Contextual cues as modifiers of cTBS effects on indulgent eating

by

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Author's Declaration

I hereby declare that I am the sole author of this thesis. This is a true copy of the thesis, including any required final revisions, as accepted by my examiners.

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Abstract

Background: Prior studies have found that continuous theta burst stimulation (cTBS) targeting the left dorsolateral prefrontal cortex (dlPFC) results in reliable increases in the 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.

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This document would not have been possible without the work of those who came before me, and the training and support I've received along the way. I would like to express my gratitude to my advisor, Dr. Peter Hall, and my colleagues both past and present in the Prevention Neuroscience Lab, without all of your help this thesis would not have been possible. I hope that over time I will be able to express my gratitude more fully than I've been able to with the words on this page. Thank you for your help, your support, and your belief in me.

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List of Abbreviations

ACC	Anterior Cingulate Cortex
AIC	Anterior Insular Cortex
APB	Abductor Pollicis Brevis
BMI	Body Mass Index
dlPFC	Dorsal Lateral Prefrontal Cortex
EF	Executive Functions
fNIRS	Functional Near Infrared Spectroscopy
FCQ-S	Food Cravings Questionnaire-State
fMRI	Functional Magnetic Resonance Imaging
fNIRS	Functional Near-Infrared Spectroscopy
IAT	Implicit Association Test
IPS	Intraparietal Sulcus
LTP	Long Term Potentiation
LTD	Long Term Depression
pOFC	Posterior Orbitofrontal cortex
RMT	Resting Motor Threshold
TBS	Theta Burst Stimulation

cTBS	Continuous Theta Burst Stimulation
tDCS	Transcranial Direct Current Stimulation
TMS	Transcranial Magnetic Stimulation
rTMS	Repetitive Transcranial Magnetic Stimulation

Chapter 1: Background

Chapter 1.1 – Understanding Obesity

Navigating the aisles of modern supermarkets has evolved into a complex obstacle course for the cognitive control centres of the brain.[1] Brightly lit shelves are stocked with a surplus of branded calorically dense snack foods, and their consumption is persistently encouraged through advertisements.[2–4] While humans have an evolved capacity for directing long-term goal-oriented behaviours,[5] the steady rise of obesity rates in Canada over the past century reveals the increasing difficulty of maintaining a balanced diet in our current food landscape.[6]

The associations between high BMI and the increased risks for developing non-communicable diseases (i.e. diabetes, heart disease, stroke and multiple cancers) have been repeatedly, and well documented.[7–11] Current estimates for the years of life lost in a person with severe obesity range from 5-20 depending on demographics and smoking status.[11] The contributions of obesity to premature mortality is especially troubling when considering the rising rates in adolescents and youth, for whom the health consequences are the greatest.[12] While childhood obesity was essentially unheard of in North America in the early 1930's (prevalence of 0% in males, 2% in females),[13] comparable estimates place the modern prevalence at 17.4%.[14]

The aging demographics of Canada and other industrialized nations[15] makes the compression of morbidity a necessity for alleviating the financial pressures being placed on the health care system.[16] It is estimated that mild obesity (BMI 30-34.9) in adults is associated with the loss of one in ten years of potential disease-free life, while severe obesity (BMI $\geq$ 40) is associated with the loss of one in four years of potential disease-free life.[8] The $3.9 billion in

direct costs and $3.3 billion in additional indirect costs to the Canadian healthcare system attributed to obesity in 2006 [17] would account for just over 5% of health care spending nationwide.[18,19]

As both public awareness and the prevalence of obesity have grown, weight management has become an increasingly global concern. Santos and colleagues in a large (n = 1,184,942) systematic review of the literature revealed that over 40% of adults in the general population are actively trying to lose weight, with long-term health as the most commonly reported motivator.[20] However, despite the motivations of the public and major initiatives put in place by both federal and provincial governments,[21] obesity rates in Canada and the rest of the world have more than tripled over the past 30 years.[7,22] At last count it was estimated that over 60% of Canadians were overweight or obese.[23] Both diet and exercise are important in the prevention of obesity,[24] however examining the efficacy of behavioural weight reduction programs Johns et al. found that dietary change was the compulsory component for ensuring long term changes in body composition while exercise was supplementary.[25]

The majority of Canadians are concerned about the healthiness of their diet and report having made recent changes to improve it by attempting to remove or reduce their snack consumption.[26] However, these health conscious attitudes are not well represented by the largest recent nutrition sampling surveys,[27,28] wherein Canadians demonstrate an affinity for eating at fast food restaurants and have almost a quarter of their caloric intake coming from “other foods” (e.g. candy, potato chips, and soda).[29] While many Canadians are voicing a desire to eat healthy, there exists a problematic gap between their intentions and actions regarding food intake.[26]

Chapter 1.2 – Dietary Behaviour and Executive Function

Dietary behaviours are complex and multifaceted.[30] While the most highly cited models of eating behaviour from the social psychological literature rely on attitudes, normative beliefs, and self efficacy as proximal predictors for consumption,[31] these socio-cognitive variables only account for a fraction of the variability seen in behavioural outcomes.[32] More recent efforts to explain dietary behaviour are working to bridge our understanding of the gap between thoughts and actions by examining neurobiological differences through the measurement of executive functions.[33] Executive functions are a set of higher-order cognitive processes (e.g. attentional control, working memory, cognitive flexibility) that are essential for carrying out long term goal-oriented behaviours.[34] The dorsolateral PFC (dlPFC) has long been implicated in self-control in the context of eating[34,35] and is thought to be an important node in the brain networks supporting executive functions.[36]

The dlPFC is a cognitive processing center that integrates projections from sensory association areas with communication from limbic structures in order to make decisions.[36] These decisions are directed to the inhibitory thalamic reticular nucleus, a central gate-keeper of thalamo-cortical communication.[36] The sensory association areas for visual, auditory, and somatosensory information handle higher order sensory information, (i.e. while the primary visual cortex interprets photoreceptor signals as a pattern of lights and edges, the higher order areas downstream can register if what they are looking at is a hamburger).[37] Within the limbic system the amygdala and hypothalamus convey information about the interior milieu (e.g. energy levels, or hunger) to the ACC and pOFC.[36] The ACC and pOFC serve as information relays within the PFC and are responsible for encoding the stimuli they receive with motives, drives and emotions**,** which are then communicated to the dlPFC.[36] By combining higher order

sensory information with the internal context provided by the limbic system the dlPFC is able to establish a basis for making decisions in line with longer term goals.[37]

Chapter 1.3 – Executive Function and Obesity

Executive functions are commonly measured through cognitive tasks examining the domains of updating, shifting and inhibition,[38] with neuroimaging studies demonstrating the relationship between each of these domains and the dlPFC.[39–41] Using the example of a trip to the grocery store we can see how everyday cognitive requirements engage the dlPFC e.g. A shopper enters a grocery store with a mental list of everything they need and figuratively crosses off items as they load their cart and *update* their attentional focus to acquiring the remaining items, if something isn't available or isn't affordable they need to *shift* and switch to finding a substitute, and throughout their journey they need to *inhibit* their impulses to grab hold of any snacks they're trying to cut back on. With a decrease in executive function (which is common under conditions of stress or fatigue),[42,43] it is possible to imagine how the grocery shopper might make less healthy decisions either through the omission of healthy items, or the addition of unhealthy items to their cart.

