

# The Effects of Continuous Theta Burst Stimulation to the Left Dorsolateral Prefrontal Cortex on Executive Function, Food Cravings, and Snack Food Consumption

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**Objectives:** Prior research has demonstrated that executive function (EF) strength is positively associated with dietary self-control. As such, the differential operation of the brain centers underlying EFs (i.e., dorsolateral prefrontal cortex [DLPFC]) may explain controlled aspects of dietary self-control. The present study was designed to examine the causal relationship between DLPFC function and two aspects of dietary self-control: visceral cravings and actual consumptive behaviors. **Methods:** The research was conducted using a within-participant design. A sample of 21 healthy female young adults aged 19 to 26 years (mean [M; standard deviation] = 21.10 [1.86] years) received both active and sham continuous theta burst stimulation (cTBS) to the left DLPFC. Before and after each session, subjective food cravings were assessed using the Food Craving Questionnaire—State. After each stimulation session, participants competed three measures of EF (Stroop, Go/No-Go, and Stop-Signal) and a bogus taste test. **Results:** Participants reported larger increases in snack food cravings after active stimulation (M = 9.98% change, standard error [SE] = 0.45) than after sham stimulation (M = -3.46, SE = 0.39,  $p = .012$ ) on the reinforcement anticipation dimension of Food Craving Questionnaire—State. Likewise, participants consumed significantly more snack foods after active stimulation (M = 70.62 grams, SE = 5.17) than after sham stimulation (M = 61.33, SE = 3.56,  $p = .006$ ). Finally, performance on the Stroop task was reduced more after active (M = 71.56 milliseconds, SE = 25.18) than after sham stimulation (M = 20.16, SE = 13.32,  $p = .033$ ); reduction in Stroop performance mediated the effect of active stimulation on increased appetitive food consumption. **Conclusion:** These results support the contention that EF strength, as modulated by DLPFC activity, is causally associated with effective dietary self-control. **Key words:** executive function, prefrontal cortex, dietary behavior, theta burst stimulation, transcranial magnetic stimulation, food cravings.

EF = executive function; DLPFC = dorsolateral prefrontal cortex; PFC = prefrontal cortex; GNG = go/no-go; SST = stop signal task; rTMS = repetitive transcranial magnetic stimulation; cTBS = continuous theta burst stimulation.

## INTRODUCTION

Humans display a strong preference for calorie-dense foods, a preference potentially driven by evolutionary pressures to optimize investment return per unit of energy-spent foraging (1,2). Through much of human history, this consumptive bias would have been adaptive, to the extent that it ensured survival under conditions of relative food scarcity or unpredictability of supply. However, in a relatively short time frame, there has been a switch from food scarcity to an oversupply of calorie-dense foods in most parts of the developed world, coupled with ubiquitous environmental cuing of such foods through media advertising (3). These differences in the modern living environment may have contributed to the dramatic increase in the prevalence and burden of obesity and other chronic illnesses over the past half century (4).

From an ecological perspective, humans are in conflict with their modern environments with respect to their dietary behavior: they prefer highly available calorie-dense foods, yet must avoid yielding to such preferences for the sake of health and longevity. The existence of executive control networks in the human cortex may enable effective negotiation of such person/environment conflicts. Executive functions (EFs) are a collection of distinguishable but interconnected, cognitive

functions (i.e., behavioral inhibition, mental flexibility, and working memory) that enable the top-down (i.e., non-stimulus-driven) control of action, emotion, and thought (5,6).

An accumulating body of literature suggests that the integrity of the executive control system is correlated with obesogenic behavior tendencies in a theoretically meaningful way (7–14). Dietary self-control is strongly dependent on inhibitory control abilities, as effective inhibitory control enables individuals to override habitual or prepotent responses to appetitive energy-dense foods and otherwise act in accordance to their behavioral intentions or other internally generated goals/aspirations (i.e., limit the consumption of energy-dense foods to maintain a healthy diet). As such, the extent in which individuals differ in their inhibitory control abilities could determine their risk for overeating and, subsequently, obesity in the modern environment.

Inhibitory control is understood to involve the operation of the prefrontal cortex (PFC), specifically the dorsolateral prefrontal cortex (DLPFC (15,16)). As such, it is plausible that the differential operation of the DLPFC drives successful self-initiated, self-regulatory processes in eating behavior. Prior research indicates that the DLPFC modulates subjective reward values of highly appetitive foods (17). Hare et al. (18) reported that individuals with effective dietary self-control as compared with those with weak dietary self-control more often made decisions about which foods they would like to consume on the basis of health rather than taste. In addition, those with effective dietary self-control had increased activity in the left DLPFC when making decisions about which foods they would like to eat, suggesting that the operation of the DLPFC may be important for regulating dietary self-control. Therefore, differences in DLPFC activity, particularly the left DLPFC, may explain individual differences in dietary choices, vis-à-vis the connection between the DLPFC and inhibitory control.

