions in drug or eating addiction. The characteristics of these studies are summarized in Table 1. Not all studies reported both craving and consumption measures, and only 5 studies evaluated both a single-session and a multi-session effect (Supplementary Table 1). Specifically, we included 44 articles on studies assessing the overall intervention effect of brain stimulation on craving (33 with single-session and 15 with multi-session interventions). In addition, we included 15 articles on studies that investigated the overall intervention effect of brain stimulation on consumption (10 with single-session and 7 with multi-session interventions). All included studies used excitatory rTMS or tDCS stimulation.

Assessment of risk of bias in the included studies

Table 1
Study and sample characteristics for included studies.

First author	Study population	Number of sessions (per condition)	Anodal Stimulation side (dlPFC)	Stimulation Technique	Participants number	Study Design	total number of pulses (per condition)	Craving measure	Consumption measure
Alcohol (12 studies)									
Boggio et al.(2008)	Alcohol dependence	1	Both	tDCS	13	W	NA	AUQ *	NA
da Silva et al.(2013)	Alcohol dependence	5	Left	tDCS	13	B	NA	OCDS *	NA
den Uyl et al. (2015)	Alcohol use disorder	1	Left	tDCS	26	B	NA	AAAQ *	NA
Herremans et al.(2012)	Alcohol dependence	1	Right	rTMS	31	B	1560	OCDS	NA
Herremans et al.(2013)	Alcohol dependence	1	Right	rTMS	29	W	1560	OCDS	NA
Herremans et al.(2015)	Alcohol dependence	1	Right	rTMS	24	W	1560	VAS	NA
Höppner et al.(2011)	Alcohol dependence	10	Left	rTMS	19	B	NA	OCDS	NA
Klauss et al.(2014)	Alcohol dependence	5	Right	tDCS	33	B	NA	OCDS	NA
Klauss et al.(2018)	Alcohol dependence	10	Right	tDCS	45	B	NA	OCDS	NA
Mishra et al.(2010)	Alcohol dependence	10	Right	rTMS	45	B	10000	ACQ *	NA
Nakamura-Palacios et al.(2012)	Alcohol dependence	1	Left	tDCS	32	W	NA	OCDS *	NA
Wietschorke et al.(2016)	Alcohol dependence	1	Right	tDCS	30	B	NA	VAS *	NA
Food (20 studies)									
Barth et al. (2011)	Healthy women who endorsed frequent food cravings	1	Left	rTMS	10	W	3000	VAS	NA
Bravo et al.(2016)	Obesity	5	Right	tDCS	10	B	NA	VAS	NA
Burgess et al.(2016)	Binge Eating Disorder (also subthreshold)	1	Right	tDCS	30	W	NA	VAS *	Calories consumed *
Claudino et al. (2011)	Bulimia Nervosa or Eating Disorder not otherwise specified	1	Left	rTMS	22	B	1000	VAS and FCQ-S *	NA
Fregni et al. (2008a)	Healthy subjects with frequent food cravings	1	Both	tDCS	21	W	NA	VAS *	Calories consumed *
Gluck et al.(2015)	Obesity	3	Left	tDCS	9	B	NA	NA	Calories consumed
Gluck et al.(2017)	Obesity	15	Left	tDCS	20	B	NA	NA	Calories consumed *
Goldman et al. (2011)	Healthy subjects with frequent food cravings	1	Right	tDCS	19	W	NA	VAS	Food consumed
Grundeis et al.(2017)	Obesity	1	Left	tDCS	23	W	NA	NA	Calories consumed
Heinitz et al.(2017)	Obesity	15	Left	tDCS	29	B	NA	NA	Calories consumed *
Jauch-Chara et al.(2014)	Healthy men with low cognitive restraint for food consumption	Both 1 and 8	Right	tDCS	14	W	NA	VAS *	Calories consumed *
Kekic et al.(2014)	Healthy women with frequent food cravings	1	Right	tDCS	20	W	NA	FCQ-S	Food consumed
Kekic et al.(2017)	Bulimia Nervosa	1	Both	tDCS	39	W	NA	VAS *	NA
Kim et al.(2018)	Obesity	4	Left	rTMS	57	B	4000	VAS	NA
Lapenta et al. (2014)	Healthy women with frequent food cravings	1	Right	tDCS	9	W	NA	VAS *	Calories consumed *
Ljubisavljevic et al.(2016)	Healthy individuals with frequent food cravings	5	Right	tDCS	27	B	NA	FCQ-S and FCI *	NA
Montenegro et al. (2012)	Overweight	1	Left	tDCS	9	W	NA	VAS *	NA
Ray et al.(2017)	Obesity	1	Right	tDCS	18	W	NA	VAS	Calories consumed
Uher et al. (2005)	Women with strong food cravings	1	Left	rTMS	28	B	1000	VAS *	Calories consumed
Van den Eynde et al. (2010)	Bulimia Nervosa or Eating Disorder not otherwise specified	1	Left	rTMS	37	B	1000	VAS *	NA
Nicotine (9 studies)									
Amiaz et al. (2009)	Nicotine dependence	10	Left	rTMS	21	B	10000	VAS and sTCQ *	Self-report Cigarettes consumed *
Boggio et al. (2009)	Smoking $\geq$10 cigarettes per day		Left	tDCS	23	B	NA	VAS *	

