Testing the relative contributions of the dlPFC and mPFC to decision-making about eating and finances across the adult lifespan

by

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Authors Declaration

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

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Abstract

***Background*:** Prior neuroimaging and neuromodulation studies have shown that the dorsolateral prefrontal cortex (dlPFC) and dorsomedial prefrontal cortex (dmPFC) are important nodes for self-control and decision-making, but through separable processes. However, very little is known about the relative contribution of both these regions in two important domains of decision making for older adults: 1) financial judgement and 2) consumption of appetitive high-caloric snacks foods.

***Objective and Hypothesis*:** The objective of the study was to examine the effects of excitatory brain stimulation (iTBS) on financial decision making and eating, as mediated through cognitive performance. Given that the PFC and its subregions are differentially sensitive to the effects of aging, it was hypothesized that age (older versus younger) might moderate the effects of stimulation. It was further hypothesized that excitatory stimulation would lead to a decrease in consumption of appetitive snack foods and improvement in financial decision making (i.e., reduced discounting of delayed rewards; delay discounting).

***Methods*:** Using a single-blinded, between-subjects experimental design, a sample of 22 younger adults and 21 older adults ($N = 43$) were randomly assigned to receive iTBS in one of the three conditions: 1) active iTBS to the left dlPFC; involved in the modulation of pre-potent responses; 2) active iTBS to bilateral dmPFC; which is involved in subjective valuation processing, or 3) sham iTBS; the control/placebo condition. After the stimulation session, participants completed two cognitive tasks (delay discounting and flanker), and a bogus taste test. Functional-near infrared spectroscopy (fNIRS) was used to validate iTBS effects on cognitive task performance via changes in blood oxygen saturation levels.

***Results*:** Results indicated null effects of iTBS on food consumption, flanker performance and delay discounting, with no moderation by age category. However, a significant moderating effect of gender emerged, such that a significant increase in calorie dense food consumption was evident among those in the dmPFC stimulation condition. This effect was mainly driven by the consumption of sweet foods. Finally, fNIRS data suggested a strong left lateralized activation on the incongruent versus congruent flanker task, with overall lower oxygen demand in the active stimulation than the sham stimulation. In contrast, medial channels were activated for the delay discounting task, with a significant increase in oxygen demand for the dmPFC condition compared to the sham condition.

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List of Abbreviations

BOLD: blood oxygenation level-dependent

cTBS: continuous theta burst stimulation

dlPFC: dorsolateral prefrontal cortex

dmPFC: dorsomedial prefrontal cortex

fMRI: functional magnetic resonance imaging

fNIRS: functional near-infrared spectroscopy

iTBS: intermittent theta burst stimulation

LTD: long-term depression

LTP: long- term potentiation

mPFC: medial prefrontal cortex

MEP: muscle evoked potential

MRI: magnetic resonance imaging

NBIS: non-invasive brain stimulation

NIR: near infrared

PFC : prefrontal cortex

RMT: resting motor threshold

rTMS: repetitive transcranial magnetic stimulation

TBS: theta burst stimulation

tDCS: transcranial direct current stimulation

TMS: transcranial magnetic stimulation

Chapter 1: Introduction

1.1 Obesity: Prefrontal Cortex on Dietary Self-Control

The prevalence of obesity is on the rise in Canada and is considered one of the leading risk factors for a wide range of chronic illnesses, such as cardiovascular diseases, cancer and type 2 diabetes (1). The rate of increase in adult obesity has been alarming; it has almost tripled in the last 40 years, from 13.8% in 1978 to 36.3% in 2018 (2,3). A recent study in 2019 projected a 10-year prevalence of obesity to steadily increase from a baseline of 261 cases per 1000 from the 2013/14 Canadian Community Health Survey to 326 cases per 1000 in 2023/24 (4). There is an urgent need to address this health risk, as its long-term impact can have a significant burden on our economic and health resources. It is important to understand the behavioral and biological mechanisms that support obesity, given the challenge that it poses to traditional public health intervention approaches (5).

Globalization has led to an increased availability and consumption of palatable energy-dense foods; foods that are preferred due to their high fat and sugar content (6). From an evolutionary perspective, palatable foods were once considered advantageous to early settlers because it provided the highest net caloric gain in times of scarcity for survival (7). Unfortunately, the same cannot be said today - as drastic changes to our modern food environment (i.e. low-cost and abundance availability of these foods) has exposed our genetic predisposition and shifted our primary purpose of food-intake; once which was solely required to satisfy our biological nutritional needs to prevent starvation, is now entered into a new era of food-intake called “non-homeostatic feeding”, or the need to feed for pleasure (6). Humans are therefore in a constant conflict between their modern food environment and maintaining their dietary behaviour; there is a preference for these calorie dense foods, but it is understood that avoiding such preferences is integral to maintaining their health and longevity. Most individuals are successful in adapting to such person/environment conflicts, but unfortunately a few succumb leading to obesogenic behavioural tendencies.

Why might there be such differences? There is evidence that suggests that individual differences toward regulation of food-intake is causally related with the maintenance of higher-

order executive functioning (7–9). It has been previously indicated that the differential operation of the prefrontal cortex could be important for determining dietary self-control (8,10,11).

The prefrontal cortex (PFC) is an important multi-modal node of the brain executive control network, that is located in the anterior frontal lobe and occupies one-third of the human cerebral cortex. It supports a variety of functions such as attention and language processing, encoding and retrieval of memory, initiating and carrying out goal directed behaviours, evaluative processing and inhibitory control interference (12,13). Dietary self-control is strongly dependent on the PFC, as it enables individuals to override habitual or prepotent responses to high caloric foods and to act in accordance to their behavioral intentions and goals/aspirations (i.e. limit the consumption for high caloric foods for health benefits) (7,8). The extent to which indulgent eating occurs (i.e. that leads to obesity), may be dependent on the attenuated inhibitory control via the operation of the prefrontal cortex (7,8).

There is an accumulating body of literature that has suggested that tendency to overconsume is stronger among individuals with weaker inhibitory control (14–20). A previous meta-analysis has reported that obese individuals showed significant deficits in inhibitory control relative to healthy weight individuals (21). Neuroimaging data revealed that these differences could be due to functional activation patterns, where lower activation of the PFC was shown to be associated with increased body weight (11,22). Similarly, the consumption of palatable foods has shown to lead deficiencies in the top-down regulation of cognitive and executive function controlled by the PFC, where the strength of inhibitory control is significantly weakened in obese individuals in comparison to normal weight individuals (10). It has been previously described that the relationship between PFC and obesity might potentially be reciprocal (8); where an increase in weight gain due to decreased PFC activation (as weak dietary control leads to increased consumption of hyperpalatable foods), could further exacerbate PFC dysfunction and executive function impairments, promoting further over-consumption, which drives the maintenance of unhealthy eating behaviours (8). Together, this highlights that PFC function is critical to understanding individual differences in food consumption and its vulnerability to obesity.

In terms of specific PFC regions, neuroimaging studies have indicated that the dorsolateral prefrontal cortex (dlPFC) as an important sub-region for executive self-control and food-related decision-making (11,22,23). Individual differences in the strength of dlPFC activation have been shown to be correlated with grey matter volume, which was shown to be positively associated with dietary self-control regulation (24). In particular, increased activity of the left dlPFC was found to be important when participants were asked to regulate or supress food cravings, which was also negatively correlated with BMI during dietary self-control (11). Furthermore, previous meta-analyses has suggested that experimental studies using non-invasive brain stimulation methods (NIBS), such as repetitive transcranial magnetic stimulation (rTMS), including theta burst stimulation (TBS), have provided causal evidence linking activity within the left dlPFC to food cravings and consumption outcomes (9). rTMS and TBS have been previously shown to be effective in manipulating the function of the dlPFC, and can reliably modulate its performance on various executive functioning tasks in theorized directions (i.e., excitatory stimulation increases, and inhibitory stimulation decreases cognitive task performance) (25).

Single-session rTMS studies have shown that the administration of excitatory left dlPFC stimulation causes reduced cravings for appetitive snack foods (26,27). Likewise, multi-session excitatory rTMS on left dlPFC was found to be effective in reducing weight loss and decreasing food intake in obese patients (28). Furthermore, continuous theta burst stimulation (cTBS; an inhibitory variant of rTMS) targeting the left dlPFC resulted in increased cravings and consumption of similar foods (29,30). Meta-analyses on the assessing the effects of the non-invasive brain stimulation techniques on the dlPFC, such as TMS and transcranial direct current stimulation (tDCS) have revealed medium effect sizes on food cravings (9,31) and consumption outcomes (32,33), both in the favour of active over sham stimulation. The effects were more pronounced with rTMS than with tDCS (9,32), in the left dlPFC than in the right dlPFC (9,32), along with a larger effect size seen in multi-session over single session studies (33). In addition, these meta-analyses have also linked left dlPFC modulation to various other types of cravings (9,29,31,32). This suggests that the lateral prefrontal cortex (especially the left) is important self-control of hedonic eating, and its role is broadly implicated across a variety of domains, ranging from cravings and consumption, to other types of judgements.

1.2 Behavioural Economics: Obesity and Delay Discounting

The rise in obesity can be conceptualized through the lens of behavioural economics; a field which looks at combining research from economics, cognitive psychology and neuroscience, in understanding how people allocate their choices between alternatives given their time, efforts and limited resources to gain access to goods (34). Behavioural choice theory has been prominent in explaining many negative decision-making around health behaviours; including those involving maintenance of positive energy balance (i.e., the demand for energy intake exceeding energy expenditure leading to obesity), drug abuse and excessive gambling (34).

One prominent theoretical approach in understanding how our choices are made in terms of time is through delay discounting (34). Delay discounting or inter-temporal discounting is a universal human phenomenon wherein rewards are discounted in value as a function of delay time until receipt. This causes small—but immediately available—rewards to be valued mire highly than delayed rewards of larger absolute magnitude (35). The delay discounting phenomenon is important because it explains human choice behavior across multiple domains, ranging from food choices to interpersonal relationships to financial decision making (35–37). This is important for understanding choice behaviour because it implies that individuals must voluntarily give up their immediate gratification for better goal-directed behaviours that improve their health in the future (34).

The concept of delay discounting can be applied to obesity and the behaviors that give rise to it; delay of gratification is required in order to avoid foods that are tasty but calorie dense, in the interest of delayed benefits to appearance and wellbeing. The same is true of exercise, which requires enduring minor discomfort and inconvenience in order to realize non-immediate benefits such as improved fitness level and longer life. Studies have shown obese individuals are indeed more likely to discount future gains than healthy weight individuals (38–41). Additionally, a recent systematic review and meta-analyses found consistent evidence across studies that steep discounting of delayed monetary and food rewards is associated with obesity (42,43).

Delay discounting is fundamentally linked to the neurophysiology of the executive control network (including the dlPFC, the superior parietal lobule, and white matter tracts connecting the two) and its functional connectivity with various brain systems implicated in hedonic response to

rewards (food-related and otherwise; the ventral tegmental area, anterior insula) (44). Neuroimaging studies have shown altered brain activation in cognitive control networks among individuals with obesity during the execution of discounting tasks; lower activation of the lateral PFC is also broadly associated with increased discounting of future rewards (45–47). The above highlights that the lateral prefrontal cortex is critical in the process of exerting self-control over immediate temptations, and moreover that inter-temporal decision-making can be a framework for understanding behavioural precursors of obesity.

The next few sections will explain how delay discounting is assessed, explore age and gender related differences in delay discounting, and emphasize key areas of the PFC that are important during inter-temporal choice.

1.3 Delay Discounting: Assessment in Literature

Delay discounting is most often assessed indirectly using decision-making patterns that involve monetary choices. For instance, the primary measurement paradigm for delay discounting involves asking individuals to make a series of judgements between two monetary offers that differ in magnitude (i.e. $5 vs. $10), but also delay in time (i.e. would you rather have $5 now or $10 in one week?). Ignoring the delay, the logical approach would be to select the higher absolute monetary value ($10) over the lower one ($5) when both are immediately available. However, when a delay is imposed for the larger option but not the smaller one, a significant number of people revert to the preference for immediately available, but smaller (in absolute terms) monetary reward (48). This phenomenon is known as “preference reversal”. The occurrence of preference reversals can be explained by understanding the shape of the discount-over-time curve (48,49).

According to several prominent theories of inter-temporal choice, the decline in value of a given option as a consequence of delay is neither a constant nor exponential function (i.e. such that the value decreases proportionately more with each unit delay of time and therefore the discount rate stays the same), but rather is a hyperbolic (48,49). Hyperbolic discounting implies that the effect of delay on value is not the same across a range of delays (48,49). At shorter delays, the value is the decreased proportionally more than at longer delays (48,49). A hyperbolic (i.e., very

steeply bowed) discounting curve would predict that if equivalent delays were added to both alternatives, (i.e. $5 in one month vs. $10 one week + one month) the preference would now switch for the delayed reward. Studies have shown evidence for preference reversal in both human and non-human subjects, in which the percent of choosing larger-later rewards increases when the smaller-sooner rewards are delayed in time (48–50).

In assessing how delay affects the value of outcomes in humans, as previously mentioned, researchers have participants complete an array of inter-temporal tasks, in which they are asked to make a series of choices between hypothetical monetary options. The purpose of these the delay discounting procedures is to identify the indifference point, which reflects the equal preference for two dichotomous reward alternatives (immediate vs. delayed) that differ in both magnitude and delay (49,51). The indifference point can be determined using one of the two techniques: 1) having a fixed list of options as described by Rachlin and colleagues (52) or 2) using an adjusted-amount procedure ("adaptive delay discounting assessment"), in which the amount of the immediate outcome is adjusted (increased or decreased) (49,51) or the delay of larger outcome is adjusted (also increased or decreased) (53) based on the participants previous choice. Both of these techniques help determine the indifference point, by taking the average amount at which the participant switches their preference (49,51).

To illustrate how the indifference point is determined, let us look at an example. Using Rachlin and colleague's simple procedure of a fixed list options method, participants were initially asked to choose between $1000 today and $1000 available in a month. Thereafter, the amount of the immediate option decreased across several trials until it reaches $1; then it increases back (in the same order) across several trials back to $1000 (52). The delayed option stays constant throughout (52). If the participant had initially chose $1000 today over $1000 available in a month, and then switched for the delayed option at $960 and stay with delayed option throughout the rest of trials till the immediate options decreased to $1 and then switched back at $940 when the immediate amounts increased back across trials, the indifference point would be the average of the two, which would be $950 (52). In addition, Rachlin and colleagues also reported that the larger the delay gets for the rewards, the smaller the indifference point becomes (52). This demonstrates that the value of reward decreases as it becomes more remote (52).

Once the data is collected and the indifference point is determined, non-linear regression techniques are used to generate discounting curves (51). Since delay discounting is hyperbolic in function, the degree of discounting, or *k*, can be estimated by using the following formula:

Equation 1:

$$V = A / (1+kD)$$

where *V* is the experimentally calculated indifference point, *A* is the amount of the reward, *D* is the time delay and *k* is the degree of discounting; the crucial parameter of interest that quantifies the steepness and how much the value is affected by the delay (48,49,51). The size of *k* is important, as it tracks the degree of discounting shown in the indifference points: a larger *k* indicates a steeper discounting curve, meaning the effect of the delay has degraded the value, indicating impulsivity (48,49,51). Conversely, a smaller *k* implies higher probability for opting for a delayed over immediate alternative.

1.4 Age-Dependent Differences in Delay Discounting

Delay discounting is pervasive in everyday life and appears to be a universal human tendency, affecting all demographic groups (48,49). However, discounting changes across the lifespan (54), with young children and adolescents frequently discounting delayed alternatives more heavily than adults (54–58). A primarily reason for steep discounting among adolescents is the underdevelopment of the prefrontal cortex; an area involved highly involved self-regulation and the capacity for far-sighted decision-making (59,60). In addition, when comparing different sub-populations of adults, younger and middle-aged adults had shown to discount future gains for short-term rewards more frequently than non-impaired older adults (61,62). However, discrepancies have been reported; Green et al.(63) reported no differences in discounting between younger and older adults after controlling for socio-economic status (SES), while Reed & Reed (64) reported the opposite results; where older adults discounted future gains more frequently than younger adults. Further research is needs to be conducted to address the inconsistency in age-

related differences in delay discounting and clarify important mediators that can impact discounting behaviour between individuals.

Despite this discrepancy, it is well known that older adults are at a higher risk for chronic illnesses that can impact decision-making, that can ultimately lead to serious consequences on their health (61). This is especially true for older adults leading up to or during their retirement years, as in part because many individuals at this stage of life frequently have fixed incomes and also have less opportunity to recover from their mistakes. The inevitable normal processes of ageing and ageing-related illnesses can hinder cognitive function and could negatively support far-sighted decision making in older adults, leaving them more vulnerable towards multiple health consequences (61,65).

1.5 Gender-Dependent Differences in Delay Discounting

Among moderators that may impact discounting behaviour, gender differences have also been considered. Men are more impulsive and likely to partake in more risky behaviours (66,67). From an evolutionary perspective, a potential reason for this inherent difference may be reproductive success, which may be increased for females who were relatively more deliberative in the ancient evolutionary context; selective pressure toward delay of gratification may have in turn been preserved (68). Consistent with this, a previous meta-analysis by Silverman (2003) reported a relatively small but reliable effect size for sex and delay of gratification, with females less likely to discount future rewards (69). However, another meta-analysis found no significant differences in delay discounting between genders (70). At the time being, the exact role of gender and discounting remains unclear but worthy of further investigation.

1.6 The Role of The Prefrontal Cortex During Intertemporal Choice

Studies using magnetic resonance imaging (MRI) and functional magnetic resonance imaging (fMRI) involving delay discounting tasks have shown that far-sighted choices are correlated with the increased cortical volume and functional activation parameters in the dlPFC, a region also subjected to disproportionate age related decline in older adults (12,71,72). McClure and colleagues' have shown that during inter-temporal decision difficulty tasks (choosing between an easy vs. difficult monetary option), greater activation of dlPFC was required when decisions

between two inter-temporal choices (the difference in dollar amount between two options) became more difficult to choose with time (71). More specifically, studies using fMRI have shown increase activation specifically in left dlPFC when subjects have a preference for larger-later rewards than smaller-sooner rewards (71,73,74). Similarly, neuromodulation studies have also confirmed the importance of the left dlPFC in the preference for larger delayed rewards. Figner et al. (2010) used inhibitory rTMS to attenuate left dlPFC function and found an increased tendency for those in the active stimulation condition to choose immediately available rewards over delayed ones (75). Similarly, in the opposite direction, Sheffer et al. (2013) found excitatory rTMS to the left dlPFC decreased the discounting of monetary gains when individuals received active verses sham stimulation (76). The above findings all strongly suggest the importance of left dlPFC in far-sighted decision-making during inter-temporal decision-making.

Among cognitive operations that might be important for inter-temporal choices, beyond self-control, evaluative processing may also be critical. Beyond executive control nodes such as the lateral PFC, the phenomenon of delay discounting—and the tendency to yield to immediate hedonic lures more broadly—may depend on evaluative processing. Evaluative processing or subjective valuation refers to the process of assigning and integrating relevant dimensions of an option (i.e. money, time) into a single metric, in order to guide decision making that should, in theory, maximize value to the decision-maker (77). An early neuroimaging study by McClure and colleagues showed that evaluative processing during intertemporal choices draw on two separate but interacting neural systems: one system corresponding to immediate options and the other system for delayed options (71). Settling for immediate choices primarily activated areas of the limbic and paralimbic system, such as the ventral striatum and posterior cingulate cortex, and also to areas that make cortical projections from the paralimbic system to PFC sub regions, such as the medial PFC (mPFC) (71). In contrast, choosing delayed options was associated more selectively with the activation the of the dlPFC (71).

However, Kable and Glimcher (2007) using psychometric-neuromeric discounting comparisons; a gold standard in precisely comparing changes in neural activity with the subjective value of possible rewards during choice, suggested an alternative model to the dual-valuation system proposed by the McClure group (78). Although the authors of the study indicate that with

some respect their hypothesis is compatible with McClure's group, in which both groups agree that mPFC is important for subjective valuation, they disagree on the fact that its role is exclusively only for immediate rewards (78). In fact, they propose that there exists a common valuation system that encodes for all intertemporal choices, regardless whether the reward is immediate or delayed (78). Using fMRI, they showed that the activation in mPFC, ventral striatum and posterior cingulate cortex, all tracked the valuation for not only immediate rewards, but also delayed monetary rewards as well (78). Their findings suggested the neural activation within these regions varied when delayed rewards changed between trials. They showed an increased activation in these regions when the objective amount of the delayed reward increases, decreased activation when the delay to reward increases, and increased activity when the delayed reward is chosen because it is found to be more valuable (78). Overall, these findings from Kable and Glimcher study suggest the potential for the mPFC to make important contributions in inter-temporal decision-making by integrating value with time delay when choosing between reward options.