Numerous studies have identified correlations between obesity and impairments in executive function across the life span.[44–47] Recent studies have also identified functional and neuroanatomical differences in the dlPFC of individuals with obesity compared to healthy controls.[48–50] While this evidence could suggest that executive function is mediating the relationship between dlPFC function and obesity, others have suggested that the causal direction is bidirectional,[51,52] or even reversed (i.e. with obesity causing impaired executive function).[46,53] However, experimental evidence from neuromodulation studies has

demonstrated that temporary changes in dlPFC activity are capable of increasing or decreasing snack food consumption within a single laboratory session.[54]

Chapter 1.4 – Neuromodulation

The association between eating, EF and brain structures like the dlPFC allows for the use of both neuroimaging and neuromodulation techniques. Different neuromodulation methods have been repeatedly demonstrated to alter dietary behaviour and food consumption.[55] While vagus nerve stimulation and deep brain stimulation are able to target deep structures within the brain to decrease and increase consumption, these invasive methods require surgical operations, and are reserved for individuals with serious clinical conditions (i.e. intractable epilepsy) necessitating their use.[55] Non-invasive brain stimulation techniques like tDCS (transcranial direct current stimulation) and TMS (transcranial magnetic stimulation) target more superficial cortical structures through the skull. tDCS operates by transmitting a direct electrical current through electrodes placed on the scalp with the intention of influencing the excitability of underlying neuron populations with the generated electrical field.[56] However, there are several limitations to this approach, due largely to the poor electrical conduction properties of the human skull.[56]

TMS however operates via the principles of electromagnetism. By rapidly charging and discharging an electrical current through coils of wire, the changing magnetic field produced is capable of inducing a smaller secondary current.[57] As the human skull is relatively permeable to magnetic fields, the TMS coil can be placed on an individual's head and aligned such that the neurons of the underlying cortical brain structure are depolarized by the current induced by an electrical pulse through the coil.[57] To elicit lasting changes in the brain, the stimulation is repeated (rTMS) with a train of pulses.[58] The nature of the effects (inhibitory vs. excitatory) depends entirely on the pattern and duration in which the stimulation is delivered.[58] rTMS is

sometimes used in the treatment of clinical conditions like depression, in order for changes in the brain to endure past a typical experimental session (i.e. 1 hour) multiple sessions of stimulation would be required, i.e. at least once a week.[59]

One variant of rTMS, continuous theta burst stimulation (cTBS), has the effect of attenuating excitability within targeted neuron populations, while another variant, intermittent theta burst stimulation (iTBS), has the effect of increasing excitability.[60] The effects of cTBS are understood to become evident after approximately 8 minutes post-stimulation, with the peak effects appearing around the 30 minute mark, falling of at 40-50 minutes post stimulation, and dissipating before 1 hour.[61] The underlying physiological mechanism behind the observed effects of rTMS are still poorly understood, but it is thought the synaptic plasticity is a result of receptor trafficking at the synapse in a manner similar to long term potentiation (LTP) and long term depression (LTD).[62]

The time course of TBS protocols is uniquely suited to the study of eating phenomena in the laboratory, particularly wherein actual eating behavior is the outcome of interest. Given that eating behavior naturally extends over tens of minutes (for snacking, or eating a meal), the time window for TBS is an ideal match. The study described in the next chapter involves the use of a TBS protocol to explore the causal role of the left dlPFC in the modulation of eating behavior, in the presence of various cue types that mimic those found in the everyday eating environment.

Chapter 2: Introduction

Modulation of the left dlPFC reliably alters responses to appetitive, calorie-dense foods.[63,64] Such effects are more reliable when using rTMS than tDCS, and when stimulation is targeting bilateral structures on the left- rather than right-hemisphere [63,65,66] see also.[67] Most neuromodulation studies involving eating [55] 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 supporting cognitive control, such as those linked to valuation, salience, and attention (i.e. the vmPFC, AIC, and IPS respectively) have the 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.[68–71]

For instance, the incentive salience of foods tend to be stronger when homeostatic feeding systems (i.e. the hypothalamus) are primed by ghrelin.[72,73] The vmPFC, AIC, IPS, and hypothalamus are all capable of communicating with the dlPFC using the ACC as an intermediary.[73–75] 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.[76–79] 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 executive function tasks predict actual consumption more so in the presence of facilitative visual cues than

in the presence of restraint cues.[80,81] 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; [82–84]) is a highly efficient variant of rTMS that reliably reduces task performance on measures of cognitive control, particularly when targeting the left dlPFC.[85] 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,[86] it was anticipated that cravings, attitudinal dimensions, and flavour experience would not mediate the cTBS effects on eating outcomes.

Chapter 3: Methods

Chapter 3.1 – 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% using the typical North American cut-off (18.5-24.9), and 63% when adjusted for ethnicity-specific cut-offs (18.5-23.4 for Asian and South Asian participants).[87]

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 (Appendix C).[59] 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.

Chapter 3.2 – Procedures

Participants were randomly assigned to one of 4 conditions: 1) active cTBS + facilitating

cues, 2) sham cTBS + facilitating cues, 3) active cTBS + inhibiting cues, or 4) sham cTBS + inhibiting cues. 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 hours 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 were conducted using SPSS V. 25 (IBM).

The study protocol is presented in ***Figure 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 minutes 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?"

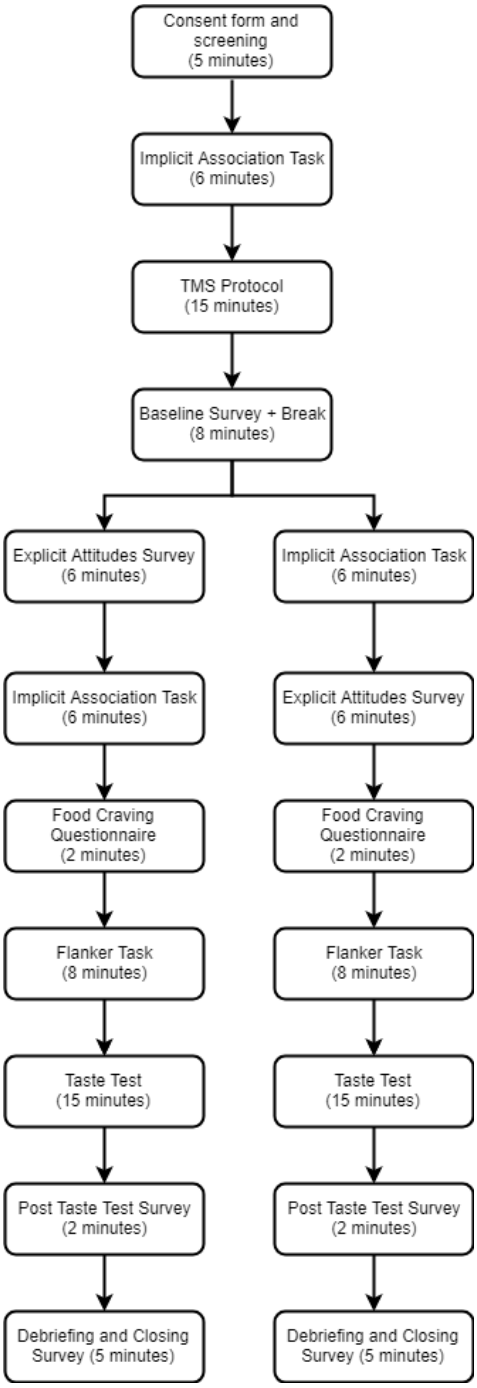

Figure 1 *– Experimental session timeline.*

Tasks were timed to coincide with the initial emergence and subsequent peak cTBS effects based on known parameters of its time course.[82,88] Specifically, the first outcome measure is completed at 8-14 minutes 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 30-45 minutes after stimulation. All other tasks fell in between these, and well within the temporal window of expected cTBS potency.

Chapter 3.3 – Brain Stimulation Protocol

The cortical stimulation protocols were applied using a 75mm 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, stimulation set up can be seen in ***Figure 2***. 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 (Appendix B). 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.

