BRAIN
STIMULATION

Contextual cues as modifiers of cTBS effects on indulgent eating

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ABSTRACT

Background: Prior studies have found that continuous theta burst stimulation (cTBS) targeting the left dlPFC results in reliable increases in consumption of calorie-dense food items. However, it is not known to what extent such effects are modified by cues in the immediate eating environment. Tempting environments (i.e., those saturated with appetitive eating cues) may lead to more reliance on cognitive control networks involving the dlPFC, thereby enhancing cTBS effects on indulgent eating.

Objective/Hypothesis: The objective was to examine the extent to which cTBS effects on indulgent eating would be modified by contextual cues. It was hypothesized that cTBS effects would be stronger in the presence of facilitating cues.

Methods: Using a single-blinded between-subjects factorial design, 107 TMS-naïve adults were randomly assigned to one of four conditions: 1) active cTBS + facilitating cues, 2) sham cTBS + facilitating cues, 3) active cTBS + inhibiting cues, 4) sham cTBS + inhibiting cues. Following stimulation participants completed a flanker paradigm and a taste test during which quantity consumed was assessed surreptitiously.

Results: Findings revealed a significant interaction between stimulation and cue type ($F(1,102) = 6.235$, $p = .014$), such that cTBS resulted in increased food consumption (compared to sham) in the presence of the facilitating cue but not in the presence of the inhibiting cue. Moderated mediational analyses showed selective mediation of cTBS effects on consumption through cTBS attenuation of flanker interference scores.

Conclusions: The effects of cTBS on indulgent eating are strengthened in the presence of facilitating cues. Methodologically speaking, facilitating cues may be a functional prerequisite for exploring cTBS effects on eating in the laboratory. Substantively, the findings also suggest that facilitating cues in the eating environment may amplify counter-intentional food indulgence in everyday life via cognitive control failure.

Introduction

Modulation of the left dlPFC reliably alters response to calorie-dense food items [1,2]. Such effects are more reliable with rTMS than tDCS, and when stimulation is left-sided than right-sided [1,3,4] see also [5]. The involvement of the dlPFC in dietary self-control and the propensity toward weight gain is corroborated by functional imaging studies that also implicate the dlPFC in dietary self-control and obesity [6].

Most neuromodulation studies involving eating consider stimulation parameters more carefully than food outcome measurement—for instance the type of food product and the nature of the eating environment. However, there is both theoretical and empirical justification for considering the latter two factors when attempting to quantify the direction and magnitude of any causal effect of dlPFC modulation on eating outcomes. In theory, brain systems that support cognitive control have potential to be more consequential for food consumption when the food is calorie-dense than otherwise, and when environmental cues impel indulgence rather than restraint [7–9].

For instance, incentive salience of foods tend to be stronger when homeostatic feeding systems are primed by ghrelin [6,10]. Likewise, meta-analytic studies have found reliable associations between cue reactivity and eating outcomes, with visual cues as powerful as the presence of real food [11–14]. For this reason, the presence of food cues in the contextual environment should

amplify the causal influence of fronto-parietal control systems on eating behavior.

Several prior studies have found evidence that individual differences in Stroop performance predict actual consumption more so in the presence of facilitative visual cues than in the presence of restraint cues [15,16]. However, to date, no experimental study has examined the potential for contextual cues to moderate the impact of dlPFC function on eating in a fully factorial experiment, crossing dlPFC modulation with cue type. The present experiment is an attempt to do this using continuous theta burst stimulation to attenuate the excitability of neuron populations in the left dlPFC and observe the effect on eating in the context of randomly assigned inhibitory versus facilitative visual cues in the eating environment.

Continuous theta burst stimulation (cTBS; [17–19]) is a highly efficient variant of rTMS that reliably reduces task performance on measures of cognitive control, particularly when targeting the left dlPFC [20]. The current study examines the joint effect of left dlPFC modulation (active vs sham) and cue type (facilitating vs. inhibiting) on calorie-dense food consumption, in order to test the hypothesis that left dlPFC attenuation will result in increased consumption more so in the presence of cues that impel indulgence than when they impel restraint. We further hypothesize that cTBS effects on snack consumption would be mediated by reductions in inhibitory control, particularly in the presence of facilitative cues. In keeping with a recent study using similar methods and outcomes [21], it was anticipated that cravings, attitudinal dimensions, and flavour experience would not mediate the cTBS effects on eating outcomes.

Methods

Participants

A total of 107 adult participants were recruited for this study. Three participants discontinued participation, leaving an effective sample size of 104 (39 males and 65 females). All participants were right-handed with a mean age of 21.9 ($SD = 3.0$; range = 18–37). Participants were primarily Asian (43.3%), Caucasian (27.9%), or South Asian (14.4%). Mean body mass index (BMI) was 23.0 ($SD = 3.6$; range = 16.8–35.4); the majority of the sample was within the "normal" range (72.8% and 63% using North American and ethnicity-specific cut-offs, respectively).

Participants were recruited over 8 months (January through August, 2018) through posters distributed around the university campus. All participants were naïve to TMS; prior to participation, individuals were screened to be free of any physical and neurological conditions that would contraindicate rTMS, using a standard screening form [22]. The study protocol was reviewed by and received clearance from the hosting institutional ethics review board. Written and informed consent was obtained from all participants prior and following to their participation. One participant discontinued due to reluctance to remove a head scarf for religious reasons and two discontinued due to discomfort during the motor threshold establishment procedure. In the latter two participants discomfort was alleviated immediately by discontinuing stimulation. No other tolerability or adverse reactions were reported by participants.