The discrepancy between the two systems of thought on subjective valuation can be partly resolved by the notion that inter-temporal choices itself are multi-component based; consisting of a valuation stage and a choice stage (77). As such, an fMRI study by Lui and colleagues, showed that subjective valuation processes that are associated with mPFC, are independent from choice processes that are associated with dlPFC, suggesting a neural dissociation during inter-temporal choice (79). Furthermore, their results suggests that the valuation component may occur before the choice component during inter-temporal choices, although this hypothesis is still immensely being debated (79). Moreover, a recently published neuromodulation study using excitatory rTMS targeting the mPFC revealed increases in delay discounting, further implicating the role of the mPFC in far-sighted decision-making (80). Halfmann and colleagues have shown that older adults with disadvantageous decision-making patterns (assessed using the Iowa Gambling Task (IGT); a complex task that incorporates emotional and cognitive skills) were more likely to discount future rewards than older adults with advantageous decision making patterns (those that scored higher IGT scores) (61). This could be due differences in mPFC activation, where decreased activation in mPFC (reduced value signals) was found in older adults with disadvantageous decision-making patterns (lower IGT scores) compared to IGT advantageous older adults (59). Interestingly, the mPFC does not manifest the age-related decline in older adults that is typically seen with the

dlPFC; this suggests differences in sensitivity of each region to the effects of the aging process (12).

Although there is rapidly accumulating understanding of the function of both the dlPFC and mPFC, very little is known about the relative contribution of each of these two structures in farsighted decision-making, especially in the context of financial judgement and eating behaviour in older individuals. This will be the first study to our knowledge, that will be use intermittent theta burst stimulation (iTBS), a variant of excitatory TMS, to understand the causal role of the dlPFC and mPFC in making far-sighted choices in an aging population.

1.7 Study Purpose and Rationale

The purpose of the current study is to examine the role of two PFC sub-regions—the dlPFC and dmPFC—in farsighted choices in the context of financial decision-making and food consumption among older adults. The two structures were chosen because of their differential roles in far-sighted decision-making (inhibition vs. evaluative processing), along with their differences in sensitivity to the effects of aging (12). Using intermittent theta burst (iTBS), a variant of rTMS, we aim to produce excitatory effects on these two sub-regions, through a process similar to long-term potentiation (LTP) and long-term depression (LTD) of synaptic connections (81,82). LTP and LTD are one of several phenomena underlying changes in neuronal synaptic plasticity, which cause long-lasting increases (LTP) or decreases (LTD) in synaptic transmission between two neurons occur following a long patterned stimulus (83). Using a between subjects' design, participants will be randomized into one of the three groups: 1) iTBS targeting the left dlPFC 2) iTBS targeting the bilateral mPFC, 3) sham stimulation. This was followed by two tasks: 1) a variant of delayed discounting paradigm as described in Koffarnus & Bickel (53), in which participants are shown a series of choices between monetary outcomes of varying magnitude and temporal dispersion and 2) a flanker task, as a measure behavioural inhibition. To validate the excitatory neuromodulation effects of TMS in our cortical regions of interest, functional near infrared spectroscopy (fNIRS) was used detect changes in blood oxygenation during both cognitive task performances (84,85). Participants will also complete a series of questionnaires on demographic background and personality traits. The purpose of collecting this information is to

control for any potential variables that might mitigate or augment decision-making choices in both financial and food consumption paradigms. The session ended with the completion of a taste test, in which participants were presented with array of calorie-dense snacks, where the researcher surreptitiously quantified the amount of food consumed.

The rationale for this study are as follows:

a) This study will use iTBS on the left dlPFC to validate previous excitatory effects on food consumption outcomes and intertemporal decision-making. Previous studies have reported excitatory brain stimulation effects on food consumption and delay discounting paradigms, particularly when targeting the left dlPFC (9,32,76,86). However, very little research has been conducted using iTBS on dlPFC under these domains, mainly in apart because TBS protocols have been relatively recently developed (25). The reason for using iTBS over the conventional rTMS is because up-regulation of cortical excitability can be achieved in a fraction of the time usually required by conventional rTMS; stimulation times can be reduced to as little as 3 minutes (i.e. this is < 10% of the time required by conventional high frequency rTMS protocols) (25,81).

b) There has been very little research conducted on examining the causal role of the mPFC in both food and finance domains under TMS paradigms. This will be the first study to date that will use iTBS on mPFC to understand its role on the consumption of appetitive snack foods among healthy subjects. With respect to delay discounting, one study to date has shown excitatory rTMS targeting mPFC to decreases discounting (80). Hence, this study would look to expand on these findings to provide further insight on the role of the mPFC on inter-temporal decision-making.

c) To examine whether iTBS faciliatory effects on delay discounting and consumption of high caloric foods are moderated by age and gender category. The beneficial effects of non-invasive brain stimulation on cognitive performance among healthy younger adults may be limited in part due to a relatively better baseline performance (i.e. ceiling effects). As such, it is possible that the effects of the stimulation on cognitive functioning might be more prominent in older adults because physiological aging has shown structural and functional changes related to neural plasticity. A previous meta-analysis reported a significant positive effect (effect size of Cohen's *d*

= 0.42) of excitatory brain stimulation methods (i.e. rTMS and tDCS) on predicting better cognitive task performance among healthy older adults (87). This will be the first non-invasive brain stimulation study to compare age-related stimulation effects on delay discounting and consumption of appetitive snack foods. In addition, this study will look to add further depth into understanding age-related differences in discounting behaviour, as well as to compare consumptive behaviour towards high caloric snack foods.

In relation to gender, this study will examine whether stimulation effects on delay discounting and consumption of appetitive snack foods are moderated by gender. There is some evidence to suggest that males consume significantly more calories than females in standard laboratory conditions and natural eating environments (88,89). This variation in consumption by gender could be driven by 1) differences in energetic demands, as males have a greater demand for caloric intake due to a larger body size, and 2) greater social pressures on females to maintain their body weight and shape, which consequently leads to lower consumption (88).

d) The would be first study to use fNIRS to validate the effects of TMS activity during inter-temporal and inhibition tasks. fNIRS is an emerging optical neuroimaging technique that offers a relatively non-invasive, safe, portable and cost-effective method of monitoring brain activity in the prefrontal cortex (84,85). More specifically, fNIRS monitors brain activity using light at different wavelengths in the near-infrared spectrum, to measure activity-dependent regional changes in concentration of oxyhemoglobin (HbO) and deoxyhemoglobin (HbR) (85). Oxygen availability is crucial for intact cognitive processes, as studies have shown that a lack of oxygen leads to a lower cognitive performance (85). An increase in neuronal activity due iTBS stimulation, is expected to result with an increase in oxygenation metabolism, to satisfy the energetic demands of the neuronal tissue when required (i.e. during a cognitive task) (85). Hence, the stimulation will trigger local cerebral hemodynamics changes and will induce an intensified blood flow to the activated regions (85). Because the local supply of blood flow is greater than its consumption in activated regions, a higher concentration of oxyHb and a lower concentration of deoxyHb will be observed (85). Previous studies using fNIRS have shown changes in prefrontal cortical activity in both delay discounting and flanker task performances (90,91), however these effects have not been observed under a TMS paradigm.

e) Explore personality predictors associated with inhibitory control, delay discounting and high caloric food consumption outcomes. Previous studies have shown structural (92,93) and functional (94,95) brain differences to be correlated with the different personality traits. However, very little is known if certain personality traits are more prominent during certain executive tasks such as inhibitory control and inter-temporal decision-making. Previously, one prior study has shown lateral activation during inhibitory control is shown to be associated with high levels of extraversion, agreeableness and conscientiousness and lower neuroticism (96). In the realm of delay discounting, extraversion predicted higher discounting tendency, while emotional stability, conscientious and openness predicted lower discounting tendencies (97–99). This study would look expand on these findings and provide further insight on personality traits that are associated with each of these outcomes. This will be the first study to look at personality predictors on high caloric food consumption.

1.8 Study Hypotheses

The study hypotheses are as follows:

1) It is hypothesized that following both active iTBS stimulation conditions, the *k* value will be smaller than the *k* value for the sham condition. ***Rationale:*** Previous findings using excitatory TMS targeting the left dlPFC and mPFC have shown to decrease discounting rates. An increase in neural activity post-stimulation using iTBS, it is expected that participants will choose delayed over immediate choices more often than in the sham condition.

2) Active iTBS (either target) will result in higher oxygen saturation within the targeted PFC region during a task blocks requiring active inhibition (i.e., during incongruent blocks of the Flanker task) than during tasks that require a simple, quick response (i.e., during congruent blocks of the Flanker task).

3) Although it is hypothesized that both active iTBS conditions will result in better far-sighted decision-making, it is anticipated that the effects of the iTBS will be more pronounced in mPFC

than in the dlPFC for the delay discounting task, as evaluative processing is preceded before choice processing during intertemporal choices, and as such a smaller k value is expected to those that receive the stimulation to dmPFC (79).

4) Active iTBS will result in less calorie dense food consumption in the taste test compared to the sham condition. ***Rationale:*** Previous studies have shown that using excitatory stimulation of the dlPFC results in decreased cravings and consumption of calorie dense foods (26,27). For instance, inhibition of the left dlPFC using cTBS was shown to induce cravings and more likely to succumb to eating calorie dense foods, than participants that received the sham condition (30,100). By increasing activity in dlPFC, we anticipate seeing the opposite: i.e., that individuals in the active stimulation conditions will be less likely to indulge in eating than the sham condition. In addition, decrease in food consumption in both these PFC sub regions will be mediated through two different processes: the left dlPFC through self-control/inhibitory processing and the mPFC through evaluative processing (**Appendix A**)

5) It is hypothesized that active iTBS will result in improved Flanker scores (i.e., a weaker interference effect) for the left dlPFC compared to the active mPFC and sham stimulation conditions. The reason for this anticipated result is behavioral inhibition is disproportionately controlled by left dlPFC.

6) The stimulation effects will be more pronounced among older adults than younger adults for each outcome variable, where these effects will be more pronounced for the dlPFC than the mPFC due to their differences in sensitivity to effects of aging.

Chapter 2: Methods

2.1 Participants

A total sample of 43 participants were recruited for the study. To assess the differences in the effects of iTBS by age, the recruitment was stratified as follows: 22 younger adults and 21 middle-to-older adults. Younger adults were between 18-30 years of age and were all recruited from the University of Waterloo campus. The middle-to-older adults were between 40-75 years of age and were recruited from the following locations: University of Waterloo campus, the Waterloo Research in Aging Participant pool as well as from local community centres and YMCA's in the Kitchener-Waterloo area. All eligible participants were right-handed, neurologically healthy and naïve to TMS.

Screening was initially completed by telephone and again prior to participation in the laboratory in order to confirm any physical and neurological conditions that could preclude TMS. The following exclusions applied: a) diagnosed with neurological or psychiatric disorder (i.e. epilepsy or seizures, depressive or anxiety disorders); b) treated with any psychiatric medication; c) have a family history of epilepsy or hearing loss; d) history of trauma (i.e. concussion); e) experience chronic and repetitive headaches or migraines; f) have any metal and/or any implanted electronic or medical devices (i.e. electronic pacemaker, implanted medication pump); g) pregnant. In addition, participants were screened for any allergies/sensitivity food products containing dairy, eggs, gluten, nuts and monosodium glutamate, as the final portion of the study included the taste test component. Participants were also excluded from the study if they were diagnosed with either Type 1 or Type 2 diabetes.

Once all the procedures, risks and benefits were explained, electronic informed consent was obtained from all participants before the start of the study. In exchange for their participation, each participant received a $25 e-gift card to Tim Hortons or Walmart of their choice. The study had been reviewed and received ethics clearance by the University of Waterloo Research Ethics Committee prior to study commencement.

2.2 Sample Size Determination

The sample size was determined using an overall effect size from a prior meta-analysis examining the effects of excitatory stimulation on food consumption (32). Using a value of Hedges $g = 0.47$, with a statistical power of 0.80 and an alpha of 0.05, using a one-tailed hypothesis, the sample size was determined to be N=114, or 57 per group. Given that this sample size was unlikely to be feasible given the start time of the data collection, we re-calculated assuming a larger effect size using largest two estimates from the meta-analysis; this resulted in revised sample size of 36, or 18 per group. We also calculated a sample size determination using a "large statistical effect" by Cohen's conventions (d =.80); this calculation yielded a minimum estimate of 42, or 21 participants per group. This latter effect size we chose as our minimum sample size requirement, given that it was the smaller of the two revised sample size estimates.

2.3 Procedure

The study employed a single-blinded between-subject design in which participants were randomly assigned to one of the three conditions: iTBS to the dlPFC, iTBS to the dmPFC and sham iTBS (**Appendix B**). Participants were asked to refrain from eating or consuming any caffeinated beverages 3 hours prior to the study; adherence to these requirements was checked with the completion of the consent and screening forms. All computer tasks were presented using the Inquisit (Millisecond Software) on a 27-inch monitor. Prior to commencing the computer tasks, participants were asked to follow the instructions that were presented on the monitor and respond as quickly and accurately as possible while completing the assigned cognitive task. The ambient lighting and temperature conditions were stable across all participants.

The experimental session began with the participant reviewing the information letter (**Appendix C**), signing the consent form (**Appendix D**) and progressing through the TMS (**Appendix E**) and food allergies/sensitivity (**Appendix F**) screening process. This was shortly followed by the iTBS protocol (see below). Once the iTBS stimulation protocol had been administered, participants were asked to rest for 10 minutes to allow for the effects of TMS stimulation to set in. During this time, participants were asked to complete a series of questionnaires on the computer collecting information on the demographics, lifestyle behaviours and personality traits.

Next, 15 minutes post-stimulation, participants were asked to complete the two computerized cognitive tasks in the following order: three blocks of the delay discounting task, followed by four blocks of the flanker inhibition task. Between each block, there was a 15 second rest period. While performing these tasks, changes in blood oxygenation levels were measured using the fNIRS protocol (see below). Following the completion of these tasks, approximately 30 minutes post stimulation, the participants were given the opportunity to sample five different calorie dense snack foods under the guise of examining the relationship between brain function and taste perception. Change in the weight of the food from pre-to-post tasting was measured surreptitiously to quantify the amount of food that was consumed. The reason for the use of mild deception (with respect to the food measurement) is that food consumption is highly sensitive to social desirability, and typically when individuals know that their consumption will be quantified in a research setting, they limit their eating substantially, resulting in floor effects on the outcome variable. As per ethical guidelines, this mild deception was explained to the participant during the debriefing session. At this stage, the researcher disclosed the appropriate study condition assigned to the participant, where the participant was given the opportunity to withdraw their data from the study. No participants chose to withdraw their data following disclosure of condition and mild deception.

2.4 Repetitive Transcranial Magnetic Stimulation Protocol

rTMS is a non-invasive brain stimulation method that involves passing a pulsed electrical current through a figure 8 coil; this in turn produces a magnetic field that is perpendicular to the plane of the coil via the principle of electromagnetic induction (101,102). The pulsed magnetic field in turn produces an endogenous electrical current that is parallel to the original plane of the coil in the cortical region of interest, but in the opposite direction of the original current flow. The pulsed magnetic field thereby changes the excitability of underlying neuron populations by synchronizing rhythmic patterns of firing (in the case of excitatory stimulation) or by causing activation of inhibitory interneurons (in the case of inhibitory / suppressive stimulation). The pattern and the amplitude of the magnetic pulses determine whether the stimulation is excitatory or inhibitory. TBS is highly efficient variant of rTMS involving a sequence of patterns that mimics theta band frequencies found in throughout the brain and implicated in memory consolidation (81). Prior studies have found that the inhibitory variant and excitatory variant (iTBS) produce increases

and decreases in cortical excitability within the dlPFC in hypothesized directions (25). TBS protocols have increased in popularity due to it efficacy in achieving excitatory or suppressive effects, which can be as little as 3 minutes for the former and 15-30 seconds for the latter (81).

iTBS targeting the left dlPFC was administered using a 75mm figure 8 coil (MCF-B65), while the iTBS stimulation for the bilateral dmPFC was administered using a 75mm figure 8 coil (MCP-B80), both which were connected to a Mag Pro (model x100) stimulation unit. Sham stimulation was delivered with a placebo version of the MCF-B65 (MCF-P-B65), targeting the left dlPFC. The iTBS stimulation intensity to the left dlPFC was individually calibrated based on each participant's resting motor threshold (RMT), as per standard practise. The RMT is defined as the lowest stimulation intensity required to induce a motor evoked potential (MEP) in the right abductor pollicus brevis muscle (the right thumb muscle) of > 50 uV peak-to-peak amplitude, respectively, in 5/10 consecutive trials of stimulating the motor cortex. This allows the researcher to calibrate the stimulation intensity for each participant individually, which is important for avoiding any under- or over-stimulation effects.

In order to guide coil placement for stimulating both the motor cortex (for determining the RMT) and the cortical target regions of interest, an EEG cap with electrodes arranged in an international 10-20 system was fitted according to standard anatomical landmarks. The determination of the RMT using the motor cortex was defined at the C3 electrode position. The iTBS stimulation site for the left dlPFC was defined to be at F3 electrode position. The iTBS stimulation site for the bilateral dmPFC and was defined to be 2/3 of the distance from the naison to the vertex, as per prior research precedent (103).

Once the RMT was determined, the stimulation intensity for the left dlPFC stimulation was set at 80% of the RMT and consisted of triplet bursts applied in the theta burst pattern (three 50 Hz pulses repeated at a frequency of 5 Hz); this was applied for 2 seconds for every 10 second period (i.e. 2 seconds of theta burst, then 8 seconds of rest), for a duration of 190 seconds, totaling 600 pulses (81). Participants assigned to the sham iTBS condition received similar procedure as mentioned above, but the stimulation was received from placebo version of the same coil (MCP-

P-B65) targeting the vertex (Cz position) instead. The sham coil is identical in nature to the active coil, except that it contains a shield coating that blocks 80% of the stimulation intensity.

The iTBS stimulation to the dmPFC condition was was set at a low, fixed intensity of 30% of the maximal stimulator output in order to maintain tolerability for participants (103). Due to the fixed stimulation intensity, RMT was not necessary to assess for participants assigned to this condition.

2.5 Demographic and Lifestyle Behaviour Questionaries'

Participants in the study were asked to complete a brief series of questionnaires measuring: 1) demographic background which included: age, gender, height, weight, household income, ethnicity and relationship status and 2) lifestyle behaviours: exercise frequency/intensity, dietary characteristics, smoking frequency, and alcohol consumption (**Appendix G**).

2.6 Levenson's Self-Report Psychopathy Scale

The Levenson's Self-Report Psychopathy scale (LSRP) is a self-reported questionnaire developed by Levenson et al. (1995) that measures anti-social behaviour among the non-institutionalized general population, separated into two items: primary psychopathy and secondary psychopathy. Primary psychopathy is characterized as individuals who are manipulative, superficial, unemotional and lack guilt, remorse, empathy or anxiety (104). In contrast, secondary psychopathy is characterized as individuals with high levels of emotional dysregulation; individuals who show extreme impulsivity (i.e. risky decision-making), low frustration tolerance, quick-temperedness and lack ability to make long-term goals (due to a self-defeating behaviour) (104).

Participants in the study were asked to give their attitudes on these 26 items using a 4-point Likert scale from ("*Disagree strongly", "Disagree somewhat", "Agree somewhat", "Agree strongly"*), where the first 16 statements assessed primary psychopathy and the remaining 10 statements assessed secondary psychopathy (**Appendix H**). A higher score on each scale reflects a greater psychopathy measure.

2.7 Ten-Item Personality Inventory

The ten-item personality inventory (TIPI) developed by Gosling et al. (2003) is brief assessment of the Big-Five personality dimensions. The Big-Five personality dimensions are defined as the following: **extraversion**; ("being social, assertive talkative, active, *not* reserved or shy"), **agreeableness**; ("being trusting, generous, sympathetic, cooperative, *not* aggressive or cold"), **emotional stability**; ("being relaxed and self-confident, *not* anxious, moody, easily upset or stressed"), **conscientiousness**; ("being hardworking, dependable, responsible, self-disciplined *not* careless or impulsive") and **openness;** ("being imaginative, curious, reflective, creative, open-mined, deep *not* conventional") (105). Each personality dimension consisted of two items, where each item represented opposite poles for the respective personality dimension as defined above **(Appendix I)**. An item consisted of two descriptors, representing a specific pole of that dimension. Participants were asked to evaluate each set of descriptors on a 7-point scale ranging from 1 (*disagree strongly*) to 7 (*agree strongly*). Once the inventory was complete, each personality dimension was scaled in the following manner: since each personality dimension consisted of two items representing opposite poles of each other, one item was scored in the reverse manner. One item was scored on the scale provided, while the other was scored in reverse (i.e. 7 replaced with a 1, 6 with a 2, etc.). Once each item was scored, the average of the two scores is taken to make up the final score for each personality dimension. The following are the items listed by number (as seen on Appendix I) that are associated with each personality trait, where "R" denotes items that have to be reverse scored once the inventory is complete: *Extraversion: 1, 6R; Agreeableness: 2R, 7; Conscientiousness; 3, 8R; Emotional Stability; 4R, 9; Openness: 5, 10R.*

2.8 Functional Near Infrared Spectroscopy Protocol

Functional Near Infrared Spectroscopy (fNIRS) is a non-invasive, optical neuroimaging technique that uses near-infrared (NIR) light sources and detectors to quantify changes in blood oxygenation levels within cortical brain tissues following neuronal activation (106,107). It is known that NIR light is able to penetrate through the human scalp, where high attenuation of NIR light in human tissue is most dominantly absorbed by hemoglobin; an oxygen transport red blood cell protein (106,107). There are two forms of hemoglobin: oxygenated (oxy-hemoglobin, HbO) and deoxygenated (deoxy-hemoglobin, HbR), where both absorb NIR light at different wavelengths (106,107). HbO absorption is at > 800 nm, whereas HbR absorption is at < 800 nm

(106,107). Hence, fNIRS is able to take advantage of chromophoric features of hemoglobin to detect changes in brain activation.