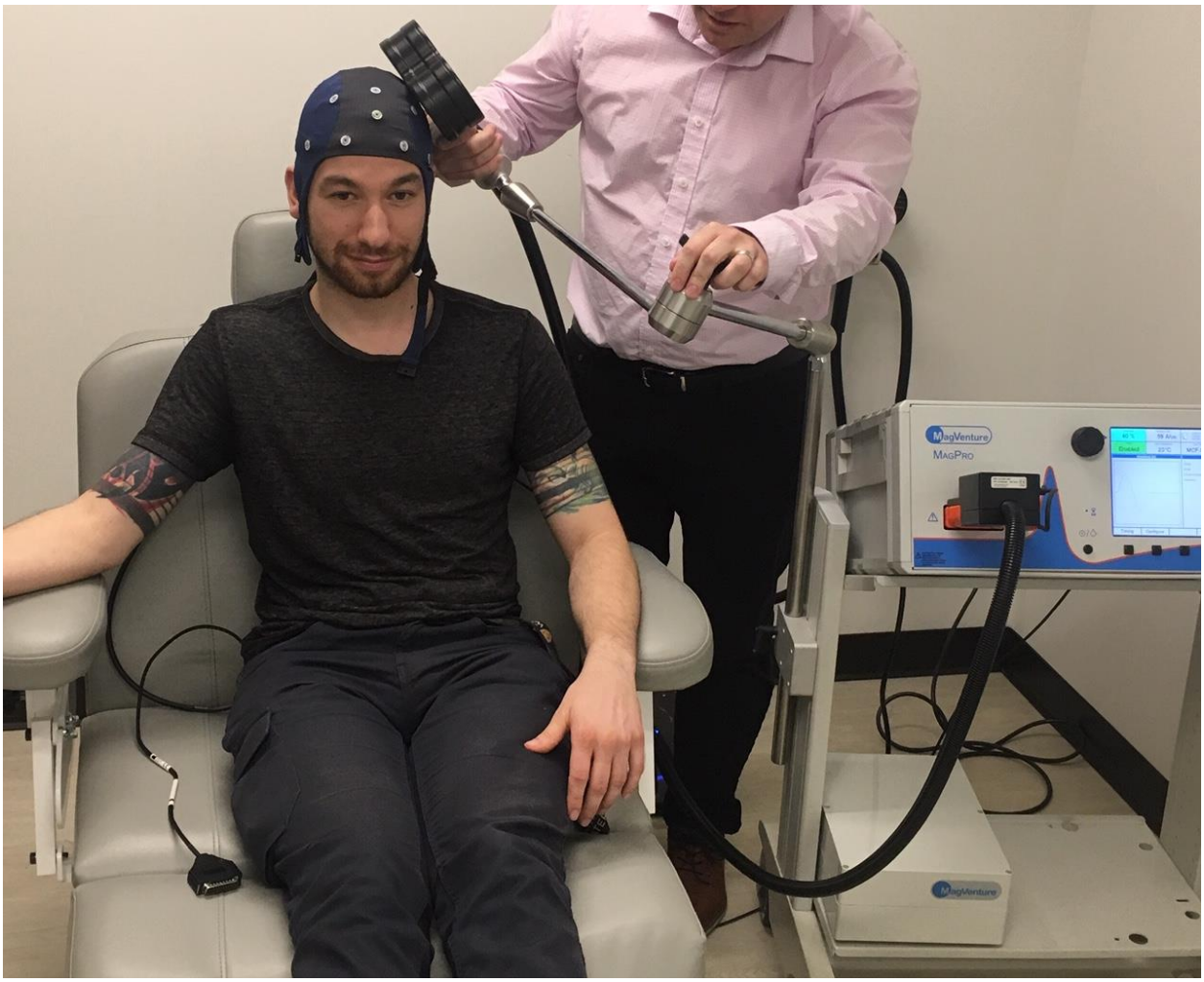

Figure 2 *– Establishing motor threshold*

Participant is seated in chair with right arm extended. Right wrist remains loose, and relaxed facing palm up while researcher looks for twitch of APB muscle following stimulation of C3

Chapter 3.4 – 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.

Chapter 3.5 – 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 (Appendix D) 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,[89] and responsive to acute manipulations of executive function

using cTBS targeting the left dlPFC.[65,86] 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."

Chapter 3.6 – 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; ***Figure 3***). Each poster was 60*cm* x 85*cm*, and was placed on the wall at a 45 degree 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).

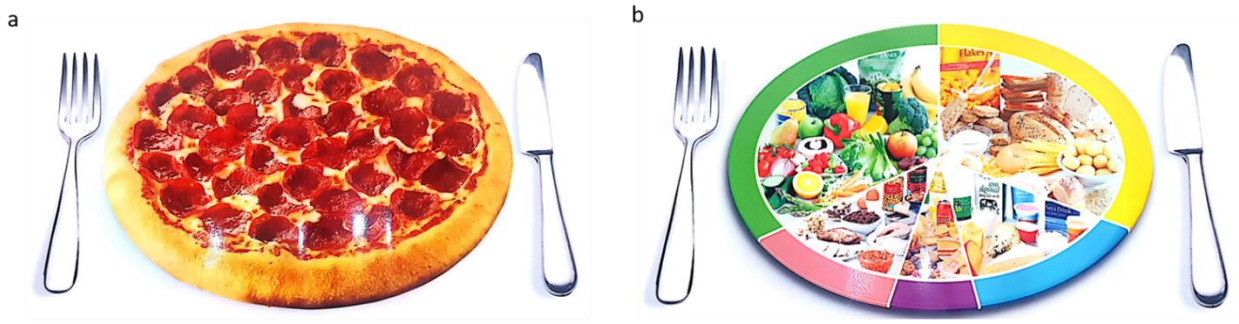

Figure 3 – *Environmental Posters*

The facilitating cue poster (a) and the inhibiting cue poster (b)

Chapter 3.7 – Implicit Attitudes

The IAT [90] 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 target food items and words (Appendix E) were selected based on their usage in prior food IAT research.[91] Based on prior evaluative ratings of words in a large normative sample,[92] 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,[90] 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 valance words.

Inhibitory control in the context of snack consumption is the primary focus of this study. However, measuring the changes in attitudes allows for examining whether the effects of the stimulation are being mediated through indirect influences on valuation centers associated with the dlPFC (i.e. the mPFC). Measuring attitudes allows us to examine the effects of food valuation by the mPFC on eating outcomes despite it not being targeted directly for stimulation, as has been done in other studies where examining the effects of cTBS on changes in attitude was the primary outcome of interest.[91]

Chapter 3.8 – Food Cravings

The Food Cravings Questionnaire-State (FCQ-S; [93]) is a 15-item scale assessing the strength of current subjective food cravings. Higher scores on the FCQ-S 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, overeating, and physiological symptoms of hunger (Appendix F).

Chapter 3.9 – 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 (Appendix G). Responses were summed such that higher scores indicated more positive explicit attitudes toward food indulgence. This scale was previously validated and employed in eating studies involving neuromodulation in our laboratory.[94]

Chapter 3.10 – 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.]" (Appendix D).

Chapter 3.11 – 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. The estimated marginal means derived from the ANCOVAs were then subjected to two-way ANOVAs for analysis.

Planned comparisons between means in the flanker and consumption measures were conducting using t-tests. The effects sizes of the means were calculated using the formula for Hedges' g. While Hedges' g and Cohen's d are the most commonly used statistics for describing

standardized mean differences and the conventions for interpreting effect sizes can be applied interchangeably (0.3 = small, 0.5 = moderate, 0.8 = large),[95] the formula for Hedges' g contains a correction factor to account for some of the upward bias seen when calculating effect sizes with small sample sizes.[96] The use of Hedges' g in place of Cohen's d makes the data presented more readily accessible for inclusion in meta-analysis where other studies may have small sample sizes.

Significant cTBS effects on mediator variables were subjected to conditional mediational analyses using the PROCESS macro [97], in order to examine whether or not the 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). The correlations between each step on the pathway of the mediational model are reported as standardized beta weights to allow for easier interpretation and comparison across the coefficients. The models display the effects of cTBS on the outcome of food consumption, the effect of cTBS on the potential mediator, the relationship between the mediator and food consumption, and finally the effects of cTBS on food consumption adjusted for the relationship between the mediator and food consumption. Only variables that were significantly affected by cTBS were further analyzed as purported mediators in formal analyses.

Chapter 4: Results

Chapter 4.1 – Overview

No significant differences were evident among the four treatment conditions with respect to age ($F(3,103)=.136$, $p=.938$), gender ($\chi(3) = 1.171$, $p = .760$), BMI ($F(3,102)=1.701$, $p=.172$), time of last meal ($F(3,103)=.561$, $p=.642$), 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 ($F(1,102)=.096$, $p=.757$), salty ($F(1,102)=1.413$, $p=.237$), sweet ($F(1,102)=0.026$, $p=.872$), greasy ($F(1,101)=.396$, $p=.531$) or globally palatable ($F(1,102)=.009$, $p=.925$), 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 ($F(1,102)=.013$, $p=.910$). The above suggests that cTBS applied to the dlPFC had negligible impact on sensory/evaluative aspects of the flavor experience.

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 9 Male	14 Female 10 Male	14 Female 11 Male	18 Female 9 Male	65 Female 39 Male
BMI	23.94 (4.39)	23.62 (3.12)	21.98 (3.07)	22.57 (3.35)*	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)

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

Chapter 4.2 – Flanker Interference Scores

With respect to interference scores, a 2-way (stimulation condition x cue type) ANOVA revealed no main effect of cue type ($F(1,102)=.008$, $p=.931$, $g=.017$), but a significant main effect of stimulation condition ($F(1,102)=8.844$, $p=.004$, $g=-.585$), 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 ($F(1,102)=.001$, $p=.976$). Variable means for all study conditions are depicted in ***Figure 4***.