Indeed, there is some evidence suggesting that the operation of the DLPFC is causally linked to dietary behaviors. A recent

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meta-analysis (19) documented modest but reliable effects (Hedge  $g = 0.476$ ) of DLPFC modulation (via various cortical stimulation methodologies) on subjective cravings to appetitive substances, including high-calorie foods. No significant differences were observed across stimulation modalities, or between left and right DLPFC stimulation. Three of the studies reviewed demonstrated that up-regulation of the DLPFC results in decreased food cravings for appetitive foods (20–22) and, in one case, decreased consumptive behavior (20). Together, these results suggest that the DLPFC plays a role in regulating food cravings. However, the relationship between DLPFC activity and consumptive behaviors is still unclear, with one study reporting that up-regulation of the DLPFC resulted in the decreased consumption of appetitive snack foods (20), and with two other studies reporting null effects (21,22). No existing studies have attempted to quantify the effects of temporary down-regulation of DLPFC function on cravings and/or consumptive behavior.

Part of the challenge inherent in examining directly observed dietary behavior is the presence of social desirability bias: participants are reluctant to overconsume unhealthy foods in an experimental context. Proper modeling of the social situation for eating to occur is difficult and may have precluded disinhibiting effects of DLPFC modulation on consumptive behavior in prior studies. Facilitating contexts (via instructional sets or cues) can potentiate the expression of individual differences in EF on consumption of high-calorie snack foods (23), and so the extent to which such cues were present in prior studies could influence the likelihood of finding an effect of DLPFC modulation on craving and consumptive behavior.

The nature of the stimulation protocol may also influence the direction and magnitude of effects observed. For instance, continuous theta burst stimulation (cTBS) is a form of repetitive transcranial magnetic stimulation (rTMS) that transiently inhibits cortical activity (24); however, cTBS is considered to be more efficient than other forms of rTMS. There is evidence that suggests that cTBS decreases cortical activity in the PFC, rather than increasing it, as would be expected of aforementioned rTMS protocols. For instance, cTBS has been previously shown to decrease regional blood flow in the PFC (25,26) and impairs performance on measures of EF and attention (27–29). Together, these results suggest that cTBS is an effective cortical stimulation methodology that can be used to transiently inhibit PFC activity. In the context of the current study, cTBS can be used to attenuate DLPFC activity and observe subsequent changes in food cravings and food consumption.

In the current study, we used a taste test paradigm with bias-minimization procedures (23) to carefully examine the effects of DLPFC stimulation (using cTBS) on craving and consumptive behavior in relation to high-calorie snack foods (i.e., those implicated in the development of obesity). It was hypothesized that active cTBS stimulation to the DLPFC (i.e., down-regulation) would result in stronger subjective craving for, and more objective consumption of appetitive calorie-dense foods (but not control foods) in relation to sham stimulation. It was also further hypothesized that changes in EF would

mediate the effects of DLPFC modulation on food consumption. Finally, it was hypothesized that the effects of DLPFC stimulation would be selective to only appetitive, calorie-dense foods and not generalize to other foods.

## METHODS

### Participants

A total of 21 healthy female participants, recruited from undergraduate psychology courses, participated in this study. Participants were recruited using an online participant recruitment system wherein participants signed up for studies in exchange for course credit or monetary reimbursement. The sample size was selected based on observed effect sizes in prior cortical stimulation studies involving dietary behavior (20,22). In exchange for their participation, participants either received \$40 or were entered into a draw for a 16 GB iPad. Participants were preselected based on strong and frequent food cravings for the experimental foods (i.e., chocolate and potato chips). All participants were neurologically healthy and naive to TMS. In addition, participants were excluded if they had been clinically diagnosed with an eating disorder and had either Type 1 or Type 2 diabetes mellitus. Written and informed consent was obtained from all participants. Each participant was debriefed at the end of the second study session. This study was reviewed by and received approval from the University of Waterloo Research Ethics Board. See Table 1 for participant demographics.

### Measures

#### Screening Measures

Several weeks before study participation, potential participants completed a prescreening questionnaire package, which included the Food Craving Scale adapted to include the experimental foods (30). The following items were used to identify participants with strong and frequent cravings for both chocolate and potato chips: a) “how often do you experience cravings to eat potato chips/chocolate?” (response scale: 1 = “never”; 10 = “all the time”) and b) “how strong are these cravings you experience to eat potato chips/chocolate?” (response scale: 1 = “extremely weak”; 10 = “extremely strong”); individuals who scored 7 or above on the response scale (i.e., the top 30%) for both items and both experimental foods were deemed eligible to participate in the study. The inclusion criteria was selected to recruit potential participants with moderate to extremely strong and frequent food cravings (i.e., those that fell within 2 standard deviations [SDs] above the mean), without limiting the sample to only

TABLE 1. Participant Characteristics

	M (SD)	% (n)
Age, y	21.10 (1.86)	
BMI, kg/m <sup>2</sup>	23.36 (4.70)	
<18		4.76 (1)
18.5-24.9		71.42 (15)
25-29.9		19.05 (4)
>30		4.76 (1)
Waist circumference, inches	31.79 (5.99)	
RMT	53.40 (4.50)	
cTBS intensity	42.70 (3.53)	
Ethnicity		
White		61.90 (13)
Asian		9.50 (2)
Hispanic		9.50 (2)
South Asian		4.80 (1)
Middle Eastern		14.30 (3)

BMI = body mass index; RMT = resting motor threshold; cTBS = continuous theta burst stimulation; M = mean; SD = standard deviation.

Average RMT and cTBS intensity are the average across stimulation conditions.

