Investigation into the neurocognitive mechanisms underlying self-regulatory processes in eating behaviours

by

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A thesis

presented to the University of Waterloo

in fulfillment of the

thesis requirements for the degree of

Doctor of Philosophy

in

Public Health and Health Systems

Waterloo, Ontario, Canada, 2017

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Author's Declaration

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

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Abstract

Prior research has demonstrated that the integrity of the executive control system is correlated with obesogenic behaviour tendencies in a theoretically meaningful way. However, due to the paucity of experimental evidence demonstrating directionality and causality of this relation, there is a need for research investigating the nature via which prefrontal-mediated executive control abilities influence vulnerability to obesity-conducive eating habits (i.e., the overconsumption of calorie dense snack foods). As such, current body of research employed experimental methodologies to assess the causal relation between the functionality of the prefrontal cortex (PFC) and dietary self-restraint as mediated via executive control. A secondary objective was to determine the capacity via which aerobic exercise and continuous theta burst (cTBS) methodologies can be used to both attenuate and optimize executive control within an experimental context. Study 1 used meta-analytic methods to determine the reliability of validity of both up-regulatory (intermittent theta burst stimulation; iTBS) and down-regulatory (cTBS) theta burst stimulation (TBS) methodologies targeting the PFC on executive function (EF) task performance. Findings suggest that TBS protocols appear to be valid and effective means of modulating EF task performance within experimental contexts. However, the attenuating effects of cTBS may be more reliable than the excitatory effects of iTBS. Study 2 utilized cTBS and EEG methodologies to assess the extent in which changes in attentional engagement to high caloric food images and cognitive control influence consumptive patterns. Findings indicated that the attenuation of activity in the left dorsolateral prefrontal cortex (dlPFC) via cTBS significantly impaired executive control abilities. Further, a significant increase in the cravings for and consumption of appetitive high caloric foods was apparent following active relative to sham cTBS, an effect that was mediated by a significant increase in the attentional engagement to high caloric food images. Most importantly, this effect was specific to high-caloric foods and did not translate to changes in cravings or consumption of low calorie foods. Study 3 sought to determine whether

aerobic exercise methodologies can be used to enhance EF following temporary perturbations in dlPFC functionality. Findings indicated that an acute bout of moderate intensity exercise mitigated the cTBS-induced decrements in EF more quickly than the very light intensity control condition. Study 4 used the same aerobic exercise methodologies as Study 3 to determine if exercise-induced enhancements in executive control results in the subsequent transfer to self-control in the dietary domain. Findings revealed that a bout of moderate aerobic exercise can both enhance inhibitory control and improve dietary choices, providing the first evidence of a direct cross-domain transfer effect of exercise-induced cognitive enhancement to an unrelated domain. Together, these findings demonstrate that the attenuation and optimization of EFs results in subsequent changes in dietary self-restraint in the theorized directions.

Acknowledgements

I have many, many, people to thank. I wouldn't have been able to get my PhD without their unwavering support throughout this journey.

First and foremost, I would like to thank my supervisor Dr. Peter Hall. Thank you for putting up with me all these years. I have grown so much as a person and researcher over the years, and I wouldn't be where I am today without your guidance and support. I would also like to thank my committee members, Dr. Richard Staines and Dr. John Mielke. Thank you for all the valuable help, guidance, and advice you provided throughout this entire process.

To past and present lab mates, thank you for all your support in data collection and all other aspects of lab life. Thank you for putting up with my quirks and my coffee habit (aka convincing you to take a break to get coffee with me) over the years.

During graduate school I was fortunate to meet some of the most wonderful and amazing people, and I will cherish those friendships deeply. Because of them, I never felt alone during this process. To Jerrica, Andrea, Robyn, Danielle, Felicia, Rachel, thank you so much for always being there to lend an ear. Thank you for all the good times, the laughs, the coffee, sushi, and wine dates, and all the support and advice over the years.

To my "book club", though we have yet to actually read a book, the wine, movie, and concert dates kept me somewhat sane through out this process.

To my better half Mike, thank you for always believing in me, even when I didn't. You have been my rock throughout this process. I never could have made it this far without your love and support. Words will never be able to express how much your support has meant to me over the years. I don't know where this journey will take us, but I am so glad that you will be by my side the entire time.

Joey, Oscar, Chloe, Carl, and Zelda, thank you for the constant stress relief and unconditional love and unwavering support you provide. You are always there to listen when I need to talk through things or practice a presentation. Special thanks to Joey and Chloe for bullying me into going for walks when I am working at home. It is almost like you know that too much sedentary time is bad for your health. And to Oscar, you make morning yoga oh so much better.

Lastly, I would like to thank coffee, tea, and all things caffeinated that made all the early mornings and late nights possible.

Table of Contents

List of Tables

List of Figures

List of Abbreviations

EF	Executive function
GNG	Go No/Go
SST	Stop signal task
PVT	Psychomotor vigilance task
TOL	Tower of London
MCST	Montreal card sorting task
BMI	Body mass index
PFC	Prefrontal cortex
dlPFC	Dorsolateral prefrontal cortex
aPFC	Anterior prefrontal cortex
dlAVC	Dorsolateral anterior visual cortex
ACC	Anterior cingulate cortex
OC	Occipital cortex
IFG	Inferior frontal gyrus
MFG	Middle frontal gyrus
SFG	Superior frontal gyrus
NAc	Nucleus accumbens
VP	Ventral striatopallidum
VTA	Ventral tegmental area
NIBS	Non-invasive brain stimulation
tDCS	Transcranial direct current stimulation
TMS	Transcranial magnetic stimulation
spTMS	Single pulse transcranial magnetic stimulation
rTMS	Repetitive transcranial magnetic stimulation
TBS	Theta burst stimulation
cTBS	Continuous theta burst stimulation
iTBS	Intermittent theta burst stimulation
MEP	Motor-evoked potential
RMT	Resting motor threshold
AMT	Active motor threshold
APB	Abductor pollicus brevis
FDI	First dorsal interosseous
LTP	Long-term potentiation
LTD	Long-term depression
NMDA	*N*-methyl-d-aspartate
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
GABA	Gamma-amino-butyric acid
BDNF	Brain-derived neurotrophic factor
CaMKII	Calcium/calmodulin-dependent kinase II
PP1	Protein phosphate 1
IGF-1	Insulin-like growth factor-1
TrKB	Tropomyosin receptor kinase B

VEGF	Vascular endothelial-derived growth factor
fMRI	Functional magnetic resonance imagining
ERP	Event-related potential
EEG	Electroencephalogram
LPP	Late positivity potential
FAA	Frontal alpha asymmetry
MCA_v	Middle cerebral artery blood velocity
RHR	Resting heart rate
RPE	Rate of perceived exertion
THR	Target heart rate
TI	Target intensity
HRR	Heart rate reserve

Chapter 1 Background

Food consumption is an essential human behaviour, yet the factors that influence consumptive decisions are complex and poorly understood. Homeostatic needs, genetic factors, central and peripheral neurobiological factors, as well as social, environmental, and cognitive factors all influence a person's motivation to consume or abstain from eating certain foods (Berthoud, 2012; Johnson, 2013; Morton, Cummings, Baskin, Barsh, & Schwartz, 2006; Morton, Meek, & Schwartz, 2014). Nonetheless, within the context of chronic disease prevention, the homeostatic drive to consume food is not of central concern. Rather, non-homeostatic consumptive behaviours (i.e., consuming food outside of homeostatic need) in conjunction with the type of food being consumed is of central concern as there is a well-established link between dietary choices and health outcomes. The overconsumption of processed carbohydrates (e.g., added sugars) and saturated fats, outside of physiological need, is a risk factor for numerous chronic diseases, including cardiovascular disease, cerebrovascular disease, type 2 diabetes mellitus (de Souza et al., 2015; Mozaffarian et al., 2015; Reedy et al., 2014; Stanhope et al., 2015), and intermediate risk factors for chronic disease, including weight gain and excess adiposity (Bailey, Sullivan, Kirk, & Donnelly, 2010; Levy et al., 2011; Swinburn, Caterson, Seidell, & James, 2004).

From a public health perspective, determining the factors that influence obesity-conducive dietary habits are of an upmost importance. Current estimates indicate that at over 2.2 billion adults are overweight, of which, an estimate 400 million are obese (Finucane et al., 2011; Ng et al., 2014). In Canada, suboptimal dietary habits are considered the leading cause of chronic disease and death, and the prevalence of nutrition-specific chronic diseases and intermediate risk factors are steadily increasing (Public Health Agency Canada, 2011a). For instance, in 2008/2009 approximately 7% of Canadians were diagnosed with type 2 diabetes mellitus, a number that has increased almost 70% from 1998 (Public Health Agency Canada, 2011b). The prevalence of hypertension and high total blood cholesterol are an estimated 27.4% and 41% respectively (Wolf-Maier et al., 2003; Statistics Canada, 2010). It is estimated that 1 in 4 Canadian adults are living with

obesity, and another 37% are overweight (Public Health Agency Canada, 2011a). This equates to two thirds of the Canadian population having an elevated risk for developing a chronic disease due to excess weight and adiposity. The economic burden (i.e., direct healthcare cost) attributable to overweight and obesity, and by extension unhealthy eating, in Canada is an estimated $11 billion annually (Janssen, 2013). It is evident that modifiable nutritional factors substantially impact individual and population level health and wellbeing. Yet, a common theoretical framework for understanding the factors that mitigate obesity-conducive eating behaviours has not emerged within the literature. Understanding these mechanisms may be essential in elucidating both the etiology of the obesity pandemic and developing effective interventions aimed at reducing problematic dietary habits.

1.1 Environmental mismatch and dietary preferences

Optimal dietary habits require individuals to forego, or at least limit, the consumption of appetitive, but unhealthy, food items (e.g., piece of coconut cream pie) in favour of the healthier alternative (e.g., apple). However, it is difficult to conceptualize the processes underlying this decision process without first considering how default food preferences intersect with environmental conditions to modulate dietary patterns. From an evolutionary perspective, individual level vulnerability to ill-health can be viewed as a function of a fundamental mismatch between the environment in which most of human evolution took place and the modern environment (Gluckman, Low, Buklijas, Hanson, & Beedle, 2011). Within the context of dietary habits, it can be argued that susceptibility to obesity is a function of a mismatch between evolutionary based food preferences and the modern environment.

Humans evolved with an innate preference for calorie dense foods, particularly for those high in sugar and/or fat (Drewnowski, 1997; Drewnowski & Greenwood, 1983; Mennella & Bobowski, 2015), making the consumption such foods the default option (i.e., humans are more likely to select the coconut cream pie over an apple when presented with both options). While such

mechanisms ensured species survival during periods of food scarcity or uncertainty, food scarcity is no longer a concern for most individuals in developed nations. Instead, modern environments are saturated with an abundance of highly appealing calorie dense foods coupled with ubiquitous consumptive cues (e.g., media advertisements). The exposure to both palatable food and food cues can induce excessive food cravings and the tendency to overindulge on calorie-dense snack foods in the absence of physiological hunger (Finlayson & Dalton, 2012; Lutter & Nestler, 2009). Such food-cue reactivity is similar across cue modalities (i.e., images versus actual food stimuli; Boswell & Kober, 2016). As such, healthy dietary choices are dependent on the ability to override autonomic visceral response (e.g., cravings) to appetitive food stimuli, especially in the modern obesogenic environment, and otherwise exert conscious control over food choices. Such abilities are modulated via executive control and by extension the operation of the prefrontal cortex (PFC).

1.2 Sex differences in eating behaviours

Converging evidence has consistently reported that clinical manifestations of eating disorders (Kjelsås, Bjørnstrøm, & Götestam, 2004; Woodside et al., 2001) and the prevalence of obesity (Flegal, Carroll, Ogden, & Curtin, 2010) is higher among individuals that are biologically female relative to male. Such sex based differences in eating behaviours and the regulation of body weight may be attributable to biological differences in food cravings and neural responsivity to food stimuli. Relative to men, women report stronger food cravings for calorie dense foods (Lafay et al., 2001), and show greater activation in the dorsolateral prefrontal cortex (dlPFC; Cornier, Salzberg, Endly, Bessesen, & Tregellas, 2010) and reward regions of the cortex, including the dorsal and ventral striatum, amygdala, and parahippocampal gyrus (Chao et al., 2017), in response to food cues. Further, reward region responsivity to food cues is associated with overeating and an elevated body mass index (BMI) in women, but not men (Chao et al., 2017). Together, these data demonstrate that females are more responsive to both food stimuli and the overindulgence of high calorie foods in response to food cues. However, the mechanisms underlying these observed sex

based differences remain unclear, and may be associated with differences in socialization regarding health beliefs or ideal body shapes and weights (Wardle et al., 2004), gonadal hormones (Asarian & Geary, 2006; Butera, 2010; Smith, Sierra, Oppler, & Boettiger, 2014), or evolutionary differences. Maternal nutrition plays a crucial role in fetal development and subsequent health in adulthood in that fetal undernutrition is associated with lower body weights at birth and an increased risk of obesity and associated health conditions in adulthood (Gluckman & Hanson, 2004; Gluckman et al., 2011). Therefore, it is plausible that females evolved with a higher preference for calorie dense foods to ensure adequate nutrition during pregnancy, thus, ensuring species survival.

1.3 Executive functions

Humans have a highly evolved PFC that enables numerous cognitive or executive processes (Friedman & Miyake, 2017; Miller & Cohen, 2001; Miller, 2000). Executive function (EF) is an overarching term used to refer those to higher-order cognitive functions implicated in the "top-down" control (i.e., non-stimulus driven control) of human behaviour (Baddeley, 1996; Miyake et al., 2000; Miyake & Friedman, 2012). Conceptually, EF consists of a unitary construct that can be further decomposed into several interconnected, but distinguishable, subcomponents that together potentiate complex processes and behaviours (e.g., planning and decision-making; Miyake et al., 2000; Miyake & Friedman, 2012). Although the subcomponents conceptualized under the domain of EF may differ among theoretical models, most models include behavioural inhibition, mental flexibility and working memory; other subcomponents may include verbal fluency and attentional control. Statistically speaking, behavioural inhibition is considered to be the most pure manifestation of EF in that factor-analytic analyses have demonstrated that performance on inhibitory control measures correlates perfectly (i.e., correlation of 1.0) with the unitary EF factor (Miyake et al., 2000; Miyake & Friedman, 2012).

1.4 Prefrontal cortex and executive control

A wealth of neuroimaging studies of EF in healthy populations have consistently performance on EF measures corresponds with subsequent activation in regions within the PFC and anterior cingulate cortex (ACC; Aron, Robbins, & Poldrack, 2014; Banich & Depue, 2015; Barbey, Koenigs, & Grafman, 2013; Crowe et al., 2013; Kim, Cilles, Johnson, & Gold, 2012; Kim, Johnson, Cilles, & Gold, 2011; Kim & Lee, 2011; Macdonald, 2010; Wager, Jonides, & Reading, 2004; Wager et al., 2005; Wager & Smith, 2003). These findings are consistent with those demonstrating that both lesions to (Alvarez & Emory, 2006) and the structural integrity of the PFC (Smolker, Depue, Reineberg, Orr, & Banich, 2014; Yuan & Raz, 2014) are associated with variations in executive functioning. Further, several lines of evidence have demonstrated that experimental (i.e., neuromodulation) and naturalistic attenuation (e.g., acute stress, sleep restriction, alcohol intoxication) of prefrontal activity results in subsequent performance deficits on EF measures (Arnsten, 2009; Cho et al., 2012; Ko et al., 2008; Marinkovic, Rickenbacher, Azma, & Artsy, 2012; Murray et al., 2012; Nilsson et al., 2005; Porcelli et al., 2008; Rossa, 2012; Sandrini, Rossini, & Miniussi, 2008). Although involvement of non-prefrontal cortical regions (e.g., parietal lobe, inferior frontal junction) has been documented (Alvarez & Emory, 2006; Derrfuss, Brass, Neumann, & von Cramon, 2005), together, these data suggest that the PFC is the main neuroanatomical region involved in executive functioning.

The extent in which functional specialization can be attributed to discrete sub regions of the PFC has been well documented. Of particular interest is the association between cortical activity in the dlPFC and executive control and self-regulation. Several lines of research have implicated the operation of dlPFC in several executive processes, including inhibitory control (Brunoni & Vanderhasselt, 2014; MacDonald et al., 2000; Tupak et al., 2013; Vanderhasselt, De Raedt, & Baeken, 2009; Xu et al., 2017; Yanagisawa et al., 2010), and self-regulation more broadly (Hare, Camerer, & Rangel, 2009; Hare, Malmaud, & Rangel, 2011; Harris, Hare, & Rangel, 2013; Kober et al., 2010). The

operation of the left dlPFC, in particular, plays a crucial role in dietary self-control (Hare et al., 2009) and cognitive regulation of visceral cravings (Kober et al., 2010; Scharmüller, Übel, Ebner, & Schienle, 2012). Consistent with this notion, prior research has demonstrated that experimental attenuation (using continuous theta burst stimulation (cTBS)) of left dlPFC activity predisposes an individual the overconsumption of calorie dense food, an effect that was mediated via stimulation-induced changes in inhibitory control (Lowe, Hall, & Staines, 2014). However, there is currently a limited amount of research examining the mediational relation between dlPFC functionality and executive control, and the underlying neural correlates potentiating such a relation; thus, further investigation is warranted.

1.5 Neurocognitive correlates of dietary self-restraint

Prior research has demonstrated that the integrity of the executive control system is indeed correlated with obesogenic behaviour tendencies in a theoretically meaningful way (Appelhans, 2009; Hall, 2016; Vainik, Dagher, Dubé, & Fellows, 2013), and the potency of this relation is amplified when environmental (consumptive) cues are facilitating in nature (Hall et al., 2014; Hall, Lowe, & Vincent, 2014). Nonetheless, while the nature and function of EF has been studied extensively, the emergence of conceptual models linking executive control to health-behaviours has only occurred within the last decade. However, there are several reasons why a common neurocognitive framework is necessary. First, most neurobehavioural frameworks of obesity-conducive consumptive behaviours have focused extensively on aberrant neural responses to food stimuli and subsequent relation to consumptive behaviour. The nature of executive control is often discounted within these models with the emphasis placed on hyper-or-hypo responsivity to food cues as the underlying factor driving the overconsumption of calorie dense foods (see Stice & Yokum, 2016a or Val-Laillet et al., 2015 for a review). These neurobehavioural models mimic that of drug addiction models, and support the contention that obesity is a product of food addiction (Davis et al., 2011; Volkow, Wang, Tomasi, & Baler, 2013; Volkow, Wang, & Baler, 2011). Further,

while reward responsivity is a potential pathway via which neural factors may increase susceptibility to obesity, such frameworks fail to account for self-regulatory abilities and by extension the capacity of the PFC to modulate activity in cortical and subcortical regions. Converging evidence has demonstrated that striatal dopaminergic neurotransmission is modulated via glutamatergic projections from the PFC to the ventral tegmental area (Taber, Das, & Fibiger, 1995; Tekin & Cummings, 2002), thus individual differences in reward sensitivity may be a direct reflection of prefrontal cortical activity (i.e., the ability of the PFC to modulate activity in reward regions of the cortex).

Second, most frameworks examining the relation between obesity and neurocognitive functioning focus on variations in executive control as an outcome rather than a predictor. Indeed, several lines of research have consistently reported that persons with obesity generally perform more poorly on measures of EF relative to their healthy weight counterparts (Gunstad, Paul, Cohen, Tate, & Gordon, 2006; Gunstad et al., 2007; Sargénius, Lydersen, & Hestad, 2017; Smith, Hay, Campbell, & Trollor, 2011), which may be attributable to structural and functional differences within the PFC (Brooks et al., 2013; Pannacciulli et al., 2006; Volkow et al., 2009; Willeumier, Taylor, & Amen, 2011). However, such frameworks do not take into account the potential reciprocal nature of prefrontal cortical activity in mitigating the risk of obesity. That is, individuals with lower executive control abilities may be more susceptible to the rewarding properties of calorie dense foods, which in turns leads to the overconsumption of such foods, resulting in the amplification of the effect via neuroanatomical changes in prefrontal structure and functionality. Thirdly, and most importantly, optimization of executive control abilities and the structure and functionality of the underlying cortical regions is possible, most notably via aerobic exercise (Chang, Labban, Gapin, & Etnier, 2012; Colcombe et al., 2006; Erickson, Hillman, & Kramer, 2015; Smith et al., 2010; Voss et al., 2010). It is important to consider the implications of this from a public health standpoint, as it is unlikely that the food environment will drastically change any time soon, at least to the extent

necessary to notice discernable differences in obesity risk and susceptibility. However, from a prevention standpoint, the use of exercise interventions and promotions at the individual and population level has the potential to reduce susceptibility to obesity via increased executive control.

To date, most studies exploring the relation between executive control and consumptive behaviours have been observational, and thus, directionality and causality cannot be ascertained. Therefore, in order to develop a convincing neurocognitive framework for understanding the factors that mitigate obesity-conducive eating behaviours the experimental manipulation of activity in the cortical regions underlying EFs is necessary to ascertain causality and directionality of the effect. A recent meta-analytic review reported the attenuation of visceral food cravings following repetitive transcranial magnetic stimulation (rTMS) or transcranial direct current stimulation (tDCS) induced enhancement of dlPFC activity. Comparison of neuromodulation methods revealed that the stimulation effect on food cravings was significant for rTMS, but not tDCS. While it is plausible that laterality effects contributed to the observed findings (i.e., all studies targeting the right dlPFC were tDCS studies), these findings indicate that rTMS methodologies are effective means to study the neural factors influencing visceral cravings (Lowe, Vincent, & Hall, 2017). Null effects were observed with respect to consumptive behaviours (Lowe, Vincent, et al., 2017), however, a recent update demonstrated that this was directly attributable to insufficient power to detect an effect rather the absence of an effect (Hall, Lowe, & Vincent, 2017); the addition of four new studies rendered the consumptive effects significant. Although these data quantitatively demonstrate the causal relation between activity in the dlPFC and food cravings and consumption, cognitive mediators of the effect were not addressed.

1.6 Non-invasive brain stimulation methodologies

Non-invasive brain stimulation methodologies are a class of neuroscience tools that are able to safely modulate cortical plasticity in research and clinical settings. Thus, such methods would allow for causal examination into the neurocognitive mechanisms underlying prefrontal

functionality and dietary self-restraint. While there has been some debate whether such methods can be considered non-invasive, these methods have made remarkable contributions, both therapeutically and experimentally, over the last 2 decades. Unlike other methodologies, NIBS allows researchers to test the causal relation between cortical functionality in specific brain regions in cognitively intact human populations while avoiding the confounds with animal models, neurosurgical procedures, or patients with uncontrollable focal brain lesions and reorganization of brain function, which may occur in the event of a brain lesion (Dayan, Censor, Buch, Sandrini, & Cohen, 2013; George & Aston-Jones, 2010; Hallett, 2000; Hallett, 2007). Further, NIBS studies can be conducted across multiple participants, and can be repeated on the same participant, allowing for controlled experimental designs; thus researchers are able to infer a causal relationship between focal brain activity and subsequent behavior (Dayan, Censor, Buch, Sandrini, & Cohen, 2013; George & Aston-Jones, 2010; Hallett, 2000; Hallett, 2007). The two most widely used NIBS are transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS).

1.61 Transcranial Direct Current Stimulation

In tDCS, saline-soaked electrodes of different polarities (anodal and cathodal) are placed in different positions on the scalp, and a battery-driven stimulator delivers a weak electrical current (≤1 mA) between electrodes (Dayan et al., 2013; Nitsche et al., 2008; Utz, Dimova, Oppenländer, & Kerkhoff, 2010); anodal stimulation is facilitatory, whereas, cathodal stimulation is inhibitory. The efficacy of tDCS is dependent on the current density, which determines the strength of the electrical field, and current strength, electrode size, and positioning of the electrodes, which determines the direction and distribution of the electrical current (Nitsche et al., 2008; Utz et al., 2010). Approximately 50 % of the applied electrical current enters the brain through the skull, and the acute modifications of cortical excitability have been attributed to stimulation-induced polarity-shifts within the resting membrane potential (Nitsche et al., 2008; Stagg & Nitsche, 2011; Utz et al., 2010). The longer-lasting after-effects have been attributed to modulation of *N*-methyl-d-aspartate

(NMDA) and gamma-amino-butyric acid (GABA) receptor efficiency in the terms of long-term potentiation (LTP) or long-term depression (LTD; George & Aston-Jones, 2010; Nitsche et al., 2008; Stagg & Nitsche, 2011). Specifically, although there is some evidence that LTP may be modulated by stimulation-induced change in GABAergic inhibition, the excitatory effects of anodal tDCS appear to be primarily associated with stimulation-induced changes in NMDA receptor efficiency. Conversely, the LTD (inhibitory) like effects of cathodal tDCS are thought to be primarily related to stimulation-induced reductions in excitatory glutamatergic transmission (George & Aston-Jones, 2010; Stagg & Nitsche, 2011).

In comparison with TMS, tDCS produces similar after effects and is easier to use, however tDCS is less focal than TMS (Dayan et al., 2013; George & Aston-Jones, 2010). Further, recent systematic and meta-analytic reviews have suggested that the effects of tDCS are not reliable across cognitive and neurophysiological measures outside of modulation of motor-evoked potentials (MEP; Horvath, Forte, & Carter, 2015a, 2015b).

1.62 Transcranial Magnetic Stimulation

The basic TMS apparatus consists of a wire coil that is placed directly on the scalp. To permit focal stimulation, two circular coils are combined to form a figure eight (George & Aston-Jones, 2010; Hallett, 2007; Wassermann & Zimmermann, 2012). The coil emits electromagnetic pulses—of varying length, form and intensity—that induce changes in cortical excitability (upwards or downwards) in the cortical region below the area of application. TMS can be applied as a single pulse (spTMS) or a repetitive train of pulses (rTMS; George & Aston-Jones, 2010; Hallett, 2007; Wassermann & Zimmermann, 2012). The duration of spTMS is less than 1 ms, whereas the duration of rTMS can typically span between 10 and 25 minutes (George & Aston-Jones, 2010; Hallett, 2007; Wassermann & Zimmermann, 2012). The type of TMS paradigm used depends on the brain behavior relation being investigated. Single pulse TMS is effective for producing short responses,

and are usually used to measure muscle movements; spTMS-induced neuronal changes only last for approximately 40-60ms, which is sufficient for studying motor movements (Dayan et al., 2013; George & Aston-Jones, 2010; Hallett, 2007; Wassermann & Zimmermann, 2012). However, stimulation and task performance must occur concurrently when using spTMS paradigm (Dayan et al., 2013; George & Aston-Jones, 2010; Hallett, 2007). Conversely, in rTMS, a train of pulses is delivered at a frequency up to 50 Hz, evoking sustained changes in neural activity (after effects) for up to 60 minutes post-stimulation (Dayan et al., 2013; George & Aston-Jones, 2010; Hallett, 2000; Hallett, 2007; Ridding & Rothwell, 2007). Generally speaking, stimulation frequencies higher than 1 Hz increases cortical excitability, whereas, stimulation frequencies lower than 1 Hz tends to produce an inhibitory after effect by decreasing cortical excitability (Dayan et al., 2013; George & Aston-Jones, 2010; Hallett, 2000; Hallett, 2007; Ridding & Rothwell, 2007).

1.63 Theta burst stimulation

Theta burst stimulation (TBS) is a variant of rTMS which consists of three short pulses (between 50-100 Hz) that are repeated every 200 ms (5Hz; Huang, Edwards, Rounis, Bhatia, & Rothwell, 2005); the parameters for TBS were designed to mimic theta rhythms (Huang, Rothwell, Chen, Lu, & Chuang, 2011). There are two types of TBS: continuous TBS (cTBS) and intermittent TBS (iTBS). In cTBS, the pulses are applied at a rate of 5 Hz for either 20 seconds (100 bursts) or 40 seconds (200) bursts, resulting in an inhibitory effect (Huang et al., 2005). Conversely, in iTBS the pulses are applied at a rate of 0.1 Hz in 2s intervals, resulting in a facilitating effect (Huang et al., 2005). Because TBS can be administered in a shorter time interval than traditional rTMS methods, it is considered to be more efficient than other forms of rTMS. As such, TBS is becoming the preferred method of administering rTMS from an experimental standpoint.

1.64 Basic principles of TMS

TMS utilizes the principles of electromagnetic induction to selectively activate or inhibit regions of the cortex (Dayan et al., 2013; George & Aston-Jones, 2010; Hallett, 2007; Wassermann & Zimmermann, 2012). A standard TMS coil can be used to stimulate cortical regions located 1.5-2 cm beneath the surface of the skull, thus limiting the brain regions that can be stimulated; therefore, standard TMS methodologies cannot be used to directly stimulate deep brain regions, such as the hippocampus. The coil produces a small magnetic field (between 1.5-2 tesla; T), that lasts for approximately a millisecond (Dayan et al., 2013; George & Aston-Jones, 2010; Hallett, 2007; Wassermann & Zimmermann, 2012). The magnetic field penetrates the skull and induces an intracranial electrical current, resulting in neuronal depolarization and subsequently an action potential (Dayan et al., 2013; George & Aston-Jones, 2010; Hallett, 2007; Wassermann & Zimmermann, 2012). Although the mechanisms responsible for TMS after effects are still unclear, the induced intracranial electrical current is thought to stimulate the axons of the neurons in the cortex and subcortical white matter, as opposed to the neuronal cell bodies (George & Aston-Jones, 2010; Hallett, 2007; Ridding & Ziemann, 2010; Ridding & Rothwell, 2007). Short term after effects (a few seconds to a couple minutes) can be attributed to changes in neural excitability (e.g., shifts in ionic balance) and disappear almost immediately after TMS cessation (Dayan et al., 2013; George & Aston-Jones, 2010; Hallett, 2007; Wassermann & Zimmermann, 2012). However, longer lasting after effects (30 to 60 minutes) are likened to changes in synaptic efficiency in the forms of LTD or LTP between neurons (Hallett, 2007; Huang et al., 2011; Ridding & Ziemann, 2010; Ridding & Rothwell, 2007).

1.623 Physiological mechanisms

LTP is thought to be directly mediated by presynaptic glutamate transmission and coincident activation of pre-and-postsynaptic neurons (Clapp, Hamm, Kirk, & Teyler, 2012; Lüscher & Malenka, 2012). Depolarization of the postsynaptic neuron occurs when glutamate is released

from the presynaptic neuron. The concurrent depolarization and binding of glutamate in the postsynaptic neuron results in an influx of calcium (Ca^{2+}) through postsynaptic NMDA receptors, subsequently activating the signalling cascades responsible for changes in synaptic efficiency (Clapp et al., 2012; Lüscher & Malenka, 2012). More specifically, binding of glutamate in the postsynaptic neuron causes an influx of sodium ions-via the fast ionotropic α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors-into the neuron. The subsequent change in voltage triggers the activation of NMDA receptors resulting in the transient increase in postsynaptic Ca^{2+} levels (Clapp et al., 2012; Lüscher & Malenka, 2012).

The influx of Ca^{2+} to the postsynaptic neuron concurrently triggers both inhibitory and excitatory pathways, and the induction of LTP (excitatory) relative to LTD (inhibitory) is dependent on Ca^{2+} entry rate and absolute levels (Clapp et al., 2012; Lüscher & Malenka, 2012). The rapid increase of Ca^{2+} into the postsynaptic neuron increases calcium concentrations in the dendritic spine, subsequently activating the calcium/calmodulin-dependent kinase II (CaMKII; Clapp et al., 2012; Lüscher & Malenka, 2012). This phosphorylation of CaMKII increases conductance of the AMPA receptor channel, triggering LTP like increases in synaptic activity and efficiency (Clapp et al., 2012; Lüscher & Malenka, 2012). In contrast, the induction of LTD appears to be dependent on the calcium/calmodulin-dependent protein phosphatase calcineurin and protein phosphate 1 (PP1; Clapp et al., 2012; Lüscher & Malenka, 2012). Calcineurin has a higher affinity for calcium than CaMKII, and thus, low-to-moderate increases in Ca^{2+} results in preferential activation of this protein and the dephosphorylation of CaMKII, which in turn decreases AMPA receptor channel conductance, and subsequent synaptic activity (Clapp et al., 2012; Lüscher & Malenka, 2012).

High-frequency TMS triggers the release of glutamate from the presynaptic neuron, subsequently activating postsynaptic NMDA receptors and the transient increase in postsynaptic Ca^{2+} levels (Clapp et al., 2012; Feldman, 2009; Huang, Chen, Rothwell, & Wen, 2007; Lüscher & Malenka, 2012; Meunier, Chameau, & Fossier, 2017). In TBS specifically, the intermittent short

trains of TBS delivered in iTBS results in the rapid change of Ca^{2+} levels, however, the absolute level remains low, resulting in an excitatory effect (Huang et al., 2007, 2011). Conversely, in cTBS the absolute levels of Ca^{2+} are sustained, however, the rate of change is low, resulting in an inhibitory effect (Huang et al., 2007, 2011). Pharmacological blockade of either Ca^{2+} or NMDA (with receptor antagonists such as memantine or dextromethorphan) receptors suppresses the after effects of TBS (Huang et al., 2007). Conversely, NMDA agonists (such as D-cycloserine) can prolong the after effects (Huang et al., 2007). Taken together, these data suggest that the TBS after effects can be attributed to LTP/LTD like changes in synaptic plasticity (Huang et al., 2007).

1.7 Exercise and Neurocognitive Functioning

The beneficial effects of regular physical activity on neurocognitive functioning are well-documented. Cross-sectional studies have consistently reported that across the lifespan higher levels of self-reported physical activity and cardiorespiratory fitness (an index of aerobic fitness) are associated with superior performance on a variety of cognitive tasks (Etnier et al., 1997; Etnier, Nowell, Landers, & Sibley, 2006; Hillman, Castelli, & Buck, 2005; Hillman, Khan, & Kao, 2015; Sibley & Etnier, 2003; Verburgh, Konigs, Scherder, & Oosterlaan, 2013). Among the different exercise modalities, aerobic exercise is particularly facilitative of cognitive improvements. Reliable increases in cognitive functioning is observed following both single-session and multi-session training formats (Chang, Labban, Gapin, & Etnier, 2012; Lambourne & Tomporowski, 2010; Ludyga, Gerber, Brand, Holsboer-Trachsler, & Pühse, 2016; McMorris & Hale, 2012; Smith et al., 2010; Verburgh et al., 2013). Exercise-induced improvements in EF, attention, and processing speed are apparent following aerobic exercise interventions lasting as little as one month, and these effects are not moderated by the age of the participant, or the duration and intensity of the exercise regime (Smith et al., 2010).

In acute bout studies, exercise-induced improvements in neurocognitive functioning have been observed following as little as 20 minutes of moderate intensity exercise, with the largest

effects being observed 11-20 minutes post-exercise (Chang et al., 2012). However, these effects are not uniform across all cognitive domains. While a general exercise-induced improvement in cognition is observed, the largest effects are observed on measures of executive functioning (McMorris & Hale, 2012), suggesting that EFs in particular may be the most sensitive to exercise-induced improvements in neurocognitive functioning. Consistent with this notion, the acute effects of aerobic exercise appear to be specific to prefrontal-dependent cognitive abilities (i.e., EF), and do not translate into changes in hippocampal-dependent cognitive functions (e.g., long-term memory; Basso, Shang, Elman, Karmouta, & Suzuki, 2015). Within the acute exercise and EF literature the majority of studies have focused predominately on the behavioural inhibition subcomponent, and collectively, these studies have demonstrated that acute exercise can improve inhibitory control in both young (Chang, Chu, Wang, Song, & Wei, 2015; Ferris, Williams, & Shen, 2007; Lowe, Hall, Vincent, & Luu, 2014; Lowe, Kolev, & Hall, 2016; Sibley, Etnier, & Masurier, 2006; Yanagisawa et al., 2010) and older adults (Barella, Etnier, & Chang, 2010; Hyodo et al., 2012, 2016; Keita Kamijo et al., 2009) for up to 52 minutes post-exercise (Joyce, Graydon, McMorris, & Davranche, 2009).

1.71 Aerobic exercise and cortical functionality

Electrophysiological studies have consistently demonstrated that the latency and amplitude of the P3 event related potential (ERP) component is especially sensitive to physical exercise. The P3—an endogenous component generated by an anatomically diffuse network of cortical and subcortical structures—is thought to reflect the neural processes underlying several higher cognitive functions typically engaged during executive control tasks (e.g., inhibition, working memory, attention, and stimulus processing; Polich, 2007). The amplitude of the P3 is thought to reflect the neural or attentional resources afforded to a given task or stimulus, whereas, the latency reflects cognitive processing speed (Polich, 2007). Across a variety of cognitive tasks, greater amounts of physical activity are associated with larger amplitudes and shorter P3 latencies (Hillman, Castelli, & Buck, 2005; Hillman, Belopolsky, Snook, Kramer, & McAuley, 2004; Polich &

Lardon, 1997; Pontifex, Hillman, & Polich, 2009). Such physical activity-related modulation of cortical functionality is substantially larger for cognitive measures requiring greater amounts of executive control (Hillman et al., 2006). Similarly, exercise-induced enhancements in P3 amplitude (Chang et al., 2017; Drollette et al., 2014; Hillman et al., 2009; Hillman, Snook, & Jerome, 2003; Kamijo et al., 2009) and reductions in P3 latencies (Chang et al., 2017; Drollette et al., 2014; Hillman et al., 2003; Kamijo et al., 2009) are observed following acute bouts of aerobic exercise, and these effects are specific to those task components involving some degree of inhibitory control. Together, these data suggest that aerobic exercise generally improves neurocognitive functioning by increasing the attentional resources afforded to a given task and cognitive processing speed during stimulus encoding.

In agreement with the above findings, functional magnetic resonance imagining (fMRI) studies have shown aerobic exercise training modulates cortical functionality, and these changes in functionality may precede structural changes. For instance, increased activation in anterior prefrontal, ACC, middle and superior frontal gyrus, and superior PFC during EF and selective attention tasks is observed following aerobic exercise interventions in normal weight and children with obesity, and older adults. Such changes in functionality were directly associated with exercise-induced improvements in neurocognitive functioning (Chaddock-Heyman et al., 2013; Colcombe et al., 2004; Krafft et al., 2014). Similar patterns of activation are observed following acute bouts of aerobic exercise. Increased activation in the right middle prefrontal gyrus, right lingual gyrus, and left fusiform gyrus during a working memory task are observed following a 20 minute bout of moderate intensity exercise (Li et al., 2014). However, the neurobiological mechanisms underlying exercise-induced improvements in cognition and cortical function are not entirely understood, and likely vary depending on the duration, intensity and frequency of the exercise (acute versus long-term). Several potential mechanistic explanations for why exercise has beneficial effects on neurocognitive functioning have been proposed, and include neurochemical mediators such as

brain-derived neurotrophic factor (BDNF) levels (Cotman, Berchtold, & Christie, 2007; Dinoff, Herrmann, Swardfager, & Lanctôt, 2017; Voss, Vivar, Kramer, & van Praag, 2013), changes in global and regional cerebral blood flow (Giles et al., 2014; Rooks et al., 2010; Tempest et al., 2014; Yanagisawa et al., 2010), as well as structural changes (Erickson et al., 2015; Kramer & Erickson, 2007). Each of these potential mechanisms will be discussed in more detail below.