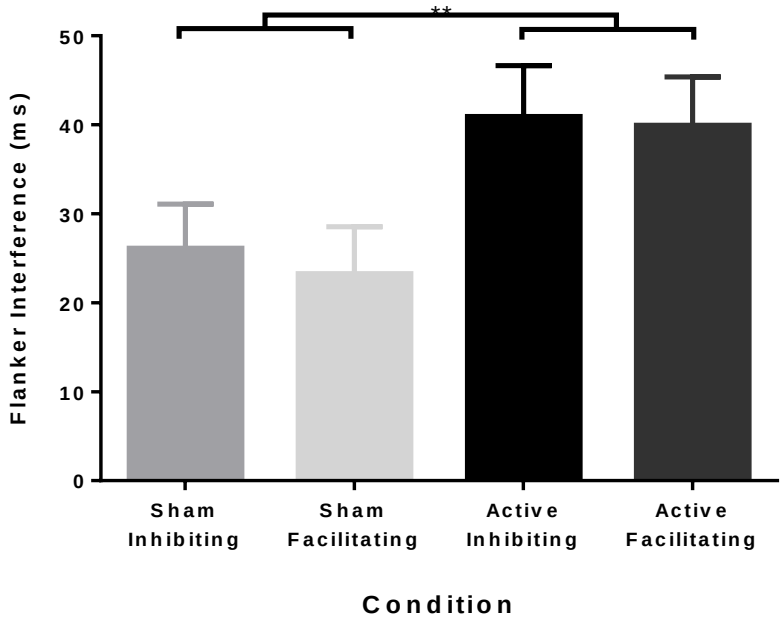

Figure 4 *– Flanker Interference Scores*

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 ($M=39.953$, $SE=5.422$).

**: $p<0.01$

Chapter 4.3 – 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 ***Figure 5***.

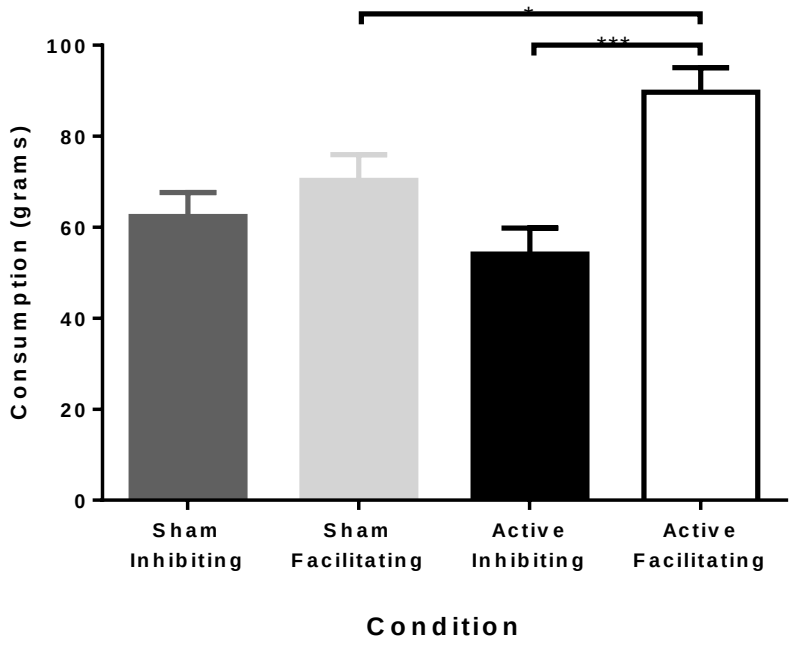

Figure 5 – *Food Consumption*

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 ($M=89.659$, $SE=5.422$).

*: $p<0.05$
***: $p<0.001$

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*=.437) but negative and small in magnitude in the inhibiting condition (*g*=.240; ***Figure 6***), suggesting that cTBS targeting the left dlPFC made consumptive behavior responsive to environmental cues in general.

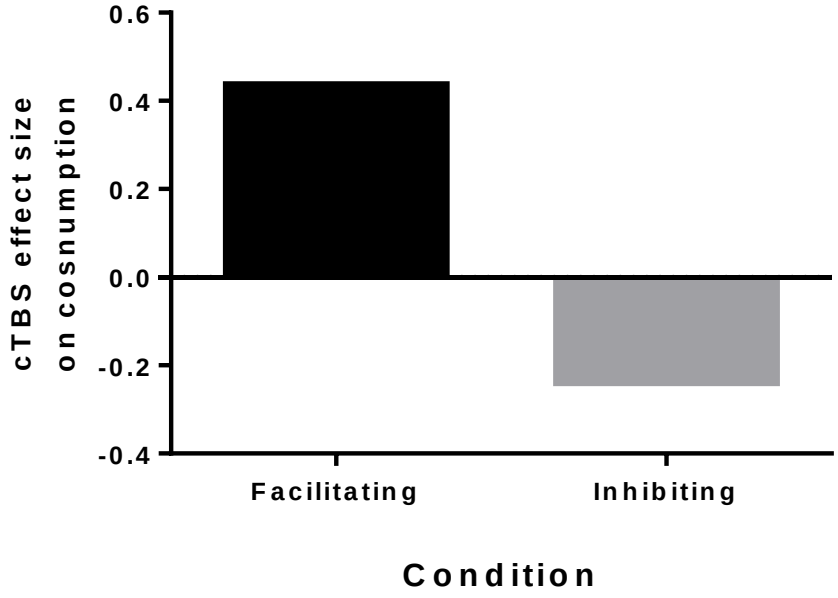

Figure 6 *– cTBS effect size on consumption*

Hedge's *g* by treatment condition; effect size of cTBS vs. Sham in the facilitating conditions (*g*=.437) contrasted with the inhibiting conditions (*g*=-.240).

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). **Figure 8** depicts the hypothesized conditional mediational model and the path coefficients for each conditional model separately.

We also observed significant differences between the amounts consumed by male (*M*=88.013, *SE*=5.456) and female (*M*=58.555, *SE*=3.256) participants across conditions (t(1,102)=4.945, p<.05), with males consuming on average 29.458 g more **Figure 7**.

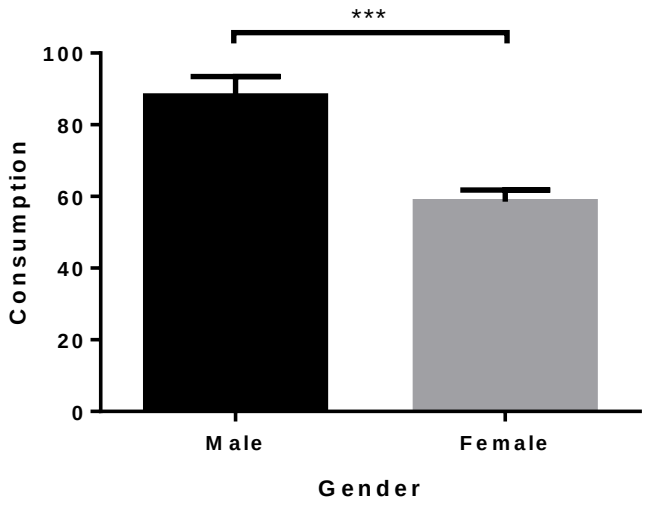

Figure 7 *– Gender differences in snack consumption*

Mean (+/-*SE*) for taste test consumption (grams) by gender; Male (*M*=88.013, *SE=5.456*), (*M*=58.555, *SD*=3.256)