## CORTICAL STIMULATION AND DIETARY BEHAVIOR

those with extremely strong and frequent food cravings (i.e., those that fell within 3 SDs above the mean). The prescreening questionnaire package was administered to all undergraduate students enrolled in an undergraduate psychology course through an online participant recruitment system. Of those, 27.4% of female respondents met the eligibility criteria.

### *Craving Measure*

Food cravings were evaluated using the Food Craving Questionnaire-State (FCQ-S (31)). The FCQ-S is a 15-item self-report questionnaire designed to measure current subjective food cravings on the following five dimensions: a) an intense desire to eat, b) anticipation of positive reinforcement that may result from eating (positive reinforcement), c) anticipation of relief from negative states and feelings as a result of eating (negative reinforcement), d) lack of control over eating, and e) craving as a physiological state (i.e., hunger). Cravings on the different dimensions were calculated as the sum of their corresponding items. Higher scores were indicative of stronger subjective food cravings.

### *Food Consumption*

The experimental foods were covertly weighed before and after the taste test, and the amount of each food consumed (in grams) was recorded. The experimental foods were divided into the following two categories: a) appetitive foods (milk chocolate and both types of Pringles) and b) control foods (dark chocolate and crackers). The variables in each category were summed together, with higher scores indicating a greater quantity of food consumed. The following item from the taste rating questionnaire was used to confirm that participants perceived the appetitive foods as more appealing than the control foods: "Overall, how would you rate this food?" (response scale: 1 = "not at all good"; 10 = "very good"). Across stimulation sessions, the appetitive foods were rated significantly more appealing than control foods ( $t(20) = 5.146, p < .001$ ).

### **EF Measures**

All EF tasks were presented on a 17-inch CRT Dell desktop computer, using E-Prime software (Psychology Software Tools, Inc). For all of the EF measures, responses were made via manual button press on the keys of a response box. In addition, for each EF task, participants were instructed to respond as quickly as possible while still being accurate.

### *Stroop Task*

The Stroop task (32) is one of the most widely used measures of response inhibition (33–35). The Stroop task used in this study (3) consisted of a mixed block of 144 trials, in which the stimulus was either a string of asterisks (72 trials), a congruent color word (12 trials) or an incongruent color word (60 trials). The stimuli were presented individually in one of six colors (blue, green, orange, red, purple, or yellow) on a black background. Participants were instructed to name the color ink each stimulus was written in. On each trial, the stimulus remained on the computer screen until the participant responded, followed by a response to stimulus interval of 1000 milliseconds minus the response time. The primary dependent variable was the Stroop interference effect. Consistent with Miyake et al. (5), the Stroop interference effect was calculated as the difference between the reaction time (RT) on correct asterisk trials in milliseconds minus the RT on correct incongruent color word trials in milliseconds. Shorter RTs were taken to reflect stronger EFs.

### *Stop Signal Task*

The stop signal task (SST (36)) is a widely used behavioral task designed to measure insufficient response inhibition (35,37). The task used in this study was modeled after the variant in Miyake et al. (5) and consisted of two blocks of trials. During the first block of 48 trials (go trials), a series of words were presented individually on the computer screen (in black ink on a white background). Participants were instructed to categorize the word as either an animal (e.g., dog) or nonanimal word (e.g., chair). Each trial began with a fixation cross (500 milliseconds). After this, participants were given up to 1500 milliseconds to categorize the word. During the second block of 96 trials, participants completed the same categorization task but were instructed to withhold their response when the stop signal was presented (i.e., stop trials). The stop signal consisted of

a 220-Hz computer emitted tone, with a duration of 100 milliseconds. The stop signal appeared randomly on 25% of the trials (24 trials). The stop signal delay (the interval between the onset of trial and the onset of the stop signal) was adjusted for each participant by subtracting 225 milliseconds minus the average RT on go trials. Consistent with Miyake et al. (5), the primary dependent variable of interest was the proportion of incorrect responses on stop trials. Lower values were taken to reflect stronger EFs (i.e., less incorrect responses).

### *Go/No-Go Task*

The go/no-go (GNG) paradigm is a widely used measure of inhibitory control. Reliability and validity are well documented (34). This variant consisted of eight blocks of 60 trials, each of which began with a fixation cross (500 milliseconds), followed by a series of uppercase and lowercase letters (1000 milliseconds). Participants were instructed to respond whenever a lowercase letter was presented, and to withhold their response whenever an uppercase letter was presented. In half the experimental blocks, uppercase letters were predominant (5:1 ratio), and in the other half of experimental blocks, lowercase letters were predominant (5:1 ratio).

The primary dependent measure of interest was error rate (measured using the  $d'$  sensitivity statistic) in the lowercase-predominant experimental blocks (i.e., the GNG blocks). Data analysis was restricted to error rates in the GNG blocks because these blocks are a more accurate measure of response inhibition than the uppercase-predominant experimental blocks (i.e., oddball blocks). In the GNG blocks, the no-go stimulus is presented infrequently, and therefore, these experimental blocks measure the ability to inhibit a dominant or prepotent response to the go stimulus. However, in the oddball blocks, the go stimulus is presented infrequently, and therefore, these experimental blocks measure more response monitoring (i.e., response to an infrequent or novel stimulus) as opposed to response inhibition. The  $d'$  sensitivity statistic reflects the ability to discriminate between different stimulus conditions (i.e., discriminate go trials from no-go trials), that is, independent from response biases. Higher values are taken to reflect better discrimination, and therefore stronger EFs. The  $d'$  sensitivity statistic was calculated as the difference between the  $z$  score-transformed (right tail value) proportion of hits (correct go trials) and false alarms (commission errors on no-go trials (38));  $d' = z(\text{hits}) - z(\text{false alarm})$ . Perfect hit rates (i.e., 100%) were assigned a  $z$  score value of 2.33. There were no perfect false alarm rates.