Procedures

Participants were randomly assigned to one of 4 conditions: 1) active cTBS + facilitating cue, 2) sham cTBS + facilitating cue, 3) active cTBS + inhibiting cue, or 4) sham cTBS + inhibiting cue. All participants were blinded to stimulation condition. Each study session was conducted 11:00am-12:30pm or 3:00pm-4:30pm from

Monday-Friday. Participants were asked to refrain from eating or consuming caffeinated beverages 3 h prior to the start of the experimental session; adherence to these requirements was checked with completion of the consent form. All computer tasks were presented using Inquisit software version 5.0.13.0 (Millisecond Software) on a 27-inch monitor. For the cognitive tasks, participants were instructed to respond as quickly and accurately as possible. The ambient lighting and temperature conditions were maintained stable across participants. All analyses was conducted using SPSS V. 25 (IBM).

The study protocol is presented in Fig. 1. The experimental session started with the consent procedure, followed by a computer task (IAT), rTMS protocol (see below), two measures of attitudes in counterbalanced order (implicit and explicit), self-report measures (food cravings), and a computerized task of behavioral inhibition (the Flanker task). Following the testing session—and approximately 30 min after stimulation—participants were given an opportunity to sample 5 different calorie-dense snack foods under the guise of examining the relationship between brain function and taste perception. Change in weight of food from pre- to post-tasting was surreptitiously assessed in order to quantify food consumption. The mild deception about the purpose of the study and presence of a sham condition was then explained in a debriefing session that followed; participants were then given the opportunity to withdraw their data as per ethical requirements, however none elected to do so. Following the disclosure of their study condition all participants in the sham condition reported being initially unaware that they were in the sham condition during the stimulation protocol, when asked the question: "during the stimulation, were you aware that you were placed in the sham condition?"

Brain stimulation protocol

The cortical stimulation protocols were applied using a 75 mm figure-8 coil (MCF-B65), with pulses generated by a MagPro (model X100) biphasic stimulation unit (MagVenture, Alpharetta, GA, USA). Individualized resting motor thresholds (RMT) were employed to calibrate stimulation intensity vis-à-vis visible twitch of the right *abductor pollicus brevis* (APB) muscle. RMT was established as lowest intensity required to induce a discernable thumb twitch in 5/10 consecutive trials. The F3 electrode position (from the international 10–20 system) was used to locate target site for the left dlPFC. Stimulation intensity was set at 80% of RMT and consisted of a 40s continuous train of 600 pulses applied in the theta burst pattern (i.e., bursts of three stimuli at 50 HZ repeated at a 5 HZ frequency). Sham cTBS was applied using the placebo version of the same coil (MCF-P-B65 coil), again targeting F3.

cTBS condition was single-blinded. To confirm the success of the sham condition, we asked sham participants following the study if they were aware that they were in the sham condition, and none indicated that they believed this to be true initially.

Flanker task

The Eriksen Flanker task paradigm presents participants with a series of selective spatial attention response trials wherein they are asked to respond to target stimuli as quickly and accurately as possible, while at times inhibiting the influence of distracting noise stimuli presented in either side of the target (i.e., "flankers"). As such, the Flanker task is primarily a measure of the behavioral inhibition facet of executive function. In the current version of the task, for each trial participants were asked to stare at a fixation cross in the middle of the screen, and when they pressed the space bar a stimulus would appear. Participants were required to identify the target letter in the center of the array, ignoring any flanking
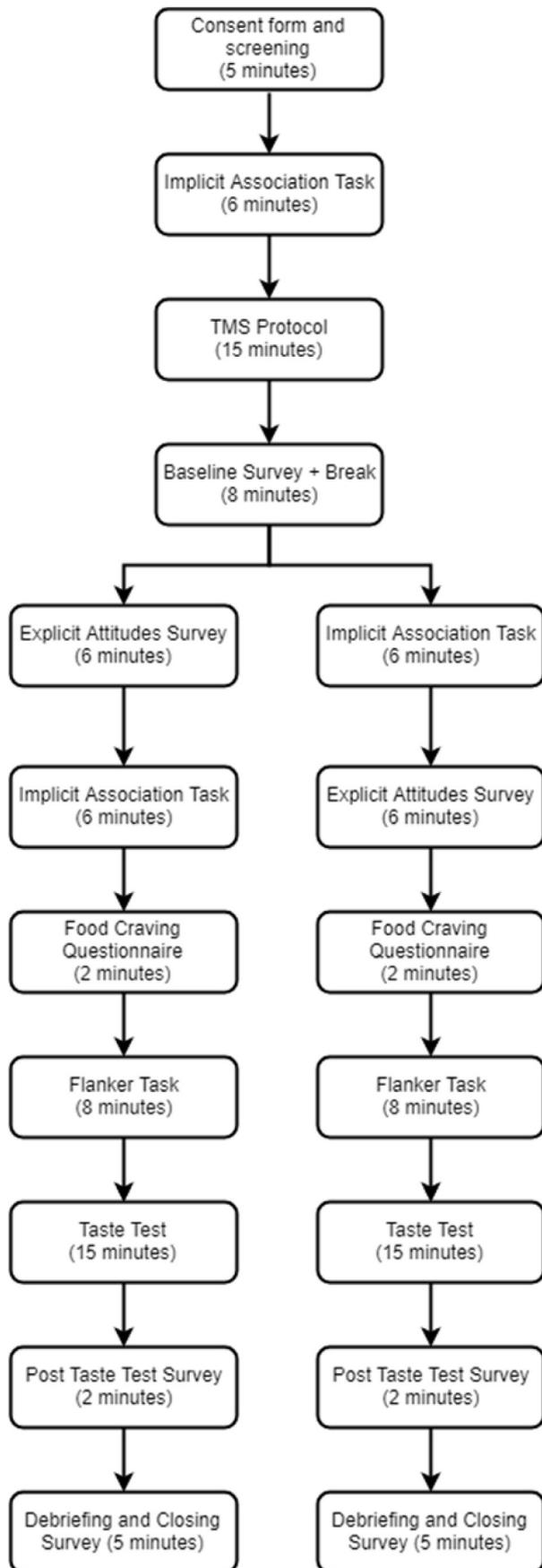
noise letters and register a response using the corresponding keyboard key. Participants could proceed at their own pace but were given a maximum of 1 s in which to respond to any given stimulus. The Flanker interference score was calculated as the difference between reaction times on correct trials in noise condition 3 (incongruent noise) and noise condition 1 (congruent noise); this served as the primary metric for subsequent analyses.

