Investigating cortical buffering effects of acute exercise:

A cTBS study targeting the left dorsolateral prefrontal cortex

By

Felicia Manocchio

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I hereby declare that I am the sole author of this thesis. This is a true copy of the thesis, including any required final revisions, as accepted by my examiners. I understand that my thesis may be made electronically available to the public.

Abstract

Objective: The beneficial effects of both single-session bouts of aerobic exercise and therapeutic exercise interventions on the cortical regions associated with executive functions (i.e., prefrontal cortex (PFC)) and memory (i.e., the hippocampus) have been well documented. However, it remains unclear whether aerobic exercise can be used to offset temporary fluctuations in cortical activity. The current study sought to determine whether a single session of moderate intensity aerobic exercise can offset the attenuating effects of continuous theta burst stimulation (cTBS) targeting the dorsolateral prefrontal cortex (dlPFC).

Methods: Twenty-two healthy right-handed participants between 18-30 years completed a 20 minute session of light intensity (10% heart rate reserve (HRR)) and moderate intensity (50% HRR) exercise in a counterbalanced order. Following each exercise session, participants received active cTBS to the left dorsolateral prefrontal cortex (dlPFC). Changes in executive functions were quantified using a flanker paradigm employed at baseline, pre-cTBS and post-cTBS time points. In addition, EEG methodologies were used to measure changes in inhibitory control specific event-related potential components (i.e., P3 and N2) in response to the flanker task.

Results: Behavioural results from the Flanker task revealed a non-significant effect of exercise on cTBS in both light and moderate intensity conditions ($F(1,21)=0.219$, $p= 0.804$). Similarly, EEG data from the P3 ($F(2,40)= .789$, $p=.461$) and N2 ($F(2,40)= 1.819$, $p=.175$) ERP components revealed a non-significant effect of amplitude across time and condition. P3 latency data revealed a significant effect of time in the light intensity condition ($F(2,40)=4.313$, $p=.020$),

such that latency was faster following cTBS. Similarly, latency data within the N2 ERP component revealed a significant effect of time on congruent trials ($F(2,40)=17.206$, $p=0.00$) in the light intensity condition; N2 latency was faster following cTBS on congruent trials.

Conclusion: The current study revealed that light and moderate intensity exercise may provide a buffer to cTBS- induced attenuation of the dlPFC. This study provides empirical and theoretical implications on the potential for exercise to promote cognitive control.

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1.1 Background

Executive Function (EF) is a general term that refers to the "top down" control of behaviour, emotion and thought via higher cortical regions and modulating connections with reward centres (Baddeley, 1996; Miyake et al., 2000; Miyake & Friedman, 2012). Executive function is implicated in the modulation of aversive emotional states, goal directed behavior, and behavioral self-regulatory processes (Lowe, Hall, Staines, 2016 ;Ochsner, Ray, Cooper, et al., 2004; Hsu, Best, Davis, et al., 2017). Several everyday activities are dependent on optimal executive functioning, including planning and decision making (Miyake et al., 2000; Miyake & Friedman, 2012), dietary self- control (Guerrieri et al., 2007; Lowe, Hall, Staines, 2014), and adherance to medications (Hinkin et al., 2004).

While executive functions have trait like properties (i.e., they are relatively stable within individuals), state fluctuations in executive functions are also apparent. Numerous factors may lead to long-term impairment to executive control, including neuropsychiatric conditions (ie., Alzheimer's (Baudic, Barba, et al., 2006), Schizophrenia (Weisbrog, Kiefer, Marzinzik, & Spitzer, 2000) autism (Happe, Booth, Charlton, Hughes, 2006), ADHD (Barkley, Edwards, Laneri, Fletcher, Metevia, 2001), prefrontal brain lesions (Rossi, Pessoa, Desimone, Ungerleider, 2008) and age related decline (O'Sullivan, Jones, Summers, 2001). Additionally, natural modulators (i.e., sleep deprivation, acute stress, alcohol intoxication) have been demonstrated to impact EF. (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; Chan, Chen, Cheung, et al, 2006).