### **Theta Burst Stimulation Procedure**

A 75-mm outer-diameter figure-8 coil (MCF-B65) connected to a MagPro (model X100) stimulation unit (Medtronic, Minneapolis, MN) was used to administer cTBS. Continuous TBS was applied according to the established cTBS protocol outlined in Huang et al. (24); 3 stimuli at 50 Hz repeated at 5 Hz for a total of 600 stimuli for 40 seconds. For active stimulation, procedures were similar to those used by Grossheinrich et al. (39) and Bolton and Staines (29) for targeting the DLPFC. The coil was placed over F3 (i.e., frontal region of scalp near the hairline) in accordance with the International 10-20 System to target the left DLPFC. The coil was positioned at a 90° angle from the midsagittal line with its center over F3. Stimulation intensity was set at 80% of the resting motor threshold for the right abductor pollicis brevis muscle. Resting motor threshold was defined as the lowest stimulator output required to produce a motor-evoked potential, with a peak-to-peak amplitude exceeding 50  $\mu\text{V}$  in at least 5 of 10 consecutive trials. For sham stimulation, the coil was again positioned over F3 but rotated 90°, such that the coil was perpendicular to the surface of the head with both the wings in contact with the scalp.

### **Procedure**

A double-blind, sham-controlled, within-participant crossover design was used, in which participants received both active and sham stimulations. Participants and the researchers, except for the researcher who applied the cTBS, were blinded to the treatment condition. The order of stimulation was counterbalanced across participants. A 1-week intersession interval was used to avoid any potential carryover effects, and each study session was identical and carried out at the same time of day. All participants were instructed to not to consume any food or caffeinated beverages 3 hours before the start of each study session, with compliance checked upon arrival (i.e., participants signed a form

indicating that they had complied to the above instructions and the time they consumed their last meal). The mean (SD) time since participants last meal was 6.46 (5.17) hours for active stimulation and 6.8 (4.75) hours for sham stimulation.

To stimulate food cravings, participants were seated in front of a desktop computer and shown two-dimensional images of the experimental foods (milk chocolate, original and flavored potato chips, and dark chocolate); one image of each experimental food was presented (5 seconds each) using PowerPoint. After viewing the images, participants completed the FCQ-S. After this, participants completed the Positive Affect and Negative Affect Schedule (PANAS (40)). The PANAS is a 20-item self-report questionnaire designed to assess state affect and consists of a list of 10 negative affect items and 10 positive affect items. State positive and negative affect ratings were calculated as the sum of each of their respective items.

After the completion of the PANAS, participants were taken to a different room where they received either active or sham cTBS. After a 5-minute post-cTBS interval, participants were again shown the food images and completed the FCQ-S and PANAS. Then, participants completed three computerized EF tasks. To avoid any potential order effects, the order of the EF tasks was counterbalanced across participants. After this, participants completed a bogus taste test. For the taste test, participants were instructed to taste and rate the subjective properties (e.g., texture, sweetness, saltiness) of each experimental food. Participants were instructed to consume as much food as they would like and were given 5 minutes per food item to eat “ad libitum.” During the “ad libitum” eating period, the researcher left the room until the 5-minute interval concluded, at which point the previous food item was removed and the participant was presented with the next food item. The experimental foods were presented in the following order: a) Lindt milk chocolate (100 grams), b) Lindt dark chocolate (100 grams), c) original potato chips (42 grams), d) sour cream and onion potato chips (42 grams), and e) soda crackers (12 grams); the foods were presented in their prepackaged quantities in grams. Participants were not provided with any macronutrient information for any of the experimental foods.

Following the second study session taste test, participants completed a series of questionnaires pertaining to demographics, food habits and attitudes, and self-control. At this time, weight (in pounds), height (in inches), and waist circumference (in inches) were measured.

## RESULTS

### Data Analytic Procedure

First, two separate  $2 \times 2$  repeated-measures analysis of variance (ANOVA; stimulation condition by food type) were conducted to determine whether there was a stimulation effect on the differential consumption of appetitive and control foods (quantified by grams consumed and then by calories consumed). After this, five separate paired-sample *t* tests were conducted to determine whether there was a differential stimulation effect on the pre-to-post percent change across the five craving dimensions of the FCQ-S. To account for multiple family-wise comparisons,

a Bonferroni correction was used. Next, separate one-way repeated-measures ANOVAs were conducted to determine if there was an effect of stimulation on Stroop (Stroop interference in milliseconds), GNG ( $d'$  sensitivity), and SST (proportion of incorrect responses on stop trials) task performance.