A modified version of the Eriksen flanker task was employed as a measure of behavioral inhibition (Eriksen et al., 1974). Following a practice block of 32 trials, participants completed 5 blocks of 108 trials (96 noise, and 12 no noise) in a mixed block design. As per the original Eriksen paradigm, blocks consisted of 5 different noise conditions; the order of the trials was selected randomly but rotated such that over the course of the experiment every permutation was equiprobable. The target letters "H" and "K" were assigned to either the "A" or "D" keyboard key, while the target letters "S" and "C" were assigned to the other alternative; letter assignment was random for each participant but maintained across trials.

Food consumption

Participants were seated in front of an array of 5 snack foods, all of which were calorie-dense (2 types of salted potato chips and 3 types of Belgian chocolate balls). Participants were given a series of self-report scales to indicate the extent to which each resulted in a different taste experience (sweet, savory, etc.). The form of the taste test is commonly used in the eating literature and has been demonstrated to be a reliable metric for food consumption. Prior validation studies have shown variability in this kind of paradigm to be responsive to food palatability and level of hunger [23], and responsive to acute manipulations of executive function using cTBS targeting the left dlPFC [3,21]. Participants were given condition specific instructions during the lead-in to the taste test: participants in the facilitation condition were instructed to "eat as much as you like in order to make your ratings" while those in the inhibition condition were instructed to "eat the bare minimum in order to make your ratings."

Visual cues

Participants were exposed to a visual cue containing an image of a calorie-dense food item (i.e., a pepperoni pizza) or a health-oriented informational image of the same size and shape (i.e., a circular food recommendation pyramid; Fig. 2). Each poster was 60 cm × 85 cm, and was placed on the wall at a 45° diagonal from the computer screen. The poster was switched for each participant in accordance with their randomly assigned cue condition. Visual cue posters were intended to be peripheral but within the visual field of each participant during the first phase of the study (e.g., consent, self-report questionnaires, and cognitive testing).

Implicit attitudes

The IAT [24] was used to measure implicit associations between calorie density (high vs. low) and semantic valence (positive vs. negative); it was administered pre- and post-stimulation. The

Fig. 1. Experimental session timeline. Tasks were timed to coincide with the initial emergence and subsequent peak cTBS effects based on known parameters of its time course. Specifically, the first outcome measure is completed at 8–14 min post-stimulation, which is the minimum time required for significant cTBS effects to manifest, and the critical outcome (food consumption) is timed to coincide with peak effects from 30 to 45 min after stimulation. All other tasks fell in between these, and well within the temporal window of expected cTBS potency.
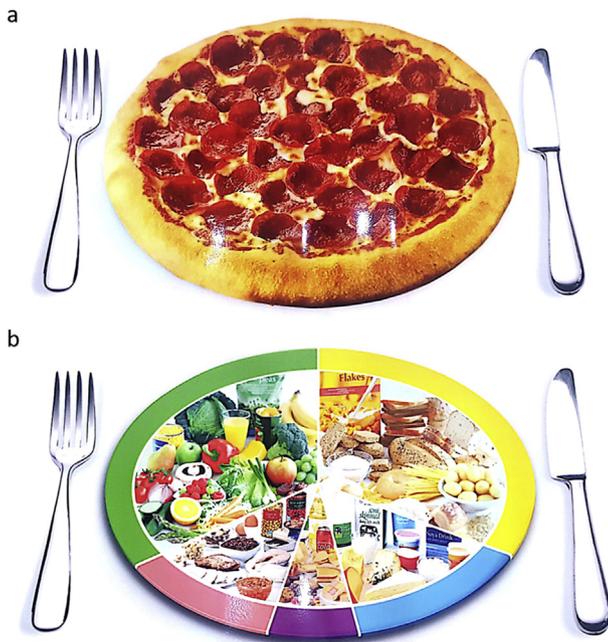
a

b

Fig. 2. The facilitating cue poster (a) and the inhibiting cue poster (b).