***: $p<0.001$

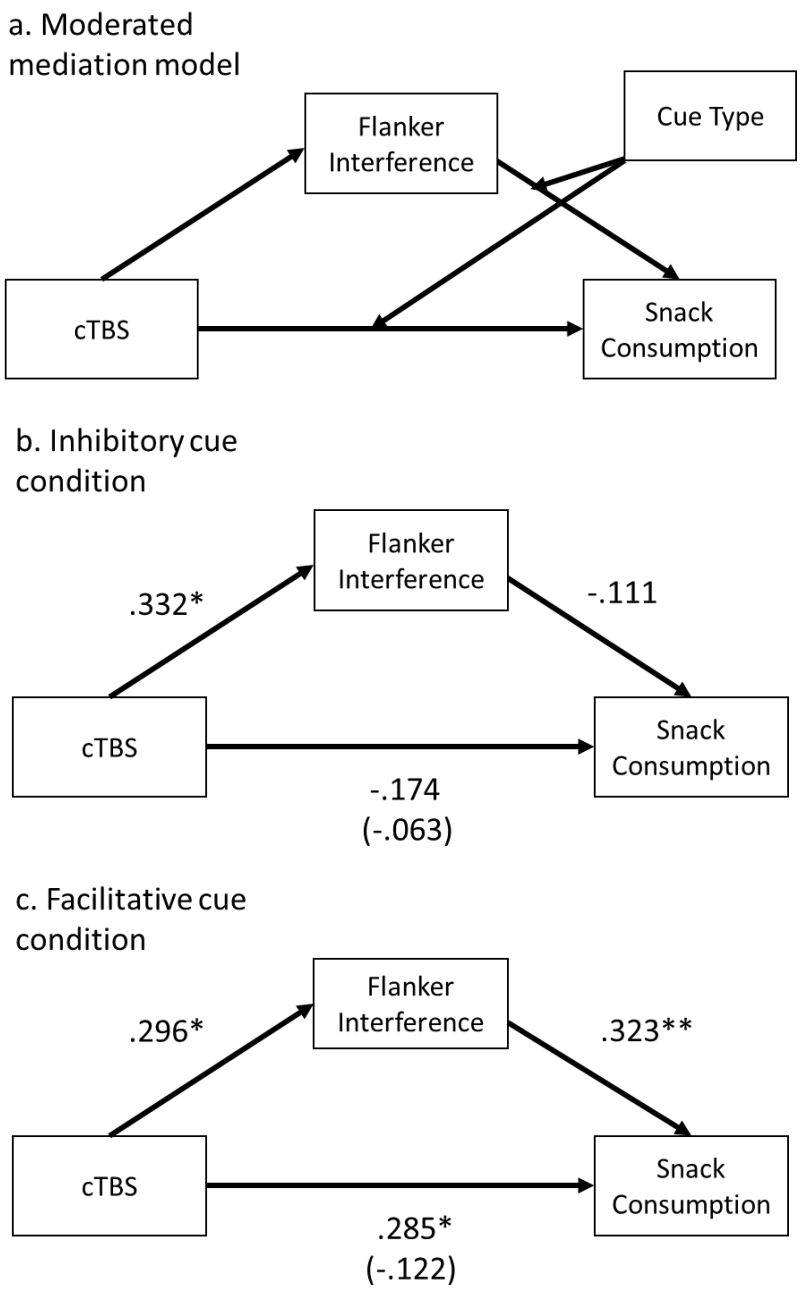

Figure 8 – *Moderated mediational model*

(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.

*: $p<0.05$
**: $p<0.01$

Chapter 4.4 – Food Cravings

The two way ANOVA examining stimulation condition x cue type revealed a main effect of cue ($F(1,102)=8.762$, $p=.004$, $g= 0.588$), such that individuals in the inhibiting cue conditions ($M=49.714$, $SD=1.355$) 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 ***Figure 9***, greater values indicate stronger cravings.

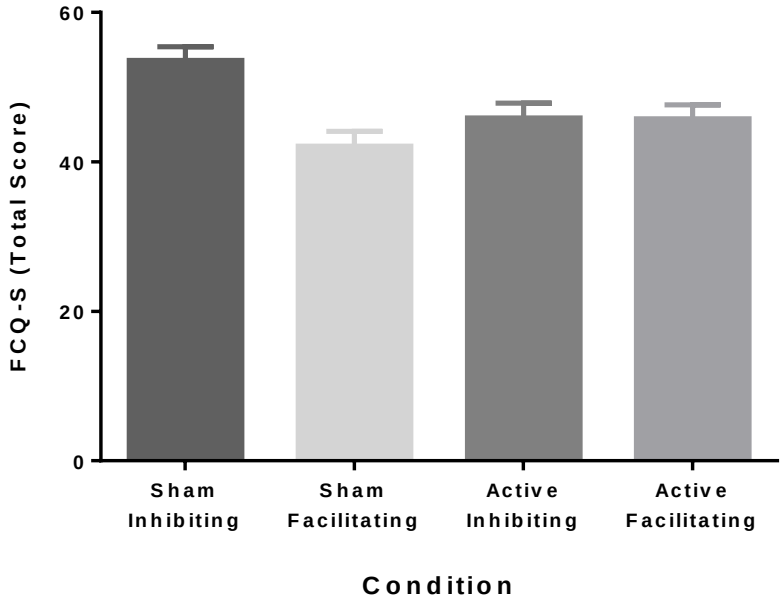

Figure 9 – *FCQ-S Scores*

Mean (+/-*SE*) for FCQ-S 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 ($M=45.753$, $SE=1.888$).

Chapter 4.5 – Attitudes

The two way (stimulation x cue type) ANOVA revealed no main effects of cue type ($F(1,102)=.934$, $p=.336$, $g=0.061$), or stimulation condition ($F(1,102)=.057$, $p=.812$, $g=0.015$) 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 ***Figure 10***.

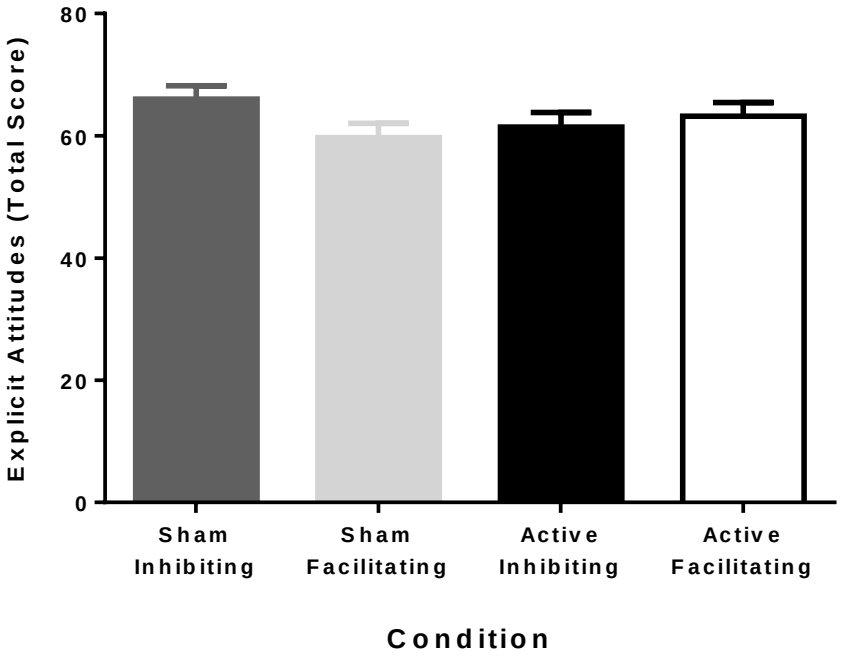

Figure 10 *– Explicit Attitude Scores*

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).

Likewise, 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 ($F(1,102)=.036$, $p=.850$, $g=0.039$), 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 ***Figure 11.***

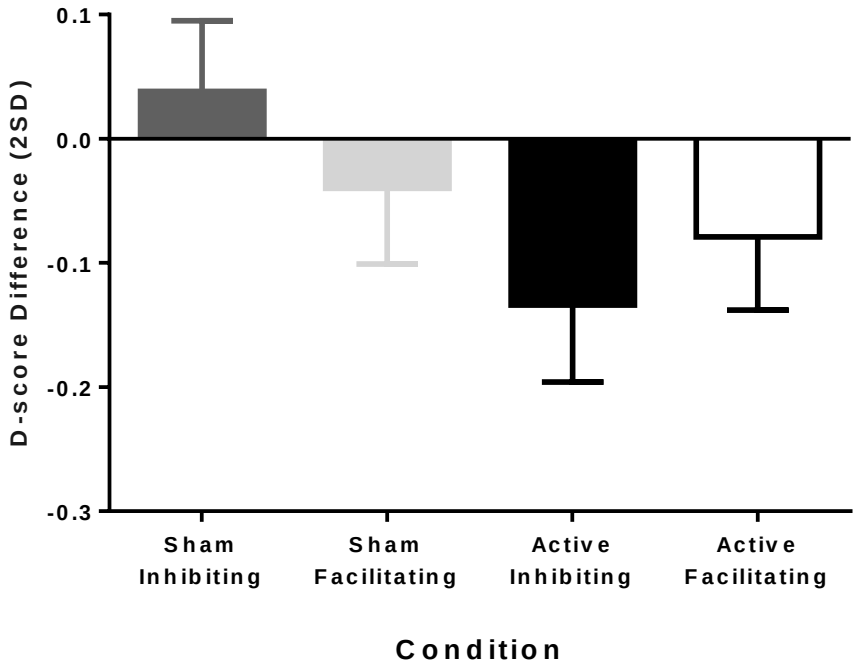

Figure 11 *– IAT D-score changes*

Mean (+/-*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).