		Craving: Both 1 and 5; Consumption: 5							Self-report Cigarettes consumed *
Fecteau et al.(2014)	Average daily intake of at least 15 cigarettes	Craving: 5 Consumption: both 1 and 5	Right	tDCS	12	W	NA	sQSU *	Self-report Cigarettes consumed *
Fregni et al. (2008b)	Smoking 15 or more cigarettes per day	1	Both	tDCS	24	W	NA	VAS *	NA
Johann et al. (2003)	Average daily intake of at least 18 cigarettes	1	Left	rTMS	11	W	1000	VAS*	NA
Li et al.(2013)	Nicotine dependence	1	Left	rTMS	14	W	3000	VAS *	NA
Li et al.(2017)	Nicotine dependence	1	Left	rTMS	10	W	3000	VAS	NA
Pripfl et al.(2014)	Nicotine dependence	1	Left	rTMS	11	W	1200	VAS *	NA
Xu et al. (2013)	Daily intake of at least 10 cigarettes	1	Left	tDCS	24	W	NA	UTS	NA
Drugs (7 studies)									
Batista et al.(2015)	Cocaine dependence	5	Right	tDCS	36	B	NA	OCCS *	NA
Boggio et al. (2010)	Marijuana use at least 3 times per week	1	Both	tDCS	17	B	NA	VAS *	NA
Sahlem et al.(2017)	Cannabis Use Disorder	1	Left	rTMS	16	W	4000	MCQ	NA
Shahbabaie et al. (2014)	Methamphetamine dependence	1	Right	tDCS	30	W	NA	VAS	NA
Shen et al.(2016)	Heroin dependence	Both 1 and 5	Left	rTMS	10	B	10000	VAS *	NA
Su et al.(2017)	Methamphetamine dependence	Both 1 and 5	Left	rTMS	30	B	6000	VAS *	NA
Shahbabaie et al.(2018)	Methamphetamine use disorder	1	Right	tDCS	15	W	NA	VAS *	NA

AAAQ: alcohol approach and avoidance questionnaire; ACQ: Alcohol Craving Questionnaire; AUQ: Alcohol Urge Questionnaire; B/W: between-subject design/within-subject design; dlPFC: dorsolateral prefrontal cortex; FCI: Food Craving Inventory; FCQ-S: Food Craving Questionnaire State; MCQ: Marijuana Craving Questionnaire; NA: not available; OCDS: Obsessive Compulsive Drinking Scale; rTMS: repetitive transcranial magnetic stimulation; sTCQ: short version of the Tobacco Craving Questionnaire; sQSU: standardized Questionnaire of Smoking Urges; tDCS: transcranial direct current stimulation; UTS: Urge to Smoke; OCCS: Obsessive-Compulsive Cocaine Scale; VAS: Visual Analogue Scale; * represent significant craving or consumption reduction after intervention, if an article reported the effect of both single-session and multi-session, this only represent the effect of the later.

protocols were more beneficial. However, the moderator analysis testing for a positive linear association between the number of sessions and effect size (β = 0.032, CI: -0.001–0.008, $Q = 2.488$, $p = 0.115$) was not significant, possibility due to the lower number of studies measuring consumption as compared to craving (Supplementary Fig. 2). The relationship between administered pulses and consumption could not be investigated since there were only two available rTMS studies. The additional analyses excluding individuals without a clinical diagnosis of eating disorder studies (Supplementary B), as well as the analyses excluding studies with partially failed blinding procedures (Supplementary C) confirmed the above findings.