target food items and words were selected based on their usage in prior food IAT research [25]. Based on prior evaluative ratings of words in a large normative sample [26], the average valence of words chosen as positive words for this version of the IAT were significantly more positive than those chosen as the negative words ($t(1,10) = 7.229$, $p < .001$). As in the original Greenwald study [24], the IAT consisted of 7 blocks of sorting trials. In every trial a word stimulus would be presented in the middle of the screen and participants are required to sort it into the appropriate category on either the left or right side of the screen using the "A" key or the "D" key on the keyboard respectively. Following training blocks in which participants were required to correctly sort words according to a single category (i.e. high-calorie vs. low-calorie, or unpleasant vs. pleasant) the categories were combined (i.e. high-calorie/pleasant vs. low-calorie/unpleasant, or low-calorie/pleasant vs. high-calorie/unpleasant). The presentation order of the combined categories was randomized between participants. The primary outcome measure was a change in the D-score between the pre- and post-stimulation administrations of the IAT. The D-score was calculated as the difference in the mean sorting response times between the different combinations of category groupings (i.e. the "high-calorie/pleasant vs. low-calorie/unpleasant" blocks and the "low-calorie/pleasant vs. high-calorie/unpleasant" blocks), divided by the inclusive standard deviation of the response times in those blocks. Reaction times for trials that were more than 2 *SD* from the mean of a participant's response times were excluded from analyses. Higher scores on the D′ metric is interpreted as a stronger positive association between high calorie foods and positive valence words.

Food cravings

The Food Cravings Questionnaire-State (FCQS; [27]) is a 15-item scale assessing the strength of current subjective food cravings. Higher scores on the FCQS indicate stronger craving responses experienced in the here and now. The scale includes items pertaining to the desire to eat, anticipated positive reinforcement from eating, anticipated negative reinforcement from eating, subjective lack of control over eating, and physiological symptoms of hunger.

Explicit attitudes

Explicit attitudes were measured using self-report. Participants were asked to rate indulgent eating using 16 sets of bipolar adjective pairs in relation to a common word stem (i.e., "for me to eat calorie dense foods would be …" wise/foolish; good/bad; etc), using a 1 to 7 scale. Responses were summed such that higher scores indicated more positive explicit attitudes toward food indulgence. This scale was previously validated and employed in an eating study involving neuromodulation in our laboratory [28].

Food evaluative dimensions

During the taste test, participants were asked to rate each snack food item on a number of taste and evaluative dimensions, in order to capture the extent to which cTBS may have affected the flavour experience and value processing. In the first subjective report item, participants were presented with 25 descriptive terms and asked to circle any that they felt applied to the food texture that they had just sampled. The next five questions asked participants to rate the extent to which the participants found the food to be appealing, salty, sweet, greasy, and generally pleasant to consume; all of these were made on a 1−10 scale where 1 = "Not at all [sweet, salty, etc.]," 5 = "Moderately [sweet, salty, etc.]," and 10 = "Very [sweet, salty, etc.]."

Statistical approach

Descriptive statistics were computed for demographic variables and evaluative/taste dimension ratings separately for each treatment group. Groups were compared on each of these to ensure baseline comparability and successful randomization. Following this, univariate generalized linear models were employed to examine the effects of stimulation condition (active vs. sham) and cue type (facilitating vs. inhibiting) using a two-way ANCOVA for each of the candidate mediators (Flanker interference scores, cravings, explicit attitudes, and IAT scores) and primary outcome (food consumption). Gender, BMI, and dieting or sports participation were included as covariates in all ANCOVAs. Significant cTBS effects on mediator variables were subjected to conditional mediational analyses using the PROCESS macro [29], in order to examine whether or not effects of cTBS on the dlPFC operated through modulation of inhibitory processes (as hypothesized) versus overall taste/evaluative ratings, cravings or attitudinal dimensions (competing hypotheses). Only variables that were significantly affected by cTBS were further analyzed as purported mediators in formal analyses.

Results

No significant differences were evident among the four treatment conditions with respect to age ($F(3,103) = 0.136$, $p = .938$), gender ($\chi(3) = 1.171$, $p = .760$), BMI ($F(3,102) = 1.701$, $p = .172$), time of last meal ($F(3,103) = 0.561$, $p = .642$), or cTBS intensity ($F(3,103) = 1.375$, $p = .255$; Table 1). cTBS also did not affect subjective rating dimensions of the taste test food items; those in the active cTBS condition did not report the food as being more appealing ($F(1,102) = 0.096$, $p = .757$), salty ($F(1,102) = 1.413$, $p = .237$), sweet ($F(1,102) = 0.026$, $p = .872$), greasy ($F(1,101) = 0.396$, $p = .531$) or globally palatable ($F(1,102) = 0.009$, $p = .925$), compared to the sham condition participants. Likewise, those in the active condition did not choose significantly more descriptive flavor dimensions to apply to the food compared to the sham condition ($F(1,102) = 0.013$, $p = .910$). The above suggests that

Table 1
Mean (*SD*) for demographic variables by treatment condition.