Chapter 5: Discussion

Chapter 5.1 – Findings and Implications

The current study employed a between-subjects factorial 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. The effect size observed in the facilitation condition (.437) is quite similar to the effect size previously reported in a meta-analysis examining the effects of neuromodulation on food consumption (.472).[63]

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 (Appendix A). 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 [85] 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, a common practice in the measurement of food cravings,[63] 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 especially in individuals who's dlPFC circuitry is still undergoing development (i.e. children and adolescents),[98] or when other acute dlPFC suppressing factors are present, such as sleep restriction,[42] stress,[43] or alcohol intoxication.[99]

The growing problem of childhood obesity has brought increasing concerns about children's food advertising to the attention of legislative bodies.[2] With some efforts like Bill S-228, promoted by Health Canada, going so far as to suggest a complete ban on all food and beverage advertising targeting children.[100] The dlPFC and other brain regions involved in executive function are not fully online until an individual is in their mid-twenties.[98] In accordance with the findings of the current study, the decreased executive function of children

has been found to render them uniquely susceptible to the influence of environmental cues in the form of advertisements.[101] Food advertising aimed at children is highly prevalent across all forms of media, exists predominately for unhealthy foods and beverages, but effectively increases consumption with even short-term exposure.[2]

While compulsory legislative approaches, like the 1990 Quebec ban on advertising fast food to children, have been found to successfully reduce the consumption of the targeted foods; globally advertising restrictions have been primarily self-imposed through industry pledges.[102,103] Despite high rates of apparent adherence to self-imposed guidelines in industry reports, countries operating under voluntary standards continue to expose children to high rates of unhealthy food advertisements.[102] The ability of environmental cues to facilitate indulgence has been well demonstrated in the current study, but also the population literature.[104–107] The unique vulnerability of children to advertisements,[101] and the potential ramifications to their health,[2] raises serious ethical concerns about food marketing efforts aimed at young audiences.[108] The enactment of legislation like Bill S-228 would be expected to decrease the consumption of unhealthy foods in young people, and have downstream benefits for public health.[102]

With over a third of adults reporting that they get less than the recommended minimum number of hours of sleep at night (i.e. <7 hours), the high prevalence of sleep restriction within the general population is a cause for public health concern.[109] In addition to the acute cognitive consequences (i.e. decreased executive function),[42] sleep restriction has been linked to obesity.[110] Sleep restricted individuals display an increased preference for fatty foods, eating out, and consuming irregular but proportionately larger meals.[111] Additionally, sleep restriction has been shown to increase the responsiveness of brain regions to appetitive food

stimuli.[112–115] Similarly, both stress and alcohol consumption reliably impair executive function, can increase the consumption of unhealthy foods, and have been linked to obesity.[116,117]

From this perspective, one strategy for successfully resisting the temptation to overindulge in foods may be to avoid the combination of appetitive cues *and* incidental attenuators of dlPFC function, an illustration of this would be shopping for groceries only when you are well rested. Alternatively, individuals seeking to improve the resiliency of their dlPFC to perturbation, might try to do so using aerobic exercise.[118] Although the above extrapolations are speculative, linking up neuromodulation findings with public health considerations is potentially informative.[119,120] 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=.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 between 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.[86] 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 [86] 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.

Chapter 5.2 – Strengths and Study Considerations

In a recent meta-analysis examining the effects of non-invasive brain stimulation on eating outcomes by Lowe et al., the analyzed studies had an average sample size of 28 participants.[63] The much larger sample (n = 107) of the current study allowed for between-condition comparisons and mediational analyses that would not have been sufficiently powered in the more conventional smaller study samples. Methodological considerations are likely a contributing factor to the smaller samples typically found. While the current study recruited from a general population of healthy undergraduates, studies typically have additional conditions restricting their recruitment pool, limiting participation to females with high reports of food cravings or drawing from clinical populations with eating disorders.[63] However, the use of a healthy university population in the current study is likely to improve the generalizability of the results found herein.

While we observed a large gender difference in the quantity of food consumed during the taste test across all 4 conditions, with men eating approximately 50% more on average, we did not have any a priori hypothesis suggesting that the interaction between TMS and cues would differ between men and women. Given the number of conditions present in the study and the differences in male to female recruitment, further stratification of the dataset to allow for a well-considered examination of potential gender differences in each of the four study conditions across outcome would necessitate the recruitment of an even larger study sample. To account for the differences in male and female consumption in the results gender was used as a covariate in the analysis model.

The systematic blinding of participants is a challenge in research utilizing TMS. The scalp muscle twitch sensations elicited by stimulation with an active coil can clue participants in to whether or not they are receiving real vs. sham stimulation, and consequently introduce bias through expectancy.[121] The use of the between-subjects design, in conjunction with a sham coil and TMS naïve participants herein, enhances the validity of the experimental conditions by reducing the ability of participants to compare stimulation sensations across conditions as they would be able to do with a within subject design.

Limitations of this study 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.

Chapter 5.3 – Future Directions

The facilitation and restraint conditions participants were assigned to incorporated both visual cues and verbal instructions, however in the current study design it is not possible to determine how much either cue type individually contributed to the observed eating outcomes. The possibility that different sensory modalities (i.e. smells, verbal instructions, and visual cues) or limited temporal presentations of facilitative or restriction cues in the eating environment could elicit different interactions with the dlPFC provides an interesting opportunity for replication and further investigation.

Studies examining varying modalities of executive function tasks (using verbal vs. visual cues) have observed differential patterns of dlPFC activation corresponding to the different sensory inputs.[39] While the brain stimulation literature has operated under the assumption that

the dlPFC is structurally and functionally homogeneous, neuroimaging evidence based on studies of the right dlPFC indicates the existence of functionally distinct anterior-ventral and posterior-dorsal subregions.[122] Here it should be noted that the current study used the left (not right) dlPFC as a target site for stimulation, because of greater consistency in the reported behaviour findings.[85]

While the anterior-ventral subregion of the right dlPFC is closely associated with attention and action inhibition, the posterior-dorsal subregion is associated with action execution and working memory.[122] This would suggest that small shifts in coil positioning during stimulation of the right dlPFC could reduce or increase the observed effects of the stimulation depending on the cognitive task being used. A systematic investigation of this research question would require the use of a neuronavigation system where ideally individualized brain images of the research participants would guide in the precise positioning of the TMS coil.[123]

While flanker interference scores serve as a reliable indicator for the cognitive capacity of the dlPFC, as demonstrated here and in other neuromodulation studies,[85] incorporating a neuroimaging measure into future studies would provide additional validation and evidence of the underlying physiological mechanisms understood to be behind the observed behavioural outcomes.[62] Functional near infrared spectroscopy (fNIRS) has previously been applied in the characterization of cognitive control through changes in dlPFC activity,[124] and has an advantage over fMRI in terms of its portability.[125] While the optical based fNIRS is limited to observing changes in cortical activity, [126] this would allow researchers to establish that changes in dlPFC activity following stimulation correspond with the expected time course,[127] and would allow for simultaneous imaging of other PFC structures like the mPFC, which is involved in valuation.[128]

Chapter 5.4 – 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. The 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.