During cognitive-demanding tasks, enhanced neural activation results an increase in arteriolar vasodilation and a subsequent surge in regional cerebral blood flow to facilitate metabolic needs, leading to changes in hemoglobin concentrations (106). This change is known as a hemodynamic response, which produces a relative increase in oxygenated hemoglobin and decrease deoxygenated hemoglobin in order to sustain neuronal activity (106). As such, by utilizing two different wavelengths of NIR light corresponding to the oxy- and deoxy- hemoglobin, light detectors are able to collect the backscattered light and measure changes light attenuation to provide an estimation of oxygenation in the cortex (106). Because NIR light has a scattering effect on the human scalp (due to different layers of the biological tissue), a method known as differential spectroscopy (also known as modified Beer-Lambert law) is applied to derive to changes in attenuation (by removing light attenuation due to scattering effects, melanin and water concentrations), that are solely dependent on HbO and HbR levels (106).

For this study, a continuous wave fNIR device 203C unit was used. This device consisted of a headband with a sensor pad, which was embedded with 4 LED light sources and 10 light detectors, joined to create 16 channels over the bilateral PFC region. In terms of identifying channels to general cortical areas of the PFC, channels 1-4 indicate the left lateral PFC, channels 5-12 to the bilateral medial PFC and 13-16 to the right lateral PFC (108) . Participants were fitted with this headband, where the sensor pad was gently placed on the participant's forehead and secured in place with cloth straps. The participant was asked to rest quietly, keep their eyes fixed at the computer screen and refrain from moving their head as much as possible. Once the head band was secure, the channels for the fNIRS system were monitored to make sure there was limited amount of ambient light. The light intensity in the 730 nm (for deoxy-hemoglobin) and 850 nm (for oxy-hemoglobin) wavelengths were recorded using the COBI Studio software.

The fNIRS headband was worn for the duration of the delay discounting and Flanker task, where the purpose of the fNIRS protocol in this study was to validate iTBS effects via documenting functional activity changes in the target regions, vis-à-vis blood oxygen saturation.

2.9 Delay Discounting Task

Participants were asked to complete a variant of the delay discounting paradigm described by Koffarnus and Bickel (2014). The task is an adjusting delay discounting task, which uses the concept of ED50 (Effective Delay 50%), to determine a delay that is effective in discounting the value of the delayed reinforcer by 50% (53). Participants were presented with three blocks, varying in magnitude by monetary value for the delayed option (Block 1: $10, Block 2: $1000, Block 3: $1,000,000). Each block consisted of five trials, where participants had to choose between two options: a fixed larger commodity for which the delay was adjusted from trial to trial verses a fixed smaller commodity that was immediately available. The magnitude of immediately available option for each block was set at half of the delayed option (Block 1: $5, Block 2: $500, Block 3: $500,000). Hence, the blocks were ordered and completed in the following manner: 1) $5 vs. $10, 2) $500 vs. $1000 and 3) $500,000 vs. $1,000,000.

The first-choice trial for each block was always set with the larger commodity delayed at 3 weeks. For subsequent trials, the delay for the larger option were adjusted depending on the participant's previous choice; delay was adjusted up if the delayed choice was chosen or down if the immediate choice was chosen on the previous trial. For the purposes of explanation, choice indices, delay series and the discounting parameters have been illustrated in **Table 1** as published in Koffarnus and Bickel (2014). It shows the first-choice trial delay being at 3 weeks (index 16), which then adjusts up or down by 8 delays (index 8 or 24) for the next choice based on the participant's previous choice. This pattern continues for next remaining three trials, with the delay index adjusting by an amount half that of the previous adjustment. Delays were conveniently chosen as whole integers of time durations that would result in a series of ED50 values that are evenly distributed as possible on a logarithmic scale (53). The reason for this consideration is because k values (inverse of ED50 values) are normally distributed among populations when logarithmically transformed (53).

ED50 and k values are determined at the end of last trial (choice no. 5). A smaller k value (higher ED50 value) is associated with a lack of discounting, thereby having a preference for delayed rewards. A higher k value (lower ED50 value) is indicative of a strong discounting rate, thereby having a preference for immediate rewards. The task was be delivered using Inquist

desktop computer software and the responses given via the clicking the option on the screen with a computer mouse. A total of 15 trials were presented to the participant, where between each block (5 trials), there was a 15 second rest period.

Table 1 Delay Series and Parameters of Choice Trials by Index for the 5-Trial Adjusting Delay Discounting Task (Adopted from Koffarnus & Bickel, 2014).

Index	***Delay***	***Choice no.***	***ED50 (days) if the last choice is:***		***k if the last choice is:***	
			Immediate	***Delayed***	***Immediate***	***Delayed***
1	*1 hour*	*5*	*0.04167*	*0.05893*	*24.0*	*17.0*
2	*2 hours*	*4*				
3	*3 hours*	*5*	*0.1021*	*0.1444*	*9.79*	*6.93*
4	*4 hours*	*3*				
5	*6 hours*	*5*	*0.2041*	*0.3062*	*4.90*	*3.27*
6	*9 hours*	*4*				
7	*12 hours*	*5*	*0.4330*	*0.7071*	*2.31*	*1.41*
8	*1 day*	*2*				
9	*1.5 days*	*5*	*1.225*	*1.732*	*0.816*	*0.577*
10	*2 days*	*4*				
11	*3 days*	*5*	*2.450*	*3.464*	*0.408*	*0.289*
12	*4 days*	*3*				
13	*1 week*	*5*	*5.292*	*8.573*	*0.189*	*0.117*
14	*1.5 weeks*	*4*				
15	*2 weeks*	*5*	*12.12*	*17.15*	*0.0825*	*0.0583*
16	*3 weeks*	*1*				
17	*1 month*	*5*	*25.28*	*43.05*	*0.0396*	*0.0232*
18	*2 months*	*4*				
19	*3 months*	*5*	*74.56*	*105.40*	*0.0134*	*0.000949*
20	*4 months*	*3*				
21	*6 months*	*5*	*149.1*	*210.9*	*0.00671*	*0.004741*
22	*8 months*	*4*				
23	*1 year*	*5*	*289.2*	*516.5*	*0.00335*	*0.00194*
24	*2 years*	*2*				
25	*3 years*	*5*	*894.7*	*1265*	*0.00112*	*0.000791*
26	*4 years*	*4*				
27	*5 years*	*5*	*1633*	*2310*	*0.000612*	*0.000433*
28	*8 years*	*3*				
29	*12 years*	*5*	*3579*	*5368*	*0.000279*	*0.000186*
30	*18 years*	*4*				
31	*25 years*	*5*	*7748*	*9131*	*0.000129*	*0.000110*

2.10 Flanker Task

Participants were asked to complete a modified version of the Eriksen Flanker task, which was used to measure behavioral inhibition. In this task, participants were presented with a stimulus consisting of a set of seven letters and were asked to make directional responses to the letter in the centre (the target stimuli) in a series of flanked letters (non-target stimuli), by pressing the corresponding keyboard key that is to assigned target stimuli. 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 alternative key. Participants were presented with two conditions: 1) congruent noise condition, in which the target letter were flanked by the letter corresponding to the same keyboard key response (i.e. HHHKHHH or CCCSCCC). And 2) incongruent noise condition, in which the target letter was flanked by the letters assigned to the other keyboard key response (i.e. CCCHCCC or HHHSHHH).

Initially for each trial, the participant was asked to stare at a fixation cross in the middle of the screen, and then to press the space bar to have the stimulus appear. Participants were then required to determine the target letter in the centre of an array, ignoring the flanking noise letters and registering their response by pressing keyboard key. Participants were allowed to progress at their own pace but were only be given a maximum of 1 second to respond to any given stimulus. The task began with a practice block, which consisted of one mixed block (incongruent + congruent) of 60 trials. This will be followed by participants 4 blocks (2 blocks of each condition), which were completed in the following order: 50 trials of the congruent task, 75 trials of the incongruent task, 50 trials of the congruent task and 50 trials of the incongruent task, totaling 225 trials for the entire task.

The flanker interference score was be calculated by taking the difference in the latency of the correct trials in congruent noise condition from the incongruent noise condition. A higher score reflected a poorer performance on the task, indicating that the noise from the flanked letters in the incongruent condition resulted in a slower behavioral response than in the congruent condition.

2.11 Bogus Taste Test and Food Ratings Questionnaire

The taste test is commonly used in the eating literature and has been demonstrated to be a reliable metric and valid measure of consumption; for example, prior studies have shown it to be responsive to food palatability (109), level of hunger (109), and responsive to acute manipulations of executive function using TMS targeting the left dlPFC (29,30).

In the current version of the paradigm, participants were presented an array of five calorie-dense snack foods (3 types of Pringles potato chips and 2 types of Belgian chocolate balls). Participants were given 15 minutes for the task, which also included completing a 7-item self-reported food ratings questionnaire for each item presented (**Appendix J**). Prior to the task, participants given a verbal cue "you can eat as much as you would like while making your taste ratings", under the guise that the main purpose of the task was in understanding their flavour experience by giving their taste ratings for each snack food item. The experimental foods were weighted before and after the taste test, where the difference (amount of food consumed) was recorded (in grams).

For the questionnaire (**Appendix J**), the first reporting item had participants select from a list of 25 descriptive terms on the texture of the food that they had sampled. The remaining six items had each participant indicate their sensory experience (*appealing, salty*, *sweet, greasy*, *healthy*) and overall rating of the food on a scale of 1 to 10; (response scale: 1 = *"Not at all ___"* ; 5 = *"Moderately ___"* ; *10 = "Very __"* , where ____ indicates the sensory experience or overall rating *("good"*, *"neutral"* or *"very good"* respectively). In terms of evaluating each of the six dimensions, an average rating (the sum from all 5 foods) was taken as a final score for each sensory dimension and compared by stimulation condition.

2.12 Statistical Approach and Data Analysis

Descriptive statistics were computed to examine the distribution of each of the continuous outcome variables of interest: i) food consumption, ii) flanker interference scores and iii) averaged delay discounting *k* values (*k* values averaged across the three delay discounting tasks) by treatment condition. Boxplots were generated to examine the shape of the distribution (i.e.

skewness and kurtosis) and identify any outliers. All the outcome variables in the dataset were subject to winsorization; a robust statistical transformation that limits the effects of extreme outliers. This was done in order to: 1) help maintain the rank ordering of outlying data points, and 2) retain statistical power given the modest sample size. The data was subject to 90% winsorization (i.e., bounded at 5% and 95%). Acceptable skewness statistics for each continuous outcome variables was determined to be between -1.0 and 1.0. Four outliers were identified for the food consumption variable: two below the 5th percentile value (34.21) and two above the 95th percentile value (173.62), which were than replaced with an assigned percentile values (i.e., corresponding with the 5th or 95th percentile, respectively). In addition, granular analyses was conducted to compare differences in type of food consumed (salty vs. sweet). Both these outcome variables were also subject to winsorization to limit any extreme outliers and preserve statistical power prior to running the general linear models (GLM's).

The flanker interference scores were first assessed for overall accuracy, which was determined by taking the percentage of the total number of correct trials. Participants with an accuracy of less 50% had their Flanker score dropped from the study, to account for lack of understanding of the task or other response sets; one participant's flanker score was dropped from the study by this procedure. Next, four outliers were identified in flanker scores; two below the 5th percentile value (7.74) and two above the 95th percentile value (139.13), which were than replaced with their assigned percentile values.

The delay discounting variable (*k*) was averaged across the three trials, to obtain an average discounting rate for each participant. Since the variable displayed significant skewness, the scores were then subject to a Log10 transformation, which improved the distributional properties. Four outliers were identified in the transformed distribution; two below the 5th percentile value (-3.39) and two above the 95th percentile value (-1.03), which were than replaced with their assigned percentile values.

In the primary statistical analysis, univariate general linear models were employed to examine the effects of the stimulation condition (active dlPFC stimulation vs. active mPFC stimulation vs. sham stimulation) on the candidate outcome variables (i.e., food consumption,

flanker performance, delay discounting). Age category was also considered as an interaction term (i.e., moderator), in order to examine the extent to which any treatment effects might differ by age group (younger adults vs. older adults). This was followed by secondary analysis examining the effects of stimulation condition and gender (females vs. males) using a two-way ANOVA for each of the candidate outcome variables, in order to examine the extent to which the experimental effects might differ by gender category. Planned comparisons were conducted using independent t-tests. Next, exploratory analysis using hierarchal linear multiple regression was performed to examine if personality dimensions predicted differences in mediator and outcome variables after controlling for treatment condition and age.

Finally, functional near infrared spectroscopy (fNIRS) data from the cognitive tasks were analyzed for differences in oxy hemoglobin concentrations between stimulation conditions for each channel, where heat maps were designed using corresponding *p*-values. Each channel was subject to winsorization prior to running the GLM's.

Chapter 3: Results

3.1 Preliminary Analysis

Demographic Variables

No significant differences were evident among the three treatment conditions with respect to age **($F(2,40) = 0.043$, $p = 0.953$)**, gender **($F(2,40)$ 0.080, $p = 0.924$)**, BMI **($F(2,40) = 1.601$, $p = 0.214$)** and time of last meal ***(*$F(2,40) = 1.724$, $p = 0.191$)**; Table 2.

Taste Rating Dimensions

Taste ratings did not differ among the three groups with respect to overall appeal **($F(2,40) = 0.671$, $p = 0.517$)**, saltiness **($F(2,40) = 0.159$, $p = 0.854$)**, sweetness **($F(2,40) = 0.651$, $p = 0.546$),** greasiness **($F(2,40) = 1.811$, $p = 0.177$)**, healthiness **($F(2,40) = 0.460$, $p = 0.634$)** or globally palatability **($F(2,40) = 0.566$, $p = 0.572$)**. Likewise, there were no interaction effects between stimulation group and age category or gender (all p's >.10). This suggests that iTBS applied to the dlPFC or dmPFC had a negligible impact on the sensory aspects of the flavour experience overall, and for each age and gender category.

Table 2
Mean (*SD*) for demographic variables by treatment condition

	dlPFC condition (n = 16)	***mPFC condition (n = 13)***	***sham condition (n= 14)***	***Overall (n = 43)***
Age (in years)	44.87 (25.69)	42.38 (24.26)	44.86 (26.43)	44.12 (24.93)
Gender	11 Female 5 Male	8 Female* 5 Male	9 Female 5 Male	28 Female 15 Male
Age Category	8 Young Adults 8 Older Adults	7 Young Adults 6 Older Adults	7 Young Adults 7 Older Adults	22 Young Adults 21 Older Adults
BMI	26.08 (4.27)	25.82 (3.53)	23.89 (2.63)	25.29 (3.63)
Last Meal (in hours)	8.55 (4.65)	7.50 (4.52)	5.71 (3.20)	7.31 (4.26)

***One participant in the mPFC condition was assigned from Other to a randomly assigned gender to female to help minimize cell drop counts due to the small sample size.**

3.2 Primary Data Analysis: Stimulation x Age Category

The primary analysis involved examining main effects of stimulation group (active dlPFC vs. active mPFC vs. sham stimulation) on each outcome, as well as the interaction between stimulation and age category on each of the same variables.

3.2.1 Food Consumption

With respect to food consumption, the two-way (stimulation x age category) ANOVA revealed no significant main effect of stimulation **($F(2,37) = 0.655$, $p = 0.526$)** or age category **($F(1,37) = 3.068$, $p = 0.088$)**. The interaction between stimulation condition and age category was also not significant **($F(2,37) = 1.231$, $p = 0.304$)**.

3.2.2 Flanker Interference Scores

With respect to flanker interference scores, the two-way (stimulation x age category) ANOVA revealed no main effect of stimulation **($F(2,36) = 0.706$, $p = 0.500$)** and no significant main effect of age category **($F(1,36) = 0.278$, $p = 0.601$)**. The interaction between stimulation condition and age category was also not significant **($F(2,36) = 1.263$, $p = 0.295$)**.

3.2.3 Log Transformed Average Delay Discounting (k values)

With respect to log transformed delay discounting *(k)* values, the two-way (stimulation x age category) ANOVA revealed no main effect of stimulation **($F(2,37) = 0.043$, $p = 0.958$)** and no significant main effect of age category **($F(1,37) = 2.684$, $p = 0.110$)**. The interaction between stimulation condition and age category was also not significant **($F(2,37) = 0.192$, $p = 0.826$)**.

3.3 Secondary Data Analysis: Stimulation x Gender

3.3.1 Food Consumption

With respect food consumption, a two-way (stimulation x gender) ANOVA was conducted to examine the effect of treatment condition and gender on food consumption. The analysis revealed no significant main effect of stimulation **($F(2,37) = 1.191$, $p = 0.315$)**, but a significant main effect of gender **$F(1,37) = 38.007$, $p < .001$)** on food consumption. The pattern of means suggests that across study conditions males **($M = 119.174$, $SE = 8.951$)** consumed nearly twice as much food as females **($M = 67.261$, $SE = 4.265$)**. In addition, a statistically significant interaction was found between gender and stimulation group on food consumption **($p = 0.040$, $F(2,37) = 3.110$)**, suggesting that the effect of stimulation on food consumption was significantly different for males and females**.** Variable means for all stimulation groups by gender are depicted in Figure 1.

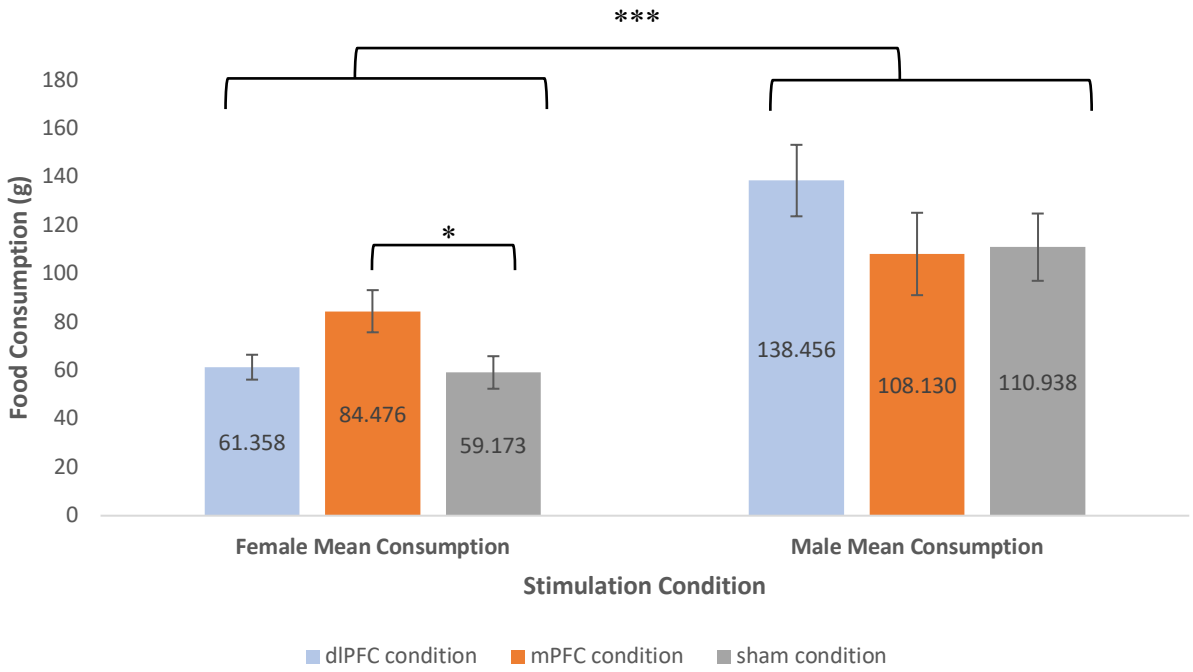

Figure 1: Mean (+/-*SE*) for food consumption (g) by gender for each treatment condition; i) Females: a) dlPFC condition ($M = 61.358$, $SE = 5.143$), b) mPFC condition ($M = 84.476$, $SE = 8.709$) and c) sham condition ($M = 59.173$, $SE = 6.720$); ii) Males: a) dlPFC condition ($M = 138.456$, $SE = 14.766$), b) mPFC condition ($M = 108.130$, $SE = 17.021$) and c) sham condition ($M = 110.938$, $SE = 13.898$). *: $p < .05$. ***: $p < .001$.

Planned comparisons indicated that compared to the sham condition (*M* = 59.173, *SE* = 6.720), females in the mPFC condition (*M* = 84.476, *SE* = 8.709) consumed significantly more food **(*t* (1,15) = 2.329, *p* = 0.034)**. In contrast, compared to the sham condition **(*M* = 110.130, *SE* = 13.898)**, males in the mPFC condition **(*M* = 108.130, *SE* = 13.898)** did not significantly consume more food **(*t* (1,8) = -.128, *p* = 0.901)**.