	Sham Inhibiting (n = 28)	Active Inhibiting (n = 24)	Sham Facilitating (n = 25)	Active Facilitating (n = 27)	Overall (n = 104)
Age	22.11 (3.57)	21.96 (2.71)	21.60 (2.68)	21.81 (2.87)	21.88 (2.96)
Gender	19 Female	14 Female	14 Female	18 Female	65 Female
	9 Male	10 Male	11 Male	9 Male	39 Male
BMI	23.94 (4.39)	23.62 (3.12)	21.98 (3.07)	22.57 (3.35)[a]	23.04 (3.59)
Last Meal	7.48 (5.35)	7.69 (5.25)	6.14 (4.54)	6.66 (4.14)	6.99 (4.82)
cTBS Intensity (% of max. output)	45.66 (5.78)	46.79 (5.18)	48.76 (5.60)	47.20 (5.78)	47.07 (5.64)

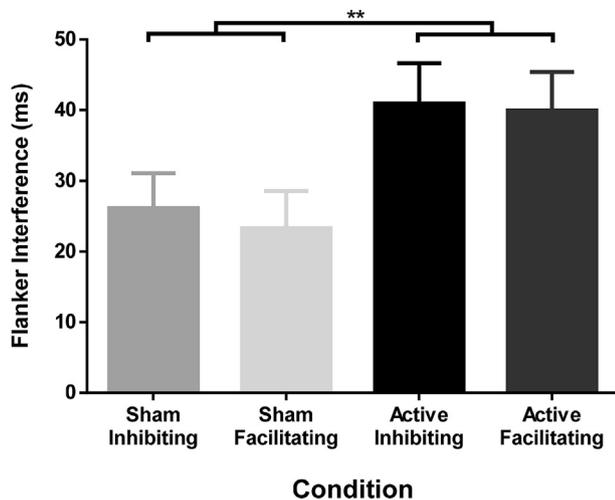[a] One participant in the Active/Facilitating Cue condition chose not to disclose their height and weight.

cTBS applied to the dlPFC had negligible impact on sensory/evaluative aspects of the flavor experience.

Flanker interference scores

With respect to interference scores, a 2-way (stimulation condition x cue type) ANOVA revealed no main effect of cue type ($F_{(1,102)} = 0.008$, $p = .931$, $g = 0.017$), but a significant main effect of stimulation condition ($F_{(1,102)} = 8.844$, $p = .004$, $g = -0.585$), such that those in the active stimulation conditions ($M = 40.446$, $SE = 3.772$) exhibited a stronger interference effect than those in the sham stimulation conditions ($M = 24.728$, $SE = 3.666$). The interaction term between stimulation condition and cue type was not significant ($F_{(1,102)} = 0.001$, $p = .976$). Variable means for all study conditions are depicted in Fig. 3.

Snack food consumption

With respect to snack food consumption, a main effect of cue type ($F_{(1,102)} = 15.067$, $p < .001$, $g = -0.771$), was evident such that individuals in the facilitating cue conditions ($M = 79.985$, $SE = 3.919$) consumed significantly more snack foods than those in the inhibiting cue conditions ($M = 58.222$, $SE = 3.890$). There was no significant main effect of stimulation ($F_{(1,102)} = 1.029$, $p = .313$, $g = -0.199$). The effect of cue type on eating was qualified by a significant two-way interaction ($F_{(1,102)} = 6.235$, $p = .014$); means are depicted in Fig. 4. Consumption was greatest among those in the active condition who were exposed to facilitating cues ($M = 89.659$, $SE = 5.422$). Planned comparisons indicated that the

difference between active and sham stimulation within the facilitation cue condition was significant ($t_{(1,50)} = 2.477$, $p < .05$) as was the difference between the cue type within the active condition ($t_{(1,49)} = 4.509$, $p < .001$). When examining the overall effects of cTBS on consumption, the effect size was positive and moderate in magnitude in the facilitating cue condition ($g = 0.437$) but negative and small in magnitude in the inhibiting condition ($g = -0.240$;
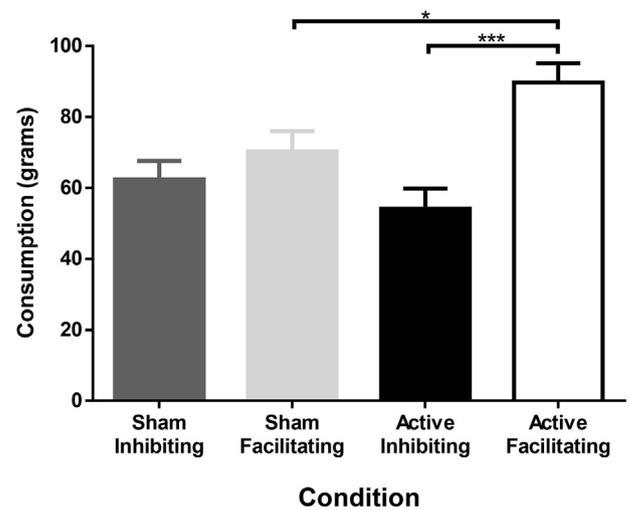
Fig. 4. Mean (+/-SE) for taste test consumption (grams) by treatment condition; "Sham Inhibiting" = sham cTBS + inhibiting cue ($M = 62.327$, $SE = 5.278$); "Sham Facilitating" = sham cTBS + facilitating cue ($M = 70.310$, $SE = 5.624$); "Active Inhibiting" = active cTBS + inhibiting cue ($M = 54.117$, $SE = 5.717$); "Active Facilitating" = active cTBS + facilitating cue ($M = 89.659$, $SE = 5.422$). *: $p < .05$. ***: $p < .001$.
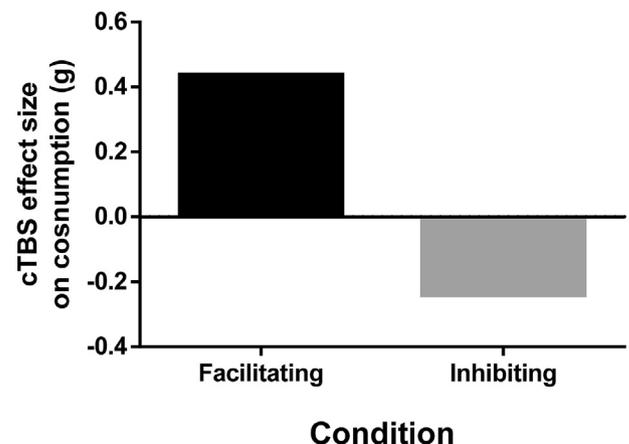