Such flucations in EF are of concern as impairments in EF may result in poor academic performance, difficulties attaining employment, suboptimal planning and reasoning, and

difficulty forming and maintaining social relationships (Chan, Shum, Toulopoulou. & Chen, 2008; Goel ,Grafman, Tajik, Gana, & Danto, 1997; Chan, Chen, Cheung, Chen, & Cheung, 2006). In addition, attenuation of EF can impact individual health and well-being, as such fluctuations may increase the likelihood individuals will overconsume, and partake in risky behaviours (Lowe, Staines, Hall, 2017; Romer, Betancourt, et al, 2009). Considering the importance of optimal EF in daily living, and the commonality of EF disrupters, determining methods to support and maintain optimal cognitive functioning is essential.

1.2 Executive Functions

EF encompasses several primary subcomponents, including most centrally, behavioural inhibition, working memory and task switching. These core elements are thought to enable more complex forms of cognitive operations such as planning, decision making, and self-regulation. Of these subcomponents, behavioural inhibition is considered the most pure indicator of EF as demonstrated by factor-analytic studies (i.e., correlation of 1.0) (Miyake et al., 2000; Miyake & Friedman, 2012).

The neurobiological mechanisms of EF have been studied quite extensively. Tasks of EF reliably elicit activation in several important nodes in the executive control network, including most broadly the prefrontal cortex (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). Lesions to the PFC have long been linked to impairment in executive control (Rossi, Pessoa, Desimone& Ungerleider, 2009); adults with left PFC lesions have demonstrated deficits in working memory, response inhibition, task switching, and sustained mental attention (Funderud, Due-Tonnessen, Meling, Lindren, 2012). It is possible to modulate EF through experimental (i.e., neuromodulation) and naturalistic attenuation (i.e., sleep deprivation, acute stress, alcohol intoxication) of the PFC (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,

alternative brain regions (ie., parietal lobe, inferior frontal junction) are involved in the process of executive control, most data suggest that the PFC is the predominant neuroanatomical region associated with executive control (Alvarez & Emory, 2006; Derfuss, Brass Neumann & Von Cramon, 2005). More specifically, the neuroanatomical region most central to EF, is the dorsolateral prefrontal cortex (dlPFC). Increased grey matter integrity in the dlPFC correlates with superior performance in specific facets of EF, namely inhibitory control and working memory (Weinsten, Voss, Prakash, Chaddock, et al., 2012; Eisenberg, Berman., 2010). FMRI studies have shown increased activation of the dlPFC during working memory tasks, and suggest that this key region aids in maintaining information through directing attention toward sensory stimuli (Curtis, D'Esposito, 2003). The dlPFC is suggested to display hemispheric lateralisation, contributing to distinct facets of working memory. Specifically, the left dlPFC is associated with increased activation during tasks involving verbal working memory, whereas the right dlPFC is associated with visual-spatial working memory (Smith, Jonides, Koeppe, 1996; Reuter-Lorenz, et al, 2000). Facets of EF depend highly on neuronal firing of the dlPFC, through expression of excitatory NMDA receptors in this region. Specifically,post mortem studies from patients with schizophrenia, bi-polar disorder and depression have detected decreased NMDA receptor expression, and perturbation of excitatory cells of the dlPFC, which has been postulated to explain the decrements to facets of EFin individuals with these conditions (Eisenberg, Berman, 2010; Mueller, Woodruff, 2004).

Given the importance of optimal executive functioning in everyday activities, it is of the utmost importance to determine methods of enhancing or optimizing executive control. Exercise has been studied extensively as a means for potentially enhancing brain health, and

specifically improving function of the systems that support executive control. A growing body of evidence has demonstrated that acute bouts of exercise and extended exercise training improve cognitive functioning (Chang, Labban, Gapin, Etnier, 2012; Smith, Jonides& et al., 1999; Daley, 2008). For instance, exercise training and acute bouts of moderate intensity aerobic exercise have been demonstrated to provide enhancements to both executive functions and underlying cortical substrates that support these processes (Pontifex,et al, 2009; Hillman, Erikson, 2008, Erikson 2014;).

A recent meta-analysis of 29 controlled intervention studies revealed a small but reliable effect of exercise training on cognitive outcomes, with especially reliable effects emerging for tasks with an executive control component (Smith, Blumenthal, Hoffman, et al., 2010; Krafft, Schwarz, Chi, et al., 2013). In at least one intervention study involving older adults with a one year follow up, findings suggested a structural benefit of exercise training as well: those in the active exercise condition evidenced structural increases in hippocampal volume, and reductions in age-related decline, together equivalent to offsetting 1 year of age related decline (Erickson, Voss, Prakash, et al., 2010). Regular exercise may facilitate neuroprotective effects, such as; neurogenesis in the hippocampus via increased blood flow, as well as survival of neural stem cells in animal models (Pereira, Huddleston, Sosunov, Brickman, et a, 2007).