Mediation of cTBS effects on food consumption by Stroop performance was assessed using the procedure outlined by Judd et al. (41) for testing mediation in the context of a within-participant design. In the first step, a mean difference score was computed for each participant in terms of grams of appetitive food consumed (active stimulation condition – sham stimulation condition). This difference score was then regressed to two predictor variables: the sum of each participant’s Stroop interference (in milliseconds) score for active and sham stimulation, and the mean difference in each participant’s Stroop interference (in milliseconds) score. Mediation is assumed if two conditions are met (separate models): a) there is a stimulation effect on Stroop task performance in the same direction as the stimulation effect on appetitive food consumption (ANOVA analyses), and b) the Stroop interference (in millisecond) difference score is a significant predictor of the appetitive food consumption difference score (regression analysis). Lastly, paired-sample *t* tests were conducted to determine if there was a stimulation effect on the pre-to-post difference in positive and negative affect ratings.

Finally, before the above analyses, frequency distributions were examined for outliers, and when necessary, imputation was performed using the next sequential value procedure. One outlier on the appetitive foods consumed variable was identified in the main analysis, and two in the mediational analysis. All statistical analyses were conducted using SPSS software (version 22; IBM Corp, 2013).

### Effects of TMS on Food Consumption

Mean (M; standard error [SE]) food consumption (grams and calories consumed) by stimulation condition are presented in Table 2. Using grams consumed as the outcome measure, results revealed a significant main effect for the stimulation condition ( $F(1,20) = 4.515, p = .046, d = 0.927$ ), such that participants consumed significantly more food in grams after active (M [SE] = 42.95 [2.56]) than sham stimulation (M [SE] = 39.71

TABLE 2. Descriptive Statistics for Study Variables by Stimulation Condition

	Active, M (SE)	Sham, M (SE)
Stroop interference, ms	71.56 (25.18)*	20.16 (13.32)
GNG $d'$ sensitivity	2.78 (0.14)	2.823 (0.13)
SST accuracy (proportion of incorrect categorization responses)	0.17 (0.53)	0.12 (0.03)
Appetitive food consumed, grams	70.62 (5.17)*	61.33 (3.56)
Control food consumed, grams	15.29 (1.76)	18.09 (2.39)
Appetitive food consumed, kcal	353.59 (30.59)	316.03 (24.15)
Control food consumed, kcal	73.004 (8.81)	88.23 (12.14)
Positive affect (pre-to-post difference)	2.40 (0.83)	-1.00 (1.09)
Negative affect (pre-to-post difference)	1.21 (0.61)	-0.50 (1.26)

GNG = go/no-go; SST = stop signal task; M = mean; SE = standard error.

\* Significantly different from sham stimulation at the  $p < .05$  level.

## CORTICAL STIMULATION AND DIETARY BEHAVIOR

[2.34]). In addition, results revealed a significant main effect of food type ( $F(1,20) = 124.123, p < .001, d = 4.862$ ), such that participants consumed significantly more appetitive food in grams (M [SE] = 65.98 [4.18]) than control foods in grams (M [SE] = 16.69 [1.80]). The main effects were qualified by a significant interaction between stimulation condition and food type ( $F(1,20) = 7.920, p = .011, d = 1.228$ ). Participants consumed significantly more appetitive food in grams after active than sham stimulation ( $F(1,20) = 9.450, p = .006, d = 1.342$ ). As predicted, there was no stimulation effect on the amount of control food in grams consumed ( $F(1,20) = 1.660, p = .21, d = 0.562$ ; see Fig. 1).

Similar results were observed when examining the interaction between stimulation condition and food type in kilocalories (calories consumed). Specifically, although there was no significant main effect of stimulation condition ( $F(1,20) = 0.925, p = .35, d = 0.420$ ), there was a significant main effect of food type ( $F(1,20) = 95.470, p < .001, d = 4.264$ ), such that participants consumed significantly more appetitive foods in kilocalories (M [SE] = 334.81 [25.79]) than control foods in kilocalories (M [SE] = 80.62 [8.97]). This main effect was qualified by a significant stimulation condition by food type interaction ( $F(1,20) = 7.005, p = .015, d = 1.155$ ). Compared with sham stimulation, participants in the active stimulation condition consumed marginally more appetitive foods in kilocalories ( $F(1,20) = 4.140, p = .055, d = 0.888$ ). There was no stimulation effect on the amount of control foods in kilocalories consumed ( $F(1,20) = 1.813, p = .19, d = 0.588$ ).

### Effects of TMS on Food Cravings

The mean % change (SE) for each FCQ-S dimension by stimulation condition is presented in Table 3. A significant stimulation effect was observed on the positive reinforcement dimension of the FCQ-S ( $t(20) = 2.776, p = .012, d = 1.212$ ); this association became marginally significant after applying the