There were no significant differences in food consumption between those in dlPFC condition and sham condition for both males **(*t* (1,8) = 1.357, *p* = 0.212)** and females **(*t* (1,18) = .263, *p* = 0.796)**.

3.3.2 Flanker Interference Scores

With respect Flanker interference scores, a two-way (stimulation x gender) ANOVA was conducted to examine the effect of treatment condition and gender on Flanker interference scores. The analysis revealed no significant main effect of stimulation **(*F*(2,36) = 0.706, *p* = 0.500)** or gender (***F*(1,36) = 2.197 , *p* = 0.147)** on Flanker performance. The interaction between stimulation and gender was also not significant **(*F*(2,36) = 0.119, *p* = 0.888)**. Variable means for all study conditions by gender are depicted in Figure 2.

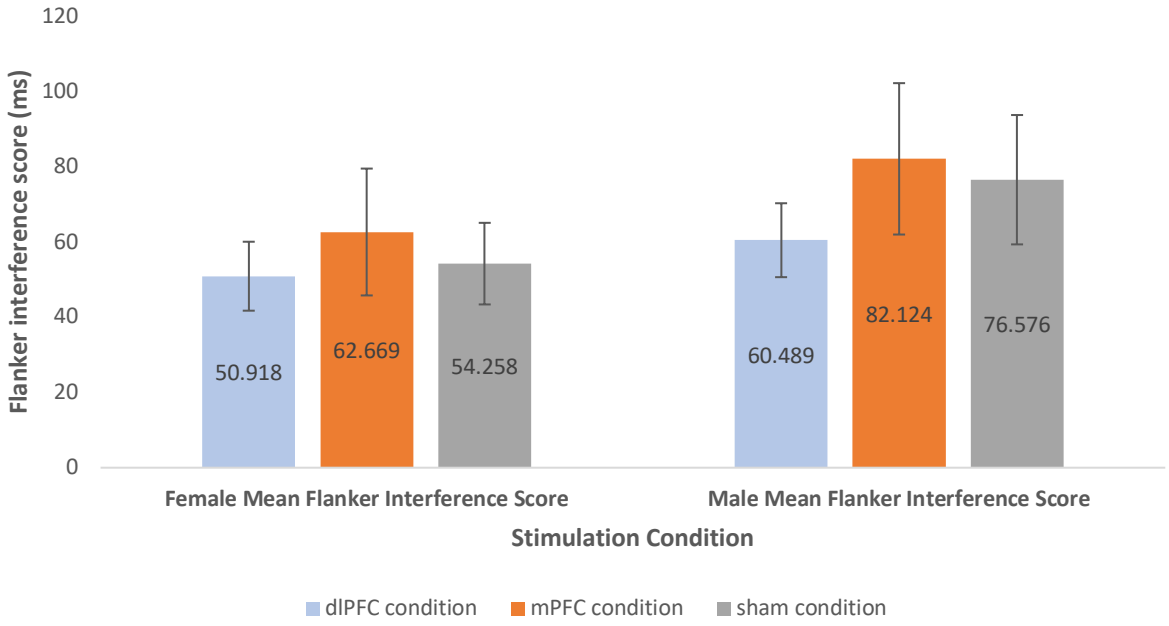

Figure 2: Mean (+/-*SE*) for Flanker interference score (ms) by gender for each treatment condition; i) Females: a) dlPFC condition (*M* = 50.972, *SE* = 9.168), b) mPFC condition (*M* = 62.669, *SE* = 16.865) and c) sham condition (*M* = 54.258, *SE* = 10.849); ii) Males: a) dlPFC condition (*M* = 60.489, *SE* = 9.828), b) mPFC condition (*M* = 82.124, *SE* = 20.126) and c) sham condition (*M* = 76.576, *SE* = 17.199).

3.3.3 Log Transformed Average Delay Discounting (k values)

With respect to log transformed delay discounting *k* values, a two-way (stimulation x gender) ANOVA was conducted to examine the effect of treatment condition and gender on log transformed delay discounting *k* values. The analysis revealed no significant main effect of stimulation **($F(2,37) = 0.083, p = 0.921$)**, and gender **$F(1,37) = 0.90, p = 0.766$)** on log transformed delay discounting *k* values. The interaction term between stimulation condition and gender was not significant **($F(2,37) = 0.181, p = 0.835$)**. Variable means for all study conditions by gender have been graphed by taking the absolute value of the log transformed *k* values in Figure 3.

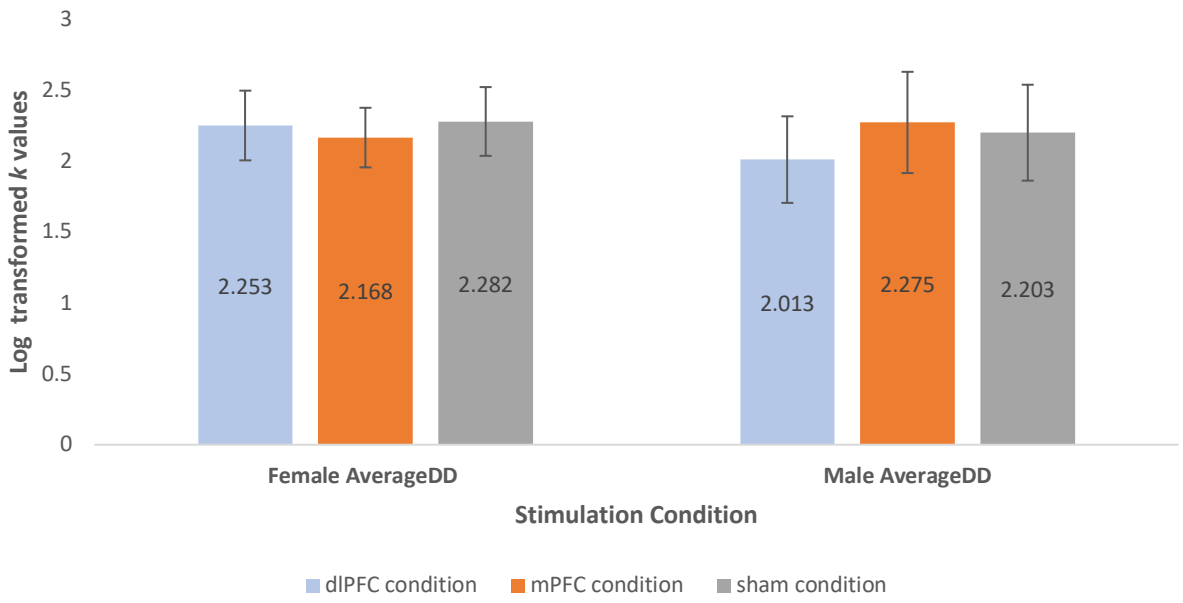

Figure 3: Mean (+/-*SE*) for Log10 transformed averaged delay discounting *k* values by gender for each treatment condition; i) Females: a) dlPFC condition (*M* = 2.253, *SE* = 0.246), b) mPFC condition (*M* = 2.168, *SE* = 0.210) and c) sham condition (*M* = -2.281, *SE* = 0.243); ii) Males: a) dlPFC condition (*M* = 2.013, *SE* = 0.306), b) mPFC condition (*M* = 2.275, *SE* = 0.357) and c) sham condition (*M* = -2.203, *SE* = 0.339).

3.4 Granular Food Choice Analyses

Additional analyses were conducted for each food type separately: potato chips (salty) and chocolate (sweet). Two-way ANOVA's were performed to determine if there were any main effects or interactions between our categorical variables of interest: stimulation, age category (young vs. old) and gender (females vs. males).

3.4.1 Total Potato Chips Consumption

With respect to potato chips consumption, a two-way (stimulation x age category) ANOVA revealed no significant main effect of stimulation **($F(2,37) = 1.850$, $p = 0.171$)** and age category **($F(1,37) = 3.733$, $p = 0.061$)**. The interaction between stimulation condition and age category was also not significant **($F(2,37) = 1.041$, $p = 0.363$)**.

A two-way (stimulation x gender) ANOVA revealed no significant main effect of stimulation **($F(2,37) = 1.265$, $p = 0.294$),** but a significant main effect for gender **($F(1,37) = 8.158$, $p = 0.007$)**. Males **($M = 49.023$, $SE = 5.368$)** consumed significantly more salty foods than females **($M = 31.615$, $SE = 3.104$)** across stimulation conditions. The interaction between stimulation condition and gender was not significant **($F(2,37) = .091$, $p = 0.913$)**. Variable means for all study conditions by gender are depicted in Figure 4.

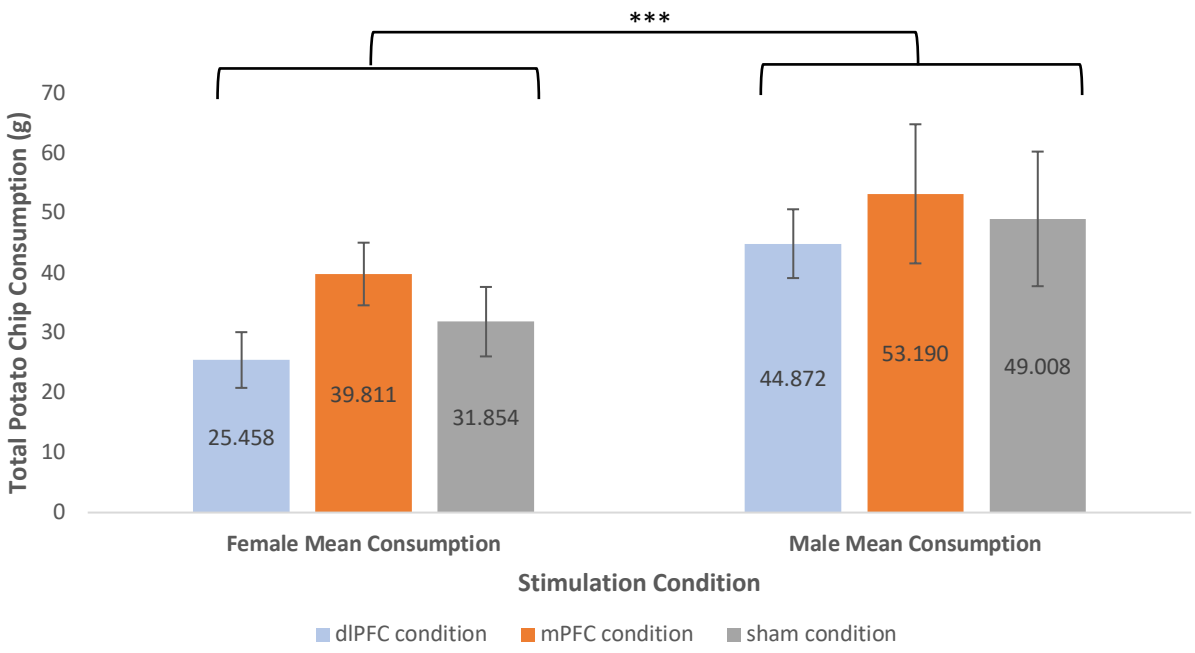

Figure 4: Mean (+/-*SE*) for total potato chips consumption (g) by gender for each treatment condition; i) Females: a) dlPFC condition ($M = 25.458$, $SE = 4.649$), b) mPFC condition ($M = 39.811$, $SE = 5.228$) and c) sham condition ($M = 31.854$, $SE = 5.797$); ii) Males: a) dlPFC condition ($M = 44.872$, $SE = 5.741$), b) mPFC condition ($M = 53.190$, $SE = 11.608$) and c) sham condition ($M = 49.008$, $SE = 11.232$). ** $p < .01$.

3.4.2 Total Chocolate Consumption

With respect to chocolate consumption, a two-way (stimulation x age category) ANOVA revealed no significant main effects of stimulation **($F(2,37) = 1.171$, $p = 0.321$)** or age category **($F(2,37) = 0.841$, $p = 0.365$)**. The interaction between stimulation condition and age category was also not significant **($F(2,37) = 2.544$, $p = 0.092$)**.

A two-way (stimulation x gender) ANOVA revealed a significant main effect of stimulation **($F(2,37) = 4.574$, $p = 0.017$)** and gender **($F(1,37) = 33.136$, $p = 0.010$),** such that those in the active stimulation conditions **(dlPFC : $M = 53.293$, $SE = 7.976$, mPFC: $M = 47.296$, SE = 5.169)** consumed more than those in the sham stimulation condition **($M = 39.602$, $SE = 5.952$)**. The results also suggest that males **($M = 68.249$, $SE = 7.342$)** overall consumed more sweet foods than females **($M = 35.651$, $SE = 2.717$)** regardless of treatment condition.

The interaction between stimulation condition and gender was also significant **($F(2,37) = 6.547$, $p = .004$),** suggesting that the effect of stimulation was significantly different for males and females**.** Variable means for all study conditions by gender are depicted in Figure 5.

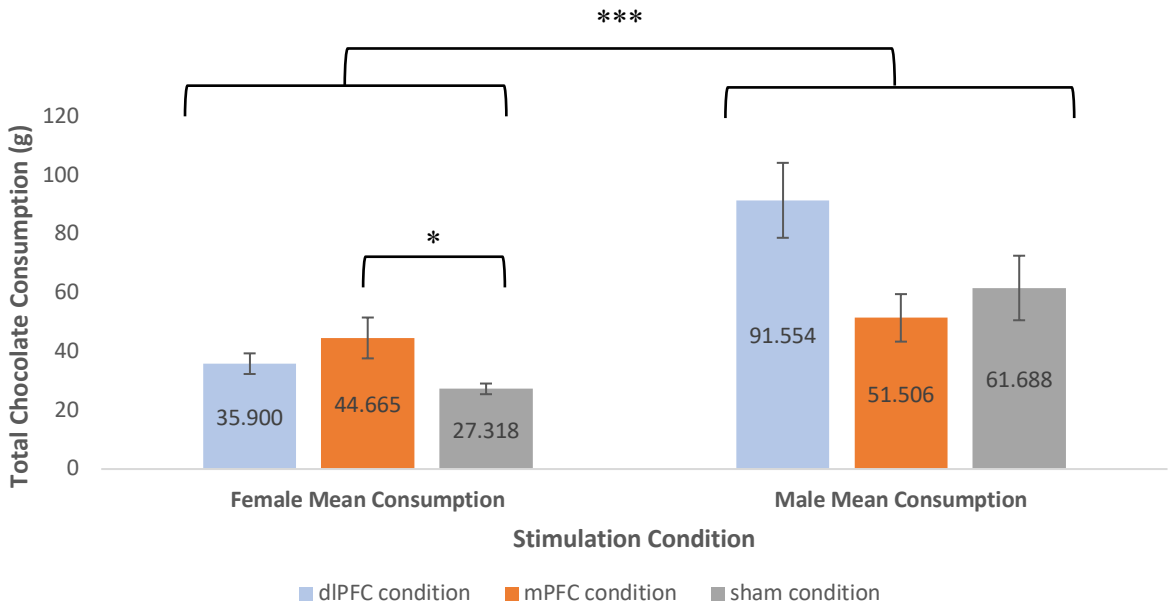

Figure 5: Mean (+/-*SE*) for total chocolate consumption (g) by gender for each treatment condition; i) Females: a) dlPFC condition ($M = 35.900$, $SE = 3.515$), b) mPFC condition ($M = 44.665$, $SE = 6.962$) and c) sham condition ($M = 27.332$, $SE = 1.815$); ii) Males: a) dlPFC condition ($M = 91.554$, $SE = 12.768$), b) mPFC condition ($M = 51.506$, $SE = 8.093$) and c) sham condition ($M = 61.688$, $SE = 10.995$). *: $p < .05$. ***: $p < .001$.

Planned comparisons indicated that compared to the sham condition **(*M* = 27.332, *SE* = 1.815)**, those females in the mPFC condition **(*M* = 44.665, *SE* = 6.962)** consumed significantly more sweet foods **(*t* (1,15) = 2.543, *p* = 0.023)**. There was also a marginal significant difference in the consumption of sweet foods between females in the dlPFC condition and sham condition **(*t* (1,18) = 2.024, *p* = 0.054)**.

Among males, it was found that those in the mPFC condition **(*M* = 51.506, *SE* = 8.093)** did not consume significantly more **(*t* (1,8) = -.746, *p* = 0.477)** food than those in the sham condition **(*M* = 61.688, *SE* = 10.995)**. In addition, there were no significant differences in the consumption of sweet foods between those in the dlPFC and sham condition for males **(*t* (1,8) = 1.773, *p* = 0.114).**

3.5 Exploratory Analyses

3.5.1 Correlational Analysis

In the first set of exploratory analyses, zero order correlations were computed to examine the relationships among personality measures (Big 5, Psychopathy dimensions), cognitive test scores and food consumption. Table 2 shows the Pearson correlation coefficiencies with corresponding *statistical significance* indicated by the asterisk.

Table 3: Zero Order Correlational Coefficiencies

Variable	*n*	*M*	*SD*	1	2	3	4	5	6	7	8	9	10
1. Food Consumption	43	85.370	36.808										
2. Flanker Interference Scores	42	61.515	35.125	-.149	-								
3. Log Transformed *k* values	43	-2.212	.697	.239	.186	-							
4. Extraversion	43	4.314	1.460	.054	.301	-.82	-						
5. Agreeableness	43	4.988	1.183	-.358*	.048	-.102	-.091	-					
6. Conscientiousness	43	5.593	1.098	-.138	.123	.139	-.037	.459**	-				
7. Emotional Stability	43	5.058	1.552	.029	-.046	-.275	.063	.545**	.287	-			
8. Openness	43	5.605	.948	-.121	.060	-.424**	.397**	.134	-.021	.322*	-		
9. Primary Psychopathy	43	26.349	6.869	.337	.130	.201	.054	-.442**	-.282	-.286	-.335*	-	
10. Secondary Psychopathy	43	19.698	4.427	.057	.121	.390**	.085	-.430**	-.364*	-.519*	-.259	.550**	-

*Correlation is significant at the 0.05 level (2-tailed)
**Correlation is significant at the 0.01 level (2-tailed)

3.5.2 Regression Analyses

In the first set of regression analyses, we examined the relationship between each personality dimension with each primary outcome, after controlling for both treatment condition and age. Following this, blocks of personality variables (Big 5 and Psychopathy dimensions) were entered simultaneously to examine the unique predictive power of each dimension while controlling for the others.

Food Consumption

Sole Predictors

Table 4:
Extraversion as a Predictor of Food Consumption After Controlling for Age and Treatment Condition

	Model 1			*Model 2*		
	ß	*t*	*p*	ß	*t*	*p*
Stimulation Group	-.084	-.556	.581	-.073	-.471	.640
Age (in years)	-.271	-1.787	.081	-.279	-1.813	.078
Extraversion				.074	.477	.636

Note. Model 1 = controlled for stimulation group and age. Model 2 = adjusted for control variables and sole personality predictor extraversion

Table 5:
Agreeableness as a Predictor of Food Consumption After Controlling for Age and Treatment Condition

	Model 1			*Model 2*		
	ß	*t*	*p*	ß	*t*	*p*
Stimulation Group	-.084	-.556	.581	-.018	-.118	.907
Age (in years)	-.271	-1.787	.081	-.146	-.866	.381
Agreeableness				-.292	-1.724	.093

Note. Model 1 = controlled for stimulation group and age. Model 2 = adjusted for control variables and sole personality predictor agreeableness

Table 6:
Conscientiousness as a Predictor of Food Consumption After Controlling for Age and Treatment Condition

	Model 1			*Model 2*		
	ß	*t*	*p*	ß	*t*	*p*
Stimulation Group	-.084	-.556	.581	-.077	-.499	.620
Age (in years)	-.271	-1.787	.081	-.257	-1.662	.105
Conscientiousness				-.093	-.602	.551

Note. Model 1 = controlled for stimulation group and age. Model 2 = adjusted for control variables and sole personality predictor conscientiousness

Table 7:
Emotional Stability as a Predictor of Food Consumption After Controlling for Age and Treatment Condition

	Model 1			*Model 2*		
	ß	*t*	*p*	ß	*t*	*p*
Stimulation Group	-.084	-.556	.581	-.085	-.553	.583
Age (in years)	-.271	-1.787	.081	-.295	-1.875	.068
Emotional Stability				.100	.638	.527

Note. Model 1 = controlled for stimulation group and age. Model 2 = adjusted for control variables and sole personality predictor emotional stability

Table 8:
Openness as a Predictor of Food Consumption After Controlling for Age and Treatment Condition

	Model 1			*Model 2*		
	ß	*t*	*p*	ß	*t*	*p*
Stimulation Group	-.084	-.556	.581	-.083	-.542	.591
Age (in years)	-.271	-1.787	.081	-.257	-1.622	.113
Openness				-.053	-.333	.741

Note. Model 1 = controlled for stimulation group and age. Model 2 = adjusted for control variables and sole personality predictor openness

Table 9:
Levenson's Primary Psychopathy as a Predictor of Food Consumption After Controlling for Age and Treatment Condition

	Model 1			*Model 2*		
	ß	*t*	*p*	ß	*t*	*p*
Stimulation Group	-.084	-.556	.581	-.128	-.841	.405
Age (in years)	-.271	-1.787	.081	-.037	-.175	.862
Primary Psychopathy				.328	1.514	.138

Note. Model 1 = controlled for stimulation group and age. Model 2 = adjusted for control variables and sole personality predictor primary psychopathy

Table 10:
Levenson's Secondary Psychopathy as a Predictor of Food Consumption After Controlling for Age and Treatment Condition

	Model 1			*Model 2*		
	ß	*t*	*p*	ß	*t*	*p*
Stimulation Group	-.084	-.556	.581	-.100	-.646	.522
Age (in years)	-.271	-1.787	.081	-.326	-1.862	.070
Secondary Psychopathy				-.113	-.642	.525

Note. Model 1 = controlled for stimulation group and age. Model 2 = adjusted for control variables and sole personality predictor secondary psychopathy.