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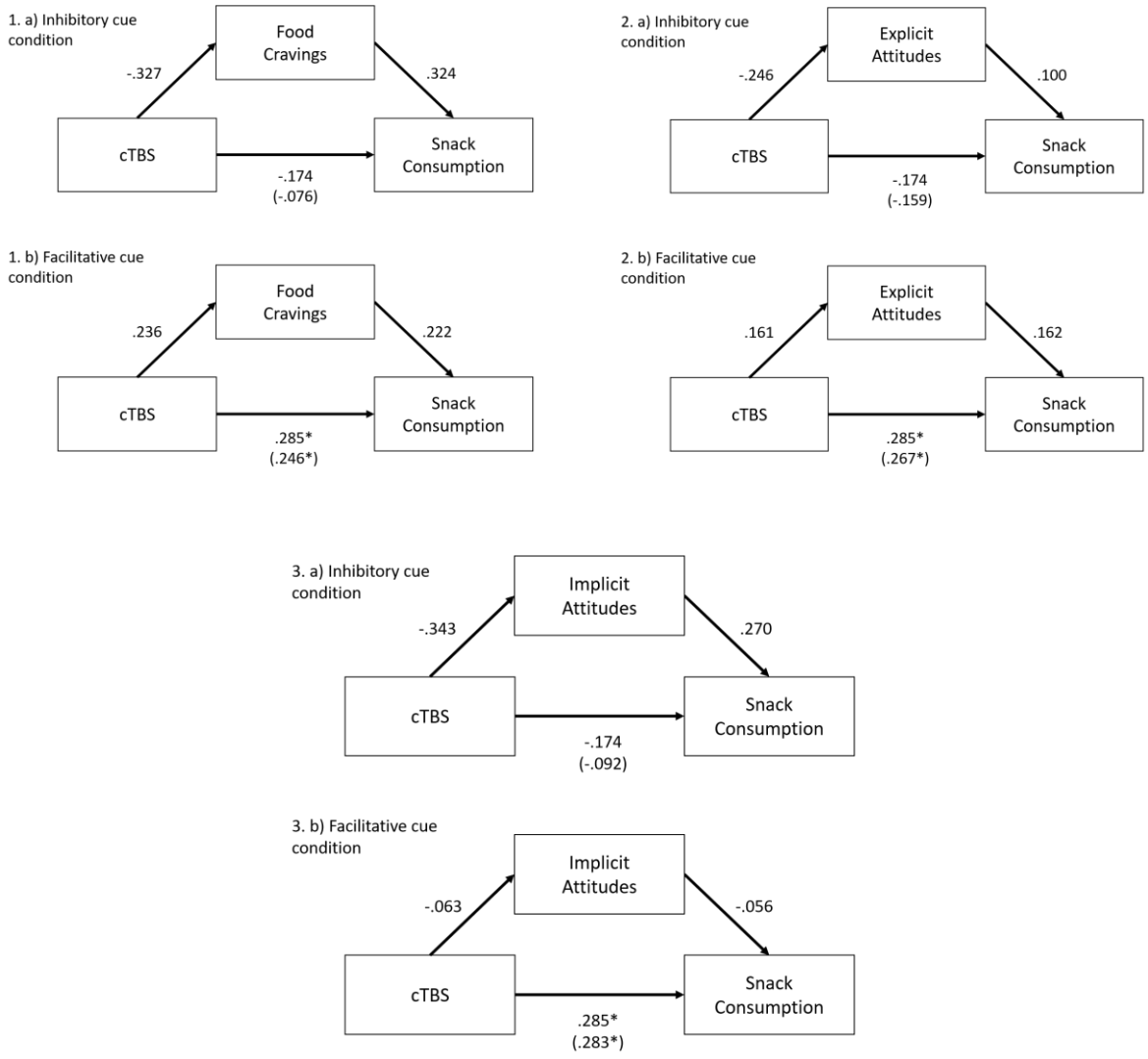
Appendices

Appendix A – Alternate Mediation Models

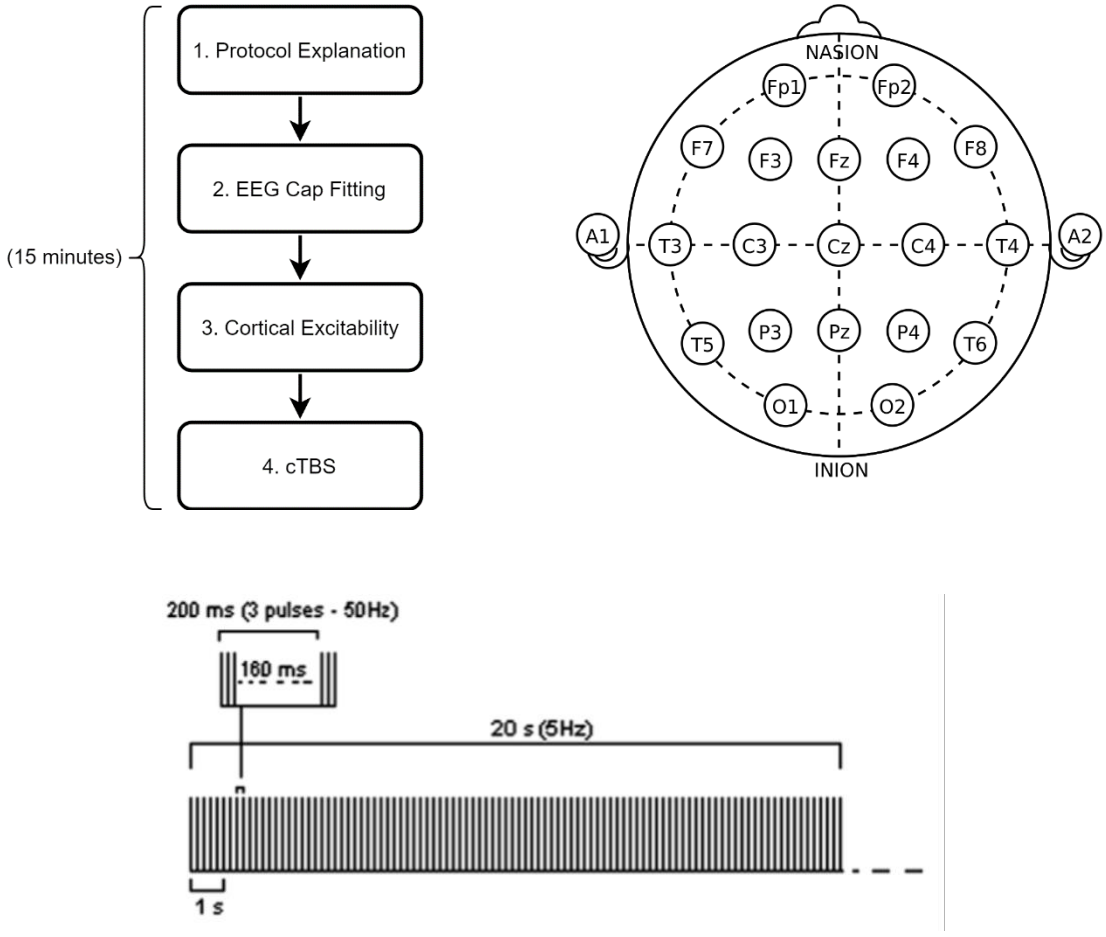


Schematic representation of alternative moderated mediational models positing mediation of cTBS effects on consumption through different outcome measures (1. Food Cravings, 2. Explicit Attitudes, 3. Implicit Attitudes) conditional upon cue type a) inhibitory vs. b) facilitative.

All coefficients are standardized Beta weights.

*: $p<0.05$

Appendix B – cTBS Protocol



cTBS protocol:

1. The cTBS procedure is explained to participants to ensure informed consent and comfort throughout the protocol

2. EEG cap fitting consists of first measuring the participant's head circumference to determining the corresponding EEG cap size. The EEG cap will be centered onto the scalp using the CZ electrode of the cap. The center point of the scalp is determined by measuring the intersection of the nasion to inion (vertical line) and the preauricular notch (horizontal line) of both ears

3. The C3 electrode position (from the international 10-20 system) was used to locate target site of the motor cortex corresponding to the right *abductor pollicus brevis* (thumb) muscle. Resting motor treshold was established as lowest intensity required to induce a discernable thumb twitch in 5/10 consecutive trials.

4. 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).[59]

Appendix C - TMS Screening Form

Below is a questionnaire used to help with decisions about who is eligible to take part in the study and who is not. This information, as well as your identity, will be kept confidential in all future publications. If you wish to indicate "YES" to any of the conditions listed below, but feel uncomfortable specifying, please inform the researcher.

PLEASE COMPLETE FORM BELOW:

Participant ID _____ Age: _____

For each one, please **CIRCLE YES or NO**:

Neurological or Psychiatric Disorder	YES	NO	Multiple Sclerosis	YES	NO
Head Trauma (e.g. Concussion)	YES	NO	Depression	YES	NO
Stroke	YES	NO	Treatment with amitriptyline and haloperidol	YES	NO
Brain surgery	YES	NO	Implanted medication pump	YES	NO
Metal in cranium	YES	NO	Intracranial Pathology	YES	NO
Brain Lesion	YES	NO	Albinism	YES	NO
Pacemaker	YES	NO	Intractable anxiety	YES	NO
History of seizure	YES	NO	Pregnant at this time	YES	NO
Family history of epilepsy	YES	NO	Headaches or Hearing problems	YES	NO
History of epilepsy	YES	NO	Family History of Hearing Loss	YES	NO
Intracorporal electronic devices or stimulators.	YES	NO	Other medical conditions (please specify)	YES	NO
Intracardiac lines	YES	NO	Are you right or left handed?	Right	Left

I hereby declare that all information given on this TMS screening form is true and complete in every respect.