1.72 Structural changes

At the neurophysiological level, higher cardiorespiratory fitness levels are associated with greater grey matter volume within the PFC (Weinstein et al., 2012) and hippocampus (Chaddock et al., 2010; Erickson et al., 2009), and white matter tract microstructural integrity within the cingulum, corpus callosum, superior corona radiate and inferior longitudinal fasciculus (Burzynska et al., 2014; Hayes, Salat, Forman, Sperling, & Verfaellie, 2015; Johnson, Kim, Clasey, Bailey, & Gold, 2012; Oberlin et al., 2016; Tian et al., 2014, 2015). In addition, the association between fitness and neurocognitive functioning is directly mediated by volumetric differences in prefrontal and hippocampal grey matter (Erickson et al., 2009; Weinstein et al., 2012), and white matter tract integrity (Oberlin et al., 2016). Further, long-term exercise interventions have yielded reliable increases in gray matter volume in the cortical regions underlying EFs and memory, specifically the PFC (Colcombe et al., 2006) and hippocampus (Erickson et al., 2011; ten Brinke et al., 2015). However, the observed structural changes are specific to long-term exercise interventions, indicating that acute sessions of aerobic exercise are not sufficient to induce structural changes in brain.

1.73 Cerebral blood flow

Increased cerebral blood flow and perfusion were proposed early on as primary mechanisms underlying the exercise-induced enhancements in cognition and cortical structure and function. Consistent with this, studies have shown that habitual engagement in aerobic exercise is associated with greater cerebral blood flow (Ainslie et al., 2008; Bailey et al., 2013; Chaddock-

Heyman et al., 2016). Likewise, aerobic exercise leads to widespread growth of blood vessels (i.e., angiogenesis) within the brain (Black, Isaacs, Anderson, Alcantara, & Greenough, 1990; Ding et al., 2006; van Praag, 2005), and this growth increases nutrient and energy supply, which helps maintain the observed exercise-induced enhancements in brain structure and function by facilitating the survival of neural stem cells and supporting neurogenesis (Blackmore, Golmohammadi, Large, Waters, & Rietze, 2009; Pereira et al., 2007; van Praag, Kempermann, & Gage, 1999; Wu et al., 2008). Finally, a more recent study found that exercise-induced volumetric changes in hippocampal gray matter are directly associated with increased cerebral perfusion (Maass et al., 2015). Together, these data suggest that exercise-induced changes in cerebral blood flow could modulate the observed structural changes following exercise interventions.

In addition, converging evidence has demonstrated that acute bouts of moderate intensity aerobic exercise increases middle cerebral artery blood velocity (MCA_v) and global cerebral blood flow by approximately 10-30 % (Jørgensen, Perko, & Secher, 1992; Ogoh et al., 2005). However, exercise-induced increases in prefrontal cerebral blood flow is only observed following moderate-to-high intensity exercise with discernible reductions occurring following high-to-very high intensity exercise (Rooks et al., 2010). This increase in cerebral blood flow is particularly pronounced in the frontal lobes, and is thought to underlie the acute exercise-related improvements in neurocognitive functioning (Endo et al., 2013; Giles et al., 2014; Guiney, Lucas, Cotter, & Machado, 2015; Ogoh et al., 2014; Tempest et al., 2014; Yanagisawa et al., 2010). For instance, exercise-induced improvements in inhibitory control are thought to be mediated, at least in part, by increased cerebral blood flow to the left dlPFC (Byun et al., 2014; Endo et al., 2013; Giles et al., 2014; Guiney et al., 2015; Yanagisawa et al., 2010). Conversely, there is some evidence suggesting that exercise-induced enhancements in EF occur despite reductions in MCA_V (Ogoh et al., 2014), indicating exercise-induced changes in cerebral blood flow alone, may not fully account for the observed changes in neurocognitive functioning.

The mechanisms via which exercise-induced increases in cerebral flood flow increases neurocognitive functioning may differ depending on whether the exercise occurs as a single bout, or as part of a longer-term training protocol. During acute bouts of low-to-moderate intensity aerobic exercise transient increases in cerebral metabolism are coupled with increases in internal carotid artery blood flow (Hellstrom, Fischer-Colbrie, Wahlgren, & Jogestrand, 1996; Sato, Ogoh, Hirasawa, Oue, & Sadamoto, 2011), and MCA_V (Ogoh, 2008; Ogoh & Ainslie, 2009), suggesting that the acute exercise-induced increases in cerebral blood flow may reflect the increased metabolic demands necessary to maintain the observed increase in neuronal activity. Conversely, the angiogenesis-specific changes in cerebral vascularization may be directly related to the long-term structural changes in that, over time, the increase in vascularization may increase the delivery of nutrients, oxygen, glucose, and peripheral growth factors, such as insulin-like growth factor-1 (IGF-1) and BDNF, which in turn promotes volumetric changes via neuronal proliferation, synaptogenesis, and dendritic branching, and protects against gray matter atrophy and white matter hyperintensities (Chieffi et al., 2017; Knaepen, Goekint, Heyman, & Meeusen, 2010; Querido & Sheel, 2007; Voss et al., 2013).

1.74 Brain-derived neurotrophic factor

Converging evidence from animal and human models have consistently demonstrated that serum BDNF levels are increased both during and following acute sessions of aerobic exercise (Cotman et al., 2007; Dinoff et al., 2017; T. Huang, Larsen, Ried-Larsen, Møller, & Andersen, 2014; Voss et al., 2013), and the magnitude of this effects is enhanced over time by habitual aerobic activity (Szuhany, Bugatti, & Otto, 2015). In addition, animal and human models have demonstrated that both short (2-14 days) and long periods (1-8 months) of aerobic exercise enhances BDNF gene expression and protein levels, and increases circulating BDNF levels (Cotman et al., 2007; Voss et al., 2013). Such exercise-induced increases in serum BDNF have been shown to mediate the effects of long-term aerobic exercise interventions on neurocognitive functioning (Leckie et al., 2014),

indicating that exercise-induced changes in BDNF levels may play a crucial role in modulating exercise intervention-specific enhancements in cognition. It should be noted that in humans peripheral serum BDNF levels are an indirect measure of levels within the cortex (i.e., brain levels are not directly measured in humans). However, BDNF can cross the blood-brain barrier in a directional nature (Pan, Banks, Fasold, Bluth, & Kastin, 1998) and an estimated 70-80% of circulating BDNF levels are thought to come from the brain (Rasmussen et al., 2009). Nonetheless, immune cells, platelets, and skeletal muscle cells also produce BDNF (Colombo et al., 2013; Fujimura et al., 2002; Matthews et al., 2009; Mousavi & Jasmin, 2006), and while the available evidence seems to suggest that skeletal muscle cell BDNF is not released into circulation (Matthews et al., 2009), the other sources can potentially confound measurements.

BDNF is a protein within the neurotrophin family that is essential for the growth, proliferation and differentiation, and survival of neurons and glial cells (Zagrebelsky & Korte, 2014). On average, a 60% increase in peripheral BDNF levels are observed following acute aerobic exercise (Dinoff et al., 2017). Such exercise-induced increases in circulating BDNF results in a cascade of neurotrophic effects that have a central role in promoting brain plasticity. Specifically, rapid exercise-induced increases in IGF-1 are observed following aerobic exercise, which in turn increases neuronal levels of tropomyosin receptor kinase B (TrKB; Cotman et al., 2007; Knaepen et al., 2010; Voss et al., 2013). BDNF utilizes TrkB to activate the signal transduction pathways thought to facilitate LTP, and promotes the structural remodeling of dendritic spines, synaptogenesis, and neurogenesis (Cotman et al., 2007; Hamilton & Rhodes, 2015; Knaepen et al., 2010; Voss et al., 2013), resulting in down-stream enhancements in cortical structure and function and subsequently cognition. Indeed, experimentally blocking either IGF-1 or BDNF signaling attenuates or ameliorates the observed exercise-induced inductions in synaptic efficiency (Cotman et al., 2007), indicating that involvement of both IGF-1 and BDNF play a crucial role in modulating exercise-induced improvements in neurocognitive functioning.

While, most prior research has focused on the exercise-induced effects on either BDNF or IGF-1 expression and levels, other potential mechanisms may play a crucial role in exercise-induced enhancements in neural plasticity. For instance, exercise-induced increases in vascular endothelial-derived growth factor (VEGF) mediates exercise-induced angiogenesis and neurogenesis (Cotman et al., 2007; Voss et al., 2013). VEGF promotes neurogenesis by stimulating cell proliferation and differentiation and increasing endothelial and astrocytic production of BDNF and IGF-1 (Cotman et al., 2007; Voss et al., 2013).

1.75 Neurotransmitter levels

Although the number of studies are limited, the available evidence has reported elevated levels of norepinephrine (Meeusen & De Meirleir, 1995), serotonin (Gomez-Merino, Béquet, Berthelot, Chennaoui, & Guezennec, 2001; Rabelo et al., 2015), dopamine (Berse et al., 2015; Goekint et al., 2012; Meeusen & De Meirleir, 1995; Winter et al., 2007), and epinephrine (McMorris et al., 2009; Zouhal, Jacob, Delamarche, & Gratas-Delamarche, 2008) following an acute bout of exercise. Such increases in neurotransmitter levels have been shown to modulate exercise-induced improvements in executive functioning. For instance McMorris et al. (2009) reported that exercise-induced increases in norepinephrine and epinephrine were significant predictors of flanker task performance during exercise. In addition, exercise-induced increases in dopamine and epinephrine are associated with success in both intermediate and long-term vocabulary retention (Winter et al., 2007).

The available evidence seems to suggest that cognitive enhancing effects of exercise-induced changes in neurotransmitter function may be specific to acute exercise modalities, however, the mechanisms via which exercise-induced increases in neurotransmitter levels modulate neurocognitive functioning likely differ depending on the neurotransmitter in question. For instance, mesocortical dopaminergic input to the frontal lobes is thought to mediate a variety of neurocognitive processes in that dopamine levels within the PFC are positively correlated with

executive functioning (Logue & Gould, 2014). In addition, serotonergic activity within the PFC is positively associated with inhibitory control and reversal learning (Cools, Roberts, & Robbins, 2008; Logue & Gould, 2014). Together, these data suggest that the acute exercise-induced improvements in neurocognitive functioning may be attributable to exercise-induced increases in dopamine and serotonin transmission within the PFC. Conversely, norepinephrine and epinephrine levels may modulate cognitive processing via increased arousal (Logue & Gould, 2014).

1.8 Specific research objectives

The current body of research presented explores the causal relation between the functionality of the PFC and dietary self-restraint as mediated via executive control. The combination of cTBS and aerobic exercise methodologies will be used to demonstrate that both the attenuation and optimization of EFs results in subsequent changes in dietary self-restraint in the theorized directions. Given the paucity of experimental studies within this area, the current body of research is necessary to develop a framework for understanding the neurocognitive factors that influence vulnerability to obesity-conducive eating habits within facilitative environments.

The specific objectives of the studies included in this dissertation are as follows:

1. To determine the effectiveness of cTBS in modulating prefrontal cortical activity as indexed by stimulation-induced changes in executive processes.
2. To investigate the neural correlates underlying stimulation-induced changes in food cravings and consumption, and whether stimulation induced changes in food-cue elicited brain activity and cognitive control mediates subsequent changes in snack food consumption.
3. To examine the potential cortical resilience promoting effects of aerobic exercise following cTBS-induced perturbations in dlPFC functionality.
4. To determine the potential of aerobic exercise to facilitate improvements in executive control, and subsequent transfer effect to dietary self-restraint.

Chapter 2

The effects of theta burst stimulation (TBS) targeting the prefrontal cortex on executive functioning: A systematic review and meta-analysis.

2.0 Outline

Continuous theta burst stimulation (cTBS) is a highly efficient variant of repetitive transcranial magnetic stimulation (rTMS) employed in experimental and clinical treatment paradigms. Despite widespread usage of TBS targeting the prefrontal cortex (PFC), there has been no systematic review of the evidence linking TBS protocols to changes in task performance on common measures of prefrontal function in general, and executive function (EF) specifically. A systematic review of the literature was conducted using Psych Info, PubMed, Web of Science and Scopus databases to identify articles examining the effects of TBS targeting the PFC on executive function task performance. Both up-regulating (intermittent theta burst stimulation; iTBS) and down-regulating (continuous theta burst stimulation; cTBS) variants of TBS were considered. Results from individual studies were converted to Hedge's *g* and random-effects models were used to estimate the overall effect size for each protocol. Age, biological sex, stimulation intensity, control methodology, and PFC target region were examined as potential moderators of the cTBS effect on EF test performance. Findings indicated a reliable negative effect of cTBS on cognitive abilities (g=-.254, Z=-5.617, p<.001); this effect was relatively uniform across included studies (Q= 13.768, p=.976, I^2=0). Although no significant moderators of the cTBS effect were identified, laterality sub analyses indicated that the magnitude of the effect was significantly higher (M_{diff}=.21, Z_{diff}= 2.348, p=.019) for left-sided (g=-.356, Z=-5.641 p<.001) than right-sided (g=-.146, Z=-2.260, p. =024) PFC stimulation. A systematic review of iTBS studies revealed considerable variability in reliability of effects though most were in the theorised direction. TBS protocols appear to be effective in modulating prefrontal cortical excitability in previously theorized directions, though the down- of cTBS may be more reliable than the up-regulating effects of iTBS.

2.1 Introduction

Repetitive transcranial magnetic stimulation (rTMS) is a family of techniques designed to modulate the function of brain systems via the application of magnetic pulses delivered in predefined patterns (Dayan et al., 2013; George & Aston-Jones, 2010). Specific brain structures are targeted by localizing the pulse-delivering coil using anatomical landmarks, an EEG cap, and/or a frameless stereotaxic system and a co-registered MRI structural brain scan. Repetitive TMS is sometimes referred to as "non-invasive" to reflect the fact that the pulses are delivered from a coil placed over the scalp, without the necessity of surgical intervention (in contrast with deep brain stimulation, for example). The non-surgical nature of rTMS has contributed to its popularity as technique for modulating brain activity either temporarily (for experimental purposes) or in a more long lasting manner (for clinical purposes) over the past two decades.

Repetitive TMS neuromodulation methods can be employed to up- or down-regulate cortical function with the objective of: 1) assessing neuroplasticity, 2) exploring the functional relation between specific cortical regions and subsequent cognitive, affective, sensory, and motor functions, or 3) achieving lasting change of function in targeted brain regions for therapeutic purposes. With increasing usage in laboratory and treatment contexts, there has been pressure to improve the efficiency by which rTMS methods achieve modulation of cognitive processes. Conventional high frequency rTMS requires 20-30 minutes to achieve its full effect, thereby making some experimental and clinical applications of the technique logistically challenging to implement. Theta burst stimulation (TBS) protocols promise to deal with the efficiency problem by employing protocols that achieve up- and down-regulation in the fraction of the time of conventional rTMS; effects are purported to be achieved in as little as 1-3 minutes (i.e., about 10% of the time required by conventional rTMS). However, given that TBS protocols have only been developed relatively recently (Huang et al., 2005), there is need to aggregate the effects observed across studies in relation to theoretically meaningful cognitive processes.

Although many TBS studies have targeted motor regions, the vast majority of clinical treatment and experimental studies involving psychiatric (e.g., depression, eating disorders) and behavioral phenomena (e.g., food cravings, addictions) have targeted the prefrontal cortex (PFC) because of its link to several aspects of executive control processes. The current systematic review will focus on this target, with cognitive test performance as the outcome.

2.12 TBS overview and theoretical mechanisms

TBS consists of three pulses applied in bursts of three at a frequency 50 Hz with a 200 ms (5Hz) inter-burst interval (Huang et al., 2005). Continuous TBS (cTBS) involves an uninterrupted train of TBS for either 20 s (300 pulses; $cTBs_{300}$) or 40 s (600 pulses; $cTBS_{600}$), which results in an inhibitory effect (i.e., decreased cortical excitability; Huang et al., 2005). Whereas the after-effects of $cTBS_{600}$ last for up to 50 minutes post-stimulation, the after-effects of $cTBS_{300}$ only lasts for approximately 20 minutes (Wischnewski & Schutter, 2015). Conversely, in intermittent TBS (iTBS) a 2 s TBS train (10 TBS bursts) is delivered every 10 seconds (8 s inter-burst interval between trains) over a total of 190 s (600 pulses), resulting in an excitatory effect for up to 60 minutes post stimulation (Huang et al., 2005; Wischnewski & Schutter, 2015). The physiological mechanisms underlying TBS after-effects have been likened to functional changes in synaptic plasticity in the form of long-term potentiation (LTP; increased synaptic efficiency) or long-term depression (LTD; decreased synaptic efficiency; Huang et al., 2011; Suppa et al., 2016).

2.12 TBS and prefrontal excitability

In contrast with existing validation work involving motor region stimulation targets, there remains uncertainty about the effects of TBS protocols on other areas of the brain. While the application of cTBS over the PFC has been shown to decrease regional blood flow to the PFC (Tupak et al., 2013) and impair task-specific dopaminergic neurotransmission in PFC-striatal network (Ko et al., 2008), the extent in which these observed physiological changes modulate PFC-dependent cognitive functions, particularly executive functions (EF), remains unclear. Conceptually, EF refers

to those cognitive processes implicated in the "top-down" control of human behaviour (Miyake & Friedman, 2012; Norman & Shallice, 1986). The exact nature and scope of EF is debated within the literature, however, most theoretical models propose that the unitary EF construct can be decomposed into at least three basic subcomponents (see Miyake & Friedman, 2012): working memory, behavioural inhibition, and task-shifting. Other subcomponents may include attentional control and verbal fluency. Together, these subcomponents potentiate complex processes and behaviours (e.g., planning and decision-making, self-regulation, reward valuation; Miyake & Friedman, 2012; Norman & Shallice, 1986). Although prefrontal, parietal, and subcortical brain regions all subserve executive processes, the PFC is thought to be an important cortical node underlying executive control (Friedman & Miyake, 2017; Miller & Cohen, 2001; Miller, 2000).

Given the recent controversies pertaining to the lack of credible effect of transcranial direct current stimulation (tDCS) on cognitive functioning (see Horvath, Forte, & Carter, 2015), it is important to quantify TBS effects on cognitive task performance, especially considering that it's intended therapeutic effects are assumed to operate via mediation by cognitive processes. That is, virtually all of the therapeutic usage of rTMS for treating psychiatric conditions and much of the single-session research paradigms for modulating craving responses target sub-regions of the PFC. In such research and clinical applications, TBS's intended effects often rely solely on TBS effects on underlying cognitive processes supported by the PFC (i.e., modulation of executive control).

The current study aggregates existing published and unpublished research findings using quantitative meta-analytic methods to examine the following questions: 1) is there a reliable effect of TBS protocols on theoretically meaningful cognitive mediators (i.e., EF) when targeting prefrontal cortex? 2) do cTBS and iTBS targeting the PFC modulate performance on EF measures in the theorized directions? 3) are cTBS and iTBS effects similar in magnitude? 4) what are moderators of the above associations? In providing this organizational framework for existing cTBS

findings targeting the prefrontal cortex, we evaluate the validity of therapeutic and research employ of such protocols, and provide a basis from which such uses can be justified.

2.2 Methods

2.21 Literature search and study Selection

A comprehensive search of PubMed, Scopus, Web of Science and Psych Info was conducted in June 2017 using the search terms *theta burst stimulation* combined with *prefrontal cortex, orbitofrontal cortex, or anterior cingulate cortex.* Relevant database-specific terms (e.g., MESH terms) were used when applicable. In addition, a search of the grey literature was conducted using Web of Science and ProQuest Dissertations Thesis databases. Reference lists of relevant articles and pertinent reviews were hand searched for additional articles. However, no additional articles were identified via either method. Results were restricted articles written in English only.

2.22 Inclusion/Exclusion criteria

Suitable studies were selected for inclusion according the following criteria; (1) healthy human study population; (2) cTBS or iTBS to the PFC; (3) comparison of active stimulation to sham stimulation or stimulation of a control site (e.g., the vertex); (4) at least one EF measure. EF was defined as any cognitive task measuring the working memory, behavioural inhibition, task-shifting or mental flexibility, attentional control, verbal fluency subcomponents, or those tasks designed to measure more complex aspects of EF, such as learning and decision making, self-regulation, or impulsive decision making. Prospective memory tasks were included in the current review as a working memory component, however, the free recall aspects were excluded from data analysis. Included studies were not restricted by publication date or age group.

Studies using episodic or memory recognition paradigms, or those examining implicit processes were excluded from the current review. Studies that did not directly compare the effects of cTBS or iTBS to sham or control simulation were also excluded. While some models include the eye fields (FEF) and pre-supplementary motor area (pre-SMA) as part of the PFC, studies targeting

these cortical regions were excluded from the current review due to the limited evidence supporting their role in the cognitive operations typically ascribed to the executive control network, beyond task specific demands (Nachev, Kennard, & Husain, 2008). To prevent homogeneity inflation due to correlated data, only one article per participant sample was included in data analyses.

2.23 Study quality

Assessment of methodological quality was assessed using the Cochrane risk of bias assessment tool. Ratings of low, high, and unclear were assigned to each dimension based on the criteria outlined by the Cochrane Collaboration (Higgins and Green, 2011). In addition, individual studies were assigned a rating of yes, no or unclear based on whether the participant sample was representative of the general population; university and other specialized sample populations were deemed unrepresentative.

2.24 Data extraction

Data extracted included sample size, participant characteristics (age, % female), type of stimulation (cTBS or iTBS), stimulation site, localization method, sham methodology or control site, stimulation intensity (% maximal stimulator output), factors related to the outcome measures, and relevant statistics (mean, SD, *F*-value, *T*-value). A Plot Digitizer program (Rohatgi, 2017) was used to estimate means and standard deviations (SD) when data was available in chart form only. When SD was not reported, it was estimated from standard error (SE) using the equation $SD = SE \times \sqrt{n}$.

2.25 Effect size calculation

Effect sizes were coded such that negative effect sizes reflect performance impairments following active stimulation. In studies using more than one cognitive measure, or those with more than one active stimulation condition (e.g., left and right stimulation, stimulation of two different cortical regions), effect sizes were averaged across measures to create a study-specific composite score. However, if studies utilized multiple active stimulation-specific subgroups, in which the

target cortical region varied between participants, but the active and sham (or control) stimulation was conducted within participants, this independent study-subgroup was treated as a separate study for all data analyses. When applicable, the correlation between outcome measures for repeated measure study designs was imputed using the paired sample *T* statistic and formulas outlined in Morris and DeShon (2002); the formula $T=\sqrt{F}$ was used to estimate the paired *T* test statistic from the one-way analysis of variance (ANOVA) *F* statistic (Lipsey & Wilson, 2001). Otherwise, a default correlation of 0.5 was imputed. This approach provides a conservative estimate of the repeated measure effect size without ignoring within-subject aspects of the study design (Follmann, Elliott, Suh, & Cutler, 1992). No significant differences between effect size estimates (Q_B=.104, *p*=.747) for studies using a within-subject (*g*=-.278) relative to a between-subject (*g*=-.340) study design were observed.

2.26 Meta analytic procedure

An insufficient number of studies utilizing iTBS protocols (*k*=5) were available to conduct a meta-analysis, and therefore, the results from these studies are presented as a systematic review. All analyses were conducted using Comprehensive Meta-analysis software (Englewood, NJ). Effect size data are reported as Hedges's *g,* as this transformation corrects for effect size inflation in studies with small sample sizes (Hedges & Olkin, 1985; Lipsey & Wilson, 2001). Data were inspected for outliers (± 3 SDs from the mean) prior to all analyses. One outlier effect size (*g*=-4.018) was identified (Zack et al., 2016) and excluded from all analyses. Inverse weighted random-effect models with the unit of analysis set as the individual study were used for all analyses. Statistical homogeneity of the effect size was assessed using the *Q* statistic, and further quantified using the I^2 statistic. I^2 calculates the percentage (between 0% and 100%) of the between study variability that is attributable to true heterogeneity between studies rather than random sampling error (small <25%, moderate 25-50%, large > 50%; Huedo-Medina, Sánchez-Meca, Marín-Martínez,

& Botella, 2006). Publication bias was assessed using the Egger regression test for funnel plot asymmetry (Egger, Davey Smith, Schneider, & Minder, 1997).

First, the average meta-analytic effect size for prefrontal cTBS was calculated. To ascertain whether the results were strongly influenced by a single study sensitivity analyses were conducted in which the overall significance and effect size were recomputed following the sequential removal of each study from the analysis. To determine whether differential effects were apparent for accuracy and reaction-time specific performance data separate meta-analytic effect sizes were calculated and the *Z* test of the difference (Z_{diff}) was used to compare the magnitude of the effect size (Borenstein, Hedges, Higgins, & Rothstein, 2009). Multiple effect size calculations were then conducted to assess the differential effect of cTBS on the various executive functioning (EF) subcomponents (i.e., working memory, inhibition, attention, and complex EF); see Table 2.3. However, these data are presented for descriptive purposes, and due to the low number of studies within each EF subcomponent the results should be interpreted carefully. As several studies employed both left and right stimulation protocols within participants, the laterality subgroup analysis was conducted by calculating separate meta-analytic effect sizes and using the *Z* test of the difference (Z_{diff}) to compare the magnitude of the effect size between left and right stimulation targets (Borenstein et al., 2009). The analog to the one-way ANOVA test for between-group differences was used to assess the moderating effect of control condition [sham stimulation versus control stimulation] and anatomical site of stimulation. In addition, biological sex (% female), age, and stimulation intensity (% of maximal stimulator output) were entered as continuous variables in separate weighted mixed-model maximum likelihood estimation regression analyses.

2.3 Results

Individual study and sample characteristics by TBS variant are presented in Table 2.1. The initial literature search resulted in 258 articles (duplicates removed) of which 43 were included in the full text review (see Figure 2.1). A total of 27 (24 cTBS; 5 iTBS) studies incorporating data from

32 different study populations met the inclusion criteria and were included in data analyses; two articles used both cTBS and iTBS protocols (Cho et al., 2010; Debarnot et al., 2015). This represented data from 683 participants with an average age of 30.96. The primary sample among included studies was young adults with only one study examining the effects of TBS (cTBS and iTBS) in an older adult population (Debarnot et al., 2015). The average reported stimulation intensity was 36.92 % of maximal stimulator output.

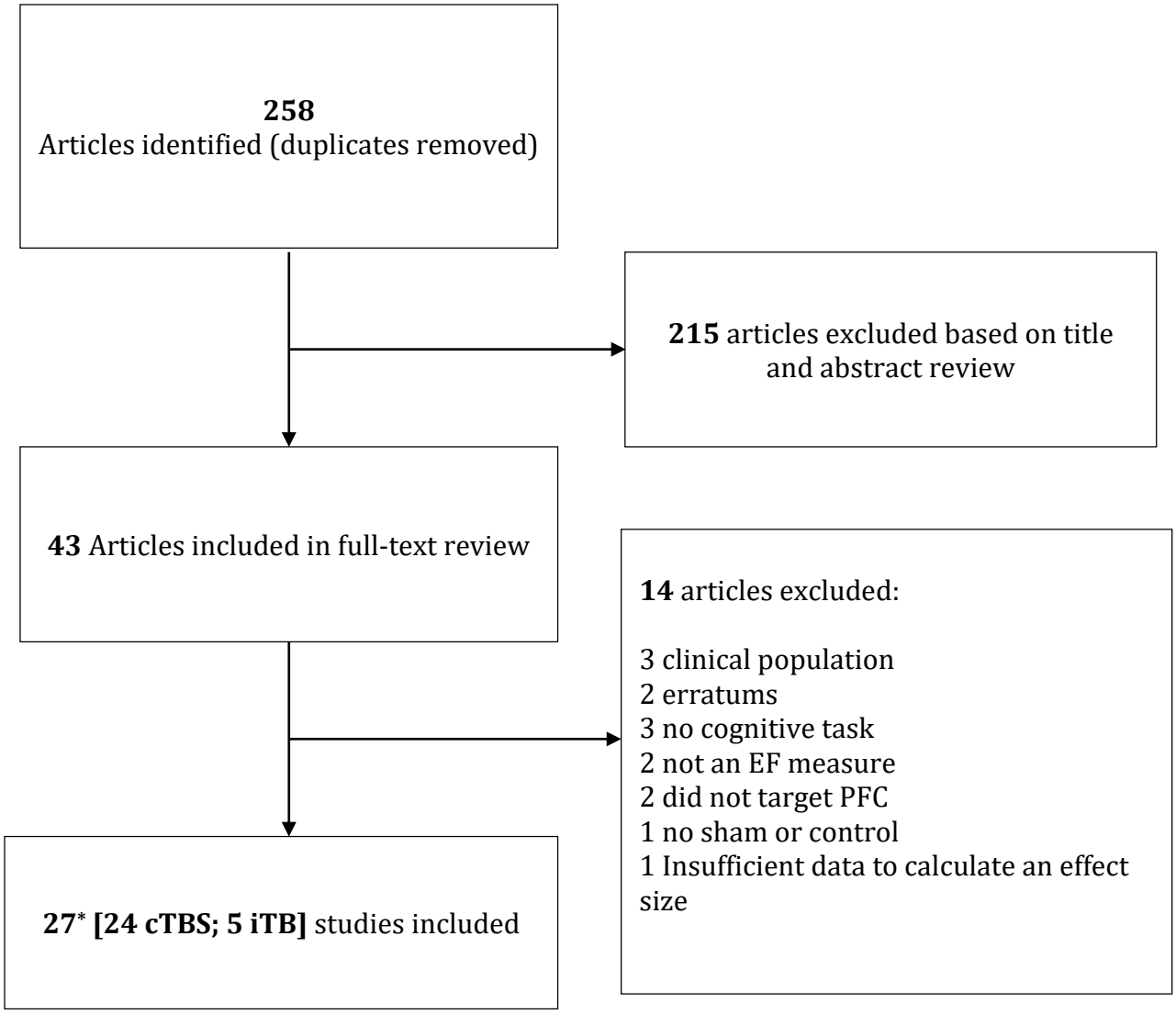

Figure 2.1: Article selection process with reasons for exclusion. * two studies used both cTBS and iTBS protocols.

Table 2.1
Study characteristics by TBS paradigm (cTBS, iTBS)

First Author, Year	*n*	Study Design	Age	% Female	Stimulation Intensity	Lateralization	Target Site	Location method	Sham/Control	Method	AMT/RMT	Hand	% Threshold	Task
cTBS														
Cameron, 2015	15	WS	20.7	40	NR	Left	dlPFC	fMRI	C	s1	RMT	FDI	80	Anti-saccade
Cho, 2010	7	WS	22.4	57.1	NR	Right	dlPFC	fMRI	S	Perpendicular	AMT	FDI	80	Delay Discounting
Cho, 2012	8	WS	22.6	50	NR	Right	dlPFC	fMRI	S	Perpendicular	AMT	FDI	80	Delay Discounting
Costa 2011	8	WS	21	50	34.8	Right	dlPFC	fMRI	C	Vertex	AMT	FDI	80	Prospective Memory
	8	WS	23.6	50	36.8	Left	dlPFC	fMRI	C	Vertex	AMT	FDI	80	Prospective Memory
Costa, 2013	12	WS	21.2	50	34	Both	aPFC	fMRI	C	Vertex	AMT	FDI	80	Prospective Memory
Dambacher, 2014	11	WS	27	NR	30.5	Right	SFG, MFG	fMRI	S	Sham Coil	AMT	VT	100	GNG, SST
Debarnot, 2015	20	BS	70.2	60	39.2	Left	aPFC	fMRI	C	Vertex	AMT	FDI	80	Prospective Memory
Dippel, 2015	18	WS	23.8	55.6	NR	Right	IFG	fMRI	S	Perpendicular	AMT	NR	70	SST
	10	WS	23.8	55.6	NR	Right	MFG	fMRI	S	Perpendicular	AMT	NR	70	SST
Drummond, 2017	13	WS	26.0	53.8	22	Right	IFG	10-20	S	Perpendicular	AMT	ECR	80	GNG
Gohil, 2016	28	WS	25	60.7	NR	Right	aPFC	fMRI	S	Perpendicular	RMT	APB	70	SST
	10	WS	NR	NR	NR	Right	MFG	fMRI	S	Perpendicular	RMT	APB	70	SST
Kaller, 2013	26	BS	24.4	50	33.9	Left	dlPFC	fMRI	S	Perpendicular	RMT	FDI	80	TOL
	26	BS	24.4	46.2	32.9	Right	dlPFC	fMRI	S	Perpendicular	RMT	FDI	80	TOL
Ko, 2008	10	WS	24	60	NR	Both	dlPFC	fMRI	C	Vertex	AMT	FDI	80	MCST
Lee, 2016	24	WS	23	25	40	Right	IFG	fMRI	S	Perpendicular			Used set intensity for all participants	SST
Lowe, , 2014	21	WS	21.1	100	42.7	Left	dlPFC	10-20	S	Perpendicular	RMT	APB	80	GNG, SST, Stroop
Lowe, 2017	28	WS	20.3	100	53.3	Left	dlPFC	10-20	S	Perpendicular	RMT	APB	80	Flanker
Morgan , 2013	17	WS	25	50	49.2	Left	IFG	fMRI	S	Perpendicular	AMT	VT	80	Working Memory Task
Obeso, 2017	19	WS	29.4	52.6		Right	IFG	fMRI[2]	S	Perpendicular	AMT	FDI	80	SST
Ott, 2011	27	BS	24.6	59.5	42	Left	dlPFC	fMRI	C	Vertex			Used set intensity for	Probabilistic Learning Task

	29	BS	24.6	59.5	42	Right	dlPFC	fMRI	C	Vertex			all participants Used set intensity for all participants	Probabilistic Learning Task
Schicktanz, 2015	40	WS	22.55	50	NR	Left	dlPFC	fMRI	S	Coil	RMT	VT	80	N-back (2,3)
Smittenaar, 2013	25	WS	24.2	60	49	Both	dlPFC	fMRI	C	Vertex	AMT	VT	90	Probabilistic Learning Task
Verbruggen, 2010	18	WS	25.9	50	30	Right	IFG	fMRI	S	Perpendicular	RMT	VT	70	SST
Volman, 2011	41	WS	21.5	0	29	Left	aPFC	fMRI	C	Vertex	AMT	FDI	80	Emotional Stroop
Xu, 2013	40	WS	21	50	NR	Right	dlPFC	10-20	S	Perpendicular	AMT	FDI	80	ANT
Zack, 2016[1]	9	WS		0	NR	Right	dlPFC	fMRI	C	Vertex	AMT	tibialis anterior muscle	80	Stroop, delay discounting
iTBS														
Cho, 2010	7	WS	22.4	57.1	NR	Right	dlPFC	fMRI	S	Perpendicular	AMT	FDI	80	Delay Discounting
Duprat, 2016	22	WS	23.2	0	NR	Left	dlPFC	fMRI	S	Sham Coil	RMT	APB	110	Probabilistic Learning Task
Debarnot, 2015	10	BS	70.2	60	39.2	Left	aPFC	fMRI	C	Vertex	AMT	FDI	80	Prospective Memory
He, 2013	30	WS	20.1	50	NR	Both	dlPFC	10-20	S	Perpendicular	RMT	APB	80	ANT
Hoy, 2016	19	WS	22.16	47.4	NR	Left	dlPFC	10-20	S	Perpendicular	RMT	NR	80	N-back (2,3)

Note: [1] not included in analyses. [2] 10-20 localization was used for 4 participants. 10-20 refers to the use of the international 10-20 system to target cortical regions. S= sham; C=control; WS= within subjects; BS= between subjects; NR= not reported; VT= any visible twitch; AMT= active motor threshold; RMT= resting motor threshold; dlPFC= dorsolateral prefrontal cortex; OC= occipital cortex; aPFC= anterior prefrontal cortex; IFG= inferior frontal gyrus; MFG= middle frontal gyrus; SFG= superior frontal gyrus; dlAVC= dorsolateral anterior visual cortex; GNG= Go No/Go; SST= Stop Signal Task; TOL= tower of London; MCST= Montreal card sorting task; PVT= psychomotor vigilance task.

2.31 cTBS and EF Task Performance

Meta-analytic and homogeneity statistics, and the results pertaining to publication bias are presented in Table 2.2. Results indicated that cTBS had a small-to-moderate, but significant, negative effect on executive functioning (g=-.261, Z=-5.785, p<.001), and that this effect was similar across studies (Q= 14.004, p=.973, I^2=0); see Figure 2.2. Minimal change in the effect size was observed following the removal of each study indicating that the overall findings were not unduly influenced by a singular study. The observed effect was significant for both accuracy (g=-.296, Z=-5.466, p<.001) and reaction-time (g=-.264, Z=-4.047, p<.001) dependent performance data, and the magnitude of the effect size did not significantly differ between performance measures (M_{diff}=-.029, Z_{diff}= -.347, p=.729). Comparable effect sizes were apparent for both accuracy (Q=21.781, p=.352, I^2=8.178) and reaction time specific data (Q=28.213, p=.079, I^2=32.66) indicating reaction-time specific effect size variability between studies. Laterality sub analyses indicated that cTBS targeting both the left (g=-.370, Z=-5.609, p<.001) and right (g=-.165, Z=-2.66, p=.008) significantly impairs performance on EF measures. However, the magnitude of effect size for left PFC stimulation was significantly larger than that for right PFC stimulation (M_{diff}=.205, Z_{diff}= 2.292, p=.022).