Research on the impacts of exercise on cognitive function has also demonstrated increased activation to regions that support executive functions (i.e., PFC). For example, overweight children involved in an exercise intervention with 20 minutes of activity per day displayed increased activation of the PFC, and subsequent improvements on executive functions as well as math performance (Davis, Tomporowski, McDowell, et al, 2012; Hillman, Eriskson, Kramer, 2014).Acute bouts of exercise have displayed similar patterns of activation

in the dlPFC following a 20 minute session of moderate intensity exercise. Increases in activation of the PFC were also associated with improvements on cognitive task scores (50% HRR) (Yaginasawa, Dan, Tsuzuki, et al, 2010; McMorris, Sproule, Turner, Hale, 2011)

In addition to structural aspects, exercise has been shown to improve functional connectivity of the default mode network (DMN), which is associated with memory formation as well as working memory (Voss, Erikson, Prakash, et al, 2010, Hampson, Driesen, Skudlarski, et al, 2006). The strength of the DMN is also associated with improved performance on cognitive tasks, and may play an important role in supporting executive functioning (Reiter, Weiss, Alfini, & Nielson, 2017; Voss, Erikson, Prakash & etal, 2010). Such evidence suggest that the brain at rest is not truly resting, rather intrinsically connected (Greicius, et al, 2003; Beckman, et al, 2005).

1.3 Acute Effects

The acute effects of aerobic exercise have been investigated considerably, such that exercise-induced improvements in cognitive abilities have been observed following a single bout of aerobic exercise (Tomporowski., 2003; Brisswalter, Collardeau, Rene., 2012), with the largest effects observed 11-20 minutes post-exercise (Chang, Labban, Gapin, Etnier., 2012). Further, exercise-induced improvements in inhibitory control have been shown to last up toapproximately 50 minutes post exercise (Chang, Labban, Gapin, Etnier., 2012). Among the strongest effects of acute exercise on the brain are its effects on the PFC and associated cognitive functions (i.e., EF). In several studies, it has been demonstrated that an acute bout of moderate intensity exercise caused increased activation of the left dlPFC, and subsequently, improvements in behavioural task scores (Yanagisawa, Dan, Tsuzuki, et al., 2010; Chang, Liu, Yu, & Lee., 2012). Proposed mechanisms underlying activation enhancements include increased cerebral blood oxygenation, specifically to the left dlPFC.

Although many studies have reported increases in prefrontal oxygenation following moderate intensity exercise (Yaganisawa, Dan, Tsuzuki, et al, 2010; Endo, Matsukawa, et al, 2013) there is increasing evidence to suggest that light intensity exercise may also result in increased cerebral blood oxygenation (Byun, Hyodo, Suwabem et al, 2014). Additional neurophysiological mechanisms that may be responsible for these exercise enhancements include: expression of brain derived neurotrophic factors (BDNF), which is hypothesised to enhance the growth and survival of excitatory neuronal cells, thereby potentially improving synaptic plasticity and neural connectivity(Ferris, Williams, Shen, 2007; Barde, 2003).

Furthermore, glycogen supercompensation may also contribute to exercise related neurophysiological improvements through increased levels of basal glycogen in key brain regions involved in memory and cognitive control; such as the hippocampus and cortex (Matsui, Ishikawa, Ito, Okamoto, et al., 2012).