Fig. 3. Mean (+/-SE) for flanker interference scores (ms) by treatment condition; "Sham Inhibiting" = sham cTBS + inhibiting cue ($M = 26.135$, $SE = 4.962$); "Sham Facilitating" = sham cTBS + facilitating cue ($M = 23.279$, $SE = 5.251$); "Active Inhibiting" = active cTBS + inhibiting cue ($M = 40.922$, $SE = 5.717$); "Active Facilitating" = active cTBS + facilitating cue ($M = 39.953$, $SE = 5.422$).**: $p < .01$.

Fig. 5. Hedge's g by treatment condition; effect size of cTBS vs. Sham in the facilitating conditions ($g = 0.437$) contrasted with the inhibiting conditions ($g = -0.240$).

Fig. 5), suggesting that cTBS targeting the left dlPFC made consumptive behavior responsive to environmental cues in general.

We examined the extent to which Flanker scores mediated observed cTBS effects on consumption, conditional upon the cue type. As hypothesized, the 95% confidence interval corresponding with the indirect effect of cTBS on consumption through Flanker performance did not include zero for the facilitating cue condition (indirect effect $= 4.741$, $SE = 2.158$; CI_{LL}: 1.146, CI_{UL}: 9.510), indicating a significant mediational effect. In the inhibitory condition, no such mediation was present (indirect effect $= -2.413$, $SE = 2.391$; CI_{LL}: -7.820, CI_{UL}: 1.675). Overall, the index of moderated mediation supported the conditional model (index $= 7.135$, $SE = 3.586$, $CI_{LL} = 1.398$, $CI_{UL} = 15.324$). Fig. 6 depicts the hypothesized conditional mediational model and the path coefficients for each conditional model separately.
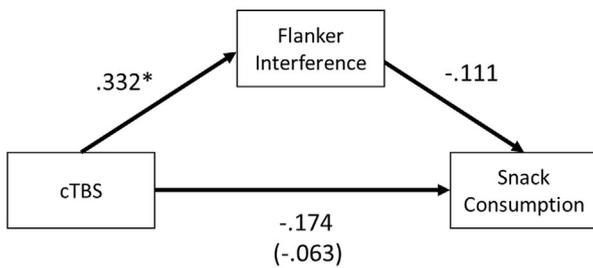
Food cravings

The two way ANOVA examining stimulation condition x cue type revealed a main effect of cue ($F(1,102) = 8.762$, $p = .004$,

a. Moderated mediation model
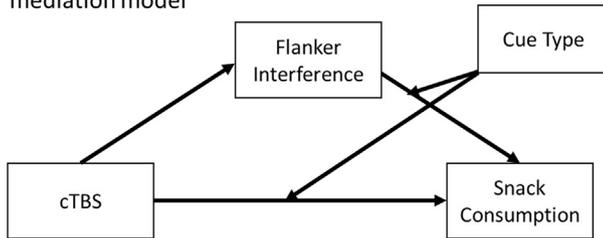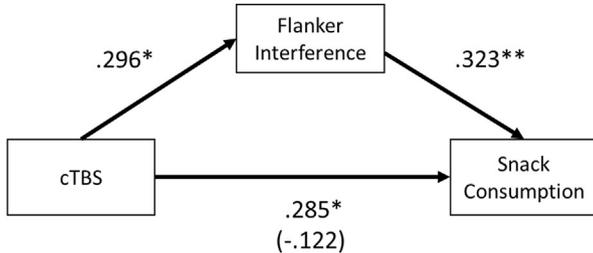
b. Inhibitory cue condition