Food Consumption

Blocked Analysis

Table 11:
All Big 5 Personality Inventory Traits as Predictors of Food Consumption After Controlling for Age and Treatment Condition

	Model 1			*Model 2*		
	ß	*t*	*p*	ß	*t*	*p*
Stimulation Group	-.084	-.556	.581	.043	.279	.782
Age (in years)	-.271	-1.787	.081	-.112	-.660	.514
Extraversion				.077	.468	.643
Agreeableness				-.494	-2.303	.027
Conscientiousness				-.010	-.057	.955
Emotional Stability				.385	2.045	.048
Openness				-.185	-1.057	.298

Note. Model 1 = controlled for stimulation group and age. Model 2 = adjusted for control variables and all big 5 personality traits (extraversion, agreeableness, conscientiousness, emotional stability and openness).

Table 12:
Levenson's Psychopathy Dimensions as Predictors of Food Consumption After Controlling for Age and Treatment Condition

	Model 1			*Model 2*		
	ß	*t*	*p*	ß	*t*	*p*
Stimulation Group	-.084	-.556	.581	-.178	-1.146	.259
Age (in years)	-.271	-1.787	.081	-.073	-.342	.734
Primary Psychopathy				.445	1.922	.062
Secondary Psychopathy				-.247	-1.340	.188

Note. Model 1 = controlled for stimulation group and age. Model 2 = adjusted for control variables, primary psychopathy and secondary psychopathy.

Exploratory analysis using hierarchical multiple regression modeling for each of the Big 5 personality dimensions on food consumption after controlling for age and treatment condition, revealed that agreeableness predicted food consumption most strongly **(Table 5)**. For every standard deviation increase in agreeableness, the amount of food consumed decreases by .292 standard deviations.

Other personality traits showed no significant effect on food consumption; extraversion/enthusiastic **(Table 4)** conscientiousness/dependable **(Table 6)**, emotional stability **(Table 7)** and openness/imaginative **(Table 8)**.

When using simultaneous entry **(Table 11)** to examine the unique power of each personality dimension while controlling for others, agreeableness (standardized beta coefficient: -.494, p = 0.027) and emotional stability (standardized beta coefficient: .385, p = 0.048) both showed strong unique effects on food consumption. The regression analysis suggests that every standard deviation increase in agreeableness, the amount of food consumed decreases by .494 standard deviations, while controlling for the other personality dimensions. Likewise, every standard deviation increases in emotional stability, the amount of food consumed increases by .385 standard deviations, while controlling for the other variables.

For the psychopathy dimensions as predictors of food consumption, primary psychopathy was found have a stronger effect **(Table 9)** on food consumption than secondary psychopathy **(Table 10)**.

Blocked analysis revealed a strong effect of primary psychopathy **(Table 12)** on food consumption. Specifically, a 1 standard deviation increase in primary psychopathy was associated with an increase in food consumption by .445 standard deviations. Interestingly, secondary psychopathy showed an opposite effect, where a 1 standard deviation increase in secondary psychopathy was associated with lower consumption of high caloric foods.

Flanker Interference Scores

Sole Predictors

Table 13:
Extraversion as a Predictor of Flanker Performance After Controlling for Age and Treatment Condition

	Model 1			*Model 2*		
	ß	*t*	*p*	ß	*t*	*p*
Stimulation Group	.106	.674	.504	.159	1.051	.300
Age (in years)	-.157	-.999	.324	-.189	-1.261	.215
Extraversion				.344	2.262	.029

Note. Model 1 = controlled for stimulation group and age. Model 2 = adjusted for control variables and sole personality predictor extraversion

Table 14:
Agreeableness as a Predictor of Flanker Performance After Controlling for Age and Treatment Condition

	Model 1			*Model 2*		
	ß	*t*	*p*	ß	*t*	*p*
Stimulation Group	.106	.674	.504	.077	.473	.639
Age (in years)	-.157	-.999	.324	-.213	-1.196	.239
Agreeableness				.125	.684	.498

Note. Model 1 = controlled for stimulation group and age. Model 2 = adjusted for control variables and sole personality predictor agreeableness

Table 15:
Conscientiousness as a Predictor of Flanker Performance After Controlling for Age and Treatment Condition

	Model 1			*Model 2*		
	ß	*t*	*p*	ß	*t*	*p*
Stimulation Group	.106	.674	.504	.094	.594	.556
Age (in years)	-.157	-.999	.324	-.182	-1.135	.263
Conscientiousness				.145	.907	.370

Note. Model 1 = controlled for stimulation group and age. Model 2 = adjusted for control variables and sole personality predictor conscientiousness

Table 16:
Emotional Stability as a Predictor of Flanker Performance After Controlling for Age and Treatment Condition

	Model 1			*Model 2*		
	ß	*t*	*p*	ß	*t*	*p*
Stimulation Group	.106	.674	.504	.106	.666	.510
Age (in years)	-.157	-.999	.324	-.155	-.944	.351
Emotional Stability				.008	-.048	.962

Note. Model 1 = controlled for stimulation group and age. Model 2 = adjusted for control variables and sole personality predictor emotional stability

Table 17:
Openness as a Predictor of Flanker Performance After Controlling for Age and Treatment Condition

	Model 1			*Model 2*		
	ß	*t*	*p*	ß	*t*	*p*
Stimulation Group	.106	.674	.504	.104	.656	.516
Age (in years)	-.157	-.999	.324	-.181	-1.110	.274
Openness				.101	.619	.540

Note. Model 1 = controlled for stimulation group and age. Model 2 = adjusted for control variables and sole personality predictor openness

Table 18:
Levenson's Primary Psychopathy as a Predictor of Flanker Performance After Controlling for Age and Treatment Condition

	Model 1			*Model 2*		
	ß	*t*	*p*	ß	*t*	*p*
Stimulation Group	.106	.674	.504	.106	.652	.518
Age (in years)	-.157	-.999	.324	-.156	-.663	.512
Primary Psychopathy				.001	.005	.996

Note. Model 1 = controlled for stimulation group and age. Model 2 = adjusted for control variables and primary psychopathy

Table 19:
Levenson's Secondary Psychopathy as a Predictor of Flanker Performance After Controlling for Age and Treatment Condition

	Model 1			*Model 2*		
	ß	*t*	*p*	ß	*t*	*p*
Stimulation Group	.106	.674	.504	.117	.729	.470
Age (in years)	-.157	-.999	.324	-.119	-.658	.514
Secondary Psychopathy				.081	.444	.660

Note. Model 1 = controlled for stimulation group and age. Model 2 = adjusted for control variables and secondary psychopathy.

Flanker Interference Scores

Blocked Analysis

Table 20:
All Big 5 Personality Inventory Traits as Predictors of Flanker Performance After Controlling for Age and Treatment Condition

	Model 1			*Model 2*		
	ß	*t*	*p*	ß	*t*	*p*
Stimulation Group	.106	.674	.504	.109	.668	.509
Age (in years)	-.157	-.999	.324	-.265	-1.490	.145
Extraversion				.373	2.181	.036
Agreeableness				.198	.880	.385
Conscientiousness				.120	-.057	.496
Emotional Stability				-.147	-.748	.460
Openness				-.001	-.008	.994

Note. Model 1 = controlled for stimulation group and age. Model 2 = adjusted for control variables and all big 5 personality traits (extraversion, agreeableness, conscientiousness, emotional stability and openness).

Table 21:
Levenson's Psychopathy Dimensions as Predictors of Flanker Performance After Controlling for Age and Treatment Condition

	Model 1			*Model 2*		
	ß	*t*	*p*	ß	*t*	*p*
Stimulation Group	.106	.674	.504	.126	.744	.462
Age (in years)	-.157	-.999	.324	-.148	-.618	.540
Primary Psychopathy				-.049	-.187	.853
Secondary Psychopathy				.096	.476	.637

Note. Model 1 = controlled for stimulation group and age. Model 2 = adjusted for control variables, primary psychopathy and secondary psychopathy.

Among the Big-5 personality traits, extraversion (**Table 13)** was a significant predictor of Flanker performance after controlling for age and treatment group. The results suggest that a 1 standard deviation increase in extraversion predicted an increase in flanker interference score by .373 standard deviations.

In addition, agreeableness **(Table 14)** and conscientiousness **(Table 15)** in our sole predictor and blocked regression analyses **(Table 20)** showed similar, but milder standardized effects to extraversion. The blocked analysis reveals that emotional stability has an opposite effect

on Flanker scores **(Table 20)**; these findings indicate that a 1 standard deviation increase in extraversion predicts a decrease in Flanker interference score by -.147 standard deviations.

Psychopathy dimensions **(Tables 18, 19, 21)**, also showed no significant effect on Flanker performance; primary psychopathy and secondary psychopathy.

Log Transformed Delay Discounting k values

Sole Predictors

Table 22:
Extraversion as a Predictor of Log Transformed Delay Discounting k values After Controlling for Age and Treatment Condition

	Model 1			*Model 2*		
	ß	*t*	*p*	ß	*t*	*p*
Stimulation Group	-.046	-.304	.762	-.055	-.355	.724
Age (in years)	-.286	-1.887	.066	-.279	-1.811	.078
Extraversion				-.059	-.377	.708

Note. Model 1 = controlled for stimulation group and age. Model 2 = adjusted for control variables and sole personality predictor extraversion

Table 23:
Agreeableness as a Predictor of Log Transformed Delay Discounting k values After Controlling for Age and Treatment Condition

	Model 1			*Model 2*		
	ß	*t*	*p*	ß	*t*	*p*
Stimulation Group	-.046	-.304	.762	-.055	-.348	.729
Age (in years)	-.286	-1.887	.066	-.303	-1.775	.084
Agreeableness				.040	.228	.821

Note. Model 1 = controlled for stimulation group and age. Model 2 = adjusted for control variables and sole personality predictor agreeableness

Table 24:
Conscientiousness as a Predictor of Log Transformed Delay Discounting k values After Controlling for Age and Treatment Condition

	Model 1			*Model 2*		
	ß	*t*	*p*	ß	*t*	*p*
Stimulation Group	-.046	-.304	.762	-.062	-.409	.684
Age (in years)	-.286	-1.887	.066	-.314	-2.068	.045
Conscientiousness				.191	1.252	.218

Note. Model 1 = controlled for stimulation group and age. Model 2 = adjusted for control variables and sole personality predictor conscientiousness

Table 25:
Emotional Stability as a Predictor of Log Transformed Delay Discounting k values After Controlling for Age and Treatment Condition

	Model 1			*Model 2*		
	ß	*t*	*p*	ß	*t*	*p*
Stimulation Group	-.046	-.304	.762	-.045	-.304	.762
Age (in years)	-.286	-1.887	.066	-.233	-1.513	.138
Emotional Stability				-.219	-1.419	.164

Note. Model 1 = controlled for stimulation group and age. Model 2 = adjusted for control variables and sole personality predictor emotional stability

Table 26:
Openness as a Predictor of Log Transformed Delay Discounting k values After Controlling for Age and Treatment Condition

	Model 1			*Model 2*		
	ß	*t*	*p*	ß	*t*	*p*
Stimulation Group	-.046	-.304	.762	-.038	-.267	.790
Age (in years)	-.286	-1.887	.066	-.189	-1.289	.205
Openness				-.374	-2.547	.015

Note. Model 1 = controlled for stimulation group and age. Model 2 = adjusted for control variables and sole personality predictor openness

Table 27:
Levenson's Primary Psychopathy as a Predictor of Log Transformed Delay Discounting k values After Controlling for Age and Treatment Condition

	Model 1			*Model 2*		
	ß	*t*	*p*	ß	*t*	*p*
Stimulation Group	-.046	-.304	.762	-.047	-.302	.765
Age (in years)	-.286	-1.887	.066	-.280	-1.271	.211
Primary Psychopathy				.008	.034	.973

Note. Model 1 = controlled for stimulation group and age. Model 2 = adjusted for control variables and sole personality predictor primary psychopathy

Table 28:
Levenson's Secondary Psychopathy as a Predictor of Log Transformed Delay Discounting k values After Controlling for Age and Treatment Condition

	Model 1			*Model 2*		
	ß	*t*	*p*	ß	*t*	*p*
Stimulation Group	-.046	-.304	.762	-.001	-.004	.997
Age (in years)	-.286	-1.887	.066	-.127	-.759	.452
Secondary Psychopathy				.328	1.940	.060

Note. Model 1 = controlled for stimulation group and age. Model 2 = adjusted for control variables and sole personality predictor secondary psychopathy

Log Transformed Delay Discounting k values

Blocked Analysis

Table 29:
All Big 5 Personality Inventory Traits as Predictors of Log Transformed Delay Discounting k values After Controlling for Age and Treatment Condition

	Model 1			*Model 2*		
	ß	*t*	*p*	ß	*t*	*p*
Stimulation Group	-.046	-.304	.762	-.060	-.399	.692
Age (in years)	-.286	-1.887	.066	-.226	-1.370	.179
Extraversion				.098	.613	.544
Agreeableness				.094	.448	.657
Conscientiousness				.195	1.194	.241
Emotional Stability				-.221	-1.206	.236
Openness				-.339	-1.983	.055

Note. Model 1 = controlled for stimulation group and age. Model 2 = adjusted for control variables and all big 5 personality traits (extraversion, agreeableness, conscientiousness, emotional stability and openness).

Table 30:
Levenson's Psychopathy Dimensions as Predictors of Log Transformed Delay Discounting k values After Controlling for Age and Treatment Condition

	Model 1			*Model 2*		
	ß	*t*	*p*	ß	*t*	*p*
Stimulation Group	-.046	-.304	.762	.030	.192	.849
Age (in years)	-.286	-1.887	.066	-.225	-1.055	.298
Primary Psychopathy				-.173	-.748	.459
Secondary Psychopathy				.380	2.069	.045

Note. Model 1 = controlled for stimulation group and age. Model 2 = adjusted for control variables, primary psychopathy and secondary psychopathy.

Hierarchal multiple regression models for each of the Big-5 personality predictors showed that openness **(Table 26)** and emotional stability **(Table 25)** are important personality dimensions for predicting delay discounting *k* values.

In addition, the model suggests for secondary psychopathy **(Table 28)**, that one standard deviation on secondary psychopathy measure predicts an increase in the delay discounting *k* value by .328 standard deviations.

Blocked analysis for the Big 5 personality **(Table 29)** and psychopathy **(Table 30)** dimensions revealed similar results, with openness, emotional stability and secondary psychopathy (impulsivity) as being important predictors for delay discounting, while controlling for the other variables in the model.

3.6 Functional Near Infrared Spectroscopy Analysis

3.6.1 Flanker Oxy-Hemoglobin Concentration

Change in oxy-hemoglobin concentration during the Flanker task for each fNIRS channel was calculated by subtracting the total congruent oxy-hemoglobin concentration from the total incongruent oxy-hemoglobin concentration:

$$\textit{Incongruent/Congruent Contrast Effect} =$$

$$(CHn\_INC1 + CHn\_INC2) - (CHn\_CON1 + CHn\_CON2)$$

where,

CHn_INC1 refers to the oxy-hemoglobin concentration for incongruent task #1 for channel *n*
CHn_INC2 refers to the oxy-hemoglobin concentration for incongruent task #2 for channel *n*
CHn_CON1 refers to the oxy-hemoglobin concentration for congruent task #1 for channel *n*
CHn_CON2 refers to the oxy-hemoglobin concentration for congruent task #2 for channel *n*

Next, each channel was subject to winsorization, which was followed by a one-way ANOVA to test for any hypothesized group differences (active iTBS vs. sham iTBS) on the contraste effect (incongruent – congruent). Differences across channels have been illustrated using a heat map, with corresponding *F*-values and *p*-values for each channel below in Figure 6.

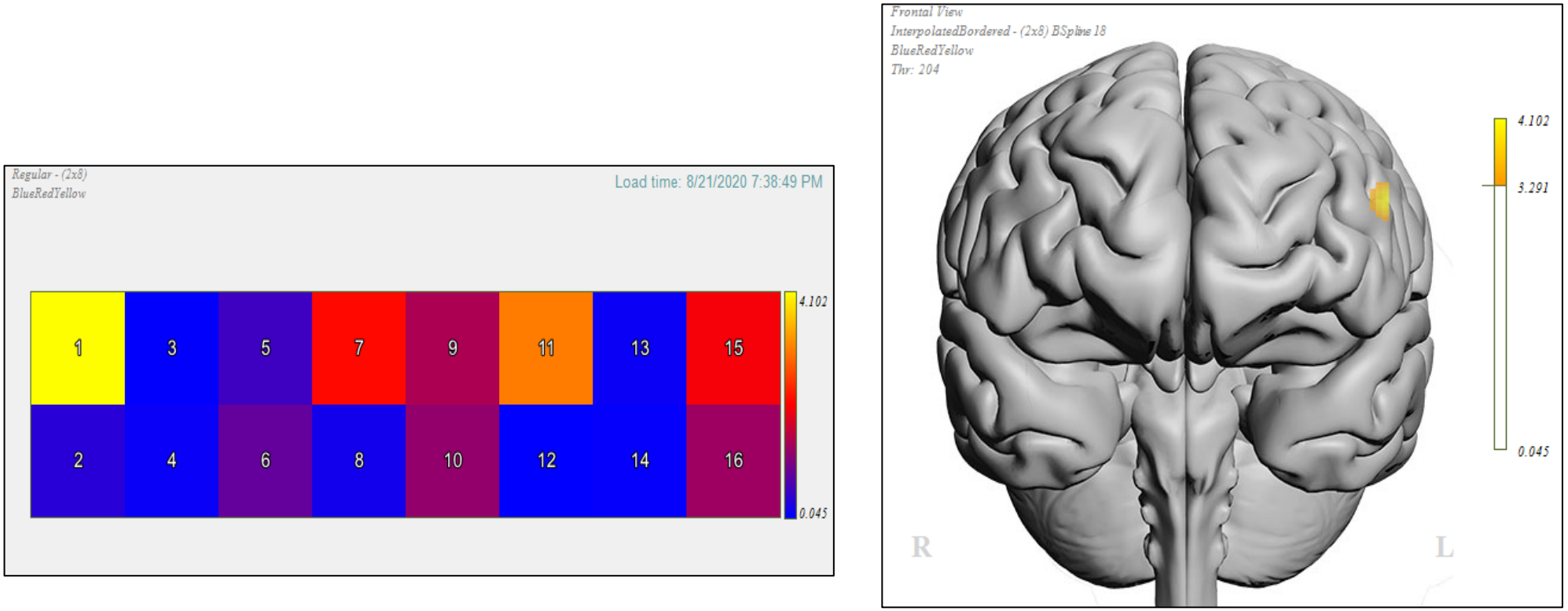

Figure 6: Heat map and 3D anatomical overlay of the active vs. sham iTBS contrast for the Flanker task. **Left**: Heat map of channels 1-16 illustrating the difference in oxy-hemoglobin concentration between active iTBS vs. sham iTBS during the Flanker task. Colour coding was represented by the strength of the *p*-values; warmer colours represent stronger active vs. sham contrast; darker shades of blue represent weak to no differences. **Right**: 3D anatomical overlay of the significant contrast difference between active vs. sham.

A significant incongruent/congruent contrast effect was observed for channel 1 **(*F*(2,29) = 4.102, *p* = .027)** comparing stimulation conditions (active iTBS vs. sham iTBS). Specifically, those in active conditions had significantly lower contrast effect **(dlPFC condition = *M* = -.646 , *SE* = .386, mPFC condition = M = .146 , *SE* = .735)** than those in the sham condition **(*M* = 2.21 , *SE* = 1.02)** when assessing the difference between the incongruent and congruent conditions. Variables means for all stimulation conditions have been depicted in Figure 7 below.