Table 2.2
Meta-analytic effect size statistics

			Meta Analytic Effect Size							**Homogeneity**			
						95 % CI							
	N	*k*	*G*	SE	V	LL	UL	*Z*	*P*	*Q*	*P*	I^2	*p* Egger
cTBS	602	28	-.261	.045	.002	-.350	-.173	-5.785	<.001	14.00	.973	0	.182
Acc		21	-.296	.054	.003	-.456	-.190	-5.466	<.001	21.78	.352	8.178	
RT		20	-.264	.065	.004	-.392	-.136	-4.047	<.001	28.21	.079	32.65	

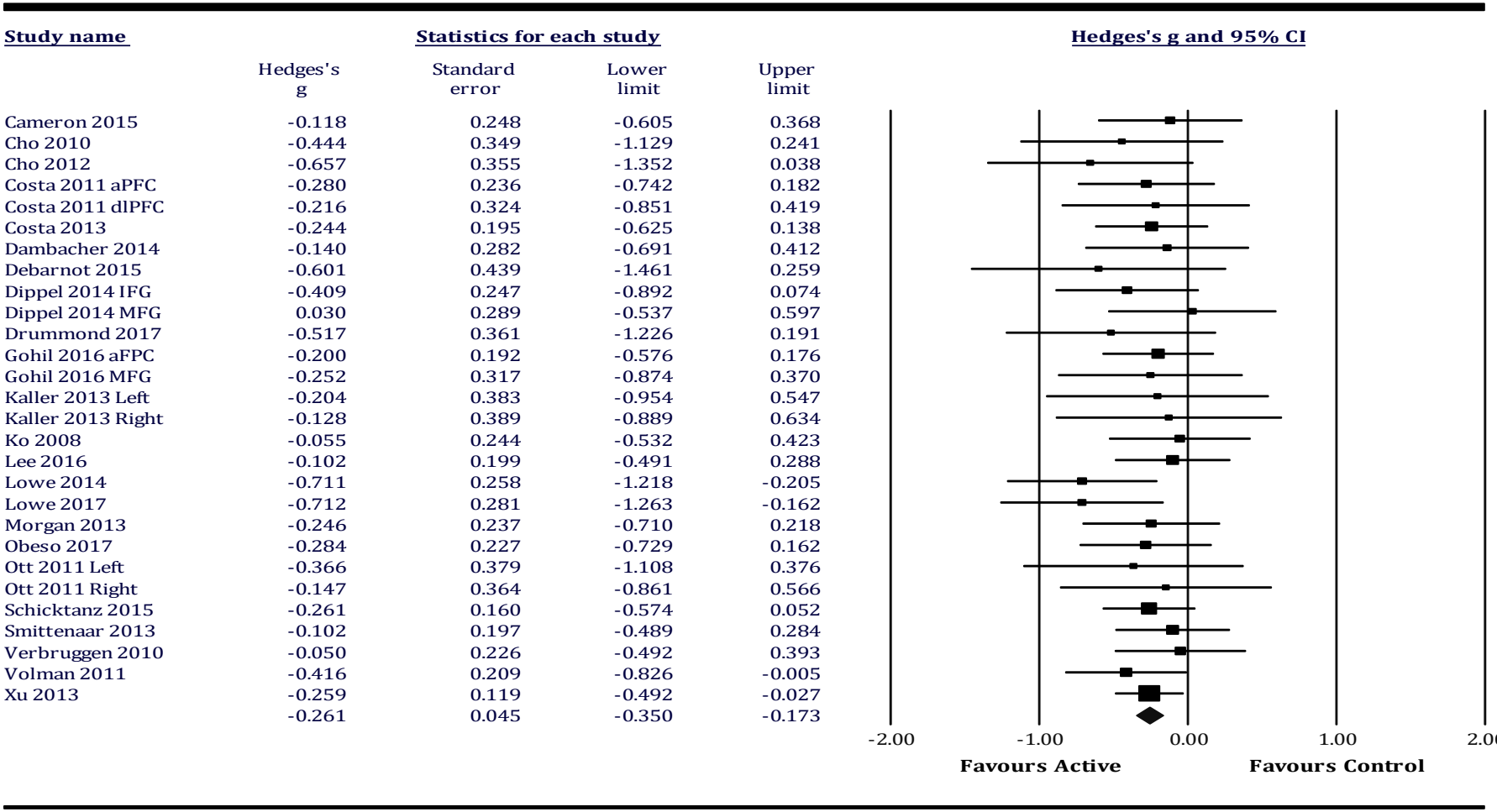

Figure 2.2: Forest plot showing the observed study-specific effect sizes with corresponding 95% confidence intervals. The diamond shows the summary estimated with using random-effects models

Table 2.3
Continuous TBS meta-analytic effect sizes as a function EF subcomponent

	Meta Analytic Effect Size							Homogeneity	
				95% CI					
	k	***G***	**SE**	**LL**	**UL**	***Z***	***p***	***Q***	***p***	***I²***
Inhibition	13	-.312	.068	.-.411	-.114	-4.085	<.001	10.126	.605	0
Working Memory	6	-.269	.093	-.451	-.087	-2.899	.004	.631	.987	0
Complex	7	-.211	.107	-.422	-.001	-1.968	.049	2.967	.813	0
Attention	1	-.259								

Moderator analyses indicated that the effect size estimate did significantly differ as a function of control stimulation methodology (Q_B=.263, p=.608); effect size estimates for individual control sites and sham methodologies are presented in Table 2.4. While effect size estimates did not differ as s function of target site (Q_B=1.125, p=.890), the largest effect size estimates were observed in those studies targeting the dorsolateral prefrontal cortex (dlPFC; g=-.315) and anterior PFC (aPFC) or frontopolar cortex (g=-.296); see Table 2.5. In addition, age (β=-.004, Z=-.42, p=.676), biological sex (β=-.003, Z= -1.00, p=.319), and cTBS stimulation intensity (β=.009 Z= .88, p=.380) were not significant moderators of the effect.

Table 2.4
Meta-analytic effect sizes by control stimulation site and sham methodology

	k	***g***	**SE**	**LL**	**UL**	***Z***	***p***
Control	10	-.227	.080	-.384	-.070	-2.830	.005
Vertex	9	-.240	.085	-.406	-.074	-2.828	.005
S1	1	-.118					
Sham	16	-.276	.056	-.387	-.166	-4.916	<.001
Coil	2	-.231	.139	-.503	.041	-1.664	.096
Perpendicular	16	-.285	.059	-.402	-.169	-4.804	<.001

Table 2.5
Meta-analytic effect sizes as a function of target site

	k	***g***	**SE**	**LL**	**UL**	***Z***	***p***
aPFC	5	-.296	.100	-.493	-.100	-2.955	.003
dlPFC	14	-.315	.084	-.479	-.151	-3.759	<.001
IFG	6	-.227	.097	-.417	-.037	-2.341	.019
MFG	3	-.131	.171	-.465	.204	-.766	.444
SFG*	1	-.090					

Note: * was excluded from moderator analyses, however, effect size is reported here for descriptive purposes. aPFC= anterior prefrontal cortex; dlPFC=dorsolateral prefrontal cortex; IFG= inferior frontal gyrus; MFG= middle frontal gyrus; SFG= superior frontal gyrus.

2.32 Systematic review of effects iTBS on EFs.

Only five studies assessed the effects of prefrontal iTBS on EF; details of these studies are presented in Table 1. All iTBS studies targeted the dlPFC. Together, the data suggest that iTBS may an effective means of modulating executive control, however, the effectiveness may be task dependent. Of note, the largest effect size estimate was observed within an older adult population (*g*=.938), highlighting the corrective function of iTBS.

2.321 Attention

He et al. (2013) reported that stimulation of the right dlPFC significantly improved alerting (*g*=.490) and executive efficiency (*g*=.783) on attention network task (ANT) compared to sham stimulation, however, no significant differences were apparent for orienting efficiency (*g*=-.077). No significant differences were observed on either alerting (g=-.219) orienting (*g*=.242), or executive efficiency (*g*=-.427) following left dlPFC stimulation.

2.322 Working Memory

Two studies assessed the effects of iTBS on working memory paradigms. Hoy et al. (2016) reported significant performance improvements on the 2-back N-back task following left dlPFC stimulation at 20 (*g*=.470) and 40 (*g*=.512) minutes post-stimulation, but no significant differences were apparent immediately following stimulation (*g*=-.015). However, no significant effects were observed immediately (*g*=.187), 20 (*g*=.196) or 40 (*g*=.193) minutes post-stimulation for the more

cognitively demanding 3-back task. Debarnot et al. (2015) reported significant improvements in the ongoing component of a virtual prospective memory paradigm following iTBS to the left dlPFC (*g*=.938) relative to both cTBS to the left dlPFC and sham stimulation within an older adult population.

2.323 Reward based learning and decision making

Two studies assessed the effects of iTBS to the dlPFC on reward responsivity or impulsive decision making using the delay discounting task (Cho et al., 2010) and a probabilistic learning paradigm (Duprat, De Raedt, Wu, & Baeken, 2016) . No significant effects were observed for either right (Cho et al., 2010; *g*=.031) or left (Duprat et al., 2016; *g*=.049) stimulation. However, Duprat et al. (2016) reported significant effects in those with higher levels of hedonic capacity (i.e., more impulsive individuals), indicating that the effectiveness of iTBS in modulating impulsive decision making may be dependent on baseline performance. Together, these data suggest that iTBS is not effective in modulating reward responsivity.

2.33 Study Quality

Methodological quality ratings are summarized in Figure 2.3. Across studies, two main areas of concern were identified (1) blinding of participants and personnel to TBS condition (active and sham) and outcomes, and (2) participant representativeness. While the use of sham and control methodologies suggest blinding, most studies failed to report whether participants and/or personnel were blinded to stimulation condition, and none reported actual blinding statistics (i.e., how many participants were able to distinguish between active and sham/control conditions).

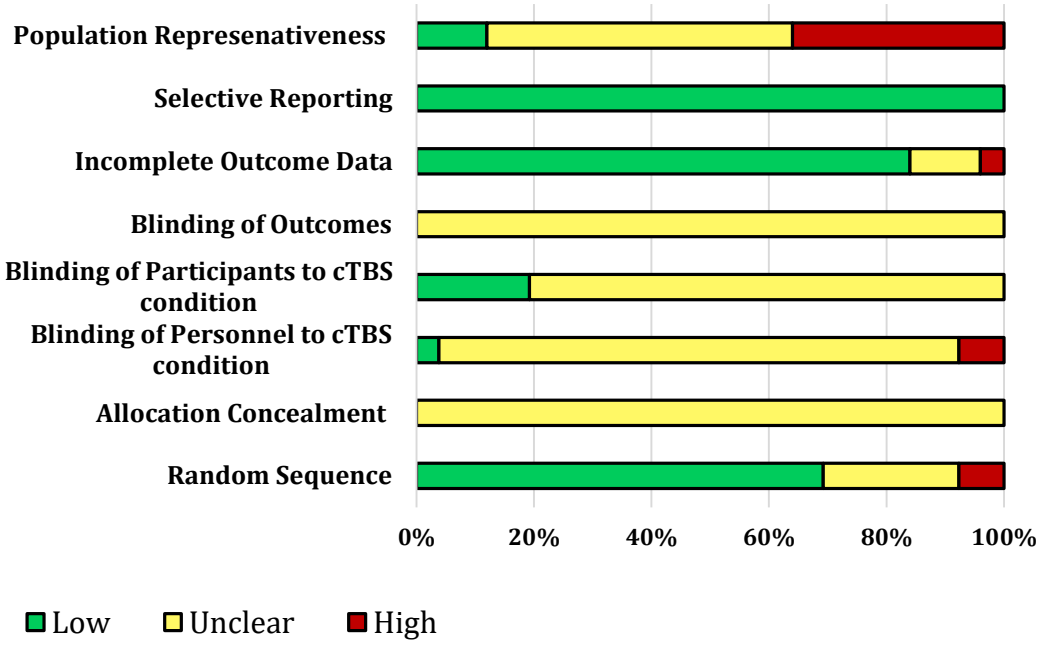

Figure 2.3: Overview of study quality and risk of bias [low, high, and unclear]. For participant representativeness yes correspond with low risk, and no with high risk. Values reflect the percentage of studies meeting the specified criteria for each rating

2.4 Discussion

The current meta-analytic review of the published research literature involving cTBS found that cTBS targeting the prefrontal cortex reliably decreases performance on measures of executive function with a high degree of uniformity across studies. Further, cTBS-induced performance decrements were not the result of a simple speed/accuracy trade off. The results for iTBS were less clear overall, in part due to the small number of studies. From the systematic review of the iTBS studies, it appears that iTBS may enhance EF task performance, but these improvements are task specific. That is, while significant improvements in working memory were uniformly apparent across studies, null effects were observed across measures of reward responsivity. The pattern of results documented here in relation to the PFC are partially similar to those observed in relation to TBS application over the motor cortex. Recent meta-analyses have reported that both cTBS and

iTBS targeting the motor cortex are effective in modulating MEP responses and corticospinal excitability (Chung, Hill, Rogasch, Hoy, & Fitzgerald, 2016; Wischnewski & Schutter, 2015).

The mixed effects of iTBS should be considered in relation to the format of stimulation, which in all cases was single-session. There have been reliable multi-session rTMS effects documented in relation to psychiatric symptomology, particularly unipolar depression (Berlim, McGirr, Rodrigues dos Santos, Tremblay, & Martins, 2017; Gross, Nakamura, Pascual-Leone, & Fregni, 2007), but the current studies do not assess such cumulative effects on cognitive mediating processes. More single- and multi-session iTBS studies will be required to more definitively quantify acute, single-session effects, as well as cumulative therapeutic effects across multiple stimulation sessions. At the current juncture, it is most prudent to conclude that single-session iTBS effects on cognition are likely reliable but additional studies would provide a more precise estimate of the effect.

It is plausible that ceiling effects with respect to the ability of iTBS to modulate cortical excitability in healthy younger adults might underlie the mixed findings across iTBS studies. Within the current body of included studies, a large effect of iTBS was observed in an older adult population (g=.938; Debarnot et al., 2015), indicating the plausibility that iTBS effects reflect a corrective function rather than the ability to augment baseline cortical excitability. This notion is consistent with that of homeostatic metaplasticity which posits that the threshold for the induction of LTP and LTD is not stable, but rather depends on prior synaptic activity in the postsynaptic neuron (Bienenstock, Cooper, & Munro, 1982; Bliem, Müller-Dahlhaus, Dinse, & Ziemann, 2008); the mechanisms underlying iTBS and cTBS induced plasticity has been likened to changes in LTP and LTD respectively (Huang et al., 2007, 2011). The threshold for further LTD-induction increases with postsynaptic excitatory activity, and vice versa, suggesting that the response to iTBS, and TBS in general, are strongly dependent on pre-stimulation cortical activity. Indeed, prior research has demonstrated that higher baseline levels of cortical connectivity precluded MEP responses in non-

responders relative to responders (Nettekoven et al., 2015). Further, priming iTBS with cTBS results in larger MEPs in young adults relative to priming with sham or iTBS. However, in older adults, priming iTBS with either cTBS, sham, or iTBS did not change MEP responses (Opie, Vosnakis, Ridding, Ziemann, & Semmler, 2017).

However, prior metaplasticity specific research has been conducted using animal models or targeting the sensory and motor cortices, thus the applicability of such findings to prefrontal modulation remains unclear. While it is likely that similar neurobiological mechanisms underlie both concepts, conceptualization of the "corrective function" hypothesis may be more applicable to prefrontal neuromodulation. That is, although intra- and inter-individual differences in state and trait cortical activity exist, healthy young adults are typically characterized by optimal prefrontal cortical activity. However, within clinical contexts, repeated administration of iTBS has been shown to improve clinical outcomes in those patients marked by suboptimal prefrontal activity (e.g., those with depression; Berlim et al., 2017), highlighting the potential deficit correcting potential of iTBS. Nonetheless, it is evident that more research is necessary to fully ascertain the mechanisms underlying prefrontal iTBS and subsequent applications to research and clinical practice.

While the between group difference was not significant, results indicated that the magnitude of the cTBS effect was larger for studies targeting the aPFC and dlPFC. Interestingly, the effect size was only marginally significant for those studies targeting the inferior frontal gyrus (IFG), and null effects were observed in those studies targeting the middle frontal gyrus (MFG). Although, this could be attributable to a power effect, these results do suggest that the effects of cTBS may be localization specific. Indeed, the dlPFC is considered to be an important cortical node subserving executive processes (Barbey et al., 2013; Cazalis et al., 2003; Fassbender et al., 2004; Miller, 2000; Miller & Cohen, 2001; Stuss, 2011; Toichi et al., 2004), thus, explaining why the largest effect is observed in studies targeting this cortical region. Furthermore, converging evidence has implicated the aPFC (or frontal poles) in supervisory attentional control (Pollmann, 2004, 2016).

Models of attention posits that performance decrements on higher order cognitive tasks are a direct function of attentional abilities (Oken, Salinsky, & Elsas, 2006; Sturm et al., 1999; Sturm & Willmes, 2001); i.e., a certain level of vigilance or attention is necessary for optimal task performance. Thus, the magnitude of the observed effect size may be directly related to the relation between aPFC cortical activity and attentional control.

The additional finding that the magnitude of the effect is larger for studies targeting the left relative to the right PFC is consistent with the notion that cognitive control is dependent on the integrity of the left PFC. For instance, patients with lesions or damage to the left PFC consistently perform worse on EF measures relative to those with right hemispheric damage (Demakis, 2004; Tsuchida & Fellows, 2013). Further, neuroimaging studies have demonstrated a leftward lateralization associated with performance on working memory and Stroop paradigms (Ambrosini & Vallesi, 2017; Banich & Depue, 2015; MacDonald et al., 2000). However, recent evidence seems to suggest that lateralization-specific functionality differences are not uniform across cognitive tasks, rather such effects are task specific (Rubia et al., 2006). In particular, left frontal activation is associated with the top-down control of attentional sets (Vanderhasselt et al., 2009) and working memory demands (Wager & Smith, 2003) whereas motor response inhibition (Aron et al., 2014) and macro-adjustments of cognitive control (Vanderhasselt et al., 2009) appear to be more dependent on rightward activation.

Physiologically, the cognitive effects of prefrontal cTBS have been likened to decreased regional blood flow (Tupak et al., 2013) and changes in prefrontal-striatal dopaminergic transmission (Ko et al., 2008). Nonetheless, there is some evidence that left frontal cTBS results in stronger physiological effects (Ko et al., 2008; Tupak et al., 2013), which may explain the observed lateralization difference in effect size magnitude. For instance, prior research has demonstrated that bilateral decreases in prefrontal blood oxygenation were only apparent following cTBS to the left dlPFC (Tupak et al., 2013); no changes in cerebral activity were observed following right-

hemispheric stimulation. However, there is no way to fully disentangle this issue with the current data, and therefore, several interpretations of the lateralization effect are plausible. The addition of more studies may allow for a more in depth examination into this issue in the future.

2.41 Future Directions and Methodological Considerations

Responsiveness to rTMS protocols are highly variable from one person to another, to the extent that stimulation-induced alterations in cortical activity are not apparent in some individuals (i.e., non-responders; Hamada, Murase, Hasan, Balaratnam, & Rothwell, 2013; Suppa et al., 2016). The mechanisms underlying such interindividual differences in responsivity are poorly understood, and several factors have been put forward, including biological sex, genetic polymorphisms, circadian factors, physical activity, and intracortical differences in functional connectivity (Hinder et al., 2014; López-Alonso, Cheeran, Río-Rodríguez, & Fernández-Del-Olmo, 2014; Suppa et al., 2016). Of note, while there is considerable variation in TBS response between individuals, intraindividual variance is substantially smaller. Levels of circulating hormones, time of day, and previous physical activity levels all influence intraindividual variance (Hinder et al., 2014; López-Alonso et al., 2014; Suppa et al., 2016); such factors are controllable from a research and clinical perspective. However, most of the research examining the factors that influence both intra-and-interindividual variance have focused on motor cortical excitability, and the applicability of such findings to prefrontal modulation remains unclear. For instance, the current findings indicated that both biological sex and age did not moderate the observed cTBS effect, suggesting the possibility that different factors may influence responsiveness to prefrontal neuromodulation; i.e., past research has demonstrated that biological females are more responsive to rTMS protocols than their male counterparts (Suppa et al., 2016). It is important to note that almost all of the included studies, except for one (Debarnot et al., 2015), were conducted in healthy young adults, and therefore, limited variation in age may account for the observed null effects of age rather than an actual difference.

Considering the variability in responsiveness among individuals, it is important to consider the impact of set stimulation parameters on the magnitude of the observed effect. While the majority of the TBS studies used the parameters outlined in Huang et al. (2005), in which the stimulation intensity is set at 80% of motor threshold, variation in the stimulation parameters did exist within the included body of studies, with some studies using a set intensity for all participants, and others using stimulation intensities ranging from 70% to 100% of motor threshold. It is unclear how such variations in stimulation parameters influenced the observed outcomes. Further, the use of set stimulation parameters for all participants is concerning, both from a methodological and safety standpoint. While no adverse effects were reported, it remains unclear the actual impact on both study outcomes and participant safety. That is, the use of a set stimulation threshold may result in suboptimal results in participants with higher motor thresholds and/or lead to adverse outcomes in those with lower thresholds.

One particular area of concern is the reliability of stimulation blinding and subsequent implications on measured outcomes. It cannot be assumed that participants are unable to differentiate between stimulation applied to the target region relative to control stimulation sites, especially when control stimulation is applied to occipital regions. Further, most studies failed to report if participants were blinded to stimulation condition (i.e., either through the use of sham stimulation and control stimulation) and actual blinding statistics (i.e., how many participants could differentiate between active and sham/control stimulation). As most studies employed a repeated measures design, it is currently unclear whether expectancy effects were apparent due to the ability of participants to differentiate between stimulation conditions. Additionally, while there was no difference in the effect size between control stimulation and sham stimulation methodologies, the lack of blinding statistics makes it impossible to determine which method is more effective in disguising stimulation conditions. Such statistics are necessary to inform future research, and therefore, researchers should consider measuring and reporting such in the future.

2.42 Strengths and Limitations

The current review had numerous strengths, including the use of a stringent inclusion/exclusion criteria, rigorous evaluation of methodological study quality, and examination of several potential moderators of the effect. The main limitation was the lack of research examining iTBS effects on cognitive outcomes. To date, only five studies met the inclusion criteria, and therefore, direct comparison of iTBS and cTBS effects were not possible. While it is possible to elucidate and control for state-dependent effects, the lack of comprehensive reporting within the included body of studies did not allow for examination into the potential impact of time of day, energy-levels, and other state-dependent attributes that may have influenced the magnitude of the effect. The inclusion of this information is both recommended and encouraged, as it would allow for a more in depth, and potentially meaningful, quantitative synthesis in the future. Finally, the primary use of healthy adult populations was a limitation worth noting. While such studies provide foundational research, it remains unclear the extent the effects of TBS differ as a function of age group, and whether differential effects are observed for cTBS and iTBS depending on age.

2.43 Conclusion

The current quantitative review demonstrated that cTBS has a small-to-moderate, but reliable, negative effect on executive function task performance. While the effects for iTBS were mixed, the available data seem to suggest the possibility of a facilitative effect of iTBS on executive processes, specifically working memory. However, in all cases, it is useful to consider what assessments of cognitive processes are sufficiently sensitive to document single- and multi-session effects. In the case of cTBS-induced down-regulation of PFC function, traditional cognitive tests appear to be sufficient to document the relatively robust effects. In the case of excitatory methods like iTBS, more sensitive methods such as EEG, fNIRS and fMRI may be more useful. Together, these data provide quantitative and systematic evidence supporting the validity of TBS as a neuromodulatory method, and provide an organizational framework that can be used to justify the

use of such protocols in future research. Nonetheless, the addition of more iTBS studies are necessary to fully ascertain the validity of such protocols.

Chapter 3

The neural mechanisms underlying food cravings and snack food consumption. A combined continuous theta burst stimulation (cTBS) and EEG study.

3.0 Outline

Regulation of food cravings is understood to be critical for modulating eating behavior, yet we do not fully understand the mechanisms by which cognitive control operates in the eating context. The current study sought to examines the causal role of the left dorsolateral prefrontal cortex in modulating visceral and behavioral responses to high calorie foods, using a combined rTMS/EEG paradigm. 28 right-handed female participants received active and sham cTBS (rTMS variant used to decrease cortical activity) targeting the left dlPFC in a counterbalanced order in order to experimentally manipulate cognitive control. Prior to and following each stimulation session participants completed a flanker and food-cue presentation (high and low calorie food) task. Following cTBS participants had the opportunity to consume both high and low calorie foods during a taste test. Findings revealed a reliable effect of cTBS on food consumption, such that participants selectively ingested significantly more calories from appetitive snack foods following active relative to sham cTBS; this effect did not translate to control food consumption. Attenuation of dlPFC activity resulted in the significant increase in N2 amplitude and P3b latency to incongruent flanker trials, and the selective significant increase in P3a amplitude in response to and the attentional bias for high calorie food stimuli. The later positively correlated with appetitive food consumption and cravings. Together, the findings provide causal evidence demonstrating that suboptimal activity in the dlPFC can predispose individuals to the overconsumption of calorie dense foods via increased reward responsivity to high calorie food stimuli.

3.1 Introduction

Neurobehavioural models of obesity have proposed several factors that could theoretically increase the risk for overeating in the modern obesogenic environment. The exposure to appetitive food images and cues, and the anticipated and actual intake of palatable calorie dense foods increases cortical activity in the regions associated with reward processing and incentive valuation, including the ventral striatum, midbrain, amygdala, and the orbitofrontal cortex OFC (Killgore et al., 2013; Kringelbach, O'Doherty, Rolls, & Andrews, 2003; O'Doherty, Deichmann, Critchley, & Dolan, 2002; Small, Veldhuizen, Felsted, Mak, & McGlone, 2008; Stice, Burger, & Yokum, 2013, 2015; Stice & Yokum, 2016a; van der Laan, de Ridder, Viergever, & Smeets, 2011; van Meer, van der Laan, Adan, Viergever, & Smeets, 2015). However, compared to their healthy weight counterparts persons with obesity show elevated cortical activity within these regions in response to high calorie food stimuli (Demos, Heatherton, & Kelley, 2012; Dimitropoulos, Tkach, Ho, & Kennedy, 2012; Gearhardt, Yokum, Stice, Harris, & Brownell, 2014; Ho, Kennedy, & Dimitropoulos, 2012; Rothemund et al., 2007). As such, most studies have focused on reward responsivity differences between persons with obesity and healthy weight individuals with a focus on aberrant neural pathologies and behaviours, specifically the similarities between food-cue responsivity and addiction.

For instance, elevated insular and striatal functional activation and dorsal striatal dopamine release in response to calorie-dense food images is positively correlated with subjective appeal ratings and subsequent *ad libitum* food intake (Lawrence, Hinton, Parkinson, & Lawrence, 2012; Scharmüller et al., 2012). Additionally, several studies have reported that reward region responsivity to calorie dense food intake and cues correlates positively with future weight gain (Demos et al., 2012; Stice et al., 2015; Stice & Yokum, 2016b; Winter, Yokum, Stice, Osipowicz, & Lowe, 2017; Yokum, Ng, & Stice, 2011). With respect to electrophysiological indicators, the amplitude of the P3 and late positivity potential (LPP) event related potential (ERP) components are larger for high caloric food images relative to non-food images, and the magnitude of this effect

positively correlates with subjective hunger (Nijs, Franken, & Muris, 2008; Nijs, Muris, Euser, & Franken, 2010), indicating that the amplitude of these ERP components may reflect attention capture by food (P3a) and motivation to eat (LPP). Indeed, an attentional bias for calorie dense foods (i.e., larger P3 amplitude) predicts both *ad libitum* food intake (Nijs et al., 2010; Werthmann, Field, Roefs, Nederkoorn, & Jansen, 2014) and future weight gain (Calitri, Pothos, Tapper, Brunstrom, & Rogers, 2010). Such reward related cortical responsivity to high caloric foods may putatively override homeostatic processes, resulting in the subsequent overindulgence in calorie dense foods (Dagher, 2010; Davis, 2017; Davis et al., 2011; Stice & Yokum, 2016a; Volkow, Wang, Tomasi, & Baler, 2013; Volkow, Wang, & Baler, 2011).

Nonetheless, while there is evidence supporting the notion that an elevated propensity to the rewarding properties of calorie dense foods and food cues can increase the risk for overeating and future weight gain (see Stice & Yokum, 2016a for a review), such neurobehavioural models fail to account for the potential for dietary self-restraint. That is, while calorie dense foods are extremely appealing, humans have the capacity to curb and control desires and cravings (or impulses) and act in accordance to behavioural intentions or goals. Within the context of dietary habits, this may involve the suppression of visceral cravings or the implementation of cognitive control strategies to mitigate consumptive habits, both of which involve engagement of the executive control network (Hall, 2016; Vainik, Dagher, Dubé, & Fellows, 2013). Thus, susceptibility to the pervasive temptation of high caloric foods in the modern environment may be partially mitigated via individual differences in inhibitory control-an important component of executive functioning associated with effective dietary self-restraint-, and by extension the cortical regions underlying executive functions (EF; i.e., prefrontal cortex (PFC)). Consistent with this notion, a growing body of evidence has consistently reported that the propensity to overconsume high calorie foods is negatively associated with executive control (Appelhans, 2009; Hall, 2016; Vainik et al., 2013). This effect is selectively amplified in the presence of facilitating consumptive cues in that

those with lower executive control are just as adept at controlling food intake as those with higher EFs when the facilitating cues are removed (Hall et al., 2014; Hall et al., 2014).

At the neural level, the operation of the PFC, and more specifically the dlPFC, has been consistently implicated in both food choice related self-control and the cognitive restraint of food intake (Hare et al., 2009; Kober et al., 2010). For instance, the selective attenuation of left dlPFC activity predisposes individuals to the overconsumption of high calorie snack foods, an effect that was directly mediated by cTBS-induced deficits in inhibitory control (Lowe, Hall, & Staines, 2014). In addition, a recent meta-analytic review reported that neuromodulatory enhancement (using either rTMS or tDCS protocols) attenuates food cravings (Lowe, Vincent, et al., 2017). While the consumption results were initially null, a recent update reported significant consumptive effects, demonstrating that the initial findings were specific to low power rather than the absence of an effect (Hall et al., 2017). Lower dlPFC activity in response to high caloric food images is associated with greater *ad libitum* energy intake (Tyron et al., 2013) and is predictive of subsequent three day *ad libitum* food intake (Cornier et al., 2010). Furthermore, higher response inhibition specific inferior frontal gyri (IFG) activity is associated with a decreased likelihood of overeating over a one week period (Lopez, Hofmann, Wagner, Kelley, & Heatherton, 2014). These findings are noteworthy, as they highlight the potential for neural activity to predict real world consumptive behaviours (i.e., outside of a laboratory setting).

It is evident that individual differences in cortical activity in response to food stimuli may mitigate individual level risk for overeating; however, to date no unifying conceptual model regarding the cognitive and neural factors that increase susceptibility to food temptation and/or predispose an individual to the overconsumption of calorie dense foods exists. Attempts at synthesizing the various neurobehavioural models of obesity have been made (see Eric Stice & Yokum, 2016a), however, these models focus heavily on reward region responsivity, and fail to fully consider the extent in which cognitive control modulates non-homeostatic food intake. This may be

partially attributable to the fact that the exact neural mechanisms underlying the relation between executive control and dietary self-restraint is unclear. That is, while the above studies are informative, causal inference regarding the exact relation between prefrontal activity and dietary self-restraint cannot be ascertained. Furthermore, while there is substantial evidence supporting the contention that the functionality of the dlPFC is positively associated with food cravings and to a lesser extent food consumption (Hall et al., 2017; Lowe et al., 2017), the exact neural mechanisms underlying this effect remain unclear. Nonetheless, an understanding of such mechanisms is essential to both treat and prevent obesity, and to identify potential neural markers that may increase individual level susceptibility to obesity. Such identification would be essential to customize individual and large-scale preventative interventions

Repetitive transcranial magnetic stimulation (rTMS) has become a powerful tool used to study the functional and causal relation between cortical activity in specific brain regions and subsequent behaviours (Dayan et al., 2013; George & Aston-Jones, 2010; Hallett, 2007). Repetitive TMS involves the application of a repetitive train of magnetic pulses that induce an electrical field in the cortex directly underlying the coil inducing a transient change in cortical activity (Dayan et al., 2013; George & Aston-Jones, 2010;Hallett, 2007). The directionality of the effect (i.e., inhibitory or excitatory) is dependent on the stimulation parameters. Continuous theta burst stimulation (cTBS) is a rTMS variant used to temporarily down-regulate cortical activity for up to one hour post-stimulation (Huang et al., 2005). The biological mechanisms underlying cTBS-induced after effects have been attributed to long-term depression (LTD) like changes in cortical plasticity (Huang et al., 2011). Prior research has demonstrated that cTBS targeting the prefrontal cortex is a reliable and effective means of modulating executive functions (EF; Lowe et al., 2017) and attentional control of somatosensory information (Bolton & Staines, 2011), and prefrontal cortical excitability as indexed via changes in cerebral blood flow (Tupak et al., 2013) and striatal dopaminergic transmission (Ko

et al., 2008). Together, these findings demonstrate that cTBS is a reliable and effective means of experimentally manipulating activity in the PFC.

The current study sought to address an important gap within the literature by investigating the neurocognitive mechanisms that enable effective dietary self-restraint, using a combination of cTBS and EEG methodologies. The high temporal resolution afforded by EEG methodologies allows researchers to explore several aspects of cognitive processing and reward responsivity that are not easily quantified with other imaging paradigms or cognitive tasks. The most widely examined stimulus-locked component is the P3 or P300. The P3 is a widespread positive potential that peaks approximately 300 ms after stimulus presentation (Polich, 2007). While they are not mutually exclusive, the P3 component can be functionally dissociated into the P3a and P3b components. The P3a is maximal at frontocentral electrodes and is thought to reflect attentional engagement. Conversely, the P3b is maximal at central and parietal electrode sites and is largely considered a measure of inhibitory control and working memory operations (Polich, 2007). Within the context of addiction and eating-related research, the amplitude of the P3a is considered an index of selective and motivated attention reflecting increased reward-responsivity to appetitive stimuli (Nijs & Franken, 2012). Thus, the selective increase in P3a amplitude in response to high calorie food images is expected following active compared to sham stimulation, and that stimulation-induced changes in P3a amplitude will be positively correlated with stimulation-induced changes in snack food consumption and food cravings; no such changes are expected in response to low calorie food images. Further, it is expected that the P3b amplitude in response to incongruent flanker trials will be significantly lower following active compared to sham stimulation, indexing stimulation-induced impairments in cognitive control. Exploratory, we also investigated the stimulation effect on the amplitude and latency of the N2 and LPP components. Although functionally distinct, the N2 is commonly observed in conjunction with the P3a and P3b (Folstein & Van Petten, 2008), and the

frontocentral N2 is considered a measure of response inhibition and cognitive control (Folstein & Van Petten, 2008).

3.2 Methods

Sample size was determined *a priori* using G*Power (Version 3.1; Faul, Erdfelder, Lang, & Buchner, 2007); results are presented in Appendix A. A total of 18-20 participants would be required to achieve 95% power to detect a cTBS effect on behavioural and electrophysiological measures of inhibitory control, and snack food consumption. In order to account for the potential loss of EEG data due to excessive muscle artifacts and the possibility of a smaller cTBS downregulation effect than previously reported a total of 36 healthy female undergraduate students were recruited to participate in the present study. However, three participants did not meet the screening criteria, four participants had motor thresholds exceeding safety limits, and one participant dropped out of the study due to discomfort during the active cTBS protocol resulting in a final sample of 28 participants. Participant characteristics and baseline measures by stimulation condition are reported in Table 1. Participants were mostly normal weight with an average body mass index (BMI) and waist circumference (inches) of 23.64 (*SD* =3.352) and 30.83 (*SD*=3.74) respectively. Only one participant had a BMI greater than 25 (BMI = 28.0), indicating that they were overweight. No participants were obese (i.e., BMI > 30) or underweight (i.e., BMI < 18.5).

Participants were recruited using an online participant recruitment system (SONA), and in exchange for their participation, they received two course credits and a $20 gift card. Prior to study participation participants were screened to be free of any major medical conditions and neuropsychiatric disorders that may contraindicate the cTBS protocol. Participants were excluded from the study if they: (1) had been diagnosed with a neurological (e.g., epilepsy) or psychiatric disorder (e.g., depression, anxiety); (2) were being treated with (any) neuropsychiatric medications; (3) had a family history of epilepsy or hearing loss; (4) had a history of head trauma (including concussions); (5) experienced chronic headaches or migraines; (6) had metal in the

cranium and/or any implanted electronic or medical devices (e.g., electronic pacemaker, implanted medication pump); (7) were pregnant. All participants were right-handed and naïve to TMS. Written and informed consent was obtained from all participants. The current study was reviewed by and received ethics clearance prior to data collection. Data collection occurred between June 2016 and April 2017.

Table 3.1
Mean (SD) participant demographics and baseline descriptives by stimulation session.

		Active	Sham
Age	20.43 (1.345)		
BMI	23.64 (3.352)		
Waist Circumference	30.83 (3.74)		
Hours since last meal		5.37 (3.297)	5.75 (4.141)
Caloric content last meal		364.667 (178.720)	366.667 (193.341)
SSS score		2.19 (.849)	2.242 (1.234)
Hours of sleep night before		7.00 (1.327)	7.435 (1.3047)
cTBS intensity		53.0286 (6.09206)	51.5143 (6.99575)

3.21 Procedure

A within-subjects crossover design was employed, such that participants received both active and sham cTBS. All participants were blinded to stimulation condition. Each study session lasted approximately 2 hours, and stimulation order was counterbalanced across participants. To account for potential carryover effects a one week intersession interval was utilized; however, due to illness, one participant had an intersession interval of 2 weeks. To account for any circadian rhythm specific variability in cognitive functioning and appetite all study sessions were conducted at the same time of day (between 1-3 PM ± 1 hour). Participants were asked to refrain from consuming any caffeinated beverages or consuming any food 3 hours prior to the start of each study session. Each study session was identical, with only the stimulation condition varying between sessions.

Upon arrival participants were asked to indicate the timing of their last meal and the foods consumed. Thereafter subjective sleepiness was assessed using the Stanford Sleepiness Scale (SSS;

Hoddes et al., 1972). Next, participants completed the Profile of Mood States-2 Adult Short (POMS-2A; Heuchert & McNair, 2014) then they were fitted with the EEG cap. Following determination of resting motor threshold (RMT) participants completed the resting EEG procedure, flanker task and food image task; task order was the same for all participants and study sessions. Following cTBS application, participants completed the POMS, resting EEG, flanker, and food image task again. The average time between cTBS application and start of the resting EEG Procedure was 3 minutes. Following completion of the above task, participants were then walked to a separate room to complete the taste test portion of the study (approximately 28 minutes following cTBS). At the end of the second study session (following the taste test), weight (lbs), height (inches), and waist circumference (inches) were objectively measured, and then participants were asked to completed a series of questionnaires pertaining to demographics, dietary habits, and physical activity patterns.