Differences in effects between different study populations

The comparison of the effect sizes in different study populations (alcohol, nicotine, illicit drugs or eating addiction) revealed no significant differences in the overall effect size for the modulation of craving ($Q = 2.545$, $p = 0.467$). In addition, when investigating each population separately, we found a significant effect with small to medium effect sizes on craving level in individuals with alcohol ($g = 0.382$, CI: 0.078–0.685; $z = 2.465$, $p = g$ =26,med

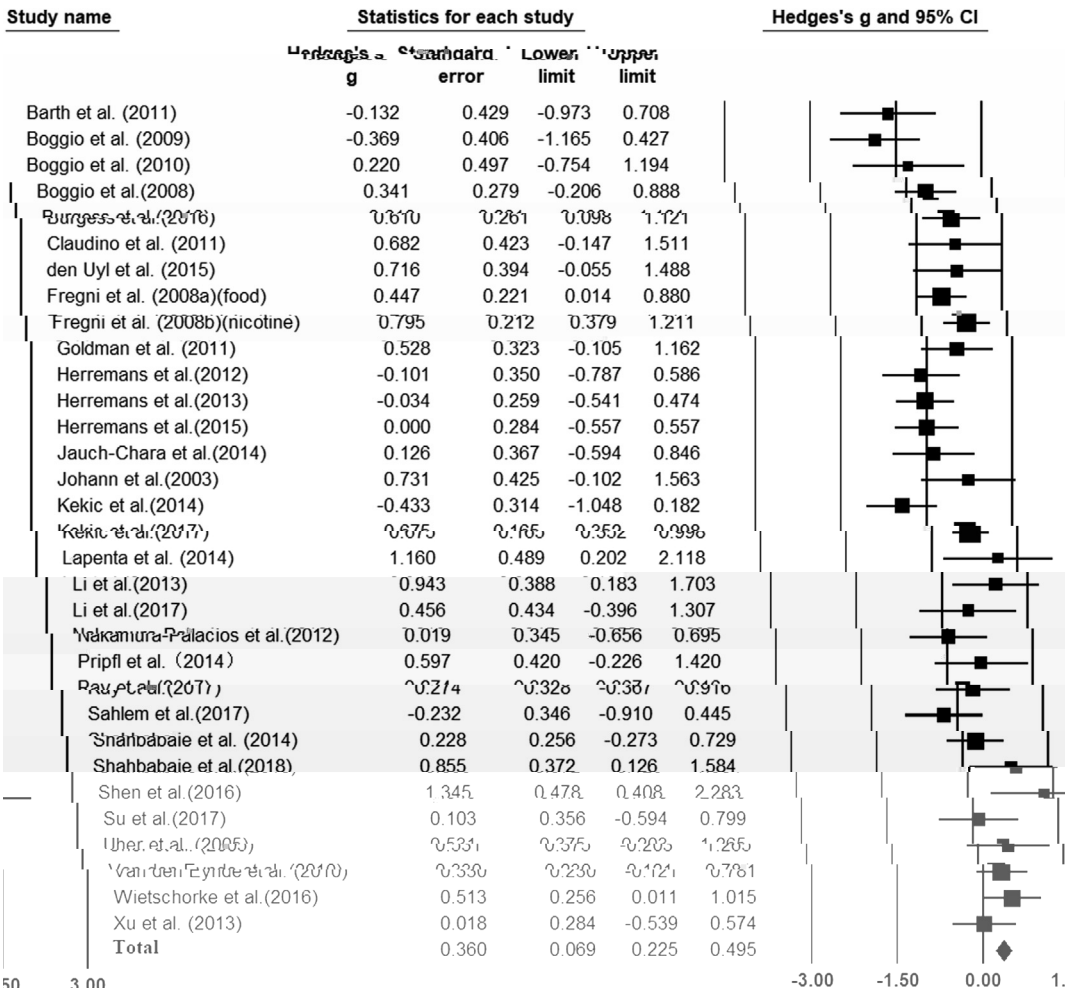

Fig. 3. The effect of single-session neuromodulation on craving.