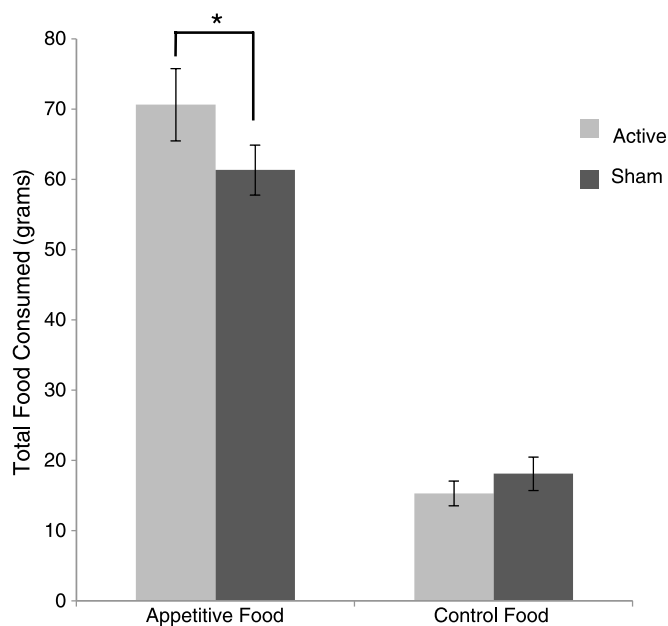


Figure 1. Mean (SE) food consumption for appetitive and control foods as a function of stimulation condition. \* Significantly different from sham stimulation at the  $p < .05$  level. SE = standard error.

TABLE 3. Pre-to-Post Percent Change in Food Craving Scores Across all Five Dimensions of the FCQ-S by Stimulation Condition

	Active, M (SE)	Sham, M (SE)
Desire to eat	-2.90 (0.66)	-14.53 (0.73)
Positive reinforcement	9.98 (0.45)*	-3.46 (0.39)
Negative reinforcement	-6.72 (0.80)	-6.77 (0.04)
Lack of control	-2.02 (0.73)	-6.65 (0.65)
Physiological state	-5.25 (0.47)	-2.08 (0.04)

FCQ-S = Food Craving Questionnaire-State; M = mean; SE = standard error. \* Significantly different from sham stimulation at the  $p < .05$  level.

Bonferroni correction (Bonferroni corrected,  $p = .010$ ). This effect was highly selective in that it did not generalize to desire to eat ( $t(20) = 1.084, p = .29, d = 0.475$ ), negative reinforcement ( $t(20) = 0.191, p = .98, d = 0.011$ ), lack of control ( $t(20) = 0.279, p = .69, d = 0.177$ ), or physiological ( $t(20) = 0.079, p = .53, d = 0.279$ ) dimensions of the FCQ-S (Fig. 2).

### Effects of TMS on EF

There was a significant effect of stimulation condition on performance on the Stroop task ( $F(1,20) = 5.261, p = .033, d = 1.001$ ), such that there was a larger Stroop interference effect in milliseconds after active as compared to sham stimulation (Fig. 3). However, there was no effect of stimulation condition on performance on the GNG ( $d'$  sensitivity;  $F(1,20) = 0.091, p = .77, d = 0.132$ ) or SST (proportion of incorrect responses on stop trials;  $F(1,20) = 1.040, p = .32, d = 0.445$ ) tasks (Table 2).

### Mediational Effect

To test whether the stimulation effect on Stroop task performance mediated the stimulation effect on appetitive food consumption, the mean difference score in appetitive food consumption in grams was regressed onto the sum of each participant's Stroop interference score in milliseconds for active and sham

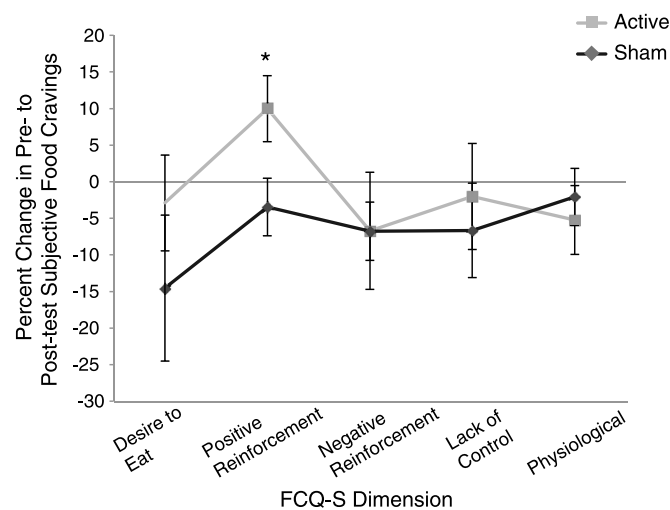


Figure 2. Mean (SE) percent change in pre-to-post subjective food cravings across all five dimensions of the FCQ-S by stimulation condition. \* Significantly different from sham stimulation at the  $p < .05$  level. SE = standard error; FCQ-S = Food Craving Questionnaire-State.

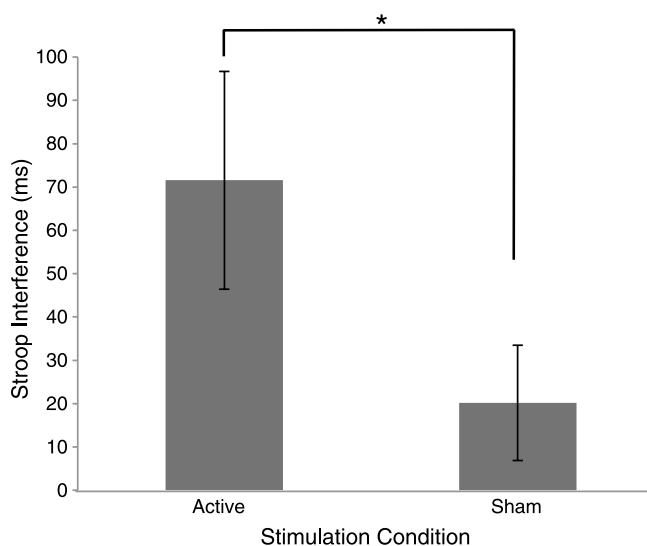


Figure 3. Mean (SE) Stroop interference effect in milliseconds (asterisk trial RT–congruent RT) as a function of stimulation condition. \*Significantly different from sham stimulation at the  $p < .05$  level. SE = standard error; RT = reaction time.