3.22 Taste Test

For the taste test, participants were instructed to taste and rate the subjective properties of five experimental foods: (1) Lindt milk chocolate truffles (91 g; 7 truffles); (2) original potato chips (42 g; two single serve containers); (3) sour cream and onion potato chips (42 g; two single serve containers); (4) plain rice cakes (22 g); (5) unsalted soda crackers (12 g; two single serve containers). With the exception of the rice cakes, the foods were presented in their pre-packaged quantities. The food items were presented simultaneously and without macronutrient information. Participants were instructed to consume as much as they would like, and were left alone to eat *ad libitum*. Participants were required to remain in the taste test room for 10 minutes, at which time the researcher entered the room and concluded the study protocol. Following the completion of the taste test, the experimental foods were weighed. Three food consumption specific variables were computed: (1) total calories (kcal) consumed; (2) total calories (kcal) consumed from appetitive foods (chocolate, potato chips); (3) total calories (kcal) consumed from control foods (rice cakes,

soda crackers). The corresponding items in each variable were summed together, with higher scores indicating a larger amount of food/calories consumed.

3.23 Measures

All stimuli were displayed and responses logged using E-Prime (Psychology Software Tools Inc, Sharpsburg, PA). Stimuli were presented on a 17-inch colour monitor (refresh rate of 60 Hz) with a viewing distance of 90 cm.

3.231 Resting EEG

Resting EEG asymmetry was measured via alternating 15 s segments of eyes-open (O) and eyes-closed (C) for 2 min in a counterbalanced order [O15s–C15s–O15s–C15s–O15s–C15s–O15s–C15s or C15s–O15s–C15s–O15s–C15s–O15s–C15s–O15s] across participants and study sessions. The 2 min resting EEG procedure has comparable reliability and internal consistency to that of the typical 8 min procedure (Allen, Coan, & Nazarian, 2004; Coan, Allen, & Harmon-Jones, 2001). During the task, participants were asked to sit quietly and to limit head and eye movement. Instructions would appear before each segment to indicate whether the participant should keep their eyes open or closed, and a tone would indicate the end of each segment.

3.232 Flanker Paradigm

Participants completed a modified version of the Eriksen flanker task (Eriksen and Eriksen, 1974) in which a five letter string composed of Hs and/or Ss was presented focally on a computer screen. Participants were instructed to indicate what the center target stimulus among four identical congruent (i.e., HHHHH or SSSSS) or incongruent (i.e., HHSHH or SSHSS) was as quickly and accurately as possible by pressing either the “S” or “H” button on a keyboard. The flanker task consisted of two blocks of 120 trials with equiprobable congruency. Each trial consisted of a flanker stimulus presented for 500ms, followed by a random inter trial interval (ITI) between 600 and 1000ms. Half the trials consisted of congruent stimuli and the other half incongruent stimuli. The

primary dependent measure was the interference score (reaction time on correct incongruent trials minus correct congruent trials); higher scores are indicative of poorer inhibitory control.

3.233 Food Image Task

This task consisted of 3 blocks of trials. Each trial was separated by a minimum 15s break. In each trial a food image depicting either a generally palatable high calorie (50) or low calorie (50) food item was presented in a random order on a computer screen. Stimuli remained on the screen for 3000 ms followed by computerized visual analogue scale (CVAS). Participants were instructed to select the spot on a 10 mm CVAS corresponding with the subjective appeal ("how much do you like the food item"; 0=not at all; 100= a lot) and their current urge to eat ("what is your current urge to eat the food item"; 0= no urge to eat; 100=extremely high urge to eat) the food item presented. No time limits were placed on CVAS ratings. Prior to the start of the task, participants were asked to indicate how hungry they were (0=not at all hungry; 100= extremely hungry), how much they think they could eat (0= nothing at all; 100= a lot), and how full they were (0=not at all full; 100= extremely full). Participants took between 8 min and 10 min to complete the task with an average time of 9.31 min.

All stimuli were selected from a food picture database (Blechert, Meule, Busch, & Ohla, 2014). High calorie food stimuli consisted solely of appealing and convenient sweet and savory snack foods (e.g., chocolate, potato chips), whereas, the low calorie food stimuli consisted of fruits, vegetables, simple salads, and plain rice cakes and crackers. Images depicting meals or other complex arrangements of food items were excluded from the current study. All pictures had the same resolution and colour depth (600 x 450 pixels. 96 dpi, 24 bpp) and were homogenous with regard to background colour, ground compositions, and camera distance. High calorie and low calorie food images did not differ in respect to image brightness ($t(98)=-.428$, $p=.670$) and contrast ($t(98)=.075$, $p=.940$), visual and subjective complexity ($t(98)=.591$ $p=.556$), recognisability ($t(98)=-1.451$, $p=.150$), or familiarity ($t(98)=-.872$, $p=.385$). The mean kcal per 100 grams was significantly

higher for high calorie (*M*=434.891; *SD*=110.602) relative to low calorie food images (*M*=68.163; *SD*=107.3854; *t*(98)=16.734, *p*<.001). In addition, the grams of dietary fat per 100 grams (*t*(98)=9.570, *p*<.001) and carbohydrates per 100 grams (*t*(98)=13.170, *p*<.001) was significantly higher for high calorie compared to low calorie food images. All image characteristics, kcal, and macronutrient data are based on the provided the normative data (Blechert et al., 2014). Image numbers and descriptions are presented in Appendix B.

3.24 Theta Burst Stimulation Procedure

Continuous TBS was administered using a 75 mm outer diameter figure-8 coil (MCF-B65) connected to a MagPro (model X100) stimulation unit (Medtronic, Minneapolis, MN, USA). A computerized frameless stereotaxic system (*Brainsight TMS,* Rogue Research, Montreal, Canada) was used to monitor head position in conjunction with an infrared camera and reflective markers placed on the participant's head and TMS coil. An anatomical scan from a previous data set and TMS neuronavigation software (*Brainsight TMS,* Rogue Research, Montreal, Canada) were used guide coil placement. Resting motor threshold (RMT) was determined using electromyography measured from the right abductor pollicus brevis (APB) muscle. Stimulation was applied over the contralateral motor cortex, at a 45˚ angle tangentially to the scalp, with the handle pointing posteriorly. RMT was defined at the lowest stimulation intensity required to produce a motor-evoked potential (MEP) with a peak-to-peak amplitude exceeding 50 μV in at least 5 out 10 consecutive trials.

For active stimulation the coil was held a 90˚angle from the mid-sagittal line with its center positioned over F3 in accordance with the International 10-20 system to target the left dlPFC. Consistent with Lowe et al. (2014) and Bolton and Staines (2011) stimulation intensity was set at 80% RMT and consisted of a 40s continuous train of 600 pulses applied in the theta burst pattern (bursts of three stimuli at 50 HZ repeated at 5 Hz frequency; Huang et al., 2005). For sham stimulation, the neuronavigation procedure and all other stimulation parameters were equal to

active cTBS, however, the coil was positioned at a perpendicular angle (90°) to the target area. Overall, cTBS was well tolerated by participants with only one participant discontinuing the protocol due to discomfort; no other adverse reactions were reported.

3.25 EEG Recording and Analyses

Continuous EEG data were recorded using a 64 Ag/AgCI electrode Neuroscan Quick-Cap (Compumedics, Charlotte, NC) referenced online to a mid-line electrode located between Cz and CPz and grounded to AFz. Online continuous data were amplified using a Neuroscan SynAmps2 amplifier (Scan 4.5, Compumedics Neuroscan, Charlotte, NC) and digitized at a sampling rate of 1000 Hz with a .1 to 70 Hz filter. EEG activity was recorded from 22 sites [FP1, FP2, FPz, Fz, F7, F5, F3, F1, F2, F4, F6, F8 FCz, FC5, FC3, FC1, FC2, FC4, FC8, Cz, CPz, Pz] placed according to the International 10-20 system (Chatrian, Lettich, & Nelson, 1985). All channel recordings had impedance values below 5kΩ. Impedance was checked before and after cTBS.

After acquisition, data were re-referenced offline to the bilateral mastoids (M1, M2). For all dependent measures, trials were visually inspected and epochs with movement and muscle artifacts were removed and excluded from analyses. ERP stimuli were averaged relative to a 100 ms pre-stimulus baseline for each flanker [incongruent, congruent] and food image [high calorie, low calorie] condition. Resting frontal alpha asymmetry (FAA) was calculated by submitting artifact-free epochs to a fast Fourier transform using a Hamming window (2.048 seconds) that tapered data at the distal 5% of each epoch to avoid spurious elements of spectral power with a 75% overlap between epochs. Overlapping compensates for minimal weighting of the distal portions of each epoch ensuring that all data are given equal weight in the final averaged spectrum (Allen, Coan, & Nazarian, 2004). FAA scores were derived by subtracting the natural log-transformed power value in the alpha band (8-13 Hz) at F3 from the corresponding homologous value at F4 (F4-F3); ln[right] – ln[left]. Alpha power is inversely proportional to the magnitude of

neural activation, thus higher asymmetry scores putatively reflect greater activity in the left dlPFC (Allen, Coan, & Nazarian, 2004).

Data for all components were extracted from electrode sites Fz, FCz, CZ, and Pz. Flanker data were segmented into condition-specific [congruent, incongruent] epochs of 100 ms before and 700 ms after stimulus onset. Stimulus-locked amplitude and latency measures for each ERP component were calculated by determining the peak amplitude (μV) for correct congruent and incongruent flanker trials within two time windows: N2 (100 to 300 ms), and P3b (300 to 600 ms). Visual inspection of the data indicated that the N2 was most pronounced at electrode sites Fz, FCz, and Cz, and therefore, amplitudes and latencies from these electrode sites were averaged together to create a frontocentral N2 cluster. Similarly, the P3b component was maximal at central parietal sites, thus, the amplitude and latencies from the electrode sites Cz, CPz, and Pz were averaged together to create a central parietal P3b cluster. Image specific [high calorie, low calorie] data were segmented into epochs of 100 ms before and 1000 ms after stimulus onset. Based on previous research (Nijs, Franken, & Muris, 2008; Svaldi et al., 2015) and visual inspection of the grand average waveform, the peak amplitude (μV) for the P3a and LPP components were determined within 200 to 400 ms and 400 to 800 ms post-stimulus time windows respectively. As both the P3a and LPP were maximal at frontocentral electrode sites the amplitudes and latencies from electrode sites Fz, FCz, Cz were averaged together to create a frontal central cluster. All offline analyses were performed using NeuroScan 4.5 software. Clearly defined components were required for inclusion in all analyses.

3.26 Data Analytic Plan

All statistical procedures were conducted using SPSS v. 24 (IBM Corp, Armonk, NY). Stimulation-induced changes in flanker interference were assessed using a 2 [pre-stimulation, post-stimulation] x 2 [active cTBS, sham cTBS] repeated measures ANOVA. Significant interactions were

followed up with simple effect ANOVA analyses. Following this, a one-way repeated measures ANOVA was conducted to determine if there was a stimulation effect on total caloric intake (kcal). It was determined *a priori* that if there was a significant difference in caloric intake as a function of stimulation condition [active vs. sham] that a food type (appetitive, control)] by stimulation condition [active, sham] repeated measures ANOVA would be conducted to determine if the consumption effects were specific to the type of food being consumed (i.e., appetitive vs. control). Significant interactions were followed up with simple effect ANOVAs.

A three-way ANOVA was conducted to determine if there was a stimulation effect on the subjective appeal and urge to consume high calorie relative to low calorie foods. Significant three-way interactions were followed up with a 2 [active, sham] x 2 [pre-cTBS, post-cTBS] repeated measures ANOVA at each food image level [high calorie, low calorie]. Significant two-way interactions were followed up with simple effect ANOVAs. Separate 2 [active, sham] x 2 [pre-cTBS, post-cTBS] repeated measures ANOVAs were conducted to determine if there was a stimulation effect on hunger, prospective consumption, and fullness ratings.

Stimulation induced differences in FAA were assessed using a 2 [pre-stimulation, post-stimulation] x 2 [active stimulation, sham stimulation] repeated measures ANOVA. Significant interactions were followed up with simple effect analyses. N2 and P3b analyses were performed using a 2 [incongruent, congruent] x 2 [pre-stimulation, post-stimulation] x 2 [active cTBS, sham cTBS] repeated measures ANOVA separately for the latency and amplitude of each component. Significant interactions were followed up with simple effect ANOVA analyses as a function of stimulation condition. Similarly, P3a and LPP were analyzed using separate 2 [high calorie, low calorie] x 2 [pre-cTBS, post-cTBS] x 2 [active cTBS, sham cTBS] repeated measures ANOVA. Significant three interactions were followed up with a 2 [active, sham] x 2 [pre-cTBS, post-cTBS] repeated measures ANOVA at each food image level [high calorie, low calorie]. For all analyses, significant interactions were followed up with simple effect ANOVAs.

3.3 Results

3.31 Behavioural data

3.311 Blinding statistics

Only 4 (14.3%) participants indicated that they could differentiate between active and sham stimulation. In addition, only 1 (3.6%) participant indicated that they were aware we were measuring food consumption during the bogus taste test. However, 6 (21.4%) participants did indicate they 'thought we might be measuring food consumption, but were unsure". Overall, these statistics suggest successful participant blinding.

3.312 Baseline comparisons

No significant differences between active and sham stimulation sessions were apparent for either cTBS stimulation intensity ($t(27)=1.102$, $p=.280$), time since last meal ($t(27)=-.044$, $p=.965$), estimated calories consumed in the last meal ($t(27)=.577$, $p=.574$), SSS score ($t(27)=-1.231$), or self-reported hours of sleep the night before the study session ($t(27)=-1.388$, $p=.179$).

3.313 Stimulation effects on mood

Examination of the stimulation effect on the total mood score indicated that both the main effect of stimulation condition ($F(1,27)=.025$, $p=.875$) and time ($F(1,27)=.148$, $p=.704$) were not significant. Likewise, the stimulation condition [active, sham] by time [pre-cTBS, post-cTBS] interaction was not significant ($F(1,27)=.189$, $p=.667$).

3.314 Taste test

A significant main effect of food type [appetitive, control] was apparent ($F(1,27)= 117.441$, $p<.001$), indicating that across stimulation conditions [active, sham] participants rated the appetitive foods ($M=7.303$; $SE=.250$) as significantly more appealing than the control foods ($M=3.966$; $SE=.227$). The main effect of stimulation condition ($F(1,27)=.010$, $p=.922$) and stimulation condition by food type interaction ($F(1,27)=2.299$, $p=.141$) were not significant.

Similarly, examination of the perceived health ratings revealed a significant main effect of food type was apparent (F (1,27)= 192.102, p<.001), indicating that across stimulation conditions participants rated the appetitive foods (M=1.603; SE=.103) as significantly less healthy than the control foods (M=4.804; SE=.268).

3.315 Stimulation effects on flanker performance

Data from one participant was excluded due to performance accuracies on the flanker paradigm at levels less than chance (i.e., < 50%). Reaction time and accuracy data as a function of stimulation condition are presented in Table 3.2. Results indicated that the main effects of stimulation condition [active, sham] (F(1,26)=4.625, p=.041) and time [pre-cTBS, post-cTBS] (F(1,26)= 18.621, p< .001) on flanker interference scores (ms) were significant. These main effects were qualified by a significant time by stimulation condition interaction (F(1,26)=9.800, p=.004). Specifically, performance on the flanker paradigm was significantly impaired following active cTBS (F(1,26)=17.537, p<.001) but not following sham stimulation (F(1,26)=1.127, p=.298). No significant differences in baseline Flanker interference scores (t(26)=-.518, p=.609) were apparent, indicating that baseline differences did not modulate the observed stimulation effect. No main effects of time [pre-cTBS, post-cTBS] (F(1,26)=.024, p=.815) and stimulation condition [active, sham] (F(1,26)=.596, p=.447) emerged for accuracy data. Likewise the time by stimulation condition interaction (F(1,26)=.039, p=.846) was not significant.

Table 3.2
Mean (SD) flanker accuracy and reaction time data by stimulation condition

	Active		**Sham**	
	Pre-cTBS	Post-cTBS	Pre-cTBS	Post-cTBS
Flanker Performance Variables				
Accuracy	87.56 (.063)	88.44 (7.905)	88.74 (7.336)	89.85 (6.304)
RT congruent trials	207.133 (82.190)	194.647 (71.828)	209.784 (88.482)	199.532 (77.902)
RT incongruent trials	220.780 (78.936)	237.912 (71.710)	228.652 (81.443)	222.003 (80.314)
Interference	16.257 (19.348)	43. 264 (31.046)	18.868 (17.546)	22.470 (13.606)

Note: Flanker interference was calculated by subtracting the reaction time on correct congruent trials from incongruent trials [incongruent-congruent]. Data is based on 27 participants, as one participant was excluded from flanker analyses due to performance accuracies at levels less than chance (i.e., < 50%).

3.316 Stimulation effect on food consumption

Examination of total calories consumed revealed a significant effect of stimulation condition ($F(1,27)=25.824$, $p<.001$), such that on average participants consumed 145.574 more calories following active cTBS ($M=576.410$; $SD=154.123$) relative to sham cTBS ($M=430.836$; $SD=123.035$). Comparison of the stimulation effects on food consumption as a function of food type (appetitive versus control) revealed significant main effects of stimulation condition [active, sham] ($F(1,27)=314.351$, $p<.001$) and food type ($F(1,27)= 25.824$, $p<.001$). As expected, these main effects were qualified by a significant stimulation condition by food type interaction ($F(1,27)= 67.664$, $p<.001$). Simple main effects analyses indicated that participants consumed significantly more calories from appetitive snack foods following active ($M=469.1.1$; $SD=127.910$) relative to sham ($M=330.264$; $SD=94.081$) stimulation ($F(1,27)=46.920$, $p<.001$). However, no significant differences in calories consumed from control foods were apparent across stimulation conditions ($F(1,27)=.353$, $p=.557$); see Figure 3.1.

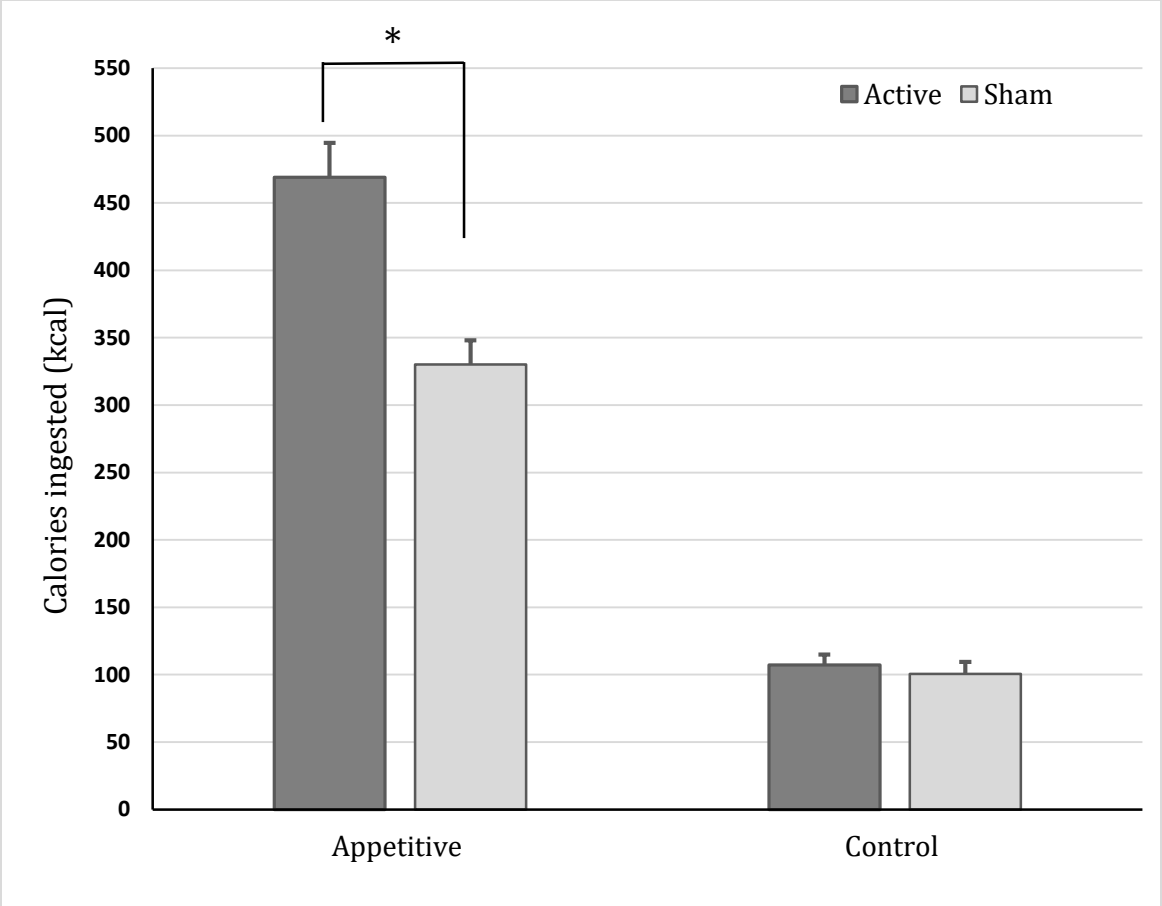

Figure 3.1: Mean (*SE*) calories ingested (kcal) during the taste test as a function of food type [appetitive, control] and stimulation condition [active, sham]. * significantly different (p<.05).

Table 3.3
Mean (SD) consumption data by food type (appetitive, control) and stimulation condition (active, sham).

	Active		**Sham**	
	Amount Consumed (g)	Calories Consumed (kcal)	Amount Consumed (g)	Calories Consumed (kcal)
Total Consumed	98.393 (24.857)	576.410 (154.123)	74.678 (18.103)	430.836 (123.035)
Appetitive Food	85.393 (24.101)	469.101 (127.910)	59.036 (17.362)	330.264 (94.081)
Milk Chocolate	38.107 (12.396)	232.877 (75.752)	31.393 (11.351)	191.845 (69.366)
Original Pringles	24.071 (14.126)	114.626 (67.268)	13.393 (9.643)	63.776 (45.919)
Sour Cream and Onion Pringles	23.214 (10.507)	121.599 (55.037)	14.250 (9.747)	74.643 (51.057)
Control Food	13.000 (4.815)	107.309 (40.520)	15.643 (5.479)	100.573 (46.525)
Plain Rice Cakes	9.107 (3.804)	90.278 (40.861)	5.321 (2.554)	55.417 (37.906)
Unsalted Crackers	3.893 (2.183)	17.031 (9.551)	10.321 (4.785)	45.156 (20.933)

3.317 Stimulation effects on food cravings and subjective appeal of high calorie and low calorie foods

A significant main effect of food type [high calorie, low calorie] was observed for both subjective appeal (F(1,27)=5.997, p=.021) and urge to eat (F(1,27)=4.618, p=.041) CVAS ratings. Across time points [pre-cTBS, post-cTBS] and stimulation conditions [active, sham] participants rated the high calorie foods (M=64.670; SE=2.296) as more appealing than the low calorie foods (M=58.164; SE=2.229), and reported stronger urges to consume the high calorie (M= 56.487; SE=3.232) relative to the low calorie (M=47.961; SE=2.327) foods. Most importantly, a significant three way interaction [food type x stimulation condition x time point] was observed for both urge to eat (F(1,27)=8.738, p=.006) and subjective appeal ratings (F(1,27)=13.549, p=.001). Results from the follow-up 2x2 [time by stimulation condition] ANOVAs at each level of food type [high calorie, low calorie] revealed a significant two-way interaction between stimulation condition [active, sham] and time [pre-stimulation, post-stimulation] for the urge to eat high calorie foods (F(1,24)=19.078, p<.001). Specifically, a significant increase in pre-to-post urge to eat ratings was apparent following active stimulation (F(1,24)=26.939, p<.001). However, no significant change in pre-to-post urge to eat high calorie food ratings were observed following sham stimulation (F(1,27)=1.004, p=.325). The time by stimulation condition interaction was not significant for low calorie foods (F(1,27)=.233, p=.634), indicating that stimulation-induced increases in food cravings is specific to high caloric foods rather than food in general. Similar effects are apparent when examining the subjective appeal of high calorie relative to low calorie foods. That is, the two-way interaction was significant for high-caloric foods only (F(1,27)= 7.317, p=.012). Furthermore, a significant increase in pre-to-post stimulation appeal ratings was observed following active stimulation (F(1,27)=9.810, p=.004); no significant differences were observed following sham stimulation (F(1,27)=1.630, p=.213).

Table 3.4
Mean (SD) CVAS ratings as a function of stimulation condition (active, sham) and food craving and hunger dimension

	Active		Sham	
	Pre-cTBS	Post-cTBS	Pre-cTBS	Post-cTBS
Food Craving Variables				
Subjective appeal high calorie foods	63.621 (11.623)	67.626 (11.220)	63.409 (13.730)	64.023 (14.655)
Subjective appeal low calorie foods	59.739 (12.892)	58.088 (13.731)	56.925 (12.120)	57.904 (12.443)
Urge to eat high calorie foods	52.923 (15.530)	61.253 (17.751)	54.492 (19.026)	55.089 (18.668)
Urge to eat low calorie foods	47.510 (11.455)	48.769 (15.805)	49.986 (13.180)	49.955 (14.447)
Hunger Variables				
Subjective hunger	61.602 (23.232)	75.321 (19.061)	64.357 (23.149)	75.571 (16.985)
Prospective consumption	67.321 (16.032)	72.536 (17.888)	68.179 (19.611)	73.679 (15.119)
Fullness*	19.607 (18.307)	24.464 (21.964)	21.615 (16.860)	27.231 (24.818)

Note: * this variable is reverse coded, such that higher numbers indicate being more full or less hungry.

3.318 Stimulation effects on subjective hunger and prospective consumption

A significant increase in pre-to-post ratings in hunger ($F(1,27)= 14.676$, $p=.001$) and prospective consumption $F(1,27)= 4.993$, $p=.034$). There were no significant differences in pre-to-post fullness ratings ($F(1,27)=1.138$, $p=.296$). The main effect of stimulation condition was not significant for hunger ($F(1,27)=.310$, $p=.582$), prospective consumption ($F(1,27)= .181$, $p=.674$), nor fullness ($F(1,27)=.541$ $p=.469$). Further, no significant interactions were observed for either hunger ($F(1,27)=.250$, $p=.621$), prospective consumption ($F(1,27)=.005$, $p=.942$), or fullness $F(1,27)=.739$, $p=.398$). Together, these data indicate that irrespective of stimulation condition, a significant increase in physiological hunger was observed following cTBS administration. No significant differences in baseline ratings for subjective hunger ($t(27)=-.636$, $p=.530$), prospective consumption ($t(27)=-.259$, $p=.798$), or fullness ($t(27)=-.009$, $p=.993$) were apparent, indicating that the increase in overall physiological hunger is not attributable to baseline differences.

3.32 Electrophysiological data

3.321 P3b amplitude and latency

All analyses were performed on correct trials only. One participant was excluded from analyses due performance accuracies less than chance. Across stimulation conditions and time points the average number of included congruent and incongruent epochs were 87.566 (*SD*=42.838) and 88.280 (*SD*=33.818) respectively. No significant main effects were apparent when examining the peak amplitude (μV) of the central parietal P3b cluster (p>.20). In addition, the three way interaction [stimulation condition by time point by congruency] was not significant (F(1,26)=1.261, p=.272). However, a significant main effect of congruency was apparent when examining the latency (ms) of the central parietal P3b cluster (F(1,26)=19.240, p<.001). Across time points and stimulation conditions, the latency (ms) of the P3b was significantly faster for congruent (*M*=407.068; *SE*=7.583) compared to incongruent (*M*=428.420; *SE*=8.210) flanker trials. This main effect was qualified by a significant three way interaction [stimulation condition by time point by congruency] interaction (F(1,27)=6.294, p=.019). The follow up 2 x 2 ANOVA as a function of stimulation condition revealed a significant time [pre-cTBS, post-cTBS] by congruency [congruent, incongruent] interaction (F(1,26)=7.295, p=.012) for active stimulation. Following active stimulation a significant increase in P3b latency to incongruent trials was observed (F(1,26)=10.224, p=.004); see Figure 3.2. However, there was no significant difference in the pre-to-post P3b latency to congruent trials (F(1,26)= .408, p=.528). While the main effect of congruency was significant (F(1.26)=4.561, p=.042), both the main effect of time (F(1,26)=.015, p=.903) and the time [pre-cTBS, post-cTBS] by congruency [congruent, incongruent] interaction (F(1,26)=.760, p=.391) were not significant in the sham condition.

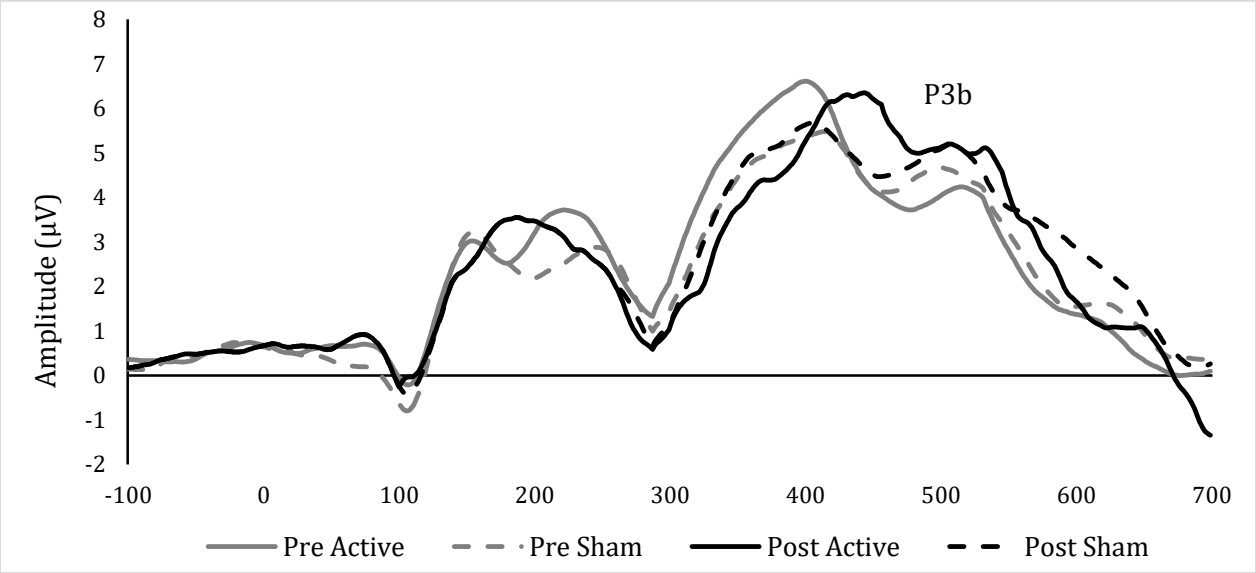

Figure 3.2: Stimulus locked grand-average waveform for incongruent flanker trials averaged across central parietal electrodes (Cz, CPz, Pz).

3.322 N2 amplitude and latency

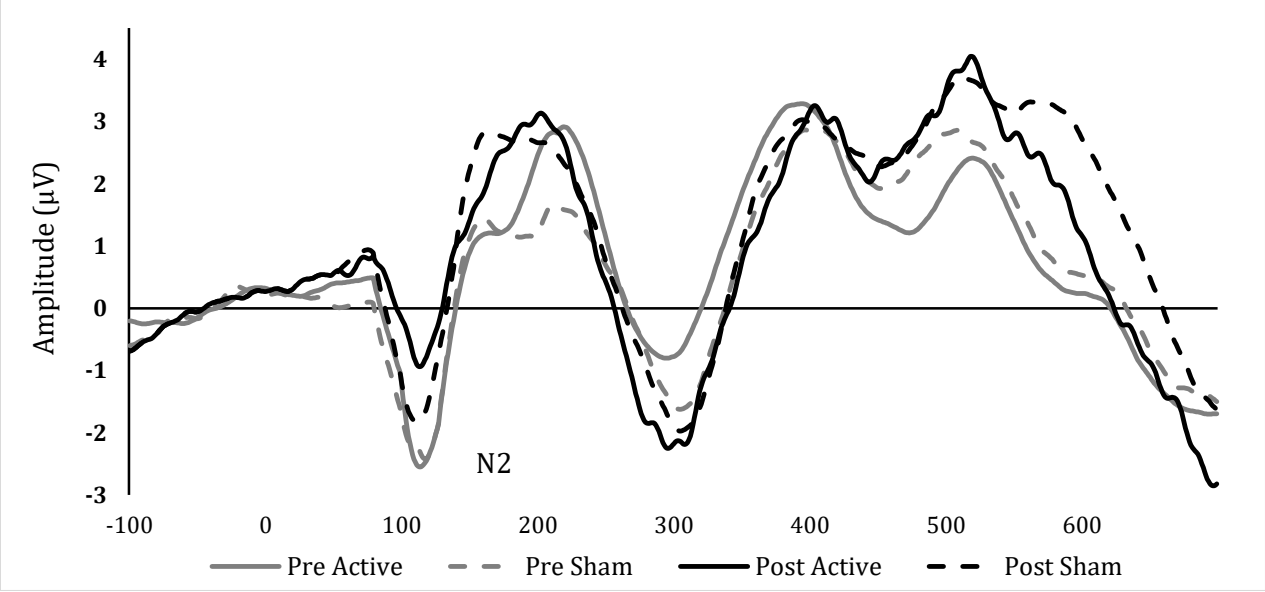

Figure 3.3: Stimulus locked grand-average waveform for incongruent flanker trials averaged across frontocentral electrodes (Fz, FCz, Cz).

When examining the peak amplitude (μV) of frontocentral N2 cluster results indicated that the time [pre-cTBS, post-cTBS] by congruency [congruent, incongruent] interaction was significant (F(1,26)=18.711 p<.001). In addition, a trend towards significance for the three-way [stimulation condition by time point by congruency] interaction was apparent (F(1,26)= 4.166, p=.052). The follow up 2 x 2 ANOVA as a function of stimulation condition [active, sham] revealed a significant time [pre-cTBS, post-cTBS] by congruency [congruent, incongruent] interaction (F(1,26)=29.544, p<.001) for active stimulation only. No significant main effects or interactions were observed for sham stimulation (p>.30). Following active stimulation, a significant reduction in the peak amplitude (μV) of frontocentral N2 cluster to incongruent trials was observed (F(1,26)=13.339, p=.001); see Figure 3.3. However, results indicated that there were no differences in the pre-to-post amplitude for congruent trials (F(1,26)=.354, p=.557). No significant main effects or interactions were apparent when examining N2 latency (p>.10).

Table 3.5
Mean (SD) peak amplitude (μV) and latency (ms) for the frontocentral N2 cluster (Fz, FCz, Cz) and central parietal P3b cluster (Cz, CPz, Pz)

	Active				**Sham**			
	Pre-cTBS		Post-cTBS		Pre-cTBS		Post-cTBS	
	Congruent	Incongruent	Congruent	Incongruent	Congruent	Incongruent	Congruent	Incongruent
P3b								
Amplitude	6.258 (2.583)	6.296 (2.678)	6.235 (2.825)	6.388 (2.240)	5.667 (3.426)	5.841 (3.106)	6.467 (2.789)	6.776 (2.951)
Latency	396.247 (64.362)	394.494 (56.905)	384.667 (52.131)	443.802 (66.110)	418.963 (93.816)	440.086 (64.597)	428.395 (72.446)	435.296 (69.851)
N2								
Amplitude	-1.642 (2.227)	-2.464 (2.065)	-1.896 (1.201)	-.9782 (1.257)	-2.356 (1.725)	-2.554 (2.029)	-1.834 (1.775)	-1.547 (2.118)
Latency	124.543 (29.368)	138.889 (50.422)	120.210 (25.802)	127.222 (32.995)	132.543 (37.361)	126.691 (31.7003)	118.901 (26.250)	111.691 (20.401)

Note: Data presented is based on a sample of 27 participants. One participant was excluded from ERP analyses due to performance accuracies on the flanker task at levels less than chance.

3.323 LPP amplitude and latency

Data from two participants were excluded from data analyses due to an insufficient number of artifact free trials. The mean number of high calorie and low calorie food epochs included the analyses were 36.13 (SD=7.65) and 34.31 (SD=8.67) respectively. A significant main effect of food

type [high calorie, low calorie] was observed ($F(1,25)=4.778$, $p=.039$), indicating that across stimulation conditions and time points the peak amplitude (μV) of the frontal LPP cluster was significantly higher in response to high calorie ($M=7.519$, $SE=.423$) relative to low calorie ($M=6.756$, $SE=.296$) food images. This main effect was qualified by a significant three-way [stimulation condition by time by food] interaction ($F(1,25)=7.230$, $p=.013$). Results from the follow-up 2x2 [time by stimulation condition] ANOVAs at each level of food type [high calorie, low calorie] revealed a significant main effect of time ($F(1,25)=11.856$, $p=.002$), indicating that across stimulation conditions that post-cTBS LPP amplitudes in response to high calorie food images ($M=8.761$; $SE=.563$) were significantly higher than pre-cTBS amplitudes ($M=6.422$; $SE=.505$). The main effect of stimulation condition ($F(1,25)=1.104$, $p=.304$) and the stimulation condition [active, sham] by time [pre-cTBS, post-cTBS] interaction ($F(1,24)=.590$, $p=.450$) were not significant. When examining the LPP amplitude in response to low calorie food images results revealed a significant main effect of time ($F(1,25)=4.660$, $p=.041$); however, the main effect of stimulation condition was not significant ($F(1,25)=3.411$, $p=.077$). The significant main effect of time was qualified by a significant stimulation condition [active, sham] by time [pre-cTBS, post-cTBS] interaction was apparent ($F(1,25)=11.963$, $p=.002$). A significant increase in the LPP amplitude to low calorie food images was observed following sham stimulation ($F(1,25)=11.764$, $p=.002$), however, no significant differences in LPP amplitude to low calorie food images were apparent following active stimulation ($F(1,25)=.267$, $p=.610$).

A significant main effect of time [pre-cTBS, post-cTBS] was observed for LPP latency ($F(1,25)=18.983$, $p<.001$), indicating that across stimulation conditions [active, sham] and food types [high calorie, low calorie] the pre-cTBS LPP latency ($M=574.356$, $SE=10.576$) was significantly faster than the post-cTBS LPP latency ($M=637.399$, $SE=18.092$). The main effects of food type ($F(1,25)=1.129$, $p=.298$) and stimulation condition ($F(1,25)=1.052$, $p=.315$) were not significant. Neither the three way [time, stimulation condition, food type] interaction ($F(1,25)=.361$, $p=.554$),

nor the time by stimulation condition (F(1,24)=2.151, p=.155) or time by food type (F(1,25)=.452, p=.508) interactions were significant. However, the significant main effect of time was qualified by a significant time [pre-cTBS, post-cTBS] by food type [high calorie, low calorie] interaction (F(1,25)=11.684, p=.002). Specifically, across stimulation conditions the latency of the LPP to low calorie food images was significantly faster (F(1,25)=29.790, p<.001) post-cTBS (M=561.642; SE=14.432) than pre-cTBS (M=666.288; SE=20.233). However, no significant differences in the LPP latency to high calorie food images were apparent (p> .250).