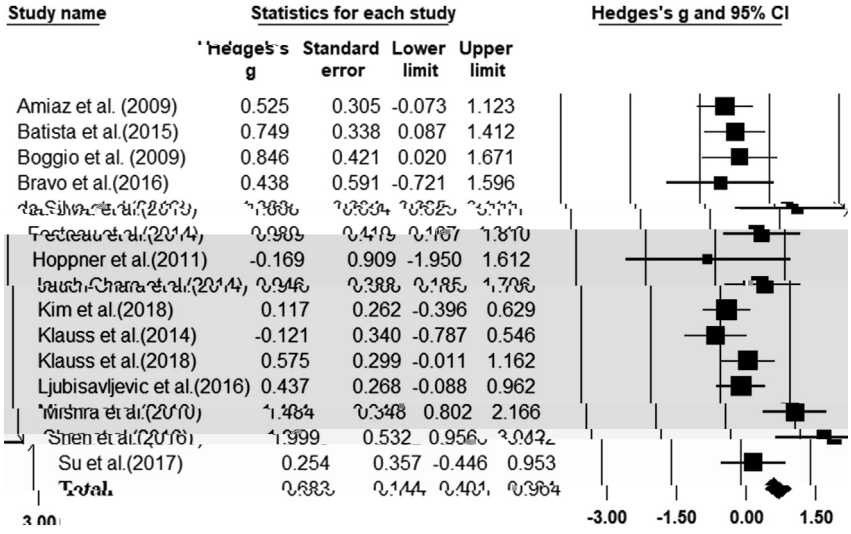

Fig. 4. The effect of multi-session neuromodulation on craving.

$p = 0.085$), revealing a slightly larger effect in individuals with nicotine addiction (with consumption levels generally being measured by cigarettes smoked per day as indicated by self-report, see Table 1) as compared to eating addiction (based on consumed food during a test after the intervention, see Table 1). When considering these two populations separately, we found a significant reduction of consumption levels in both populations, with a large effect size in smokers ($g = 1.138$, CI: 0.543–1.733; $z = 3.751$,

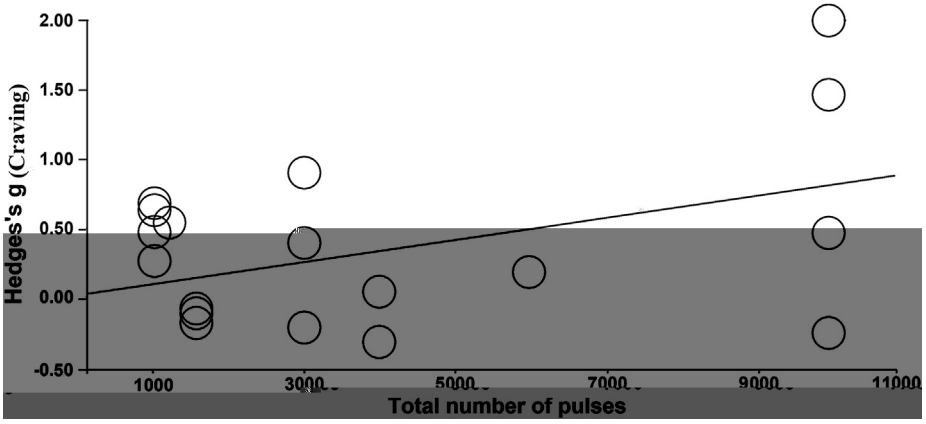

Fig. 5. Regression of the total number of pulses on the effect size of neuromodulation of craving. β = 0.0001, 95% CI: 0.00002–0.00013, Q = 8.465, p = 0.004.