Electrophysiological methods such as electroencephalography (EEG) provide information about brain function during cognitive tasks, as measured by event related potential (ERP) components. The components of interest regarding executive function are, most centrally, P3 and N2 (Hillman, Castelli, & Buck, 2005; Hillman, Belopolsky, Snook, Kramer, & McAuley, 2004; Polich & Lardon, 1997; Pontifex, Hillman, & Polich, 2009). The P3 component is predominantly involved in attentional control, and central in detecting auditory and visual stimuli, with amplitudes representing the extent of attentional resources allocated to a task (larger amplitudes representing greater resource allocation).Further, latencies within the P3 component are considered to denote evaluation speed and stimulus classification speed, regardless of the response selected (shorter latencies accompany with faster processing speed) (Karch, Feuerecker, Leicht, et al., 2010 ;Polich, 2007; Duncan-Johnson, 1981). The P3 component is related to latero-frontal and temporo-parietal neuroanatomical regions, both of which are implicated in executive control (Karch, Feuerecker, Leicht, et al., 2010; Polich, 2007). The N2 component is associated with conflict monitoring and inhibitory control as well as decision-making, with the amplitude signifying the ability to respond to the conflicting stimuli (larger amplitude coincides with greater conflict resolution) (Schmitt, Munte, &Kutas, 2003). Potentials in the N2 component involve the medial-frontal and latero-frontal neuroanatomical regions (Karch, Feuerecker, Leicht, et al., 2010). Following exercise, the amplitude and latencies of the N2 component has been demonstrated to decrease, indicating

greater inhibitory control during cognitive tasks (Drollette, Scudder, &Raine., 2014). The P3 component characteristically demonstrates greater amplitudes and shorter latencies following exercise, indicating greater attentional control and faster processing speeds (Drollette, Scudder, &Raine., 2014; Hillman, Castelli, & Buck, 2005; Hillman, Belopolsky, Snook, Kramer, & McAuley, 2004; Polich & Lardon, 1997; Pontifex, Hillman, & Polich, 2009). Electrophysiological data following aerobic exercise suggests improvements in cognitive functioning through faster processing speeds and greater inhibitory and attentional control.

1.4 Theta Burst Stimulation

While there are several natural modulators of EF (i.e., sleep deprivation, acute stress, alcohol intoxication)(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), neuromodulation methods are increasingly popular approaches for experimentally manipulating PFC function in research paradigms (Cho & Strafella, 2009; Kimbrell, Wassermann, Repella, et al., 2000; Strafella, Puas, Barret, Dagher 2001; Knoch,Lorena, Gianotti, et al., 2006). Experimentally-induced manipulations provide specificity to target cortical regions, and are more easily induced compared with natural modulators. Among neuromodulation methods, transcranial magnetic stimulation (TMS) shows considerable promise. TMS involves passing eletrical current through a coil (typically a figure 8 coil) in varying frequencies over a cortical region. The electrical energy creates a magnetic field perpendicular to the coil which, in turn, induces a small electric current thatalters nerve cell polarization (Butler, 2007). rTMS—in contrast with single pulse TMS—can induce long term effects lasting from minutes to days or weeks following consecutive sessions (Oberman, 2014)

Continuous theta burst stimulation (cTBS) involves delivery of continuous trains of pulses in order to transiently inhibit a target region. cTBS over the prefrontal cortex can lead to temporary attenuation of function as demonstrated by performance on EF-dependent cognitive tasks (i.e., Stroop, Flanker) and decreased prefrontal oxygenation (i.e., fNIRS; Tupak, Dresler,

Badewien, et al, 2011). cTBS neuromodulation has increased in popularity due to its efficacy in suppressing target brain regions and in mimicking natural attentuators of executive control.