Table 3.6
Mean (SD) peak amplitude (μV) and latency (ms) for the frontocentral P3a cluster (Fz, FCz, Cz) and frontal LPP cluster (Fz, FCz) as a function of stimulation condition and food image type.

	Active				**Sham**			
	Pre-cTBS		Post-cTBS		Pre-cTBS		Post-cTBS	
	High Calorie	Low Calorie	High Calorie	Low Calorie	High Calorie	Low Calorie	High Calorie	Low Calorie
P3a								
Amplitude	5.592 (2.646)	4.347 (2.651)	9.053 (2.907)	5.815 (3.912)	6.655 (3.065)	5.350 (2.659)	6.976 (4.987)	5.992 (2.834)
Latency	257.756 (39.036)	245.590 (36.5300	261.077 (47.742)	259.833 (49.339)	263.628 (57.123)	246.897 (53.123)	255.538 (51.779)	259.026 (53.924)
LPP								
Amplitude	6.544 (3.361)	6.497 (2.777)	9.290 (3.497)	6.118 (2.929)	6.299 (3.443)	5.640 (1.957)	8.234 (3.396)	8.927 (4.419)
Latency	639.923 (165.897)	699.996 (165.467)	598.327 (107.185)	545.135 (122.908)	602.596 (128.758)	639.040 (101.801)	598.827 (111.586)	569.772 (67.087)

3.324 P3a amplitude and latency

Grand average waveforms as a function of stimulation condition are presented in Figure 3.4 Results from the 2 [pre-cTBS, post-cTBS] X 2 [active, sham] X 2 [high calorie, low calorie] revealed a significant main effect of food type (F(1,25)= 20.407, p<.001) indicating that across stimulation conditions and time points the P3a amplitude to high caloric food images (M=7.182, SE=.469) was significantly higher than low caloric food images (M=5.376; SE=.343). Most importantly, a significant three way interaction [food type x stimulation condition x time point] was observed (F(1,25)=4.629, p=.041). Results from the follow-up 2x2 [time x stimulation condition] ANOVAs at

each level of food type [high calorie, low calorie] revealed a significant two-way interaction between stimulation condition [active, sham] and time [pre-stimulation, post-stimulation] for P3a amplitude in response to high caloric food images ($F(1,25)=14.259$, $p=.001$). A significant increase in P3a amplitude was apparent following active stimulation ($F(1,25)=35.528$, $p<.001$), however, no significant differences in P3a amplitude were observed following sham stimulation ($F(1,25)=.169$, $p=.684$). Further, the stimulation condition [active, sham] by time [pre-cTBS, post-cTBS] interaction was not significant for low calorie food images ($F(1,25)=1.061$, $p=.313$), indicating that the stimulation-induced increase in P3a amplitude was specific to high caloric food images. No significant effects were apparent when examining P3a latency ($p>.10$).

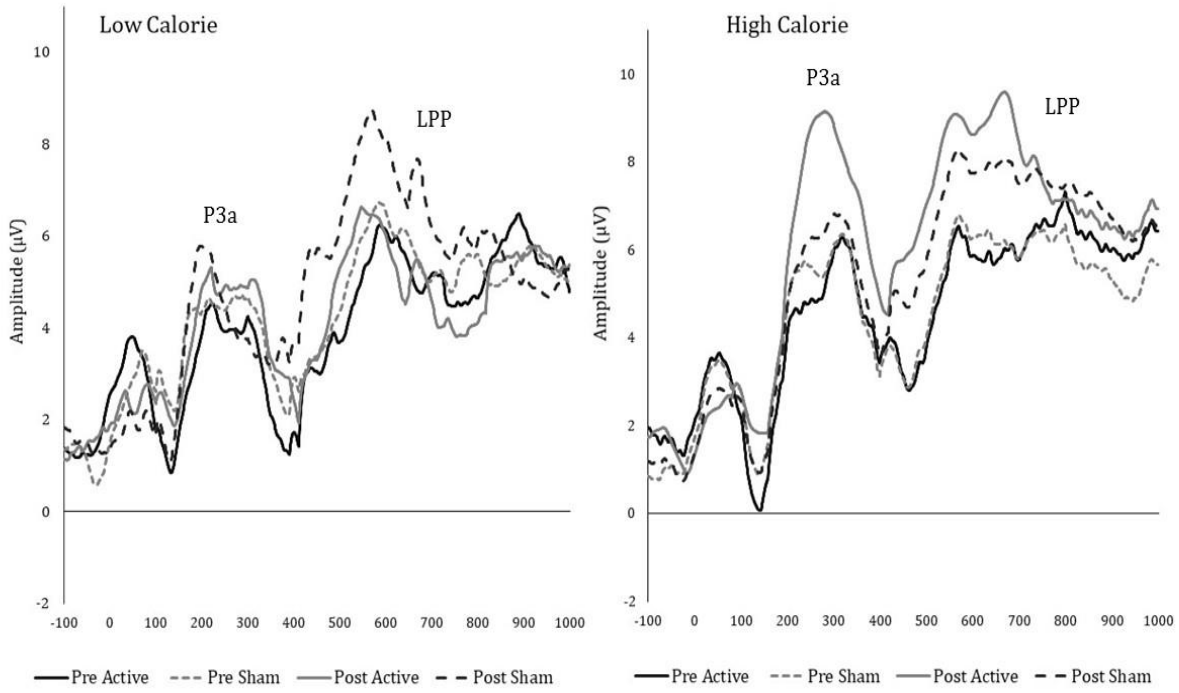

Figure 3.4: Grand-average high calorie and low calorie elicited waveforms for the frontocentral electrode cluster (averaged across Fz, FCz, Cz)

3.325 Attentional bias for high calorie food stimuli

Additional analyses were conducted to determine if there was a stimulation effect on P3a amplitude bias to high calorie food stimuli (i.e., attentional bias for high calorie foods). The amplitude bias was calculated by subtracting the P3a amplitude to low calorie food images from that to high calorie food images. Results indicated that the main effect of time (F(1,25)=1.778, p=.194) and stimulation condition (F(1,25)=3.296, p=.081) were not significant. However, a significant stimulation condition [active, sham] by time [pre-cTBS, post-cTBS] interaction (F(1,25)=4.629, p=.041) was observed. Planned simple effects analyses revealed that the amplitude bias to high calorie food stimuli was significantly higher following active stimulation (F(1,25)= 6.627, p=.016), however, there was no significant change in amplitude bias following sham stimulation (F(1,25)=.086, p=.771); see Figure 3.3.

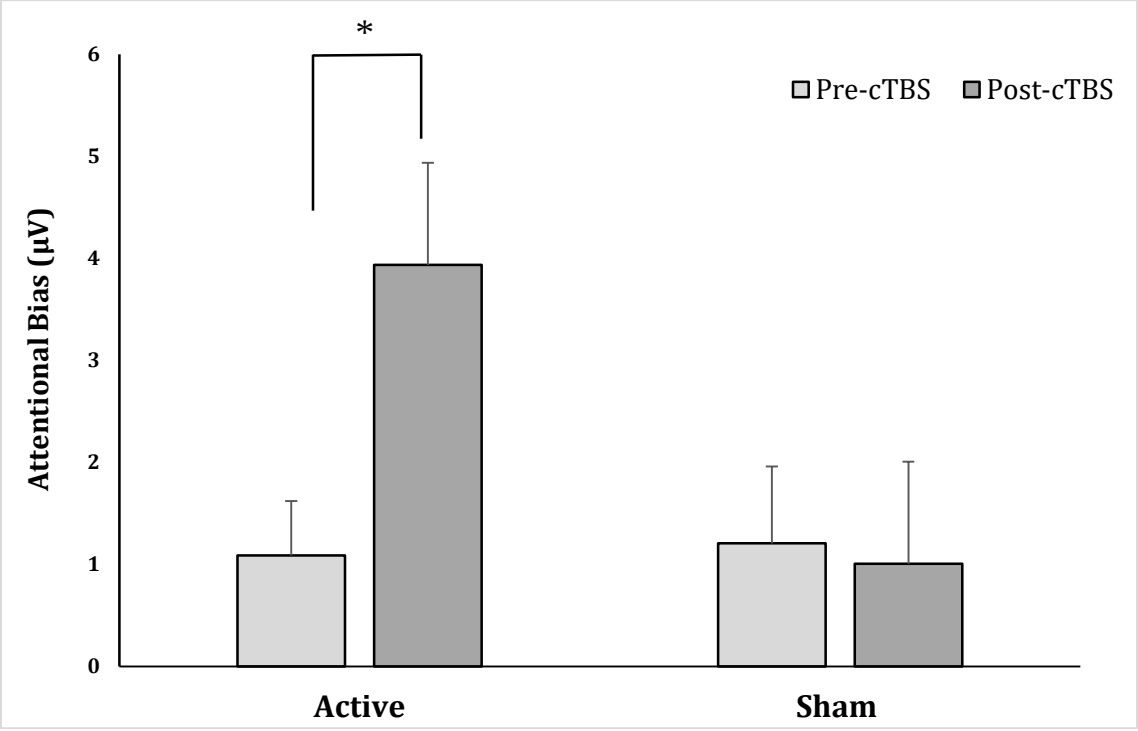

Figure 3.5: Mean (SE) attentional bias to high calorie food images by stimulation condition. A significant increase in the pre (M=1.578; *SE*=.530)*-to-post* (*M*=3.270; *SE*=.906) *attentional bias was apparent following active stimulation. No change in the pre* (*M*=1.247; *SE*=.730)*-to-post* (*M*=1.104*; SE*= .924) *attentional bias was observed following sham stimulation. * p*<.05

3.326 Mediational analyses

Pearson correlations were calculated to assess the potential mediational relationship between stimulation-induced changes in P3a amplitude [post-cTBS P3a – pre-cTBS P3a amplitude] and the attentional bias for high calorie foods [post-cTBS attentional bias –pre-cTBS attentional bias] and stimulation-induced changes in hunger, the prospective consumption , the subjective appeal of high calorie foods, the urge to consume high calorie foods, total calories consumed, and calories consumed from appetitive and control foods. All correlations were conducted for the active stimulation condition only. Strong positive correlations were observed for both stimulation-induced gains in P3a amplitude and the attentional bias for high calorie foods between stimulation-induced changes in subjective hunger (attentional bias: r=.559, p=.003; P3a: r=.394, p=.046) and prospective consumption (attentional bias: r=.751, p<.001; P3a: r=.429, p=.029) CVAS ratings; see Figure 3.4. Further, stimulation-induced changes in the attentional bias for high calorie foods correlated with the change in subjective appeal ratings (r=.418, p=.034) but not urge to eat (r=.245, p=.227) CVAS ratings. Conversely, stimulation-induced changes in P3a amplitude correlated with the change in urge to eat (r=.452, p=.020), but not subjective appeal (r=.298, p=.139). The active-stimulation induced gains in the attentional bias for high calorie foods and P3a amplitude were significantly correlated with total calories consumed during the taste test (attentional bias: r=.394, p=.047; P3a: r=.452, p=.020), and calories from appetitive foods (attentional bias: r=.422, p=.032; P3a: r=.459, p=.018). There was no association between either variable and control food consumption (attentional bias: r=.230, p=.258; P3a: r=.216, p=.289) This remained robust after controlling for BMI, time since last meal, calories ingested in the last meal, and waist circumference (see Table 3.5).

Stimulation-induced changes in LPP amplitude to high calorie foods [post-cTBS LPP – pre-cTBS LPP] were positively correlated with pre-to-post cTBS changes in the prospective consumption (r=.520, p=.007) and hunger (r=.406, p=.032) CVAS ratings. However, there was no

association between stimulation-induced changes in subjective appeal (r=.092, p=.662) or urge to eat (r=.087, p=.679) ratings, nor total calories consumed (r=.059, p=.780), calories from appetitive snack foods (r=.122, p=.562), or calories from control foods (r=-.155, p=.459).

Table 3.5
Correlational analyses between stimulation-induced changes in P3a amplitude (μV) to high calorie food stimuli and the amplitude bias for high calorie foods (μV) and stimulation-induced changes in hunger, food cravings, and calories ingested after controlling for BMI, waist circumference, time since last meal, and estimated calories consumed in last meal.

	1	2	3	4	5	6	7	8	9
1. Change in Attentional Bias	1								
2. Change in P3a amplitude	.780 (<.001)	1							
3. Change in hunger	.506 (.019)	.600 (.004)	1						
4.Change in prospective consumption	.542 (.011)	.707 (<.001)	.648 (.001)	1					
5. Change urge to eat high calorie foods	.383 (.105)	.461 (.035)	.366 (.103)	.355 (.115)	1				
6. Change in the subjective appeal of high calorie foods	.463 (.035)	.377 (.101)	.545 (.011)	.097 (.677)	.409 (.066)	1			
7. Total Calories ingested	.465 (.034)	.495 (.023)	.117 (.612)	.310 (.171)	.365 (.104)	.281 (.217)	1		
8. Calories ingested from appetitive foods	.456 (.038)	.495 (.023)	.126 (.585)	.355 (.114)	.465 (.033)	.272 (.233)	.976 (<.001)	1	
9. Calories ingested from control foods	.328 (.146)	.318 (.160)	.047 (.841)	. 055 (.812)	-.088 (.704)	.211 (.359)	719. (<.001)	.552 (.009)	1

Note: All change variables reflect the pre-to-post difference following active stimulation only.

3.4 Discussion

The current study sought to address an important gap within the literature by determining the causal relation between prefrontal functionality and food-specific reward responsivity. A core theme underlying the predominate neurobehavioural models of obesity is that individuals with obesity are more attuned to the rewarding aspects of calorie dense foods and food cues, and this heightened reward sensitivity predisposes them to the overconsumption of such foods (Boswell & Kober, 2016; Dagher, 2010; Davis et al., 2011; Stice & Yokum, 2016a; Val-Laillet et al., 2015; Volkow et al., 2013). More specifically, such heightened reward sensitivity to calorie dense food stimuli is

thought to be a direct function of aberrant dopaminergic signalling within the mesolimbic reward regions of the brain (e.g., ventral striatum; Stice & Yokum, 2016a; Volkow, Wang, Tomasi, & Baler, 2013). While there is substantial evidence that non-homeostatic food consumption is (at least in part) modulated by activity in the cortical and subcortical reward regions of the brain, much less attention has been given to identifying the neural mechanisms that enable individuals to exert conscious control over food choice. The current findings build previous models by providing direct evidence that the functionality of the PFC also plays a pivotal role in modulating reward responsivity and non-homeostatic consumptive habits.

Specifically, consistent with prior research (Lowe, Hall, & Staines, 2014), we found that cTBS-induced attenuation of left dlPFC activity resulted in the significant increase in the consumption of and cravings for appetitive calorie dense foods. This was highly specific for palatable high calorie foods and food stimuli, and did not translate into stimulation-induced changes in the cravings for low calorie foods or control food consumption. Further, as expected, across stimulation conditions and time points the amplitude of the P3a and LPP components were significantly higher in response to high calorie relative to low calorie food images, indicating higher reward responsivity to and motivation to consume high calorie foods. These findings are in line with several other studies reporting positive associations between ERP indices of attentional engagement and motivation (i.e., P3a and LPP amplitude) to food stimuli and subjective food cravings (Nijs et al., 2010; Nijs et al., 2008; Werthmann et al., 2014). The additional finding that a significant increase in P3a amplitude to high calorie food images and the attentional bias for high calorie foods was apparent following active compared to sham stimulation provides important insight into the mechanisms underlying prefrontal-mediated self-regulatory behaviours. Such stimulation-induced increases in P3a amplitude and the attentional bias to high calorie food stimuli were positively associated with the total calories consumed from appetitive calorie dense foods, but not control foods. This association remained robust after controlling for BMI, waist circumference,

time since last meal, and estimated calories consumed during the last meal. Together, these data provide causal evidence demonstrating that suboptimal prefrontal cortical activity in a normal healthy population (only one participant had a BMI > 25) results in the heightened reward responsivity to high caloric food stimuli, subsequently predisposing an individual to the specific overconsumption of appetitive calorie dense snack foods. Further, these findings suggest that the heightened attentional bias to high-caloric food stimuli precedes weight gain, rather than obesity itself contributing to the development of attentional biases for food stimuli.

Such findings have important implications for how we conceptualize individual level risk for obesity, and could be used to inform preventative interventions and treatment programs. That is, prefrontal functionality can be optimized, and thus, interventions aimed at optimizing prefrontal functionality may be beneficial both from a preventative standpoint and in conjunction with current obesity treatments. For instance, several lines of research have demonstrated that both acute bouts of aerobic exercise and long-term exercise interventions has beneficial effects on cortical structure and functionality, particularly in the areas underlying executive control (Erickson et al., 2015; Erickson, Leckie, & Weinstein, 2014; Hillman, Erickson, & Kramer, 2008; Weinstein et al., 2012). Therefore, it is plausible that exercise-induced enhancements in prefrontal structure and function may translate to increased dietary self-restraint, suggesting that aerobic exercise interventions may be beneficial both as a preventative measure and in conjunction with current obesity treatments.

Although, they are not mutually exclusive, prior research suggests that there is a neural and physiological distinction between wanting and liking of appetitive substances. The subjective appeal or liking of high calorie foods may represent a hedonic reaction to the pleasure obtained from consuming such foods whereas wanting (urge to consume) represents the motivational value of the stimulus (Berridge, 2009; Finlayson & Dalton, 2012). To date, most prior research has focused on how mesolimbic circuitry and functionality influences the wanting and liking of high caloric food cues. Specifically, liking is thought to be primarily driven by dopaminergic transmission

within the nucleus accumbens (NAc) and ventral striatopallidum (VP), whereas, wanting is more widely distributed within the mesolimbic circuit such as the ventral tegmental area (VTA) and dorsal striatum (Berridge, 2009; Castro & Berridge, 2014). The current findings demonstrate that prefrontal functionality also plays a pivotal role in modulating the liking and wanting of appetitive foods in that attenuation of left dlPFC resulted in significant increases in both the subjective appeal (liking) and the urge to consume (wanting) of high calorie foods. Likewise, the stimulation-induced change in P3a amplitude to high calorie food images was positively correlated with the urge to consume (or wanting) of high calorie foods, whereas, the stimulation-induced change in the attentional bias to high calorie foods was associated with the stimulation-induced change in subjective appeal. These findings suggest that prefrontal-mediated changes in liking and wanting are modulated via different neural mechanisms, such that liking is driven by the attentional bias for high calorie foods, whereas, wanting is a direct function of the neural responses afforded to high calorie food stimuli or reward responsivity. However, only stimulation-induced changes in the wanting of high calorie foods was associated with appetitive snack food consumption, indicating reward responsivity in particular plays a pivotal role in consumptive habits.

A significant increase in the LPP amplitude to high calorie food images was observed following both active and sham stimulation, and the stimulation-induced change in LPP amplitude was positively correlated with changes in physiological hunger and prospective consumption. However, there was no association between LPP amplitude and the subjective food craving measures or actual consumptive behaviours. Thus, the P3a and LPP components may reflect differential mechanisms underlying food choice. Converging evidence has suggested that the LPP reflects motivated attention towards evolutionary relevant stimuli (Littel, Euser, Munafò, & Franken, 2012), and that the amplitude of the LPP component is amplified when participants are hungry (Nijs et al., 2010; Nijs et al., 2008; Stockburger, Weike, Hamm, & Schupp, 2008). No differences in food-specific LPP amplitude is observed between persons with obesity and normal

weight individuals (Nijs et al., 2010; Nijs et al., 2008) or among individuals with strong and low cravings for chocolate (Asmaro et al., 2012). Together, these data suggest that the amplitude of the LPP component may reflect the motivation to eat, driven primarily by physiological and homeostatic needs, rather than reward responsivity. Nonetheless, as participants were aware that they would be asked to complete a bogus taste test following the post-stimulation food image task, the selective increase in the LPP amplitude to low calorie food images following sham stimulation may reflect cognitive regulation of food-choice. For instance, (Meule, Kübler, & Blechert, 2013) reported that the amplitude of the LPP component to high calorie food images was significantly increased when participants were instructed to think about the long-term consequences of consuming such foods, suggesting that the LPP is associated with the cognitive reappraisal of food value. Therefore, the selective increase in LPP amplitudes to low calorie food images following sham stimulation may reflect an attempt to selectively control appetitive food intake, as a significant increase in hunger and prospective consumption was apparent across stimulation conditions. Further, the fact that this was not observed following active stimulation suggests that attenuation of prefrontal activity may predispose individuals to the overconsumption of high caloric foods via both the increased attentional bias for high calorie foods and a reduction in motivational aspects to consume to LC foods.

While a significant stimulation effect was apparent for the behavioural data, this did not manifest as changes in P3b amplitude. However, a selective stimulation-induced increase in P3b latency to incongruent trials was apparent. Further, a significant reduction in the amplitude of the frontocentral N2 cluster to incongruent trials was observed following active stimulation. In general, the amplitude of the P3 and N2 ERP components are thought to reflect the neural resources afforded to a given task , whereas, the latency is thought to be an index of cognitive processing speed or the speed at which an individual is able to classify and evaluate a stimulus (Folstein & Van Petten, 2007; Polich, 2007). Therefore, the reduction in P3b latency may be indicative of cognitive

slowing, rather than stimulation-induced impairments in inhibitory control *per say*. However, it is also plausible that the N2 is a better electrophysiological measure of inhibitory control. For instance, several lines of research have demonstrated that the frontocentral N2 represents the capacity to control incorrect responses and otherwise exert cognitive control during the early stages of response inhibition (Folstein & Van Petten, 2008; Tillman & Wiens, 2011; Veen & Carter, 2002). That is, the amplitude of the N2 is larger (i.e., more negative) when an individual exerts inhibitory control (i.e., for incongruent compared to congruent trials) to suppress an automatic or dominant response(Bartholow et al., 2005; Heil, Osman, Wiegelmann, Rolke, & Hennighausen, 2000; Kopp, Rist, & Mattler, 1996; Tillman & Wiens, 2011; Yeung, Botvinick, & Cohen, 2004). Nonetheless, computational and response-locked modelling has demonstrated that the amplitude of the N2 is positively correlated with reaction time, suggesting that the N2 component is time-locked to the response rather than the presentation of the stimulus (Nieuwenhuis, Yeung, van den Wildenberg, & Ridderinkhof, 2003; Yeung et al., 2004). Together, these findings suggest that the selective attenuation of dlPFC activity in healthy young adults impairs cognitive processing speed, subsequently manifesting as impairments in cognitive control. Considering that the stimulation-induced increase in Flanker interference appears to be primarily driven by a reaction time increase to incongruent trials, such stimulation-induced changes in cognitive processing speed would explain the observed pattern of findings.

These findings are consistent with prior rTMS studies. To date, only a handful of studies have used rTMS methodologies to examine the effects of excitatory and inhibitory stimulation of the dlPFC on ERP indices of cognitive control. For instance, stimulation-induced reductions in the latency of the P3 component is observed following both 10Hz and 20Hz (i.e., excitatory stimulation) rTMS targeting the left PFC (Evers, Böckermann, & Nyhuis, 2001; Rektor, Baláž, & Bočková, 2010). However, the findings from low-frequency rTMS (i.e., inhibitory stimulation) studies are mixed, with some studies showing attenuation of left dlPFC activity results in the subsequent increase in

oddball-induced P3 latencies (Evers et al., 2001; Hansenne, Laloyaux, Mardaga, & Ansseau, 2004; Jing, Takigawa, Hamada, et al., 2001; Jing, Takigawa, Okamura, Doi, & Fukuzako, 2001), and others reporting null effects (Upton, Cooper, Laycock, Croft, & Fitzgerald, 2010). Further, the evidence regarding the effects of inhibitory rTMS on early ERP measures of cognitive control are equally mixed. For instance, Upton, et al. (2010) reported that 1 Hz rTMS targeting the left and right dlPFC did not result in subsequent stimulation-induced changes on either behavioural measures or ERP indices of cognitive control (i.e., N2, P3) during a stop-signal paradigm. However, Grossheinrich et al. (2013) reported reductions in the Go Nogo induced N2 amplitude following inhibitory rTMS to the left dlPFC. Further, Li et al. (2017) reported a significant increase in N2 amplitude to congruent and incongruent Stroop trials following 7 days of active stimulation targeting the left dlPFC.

3.41 Possible physiological mechanisms

Several lines of research have demonstrated that acute neuromodulation targeting the dlPFC results in subsequent changes in the cravings for and consumption of palatable calorie dense foods (Hall et al., 2017; Lowe et al., 2017). However, the exact mechanisms underlying this effect remain unclear. This may be partially attributable to the fact that the biological mechanism underlying stimulation-induced changes in cortical activity are complex and are not completely known. While most research has converged on the notion that rTMS after effects are due to changes in synaptic plasticity (George & Aston-Jones, 2010; Hallett, 2000; Hallett, 2007) other lines of evidence have demonstrated that acute stimulation results in subsequent changes in cerebral blood flow (Hubl et al., 2008; Tupak et al., 2013) and neurotransmitter transmission (Keck et al., 2002; Ko et al., 2008). For instance, acute stimulation of the prefrontal brain regions has been shown to increase subcortical dopamine transmission and firing rate of dopaminergic neurons within the reward regions of the brain, specifically the striatum, substantia nigra, and VTA (Keck et al., 2002; Ko et al., 2008). Therefore, the observed stimulation-induced enhancements in reward responsivity may be a direct function of stimulation-induced enhancements in cortical activity within these

regions. Nonetheless, while changes in dopaminergic transmission may explain the observed pattern of findings within the current study, it does not account for the general improvements in dietary self-regulation observed in studies enhancing cortical function (Hall et al., 2017; Lowe et al., 2017). That is, while some lines of research suggest that hypofunctionality of the dopaminergic system contributes to obesity, several other lines suggest that hyperfunctionality of this system is what underlies individual level susceptibility to obesity (Stice & Yokum, 2016a; Val-Laillet et al., 2015). Consistent with this notion, heightened cortical activity within the gustatory, attention, and reward regions of the cortex is associated with energy intake (Burger & Stice, 2013), and hyperresponsivity within the reward regions, particularly the striatum is predictive of future weight gain (Stice & Yokum, 2016b; Winter et al., 2017; Yokum et al., 2011). Therefore, it would be expected that if stimulation-induced increases in dopamine transmission were the primary mechanism underlying changes in dietary behaviours, the excitatory effects would mimic the inhibitory effects.

Converging evidence has demonstrated that striatal dopaminergic neurotransmission is modulated via glutamatergic projections from the PFC to the ventral tegmental area (Taber et al., 1995; Tekin & Cummings, 2002), thus, the observed stimulation-induced changes in food cravings and consumption, and reward sensitivity may be a direct reflection of the ability of the PFC to modulate activity in reward regions of the cortex. Consistent with this notion, Kober et al. (2010) reported that the association between left dlPFC activity and the cognitive control of food cravings was directly mediated by changes in striatal activity, suggesting that prefrontal modulation of the striatum is necessary for the effective control of food cravings. This is consistent with several other lines of evidence that have demonstrated that the functionality and connectivity of the frontostriatal network is associated with individual level differences in impulsivity, delay discounting, and reward responsivity to food and monetary stimuli (Hampton, Alm, Venkatraman, Nugiel, & Olson, 2017; Kohno, Morales, Guttman, & London, 2017; McClure, Laibson, Loewenstein, &

Cohen, 2004; van den Bos, Rodriguez, Schweitzer, & McClure, 2014). By extension, the stimulation-induced reductions in behavioural and electrophysiological indices of inhibitory control (i.e., reduced N2 amplitude to incongruent trials) may represent the inability or the slowing of the PFC to employ cognitive control over eating behaviours. Consistent with this notion, prior studies have reported that the amplitude of the N2 is associated with food-related inhibitory control, in that larger amplitudes are apparent when participants have to inhibit responses towards food stimuli (Lapenta, Sierve, de Macedo, Fregni, & Boggio, 2014; Watson & Garvey, 2013).

3.42 Strengths and Limitations

Strengths of this study include the actual measurement of *ad libitum* food consumption, rather than just food cravings, and the use of high calorie and low calorie food stimuli rather than high calorie and control stimuli. This allowed us to demonstrate that the operation of the dlPFC modulates reward responsivity to high calorie food stimuli specifically, rather than food stimuli in general. In addition, the use of a healthy population provided insight into the mechanisms underlying individual level susceptibility to obesity rather than focusing on differences between persons with obesity and healthy controls. Finally, to date, the current study is only one of two (Lapenta et al., 2014) that have combined EEG and neuromodualtion methodologies to assess the neurocognitive mechanisms underlying dietary self-restraint; however, prior research was limited by the small sample size (n=9; Lapenta et al., 2014). The current study used a more well-powered design, and is currently the only neuromodulation and EEG study that specifically examined the relationship between prefrontal activity and high calorie food-specific reward responsivity.

Of course, the current study is not without limitations, including the inability to conduct source analyses due to the use of a select number of electrode sites rather than the whole EEG cap, therefore, limiting the ability to conclude the effects were attributable to the specific attenuation of left dlPFC activity; nonetheless, the actual effects, no matter the direct source, were specific to modulation of activity in the left dlPFC. In addition, while the use of healthy young adult sample

provided important insights into neural factors that may increase vulnerability to obesogenic eating behaviours, it limits the generalizability of the effects. Finally, it is plausible that participant expectancy effects could have attributed to the observed pattern of findings, especially in those individuals that could differentiate between active and sham stimulation, or those that were aware we were measuring actual food consumption; however, blinding statistics suggest that this effect was minimal. The use of a between subject design and/or better sham methods in future research (e.g., a sham coil) may help mitigate expectancy effects.

3.43 Conclusion

In conclusion, the current study expands our understanding of the neurocognitive mechanisms underlying non-homeostatic consumptive behaviours. Together, the findings provide causal evidence demonstrating that the functionality of the PFC plays a crucial role in modulating the consumption of appetitive calorie dense snack foods, and that this relationship may be mediated by PFC regulation of reward responsivity to high calorie food stimuli. Such findings provide important insights into the neural factors underlying individual level susceptibility to obesogenic behaviours. However, it is presently unclear whether the behavioural and electrophysiological pattern of findings reflect those observed in individuals with obesity. Determining if stimulation-induced changes in such measures mimics that observed normally in persons with obesity would provide important insight into the neural factors that influence individual level susceptibility to obesogenic eating behaviours.

Chapter 4

Effects of moderate exercise on cortical resilience: A transcranial magnetic stimulation study targeting the dorsolateral prefrontal cortex

4.0 Outline

The beneficial effects of exercise on the brain regions that support cognitive control and memory are well-documented. However, examination of the capacity of acute exercise to promote cortical resilience—the ability to recover from temporary perturbation—has been largely unexplored. The present study sought to determine whether single session of moderate intensity aerobic exercise can accelerate recovery of inhibitory control centres in the dorsolateral prefrontal cortex (dlPFC) following transient perturbation via continuous theta-burst stimulation (cTBS). Using a within subjects experimental design, 28 female participants, aged 18-26 (M=20.32; SD=1.79), completed a session each of moderate intensity and very light intensity exercise, in a randomized order. Prior to each exercise session, participants received active cTBS to the left dlPFC. The Stroop task was employed to quantify both the initial perturbation and subsequent recovery effects on inhibitory control. Results revealed a significant exercise condition [moderate intensity exercise, very light intensity exercise] by time [pre-stimulation, post-stimulation, post-exercise] interaction (F (2,52)=5.93, p=.005,d=.38). Specifically, the proportion of the cTBS-induced decrement in inhibition recovered 40 minutes post-exercise was significantly higher following a bout of moderate intensity exercise (101.26%) compared to very light intensity exercise (18.36%; t(27)=-2.17, p=.039, d=-.57, 95 % CI [-161.40, -4.40]). These findings support the hypothesis that exercise promotes cortical resilience, specifically in relation to the brain regions that support inhibitory control. The resilience promoting effects of exercise have empirical and theoretical implications for how we conceptualize the neuroprotective effects of exercise.

4.1 Introduction

Consistent implementation of many behaviours relies on the integrity of the brain systems that support executive functions (EF). Such behaviours include coordination of activities of daily living (Best, Davis, & Liu-Ambrose, 2015; Vaughan & Giovanello, 2010), emotional regulation efforts (Gyurak, Goodkind, Kramer, Miller, & Levenson, 2011; Ochsner, Silvers, & Buhle, 2012), medication adherence (Hinkin et al., 2004; Insel, Morrow, Brewer, & Figueredo, 2006), and dietary self-restraint (Guerrieri et al., 2007; Hall, 2012; Hall & Marteau, 2014; Lowe, Hall, & Staines, 2014; Nederkoorn, Guerrieri, Havermans, Roefs, & Jansen, 2009; Chantal Nederkoorn, Houben, Hofmann, Roefs, & Jansen, 2010). These findings suggest that suboptimal function of the executive control network may, over many years or decades, have profound implications for health and well-being. Indeed, prospective studies have demonstrated that relatively intact EFs predict better functional status, functional independence, and long-term survival among older adults with and without chronic health conditions (e.g., diabetes, heart disease, mild cognitive impairment; Duff, Mold, & Gidron, 2009; Hall, Dubin, Crossley, Holmqvist, & D'Arcy, 2009; Johnson, Lui, & Yaffe, 2007; Vu, Dean, Mwamburi, Au, & Qiu, 2013). Naturally occurring sources of disruption of the brain centres that support executive control (i.e., the prefrontal cortex; PFC) include recurring sleep deprivation (Killgore, 2010; Wilckens, Woo, Kirk, Erickson, & Wheeler, 2014), depression (Rock, Roiser, Riedel, & Blackwell, 2014), and exposure to chronic stressors (Mika et al., 2012; Shields, Bonner, & Moons, 2015). Acute sleep disruption (Chuah, Venkatraman, Dinges, & Chee, 2006; Jennings, Monk, & Van der Molen, 2003; Nilsson et al., 2005), mood fluctuations (Mitchell & Phillips, 2007) and episodic stress (Qin, Hermans, van Marle, Luo, & Fernández, 2009; Schoofs, Preuß, & Wolf, 2008) appear to have similar adverse effects on EFs and associated neural processes. Given the importance of optimal EFs in everyday consequential behaviours, determining methods to enhance cortical resilience to acute and chronic disruptions is of the upmost importance.

Along these lines, there is mounting evidence at the behavioural, neurophysiological, and molecular levels that physical exercise exerts a wide range of beneficial effects on the brain; the most well-documented effects include exercise-induced enhancements in prefrontal structure and function (Chang et al., 2012; Erickson et al., 2015; Hillman, Erickson, & Kramer, 2008; Kramer & Erickson, 2007; Lambourne & Tomporowski, 2010; McMorris & Hale, 2012; Smith et al., 2010). Exercise interventions have been shown to enhance EF task performance in a wide variety of populations (Colcombe & Kramer, 2003; Smith et al., 2010; Voss, Nagamatsu, Liu-Ambrose, & Kramer, 2011). On a neurophysiological level, such interventions have also yielded reliable increases in gray and white matter volume in the cortical substrates underlying EFs (the PFC; Colcombe et al., 2006) and memory (hippocampus; Erickson et al., 2011), which may account for the observed cognitive performance benefits. The neuroprotective effects of regular exercise is further supported by animal models, which have demonstrated that aerobic exercise facilitates the survival of neural stem cells, and supports neurogenesis in the hippocampus via increased blood flow to the dentate gyrus (Blackmore et al., 2009; Pereira et al., 2007; van Praag et al., 1999; Wu et al., 2008).

The acute effects of aerobic exercise are also well-documented. Exercise-induced improvements in EFs have been observed following a single session of aerobic exercise lasting as little as 20 minutes, with the largest effects being observed 11-20 minutes post-exercise (Chang et al., 2012). The acute effects of aerobic exercise appear to be specific to prefrontal-cortical dependent cognitive abilities (i.e., EF), and do not translate into changes in hippocampal-dependent cognitive functions (e.g., long-term memory; Basso, Shang, Elman, Karmouta, & Suzuki, 2015). The majority of the studies within the acute exercise and EF literature have focused predominately on behavioural inhibition, a subcomponent of the latent EF factor; collectively these studies have demonstrated that acute exercise can improve inhibitory control in both young (Chang, Chu, Wang, Song, & Wei, 2015; Ferris, Williams, & Shen, 2007; Lowe, Hall, Vincent, & Luu, 2014; Sibley, Etnier,

& Masurier, 2006; Yanagisawa et al., 2010) and older adults (Barella et al., 2010; Hyodo et al., 2012, 2016; Keita Kamijo et al., 2009) for up to 52 minutes post-exercise (Joyce et al., 2009).

The neurobiological mechanisms underlying exercise-induced improvements in cognition are not entirely understood, and likely vary depending on the duration, intensity and frequency of the exercise (acute versus long-term). Acute exercise-related improvements in EF strength are most commonly attributed to increased neuronal activity in the PFC, measured via changes in cerebral blood oxygenation (Endo et al., 2013; Giles et al., 2014; Guiney et al., 2015; Ogoh et al., 2014; Tempest et al., 2014; Yanagisawa et al., 2010). Exercise-induced improvements in Stroop task performance are thought to be mediated, at least in part, by increased cerebral blood flow to the left dorsolateral prefrontal cortex (dlPFC), indicating a potential lateralization of exercise effects on inhibitory control (Byun et al., 2014; Yanagisawa et al., 2010). Augmented prefrontal oxygenation is, however, only observed following moderate-to-high intensity exercise, and discernible reductions in blood oxygenation occur following high-to-very high intensity exercise (Rooks et al., 2010). Conversely, there is some evidence suggesting that exercise-induced enhancements in EF occur despite reductions in middle cerebral artery blood flow velocity (Ogoh et al., 2014), indicating that fluctuations in cerebral blood flow, alone, may not fully account for the observed exercise-induced changes in both prefrontal blood oxygenation and EF strength. Other non-exclusive mechanisms include the increased expression of brain derived neurotrophic factor (BDNF; Ferris et al., 2007; Tsai et al., 2014), or exercise-induced brain glycogen supercompensation (Matsui et al., 2012). While more research is necessary to ascertain the mechanisms underlying exercise-induced improvements in EF, and the subsequent changes in cortical structure, it is evident that both acute exercise and long-term training induces positive changes in executive control abilities, potentially via exercise-induced enhancements in brain structure and function.

However, despite the growing evidence that aerobic exercise has positive effects on the brain, the exact neurophysiological mechanisms underlying these effects remain unclear; it is

plausible that these effects may be attributed to changes or improvements in cortical resilience or neural plasticity. By definition, neural plasticity involves medium- or long-term enhancement in synaptic connectivity, growth of new neurons, or other structural changes (e.g., pruning to increase efficiency). Such changes might be expected to occur more in relation to extended exercise training than acute exercise bouts (see Erickson & Kramer, 2009). Cortical resilience, however, refers to the ability of brain tissue to rebound from acute perturbations on a short time frame, and this phenomenon may be more closely linked to the neurophysiological mechanisms underlying the acute effects of aerobic exercise on the brain (e.g., increased cerebral blood oxygenation, or other momentary mediators), rather than changes in neural plasticity *per se*.