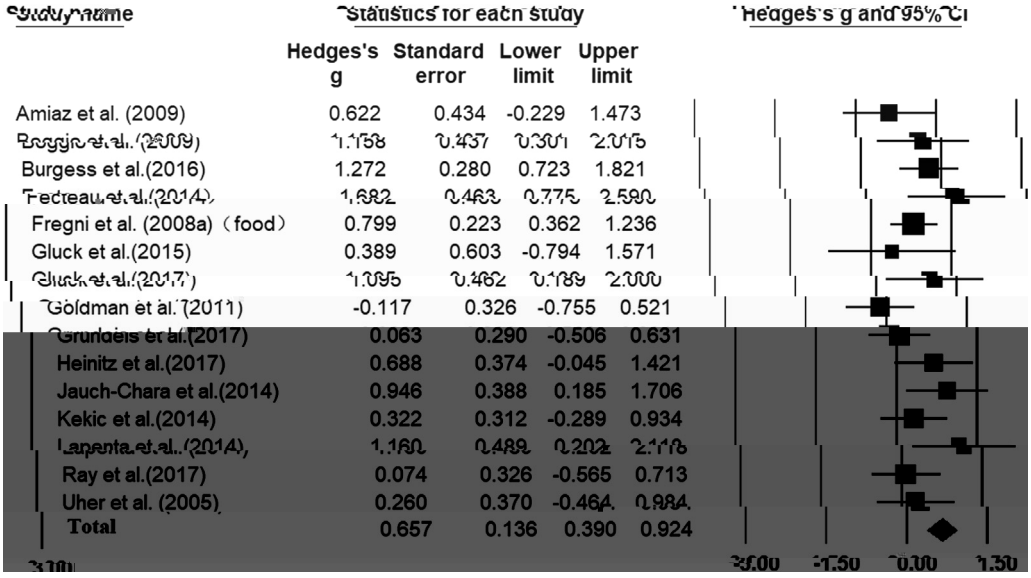

Fig. 6. The overall effect of neuromodulation on consumption.

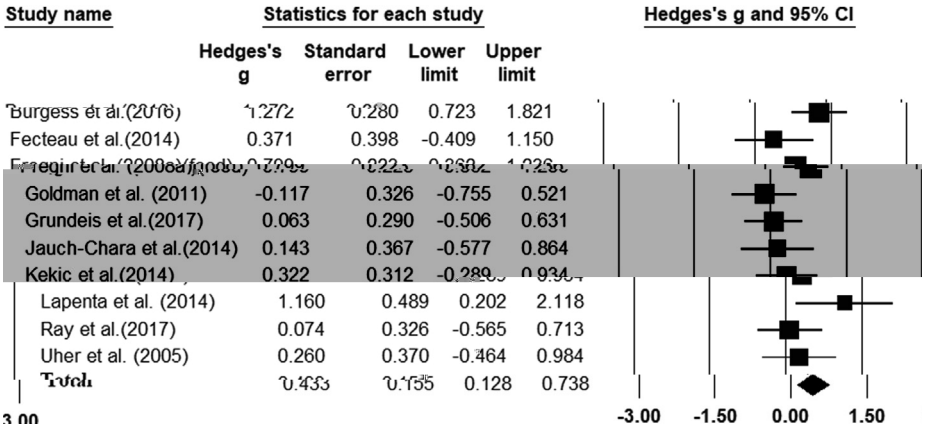

Fig. 7. The effect of single-session neuromodulation on consumption.

p < 0.0001) and a medium effect size for the reduction of food consumption (g = 0.560, CI: 0.279–0.841; z = 3.908, p < 0.0001). No study has investigated the effect of neuromodulation on consumption in individuals with alcohol or illicit drug addiction.

Comparing different stimulation techniques

The comparison of the two stimulation techniques (rTMS vs. tDCS) showed no significant differences in their overall

effectiveness for down-regulating craving ($Q = 0.307$, $p = 0.579$); with a significant effect for tDCS ($g = 0.490$, CI: 0.347–0.633; $z = 6.710$, $p < 0.0001$) and rTMS interventions ($g = 0.411$, CI: 0.170–0.651; $z = 3.350$, $p = 0.001$). When separately considering the effect on craving within single-session ($Q = 0.398$, $p = 0.528$) or multi-session interventions ($Q = 0.054$, $p = 0.816$), we also found no significant differences in the effectiveness between the two stimulation techniques. There were not enough studies to assess the session effect for consumption.