1.5 Current Study

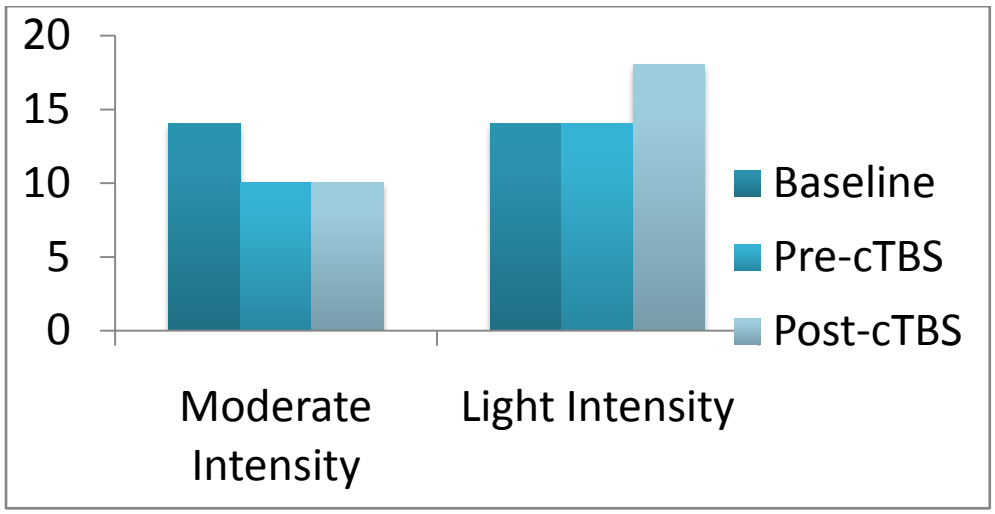
Recently, Lowe, Hall & Staines, 2016, demonstrated that aerobic exercise has the capacity to promote "cortical resilience" (i.e., the ability of brain tissue to rebound from temporary perturbations) in the dlPFC. In this original study, participants received cTBS targeted to the left dlPFC followed by either moderate or light exercise; following moderate exercise, dlPFC function recovered at a faster rate compared with the mild exercise condition. Specifically, at the 40 minute post-stimulation point, 71% of the attenuation in Stroop performance was recovered in the moderate exercise group, but only 4% in the mild exercise control group. These results have important implications on the recovery effects of exercise on the brain, and supports therapeutic approaches to improving cognitive function.

One question that remains unclear is whether a single session of exercise can offset cTBS- induced mitigation to inhibitory control. The application of cTBS induces temporary fluctuations in cortical excitability for up to 50 minutes following stimulation (Huang, et al, 2005). Currently, there is evidence to suggest that a single bout of moderate intensity exercise can promote cortical resilience in the prefrontal cortex (Lowe, Hall, Staines, 2017) as well as the motor cortex(Singh, Duncan, Staines, 2016). However the notion of whether exercise can act as a buffer (i.e., to reduce the attenuating effect of cTBS) for regions that support executive control (i.e., dlPFC) has been largely unexplored.

The overall purpose of the current study was to test the perturbation-buffering potential of exercise in relation to cTBS. It was hypothesized that moderate intensity exercise would

reduce cTBS-induced attenuation of dlPFC function, compared to light intensity exercise. It was further hypothesized that such attenuation would be evidenced on behavioral (i.e., task performance) and electrophysiological (i.e., ERP components, P3 and N2) indicators of executive control.

Figure 1.1. Hypothesized Results of Mean Flanker Interference Scores



1.6 Methods

A sample of 22 students were recruited to participate in this study using an online recruitment system (i.e.,SONA) and recruitment posters on campus; ages ranged from 18-30 years(*M*=21.83).Participants were right-handed individuals free of any neurological conditions and naïve to TMS. In exchange for their participation they received $20 in gift cards. This study was reviewed and approved for ethics clearance through the University of Waterloo Research Ethics Committee.

Before participation, participants were screened for any neurological or neuropsychiatric conditions that could have harmful effects or interfere with cTBS and aerobic exercise. Participants were excluded from the study if they had a) been diagnosed with a neurological or psychiatric condition (i.e., epilepsy, depression, anxiety), b) being treated with any psychiatric medications; c) had a family history of epilepsy or hearing loss; d) history of head trauma (i.e., concussion); e) experienced chronic headaches or migraines; f) has metal in the cranium and/or any implanted electronic or medical devices (i.e., electronic pacemaker, implanted medication pump); g) were pregnant; h) answered "yes" to any of the questions of the Physical Activity Readiness Questionnaire.

1.7 Procedure

This study was a within-subjects study design, in which participants performed both moderate intensity and light intensity exercise on separate occasions. The order of the light and moderate intensity exercise sessions was counterbalanced across participants. Participants were to wait a minimum ofapproximately 1 week between the first and second session to avoid any potential carry over effects of cTBS. Session one and two were identical, with the exception that a demographic survey was added at the end of the second session.