The present study was designed to determine whether a single session of moderate intensity aerobic exercise accelerates inhibitory control recovery following momentary distributions in prefrontal cortical activity via continuous theta burst stimulation (cTBS) to the left dlPFC. cTBS is a variant of repetitive transcranial magnetic stimulation (TMS) that temporarily suppresses cortical excitability for up to 50 minutes post stimulation (Huang et al., 2005; Wischnewski & Schutter, 2015). In this within-subjects experiment, participants received active cTBS paired with either moderate intensity aerobic exercise, or a control activity (very light intensity exercise). The Stroop task was employed to quantify both the initial perturbation of inhibitory control and subsequent recovery effects. Based on past non-invasive neuromodulation studies (Cho et al., 2012; Ko et al., 2008; Lowe, Hall, & Staines, 2014) it was hypothesized that cTBS to the dlPFC would temporarily impair inhibitory control, but that moderate intensity exercise would selectively promote accelerated recovery (i.e., enhanced cortical resilience) following moderate intensity exercise compared to the control condition.

4.2 Methods

4.21 Participants

Participant characteristics are presented in Table 4.1. Sample size was determined using G*Power (Version 3.1; Faul et al., 2007). Results indicated that 22 participants would be required to achieve 90% power to detect the cTBS suppression effect on Stroop task performance, assuming an effect size of 1.00 (Cohen's *d;* estimated from Lowe, Hall, & Staines, 2014) with an alpha set to .05. In order to allow for the possibility of a smaller cTBS downregulation effect than previously reported, and the partial correction of the cTBS effect in the second part of the protocol, a total of 28 healthy female undergraduate students aged 18-26 (*M*=20.32; *SD*=1.79) were recruited to participate in the present study. Participants were recruited using an online participant recruitment system, and in exchange for their participation, they received two course credits and a $10 gift card.

Prior to study participation participants were screened to be free of any major medical conditions and neuropsychiatric disorders that may contraindicate either the cTBS or aerobic exercise protocols. Participants were excluded from the study if they: (1) had been diagnosed with a neurological (e.g., epilepsy) or psychiatric disorder (e.g., depression, anxiety); (2) were being treated with (any) neuropsychiatric medications; (3) had a family history of epilepsy or hearing loss; (4) had a history of head trauma (including concussions); (5) experienced chronic headaches or migraines; (6) had metal in the cranium and/or any implanted electronic or medical devices (e.g., electronic pacemaker, implanted medication pump); (7) were pregnant; (8) answered "yes" to any of the questions of the Physical Activity Readiness Questionnaire (PAR-Q). All participants were right-handed and naïve to TMS.

Written and informed consent was obtained from all participants. The current study was reviewed by and received ethics clearance from the University of Waterloo's Research Ethics Committee, and the TMS safety guidelines outlined in (Grossheinrich et al., 2009; Wassermann, 1998) were strictly adhered to. Data collection occurred between September 2014 and June 2015.

Table 4.1
Participant characteristics

	Mean (SD)	n (%)
Age	20.32 (1.79)	
BMI	21.27 (2.77)	
Hours of PA last week	2.89 (2.56)	
Predicted hours of PA next week	3.60 (2.92)	
Ethnicity		
Caucasian		10 (35.7)
Asian		11 (39.3)
South Asian		5 (17.9)
Middle Eastern		1 (3.6)
Indigenous		1 (3.6)

Note: Self-reported physical activity (PA) was assessed by asking participants "During the PAST WEEK, how much total time (hours) did you spend doing vigorous physical activity?" and "During the NEXT WEEK, how much time (hours) do you plan to spend doing vigorous physical activity?"

4.22 Procedure

A within-subjects crossover design was employed, such that participants completed a single 20-minute session of moderate intensity aerobic exercise and very light intensity aerobic exercise. Each study session lasted approximately 90 minutes, and study sessions were separated by a one week intersession interval; session order was allocated via random assignment [13 participants completed the very light intensity exercise condition first, 15 participants completed the moderate intensity exercise condition first]. To account for any time-related variability in physiological parameters, all study sessions within subjects were conducted at the same time of day; between subjects, timeslots were available between 10am -12pm or 2pm-4pm. Participants were asked to refrain from consuming any caffeinated beverages or consuming any food 2 hours prior to the start of each study session, with compliance checked upon arrival (i.e., participants signed a form confirming compliance to the above instructions).

Upon arrival, participants were seated in front of a desktop computer where they completed the Stroop task; the duration of the Stroop task was approximately 5 minutes. Immediately following the completion of this task, participants were walked to a different room, where they received active cTBS to the left dlPFC. Following a 5 minute post-stimulation interval,

participants completed the Stroop task again. Immediately thereafter, participants completed the aerobic exercise procedure. Following a 10-minute post-exercise interval participant completed the Stroop task again (40 minutes post-cTBS). At the end of the second study session (following the post-exercise Stroop task), participants completed a series of questionnaires pertaining to demographics, physical activity patterns, and other heath behaviours.

4.221 Stroop task

The Stroop task (Stroop, 1935) is one of the widely used EF paradigms; Stroop interference (reaction time) test-retest reliability correlations range from .79 to.91; Friedman et al., 2008; Vainik et al., 2013). The Stroop paradigm used in this study was modelled after the variant in Miyake and colleagues (Miyake et al., 2000). The task consisted of a mixed block of 144 experimental trials, in which either a string of asterisks (neutral trials; 72 trials), an incongruent colour word (60 trials), or a congruent colour word (12 trials) were presented on computer screen. The stimuli were presented individually in one of six colours (blue, green, yellow, orange, purple, or red) on a black background. Participants were instructed to indicate the colour font each stimulus was written in, via button press, as quickly and accurately as possible. The stimulus remained on the computer screen until the participant responded, followed by a response to stimulus interval of 1000 ms minus the response time. Prior to the start of the experimental trials, participants completed 10 practice trials. The Stroop task was administered using E-Prime software (Psychology Software Tools, Inc) on a Dell desktop computer CRT monitor (17 inches). The primary dependent measure was the Stroop interference score (in ms), calculated as the reaction time (RT) difference between correct incongruent colour word trials and correct asterisk (neutral) trials. Lower scores (i.e., less interference) reflects stronger inhibitory control.

4.23 Aerobic exercise protocol

Prior to the start of the exercise protocol, participants were fitted with a Polar FT1 heart rate monitor. Resting heart rate (RHR) was obtained after participants remained sitting for one

minute. For both exercise conditions, participants walked on the treadmill for 20 minutes, and the speed and incline were gradually adjusted until the target heart rate (THR) was achieved. THR was determined using the Karvonen formula, in which heart rate reserve (HRR; the difference between age-predicted maximal heart rate [220-age] and RHR) is multiplied by the target intensity (TI), and then added to RHR; THR= RHR+ (TI*([220-age]-RHR). TI was set at less than 10 percent HRR for the very light intensity exercise condition, and 50 percent HRR for the moderate intensity exercise condition. Exercise descriptives by condition are presented in Table 4.2.

Table 4.2
Exercise descriptives as a function of exercise condition

	Moderate Intensity	Very Light Intensity
	Mean (SD)	Mean (SD)
% HHR	50	< 10
Resting Heart Rate (BPM)	85.61 (10.38)	88.54 (8.26)
Change in Heart Rate (BPM)	54.70 (8.26)	6.51 (8.05)
Average Speed	3.79 (1.49)	1.61 (.20)
Average RPE	11.74 (1.81)	7.24 (1.28)
Average Incline	4.48 (2.36)	

Note: There was no incline for the very light intensity exercise condition. Heart rate reserve (HHR) is the difference between age-predicted maximal heart rate [220-age] and resting heart rate.

4.24 Theta burst stimulation procedure

Continuous TBS was administered using a 75 mm outer diameter figure-8 coil (MCF-B65) connected to a MagPro (model X100) stimulation unit (Medtronic, Minneapolis, MN, USA). A computerized frameless stereotaxic system (*Brainsight TMS,* Rogue Research, Montreal, Canada) was used to monitor head position in conjunction with an infrared camera and reflective markers placed on the participant's head and TMS coil. Coil guidance was performed using an anatomical scan from a previous data set (the same scan was used for all participants) and TMS neuronavigation software (*Brainsight TMS,* Rogue Research, Montreal, Canada). Resting motor threshold (RMT) was determined using electromyography measured from the right abductor pollicus brevis (APB) muscle. Stimulation was applied over the contralateral motor cortex, at a 45˚ angle tangentially to the scalp, with the handle pointing posteriorly. RMT was defined at the lowest

stimulation intensity required to produce a motor-evoked potential (MEP) with a peak-to-peak amplitude exceeding 50 μV in at least 5 out 10 consecutive trials.

Stimulation was applied according to the protocol outlined in (Huang et al., 2005); a 40 second continuous train consisting of 600 pulses applied in the theta burst pattern (bursts of three stimuli at 50 HZ repeated at 5 Hz frequency). Similar to that used previously (Bolton & Staines, 2011; Lowe, Hall, & Staines, 2014), the International 10-20 system was used to target the left dlPFC (Herwig, Satrapi, & Schönfeldt-Lecuona, 2003). The coil was held a 90˚angle from the mid-sagittal line with its center positioned over F3, and stimulation intensity was set at 80% RMT. The average cTBS stimulation intensity for the moderate intensity and very light intensity exercise condition were 38.76 (*SD*=6.15) and 38.61 (*SD*=6.12) respectively.

4.25 Data analysis

All statistical analyses were conducted using SPSS (version 22; IBM Corp, Armonk, NY). Prior to data analysis, outlier scores (± 3 *SD*s from the mean) were imputed using Maximum Likelihood Estimation methods. Two outlier scores in the pre-stimulation [moderate intensity exercise], one in the post-stimulation [moderate intensity exercise] Stroop interference variables, and two outlier scores in the percent reduction in the cTBS effect variables [1 moderate intensity exercise, 1 very light intensity exercise] were identified. Performance accuracy was uniformly high across time points and exercise conditions (see Table 4.3), indicating a potential ceiling effect. Therefore, analyses focused on interference scores instead; interference scores were calculated using the reaction time data from correct trials only.

The proportion of the cTBS-induced decrement in inhibition recovered 40 minutes post-exercise (i.e., percent reduction in cTBS effect variable) was calculated using the following formula: (cTBS change score * 100)/ exercise change score. The cTBS change score (i.e., the change in Stroop interference from pre-stimulation to post-stimulation) was calculated by subtracting pre-stimulation scores from post-stimulation scores [post-stimulation - pre-stimulation]. The exercise

change score (i.e., the change in Stroop interference from post-stimulation to post-exercise) was calculated by subtracting post-stimulation scores from post-exercise scores [post-exercise - post-stimulation] respectively. The change score variables were reversed scored, such that higher values were indicative of an improvement in Stroop task performance.

The stimulation effects on Stroop task performance were assessed using a mixed 2 x 3 factor analysis of variance (ANOVA). Exercise condition [moderate intensity, very light intensity] and time [pre-stimulation, post-stimulation, post-exercise] were entered as the within subject factors, and exercise session order [moderate intensity or very light intensity first] as the between subject factor. Significant main effects were followed-up with planned Fisher's LSD comparisons. The stimulation effects on cortical resilience were assessed using a paired sample t-test with the percent reduction in the cTBS effect as a function of exercise condition as the primary dependent measure.

4.3 Results

4.31 Baseline comparability of conditions

There were no significant differences in pre-stimulation Stroop interference scores ($t(27)=-.048$, $p=.96$, $d=-.02$, 95% CI[-17.84,17.02]), resting heart rate estimates ($t(27)= -1.20$, $p=.240$, $d=-0.23$, 95% CI[-7.93, 2.07]), or cTBS stimulation intensities ($t(27)=.29$, $p=.78$, $d=.06$, 95% CI[-.90, 1.20]) between exercise conditions [moderate intensity, very light intensity].

Table 4.3: Mean (SE) performance accuracy and reaction time data for the Stroop task as a function of exercise condition and time.

	Moderate Exercise				Minimal Exercise			
	Pre-Stimulation	Post-Stimulation	Post-Exercise		Pre-Stimulation	Post-Stimulation	Post-Exercise	
Stroop Accuracy	.98(.004)	.98(.005)	.98(.003)		.98(.005)	.97(.007)	.98(.003)	
RT Incongruent Trials	870.08(27.03)	895.35(31.91)	823.77(31.31)		861.45(31.02)	854.75(30.55)	828.71(26.59)	
RT Neutral Trial	855.34(26.27)	831.72(26.004)	807.80(29.24)		846.88(31.00)	810.21(26.82)	789.68(23.96)	
Stroop Interference	16.46(7.55)	63.32(11.83)	15.97(5.62)		14.57(7.23)	44.54(8.26)	39.03(6.01)	
Change in EF following cTBS				-46.86(10.79)				-29.97(10.36)
Change in EF Following Exercise				47.35(11.35)				5.51(7.03)
% reduction in cTBS effect (40 minutes post-stimulation)				101.26(35.78)				18.36(15.48)

Note: All reaction time (RT) data are presented in ms. The incongruent and neutral RTs presented in this table were corrected for outliers by removing outlier data points [2 pre-stimulation, 1 post-stimulation; moderate intensity exercise] prior to calculating the mean(SE). The change in EF as a function of cTBS and exercise was calculated by subtracting pre-stimulation interference scores from post-stimulation interference scores [cTBS change score] and post-stimulation interference scores from post-exercise interference scores [exercise change score] respectively; these values were reversed scored, so that higher values were indicative of an improvement in Stroop task performance. The % reduction in the cTBS effect was calculated by multiplying the standardized cTBS change score by 100 then dividing this value by the standardized exercise change score.

4. 32 Suppression and recovery effects

Performance accuracy, reaction times on incongruent and neutral trials and Stroop interference scores as a function of exercise condition [moderate intensity, very light intensity] and time [pre-stimulation, post-stimulation, post-exercise] are presented in Table 4.3. Results indicated that the main effect of exercise condition [moderate intensity, very light intensity] was not significant ($F(1,26)=.011$, $p=.92$, $d=.004$). However, a significant main effect of time [pre-stimulation, post-stimulation, post-exercise] was observed ($F(2,52)=7.65$, $p=.001$, $d=.76$). Across exercise conditions post-stimulation interference scores ($M=47.91$; $SE=5.38$) were significantly higher than pre-stimulation interference scores ($M=15.93$; SE=8.19; $p=.002$; 95% CI[13.20, 50.76]); indicating that cTBS to the left dlPFC significantly impaired inhibitory control irrespective of exercise condition. In addition, across exercise conditions post-exercise interference scores ($M=$ 26.79; $SE=5.82$) were significantly lower than post-stimulation interference scores ($p=.001$; 95 % CI[-32.63, -9.61]). There were no significant differences between pre-stimulation and post-exercise interference scores ($p=.27$; 95% CI[-8.92, 30.64]).

Table 4.4
Stimulation and exercise effects on inhibition: ANOVA results

	F (*df*)	*p*	Cohen's *d*
Exercise	.011 (1,26)	.92	.004
Time	7.65 (2,52)	.001	.76
Exercise X Time	5.96 (2,52)	.005	.38
Exercise X Order	.013 (1,26)	.91	.004
Time X Order	.089 (2, 52)	.92	0.006
Exercise X Order X Time	.747 (2,52)	.48	.06

There were no significant interactions between session order and exercise condition, or session order and time (see Table 4.4). The main effect of time was, however, qualified by a significant exercise condition [moderate intensity, very light intensity] by time [pre-stimulation, post-stimulation, post-exercise] interaction (F (2,52)=5.96, $p=.005$,$d=.38$). The simple main of time

was significant for both moderate intensity ($F(2,54)=13.65$, $p<.001$, $d=.71$) and very light intensity ($F(2,52)=6.12$, $p=.004$, $d=.38$) exercise conditions. Planned comparisons revealed that Stroop task performance was significantly impaired following cTBS in both moderate intensity ($p<.001$; 95% CI[-69.01, -24.72]) and the very light intensity ($p=.007$; 95% CI[-51.22, -8.72]) exercise conditions. Significant improvements in Stroop task performance were observed following the moderate intensity exercise bout ($p<.001$; 95% CI[24.05, 70.66]), however, there were no significant differences between post-stimulation and post-exercise inference scores following the very light intensity exercise bout ($p=.44$; 95% CI[-8.91, 19.93]). Finally, there were no significant differences between pre-stimulation and post-exercise interference scores in the moderate intensity exercise condition ($p=.96$; 95% CI[-18.22, 17.23]), but post-exercise interference scores were significantly higher than pre-stimulation interference scores ($p=.017$; 95% CI[8.72, 51.22]) in the very light intensity exercise condition. Together these findings suggest that an acute bout moderate intensity aerobic exercise can offset the effects of cTBS on Stroop task performance, such that performance on the task post-exercise is comparable to pre-stimulation task performance. Very light intensity exercise, however, had no effect on Stroop task performance (see Figure 4.1).

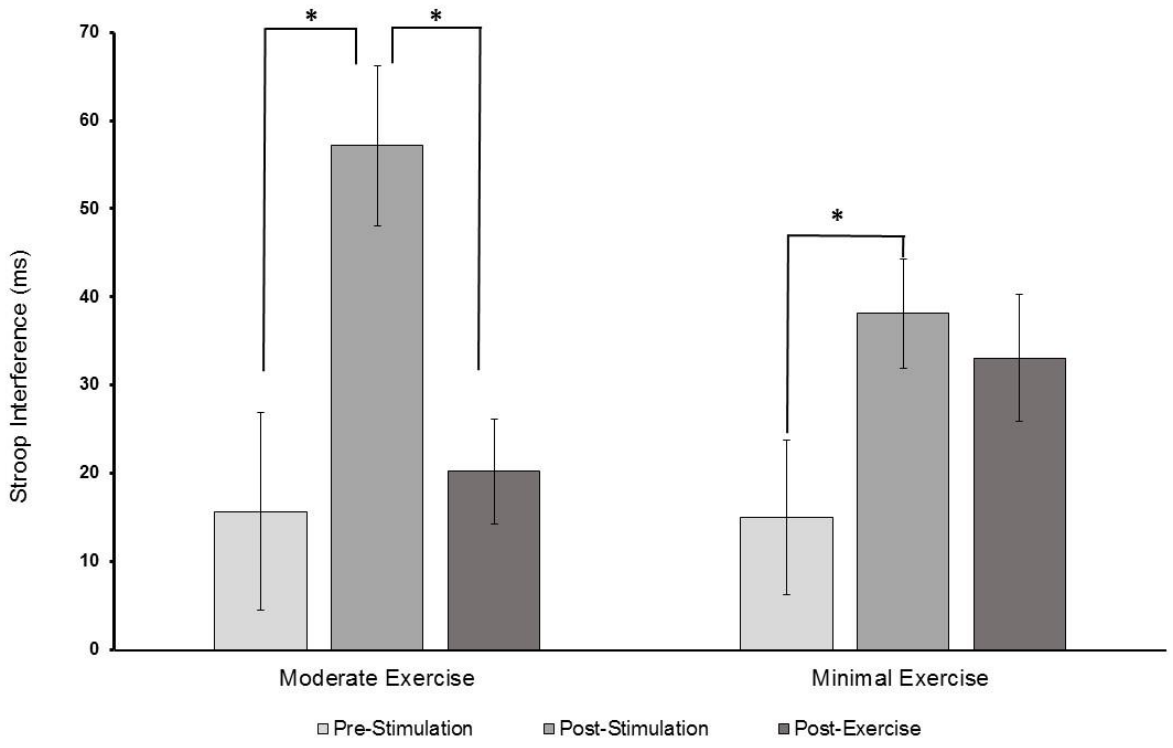

Figure 4.1: Mean (± SE) pre-stimulation, post-stimulation, and post-exercise Stroop interference scores (ms) across exercise conditions. * Significantly different at the $p<.05$ level.

4.33 Cortical resilience

Compared to very light intensity exercise, a significant attenuation of the deleterious cTBS effects on Stroop performance was observed following moderate intensity aerobic exercise ($t(27)=-2.17$ $p=.039$, $d=-.57$, 95 % CI [-161.40, -4.40]). On average, the cTBS effect following moderate intensity exercise was reduced by 106.26%, compared to a 18.36% reduction following very light intensity exercise; see Figure 4.2.

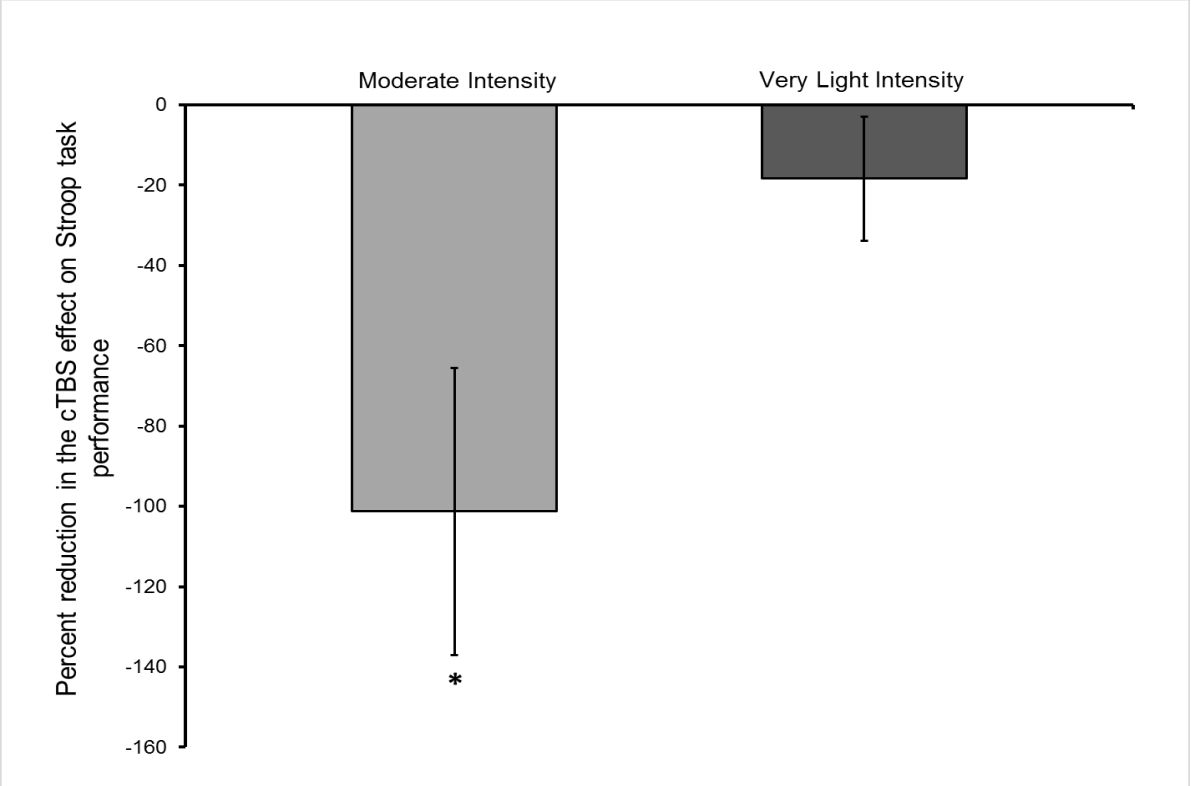

Figure 4.3: Mean (±SE) percent reduction in the cTBS effect on Stroop task performance following moderate intensity and very light intensity exercise. * Significantly different from the very light intensity exercise condition.

4.4 Discussion

The purpose of the current study was to explore the neuroprotective effects of acute exercise using a cortical stimulation protocol to induce an acute disruption in response inhibition by temporarily decreasing activity in the left dlPFC, an important node in the executive control network. The Stroop task was employed to quantify both the initial perturbation in inhibitory control and subsequent recovery effects. Using a within subjects design, we specifically examined the proportion of the cTBS-induced decrement in inhibitory control recovered following a bout of moderate intensity or very light intensity exercise. Approximately 40 minutes post-stimulation, the deleterious effects of cTBS were attenuated by 101.6% in the moderate intensity exercise condition, compared to only 18.36% in the very light intensity exercise condition. These findings support the

contention that exercise promotes cortical resilience, specifically in relation to the brain regions that support behavioural inhibition.

The current findings provide further support for the cognitive benefits of exercise, which have now been widely documented (Chang et al., 2012; Erickson et al., 2015; Hillman et al., 2008; Kramer & Erickson, 2007; Lambourne & Tomporowski, 2010; Smith et al., 2010). Prior studies have reported, using randomized experiments, that exercise—both in acute and long-term training formats—can enhance cognitive function, and that these effects are particularly pronounced in the areas of the brain that support executive function and memory (e.g., Colcombe et al., 2006; Erickson, Leckie, & Weinstein, 2014; Weinstein et al., 2012), and selective attentional regulation of somatosensory information (Popovich & Staines, 2015). The current findings add to these well-documented effects by demonstrating that exercise may accelerate recovery from artificial perturbation in the laboratory context. This "resilience promoting" mediational mechanism for the effects of exercise on the brain has not been elaborated in detail, and may differ fundamentally from other mechanisms proposed (see Kramer & Erickson, 2007 for a review).

Although the mechanisms underlying this effect cannot be elucidated by the present study, changes in neuronal activity (quantified via cerebral oxygenation) may be one potential mediator. The inhibitory effects of cTBS has been attributed to attenuated prefrontal oxygenation at both the ipsilateral (Cho et al., 2012; Hubl et al., 2008; Tupak et al., 2013) and contralateral (Mochizuki et al., 2007) site of stimulation. Considering that exercise-induced enhancements in response inhibition are most prominently associated with increased prefrontal blood oxygenation in the left dlPFC (Endo et al., 2013; Giles et al., 2014; Guiney et al., 2015; Yanagisawa et al., 2010), it is plausible that moderate intensity aerobic exercise attenuated the cTBS-induced decrements in inhibitory control by accelerating restoration of prefrontal blood oxygenation to post-stimulation levels. However, it is also plausible that neurochemical changes in synaptic monoamine levels mediated the exercise-induced improvements in cortical resilience; elevated levels of norepinephrine (Meeusen & De

Meirleir, 1995), serotonin (Gomez-Merino et al., 2001; Rabelo et al., 2015), dopamine (Berse et al., 2015; Goekint et al., 2012; Meeusen & De Meirleir, 1995; B. Winter et al., 2007), and epinephrine (Zouhal et al., 2008) are observed following an acute bout of physical activity. Regardless, it is clear that more research is necessary to determine the specific neurophysiological processes underlying cortical resilience.

While we utilized an experimental neuromodulation protocol in this study, there are in fact many everyday naturally occurring, transient factors that down-regulate EFs, including acute sleep disruption (Chuah et al., 2006; Jennings et al., 2003; Nilsson et al., 2005), mood fluctuations (Mitchell & Phillips, 2007), momentary stressors (Qin et al., 2009; Schoofs et al., 2008), and bouts of alcohol consumption (Marinkovic et al., 2012). As such, the resilience-promoting effects of exercise might be of some practical importance when considering its potential to offset the adverse influence of each of these factors in day-to-day life. With an understanding of exercise effects on the brain via improved resilience it may be possible to engineer more effective interventions for overcoming naturally occurring perturbations mentioned above. For instance, the strategic integration of aerobic exercise into existing behavioural interventions might optimize treatment outcomes, especially when effective self-regulatory abilities are crucial to both achieve and maintain the desired outcomes (e.g., weight loss and smoking cessation interventions); successful self-regulation is at least partially dependent on the optimal operation of the left dlPFC (Hare et al., 2009; Hayashi, Ko, Strafella, & Dagher, 2013; Kober et al., 2010; Yoshikawa, Tanaka, Ishii, Fujimoto, & Watanabe, 2014).

Strengths of the current study include the use of a within subjects design to reduce inter-individual sources of variability, and the use of a reliable and well established neuromodulation protocol from which to test the exercise-related mitigation effects. Limitations included reliance on healthy young adults whom may have experienced less (or more) initial downregulation, and also less recovery from exercise than older adults might have; each of these factors could in turn have

unpredictable impact on effect size. Additionally, the cTBS effect was slightly lower (though not significantly) in the very light intensity exercise condition, and this may have reduced the amount of recovery expected. Furthermore, it is plausible that inter individual differences in stress, sleep deprivation, and alcohol use could have negatively impacted the observed effect size, as these confounders may have slightly impaired initial inhibitory control abilities, subsequently dampening the cTBS effect (i.e., a potential floor effect).

One final limitation pertains to practise effects. Given that each participant completed the Stroop on 6 occasions, it is likely that scores would improve steadily across repeated administrations of the same task. However, such practise effects would be a main effect over time, and the counterbalancing of treatment condition order should minimize any possible interaction between practise effects and treatment condition. Further, the Stroop interference score was the primary dependent measure, which is based on reaction time (rather than accuracy per se). Although ceiling effects in accuracy would be expected, the same is not true for reaction times. As such, the presence of practise effects would not be a threat to the validity of our findings.

Future studies may build on the current findings examining the effects of cTBS on other brain regions not explored here, and to replicate this study on other samples and target groups (e.g., older adults). It would also be quite interesting to explore the possibility of using exercise to promote recovery of EFs following naturally occurring modulators, such as those mentioned above (sleep deprivation, alcohol consumption, and acute stress). Finally, it would be potentially informative to examine whether exercise can amplify or augment beneficial effects of upregulation via rTMS protocols designed to enhance cortical activity via changes in long-term potentiation. Such an examination might be elucidating with respect to understanding exercise effects as "deficit correcting" versus "true enhancement" of function.

4.41 Conclusion

In conclusion, using a cTBS protocol to induce downregulation of EF, we found that acute moderate intensity exercise has positive effects on EF recovery. Specifically, moderate intensity exercise mitigated the cTBS-induced decrements in inhibitory control more quickly than the very light intensity control condition. These findings have empirical and theoretical implications for how we conceptualize the neuroprotective effects of exercise and provides practical implications for using exercise to offset the influence of naturally occurring down-regulators of EF in everyday life.

Chapter 5

An exploration of exercise-induced cognitive enhancement and transfer effects to dietary self-control

5.0 Outline

The primary objective of this study was to examine the effects of aerobic exercise on executive function, specifically inhibitory control, and the transfer to self-control in the dietary domain. It was hypothesized that exercise would enhance inhibitory control, and that this enhancement would facilitate self-control in a laboratory taste test paradigm. Using a crossover design, 51 participants completed counterbalanced sessions of both moderate exercise (experimental condition) and minimal effort walking (control condition) using a treadmill; the intersession interval was 7 days. Prior to each exercise bout participants completed a Stroop task. Following each bout participants completed a second Stoop task, as well as a bogus taste test involving three appetitive calorie dense snack foods and two control foods; the amount of each food type consumed during the taste test was covertly measured. Results revealed that moderate exercise significantly improved performance on the Stroop task, and also reduced food consumption during the taste test for appetitive calorie dense snack foods; there was no exercise effect on control food consumption. Exercise-induced gains in Stroop performance mediated the effects of moderate exercise on appetitive snack food consumption. Together these findings provide evidence that a bout of a moderate aerobic exercise can enhance inhibitory control, and support for cross-domain transfer effects to dietary self-control.

5.1 Introduction

On a global basis, a substantial proportion of the chronic disease burden may be attributed to individual level behaviours (e.g., overconsumption of calorie dense foods, physical inactivity, smoking); these behaviours are recognized as being detrimental to one's health, yet, consistently implemented despite the consequences. The maintenance of healthy dietary habits in particular may be essential to prevent the onset of numerous chronic diseases, as the overconsumption of calorie dense foods is associated with an increased risk for excessive adiposity and subsequently obesity, type 2 diabetes, coronary artery disease, and cerebrovascular disease (Bailey, Sullivan, Kirk, & Donnelly, 2010; Du et al., 2009; Misra, Singhal, & Khurana, 2010; Rosenheck, 2008). However, calorie dense foods are somewhat hard to resist, partially due to an evolved preference for foods that are high in fat and sugar, which makes the consumption of such foods the natural default (Drewnowski, 1997; Drewnowski & Greenwood, 1983; Drewnowski, Kurth, Holden-Wiltse, & Saari, 1992). As such, individual health and wellbeing is in part dependent on our capacity to resist the allure of appetitive food stimuli, and otherwise exert dietary self-restraint to limit the consumption of such foods. Such self-regulatory abilities may partially depend on neurobiologically-based cognitive abilities such as executive functions (Hall & Marteau, 2014; Hall, 2016; Vainik, Dagher, Dube, & Fellows, 2013).

Executive function (EF) is an overarching term that encapsulates a variety of higher level cognitive processes implicated in the reflective top-down (i.e., non-stimulus driven) control over behaviour, thought, and emotion (Baddeley, 1996; Miyake et al., 2000; Miyake & Friedman, 2012). Conceptually, the unitary EF construct can be decomposed into three interconnected, but dissociable, basic subcomponents: working memory, mental flexibility, and inhibition. Of these subcomponents, inhibition is (from a statistical standpoint) a pure manifestation of executive abilities, as it perfectly correlates (1.0) with the unitary EF factor; working memory and task switching consist of a mixture of this fundamental EF construct and unique, but unrelated

processes. A definitive aspect of behavioural inhibition is the capacity to temporarily override reflexive (i.e., prepotent) responses to stimuli, and behave in a goal-directed manner. In the context of dietary behaviours, the capacity to override visceral (autonomic) responses to appetitive food stimuli is crucial to effectively regulate the consumption of calorie dense foods; therefore, inhibition may be more pertinent to dietary self-regulation than the other EF facets.

Indeed, prior observational studies have confirmed that stronger (i.e., better) executive control abilities are associated with the reduced consumption of calorie dense snack foods, and that this effect is evident when food consumption is assessed via self-report or objectively, and is independent of important demographic confounders (Allan, Johnston, & Campbell, 2010; Allan, Johnston, & Campbell, 2011; Allom & Mullan, 2014; Hall, Elias, & Crossley, 2006; Hall & Fong, 2013; Hall, 2012; Kakoschke, Kemps, & Tiggeman, 2015a; Kakoschke, Kemps, & Tiggeman, 2015b; Riggs et al., 2010; Riggs, Chou, Spruijt-Metz, & Pentz, 2010; Riggs, Spruijt-Metz, Sakuma, Chou, & Pentz, 2010; Vainik et al., 2013). Likewise, carefully controlled behavioural experiments have identified specific situational contexts in which such effects emerge; specifically, when eating environments include cues that suggest consumption is normative or expected, EF has a more pronounced effect on eating behaviour (Hall, Lowe, & Vincent, 2014; Hall et al., 2014b). Given the significance of EFs in explaining successful dietary self-restraint, particularly in facilitating contexts, it is important to understand how such abilities can be optimized.

The dorsolateral prefrontal cortex (dlPFC) is considered to be the central neural substrate underlying inhibitory control, and EFs more broadly (Floden, Vallesi, & Stuss, 2011; Miller & Cohen, 2001; Smolker et al., 2014; Stuss, 2011). In addition, an accumulating body of evidence has demonstrated that the differential operation of the dlPFC is implicated in the successful, self-initiated control of dietary behaviours, such as the cognitive regulation of hedonic food cravings (Kober et al., 2010), effective dietary self-control (Hare et al., 2009), and suppressing the motivation to eat (Yoshikawa et al., 2014). These findings suggest that cortical activity in the dlPFC

in response to appetitive food stimuli may predict individual differences in dietary self-control, such that attenuated activity may predispose individuals to self-regulatory failures. Therefore, optimizing activity in the dlPFC could theoretically improve dietary self-restraint, potentially via enhanced inhibitory control abilities. Consistent with this notion, at least six laboratory studies involving cortical stimulation methods have demonstrated that increasing activity in the dlPFC reduces both subjective snack food cravings following cue exposure , as well as objectively measured consumption (Fregni et al., 2008; Goldman et al., 2011; Jauch-chara et al., 2014; Lapenta et al., 2014; Uher et al., 2005). Further, Lowe et al. (2014) reported that temporary disruptions in the executive control network-via inhibitory transcranial magnetic stimulation to the left dlPFC-resulted in enhanced cravings for, and consumption of, appetitive calorie dense snack foods; this effect was mediated by changes in inhibitory control abilities. Together, these findings support the contention that the integrity of the executive control network can causally influence dietary self-restraint.

Given the causal significance of inhibitory control in relation to dietary behaviours, there is continuing interest in EF enhancement strategies. One promising avenue is physical exercise, which has been shown to enhance cognitive function both broadly, and specifically in relation to EFs (Chang et al., 2012; Lambourne & Tomporowski, 2010; McMorris & Hale, 2012; McMorris et al., 2011; Smith et al., 2010). At least 20 minutes of acute aerobic exercise is necessary to observe a positive effect on cognitive functions, with the largest effects being observed 11-20 minutes following the exercise bout (Chang et al., 2012); these effects are present for up to 52 minutes after exercise cessation (Joyce et al., 2009). In addition, there is some evidence that the beneficial effects of physical exercise may vary depending on initial EF strength, such that individuals with poor EFs are the most amendable to exercise induced improvements in EF (Drollette et al., 2014).

Although the mechanisms underlying exercise-induced improvements in EF are not entirely understood, prior research has suggested several non-exclusive possibilities (Erickson et al., 2015),

including (1) increased cerebral blood flow to the prefrontal cortex (Endo et al., 2013; Giles et al., 2014; Rooks, Thom, McCully, & Dishman, 2010; Yanagisawa et al., 2010), (2) increased expression of brain derived neurotropic factor (BDNF; Ferris et al., 2007; Tsai et al., 2014), or (3) exercise-induced brain glycogen supercompensation (Matsui et al., 2012). While it is evident that further research is needed to develop a convincing model outlining the mechanisms underlying the exercise-induced effects on EF, it remains clear that aerobic exercise, undertaken both acutely and over an extended period of time, can be used to enhance EFs by optimizing the brain structures and associated neurochemistry supporting them.

It is possible that acute exercise may also improve dietary self-control via this same route. Yet, the direct application of exercise-induced EF enhancement to the problem of dietary self-restraint remained largely unexplored. Only one prior study has examined EF as a mediator of exercise effects on eating behaviour, but the results were ambiguous due to methodological limitations (Lowe, Hall, Vincent, et al., 2014). Several prior studies have documented improvements in dietary self-restraint following acute exercise (i.e., reduced food intake; Balaguera-Cortes et al., 2011; Guelfi et al., 2013; Hagobian et al., 2013; Martins et al., 2008; Schubert et al., 2013; Sim et al., 2014; Thivel et al., 2012), but without considering (or measuring) EF as a mediator. At present, the mechanisms underlying effect of exercise on dietary behaviour have remained obscure, and exercise-induced improvements in EF have not been previously considered as a potential mediating pathway.