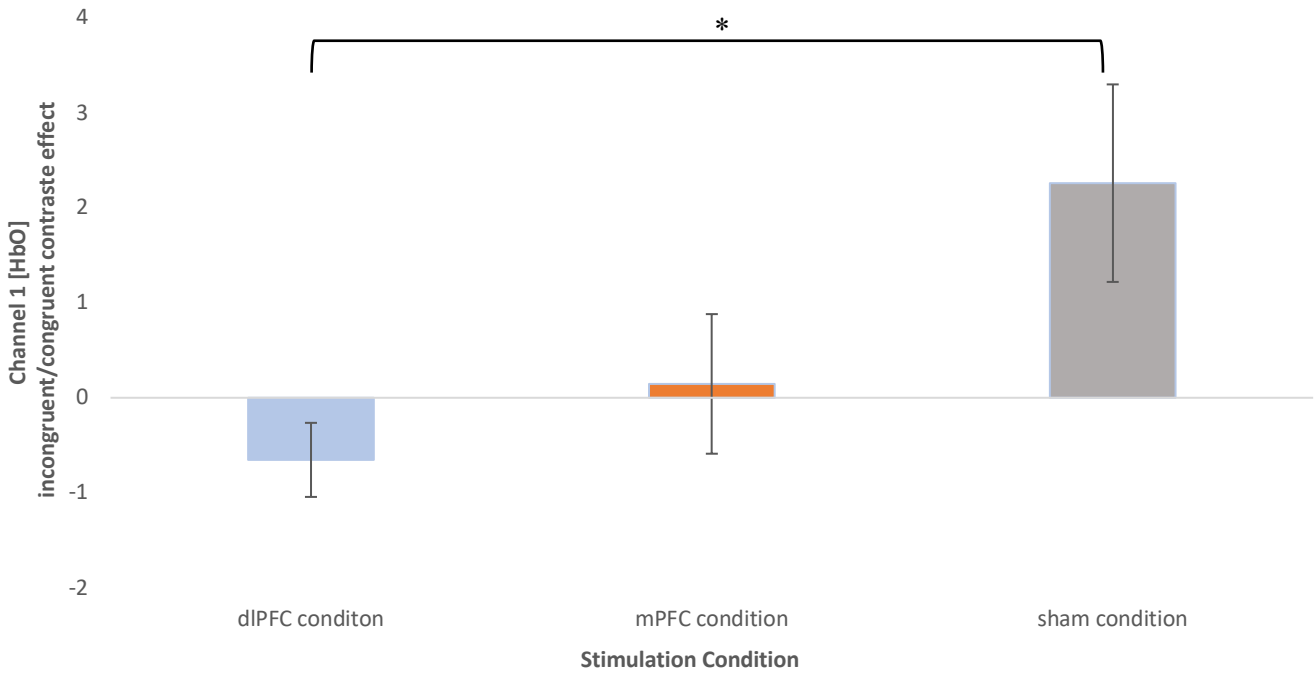

Figure 7: Means (+/-*SE*) for channel 1 oxy-hemoglobin concentration for each stimulation condition on the incongruent/congruent contrast effect; a) dlPFC condition (*M* = -.646 , *SE* = .386), b) mPFC condition (*M* = .146 , *SE* = .735) and c) sham condition (*M* = 2.21 , *SE* = 1.02). *: p < .05.

Planned comparisons for channel 1 indicated that compared to the sham condition, those in the dlPFC condition had significantly lower concentration of oxy hemoglobin **(*t* (1,21) = -2.706, *p* = 0.013)** on Flanker performance (incongruent – congruent). In contrast, compared to the sham condition, those in mPFC condition had no significant differences in oxy hemoglobin concentrations **(*t* (1,18) = 1.574, *p* = 0.133)** on incongruent/congruent contrast effect.

In addition, two-way ANOVA's (stimulation x age category and stimulation x gender) were generated for both this channel to determine if contrast effect was further moderated by age or gender, and to determine if any interaction effects exist.

Interaction Analyses

Channel 1

With respect to oxy-hemoglobin concentrations for the Flanker incongruent/congruent contrast effect, the two-way (stimulation x age category) ANOVA revealed a significant main effect of stimulation **(*F*(2,26) = 3.699, *p* = .039)**, but no significant main effect of age category **(*F*(1,26) = 3.052, *p* = .092)**. The interaction between stimulation condition and age category was not significant **(*F*(2,26) = .749, *p* = .483)**.

With respect to oxy-hemoglobin concentrations for the Flanker incongruent/congruent contrast effect, the two-way (stimulation x gender) ANOVA revealed a marginal effect of stimulation **(*F*(2,26) = 3.047, *p* = .065)**, but no significant main effect of gender **(*F*(1,26) = .544, *p* = .467)**. The interaction between stimulation condition and gender was significant **(*F*(2,26) = 6.674, *p* = 0.005)**; the pattern of means suggests differences in the effects of the stimulation on the incongruent/congruent contrast between males and females for channel 1. Variable means for all stimulation conditions by gender for channel 1 have been depicted in Figure 8.

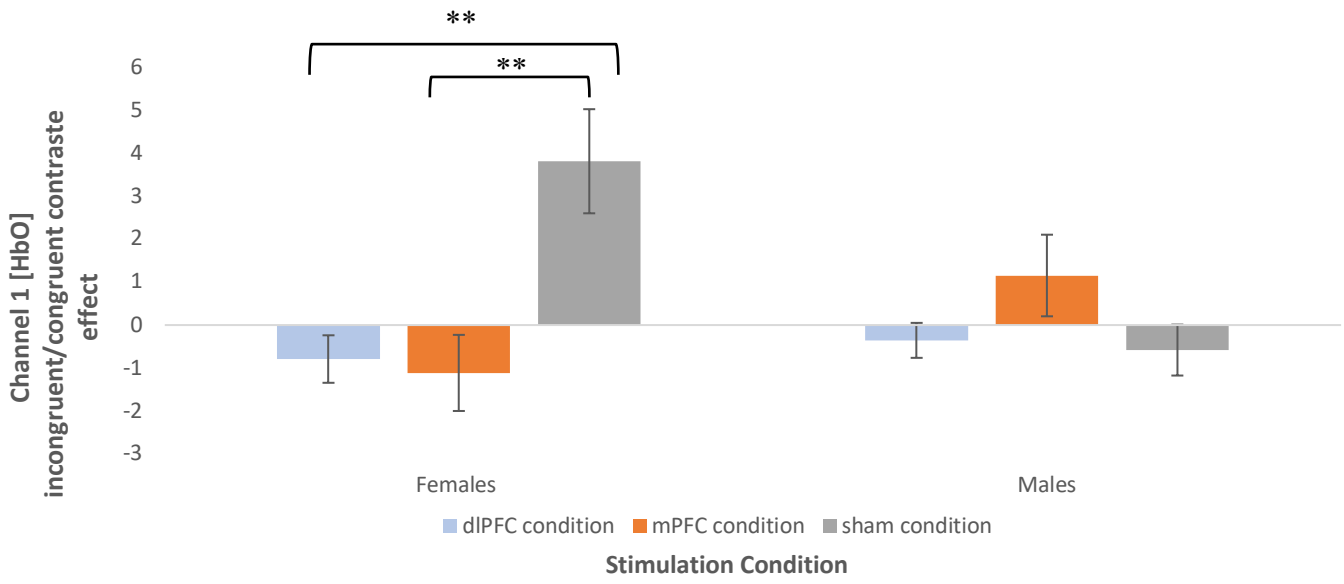

Figure 8: Means (+/-*SE*) for channel 1 oxy-hemoglobin incongruent/congruent contraste effect by gender for each treatment condition; i) Females: a) dlPFC condition (*M* = -.791, *SE* = .553), b) mPFC condition (*M* = -1.114, *SE* = .886) and c) sham condition (*M* = 3.814, *SE* = 1.212); ii) Males: a) dlPFC condition (*M* = -.356, *SE* = .407), b) mPFC condition (*M* = -1.154, *SE* = .950) and c) sham condition (*M* = -.582, *SE* = .593). **: p < .01.

Planned comparisons indicated that compared to the sham condition (*M* = 3.814, *SE* = 1.212), females in the dlPFC (*M* = -.791, *SE* = .553) had a significantly lower incongruent/congruent contrast effect **(*t* (1,13) = -3.612, *p* = 0.003)**. In contrast, compared to the sham condition (*M* = -.582, *SE* = .593), males in the dlPFC condition (*M* = -.356, *SE* = .407) did not show any significant differences on the incongruent/congruent contraste effect **(*t* (1,6) = .315, *p* = 0.764)**.

In addition, compared to the sham condition (*M* = 3.814, *SE* = 1.212), females in the mPFC condition (*M* = -1.114, *SE* = .886) also had a significantly lower incongruent/congruent contrast effect **(*t* (1,9) = -2.797, *p* = 0.021)**. In contrast, compared to the sham condition (*M* = -.582, *SE* = .593), males in the mPFC condition (*M* = -1.154, *SE* = .950) did show have any significant differences on the incongruent/congruent contrast effect **(*t* (1,7) = 1.451, *p* = 0.190)**.

3.6.2 Delay Discounting Oxy Hemoglobin Concentration

The delay discounting oxy hemoglobin concentration was calculated by taking the average oxy hemoglobin concentration across the three delay discounting tasks for each channel:

Delay Discounting Oxy-Hemoglobin= (CHn_DD1 + CHn_DD2 + + CHn_DD3)/3

where,

CHn_DD1 refers to the oxyhemoglobin concentration for the delay discounting task #1 for channel *n*
CHn_DD2 refers to the oxyhemoglobin concentration for the delay discounting task #2 for channel *n*
CHn_DD3 refers to the oxyhemoglobin concentration for the delay discounting task #3 for channel *n*

Following the calculation for delay discounting oxy hemoglobin, each channel was subject to winsorization. Next, each channel was subject to a one-way ANOVA to test for any hypothesized group differences (active iTBS vs. sham iTBS). Differences across channels have been illustrated using a heat map using corresponding *p*-values for each channel below in Figure 9:

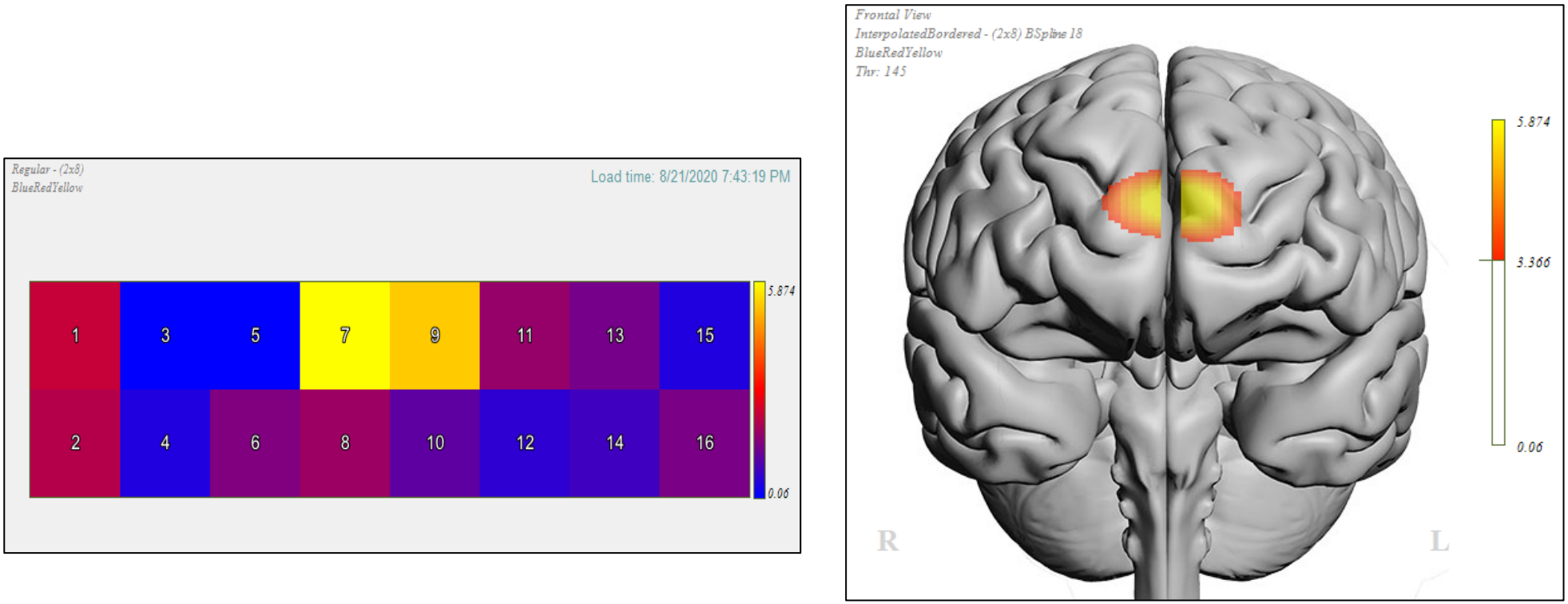

Figure 9: Heat map and 3D anatomical overlay of the active vs. sham iTBS contrast for the delay discounting task. **Left**: Heat map of channels 1-16 illustrating the difference in oxy-hemoglobin concentration between active iTBS vs. sham iTBS during the delay discounting task. Colour coding was represented by the strength of the *p*-values; warmer colours represent stronger active vs. sham contrast; darker shades of blue represent weak to no differences. **Right**: 3D anatomical overlay of the significant contrast difference between active vs. sham.

Analysis revealed channel 7 **($F(2,34) = 5.874$, $p = .006$)** and channel 9 **($F(2,33) = 5.289$, $p = .010$)** to have significant differences in oxy-hemoglobin concentrations between stimulation conditions (active iTBS vs. sham iTBS). Variable means for both channels by stimulation condition have been depicted in their respective figures below (Figures 10 and 11).

Planned comparisons for channel 7 indicated that compared to the sham condition, those in the mPFC condition had significantly higher concentrations of oxy hemoglobin **($t(1,21) = 3.154$, $p = 0.005$)** on delay discounting task. In contrast, compared to the sham condition, those in dlPFC condition had no significant differences in oxy hemoglobin concentrations **($t(1,24) = .872$, $p = 0.392$)** on the delay discounting task.

In addition, a similar trend was seen for channel 9; compared to the sham condition, those in the mPFC condition had significantly higher concentrations of oxy hemoglobin **($t(1,20) = 2.902$, $p = 0.009$)** during delay discounting task. In contrast, compared to the sham condition, those in dlPFC condition had no significant differences in oxy hemoglobin concentrations **($t(1,23) = -.085$, $p = 0.933$)** on the delay discounting task.

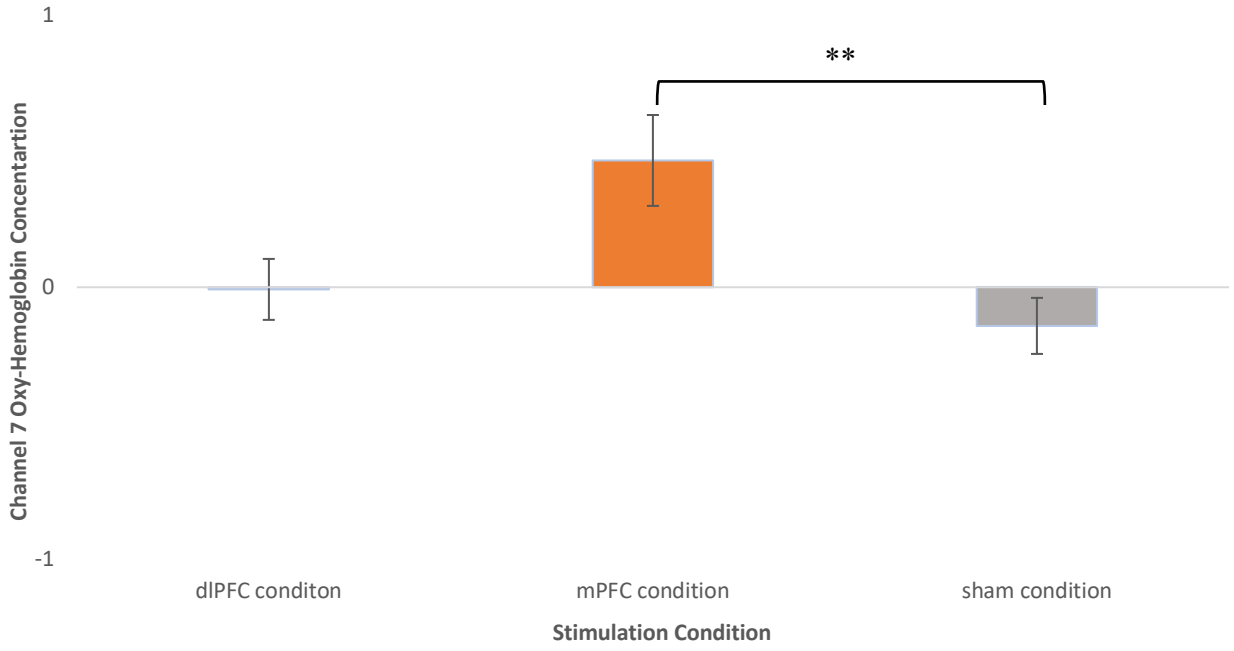

Figure 10: Means (+/-*SE*) for channel 7 oxy-hemoglobin concentration for each treatment condition averaged across the three delay discounting tasks; a) dlPFC condition ($M = -.00787$, $SE = .112$), b) mPFC condition ($M = .466$, $SE = .167$) and c) sham condition ($M = -.142$, $SE = .103$). **: $p < .01$.

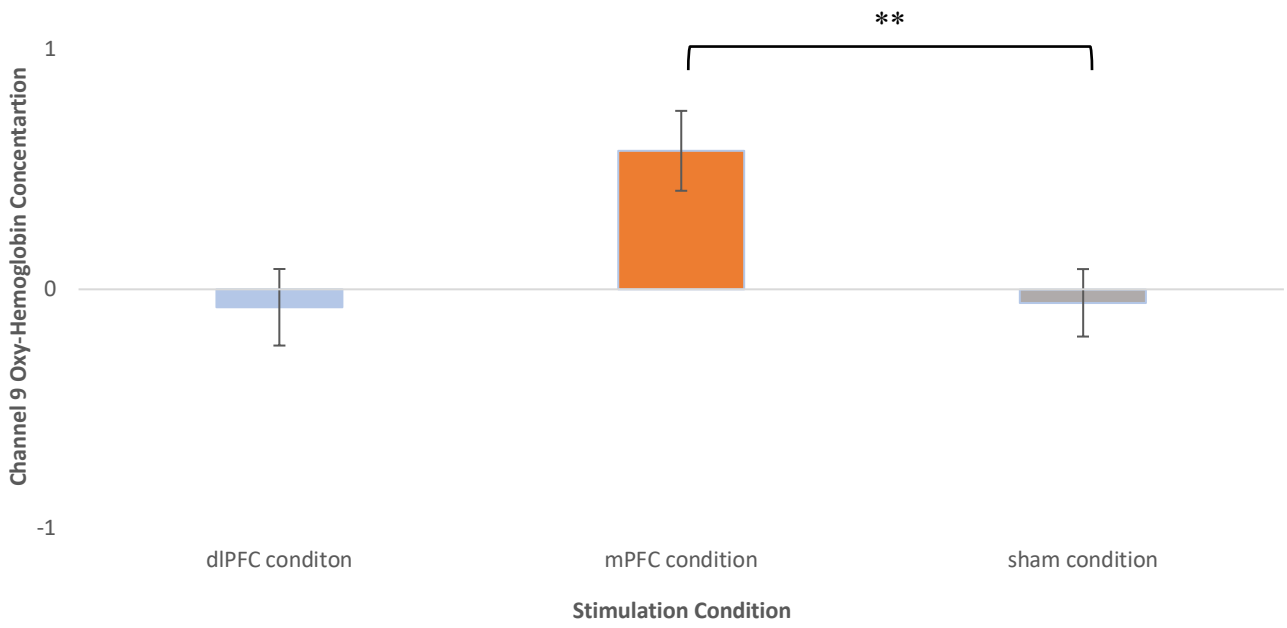

Figure 11: Means (+/-*SE*) for channel 9 oxy-hemoglobin concentration for each treatment condition averaged across the three delay discounting tasks; a) dlPFC condition (*M* = -.0750 , *SE* = .160), b) mPFC condition (*M* = .579 , *SE* = .167) and c) sham condition (*M* = -.0564 , *SE* = .141). **: p < .01.

Interaction Analyses

Channel 7

With respect to delay discounting oxy-hemoglobin concentrations, the two-way (stimulation x age category) ANOVA revealed a significant main effect of stimulation **(*F*(2,31) = 5.370, *p* = .010)**, but no significant main effect of age category **(*F*(1,31) = 1.032, *p* = .318)**. The interaction between stimulation condition and age category was not significant **(*F*(2,31) = .518, *p* = .601)**.

With respect to delay discounting oxy-hemoglobin concentrations, the two-way (stimulation x gender) ANOVA revealed a significant main effect of stimulation **(*F*(2,31) = 5.159, *p* = .012)**, but no significant main effect of gender **(*F*(1,31) = .544, *p* = .467)**. The interaction between stimulation condition and gender was not significant **(*F*(2,31) = .700, *p* = .504)**.

Channel 9

With respect to delay discounting oxy-hemoglobin concentrations, the two-way (stimulation x age category) ANOVA revealed a significant main effect of stimulation **(*F*(2,30) = 4.573, *p* = .016)**, but no significant main effect of age category **(*F*(1,30) = .341, *p* = .564)**. The interaction between stimulation condition and age category was found not to be significant **(*F*(2,30) = 1.424, *p* = .257)**.

With respect to delay discounting oxy-hemoglobin concentrations, the two-way (stimulation x gender) ANOVA revealed a significant main effect of stimulation **(*F*(2,30) = 6.587, *p* = .004)**, but no significant main effect of gender **(*F*(1,30) = 1.323, *p* = .259)**. The interaction between stimulation condition and gender was not significant **(*F*(2,30) = 2.219, *p* = .126)**.