c. Facilitative cue condition

Fig. 6. a) Schematic representation of the moderated mediational model positing mediation of cTBS effects on consumption through Flanker inhibition score, conditional upon cue type (facilitative vs. inhibitory). Analyses using the PROCESS Macro revealed that, as hypothesized, the mediational model was conditional on the cue condition. Specifically, mediation of cTBS effects on eating through flanker performance was not evident in the inhibiting cue condition (b) but full mediation was evident in the facilitating cue condition (c). All coefficients are standardized Beta weights. *: $p < .05$. **: $p < .01$.
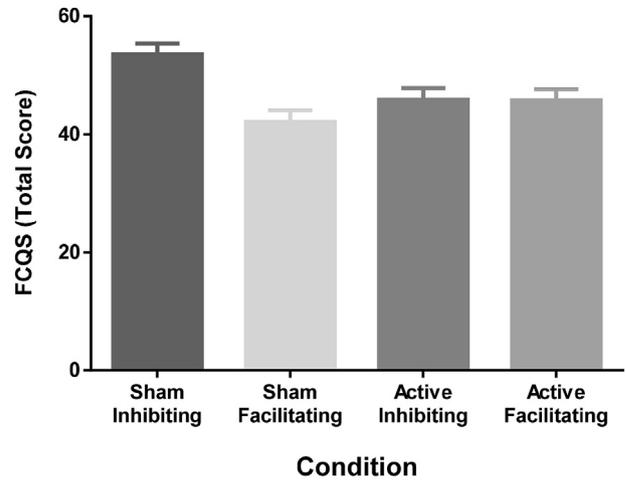

Fig. 7. Mean ($+/-SE$) for FCQS total scores by treatment condition; "Sham Inhibiting" = sham cTBS + inhibiting cue ($M = 53.569$, $SE = 1.838$); "Sham Facilitating" = sham cTBS + facilitating cue ($M = 42.114$, $SE = 1.959$); "Active Inhibiting" = active cTBS + inhibiting cue ($M = 45.859$, $SE = 1.991$); "Active Facilitating" = active cTBS + facilitating cue ($M = 45.753$, $SE = 1.888$).

$g = 0.588$), such that individuals in the inhibiting cue conditions ($M = 49.714$, $SE = 1.355$) reported increased cravings for high calorie foods compared to those in the facilitating conditions ($M = 43.934$, $SE = 3.890$). There was no significant main effect of stimulation ($F(1,102) = 1.134$, $p = .290$, $g = 0.209$). The effect of cue type on eating was qualified by a two-way interaction ($F(1,102) = 8.718$, $p = .004$). Means are presented in Fig. 7, greater values indicate stronger cravings.

Attitudes

The two way (stimulation x cue type) ANOVA revealed no main effects of cue type ($F(1,102) = 0.934$, $p = .336$, $g = 0.061$), or stimulation condition ($F(1,102) = 0.057$, $p = .812$, $g = 0.015$) on explicit attitudes towards calorie dense foods. The interaction term between stimulation condition and cue type was also not significant ($F(1,102) = 3.100$, $p = .081$). Means are presented in Fig. 8. Likewise,
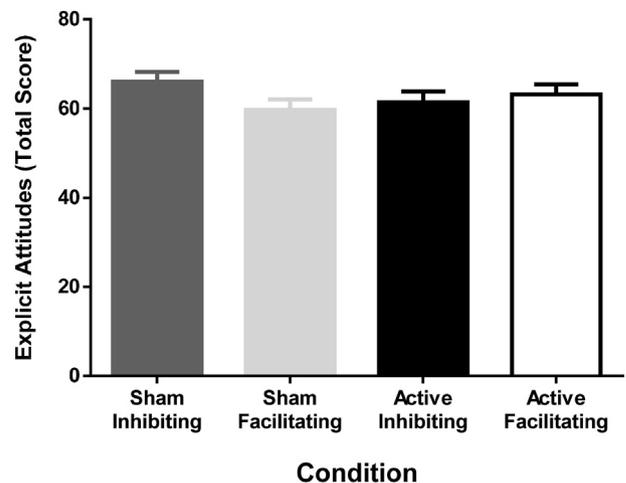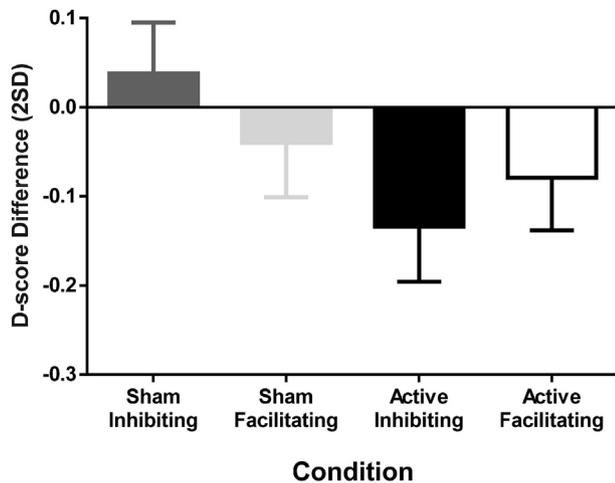

Fig. 8. Mean ($+/-SE$) for Explicit Attitudes questionnaire total scores by treatment condition; "Sham Inhibiting" = sham cTBS + inhibiting cue ($M = 66.007$, $SE = 2.198$); "Sham Facilitating" = sham cTBS + facilitating cue ($M = 59.703$, $SE = 2.343$); "Active Inhibiting" = active cTBS + inhibiting cue ($M = 61.414$, $SE = 2.381$); "Active Facilitating" = active cTBS + facilitating cue ($M = 63.204$, $SE = 2.258$).