The present study used within-subjects crossover design to test the effects of a bout of acute aerobic exercise on dietary self-control via exercise-induced improvements in inhibitory control (i.e., direct cross-domain "transfer" effect). The primary hypotheses are: 1) that acute aerobic exercise will enhance inhibitory control, and 2) acute exercise will facilitate dietary self-control in a subsequent laboratory taste test, and 3) that the former effect will mediate the latter. Secondary hypotheses are that the exercise-induced enhancements in inhibitory control will be strongest for

those with relatively weak baseline EF, and that the transfer effects to dietary self-control will be specific to calorie-dense snack food, and will not generalize to less calorie dense control foods.

5.2 Methods

5.21 Participants

A sample of 51 female undergraduate students, aged 17 to 28 (*M*=19.08; *SD*= 1.736), participated in this study. Participants were predominately Caucasian (64%) with a normal body mass index (BMI; *M*=21.81; *SD*=3.071). All participants were recruited from undergraduate psychology courses using an online participant recruitment system. In exchange for their participation, participants received two course credits. Similar to the procedure reported in (Lowe, Hall, & Staines, 2014; Lowe, Hall, Vincent, et al., 2014)participants were preselected based on self-reported food cravings for milk chocolate and potato chips. Participants were excluded if they had been clinically diagnosed with an eating disorder. This study was reviewed, and received ethics approval from the host University's Research Ethics Board; the authors confirm that this research was conducted in accordance with the Helsinki declaration.

5.22 Procedure

This study utilized a randomized cross-over design, in which participants attended two, 1 hr laboratory sessions; to avoid any potential carryover effects, a 7-day intersession interval was used. Each study session was conducted at the same time of day within participants (either between 11:00am-1:00pm, or 3:00pm-5:00pm). All participants were asked to eat something at least 6 hours prior to the start of each exercise session, but to refrain from consuming any food or caffeinated beverages 3 hours prior to the start of each exercise session. Prior to the start of the first study session, written and informed consent was obtained, and following consent participants completed the Physical Readiness Questionnaire (PAR-Q) to screen for any medical conditions that may be exacerbated by aerobic activity; no participants were excluded due to pre-existing medical conditions.

Upon arrival, participants were seated in front of a desktop computer, where they completed the Food-Craving Questionnaire-State (FCQ-S; Cepeda-Benito, Gleaves, Williams, & Erath, 2000), and subsequently the Stroop paradigm to assess EFs. Immediately following the completion of both of these tasks, participants completed 20 minutes of moderate (experimental condition) or minimal (control condition) aerobic exercise; exercise bout order was counterbalanced across participants. After a 10 minute post exercise interval, participants completed the FCQ-S and Stroop task again. Next, participants completed the bogus taste test portion of the study.

For the taste test portion of the study, participants were instructed to taste and rate the subjective properties (e.g., texture, sweetness, saltiness) of five experimental foods: (1) Lindt milk chocolate (100 g); (2) original potato chips (42 g); (3) sour cream and onion potato chips (42 g); (4) plain rice cakes (22 g); (5) unsalted soda crackers (12 g). Specifically, participants were asked to rate each of the five foods based on texture, taste (sweetness and saltiness), perceived health, and overall appeal; with the exception of the texture component (participants were asked to circle descriptive words), ratings were made using a 10 point Likert scale. The foods presented simultaneously in their pre-packaged quantities, with the exception of the rice cake. Participants were instructed to consume as much food as they would like to make their taste ratings, and were given 15 minutes to complete the taste test, during which time the researcher left the room; participants had to remain in the room for the full 15-minute duration. Nutritional information was not provided for any of the experimental foods.

The second study session was identical to the first, however, if participants completed the moderate intensity exercise during the first session, they completed the minimal intensity exercise during the second session and vice versa. In addition, at the end of the second study session, participants completed several questionnaires pertaining to demographics, physical activity frequency, and food habits, and were subsequently debriefed about the true purpose of the study.

5.23 Exercise procedure

Participants completed a 20 minute bout of moderate or minimal aerobic exercise using a treadmill; see Table 5.1 for descriptive statistics. Heart rate was measured continuously using a Polar FT1 heart rate monitor, and was recorded every five minutes. Resting heart rate (RHR) was measured after the participants rested for one minute prior to the start of both exercise bouts. Perceived exertion was measured every five minutes during using the Borg Scale of Perceived Exertion (Borg, 1982).

For the moderate exercise condition, participants began walking at 1.5 MPH, and the speed was gradually increased over the first two and half minutes until participants were walking briskly, but not jogging; treadmill speed did not exceed 4.0 MPH. The incline was gradually increased until the participant reached the calculated target heart rate (THR). THR was calculated using formula for heart rate reserve (HRR). HHR is calculated as maximal heart rate (MHR; 220-age) minus RHR multiplied by the target intensity (TI %). Next, this value was added to the RHR; THR=RHR+ (MHR-RHR) TI%. The TI% for moderate intensity was 50%. For the minimal exercise condition, participants walked at a slow and steady rate, without drastically increasing their heart rate; TI% was no greater than 10%. The treadmill speed did not exceed 2.0 MPH, and there was no incline for the minimal exercise condition. In both conditions, HRR was calibrated to the RHR taken prior to the start of the exercise condition.

5.23 Measures

5.231 Stroop task

The Stroop task (Stroop, 1935) is a reliable measure of response inhibition (test-retest reliability correlation ranges from .79 to .87; Vainik et al., 2013), and is one of the most widely used EF measures. The Stroop paradigm used in this study was modelled after the variant in Miyake et al. (2000), and consisted of a mixed block of 144 trials. The stimuli consisted of either a string of asterisks (72 trials), an incongruent colour word (60 trials), or a congruent colour word (12 trials).

The stimuli were presented individually using E-Prime software (Psychology Software Tools, Inc) on a Dell desktop computer CRT monitor (17 inches). Participants were instructed to indicate the colour font the stimuli both the colour words and asterisks were presented in (blue, green, yellow, orange, purple, or red) as quickly and accurately as possible. All participant responses were made via button press and a response box. The stimuli remained on the computer screen until the participant responded, followed by a response to stimulus interval of 1000 (ms) minus the response time. Similar to Miyake et al. (2000) the dependent measure was the Stroop interference, calculated as the reaction time on correct incongruent colour word trials (ms) minus the reaction time on correct asterisk trials ms. Lower Stroop interference scores (ms) were taken to reflect stronger (i.e., better) inhibitory control abilities.

5.232 Food consumption

Following the completion of the taste test, the experimental foods were weighed, and the total amount of food consumed across each exercise condition was calculated. Three food variables were calculated: (1) total amount of food consumed (g); (2) amount of appetitive foods consumed (g); (3) amount of control foods consumed (g). The appetitive foods consisted of the milk chocolate and potato chips, whereas the control foods consisted of the rice cakes and soda crackers. The corresponding items in each variable were summed together, with higher scores indicating a larger amount of food consumed.

5.233 Food craving

The Food-Craving Questionnaire-State (FCQ-S; Cepeda-Benito et al., 2000) is a 15-item self-report questionnaire designed to measure subjective state (i.e., current) cravings for food on the following five dimensions: 1) an intense desire to eat, 2) anticipation of positive reinforcement that may result from eating (positive reinforcement), 3) anticipation of relief from negative states and feelings as a result of eating (negative reinforcement), 4) lack of control over eating, 5) craving as a

physiological state (i.e., hunger). Cravings on the different dimensions were calculated as the sum of their corresponding items, with higher scores reflective of stronger subjective cravings.

5.234 Demographic variables

Age, weight, height, ethnicity, average household income, and relationship status were self-reported by participants. Body mass index (BMI) was calculated from the weight and height measures. The Meat/Snack section of the Block Rapid Food Screener (Block, Gillespie, Rosenbaum, & Jenson, 2000) was used to assess the frequency of fatty food consumption. The Spearman rank-order correlation coefficients between the Block Food Frequency Questionnaire (used as the gold standard), and the meat/snack section was .71 (p<.0001; Block et al., 2000). The fruit and vegetable portion was omitted, as prior research has demonstrated that EF strength is associated with the frequency of fatty food consumption, but this effect is selective to fatty foods, and does not generalize to the consumption of non-fatty foods (Hall, 2012). In order to measure current dietary fat consumption, the time frame and response options were modified to reflect the intake of dietary fats over the previous week. Self-reported physical activity was assessed by asking participants "During the PAST WEEK, how much total time did you spend doing vigorous physical activity?"

5.24 Data analytic approach

All statistical analyses were conducted using SPSS version 22 (IBM Corp, Armonk, NY). Prior to the primary analyses, frequency distributions were used to identify outlier scores, defined as 3SD or more beyond the mean. Two outliers in the Stroop interference variables (post minimal and pre moderate), and two outliers in the food consumption variables were replaced with a corresponding value imputed using maximum likelihood estimation (MLE). One participant was dropped from the data analysis due to outlier scores across all Stroop variables, resulting in a final sample of 50 participants. Finally, four data points were imputed because of an accuracy around or below chance levels (i.e., <.50), as these suggested a lack of understanding the task instruction.

First, the zero-order correlations between pre-exercise Stroop interference scores (averaged across exercise conditions), fatty food consumption, hours of vigorous physical activity in the last week, and BMI were calculated. Following this, paired sample t-tests were conducted to determine if there was a difference in the pre-exercise Stroop interference scores, resting heart rate, and the time lag between the participant's last meal and start of the exercise session between exercise sessions [moderate, minimal]. Next, five separate paired sample t-tests were conducted to determine if there was a differential exercise effect on the pre-to-post exercise bout change in food cravings across the five different dimensions of the FCQ-S. To assess whether the subjective ratings of overall appeal and health differed as a function of both food type [appetitive, control] and exercise condition [moderate, minimal] two separate 2x2 repeated measure analysis of variance (ANOVA) were conducted [exercise condition (moderate vs. minimal) by food type (appetitive vs. control)]. Significant main effects were followed up with planned Fisher's LSD comparisons.

The exercise effects on inhibitory control were assessed using a 2x2 repeated measure ANOVA (exercise condition [moderate vs. minimal] by time [pre-exercise vs. post-exercise]); significant main effects were followed up with planned Fisher's LSD comparisons. Next, a paired sample t-test was conducted to determine if the gains in inhibitory control as a function of exercise differed between exercise conditions [moderate vs. minimal]. The gains in inhibitory control as a function of moderate and minimal exercise was calculated by subtracting the corresponding pre-exercise interference score from the post-exercise interference score (post-exercise- pre-exercise). In order to show the data in more intuitive manner (i.e., as an improvement in Stroop task performance) this variable was reversed scored, meaning that higher gain scores reflect a greater increase in inhibitory control strength.

Hierarchal linear regression analyses were conducted to determine if the moderate exercise-induced gains in inhibitory control differed depending on individual differences in pre-moderate exercise interference scores. Similar to the gains variable, and for the same reason, pre-

moderate exercise Stroop interference scores were reverse scored, meaning that higher values are indicative of stronger (better) inhibitory control abilities. The pre-moderate exercise interference score and gain variable were centered and combined to form an interaction term. The pre-moderate exercise interference score was entered on the first step, and the interaction term was entered on the second step. In the second model, the covariates (age, BMI, ethnicity, and hours of physical activity in the last week) and pre-moderate exercise interference score were entered in the first step, and the interaction term on the second step. For both models, the criterion variable was the moderate exercise-induced gains in inhibitory control.

Following this, a one way repeated measures ANOVA was conducted to determine if there was an exercise effect [moderate vs. minimal] on the total amount of food consumed (g). It was determined *a priori* that if there was a significant difference in the total amount of food consumed as a function of exercise condition [moderate vs. minimal] that a 2x2 repeated measures (food type {appetitive, control] by exercise condition [moderate, minimal]) ANOVA would be conducted to determine if the consumption effects were specific to the type of food being consumed (i.e., appetitive vs. control). Significant main effects were followed up with planned Fisher's LSD comparisons.

To determine whether moderate exercise-induced gains in inhibition mediated exercise-induced dietary restraint, within subject's mediation was assessed using the procedure outlined in Judd et al., (2001). The mean difference in appetitive snack food consumption across exercise conditions was regressed onto the sum of each participant's gain in inhibition, and the mean difference in each participant's gain in inhibition as a function of exercise condition.

5.3 Results

Table 5.1
Descriptive statistics for the study variables, and the exercise procedure by exercise condition.

	Moderate		Minimal		
	M	*SD*	*M*	*SD*	*p*
Time Since Last Meal (hours)	4.060	1.752	4.955	3.026	.177
EF Variables					
Pre Exercise Stroop Accuracy	.977	.071	.961	.098	
Post Exercise Stroop Accuracy	.986	.013	.966	.096	
Pre Exercise Stroop Interference (ms)	65.230	78.946	48.572	66.568	.111
Post Exercise Stroop Interference (ms)	32.592	54.987	43.420	64.007	
Change in EF Strength (ms)	32.638	62.285	5.152	89.641	.009*
Food Consumption					
Total Amount of Food (g)	73.048	25.223	83.520	26.897	.002*
Total Amount of Appetitive Food (g)	54.077	23.008	64.640	24.555	.001*
Total Amount of Control Food (g)	19.220	7.405	18.880	7.682	.765
Pre-to-Post Change in FCQ-S					
Desire to Eat	.300	2.41	.040	2.030	.465
Positive Reinforcement	.120	2.264	.140	1.863	.802
Negative Reinforcement	.220	2.485	.120	1.891	.944
Lack of Control Over Eating	.400	2.060	.460	1.764	.875
Hunger	.860	1.969	.760	2.066	.745
Taste Test Variables					
Perceived Health Appetitive Foods	1.973	.776	2.113	.856	
Perceived Health Control Foods	5.540	1.714	5.390	1.915	
Subjective Appeal Appetitive Foods	7.133	1.716	7.153	1.542	
Subjective Appeal Control Foods	4.480	1.389	4.460	1.273	
Exercise Descriptives					
Rate of Perceived Exertion	12.775	5.210	7.313	1.053	
Speed (MPH)	3.566	.283	1.645	.371	
Incline (% Grade)	4.520	2.685			
Distance Walked (Miles)	1.069	.104	.540	.099	
Resting Heart Rate (BPM)	83.66	9.973	84.88	10.215	.099
Change in Heart Rate (BPM)	49.864	14.679	3.115	11.507	

Note: Gains in inhibitory control as a function of exercise condition was calculated by subtracting the pre-exercise Stroop interference scores (ms) from post-exercise Stroop interference scores (ms), and reverse scoring the value; higher values reflect a larger gain in inhibition strength post exercise. The pre-to-post change in FCQ-S was calculated by subtracting the sum of the corresponding pre-exercise items for each dimension from the post-exercise sum of the corresponding items. There was no incline in the minimal exercise condition. Subjective appeal and perceived health ratings were measured using the following items respectively: a) "overall, how would you rate this food? (response scale: 1= "not at all good"; 10= "very good"), and b) "how healthy do you think this food is? (response scale: 1=" not at all healthy"; 10= "very healthy"). * significantly different from minimal exercise condition.

5.31 Baseline group comparisons

Descriptive statistics for all study variables, and the exercise procedure are presented in Table 5.1. There were no significant differences in the pre-exercise Stroop interference scores (ms), resting heart rate estimates ($t(49)=-1.680$, $p=.099$) or the time lag between participants last meal and the start of the exercise session ($t(49)=-1.370$, $p=.177$) between exercise conditions [moderate, minimal]. Zero-order correlations between pre-exercise Stroop inference scores, fatty food consumption, hours of vigorous physical activity in the last week, and BMI are presented in Table 5.2.

Table 5.2
Zero-order correlations between EF, fatty food consumption, hours of vigorous physical activity, and BMI

Variables	1	2	3	4	5
1. Pre-exercise Stroop interference					
2. Frequency of Fatty Food Consumption	-.342*				
3. Frequency of Fatty Food Consumption: Meat/Animal Products	-.184	.929**			
4. Frequency of Fatty Food Consumption: Snack Food	-.485**	.503**	.147		
5. Hours of Vigorous Physical Activity in the Last Week	.253	-.271	-.171	-.326*	
6. BMI	.075	-.158	-.161	-.048	.189

Note: *$p<.05$, **$p<.001$. The pre-exercise Stroop interference variable was computed by averaging the minimal and moderate pre-exercise scores. There was a marginal association between hours of vigorous physical activity in last week and EF ($p=.076$), and the frequency of fatty food consumption ($p=.057$). It was decided *post hoc* that the frequency of fatty food consumption variable would be divided into two components (1) fatty food consumption from meat and animal products (e.g., butter), and (2) fatty food consumption from snack foods (e.g., donuts, potato chips, cookies, and etc.).

5.32 Food craving effects

There were no significant differences between exercise conditions [moderate, minimal] on the pre-to-post exercise bout change on the desire to eat ($t(49)=.736$, $p=.465$), negative reinforcement ($t(49)=.252$, $p=.802$), positive reinforcement ($t(49)=-.070$, $p=.944$), lack of control over eating ($t(50)=-.159$, $p=.875$), or physiological state (i.e., hunger; $t(49)=.327$, $p=.745$) dimensions of the FCQ-S; see Table 5.1

5.33. Taste test results

Results revealed a significant main effect of food type [appetitive, control] on the perceived health ratings of the experimental foods ($F(1,49)=190.234$, $p<.001$), such that across exercise conditions [moderate, minimal] participants rated the appetitive foods as significantly less healthy than the control foods ($p<.001$). The main effect of exercise condition [moderate, minimal] ($F(1,49)=.002$, $p=.963$), and the food type [appetitive, control] by exercise condition [moderate, minimal] interaction ($F(1,49)=1.715$, $p=.196$) were not significant. Similar results were observed when examining the exercise effects on the subjective appeal of the experimental foods. The main effect of food type [appetitive, control] was significant ($F(1,59)=81.304$, $p<.001$), such that the appetitive foods were rated as significantly more appealing than the control foods across exercise conditions ($p<.001$). However, the main effect of exercise condition [moderate, minimal] ($F(1,49)=.000$, $p=1.00$), and the exercise condition [moderate, minimal] by food type [appetitive, control] interaction ($F(1,49)=.030$, $p=.862$) were not significant. These findings indicate that across exercise conditions, participants perceived the appetitive foods to be significantly more appealing and less healthy than the control foods.

5.34 Exercise effects on Stroop performance

A significant main effect of time [pre-exercise, post-exercise] was observed ($F(1,49)=6.326$, $p=.015$); there was no significant main effect of exercise condition [moderate, minimal], $F(1,49)=.126$, $p=.724$. The main effect of time was qualified by a significant time by condition interaction ($F(1,49)=7.498$, $p=.009$). Simple effect analyses revealed that performance on the Stroop task differed as a function of exercise condition [moderate vs. minimal], such that task performance was significantly better following an acute bout of moderate aerobic exercise ($F(1,49)=13.729$, $p=.001$), whereas, there was no significant change in Stroop task performance following minimal aerobic exercise ($F(1,49)=.310$, $p=.580$). In addition, the Stroop interference score gains as a function of exercise condition were significantly higher following moderate

exercise (*M*=32.638; *SD*=62.285) as compared to the control condition (*M*=5.152; *SD*= 89.641; *t*(49)=2.738, *p*=.009; see Figure 5.1), indicating that exercise-induced improvements in inhibitory control are larger following moderate as compared to minimal exercise. Together, these data indicate that moderate aerobic exercise can enhance inhibitory control abilities, whereas, minimal exercise has little to no effect.

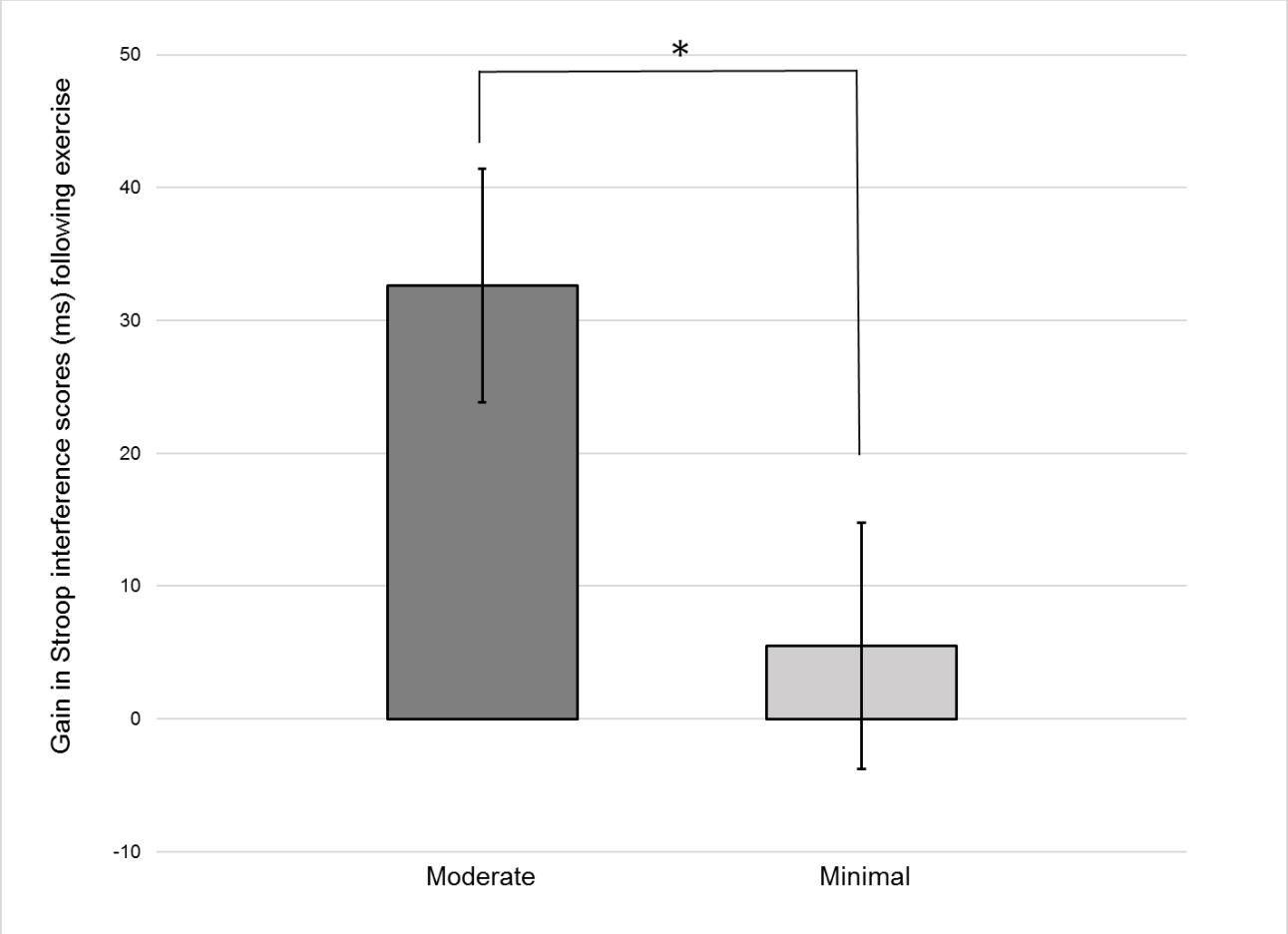

Figure 5.1: Mean (±SE) gains in EF (ms) as a function of moderate and minimal aerobic exercise. Change in EF as a function of exercise condition was calculated by subtracting the pre-exercise Stroop interference scores (ms) from post-exercise Stroop interference scores (ms), and reverse scoring the value; higher values reflect a larger gain in EF strength post exercise. * Significantly different from minimal exercise at the $p<.05$ level.

To explore whether the moderate exercise inducted gains in inhibitory control differed depending on pre-moderate exercise Stroop interference score, moderated hierarchical regression analyses were employed. Findings revealed a significant main effect of pre-moderate exercise Stroop interference scores (β=-.295, *t*=-2.572, *p*=.013). This main effect was qualified by a

significant pre-moderate exercise by gains in inhibitory control interaction (ΔR^2= .696, β=-.763, *t*=-5.214, *p*<.001). The interaction remained robust after controlling for age, BMI, ethnicity, and hours of vigorous physical activity in the last week (ΔR^2= .856, β=-.605, *t*=-5.030, *p*<.001). The gains in inhibitory control following moderate exercise were larger in those with lower pre-exercise inhibitory abilities, indicating that individuals with weaker inhibitory control are more amendable to the beneficial effects of moderate exercise. In the current sample, following moderate exercise, improvements in inhibition were observed in 91.67 % of individuals with weaker initial inhibitory control (65.810 *ms* on average) compared to 53.85% of individuals with stronger initial inhibitory control abilities (5.259 *ms* respectively; Figure 5.2).

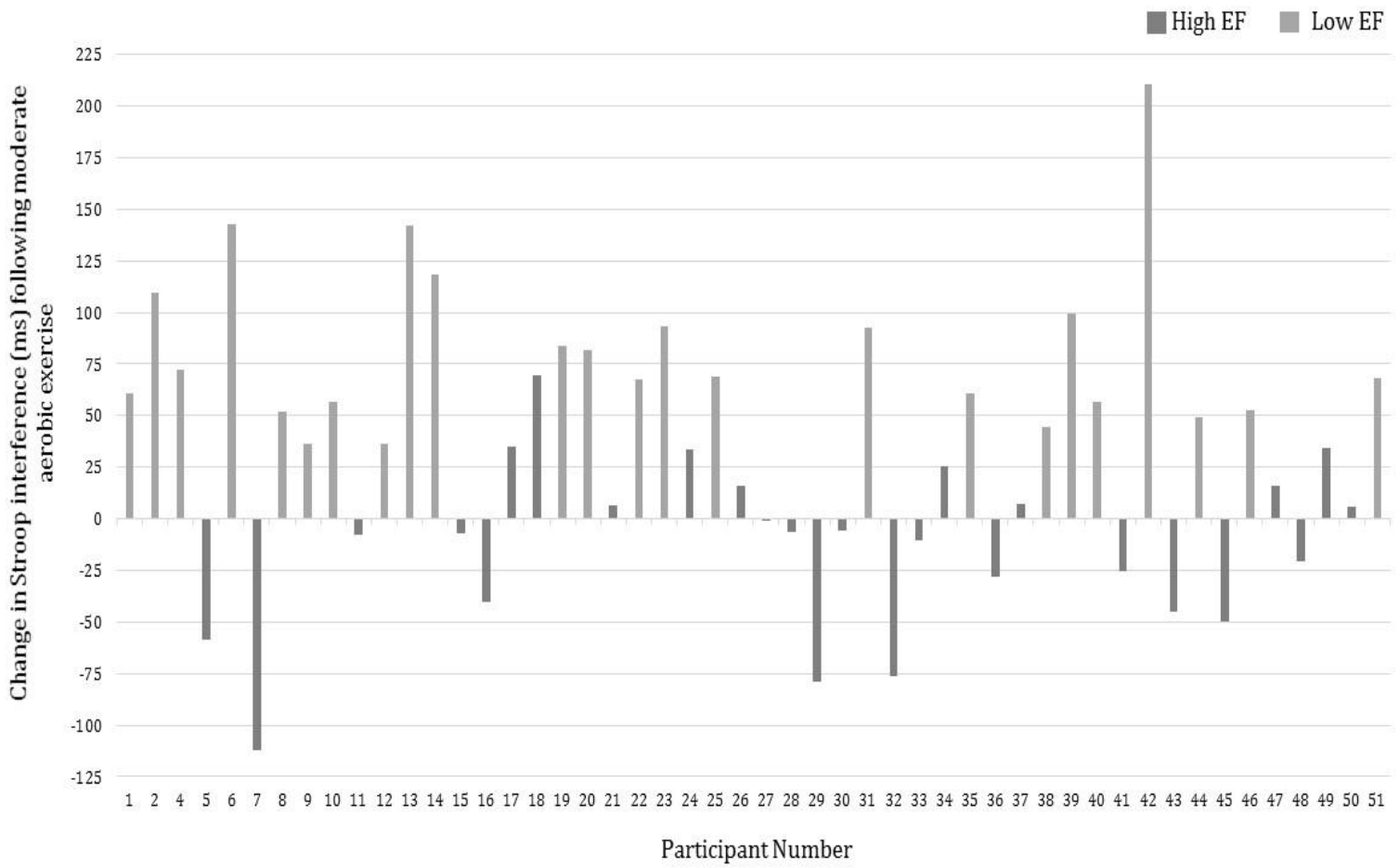

Figure 5.2: Individual gains (post-exercise minus pre-exercise, and reverse scored) in EF following moderate aerobic exercise by initial EF. Participants were divided into low and high initial EF categories using a median spilt on the pre-moderate Stroop interference scores (ms). Each bar represents an individual participant's gain in EF.

5.35 Exercise effects on calorie dense food consumption

Participants consumed significantly less food overall (g) following moderate exercise (*M*=73.048; *SD*=25.223) as compared to the control condition (*M*=83.520; *SD*=26.897; *F*(1,49)=10.871, *p*=.002). When comparing the exercise effects on food consumption as a function of food type (appetitive versus control), results revealed significant main effects of exercise (*F*(1,49)= 11.039, *p*=.002) and food type (*F*(1,49)= 179.236, *p*<.001); participants consumed more appetitive than control foods (g) across exercise conditions. As expected, these main effects were qualified by a significant condition by food type interaction (*F*(1,49)= 12.751, *p*=.001). Simple effects analyses revealed that participants consumed significantly less appetitive snack foods following moderate exercise (*M*=54.077 *SD*=23.008) relative to minimal exercise (*M*=64.640; *SD*=24.555), *F*(1,49)=13.746, *p*=.001. This effect was highly specific to appetitive snack foods, as there was no exercise effect on control food consumption (*F*(1,49)=.090, *p*=.765; see Figure 3). These findings indicate that moderate aerobic exercise enhances dietary self-regulation by modulating the type of food being consumed.

5.36 Transfer (mediation) effect

The mean difference in Stroop gains as a function of condition was a significant predictor of the mean difference in appetitive snack food consumption between exercise conditions (β=-.358, *t*=-2.408, *p*=.020). These findings remained robust after controlling for age, BMI, and ethnicity (β=-.302, *t*=-2.126, *p*=.039). This effect—in conjunction with the significant exercise effect on gains on Stroop performance, and the significant exercise effect on appetitive snack food consumption—satisfies the assumptions underlying mediation in within subjects designs.

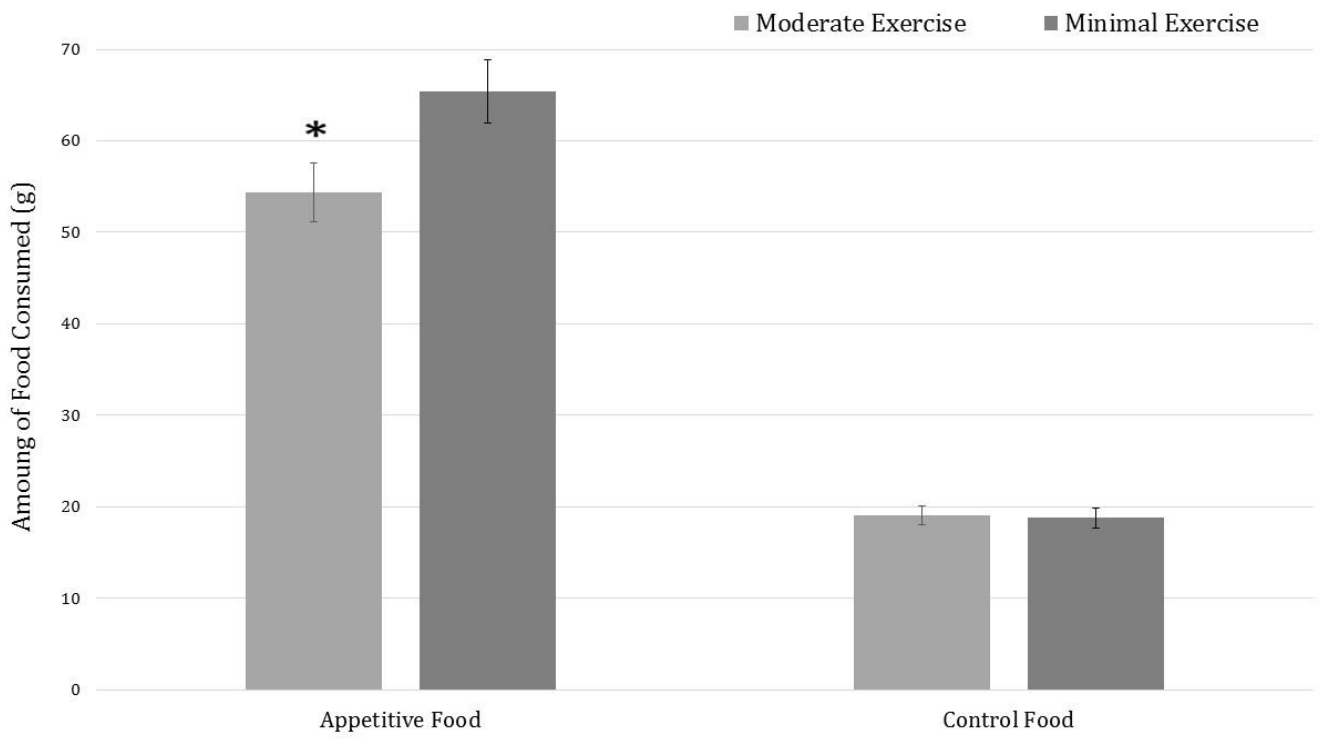

Figure 5.3: Mean (±SE) appetitive snack food (g) and control food (g) consumption as a function of moderate and minimal aerobic exercise conditions. * Significantly different from minimal exercise at the $p<.05$.

5.4 Discussion

In the present study we examined the effects of acute aerobic exercise on inhibitory control, and explored possible cross-domain transfer effects to dietary self-control. As expected, significant gains in inhibitory control strength were observed following a bout of moderate exercise; this effect appeared to be most pronounced among those with relatively weaker initial inhibitory control. Moderate exercise also improved dietary self-restraint in a subsequent taste test, an effect that appeared to be mediated by exercise-induced enhancements in inhibitory control. The results from the present study provide the first evidence of a direct transfer effects of exercise effects on the brain to an arm's length domain; such effects were highly specific to appetitive, calorie dense snack foods, as hypothesized. The interpretation of the pattern of findings as transfer *per se* was supported by the mediational analyses demonstrating that the gains in inhibitory control following

moderate aerobic exercise statistically accounted for the exercise effect on calorie dense snack food consumption.

One prior study has examined the possibility of dietary transfer effects of exercise-induced cognitive enhancement (Lowe et al., 2104b). However, this study found only evidence of an indirect transfer effect, in that those in the moderate exercise condition ate more control foods, possibly in an effort to consume bulk amounts of filling (but lower calorie) foods to satiate themselves. Several methodological improvements were included in the current study, such as the use of a more powerful within subject's design, larger sample size, and the simultaneous presentation of the experimental foods to allow differential allocation of attention to competing food choices. Therefore, the current findings can be considered more definitive, and may provide important insights into the neural mechanisms underlying the observed reductions in post-exercise food intake that have been previously documented (Balaguera-Cortes et al., 2011; Guelfi et al., 2013; Hagobian et al., 2009; Martins et al., 2008; Schubert et al., 2013; Sim et al., 2014; Thivel et al., 2012), conceptually linking the EF and exercise, and the post-exercise energy intake literatures.

The finding of exercise-induced improvements in EF is in keeping with the current body of literature on acute exercise benefits on cognition (Chang et al., 2012; Lambourne & Tomporowski, 2010; McMorris & Hale, 2012; McMorris et al., 2011; Smith et al., 2010); the observed moderation of this effect by pre-exercise inhibitory control strength is consistent with at least one prior study (Drollette et al., 2014). There are several potential mechanistic explanations for why exercise has beneficial effects on EF, including neurochemical mediators such as BDNF levels (Ferris et al., 2007), glycogen supercompensation (Matsui et al., 2012), increased neuronal activity indexed by increased blood oxygenation (Giles et al., 2014; Rooks et al., 2010; Tempest et al., 2014; Yanagisawa et al., 2010), as well as associated structural changes to cognitive control substrates (Erickson et al., 2015; Kramer & Erickson, 2007). It is plausible that individuals with relatively weaker inhibitory control abilities are more amendable to these effects due to slight decrements in all or some of

these mechanisms, while those with stronger inhibitory control do not benefit (as much) from further cognitive bolstering due to fully optimized PFC structure, and/or function.

In the context of dietary self-regulation, the consumptive effects suggest that moderate aerobic activity enhances dietary self-regulation by modulating the type of consumptive behaviour (i.e., hedonic versus homeostatic). While it is plausible these findings may be attributed to differences in caloric expenditure between exercise conditions (i.e., a compensatory effect), there was no difference in self-reported hunger ratings between exercise conditions, suggesting that these effects may not be attributed to energy regulation or hormonal changes alone. Indeed, hedonic food intake can occur independent of hunger signals, and is strongly influenced by social and environmental factors, as well as the sensory properties of food (Graham et al., 2012; Lutter & Nestler, 2009). In addition, considering that the exercise effects on food intake were highly specific for appetitive calorie dense snack foods (foods that were rated as both more appealing and less healthy across exercise conditions), and did not translate into changes in control food intake, it is unlikely that a (direct) compensatory effect occurred; if the food intake results were due to homeostatic reasons, it is likely that there would be no difference in the type (appetitive vs. control) of food consumed, rather the exercise effects would be specific to the amount of food consumed. Further, both initial inhibitory control abilities (pre-exercise) and hours of vigorous aerobic exercise in the past week were significantly (negatively) correlated with the amount of snack food consumed in the past week. Together, these findings indicate that aerobic exercise may facilitate effective dietary self-regulation by modulating the type of food consumed, rather than reducing overall food consumption, supporting the notion that the dietary transfer effect is specific to the type of consumptive behaviour (i.e., hedonic food consumption).

Considering that the dlPFC is the primary neural substrate underlying EFs, the observed exercise-induced augmentations in both inhibitory control and dietary self-regulation and may be attributed to enhanced cortical activity in the dlPFC. Prior research has reported that moderate

exercise-induced improvements in response inhibition (measured using the Stroop paradigm) can be attributed to increased cerebral blood flow to the dlPFC (Yanagisawa et al., 2010), indicating that exercise-induced enhancements in inhibition are a product of increased activity in the dlPFC. In addition, the operation of the dlPFC has been consistently implicated in both the cognitive regulation of food cravings (Kober et al., 2010), and successful self-initiated dietary regulation (Hare et al., 2009). Further, at least two fMRI studies have reported increased dlPFC activity in response to high caloric food images following moderate-to-vigorous aerobic activity (Crabtree et al., 2014; Evero et al., 2012). This pattern of cortical activity suggests an enhanced inhibitory control response -via increased cortical activity in the dlPFC- to calorie dense food stimuli post aerobic activity. Therefore, it is plausible that the observed exercise-induced changes in hedonic food consumption may be attributed to exercise-induced changes in the integrity of the executive control network (i.e., enhanced dlPFC activity), which in turn facilitates improvements in dietary self-regulatory abilities via enhanced inhibitory control.