Comparing different stimulated hemispheres

The comparison of the overall effect size depending on the side of stimulation (right versus left hemisphere) revealed no significant differences for an effect on craving ($Z = 0.028$, $p = 0.9778$), with similar effects for each hemisphere separately (left: $g = 0.438$, CI: 0.254–0.623; $z = 4.651$, $p < 0.0001$; right: $g = 0.464$, CI: 0.300–0.628; $z = 5.545$, $p < 0.0001$). This was replicated when considering only single-session ($Z = 0.01$, $p = 0.992$) or multi-session interventions ($Z = 0.088$, $p = 0.930$). Similarly, the side of stimulation did not influence the overall effectiveness of the intervention in reducing consumption levels ($Z = 0.045$, $p = 0.964$), with similar effects per targeted hemisphere (left: $g = 0.602$, CI: 0.305–0.899; $z = 3.966$, $p < 0.0001$; right: $g = 0.648$, CI: 0.220–1.076; $z = 2.968$, $p = 0.003$).

Influence of study design

Finally, when investigating the influence of the chosen study design, we found a significant craving reduction both in studies with a between-subject design ($g = 0.541$, CI: 0.332–0.750; $z = 5.078$, $p < 0.0001$) and a within-subject design ($g = 0.399$, CI: 0.237–0.561; $z = 4.828$, $p < 0.0001$); there was no significant difference in the effect size between the two study designs ($Q = 1.114$, $p = 0.291$). Consistent with this pattern, we found a significant reduction of consumption levels in studies using a between-subject design ($g = 0.690$, CI: 0.346–1.034; $z = 3.930$, $p < 0.0001$) or a within-subject design ($g = 0.645$, CI: 0.261–1.029; $z = 3.289$, $p = 0.001$); and again no difference in the effect size between the two designs ($Q = 0.029$, $p = 0.865$).

Discussion

The current meta-analysis of 48 studies revealed a significant overall effect of neuromodulation interventions targeted at the dlPFC (over sham stimulation), with small to medium effect sizes for the reduction of craving and small to large effect sizes for the reduction of consumption levels across different addicted populations. More importantly, the current results showed for the first time that multi-session protocols are more effective than single-session protocols. We found significantly larger effects of multi-session interventions both on craving reduction and for ability to refrain from consumption, with a linear dose-response effect such that an increased number of sessions or administered pulses had a larger effect on the craving level.

These results are in agreement with the general pattern of prolonged neuromodulation: compared to single pulse TMS, repeated pulses induce more prolonged effects in the brain, an effect which scales with the number of pulses applied [37]. Moreover, multi-session excitatory rTMS with its multifold total number of pulses has more prolonged effects than single-session rTMS does, generating a cumulative long-term potentiation (LTP) of synaptic connections [37]. Similarly, the length of stimulation in tDCS neuromodulation is crucial to achieving sustained effects [39]. The current meta-analytical results are also consistent with previous individual studies showing a larger effect of multi-session as compared to single-session interventions [45–47,65,66], which reported a linear dose-response effect of neuromodulation [46]. While we would expect a saturation of this dose-response

effect (medium-sized) for a craving reduction in illicit drug users (e.g., cannabis, cocaine, heroin, methamphetamine) by brain stimulation, hence suggesting consistent effects across all four included populations (alcohol vs. nicotine vs. illicit drugs vs. eating addictions).

Moreover, regarding the effect of neuromodulation on consumption, the current analysis (covering 12 studies) is consistent with a previously updated meta-analysis (covering 8 studies) focusing on individuals with excessive eating, which found an effect of brain stimulation on food consumption [43]. Furthermore, the current results demonstrated for the first time that non-invasive brain stimulation targeted at dlPFC can lead to a large-sized effect in the consumption reduction of cigarette smoking. When comparing smokers to excessive eaters, we found a marginally significant difference in the effect sizes for reduction of consumption, with a large effect size for smokers and a medium effect size for eating addiction. However, this difference between the reduction in cigarette and food consumption may be in part due to differences in the used measurement instruments, as the reduction in cigarette consumption was mainly assessed by self-report whereas the reduction in food taking was generally assessed with the real consumption (e.g., the amounts of calories consumed) after the intervention. There was no difference in effect sizes between populations when craving was used as an outcome measure.