Fig. 9. Mean ($+/\text{-}SE$) for changes in D-score in IAT performance pre- and post-stimulation by treatment condition; "Sham Inhibiting" = sham cTBS + inhibiting cue ($M = 0.038$, $SE = 0.057$); "Sham Facilitating" = sham cTBS + facilitating cue ($M = -0.040$, $SE = 0.061$); "Active Inhibiting" = active cTBS + inhibiting cue ($M = -0.134$, $SE = 0.062$); "Active Facilitating" = active cTBS + facilitating cue ($M = -0.079$, $SE = 0.059$).

no significant main effects or interactions emerged involving implicit attitudes toward indulgent eating. The two way (stimulation x cue type) ANOVA revealed no main effects of cue ($F(1,102) = 0.036$, $p = .850$, $g = 0.039$), or stimulation ($F(1,102) = 3.149$, $p = .079$, $g = 0.353$) on a change in implicit attitudes. The interaction term between stimulation and cue type was also not significant ($F(1,102) = 1.224$, $p = .271$). Means are presented in Fig. 9.

Discussion

The current study employed a between-subjects factorial to design to test the hypothesis that the left dlPFC modulation of eating behavior would be more apparent when cues were facilitative of indulgence than otherwise. Consistent with our hypothesis, we found that active cTBS resulted in significantly more food consumption when environmental cues were facilitative than when they were inhibiting. When examining the cTBS effect sizes directly, the effect sizes were positive and of moderate magnitude in the presence of facilitating environmental cues, but negative and small magnitude in the presence of inhibiting cues. Accordingly, attenuation of the left dlPFC appears to make eating behavior more responsive to environmental cues, broadly speaking.

An analysis of mediational mechanisms suggests that inhibitory control was significantly reduced by the cTBS manipulation. Likewise, Flanker interference scores predicted food consumption in a manner consistent with our hypotheses, such that they predicted consumption only in the presence of facilitative cues. The same was not true of any other candidate mediators, as none of them were affected by cTBS or predicted consumption. As such, our pattern of findings was consistent with the notion that cTBS effects on indulgent eating were mediated by cTBS-induced changes in inhibitory control.

Our findings augment existing experimental neuromodulation research involving eating by identifying an important contextual parameter of the eating environment that may determine the magnitude of experimental effect to be expected. Variability in findings of dlPFC modulation and eating outcome in the existing research literature [1,4] could potentially be explained by unintended variability in the eating environment and the extent to which available cues impel restraint or indulgence, even indirectly.

Although our visual cue manipulation was one that was relatively obvious, it is possible that more subtle cues could have similar effects. For example, an experimental setting that contains incidentally visible food images that are appetizing might introduce expected (i.e., disinhibiting) effects of dlPFC attenuation on eating; likewise, protocols wherein participants are presented with large numbers of appetitive food images may have similar effects. On the other hand, studies with inhibiting cues may have the opposite effect, making eating behavior *less* disinhibited (rather than more).

The current findings also may have substantive meaning beyond the methodological implications. Given that advertising for food items in the modern living environment rely on appetizing images, it is possible that such advertising may result in acute susceptibility to indulgence, particularly when other acute dlPFC suppressing factors are present, such as sleep deprivation [30], stress [31], or alcohol intoxication [32]. From this perspective, one strategy for successfully resisting temptation to overindulge in foods may be to avoid both appetitive cues *and* incidental attenuators of dlPFC function. Although the above extrapolations are speculative, linking up neuromodulation findings with public health considerations is potentially informative [8,33]. Along these lines, the power of cues on indulgent eating is attested to by the large main effect of cue type, which is in fact the largest effect observed in the current study ($g = 0.771$).

With respect to food cravings, the findings revealed an unanticipated main effect of cue type such that craving was reported as stronger following the inhibiting cue than following the facilitating cue. This cue effect was most apparent in the sham group. The groups were randomized which reduces the likelihood that the differences in cue response represent baseline differences in participant characteristics the two sham conditions. Yet the rank order of the means is not consistent with what we have found in other studies involving cTBS using the same craving measure [21]. Further studies will be required in order to examine the reliability and interpretability of this finding. We should note that craving is not a necessary pre-condition for consumption, though it is commonly assumed to be the case. Consistent with the current findings, one prior study [21] involving similar stimulation methods and outcomes did not find support for a mediational model involving cravings. This null mediational effect was also replicated in the current sample.

Strengths of this study include: 1) the large sample size, allowing for between-condition comparisons and mediational analyses that would not be sufficiently powered in more conventionally sized neuromodulation study samples, 2) the employ of a between-subjects design, which enhances the validity of the findings by reducing the chance of loss of blinding, 3) the use of sham coil which, in conjunction with the between-subjects design, further enhances the validity of the experimental conditions and reduces the ability of participants to compare stimulation sensations across conditions, and 4) the inclusion of a conditional mediational analysis (including consideration of competing mediators) for cTBS effects on indulgent eating. Limitations include the lack of double blinding and functional imaging. With respect to the latter, cTBS effects on the dlPFC were inferred only via flanker performance; future studies would benefit from using imaging paradigms to directly assess cTBS-induced changes in functional activation patterns in the target cortical region of interest.

Conclusion

In conclusion, the current study found evidence that the effect of cTBS targeting the left dlPFC on food consumption is stronger in the presence of facilitating cues. Findings suggest that

neuromodulation studies involving eating should include appetitive cues in the eating environment and/or avoid incidental exposure to inhibiting cues. Perhaps even more important are the implications of the current findings for when self-restraint would be expected to be more taxing of cognitive control networks in everyday life.

Acknowledgements

Conflicts of interest

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2019.05.003.

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