_____ _____

Signature of Participant Date

_____ _____

Signature of Witness Date

Appendix D – Taste Rating Form

1. How would you describe the texture of this food (please circle all that apply):

Crisp	Velvety	Mushy	Creamy	Light
Chewy	Moist	Dry	Soft	Fluffy
Crunchy	Juicy	Smooth	Stringy	Oily
Rich	Luscious	Doughy	Dense	Brittle
Sticky	Watery	Tough	Flaky	Fibrous

2. Based on appearance, how appealing is this food?

1	2	3	4	5	6	7	8	9	10
Not at All Appealing				Moderately Appealing					Very Appealing

3. How salty is this food?

1	2	3	4	5	6	7	8	9	10
Not at All Salty				Moderately Salty					Very Salty

4. How sweet is this food?

1	2	3	4	5	6	7	8	9	10
Not at All Sweet				Moderately Sweet					Very Sweet

5. How greasy is this food?

1	2	3	4	5	6	7	8	9	10
Not at All Greasy				Moderately Greasy					Very Greasy

6. How healthy do you think this food is?

1	2	3	4	5	6	7	8	9	10
Not at All Healthy				Moderately Healthy					Very Healthy

7. Overall, how would you rate this food?

1	2	3	4	5	6	7	8	9	10
Not at All Good				Neutral					Very Good

Appendix E – Food Craving Questionnaire - State (FCQ-S)

Options:

Using the following scale

1="Strongly Disagree"; 2="Disagree"; 3="Neutral"; 4="Agree"; 5="Strongly Agree"

Please indicate the extent to which you agree with the following statements right now, at this very moment.

Questions:

1. "I have an intense desire to eat chocolate or potato chips"
2. "I'm craving chocolate or potato chips"
3. "I have an urge for chocolate or potato chips"
4. "Eating chocolate or potato chips would make things seem just perfect"
5. "If I were to eat what I am craving, I am sure my mood would improve"
6. "Eating chocolate or potato chips would feel wonderful"
7. "If I ate something, I wouldn't feel so sluggish and lethargic"
8. "Satisfying my craving would make me feel less grouchy and irritable"
9. "I would feel more alert if I could satisfy my craving"
10. "If I had chocolate or potato chips, I could not stop eating it"
11. "My desire to eat chocolate or potato chips seems overpowering"
12. "I know I'm going to keep on thinking about chocolate and potato chips until I actually have it"
13. "I am hungry"
14. "If I ate right now, my stomach wouldn't feel as empty"
15. "I feel weak because of not eating"

Appendix F – IAT

Sequence of trial blocks in the IATs. In half of participants the position of blocks 1, 3 and 4 were switched with those of blocks 5, 6 and 7

Block	Number of Trials	Left-key	Right-Key
1	24	High Calorie	Low Calorie
2	24	Positive	Negative
3	16	High Calorie - Positive	Low Calorie - Negative
4	32	High Calorie - Positive	Low Calorie - Negative
5	24	Low Calorie	High Calorie
6	16	Low Calorie – Positive	High Calorie - Negative
7	32	Low Calorie – Positive	High Calorie - Negative

List of words used in the IAT with norms of valence, arousal[129]

Foods

HIGH CALORIE			**LOW CALORIE**		
	Valence	Arousal		Valence	Arousal
CHOCOLATE	7.63 (2.01)	5.14 (2.85)	CUCUMBER	5.71 (1.68)	2.81 (1.57)
COOKIE	7.32 (1.63)	4.7 (2.43)	CELERY	5.8 (2.07)	2.68 (2.1)
PIZZA	7.89 (1.29)	4.58 (2.72)	TOMATO	5.79 (2.07)	3.91 (2.81)
CAKE	7.58 (1.43)	5.33 (2.5)	CARROT	5.81 (1.94)	3.43 (2.06)
BURGER	6.95 (2.16)	3.65 (2.6)	SPINACH	5.84 (1.86)	3.64 (2.66)
CANDY	7.27 (1.78)	5.03 (2.33)	LETTUCE	6.47 (1.74)	3.17 (2.3)
Average	7.44	4.74		5.90	3.27

Attributes

positive			**negative**		
	Valence	Arousal		Valence	Arousal
love	8 (1.39)	5.36 (3.23)	ugly	2.47 (1.93)	4.43 (2.18)
joy	8.21 (1.18)	5.55 (2.85)	pain	2 (1.28)	6.27 (2.59)
friend	6.79 (2.49)	4.29 (2.69)	evil	2.34 (1.61)	5.67 (2.93)
fun	8.37 (0.96)	6.32 (2.62)	death	1.89 (1.24)	5.53 (2.62)
happy	8.47 (1.28)	6.05 (2.13)	failure	2.15 (1.17)	5 (2.49)
peace	7.75 (1.5)	4.65 (2.77)	murder	1.48 (0.81)	6.24 (2.76)
	7.93	5.37		2.06	5.52

Appendix G – Explicit Attitude Questionnaire

On a scale from 1 to 7

Please indicate the extent to which you agree with the following statements

"To me, eating high-calorie foods frequently is":

1 = "Harmful"; 2 = ""; 3 = ""; 4 = "Neutral"; 5 = ""; 6 = ""; 7 = "Beneficial"

1 = "Quick"; 2 = ""; 3 = ""; 4 = "Neutral"; 5 = ""; 6 = ""; 7 = "Time Consuming"

1 = "Convenient"; 2 = ""; 3 = ""; 4 = "Neutral"; 5 = ""; 6 = ""; 7 = "Inconvenient"

1 = "Unpleasant"; 2 = ""; 3 = ""; 4 = "Neutral"; 5 = ""; 6 = ""; 7 = "Pleasant"

1 = "Cheap"; 2 = ""; 3 = ""; 4 = "Neutral"; 5 = ""; 6 = ""; 7 = "Expensive"

"To me, eating high-calorie foods frequently makes me feel":

1 = "Happy"; 2 = ""; 3 = ""; 4 = "Neutral"; 5 = ""; 6 = ""; 7 = "Unhappy"

1 = "Self Conscious"; 2 = ""; 3 = ""; 4 = "Neutral"; 5 =""; 6 = ""; 7 = "Self Assured"

1 = "Inadequate"; 2 = ""; 3 = ""; 4 = "Neutral"; 5 = ""; 6 = ""; 7 = "Capable"

1 = "Enticed"; 2 = ""; 3 = ""; 4 = "Neutral"; 5 = ""; 6 = ""; 7 = "Disgusted"

1 = "Guilty"; 2 = ""; 3 = ""; 4 = "Neutral"; 5 = ""; 6 = ""; 7 = "Carefree"

1 = "Lethargic"; 2 = ""; 3 = ""; 4 = "Neutral"; 5 = ""; 6 = ""; 7 = "Energetic"

1 = "Unashamed"; 2 = ""; 3 = ""; 4 = "Neutral"; 5 = ""; 6 = ""; 7 = "Ashamed"

1 = "Disappointed"; 2 = ""; 3 = ""; 4 = "Neutral"; 5 = ""; 6 = ""; 7 = "Gratified"

1 = "Well"; 2 = ""; 3 = ""; 4 = "Neutral"; 5 = ""; 6 = ""; 7 = "Unwell"

1 = "Content"; 2 = ""; 3 = ""; 4 = "Neutral"; 5 = ""; 6 = ""; 7 = "Discontent"

1 = "Worried"; 2 = ""; 3 = ""; 4 = "Neutral"; 5 = ""; 6 = ""; 7 = "Calm"

1 = "Unenthusiastic"; 2 = ""; 3 = ""; 4 = "Neutral"; 5 = ""; 6 = ""; 7 = "Enthusiastic"

Appendix H – Nutrition Content of the Experimental Foods

Food	Units	Weight Displayed	Total Calorie Content
Pringles Original	20 Chips	35 g	187.5 kJ [130]
Milk Chocolate Truffle	6 Balls	78 g	480 kJ [131]
Pringles BBQ	20 Chips	37.3 g	200 kJ [132]
Salted Chocolate Truffle	6 Balls	72 g	440 kJ [133]
Pringles Sour Cream & Onion	20 Chips	37.3 g	200 kJ [134]
		= 259.6g	= 1507.5 kJ