stimulation, and the mean difference in each participant's Stroop interference score in milliseconds. Results revealed that the mean difference in Stroop interference in milliseconds was a significant predictor of the mean difference in appetitive food consumption in grams ( $\beta = 0.730$ ,  $t = 3.215$ ,  $p = .005$ ,  $d = 2.193$ ). In addition, a significant stimulation effect on Stroop task performance and appetitive food consumption was observed (see above ANOVA analyses). Together, these findings demonstrate that the assumptions underlying within participants mediation have been met, indicating that the stimulation effect on Stroop task performance mediated the stimulation effect on appetitive food consumption.

#### Effects of TMS on Affect

There was no significant stimulation effect on the pre-post difference in positive ( $t(20) = -0.334$ ,  $p = .74$ ,  $d = 0.147$ ) and negative ( $t(20) = -1.097$ ,  $p = .29$ ,  $d = 0.475$ ) affect ratings (see Table 2).

#### DISCUSSION

The present study was designed to examine the effects of cTBS to the left DLPFC on cravings for, and the consumption of appetitive calorie-dense foods, foods often implicated in the development of obesity. As expected, participants consumed significantly more calorie-dense foods following active stimulation as compared with sham stimulation. This effect was highly selective to appetitive snack foods and did not generalize to the control foods (i.e., less appealing foods). In addition, participants reported stronger food craving after active stimulation; this effect was also highly specific, in that only the "anticipated positive reinforcement" dimension of craving was influenced. Furthermore, there was a significant stimulation effect on Stroop task performance, confirming that TMS application did indeed influence at least one aspect of EF. Finally, the stimulation effect on Stroop task performance mediated the relationship between DLPFC stimulation on appetitive food consumption. The observed effects were highly selective to appetitive foods as

predicted. Together, these findings suggest that the DLPFC modulates both subjective hedonic responses to appetitive foods, as well as subsequent consumptive behavior, and that the effect is mediated by inhibitory control strength.

The current finding of a significant stimulation effect on appetitive food cravings is consistent with several other studies using cortical stimulation techniques on healthy adults (20–22). The additional finding of an effect on the selective consumption of appetitive high-calorie foods provides additional evidence that actual eating behavior can also be influenced, a finding that has been demonstrated only in one prior study (20). In general, the finding that the DLPFC modulates craving and consumptive behavior selectively for appetitive foods supports several recent theoretical conceptualizations of dietary behavior, including Temporal Self-regulation Theory, which posits this modulating role explicitly, particularly when consumption is rendered prepotent by the presence of facilitating cues (42). In addition, to our knowledge, this is the first study to demonstrate that down-regulating DLPFC activity (via cTBS) resulted in increased food cravings and food consumption; prior cortical stimulation and dietary behavior studies have used cortical stimulation methodologies to up-regulate DLPFC activity. Moreover, this study was the first to demonstrate that the stimulation effect on food cravings was specific to the reward anticipation. Finally, the results from this study demonstrated that modulating DLPFC activity resulted in craving and consumption effects through reduced EF strength, a mediational pathway often assumed but not previously measured.

At the basic neurobiological level, these findings provide direct evidence that the DLPFC plays a role in modulating one specific facet of food cravings: reward anticipation. There is some evidence that suggests that individual differences in reward sensitivity and valuation (i.e., preference for immediate versus delayed rewards) are associated with an extent that the PFC modulates the activity in the brain regions associated with motivation and reward valuation (e.g., orbitofrontal cortex and striatum (43,44)). This contention is further supported by evidence from cortical stimulation studies (45–47). Together, these results suggest that reward sensitivity is dependent on the differential operation of the PFC, such that reward sensitivity is negatively associated with the operation of the PFC.

As such, craving regulation may depend on the extent that the DLPFC can modulate the activity in the striatum (i.e., decrease the rewarding properties of appetitive substances). For example, a recent neuroimaging study demonstrated that activity in the ventral striatum mediated the relationship between DLPFC activity and food and cigarette cravings, such that when cognitive reappraisal strategies were used to decrease cravings, activity in the DLPFC increased, and activity in the ventral striatum decreased (48). These findings suggest that effective craving regulation requires the brain regions associated with self-control (i.e., DLPFC) to modulate the activity in the brain regions associated with reward and motivation (i.e., striatum). In addition, Ko et al. (27) reported that cTBS to the DLPFC resulted in a subsequent increase in striatal dopamine levels, and these effects were specific to stimulation of left DLPFC. The authors concluded that

## CORTICAL STIMULATION AND DIETARY BEHAVIOR

the hemisphere laterality effect can be attributed to the association between left DLPFC activity and EF, specifically task switching (i.e., task switching is often impaired after lesions to the left DLPFC). Therefore, the observed increase in reward anticipation after active as compared with sham stimulation may be attributed to the inability of the DLPFC to modulate activity in the striatum, resulting in increased reward sensitivity (i.e., participants were more sensitive to the rewarding properties of palatable high caloric foods).