Chapter 4: Discussion

The purpose of the current study was to examine the effects of excitatory brain stimulation (iTBS) on older adults' choices about finances and calorie-dense food consumption, and to examine potential demographic moderators of these. Two prefrontal stimulation targets—the dlPFC and the mPFC—were of specific interest because of their differential roles on self-control and evaluative processing, respectively. Primary findings suggested that iTBS targeting the dlPFC and mPFC did not result in significantly more consumption of calorie dense foods, nor changes in performance on cognitive tasks assessing inhibition or evaluative processing. Likewise, there was no evidence of moderation by age category. However, there was evidence of moderation by gender: specifically, the effect of the dmPFC stimulation was more pronounced in females than in males when comparing the amount of food consumed between active verses sham conditions. This reliable, stimulation-induced increase in consumption was in the opposite direction of the initial hypothesis, suggesting that enhancement of evaluative processing may have stimulated appetite in the presence of an eating opportunity for calorie dense foods. Granular analysis by food sub-type revealed that these eating effects were mostly driven by the consumption of sweet snack foods rather than salty snack foods. Despite null effects on the cognitive tasks, fNIRS data suggested iTBS resulted in differences in functional activation patterns in specific channels; the left lateral channel during the inhibitory task (incongruent/congruent contrast), the medial channels for the delay discounting task. Several personality variables predicted food consumption across study conditions, including agreeableness, emotional stability, and psychopathy.

4.1 Gender Differences

Variation in food consumption between genders may have been driven by differences in the sensitivity to social context and perceived expectations, as females have shown to be more sensitive to their external surroundings (110). The experimental environment in this study involved semantic and visual cues that were generally conducive to indulgent eating. The sight of appealing snack food in the context of previous self-deprivation (part of the current protocol) would have set the stage for such effects as well. When such environmental cues are impelling of consumption, stimulation-enhanced evaluative processing capacity may have accentuated the value of whatever stimuli were most obvious, depending on valence (and in this case, that valence would likely have been positive for food stimuli). Given that females are prone to higher dietary restraint than men

(REF), females may have experienced relatively more potentiated evaluative processing in relation to tempting food cues in the eating environment.

Beyond contextual and social-cognitive effects, there is also some evidence from previous studies that has shown that woman are more responsive to cortical brain stimulation than men. For example, when Korb and colleagues (2015) applied rTMS over motor and somatosensory cortices, they found reduced effects of facial mimicry and emotional cognition only among females (111). Similarly, Huber et al. (2003) found that rTMS targeting the dlPFC in women with schizophrenia significantly increased their performance on the number-connection task, whereas no pre-post stimulation differences were seen across men (112). At a neurobiological level, a few studies have reported differences in cortical brain modulation between genders due to hormonal influences (113) or differences in cranial bone density (114).

In summary, candidate explanations for why the iTBS effects were in the opposite direction to the initial hypothesis, and why the findings were stronger for females include: higher sensitivity to contextual cues, higher prevalence of dietary self-restraint, and increased susceptibility to iTBS neuromodulation effects on a physiological level, due to hormonal factors and/or bone density of the skull.

4.2 Paradoxical iTBS Effects on mPFC Food Consumption Outcomes

As mentioned above, the observed paradoxical dmPFC effects on enhanced consumption can potentially be explained by the complexity of the mPFC's role in self-evaluative processing. Initially, it was hypothesized that excitatory modulation to the dmPFC would result in lower consumption of high caloric foods by evaluative self-control measures. This hypothesized effect was assumed to be mediated by stimulation effects seen in increasing far-sighted decision-making in the delay discounting paradigm. This was theorized based upon a previous TMS study that had shown that excitatory neuromodulation to mPFC resulted in lower discounting tendency of future rewards thereby increasing the preference for larger-delayed options in comparison to the control condition (80).

Although iTBS to the dmPFC did not influence delay discounting in this study, the effect of the stimulation did increase consumption of appetitive snack foods among females. Excitatory iTBS effects on the dmPFC facilitated evaluating processes as expected (81), but not towards self-control, but possibly in self-indulgence. This seems likely given participants were self-deprived in the presence of a favorable stimulus, as palatable food cues have shown to lead to greater tendencies to overeat (109). Since the experimental environment supported indulgence rather than restraint, combined with excitatory rTMS to the mPFC, this may have been enhanced evaluative measures to self-indulge, over-riding any self-control mechanisms.

This is only experimental study to date that has used excitatory rTMS on the dmPFC to assess individual differences on actual eating outcomes among healthy subjects. One prior case study (115) reported the use of high frequency excitatory rTMS on dmPFC increased the ability to control dysfunctional eating behaviour in a patient with bulimia. This perhaps suggests differences in excitatory stimulation effects on the dmPFC between healthy and vulnerable individuals, which could be due to differences in frontal-striatal activity (115). As such, there is a need for future research to fully understand the effects of rTMS/TBS on the mPFC and its underlying mechanisms on food choices.

4.3 iTBS Effects on dlPFC Food Consumption

Excitatory neuromodulation using iTBS on the left dlPFC did not result in decreased consumption of calorie dense foods as expected. This excitatory effect was hypothesized based on initial findings that suggested that iTBS was reliable in facilitating cortical excitability among neuronal populations (81). Previous meta-analyses have indicated that excitatory brain stimulation paradigms targeting the dlPFC can reliably reduce indulgent eating (9,32). However, excitatory stimulation using iTBS on dlPFC in this study did not produce this intended eating effect. A potential explanation for this null finding is possibly due to no stimulation effects observed on the behavioural inhibitory task. This proposed notion stems from an earlier finding that had shown successful facilitation of the left dlPFC using excitatory rTMS resulted in decreased chocolate consumption in comparison to sham, only when associated with a prior go/no-go inhibitory task (116). Hence, since no differences on cognitive performance were seen across stimulation

conditions, this may explain why iTBS effects on dietary control were not observed between participants in this study.

It might be that among TBS protocols, iTBS effects are simply not as reliable as cTBS effects across neuromodulation studies. For example, studies examining the effects of iTBS on executive functioning tasks have been mixed and more variable across specific tasks (25). It could also be the case that iTBS only achieves excitatory effects when stimulation effects on neuronal populations are aggregated across several stimulation sessions over long periods of time. For instance, a meta-analysis reported that a decrease in the consumption of appetitive snack foods post excitatory stimulation was only seen for multi-session studies, as opposed to single session studies (9,32). Overall, due to the small number of studies utilizing iTBS protocols, it would be of interest to conduct additional research in validating the efficacy of iTBS on improvement of executive functioning and its impact on dietary control.

4.4 iTBS Effects on Financial Decision Making

This study investigated whether iTBS on the left dlPFC and bilateral dmPFC could influence financial decision-making using a delay discounting paradigm. The results evidently showed iTBS effects did not induce changes in discounting behaviour when applied over both targeted regions of the PFC. Consistent with current findings, prior studies have found null effects of iTBS on discounting behaviour when applied over the right dlPFC (82) or left dlPFC (117). However, it was shown that cTBS modulation on dlPFC did profoundly increase discounting behaviour among study subjects (82). The findings presented in this study contribute to growing evidence of the possibility that iTBS may not be able to alter cognitive impulsivity within a single session.

Apart from the stimulation effects, current findings also report no significant differences in delay discounting rates (k values) between younger and older adults. These findings are meaningful as they suggest that evaluative processing measures are not influenced by the natural aging process. This suggests that among relatively healthy individuals, differences in discounting tendencies may remain intact throughout the entire adult lifespan. Lastly, the findings presented

here add depth and elicit further discussion as to whether discounting tendencies differ during different stages of adulthood. Previous studies have reported higher discounting tendencies among adolescents (54–58), perhaps due to an under-developed prefrontal cortex (59,60). Discounting during adulthood have been subject to discrepancies; while some have reported younger adults to discount future gains more heavily than older adults (61,62), others have reported no differences after controlling for SES (64).

4.5 fNIRS Validates iTBS Neural Effects

The purpose of the using fNIRS in this study was to directly assess whether iTBS induced changes in functional activation patterns via BOLD signalling in the target cortical region of interest. The analysis conducted using the neuroimaging data revealed channels that showed significant changes in BOLD activity between active vs. sham stimulation conditions while performing each cognitive task.

For the Flanker incongruent/congruent contrast effect, significant differences in [HbO] between iTBS conditions were observed for only channel 1, a channel that is positioned on the left lateral side of PFC. Interestingly, results from this channel indicated that excitatory stimulation to the left dlPFC resulted in significantly lower oxygen consumption on the flanker incongruent task (relative to the flanker congruent task) when compared to the sham stimulation. This implies that excitatory stimulation to lateral PFC facilitated in lower demand of oxygenated resources on task performance, indicating a potential neural efficiency effect. In addition, stimulation and gender interaction revealed significant differences in incongruent/congruent contraste effect across conditions among females only. This preliminary finding using fNIRS perhaps suggest a possibility as to why females are perhaps more susceptible to cortical stimulation than men. Neuroimaging data from the delayed discounting task suggest significant differences in [HbO] between stimulation conditions were observed in the medial channels (channel 7 and 9). The results from both these channels indicate a significant increase in oxygen consumption was evident only in those that received iTBS to the dmPFC.

Although behavioural data indicates no differences in flanker interference latency scores or discounting tendencies between stimulation conditions, it could be that case that iTBS might have had an effect at the neural level (as seen with the fNIRS data), which may have not manifested at the behavioural level. Previously it has been shown that iTBS is more likely to alter neurophysiological markers than to cause behavioural changes (118). As such, excitatory TMS in this study did result in functional changes via BOLD signalling to lateral and medial areas of the PFC, which did not manifest at the behavioural level.

The fNIRS data presented in this study can be used as a proxy to validate the importance of combining neuroimaging techniques with neuromodulation methods in determining areas of the PFC involved in executive functioning. The findings presented are in agreement with previous studies that have shown neural recruitment of the lateral areas of the PFC to be important for inhibitory/anticipatory mentally effortful tasks (119,120), whereas activation of medial PFC is seen during intertemporal decision-making (121–123).

4.6 Personality Predictors

In contrast with the experimental results, regression analyses revealed significant personality predictors of food consumption and cognitive mediators, when analyses were collapsed across all study conditions. For example, individual differences in agreeableness predicted food consumption, such that those who scored higher in agreeableness consumed less food during the taste test. Likewise, higher scores on primary psychopathy predicted more food consumption in the taste test, whereas higher scores on secondary psychopathy predicted less consumption. Extraversion was a strong predictor on the flanker interference score, suggesting that individuals who scored higher on extraversion performed poorer on the flanker task.

A previous study has linked high levels of extraversion to be associated with activation of lateral areas of the PFC under conditions of inhibitory control (96). Along with extraversion, although not statistically significant, emotional stability was shown to be associated with better cognitive task performance. This pattern is consistent with previously published literature that has proposed neuroticism (lower emotional stability) to be associated with poor performance on multiple executive functioning domains: such as episodic memory, speed-attention, verbal

fluency, visual spatial ability and numeric reasoning (124,125). Lastly, individual differences in openness predicted differences in delay discounting, such that individuals that are more open to experience are less likely to discount future gains (have lower *k* values). Higher levels of openness is generally associated with greater IQ and overall better performance on most cognitive tasks (124,126,127) and less delayed discounting (99). In addition, regression analyses predicted that individuals who displayed traits of impulsivity are more likely to discount future gains (have higher *k* values). Impulsivity is generally associated with higher rates of delayed discounting (128). This prediction is consistent with previous literature that has reported higher rates of discounting among individuals with alcoholism (129,130), frequent cigarette consumption (131,132), pathological gambling (133) and obesity (39,134).

4.7 Strengths and Limitations

The key strengths of this study included the implementation of a single-blinded, randomized and between subjects' experimental design that minimized any selection bias and enhanced the validity of the findings by reducing the chance of loss of blinding. In addition, the use of a sham coil serves as basis of comparison to the experimental condition and mimics experimental auditory and somato-sensory effects to those in the active condition. Recruitment by age category allowed for not only demonstrating the possibility of iTBS effects by age, but also allowed to negate any plausible ceiling effects on up-regulating potential as previously assumed while using only iTBS on a healthy younger adult sample (25). Moreover, functional neuroimaging technology was used to directly assess iTBS-induced changes in functional activation patterns in the targeted cortical regions of interests. Furthermore, the use of a food consumption paradigm was a strength; this was superior to employing only a food cravings or other self-report outcome, as it more directly assess the impact stimulation effects on high caloric food consumption. Lastly, the inclusion of standardized measures of executive function and evaluative processing was a strength.

Limitations of this study include a small-to-moderate sample size (though typical of neuromodulation studies), which may have decreased the statistical power. This is significant because reducing the power of the study ultimately impacts the likelihood of a detecting a significant effect. Other limitations of this study include the lack of double blinding and sample

generalizability, both of which are also typical for neuroimaging experiments. With respect to the later, most older adults in the study were recruited from YMCA's and community centres, thus this sample may not have been representative of the general older population. Similarly, the younger adult sample were recruited from a single university campus, hence this sample may not have been representative of the younger-adult population. This study may also be subject to self-reporting biases as participants may have inherently responded inaccurately on the life-style behaviour and personality trait questionnaires due to social desirability or selective recall issues. It is important to note that the effects of stimulation to the dmPFC were received at low baseline of 30% of the maximum stimulation output, hence it is possible that effects of the stimulation would have been more pronounced had we measured the resting motor threshold. These could potentially all contribute to null effects observed as well.

4.8 Conclusions and Future Directions

In conclusion, the findings from this study suggest that there is a considerable amount of complexity in stimulation effects on eating and inter-temporal choice, when targeting these prefrontal sub-regions. Current novel findings demonstrate that single-session iTBS to the dmPFC increased food consumption of calorie-dense snack foods (i.e. selective foods that are strongly associated with development of obesity), but only among females. These findings shed a light on a potential role of the mPFC on high-caloric consumption and confirm differences in the effects of cortical stimulation between genders that have previously been highlighted in other experimental studies. Excitatory iTBS did not show any differences on the discounting task performance. Discounting rates did not differ significantly between younger and older adults indicating that perhaps intertemporal decision-making among healthy adults remains consistent throughout the adult lifespan. fNIRS data is in agreement with previous findings that have suggested that iTBS might have effect at the neural level, which does not manifest at the behavioural level. In addition, fNIRS data also suggested left lateral PFC activation during the inhibitory control, while medial PFC activation during tasks for evaluative processing. Furthermore, the use of a quick and cost-effective neuroimaging (relative to fMRI) method to validate TMS effects on the PFC and should be implemented as a standard practice in all future neuromodulation studies. Future studies should examine the reliability of the iTBS effects, explore whether a bi-directional relationship exist using both TBS variants on both sub regions, to fully

appreciate and understand the relationship of inhibitory control and evaluative processing measures on finance and food choice preferences. This would ultimately strengthen our understanding on the role of the prefrontal cortex on impulsive decision-making and could help navigate future interventions that reduce the risk for obesity.

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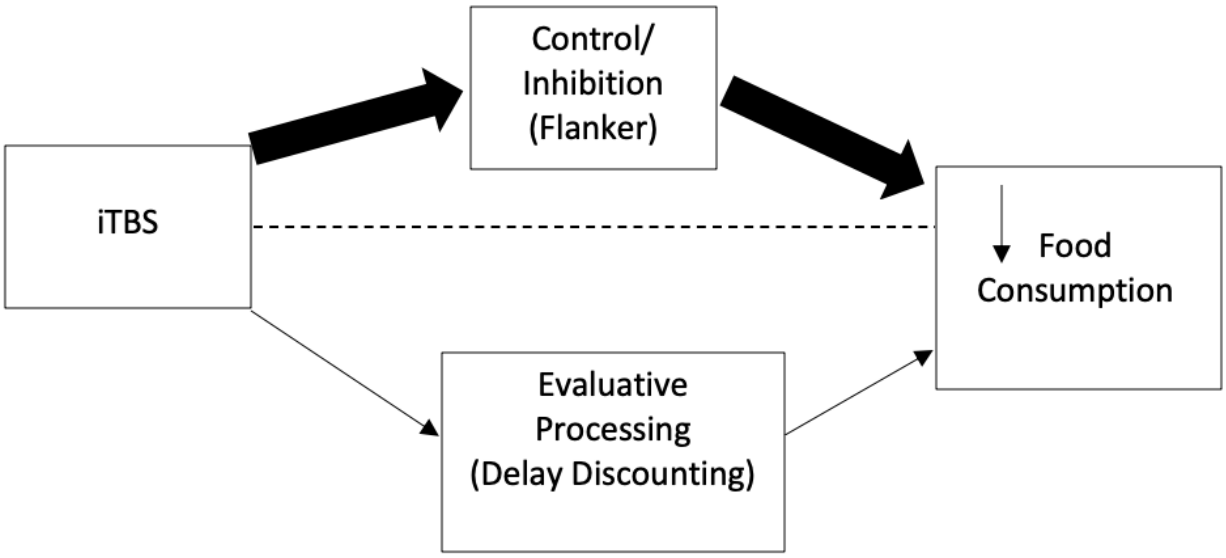
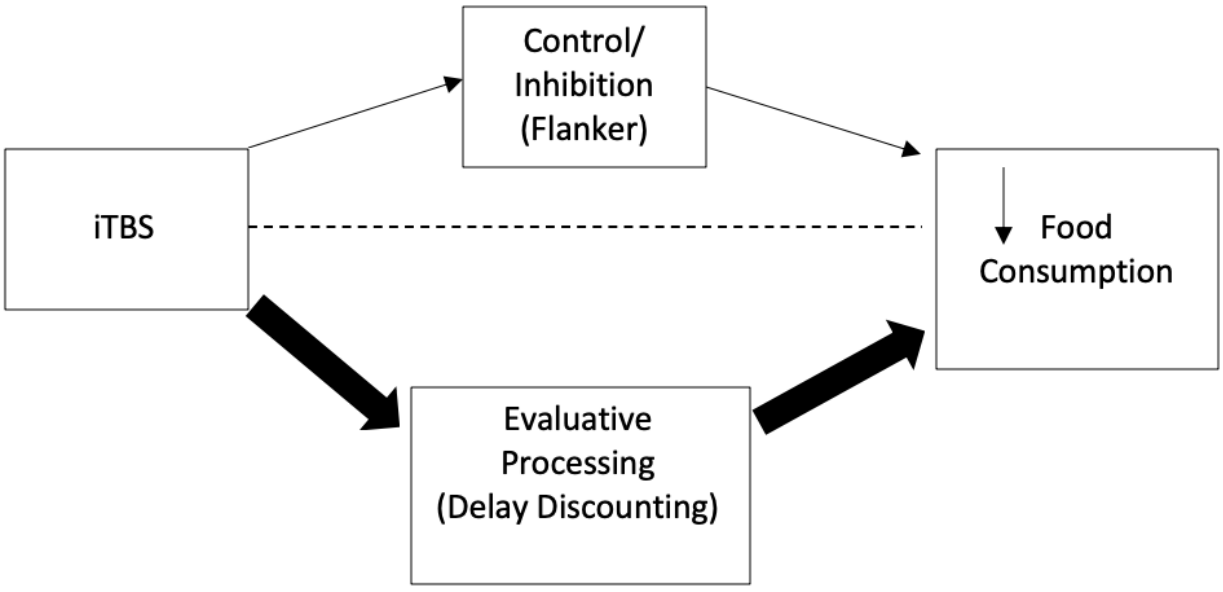
Appendices