Prior to participation in the study, participants were asked to wear appropriate exercise apparel (i.e., running shoes) and were given a bottle of water during each exercise session. Upon beginning the study, they were fitted with an EEG cap and EMG electrodes were placed on the right *abductor pollicis brevis*(APB) muscle which acts as an abductor of the thumb. Single pulse TMS was then deliveredover the motor cortex, to stimulate action potential of the APB muscle to determine resting motor threshold (i.e., to guide cTBS stimulation intensity). The resting motor threshold was determined as being the stimulation intensity that yielded five consecutive motor evoked potentials (MEP) at 50mv or greater. Once the threshold was determined, a 64-channel cap was fitted. Baseline Flanker was then obtained. Following the baseline cognitive tasks, each participant completed one session of either light intensity or moderate- intensity exercise in a counterbalanced order. Light intensity exercise was calculated as 10% of heart rate reserve; 50% heart rate reserved was the target for moderate intensity exercise. Heart rate reserve was determined using the Karvonen formula (maximum heart rate – resting heart rate X percent intensity) (Karvonen, Kentala, Mustala, 1957). Light intensity heart rate reserve was chosen as 10% to allow participants to walk as slowly as possible while still

maintaining movement. Moderate intensity heart rate reserved was selected as 50% as to allow participants to walk at a fast pace without running. According to the meta analysis by Chang, Labban, et al, 2012, exercise with an intensity of less than 50% heart rate reserve did not results in improvements on cognitive task scores, whereas exercise performed above 50% heart rate reserve.Each exercise bout was comprised of walking on a treadmill for 20 minutes, including warm-up, and wore a Polar heart rate monitor around the chest to measure heart rate during exercise. All participants reported their rated perceived exertion (RPE) 5, 10, 15 and 20 min during exercise. Following exercise, participants had a 10 minute seated rest period, during which they completed the mood questionnaire. After the mood questionnaire, participants completed the flanker task. Participants then received active cTBS to the left DLPFC in both sessions. Following cTBS, the mood questionnaire was completed, as well as the flanker and frontal asymmetry task. Following the end of the second session, participants were asked to complete a demographics survey, which reported food habits, demographics, and exercise habits.

The EriksenFlanker task is used as a behavioral measure of initial perturbation effects. This task involves a sequence of 7 letters (H and S) in either a congruent or incongruent manner. The congruent sequence consists of a target letter that matches the flankers (i.e., HHH**H**HHH), and the incongruent stimulus would consist of the target letter being different from the flankers (i.e., HHH**S**HHH). The participant is required to press the letter on the keyboard that corresponds to the letter in the middle of the sequence. Reaction times are recorded for both congruent and incongruent trials and are compared to determine possible interference in response time (Eriksen, Eriksen, 1974). The Flanker task is administered before exercise, after exercise and

after active cTBS. During the Flanker tasks, EEG data were also recorded to provide more sensitive neural activity, which may help to explain behavioral results. The EEG components of interest are P3 and N2. The EEG electrodes that were used are the electrodes from FP1, FP2, FPz, Fz, F3, F4, FCz, Cz, CPz, Pz. Specifically, the P3 ERP component is considered to be maximal at Cz, CPz, and Pz, whereas the N2 ERP component is maximal at sites FPz, Fz, and FCz. FP1 and FP2 were selected to control for eye blinks and F3 and F4 were selected as they guide the anatomical location of the dlPFC.

1.71 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). Consistent with Lowe et al. (2016), active stimulation was applied to the dlPFC using neuronavigation software system coupled with a frameless stereotaxic system (Brainsight TMS, Rogue Research, Montreal, Canada); an infrared camera and reflective markers placed on the participant's head and TMS coil were used to guide coil placement in relation to an aggregate structural MRI image (from participants of similar age and demographics). Stimulation intensity was set at 80% resting motor threshold (RMT). 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, assessed using EMG. Another commonly used procedure for defining stimulation intensity is active motor threshold (AMT), which requires a slight muscular contraction of 20% of maximal strength (Groppa, Oliviero, Eisen, et, al., 2012).For active stimulation the figure 8 coil head was held at a 90˚angle from the mid-sagittal line with its center positioned over F3 as the landmark for the dlPFC. A reference MRI brain scan was used for neuronavigation of the coil over the F3 site. Continuous TBS 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).

1.8 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 10sites [FP1, FP2, FPz, Fz, F3, F4,FCz, Cz, CPz, Pz] placed according to the International 10-20 system (Chatrian, Lettich, & Nelson, 1985). All channel recordings had impedance values below 5kΩ, and impedance was monitored before and after cTBS and exercise.