Conceptually, these findings provide a theoretical framework that can be used to shape effective public health interventions. The results from this study support the contention that the operation of the DLPFC drives successful self-initiated self-regulatory processes in eating behavior, via the causal association between DLPFC activity and EF strength. Effective inhibitory control abilities are imperative to regulate the consumption of energy-dense foods, especially under facilitating environmental conditions (23). Individuals with weak EFs may lack the dietary self-control necessary to regulate snack food consumption in the modern obesogenic environment (i.e., one that is saturated with highly salient facilitating cues to consume energy-dense foods), which, in turn, increases the likelihood of such individuals to become overweight or obese. Interventions aimed at enhancing or preserving DLPFC function in healthy populations may reduce the likelihood of adiposity and other chronic conditions. In addition, interventions aimed at enhancing DLPFC activity in clinical populations, may subsequently result in improved disease management. For instance, numerous cross-sectional (49–51) and longitudinal studies (52–54) have reported that there is an association between Type 2 diabetes mellitus (T2DM) and impaired EF. However, dietary self-control is particularly important for this population because healthy dietary habits are essential for effective glucose management. Because of the cognitive deficits associated with T2DM, individuals with T2DM may lack the dietary self-control needed to maintain healthy dietary habits. Therefore, interventions focused at enhancing DLPFC activity, through aerobic exercise or other means, may result in increased dietary self-control and, subsequently, improve disease management in individuals with T2DM.

### Strengths and Limitations

The key strengths of this study include the inclusion of the standardized measures of EF, which has not been done in previous research. By including these measures, we were able to demonstrate that the stimulation effects on food cravings and food consumption may occur through the down-regulation of EF strength. In addition, the use of the FCQ-S provided a more comprehensive measure of food cravings, and thus, we were able to demonstrate that the DLPFC modulates a highly specific aspect of food cravings (i.e., reward anticipation). Moreover, a blinding procedure (i.e., the bogus taste test) was implemented to minimize any social desirability and expectancy effects. Furthermore, the categorization of the experimental foods into appetitive and control foods is something that has not been attempted in prior cortical stimulation studies. Although it can be argued that dark chocolate and soda crackers are appetitive

snack foods, the appetitive foods were rated as significantly more appealing than the control foods across stimulation sessions. It is also important to note that there was no stimulation effect on affect, and therefore, mood would not have influenced the stimulation effect on food cravings and consumption.

There are a few limitations that warrant mention. First, stimulation effects were observed on the Stroop but not the GNG and SST, suggesting the possibility that the operation of the DLPFC may regulate different dimensions of inhibition. Indeed, an accumulating body of evidence suggests that the operation of the inferior frontal gyrus and the presupplementary motor areas are implicated in the inhibition of motor responses during the GNG and SST paradigms (55–57). Therefore, it is possible that the performance on these measures is associated with the differential operation of the inferior frontal gyrus and presupplementary motor areas as opposed to the DLPFC, thus explaining why no stimulation effect on GNG and SST performance was observed. It is also plausible that there was an effect, but the sample size was too small to detect an effect. However, based on the observed effect sizes for the stimulation effect on SST ( $d = 0.445$ ) and GNG ( $d = 0.132$ ), a sample of 64 to 711 participants would be necessary to achieve a statistical power of 0.80 for both paradigms, respectively. Alternatively, these null findings could be attributed to a potential ceiling effect. The study population consisted of healthy young adults, with relatively strong performance, rendering the measures only partially sensitive to manipulation. Therefore, it is plausible that different effects may have been observed in a community sample or older adult sample, where a larger range of EF scores would have been observed.

In addition, the sample was limited to female participants, and therefore, the results of this study can only be generalized to women; it is currently unknown whether the observed experimental effects would generalize to men. However, the study was designed to measure the experimental effects in a specific population (i.e., women), and therefore, the results from this study were intended to generalize to this specific population as opposed to the general population (i.e., both men and women). As such, the fact that the experimental effects cannot be generalized to men may not be a threat to the internal validity of the study. Finally, overall reward sensitivity was not directly measured, and therefore, it is currently unknown whether the increase in (food cravings) reward anticipation after active stimulation is accompanied by an increase in overall reward sensitivity.

### CONCLUSIONS

In conclusion, the current findings demonstrate that cTBS to the left DLPFC increases food cravings and the selective consumption of calorie-dense snack foods (i.e., those most strongly implicated in the development of obesity). The pattern of findings suggests that the effects of DLPFC stimulation on cravings and behavior may occur via attenuation of executive control. These findings shed light on the role of the DLPFC in food cravings (specifically reward anticipation), the consumption of appealing high-caloric foods, and the relation between

self-control and food consumption. Future studies should examine the reliability of the current effects, and explore the possible situational parameters within which such effects are maximized. In addition, close examination of the possible mitigating effects of cognitive re-appraisal strategies (58) on experimentally attenuated executive control networks would be a potentially important step forward in understanding self-regulatory processes in calorie-dense snack food consumption.

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## CORTICAL STIMULATION AND DIETARY BEHAVIOR

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