Appendix A: Brain Systems and Mediators

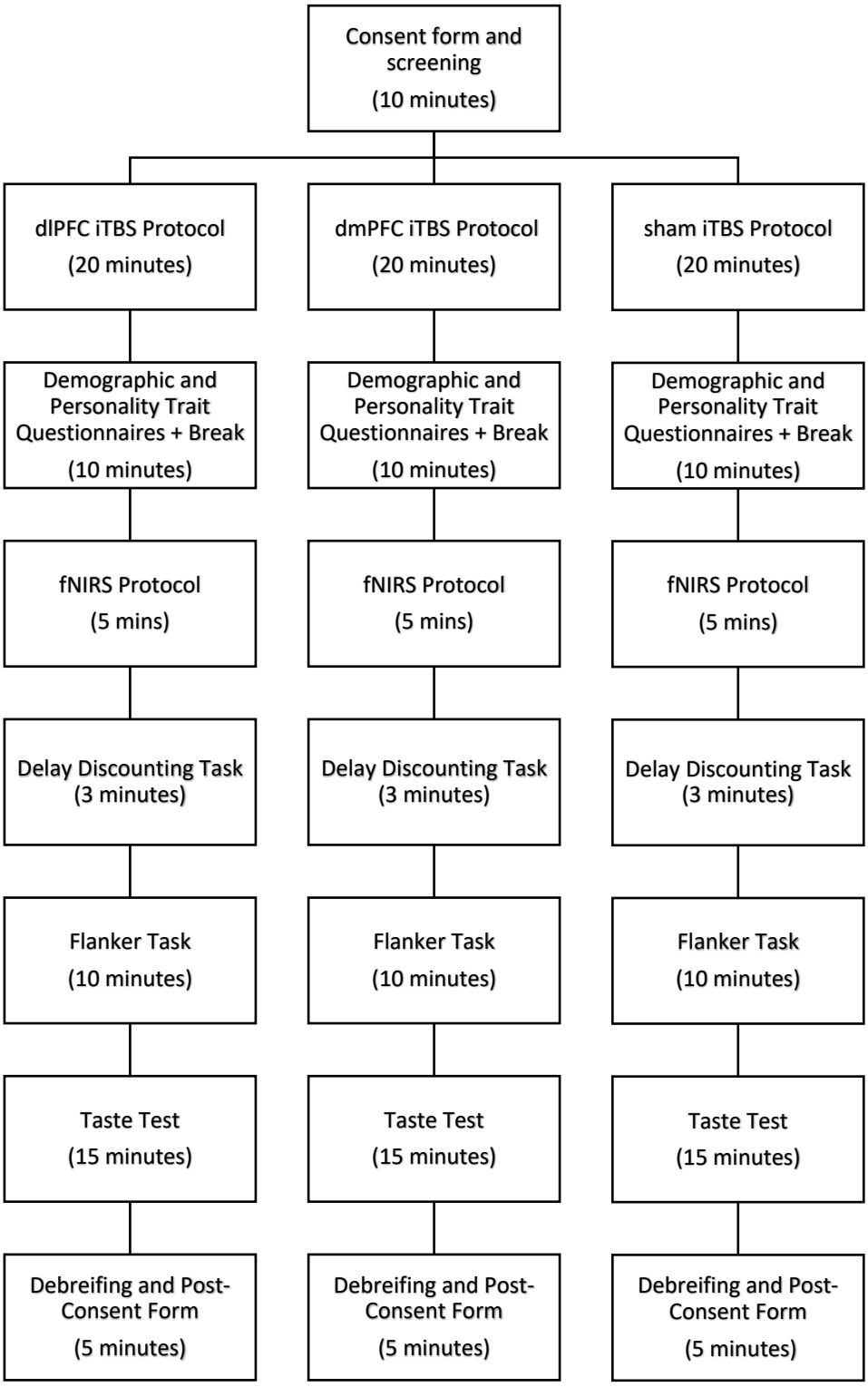
Target dlPFC:



Target mPFC:



Appendix B: Experimental Session Protocol



Appendix C: Information Letter

Study Title: Testing the causal role of brain networks in near and far-sighted decision-making

Principal Investigators: Dr. Peter Hall (pahall@uwaterloo.ca), Dr. Amer Burhan (amer.burhan@sjhc.london.on.ca)

Student Investigators: Idris Fatakdawala (ifatakda@uwaterloo.ca), Adrian Safati (absafati@uwaterloo.ca), Mohammed Nazmus Sakib (mn2sakib@uwaterloo.ca)

You have been invited to participate in a study examining the role of brain networks in decision making. Specifically, we will be testing the effects of a non-invasive brain stimulation technique (applied to one of two brain structures) on decision-making processes in two domains (taste perception and financial judgement). For the purposes of this study we will be stimulating one of the two structures in the front of the brain: dlPFC (dorsolateral prefrontal cortex) or the dmPFC (bilateral dorsomedial prefrontal cortex), temporarily increasing activity in these regions. After receiving the stimulation targeting one of the two structures, you will be asked to complete two computer tasks: one will ask you to make judgements about symbols appearing on the screen. The other will ask you to make judgements about money. These two computer tasks will be followed by a food tasting opportunity, wherein we will ask you to taste a number of common snacks and make decisions about them.

The study consists of a single laboratory session that will take approximately 1 hour to complete. In exchange for your participation you will receive **a $25 gift card to Tim Hortons or Walmart**.

Exclusion/Inclusion Criteria

Healthy individuals **between the ages of 18-30 or 40-75, that are right-handed and have never participated in a study involving brain stimulation are eligible to participate in this study**. Due to the taste test portion, persons with **known food allergies to dairy, gluten, or nuts, and/or persons diagnosed with type 1 or type 2 diabetes mellitus must not participate in this study**. Due to the use of the brain stimulation paradigm (known as "repetitive transcranial magnetic stimulation," or rTMS), persons with any metal or magnetized objects in the upper body/head, such as cardiac pacemakers, or surgical clips (e.g., aneurysm clips in the head), artificial heart valves, electronic ear implants, metal fragments in the eye, electronic stimulators, and implanted pumps must not participate in this study. Furthermore, persons that have been diagnosed with any neurological or psychiatric disorders (e.g. depression, anxiety), and/or have a history of experiencing seizures or head trauma (e.g. concussions) must not participate in this study. Individuals who experienced only a mild concussion (one that did not result in a loss of consciousness, or post-concussion syndrome) over 5 years ago can still participate if all other eligibility criteria are met.

Prior to the start of the laboratory session, you will be asked to complete a TMS screening form to determine if you are eligible to participate in this study. The TMS screening form will be used to screen for any medical conditions (e.g., epilepsy) that might put you at any additional risk for the TMS procedures. In addition, you also be asked to complete a food allergies/restriction screening form to determine any potential dietary restrictions that may prevent you from participating in the study. If you have any questions regarding your eligibility, please ask the researcher now.

Due to the nature of our study and the data being collected we require that all participants abstain from eating or consuming any caffeine in the 3 hours prior to participating in the study, which you will have already indicated on the food allergies/restriction screening form.

Procedure:

A researcher who is trained in CPR and First Aid will be present at all study sessions.

In this study, we will use a non-invasive technique to temporarily modulate brain function by stimulating specific areas of the brain. The method is called Transcranial Magnetic Stimulation (TMS). TMS will be used to stimulate the left dorsolateral prefrontal cortex (dlPFC) or the bilateral dorsomedial prefrontal cortex (dmPFC). This is a procedure involving the application of a coil above the surface of the scalp to deliver repeated trains of electromagnetic pulses to temporarily modulate the activity of cortical structures underneath.

At the start of this study, we will randomly assign you to one of the three groups: 1) active stimulation targeting the left dlPFC, 2) active stimulation targeting bilateral dmPFC or 3) sham stimulation (control). You will only be told to which group you were assigned to once the study has been completed.

During the TMS procedure, the head will need to be kept as still as possible. The stimulation equipment uses a magnetic stimulator which is essentially a set of capacitors that can store and rapidly discharge electricity into a coil encased in plastic. The plastic case rests against the head. As current flows through the coil, a magnetic field is generated that penetrates the skull and induces a second electrical flow of current in the brain identical to that created by the body during normal everyday movement; that is, the mechanism by which TMS affects brain function is via magnetic pulses generated by the coil, which in turn generate endogenous neuroelectric activity in the targeted brain regions. This procedure is not normally painful or otherwise uncomfortable. Clicking noises will be heard as the current flows through the coil and involuntary activation (i.e. twitching) of scalp muscles may be experienced depending on the position of the coil over the head.

To locate and mark the target area for stimulation (i.e., the left dlPFC or bilateral dmPFC) we will be using a cloth or lycra EEG cap (resembling a swim cap) arranged in the International 10-20 system. The EEG cap will be placed over the head and the location of each of these target areas will be used to guide the coil placement.

In single session format, repetitive TMS pulses (rTMS) can induce short-term changes in targeted areas of the brain. In the present study, we will be applying rTMS pulses in the excitatory intermittent theta burst (iTBS) pattern to temporarily increase activity in the left DLPFC (or bilateral dmPFC). Everyone has a different level of baseline cortical excitability threshold for TMS (i.e., the stimulation intensity needed to produce the desired effect). As such, we will first determine the participant's resting motor threshold (RMT), as an approximation of baseline excitability. RMT in this case will refer to the lowest stimulation intensity required to produce a detectable motor response in the right thumb in at least 5 out 10 consecutive trials. The intensity of the iTBS will be set to 80% of the RMT. The RMT will be established by stimulating the motor cortex.

Following the determination of RMT, iTBS will be applied to the left DLPFC (or bilateral dmPFC). The iTBS stimulation pattern consists of three 50 Hz pulses that are repeatedly applied for 2 seconds train of iTBS for every 10 seconds, we will apply this stimulation for a duration of 3 minutes, totaling 600 pulses.

The up-regulating effects of the stimulation will peak at 20-30 minutes post stimulation and dissipate completely in under 60 mins. All TMS procedures will be performed by a trained researcher.

Following the TMS procedure, you will be given 8-minute break for you to rest and to allow for the effects of TMS to set in. You will then undergo non-invasive neuroimaging protocol using functional near infrared spectroscopy (fNIRS). This is a technique that uses pairs of LED lights and light sensors to quantify slight changes in blood oxygenation within brain tissues during tasks and at rest. You will be outfitted with a head band, containing the pairs of lights ("illuminators") and light sensors ("detectors") and asked to rest quietly while fixating on a fixation point on the computer screen for 5 minutes. Near-infrared light is able to pass the tissues like skin and bone but is absorbed by proteins responsible for carrying oxygen in the blood. By placing near-infrared light emitters, we are able to detect and measure blood volume and oxygenation levels. By observing relative differences in blow oxygenation and flow, it is then possible infer activity in those specific brain regions.

You will then be asked to complete an adjusting delay, a 5-trial adjusting delay task. In this task we will present you with a series of two monetary options, each presented with the time it will be available. In every trial, you will choose your preferred option by pressing the corresponding left or right button. You will then be asked to complete the flanker task, in which you will be shown a five-letter string (e.g., HHHHH, SSHSS), and you will be asked to indicate what the middle letter is.

Lastly, you will then be asked to complete the taste perception task for the study. For the task, you will be asked to taste and rate the subjective properties of 2 different flavours of chocolate (Milk Lindor and Sea Salt Milk Lindor) and 3 different flavours of potato chips (Original Pringles, Barbeque Pringles and Sour Cream and Onion Pringles). You will be asked to complete a series of questionnaires that will have you rank your answers to questions on a 10-point scale. This purpose of this is taste task is to understand the effect of flavour perception post brain-stimulation.

You will have 15 minutes to complete the taste task portion of the study, during which time the researcher will leave the room.

During the 8-minute break, you will be asked to fill out several questionnaires pertaining to demographics (e.g., age, relationship status, household income, height, weight, education) and lifestyle (physical activity frequency/intensity, alcohol consumption, dietary habits). This is will also include on questionnaires on personality traits. We need this information to control for potential confounding effects (i.e., variables that may influence the results outside the experimental manipulation), and to describe the study sample in future publications.

Risks: The risks associated with this study are described below.

There are no known risks associated with fNIRS. The technique relies on passive light detection via sensors placed externally to the scalp during tasks and resting states.

Several tolerability and safety issues have been identified with TMS; these are described below. There is no evidence that the procedure is harmful if appropriate guidelines are followed[1,2,3].

a) The procedure is painless, though it can cause muscles to contract immediately after stimulation, which may lead to residual soreness caused by muscle fatigue over the duration of the experiment.
b) Approximately 1 in every 10 research participants undergoing TMS experience headaches or dizziness, which are believed to be due to excessive muscle tension. Acetaminophen promptly resolves the discomfort in most cases. In the event Acetaminophen does not resolve discomfort

within a short duration, the participant will be directed to UW Health Services, or to a walk-in clinic or family doctor appointment of their choice.

c) Approximately 1 in every 100 research participants undergoing TMS experiences neck stiffness and pain. This is believed to be due to the straight posture of the head and neck during the application of TMS. Acetaminophen promptly resolves the discomfort in most cases. Participants are asked to advise the researcher at the first opportunity if they experience any neck stiffness or soreness. In this situation, the participant may opt to withdraw from the study or to rest and change posture for several minutes before the procedures are resumed. If neck stiffness and pain persist, and Acetaminophen does not resolve the discomfort, the participant will be directed to UW Health Services, or to a walk-in clinic or family doctor appointment of their choice.

d) TMS produces a loud clicking noise when the current passes through the coil. This loud click can result in tinnitus (i.e., "ringing" in the ears) and temporary decreased hearing if no ear protection is used. To prevent this adverse effect all research participants receiving TMS and those researchers delivering TMS will be expected to wear earplugs.

e) The use of single, paired pulse, or very low frequency (repetitive) TMS has never induced a seizure in a healthy participant; likewise, the variant of TMS used here has never induced a seizure in a healthy participant when targeting the brain region that we are targeting. However, there is the possibility that TMS can induce a convulsion even in the absence of brain lesions, epilepsy or other risk factors for seizures. Only 7 cases of convulsions have been reported using single pulse TMS in patients with pre-existing brain damage despite extensive use in both the healthy and patient population. In the case of high frequency repetitive TMS the risk of seizure is reported at less than 1% in healthy young adults and only one seizure has ever been reported in a normal subject following cTBS[3]. The overall risk for seizures during TMS is thought to be in the order of 1 in 1000 studies. In the event a participant does experience a seizure, emergency services via 911 will be contacted.

If at any time during the experiment you feel uncomfortable, or experience and headaches or dizziness, please inform the researchers.

Participants should inform the researchers after seeking treatment, so researchers are aware at all time about situation and that they can inform the research ethics committee. Researchers will follow-up with the participants to ensure all the issues are resolved.

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Participation

Your participation is completely voluntary, and you may withdraw from this study or decline answering any questions on the questionnaire, with no penalty. The TMS sessions can be stopped at any time, and withdrawal from the study may occur at any time with no penalty (i.e., you will still receive your remuneration for your time in the study. If you wish to stop participating in the study, please inform the researchers. If you require a small break during the study, please inform the researchers.

Remuneration

In appreciation for your participation, you will receive a $25 gift card to Tim Hortons or Walmart. *The amount received is taxable. It is your responsibility to report this amount for income tax purposes.*

Confidentiality and security of data

Your identity in this study will be confidential. Your name will be never be associated with your individual data. The de-identified data will be accessible by the study investigators as well as the broader scientific community. More specifically, the data may be made available to other researchers upon publication so that data may be inspected and analyzed by other researchers. The data that will be shared in any future publications, and again will not contain any information that can identify you.

All information acquired will be kept for at least 7 years in the University of Waterloo Prevention Neuroscience Lab (LHN 2105) where only authorized researchers will have access. Any electronic information will be retained on a secure password protected server. All data will be averaged together for potential publications and/or presentations, and only these averages will be displayed.

Benefits
This study will not provide any direct benefit to you, but the information it provides will lead to better understanding of the brain networks involved in farsighted decision-making.

Funding
This study is being funded by the Royal Bank of Canada.

Concerns about Your Participation

This study has been reviewed and received ethics clearance through a University of Waterloo Research Ethics Committee (ORE #40271). If you have questions for the University of Waterloo Ethics Committee, at 1-519-888-4567 ext. 36005 or ore-ceo@uwaterloo.ca.

If after receiving this letter, you have any questions about this study, or would like additional information to assist you in reaching a decision about participation, please feel free to please feel free to contact the student investigator Idris Fatakdawala anytime through email at ifatakda@uwaterloo.ca.

Appendix D: Consent Form

CONSENT FORM **#ID: _____**

Study Title: Testing the causal role of brain networks in near and far-sighted decision-making

Principal Investigators: Dr. Peter Hall (pahall@uwaterloo.ca), Dr. Amer Burhan (amer.burhan@sjhc.london.on.ca)

Student Investigators: Idris Fatakdawala (ifatakda@uwaterloo.ca), Adrian Safati (absafati@uwaterloo.ca), Mohammed Nazmus Sakib (mn2sakib@uwaterloo.ca)

By signing this consent form, you are not waiving your legal rights or releasing the investigator(s) or involved institution(s) from their legal and professional responsibilities.

I have made this decision based on the information I have read in the Information letter. All the procedures, any risks and benefits have been explained to me. I have had the opportunity to ask any questions and to receive any additional details I wanted about the study. If I have questions later about the study, I can ask one of the researchers. I am aware that I may withdraw from the study at any time without penalty by telling the researcher.

This study has been reviewed and received ethics clearance through a University of Waterloo Research Ethics Committee (ORE# 40271). If you have questions for the Committee contact the Office of Research Ethics, at 1-519-888-4567 ext. 36005 or ore-ceo@uwaterloo.ca. If you have any other questions about the study, please feel free to contact the student investigator Idris Fatakdawala anytime through email at ifatakda@uwaterloo.ca.

Placing your signature below indicates that you have read the entire information-consent letter, and that you agree to participate in the study.

Signature of volunteer_____ Print name _____

Signature of investigator_____ Print name_____

Date_____

Appendix E: 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 F: Food Allergies/Restriction Screening Form

Please answer the following questions (circle).

Have not eaten any food during the past 3 hours? YES NO

Have not consumed any caffeinated beverages during the past 3 hours? YES NO

Do you have any food allergies to dairy, eggs, gluten, or nuts? YES NO

Do you have any allergies or sensitivity to products containing monosodium glutamate (MSG)?

YES NO

How many hours has it been since your last meal (approximately)? _____

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

_____ _____

Signature of Participant Date

_____ _____

Signature of Witness Date

Appendix G: Demographics and Lifestyle Behaviour Questionnaire

Questions:

"Please answer the following:"

1. "Age in years"

2. "Height (specify units):"

3. "Weight (specify units):"

4. "Gender:"
"Male", "Female", “Other”

5. "Estimated prior household income (i.e. Family income: all sources, including living assistance and/or social security):"
"$0 - $19,999", "$20,000 – 39,999", "$40,000 – 59,999", "$60,000 – 79,999", "$80,000 – 99,999", "$100,000 +"

6. "Ethnicity:"
"Asian", "Black/African", "Hispanic", "Indigenous ", "Middle Eastern", "Pacific Islander", "South Asian", "West Indian", "White/Caucasian", "Other, not listed"

7. "Relationship status:"
"Single", "Exclusive dating relationship", "Cohabitating exclusive relationship (non-married)", "Married", "Separated", "Divorced", "Other"

8. "How often do you consume high-calorie foods?"
"Never", "Occasionally", "Once A Month", "Once Every 2 Months", "Once Every 2 Weeks", "Once A Week", "2-3 Times A Week", "4-6 Times A Week", "Once A Day", "More Than Once A Day"

9. How often do you smoke?"
"Never", "Occasionally", "Once A Month", "Once Every 2 Months", "Once Every 2 Weeks", "Once A Week", "2-3 Times A Week", "4-6 Times A Week", "Once A Day", "More Than Once A Day"

9. “How often do you exercise?”

"Never", "Occasionally", "Once A Month", "Once Every 2 Months", "Once Every 2 Weeks", "Once A Week", "2-3 Times A Week", "4-6 Times A Week", "Once A Day", "More Than Once A Day"

10. “How often do you consume alcohol?”

"Never", "Occasionally", "Once A Month", "Once Every 2 Months", "Once Every 2 Weeks", "Once A Week", "2-3 Times A Week", "4-6 Times A Week", "Once A Day", "More Than Once A Day"

11. "Is English your first language?"
"Yes", "No"

11a). "How old were you when you learned English? (skip if first language)"

Appendix H: Levenson's Self-Report Psychopathy Scale (LSRP)

Options:

1- "Disagree strongly", 2-"Disagree somewhat", 3-"Agree somewhat", 4-"Agree strongly"

Questions:

1. Success is based on survival of the fittest; I am not concerned about the losers.
2. For me, what's right is whatever I can get away with.
3. In today's world, I feel justified in doing anything I can get away with to succeed.
4. My main purpose in life is getting as many goodies as I can.
5. Making a lot of money is my most important goal.
6. I let others worry about higher values; my main concern is with the bottom line.
7. People who are stupid enough to get ripped off usually deserve it.
8. Looking out for myself is my top priority.
9. I tell other people what they want to hear so that they will do what I want them to do.
10. I would be upset if my success came at someone else's expense.
11. I often admire a really clever scam.
12. I make a point of trying not to hurt others in pursuit of my goals.
13. I enjoy manipulating other people's feelings.
14. I feel bad if my words or actions cause someone else to feel emotional pain.
15. Even if I were trying very hard to sell something, I wouldn't lie about it.
16. Cheating is not justified because it is unfair to others.
17. I find myself in the same kinds of trouble, time after time.
18. I am often bored.
19. I find that I am able to pursue one goal for a long time.
20. I don't plan anything very far in advance.
21. I quickly lose interest in tasks I start.
22. Most of my problems are due to the fact that other people just don't understand me.
23. Before I do anything, I carefully consider the possible consequences.
24. I have been in a lot of shouting matches with other people.
25. When I get frustrated, I often 'let off steam' by blowing my top.
26. Love is overrated.

Appendix I: Ten Item Personality Inventory (TIPI)

Options:

1- "Disagree strongly", 2- "Disagree moderately", 3- "Disagree a little",
4- "Neither agree nor disagree", 5- "Agree a little", 6 -"Agree moderately", 7 -"Agree strongly"

Questions:

"Here are a number of personality traits that may or may not apply to you. Please indicate on the provided scale the extent to which you agree or disagree with that statement. You should rate the extent to which the pair of traits applies to you, even if one characteristic applies more strongly than the other."

1. Extraverted, enthusiastic
2. Critical, quarrelsome
3. Dependable, self-disciplined
4. Anxious, easily upset
5. Open to new experiences, complex
6. Reserved, quiet
7. Sympathetic, warm
8. Disorganized, careless
9. Calm, emotionally stable
10. Conventional, uncreative

Appendix J: Taste Ratings Questionnaire

ID#: _____ Food Item: _____

Taste Ratings

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