The current results, also converging with a previous meta-analysis of 17 studies [41], showed that the stimulation technique *per se* did not significantly affect the reduction of craving across different populations. This pattern was different from a previous meta-analysis (covering 12 studies, including 8 tDCS) [42,43] which showed a stimulation effect on food cravings that was statistically significant for rTMS but not tDCS. When we restricted our analysis to studies on food craving only (covering 16 studies, including 11 for tDCS), we showed a significant brain stimulation effect for both rTMS ($g = 0.287$, CI: 0.014–0.559; $z = 2.061$, $p = 0.039$) and tDCS ($g = 0.479$, CI: 0.266–0.692; $z = 4.400$, $p < 0.001$).

In the current meta-analysis, we examined the potential effect of lateralized neuromodulation targeted at a specific hemisphere (left versus right) but found no effect for this factor, consistent with a previous meta-analysis [41], but inconsistent with a second meta-analysis, which only investigated the effect on food craving [43]. When restricting our analysis to include only studies on food craving we did not find a difference between the targeted site ($Z = 0.170$, $p = 0.865$). However, it would be premature to conclude that the mechanism of intervention may not be lateralized, as there are strong anatomical connections between the left and right dlPFC, likely leading to the presence of neuromodulation in both hemispheres. Finally, we examined the potential effect of study design (within-versus between-participant) for the first time, and again found no effect of this variable, confirming the independence of our results from these operational parameters.

Despite its strengths, the current meta-analysis has several limitations. First, the currently available literature does not allow for a systematic investigation of long-term outcomes of brain stimulation, as studies with a follow-up visit were scarce. The few studies that did include long-term outcome measures had somewhat inconsistent findings: some studies observed a long-term reduction of craving 10 days [72], 25 days [73] or one month [74] after the last brain stimulation of dlPFC or a long-term reduction of consumption nine days [65], 14–21 days [75] or six months [76] after the last stimulation; other studies observed no such long-term effects on craving either 1–3 days [77] or six months [78] after the last treatment. Second, due to the large heterogeneity in the used stimulation protocols, we were not able to evaluate the potential effects of many variables involved in the protocols. For example, we could not explore whether the frequency (10 versus 20 Hz) used in rTMS protocols influence the modulation effects, as only five studies used 20 Hz protocols [77,79–82]. Similarly, we could not evaluate the influence of the electric current intensity used in tDCS studies (1 vs 2 mA), as only four studies adopted an 1 mA protocol [47,83–85]. In the current meta-analysis we further excluded studies using (inhibitory) low-frequency rTMS ($\leq$1 Hz). In contrast to excitatory high frequency ($\geq$5 Hz) rTMS intervention, low frequency rTMS studies targeted at dlPFC have been shown to increase craving levels in methamphetamine users [86], however, other studies have found opposite results in methamphetamine users [87] and pathological gamblers [88]. These discrepancies need to be further explored, as only a limited number of studies is currently available. Third, we only focused on excitatory brain stimulation of the dlPFC, studies that targeted at brain regions other than dlPFC (e.g., medial PFC [89]; cathodal frontal-parietal-temporal [90]) were not evaluated due to the limited numbers of relevant studies. Initial pilot studies employing inhibitory forms of TMS (cTBS = continuous bursting frequency TMS) targeting ventral medial prefrontal cortex (vmPFC) demonstrated the feasibility of this approach for attenuating reactivity of the reward network and reducing craving [91,92]. Overall, the optimization of stimulation protocols and definition of neural targets certainly remain an important goal for future research.

Conclusions

The current meta-analysis found significant effects of neuromodulation approaches targeted at the dlPFC for reducing craving and consumption in both eating and drug addiction. Importantly, multi-session interventions and longer sessions had larger effects than single-session interventions, with a linear dose-response effect. Overall, the current findings support the efficacy of neuromodulation approaches as a clinical treatment for individuals with drug or eating addiction.

Conflict-of-interest statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2018.12.975.

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