The present study improved on previous work with a more powerful design, increased ecological validity, and improved measurement. In terms of design, in comparison with Lowe et al (2014), here we utilize a more powerful within-subjects experimental design with was sufficiently powerful to test both the hypothesized interaction effects and the mediational effect. Additionally, the simultaneous presentation of the foods during the snack food consumption resembles real-world food-choice conditions, thereby enhancing ecological validity of the findings, while maintaining an ability to measure the outcome precisely. Despite these improvements, several limitations of the current study remain, including the use of an undergraduate sample, which may compromise the generalizability of the results and reduce the variability of EF scores, as well as the somewhat artificial nature of the laboratory based food selection outcome measure. Additionally, given that exercise intensity was determined using resting heart rate estimates, actual exercise intensity would have varied due to intra and inter-individual differences in cardiac frequency pre-

exercise. However, resting heart rate was measured prior to each exercise bout, and exercise intensity was calibrated to this; this controls for some of the aforementioned problematic variability.

Future studies would benefit from more demographically diverse samples, as well as examination of other variations of the food choice paradigm used here. As well, more research is needed to examine the temporal factors underlying exercise-induced dietary self-control improvements, in order to determine the dose/response relationship needed to produce long term changes in dietary self-control. In addition, the findings regarding energy overcompensation post exercise are mixed (Hopkins, Blundell, & King, 2013), and there is some evidence supporting immediate (Finlayson et al., 2009), and delayed (Rocha, Paxman, Dalton, Winter, & Broom, 2013) overcompensation effects. These effects appear to be dependent on individual differences in either implicit food attitudes (Finlayson et al., 2009), overall fitness level (Charlot & Chapelot, 2013), eating behaviours (Hopkins et al., 2013), and gender (see Martins et al., 2008). It is evident that more research is needed to tease apart the interaction between individual differences and exercise-induced overcompensation, to determine which factors mediate energy overcompensation following physical activity. Future studies would benefit from the inclusion of calorimetry to examine (more precisely) the possibility of compensatory effects that might differ by condition.

5.41 Conclusion

The present study demonstrated that a bout of moderate aerobic exercise can both enhance inhibitory control and improve dietary choice. Mediational analyses confirmed that the exercise effects on inhibitory control mediated the exercise effects on appetitive snack food intake, providing the first evidence of a direct cross-domain transfer effect of exercise-induced cognitive enhancement to an unrelated domain. Future studies might benefit from examining the possibility of exercise transfer effects in other behavioural domains beyond diet, and utilization of more

demographically diverse samples, particularly with respect to age, given the larger range of EF in older adult groups.

Chapter 6

General Discussion

Using meta-analytic methods, Study 1 demonstrated that TBS methodologies targeting the PFC are a reliable and effective way to experimentally manipulate EFs in healthy adults. Specifically, findings indicated a reliable negative effect of cTBS on executive functioning (g=-.254), and this effect was relatively uniform across included studies. Further, the magnitude of the effect was significantly higher for left-sided relative to right-sided stimulation. However, a systematic review of iTBS studies revealed considerable variability in the reliability of the effects across studies, indicating that the down-regulating effects of cTBS may be more reliable than the up-regulating effects of iTBS in healthy populations. Together, these data suggest that TBS protocols appear to be effective in modulating prefrontal cortical excitability in previously theorized directions. Study 2 applied cTBS and EEG methodologies to assess the causal relation between suboptimal PFC activity and dietary self-restraint as modulated via electrophysiological changes in reward responsivity and cognitive control. Consistent with prior research (Lowe et al., 2014), participants reported significantly higher cravings for and selectively consumed more appetitive high calorie foods following active compared to sham stimulation. The additional finding that attenuation of left dlPFC activity results in the significant increase in both reward responsivity and the attentional bias for high calorie foods provides important insight into the neurocognitive mechanisms underlying dietary self-restraint. That is, temporary perturbations in prefrontal activity may result in the inability of the PFC to modulate reward specific cortical activity in the mesolimbic regions of the brain, subsequently predisposing individuals to the overconsumption of highly appealing calorie dense snack foods. Therefore, failures in dietary self-restraint may stem from situations in which the appetitive drive of high calorie foods overpowers inhibitory control capabilities. Thus, optimizing inhibitory control would potentially decrease the likelihood of this occurring.

Study 3 and 4 sought to determine if optimizing prefrontal cortical activity (1) results in subsequent improvements in inhibitory control, and (2) if these improvements translate to subsequent enhancements in dietary self-restraint. Study 3 demonstrated that an acute session of

moderate intensity mitigated the cTBS-induced decrements in inhibitory control more quickly than a session of light intensity exercise. These findings demonstrate that acute exercise can be used to promote cortical resilience, and provide practical implications for the use of such exercise protocols to offset the influence of naturally occurring down-regulators of EF in everyday life (e.g., acute stress, sleep restriction). Study 4 employed the same exercise methodologies to determine if exercise-induced improvements in inhibitory control transfers to increased self-control in the dietary domain. Compared to very light intensity exercise, significant improvements in inhibitory control were apparent following a bout of moderate intensity exercise. Further, participants consumed significantly less appetitive calorie dense foods following moderate relative to very light intensity exercise. Most importantly, the exercise-induced gains in inhibitory control mediated the effects of moderate exercise on appetitive snack food consumption. Together these findings provide evidence that a bout of a moderate aerobic exercise can enhance inhibitory control, and support for cross-domain transfer effects to dietary self-control.

6. 1 Implications

Obesity is considered a major global public health challenge not only because of the established health risks, but also due to the fact that unlike other global health concerns, such as tobacco use and child malnutrition, the prevalence of obesity is steadily increasing (Ng et al., 2014), particularly among middle-aged to older adults (Ogden et al., 2016). Current worldwide estimates indicate that approximately 2.2 billion individuals are overweight with least 400 million of those persons living with obesity (Finucane et al., 2011; Ng et al., 2014). This is of concern as obesity has consistently been implicated as a pivotal risk factor for cardiovascular disease, stroke, type 2 diabetes mellitus and other metabolic syndromes, and depression and other mental health disorders (Bruce-Keller, Keller, & Morrison, 2009; Flegal, Graubard, Williamson, & Gail, 2007; Ng et al., 2014). Obesity itself is thought to be associated with over 3.4 million deaths worldwide equating to 3.9 % of years lost due to early mortality and 3.8% of years lost due to ill health (disability-

adjusted life years; Ng et al., 2014). Furthermore, national interventions and strategies appear to be ineffective in reducing the prevalence of obesity, indicating that current prevention programs are not working at the level needed to make a large-scale impact (Ng et al., 2014). As such, a different approach to tackling the obesity pandemic is clearly necessary.

While numerous factors influence body fat and weight gain, the combination of the availability and low cost of highly palatable calorie dense foods is thought to be a primary factor underlying the rapid increase in the prevalence of obesity (Finkelstein, Ruhm, & Kosa, 2005; Levy et al., 2011; Swinburn, Caterson, Seidell, & James, 2004; Swinburn, Caterson, Seidell, & James, 2004). In fact, the modern environment is often referred to as being "obesogenic" in that the relative ease of access and low cost of calorie dense foods in conjunction with the ubiquitous cuing to consume such foods via media advertisements promotes non-homeostatic food consumption. Both the exposure to appetitive food images and cues, and the anticipated and actual intake of palatable calorie dense foods increases cortical activity in the regions associated with reward processing and incentive valuation, such as the ventral striatum, midbrain, amygdala, and the orbitofrontal cortex OFC (Killgore et al., 2013; Kringelbach, O'Doherty, Rolls, & Andrews, 2003; O'Doherty, Deichmann, Critchley, & Dolan, 2002; Small, Veldhuizen, Felsted, Mak, & McGlone, 2008; Stice, Burger, & Yokum, 2013, 2015; Stice & Yokum, 2016a; van der Laan, de Ridder, Viergever, & Smeets, 2011; van Meer, van der Laan, Adan, Viergever, & Smeets, 2015). Such reward-related cortical responsivity to high caloric foods is thought to putatively override homeostatic processes, resulting in the subsequent overindulgence in calorie dense foods (Stice et al., 2015; Stice & Yokum, 2016a; Val-Laillet et al., 2015). Indeed, energy intake from calorie dense foods has increased to the point that approximately 40 % of adults and children's total energy intake and total fat intake comes from such foods (Rangan, Randall, Hector, Gill, & Webb, 2008).

However, it is unlikely that the modern environment is going to change drastically enough within the necessary timeframe needed to notice a substantial change in the prevalence of obesity.

Therefore, from a public health perspective, it is important to focus on individual level preventative measures. Specifically, how can we enable individuals to resist the temptation of highly appealing, but unhealthy, food items and otherwise maintain a healthy diet. The current body of work demonstrated that optimal functionality of the executive control network is essential for successful dietary self-restraint. Such findings have important implications for both the treatment and prevention of obesity. First, they build on current neurobehavioural models of obesity by providing causal evidence that the operation of the PFC plays a crucial role in regulating appetitive snack food consumption via changes in reward responsivity to high calorie food stimuli. This finding is of substantial importance as PFC activity can be optimized, and therefore, interventions aimed at enhancing prefrontal functionality may equate to improvements in dietary self-restraint at the population level. Thus, incorporating methods of optimizing PFC activity into ongoing treatment programs may prove to be more fruitful than traditional efforts. Finally, the current findings also suggest that the relationship between obesity and poor neurocognitive health is reciprocal in that suboptimal PFC activity can predispose an individual to the overconsumption of palatable calorie dense food, which subsequently amplifies obesity associated changes in cognitive functioning and cortical structure and functionality. Together, these findings can be used to inform strategic preventative interventions and improve on current treatments.

6.12 Builds upon current neurobehavioural models of obesity

Identification of subtle neurocognitive markers that predispose an individual to weight gain can be used to customize both prevention and intervention strategies, and improve current treatments. Current neurobehavioural models have noted that overlapping patterns of activation in reward regions of the brain in response to appetitive stimuli are observed in persons with obesity and drug users and abusers (Levy et al., 2013; Stice & Yokum, 2016a; Tang, Fellows, Small, & Dagher, 2012; Volkow, Wang, Tomasi, & Baler, 2013) which has led to the concepulatizion of the food addiction models of obesity (Davis et al., 2011). Specifically, these models have postulated that persons with

obesity are hypersensitive to the incentive or reward associated with high caloric food stimuli, which in turn fosters overindulgence in the absence of homeostatic or physiological need (Burger & Stice, 2011; Stice & Yokum, 2016a; Volkow et al., 2013). For instance, persons with obesity show elevated responsivity in the ventral striatum, amygdala, and orbitofrontal cortex in response to high caloric food images (Demos, Heatherton, & Kelley, 2012; Dimitropoulos, Tkach, Ho, & Kennedy, 2012; Gearhardt, Yokum, Stice, Harris, & Brownell, 2014; Ho, Kennedy, & Dimitropoulos, 2012; Murdaugh, Cox, Cook, & Weller, 2012; Rothemund et al., 2007; Stice et al., 2013). Notably, several prospective fMRI studies have demonstrated that elevated cortical responses in these regions in response to high calorie food images and commercials, and palatable food odors is predictive of future weight gain (Demos et al., 2012; Stice et al., 2015; Stice & Yokum, 2016b). Conversely, the reward deficit models posits that overeating is a function lower dopaminergic signalling with the mesolimbic reward regions in that persons with obesity overeat to compensate for this deficiency (Volkow et al., 2009; Wang, Volkow, & Fowler, 2002). Nonetheless, while reward system responsivity may play a crucial role in modulating non-homeostatic eating behaviours, these models often discount or downplay the contribution of the PFC, and by extension inhibitory control abilities.

Successful self-regulation requires humans to control impulses and regulate appetitive behaviours particularly in the presence of rewarding cues (Heatherton, 2011; Kelley, Wagner, & Heatherton, 2015). Within the context of dietary habits, successful dietary self-restraint can be conceptualized as the capacity to resist the temptation to consume highly appealing calorie dense foods and otherwise choose the healthier alternative. Consistent with this notion, several observational studies that have demonstrated that inhibitory control abilities are associated with obesogenic behaviours in a theoretically meaningful way (Hall, 2016; Appelhans, 2009; Vainik, Dagher, Dubé, & Fellows, 2013). The propensity to consume calorie dense foods is higher in individuals with poorer inhibitory control (Allan, Johnston, & Campbell, 2010, 2011; Guerrieri et al.,

2007; Hall et al., 2014; Hall, Lowe, & Vincent, 2014; Hall, 2012; Nederkoorn, Guerrieri, Havermans, Roefs, & Jansen, 2009), and this effect is amplified when environmental cues encourage consumption (Hall et al., 2014; Hall et al., 2014). The current body of work adds to this line of research by providing experimental evidence supporting the notion that the integrity of the executive control network is causally associated with successful dietary self-restraint in the theorized directions.

The additional findings that the operation of the PFC is causally related to both dietary self-restraint and reward responsivity to high calorie food stimuli builds on existing evidence that has demonstrated that prefrontal functionality is associated with both successful dietary self-regulation (Hare et al., 2009, 2011; Harris et al., 2013) and the cognitive regulation of food cravings (Kober et al., 2010; S Yokum & Stice, 2013), and provides important insight into potential neural markers that increase the susceptibility to overconsumption in the modern environment. The findings from Study 2 demonstrated that individual differences in reward responsivity are at least in part modulated by the functionality of the PFC in that a significant increase in the amplitude of the P3a component to high calorie food stimuli and the attentional bias for high calorie foods was apparent following temporary perturbations in left dlPFC activity. Such increases in reward responsivity were directly associated with the specific consumption of appetitive calorie dense snack foods. Together, these findings suggest that suboptimal prefrontal functionality can increase the propensity to overindulge on high calorie food items via increased reward responsivity to food stimuli.

While more research is necessary to fully elucidate the exact mechanisms via which prefrontal modulation of reward responsivity modulates dietary behaviours, the findings from the current body of work provide the foundational work that can be used to both develop a convincing neurocognitive framework for understanding the factors that mitigate obesity-conducive eating behaviours, and bridges current neurobehavioural models of obesity with executive control models

of eating behaviours. Most importantly, the current body of work suggests that the structure and the functionality of the PFC may play a crucial role in modulating obesogenic consumptive habits. This finding is of substantial importance from a public health perspective as prefrontal cortical activity can be optimized.

6.13 Optimization of PFC activity and implications for obesity prevention and treatment

Prefrontal functionality can be optimized, and thus, interventions aimed at optimizing prefrontal functionality may be beneficial both from a preventative standpoint and in conjunction with current obesity treatments; particularly considering that drastic changes to the modern environment are likely not going to happen any time soon. Thus, investigation into various methods of prefrontal optimization and applications to eating behaviours is of the utmost importance from a research and broader public health perspective.

While the findings regarding iTBS methods are mixed, the results from Study 1 suggest that TBS methodologies are a reliable and effective means of modulating prefrontal excitability as indexed by changes in EF. Therefore, by extension, therapeutic neuromodulation targeting the PFC may potentially improve dietary self-restraint via long-term improvements in prefrontal functionality. Consistent with this notion, Jauch-chara et al. (2014) reported that the consecutive application of anodal tDCS to the dlPFC over 8 days resulted in an approximate 14% reduction in total calories consumed. Similarly, the tendency to consume less calories, particularly from soda and fat, and a significant reduction in food cravings in persons with obesity is observed following 9 days of anodal tDCS targeting the left dlPFC relative to sham stimulation (Gluck et al., 2015). Such stimulation-induced changes in food cravings have been observed for up to 30 days post-treatment (Ljubisavljevic, Maxood, Bjekic, Oommen, & Nagelkerke, 2016); however, more well-designed and well-powered studies are necessary to confirm and replicate this effect. Finally, preliminary findings suggest that therapeutic neuromodulation may an effective treatment for bulimia and binge-eating disorders (Hall, Vincent, & Burhan, 2017), suggesting that such methods can produce

positive effects on aberrant consumptive patterns and behaviours. Nonetheless, while these findings are promising, more research is necessary to establish whether therapeutic neuromodulation is an effective treatment for obesity, and whether the effects result in long-term reductions in weight and adiposity. Furthermore, to ensure patient safety and procedural compliance, such methods should be administered within a clinical setting by trained personnel. Therefore, while therapeutic neuromodulation may prove to the be a useful treatment for more extreme cases, from a public health standpoint, such treatments are not feasible or desirable for large scale dissemination

Another well-documented method of prefrontal optimization is aerobic exercise. Several lines of evidence have demonstrated that both acute and long-term exercise interventions have beneficial effects on neurocognitive functioning and cortical structure and functionality (Chang, Labban, Gapin, & Etnier, 2012; Erickson, Hillman, & Kramer, 2015; Hillman, Erickson, & Kramer, 2008; Kramer & Erickson, 2007; Lambourne & Tomporowski, 2010; Smith et al., 2010). The cortical effects are particularly pronounced in the areas of the brain that support executive function and memory (e.g., hippocampus and prefrontal cortex; Colcombe et al., 2006; Erickson, Leckie, & Weinstein, 2014; Weinstein et al., 2012). The current body of work provides further support for the beneficial effects of exercise. In Study 4, significant improvements in inhibitory control abilities were observed following an acute session of moderate intensity exercise. The additional findings that aerobic exercise can be used to enhance cortical resilience add to these well-documented effects by demonstrating that exercise may accelerate recovery from artificial perturbation in the laboratory context. Such findings are of importance, as several natural everyday down-regulators of prefrontal functionality exist, such as acute stress (Porcelli et al., 2008; Qin et al., 2009), alcohol intoxication (Marinkovic et al., 2012; Spinola, Maisto, White, & Huddleson, 2017), and sleep-restriction (Lowe, Safati, & Hall, 2017). Therefore, over time, such perturbations in executive control may have profound effects on overall health and well-being. As such, the resilience-

promoting effects of exercise might be of some practical importance when considering its potential to offset the effects of these factors.

Further, the strategic integration of aerobic exercise into existing obesity interventions might optimize treatment outcomes via enhanced dietary self-restraint. Consistent with this notion Lowe et al. (2016) reported significant improvements in inhibitory control abilities following an acute bout of moderate aerobic exercise, and such exercise-induced improvements in translated to enhanced dietary self-restraint. In addition, a significant reduction in P3 and LPP amplitudes in response to food stimuli are observed in both adults (Hanlon, Larson, Bailey, & Lecheminant, 2012) and adolescents (Fearnbach et al., 2016) following an acute bout of moderate intensity exercise, suggesting that aerobic exercise can be used to reduce food specific reward responsivity. Such exercise-induced reductions in reward responsivity were associated with subsequent reductions in *ad libitum* food intake post-exercise (Fearnbach et al., 2016). While the long-term effects of aerobic exercise on dietary self-restraint are currently unknown, the above suggest that aerobic exercise interventions may be beneficial both as a preventative measure and in conjunction with current obesity treatments. From a public health perspective, the implementation of large scale exercise interventions within both schools and workplaces may be more feasible than therapeutic neuromodulation interventions or large overhauls in the modern environment. Thus, further consideration into the potential of aerobic exercise to improve dietary self-restraint is warranted.

6.13 Potential reciprocal relationship between prefrontal functionality and obesity

Converging evidence has noted an association between obesity and neurocognitive health. Specifically, across the lifespan, persons with obesity perform more poorly on measures of global cognition, semantic and episodic memory, processing speed, and most notably, EF (Hayes, Eichen, Barch, & Wilfley, 2017; Smith et al., 2011). Such cognitive deficits may be a direct function of the several structural and functional neurocognitive deficits observed within persons with obesity. Compared to normal weight individuals, persons with obesity typically have smaller brain volumes

(Brooks et al., 2013; Debette et al., 2010) and show reductions in grey matter volume in several brain regions, including the hippocampus, anterior cingulate gyrus, dlPFC, orbitofrontal cortex, ventromedial PFC, frontopolar cortex, and cerebellum (Brooks et al., 2013; Ho et al., 2010; Jagust, Harvey, Mungas, & Haan, 2005; Medic et al., 2016; Raji et al., 2009; Walther, Birdsill, Glisky, & Ryan, 2010). In children and adolescents with obesity the observed reductions in grey matter volume are most pronounced in the frontal and limbic regions of the cortex (Alosco et al., 2014), indicating that these regions may be the most sensitive to obesity-related structural brain alternations. In addition, obesity is associated with reductions in white matter integrity in the form of demyelination or lesions in the white matter (white matter hyperintensities; Gupta et al., 2015; Ho et al., 2010; Jagust et al., 2005; Kullmann, Schweizer, Veit, Fritsche, & Preissl, 2015). These obesity-related changes in white matter connectivity are most consistently observed in the tracts connecting the frontal and limbic regions (Kullmann et al., 2015). Considering that the PFC is considered to an important cortical node underlying executive control, the observed reductions in grey matter may explain the cognitive deficits observed in persons with obesity.

Obesity is associated with several cardiovascular and metabolic syndromes and diseases, thus, the compounding negative effects of these conditions may explain the observed associations between peripheral adiposity and neurocognitive health. For instance, converging evidence has demonstrated that obesity-associated insulin resistance also manifests as reductions in brain insulin sensitivity, and this can negatively impact both neurocognitive functioning and synaptic and structural plasticity within the hippocampus, dlPFC, and medial and temporal cortices (Blázquez, Velázquez, Hurtado-Carneiro, & Ruiz-Albusac, 2014; Cheke, Bonnici, Clayton, & Simons, 2017; Heni, Kullmann, Preissl, Fritsche, & Häring, 2015; Mainardi, Fusco, & Grassi, 2015). Peripheral insulin resistance and hyperinsulemia are both consequences of obesity that affect kidney function. The associated increase in sodium reabsorption ultimately results in hypertension or elevated blood pressure (Wickman & Kramer, 2013). High arterial blood pressure promotes endothelial

dysfunction and atherosclerosis resulting in deficits in systematic and cerebral perfusion, which in turn exacerbates global and regional brain atrophy and white matter hyperintensities (Alosco et al., 2013; Jefferson, Poppas, Paul, & Cohen, 2007; Kumar et al., 2011; Strassburger et al., 1997). Alternatively, excess adipose tissue secretes a variety of inflammatory adiopokines/cytokines, such as fibrinogen, interleukin (IL)-1β, IL-6, and C-reactive protein (Doupis et al., 2011; Ouchi, Parker, Lugus, & Walsh, 2011). These inflammatory cytokines are able to cross the blood brain barrier and stimulate the production and activation of central inflammatory mechanisms (Takeda, Sato, & Morishita, 2014; Vitkovic et al., 2000) that prompt volumetric changes in global and regional grey matter and hippocampal neurodegeneration (Jefferson et al., 2007; Marsland et al., 2015; Marsland, Gianaros, Abramowitch, Manuck, & Hariri, 2008; Takeda et al., 2014).

It is evident that obesity is associated with poor neurocognitive health, however, the question remains does excess adiposity lead result in alterations in brain structure and function or are such deficits a precursor to weight gain? The findings from the current body of work seem to suggest the latter, as temporary perturbations in prefrontal activity predisposed healthy normal weight individuals to the overconsumption of calorie dense foods. However, it is more likely that the relationship is reciprocal in nature in that individuals with lower executive control abilities may be more susceptible to the rewarding properties of calorie dense foods, prompting the increased intake of such foods. Thus, over time, the repeated overindulgence in calorie dense foods could manifest as excessive adiposity, which in turn, via the mechanisms described above, results in the marked neurocognitive impairments observed among persons with obesity. Consistent with this notion, converging evidence has suggested that repeated intake of calorie dense foods results in the elevated cortical responsivity within the striatum and ventral pallidum in response to food-predictive cues, but not in response to food receipt (Berridge, Ho, Richard, & DiFeliceantonio, 2010; Tobler, Fiorillo, & Schultz, 2005). This implies that a period of overindulgence in calorie dense foods is necessary to give rise to the observed hyperresponsivity of the reward regions in response to

food cues observed among persons with obesity, and therefore, may contribute to the maintenance of poor dietary habits rather than the processes contributing to initial overeating of calorie dense foods.

In addition, prior research has demonstrated that the acute and repeated administration of a high caloric high fat diet results in subsequent impairments in attention, processing speed, memory, and global cognitive abilities (Edwards et al., 2011; Francis & Stevenson, 2011; Holloway et al., 2011; Micha, Rogers, & Nelson, 2011). Further, animal models have consistently reported that the administration of a diet high in fat or sugar impairs hippocampal neurogenesis (Boitard et al., 2012; Boitard et al., 2014), reduces striatal dopamine levels (Levy et al., 2015; Nguyen et al., 2017), and increases the permeability of the blood brain barrier (Davidson et al., 2012). These results are noteworthy as the operation of the hippocampus has been implicated in energy regulation. Increased caloric intake is apparent following hippocampal lesions, which in turn leads to increases in body weight and adiposity (Davidson et al., 2009).

While more research, particularly in human models, is necessary to fully elucidate the relationship between neurocognitive health and obesity, the available evidence seems to suggest a reciprocal relationship rather than a direct cause and effect. That is, individuals with lower prefrontal functionality may be more susceptible to the overindulgence in calorie dense foods, which in turn amplifies reward region responsivity to such foods and food cues, leading the maintenance of poor dietary habits. The consistent consumption of a high caloric high fat diet in turn results in impairments in cognitive control, amplifying the initial relationship between executive control and dietary self-restraint. Consideration of the reciprocal nature may be important from a preventative standpoint, as interventions aimed at enhancing prefrontal functionality in at risk populations (i.e., those populations marked by suboptimal prefrontal activity or enhanced reward responsivity) may reduce individual level risk for obesity.

6.2 Limitations

Two main limitations exist with the current body of work. First, the focus on a specific population, healthy young adult females, limits the generalizability of the effects. Future research is necessary to determine if the same mechanisms are observed both across sexes and the lifespan. Second, the current body of work included in this dissertation focused solely on one component of EF: inhibitory control. While there is substantial evidence linking inhibitory control abilities to dietary self-restraint (see Hall, 2016 for a review), it is important to consider how other cognitive processes might be relevant for both dietary self-regulation and the maintenance of healthy dietary habits overall. For instance, working memory operations may be important for aspects such as meal planning, whereas, task switching might enable the ability to adjust regulation strategies to changing environmental contexts.

In conjunction to the above, the current body of work used an experimental paradigm to selectively down-regulate cortical activity. However, it is currently unknown whether the magnitude of this effect mimics that of naturally occurring down-regulators (e.g., acute stress sleep restriction). In order to make more firm conclusions regarding the real-world significance future research is necessary to ascertain whether similar patterns of findings are apparent under more natural conditions. Finally, while the use of a within subject design increases statistical power, it is impossible to fully control for expectancy expects; such effects maybe especially pertinent when it comes to consumptive habits. This may be especially true for Study 4 in that it was impossible to blind participants to exercise condition (i.e., participants were able to distinguish between moderate and very light intensity conditions). Nonetheless, across studies less than 30% of participants indicated that they were aware (3.6% Study 2; 5.8% Study 4) or thought that we might be measuring actual food consumption (21.4% Study 2; 23.5% Study 4), suggesting that while expectancy effects may have contributed to the overall effects, the actual impact may have been

minimal. The use of between-subject study designs in future research would mitigate some of the expectancy effects, however, larger sample sizes are necessary.

6.3 Future Directions

6.31 The brain as a predictor of health intervention effectiveness

The concept that neural activity can predict individual responsivity to health interventions is a new and exciting area of research. This conceptualization of neural predictors of responsivity to health interventions is novel and provides important insight into which interventions and treatments may be the most effective at the individual and population level. For instance, Falk, Berkman, and Lieberman (2012) reported that those smoking cessation ad that elicited the greatest activity in the medial PFC was predictive of real-world behaviour change. However, self-reported judgements of ad efficacy were inversely related to behaviour change, indicating that neural predictors are a more reliable measure of health campaign effectiveness. Within the context of dietary behaviours, investigation into the neural predictors individual responsivity to dietary-specific health campaigns may provide insight into which interventions are most effective for individuals with lower executive control abilities; the focus on individuals with lower EFs is essential, as these individuals are the one's most in need of interventions to enhance dietary self-restraint. That is, are individuals with lower EFs receptive to calorie labelling, or would other interventions be more effective in this population (e.g., cuing to control food consumption or to think about the consequences of overeating). Such findings could help develop and tailor interventions aimed at increasing dietary self-restraint at the population level.

6.32 Long-term effects of aerobic exercise on dietary self-restraint

Evidence from randomized control trials have consistently reported increased gray matter volume within the PFC and hippocampus following long-term exercise interventions (Colcombe et al., 2006; Erickson et al., 2015; Erickson et al., 2011). However, it remains unclear whether such improvements would translate into increased dietary self-restraint in the long-term. Considering

that higher levels of physical activity are associated with increased gray matter volume within the inferior frontal gyrus, and dlPFC, and that this association mediated the relationship between cardiorespiratory fitness and performance on EF measures (Weinstein et al., 2012), it is plausible that exercise-induced improvements in brain structure and function might transfer to increase dietary self-restraint. Investigation into this potential relationship would allow researchers to fully ascertain the effectiveness of adding exercise interventions to current obesity treatments.

6.33 Prefrontal development and implications for dietary self-restraint

Converging evidence has indicated that the structure and functionality of cortical and subcortical regions are highly susceptible to variations in environmental quality in early childhood and adolescence, even when that variation falls within normative ranges. For instance, childhood adversity within normative ranges (e.g., changing schools, death of a grandparent) results in increased cortical activity in the ventral striatum during reward based learning and temporal discounting tasks (Kamkar, Lewis, van den Bos, & Morton, 2017), indicating that even subtle changes in environmental quality can modulate responsivity within the reward regions of the brain. Determination of the factors that influence the development of the prefrontal cortex during childhood and adolescence would allow for the identification of 'at risk" populations that would benefit the those from the implementation of strategic prevention programs aimed at optimizing prefrontal cortical activity.

The capacity to control impulses or delay gratification to immediate rewards, particularly in the presence of appetitive cues or stimuli, and otherwise act in goal directed manner is critical for the maintenance of both physical and mental health. Therefore, such interventions could have profound impacts on individual level health across the lifespan. For instance, self-regulatory abilities in childhood are predictive of numerous behavioural outcomes throughout the lifespan, including academic performance, substance use and abuse, ability to cope with stress, self-esteem or self-worth, psychosocial adjustment, socioeconomic status, and the likelihood of being convicted

of a criminal offense (Mischel et al., 2011; Moffitt et al., 2011). Individual differences in self-regulation and EFs during childhood are even predicative of weight gain and excess adiposity during adolescence (Francis & Susman, 2009; Goldschmidt, Hipwell, Stepp, McTigue, & Keenan, 2015; Seeyave et al., 2009). Considering that obesity is associated with both poor neurocognitive functioning (Smith et al., 2011) and the elevated risk for numerous detrimental health conditions, including cardiovascular disease, type 2 diabetes mellitus, depression, and Alzheimer's disease and other dementias (Flegal et al., 2007; Jagust et al., 2005), such associations highlight the potential real-world impact of poor self-regulatory abilities on physical and mental health. Thus, the early identification of children for whom there is an increased risk of developmental impairments in the regulation of behaviour or EF is an important research and policy concern across national contexts, as it would inform targeted and strategic policies and priorities, and allow for the implementation of early preventative measures aimed at mitigating the adverse effects of poor self-regulation in at risk populations.

6.4 Conclusion

Although considerable conceptual and empirical models linking executive control abilities to dietary behaviours exist (Appelhans, 2009; Hall, 2016; Vainik, Dagher, Dubé, & Fellows, 2013), to date, there is a lack of causal experimental studies designed to assess whether deficits in EF predispose an individual to the overconsumption of appetitive calorie dense foods, and whether interventions aimed at enhancing EF can improve dietary self-restraint. As such, the causal and directional nature of this relationship has remained unclear. Taken together, the current body of studies provide causal and directional evidence supporting the contention that individual differences in dietary self-restraint are at least in part mediated by individual differences in executive control, and by extension prefrontal functionality. While more work is necessary to fully ascertain the exact nature prefrontal functionality plays in modulating eating behaviours, specifically in the context of modulating reward responsivity to high calorie food stimuli, these

findings provide the foundational work necessary to bridge neurobehavioural models of obesity with executive control models of eating behaviours, and have important implications for both the prevention and treatment of obesity and obesity associated health conditions.

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Appendix A: Sample Size Determination

Sample size was determined *a priori* using G*Power (Version 3.1; Faul, Erdfelder, Lang, & Buchner, 2007); results are presented in Appendix A. A total of 18-20 participants would be required to achieve 95% power to detect a cTBS effect on behavioural and electrophysiological measures of inhibitory control, and snack food consumption.

	Effect Size	Estimated From	Estimated Sample Size
cTBS effects on inhibitory control			
	d=1.0	Lowe, Hall & Staines (2014)	22
	d=.79*	Lowe, Staines & Hall (2017)	20*
	d=.78	Vollman et al., 2011	20
cTBS effects on snack food consumption			
	d=.93	Lowe, Hall & Staines (2014)	23
cTBS effects on P3 amplitude			
	d=91	Gohil et al., (2016)	15

Note: * reflects average stimulation effect across exercise conditions.

Appendix B: Image descriptives for the food images used in Study 2

The table below provides the image number, description of the image, and macronutrient information for all the images used in the food image task. All information was derived from the normative data provided.

Image Number	Description	Fat/100g	Carbs/100g	kCal/100g
4	chocolate cookie	26	63	510
8	snack mix	0.5	75.3	347
21	raspberry candies	0	97	388
26	chips	35	48	539
27	opened chips bag	39.4	40.6	535
41	donut with chocolate sprinkles	23	42	454
43	chips	39.4	40.6	535
49	chocolate popsicles	19	29	300
63	pretzels	7.5	68	392
104	tortilla chips	22	62	478
111	bar of chocolate with nuts	36	49	555
113	chips	35	49	543
116	chocolate popsicle with nuts	19.77	29.07	314
117	chips	35	48	539
125	hard candies	0.3	95	391
127	Sacher cake	15.4	51.5	375
149	NicNac (crusty peanuts)	33	40	529
150	popcorn	15.2	53.3	397
153	gummi candy (cola)	0	78	343
154	gummi candy and licorice mix	2	79.8	352
157	gummi candy (gold bears)	0.1	77.4	340
159	mini chocolate cake bar	33.1	45.5	508
160	nuts covered in chocolate	21.5	64.8	486
163	chocolate cake	26	48	451
165	cornflakes and almonds covered in chocolate	27.5	57.3	505
167	some bars of chocolate (stacked)	29.5	58.5	530
168	puffed rice covered in chocolate	29.1	60.5	533
172	Toffifay (filled caramel cup)	28.6	58.5	514
174	chocolate pieces	36	46.5	545
186	pretzel sticks	0.5	75.3	347
286	bar of chocolate	29.5	58.5	530
287	chocolate (candy) bar	17.1	68.9	449

289	chocolate cookies	21.1	67.3	471.1
291	chocolate truffle	32.21	53.5	519
293	KitKat (chocolate wafer bars)	25.58	65.11	488
294	popcorn	18	55	424
295	Toblerone	29	60	525
296	colored chocolate beans	20.88	70.98	501
298	cookies (oreos)	20.58	73.52	470
313	strawberry ice cream cone	9.78	39.13	255.43
339	wine gum	0	79	342
374	doughnut / donut icing	13.5	45.8	318
375	doughnut / donut jam	30.6	44.8	478
376	french cruller	9	29	215
492	vanilla and chocolate icecream cone	8.6	23.5	182
494	pretzel	16	64	440
499	pieces of chocolate	38	47	559
501	chocolate bar , bite	28	54	487
510	chocolate bar, broken	16.6	70.1	448
511	marzipan chocolate	34	53.5	535
Low Calorie Foods				
192	apple	0.4	11.4	52
193	crisp bread	5.26	69	372
197	Tomatoes	0.2	2.47	16
198	paprika peppers	0.37	4.87	29
199	watermelon	0.09	3.64	17
201	salad plate	0.3	3.9	31
202	Blueberries	0.6	7.3	41
221	Oranges	0.2	9.19	47
224	wildberries mix	0.5	6	43
226	crisp bread	2.5	62	350
232	bowl of salad	0.4	4	32
234	strawberries	0.39	5.33	31
244	rice waffles	3.8	79.8	380
249	cauliflower	0.17	1.45	14
250	broccoli	0.13	1.63	17
253	pickles	0.18	1.82	16
254	figs	0.49	12.77	62
255	pomegranate	0.21	5.84	27
256	grapefruit	0.1	5.91	33
257	lettuce	0.2	1.3	21
258	radishes	0.09	1.34	9
259	red cabbage	0.14	2.76	18
260	asparagus	0.1	1.43	12
261	soybean sprouts	1.2	4.68	52

262	celery	0.13	1.37	11
267	cucumber with slices	0.14	1.3	9
270	corn (on a cob)	1.5	10.4	67
273	arugula	0.1	1.2	25
274	spinach	0.3	0.55	17
275	tomatoes	0.2	2.47	16
280	cherries	0.3	13.3	63
281	grapes	0.3	15.6	71
283	avocado	23.5	0.4	217
285	pineapple	0.08	7.1	32
325	fruit salad	0.3	11.6	53
334	carrots	0.2	5.2	26
364	green beans	0.1	4.7	27
365	orange	0.14	6.62	34
379	banana	0.18	21.39	95
407	blackberries	1	2.7	30
413	kiwis	0.55	9.37	53
417	pea pod	0	7	42
424	peas cooked	0.2	15.6	84
436	carambola / star fruit	0.3	6.7	31
466	green apple	0	11.43	52
467	raspberry	0.3	4.8	34
479	papaya	0.07	1.73	9
508	head of green lettuce	0.22	1.06	12
528	peaches	0.1	9.4	41

Appendix C: Nutrition content of the experimental foods

Below is a breakdown of the nutritional content for the experimental foods used in Study 2 and Study 4. Servings presented refers to the servings available for consumption during the taste test.

Food Item	Serving Size	Calories Per Serving	Servings Presented	Total Calories Presented
Lindt Milk Chocolate Bar	30 g	170	3.33	566.1
Lindt Milk Chocolate Truffles	13 g	80	7	560
Original Pringles	21 g	100	2	200
Sour Cream and Onion Pringles	21 g	110	2	220
Premium Unsalted Soda Crackers	12 g	50	2	100
Quaker Plain Rice Cakes	9 g	35	2	70

Appendix D: Taste rating sheet

Below is the taste rating sheet used in Study 2 and 4. One sheet was given per food item.

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