Data was analyzed by re-referencing offline to the bilateral mastoids (M1, M2). For dependent measures, trials were visually inspected and epochs with movement and muscle artifacts wereremoved and excluded from analyses. ERP stimuli were averaged relative to a 100 ms pre-stimulus baseline for each flanker [incongruent, congruent]. Data for all components was extracted from electrode sites Fz, FCz, CZ, and Pz. Flanker data was separated into condition-specific [congruent, incongruent] epochs of 100 ms before and 800 ms after stimulus onset. Stimulus-locked amplitude and latency measures for each ERP component was 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 600ms). Amplitudes and latencies for the N2 component were measured from electrode sites Fz, FCz, and Cz, and were averaged together to create a frontocentral N2 cluster. The P3b component were measured from central parietal sitesCz, CPz, and Pz, and were averaged together to create

a central parietal P3b cluster. All offline analyses were performed using NeuroScan 4.5 software.

SPSS (version 22;IBM Corp, Armonk, NY) was used to conduct all statistical analyses. Performance accuracy was determined by calculating interference scores, which was measured as the reaction time data from congruent trials minus incongruent trials. Only the correct trials were used to calculate interference scores. Baseline Flanker interference scores were not normally distributed, therefore interference scores for all time points were subject to a square root transformation. A paired-sample *t* test was used to assess square root transformed baseline differences.

The cTBS effects on Flanker task performance were assessed using a repeated 2 x 3 factor analysis of variance. Time (Baseline, pre-stimulation and post-stimulation) and exercise condition (light and moderate intensity) were assessed as within subject factors. Differences in cTBS stimulation intensities were measured using a paired-sample *t* test. Additional descriptive analyses were performed on interference scores pre and post cTBS normalized to condition baselines. Finally, when using EEG components as outcome variables (P3+N2 latencies and amplitudes), identical procedures for testing group differences were followed as per the above procedures pertaining to interference scores.

1.9 Results

Baseline Comparability of Conditions:

Flanker interference scores (Congruent scores minus incongruent scores) were not normally distributed, therefore these values were subjected to a square root transformation in order to improve distributional characteristics. All subsequent analyses make use of these transformed variables. No significant differences in baseline interference scores were observed ($t(21) = 1.838$, $p = 0.080$, 95% CI= -1.167 to 1.892), indicating comparable baseline performance between minimum (M= 6.58, SE= 0.308) and moderate (M= 5.70, SE= 0.361) exercise conditions. No significant differences in cTBS stimulation intensities ($t(20) = -0.157$, $p = 0.877$, 95% CI= -2.042 to 1.757) were observed between exercise conditions using raw values.

1.91Cortical Buffering Effects

Performance accuracy, reaction times on incongruent and congruent trials and flanker interference scores as a function exercise condition (light or moderate intensity exercise) and time (pre-stimulation, post-exercise, post CTBS) are presented in Table 1. Results from the 3 [baseline, pre-cTBS, post-cTBS] by 2 [moderate, light intensity] by 2 [session order] repeated measures ANOVA indicated that there were no significant interactions between session order and exercise condition ($F(1,21) = 0.951$, $p = 0.341$), session order and time ($F(1,21) = 0.000$, $p = 0.986$), and no significant order by exercise condition by time interaction ($F(1,21) = 0.532$, $p = 0.474$). All subsequent analyses were conducted with a reduced model, removing the order variable.

The primary analyses revealed a main effect of exercise condition ($F(1,21) = 7.715$, $p = 0.011$,), such that across time points [baseline, pre-cTBS, post-cTBS] exercise interference scores were significantly lower in the moderate intensity condition (M=12.15, SE= 2.35), compared to minimum intensity condition (M= 23.96, SE= 3.04). However, the main effect of time ($F(1,21) = 0.219$, $p = 0.804$) was not significant. Likewise, the exercise condition [moderate, very light intensity] by time [baseline, pre-cTBS, post-cTBS] interaction was not significant ($F(1,21) = 1.503$, $p = 0.234$), indicating that the effect of cTBS on interference scores from pre to post stimulation did not differ by group. [1]

[1]In order to explore the findings correcting for baseline differences between conditions, a secondary analysis was performed

The analyses based on baseline-normalized data should be interpreted with caution however, given that the baseline levels of the two exercise conditions were highly divergent. Specifically, the normalized value of the minimum condition may have been abnormally high or the moderate condition abnormally low, producing a regression to the mean effect in either or both conditions. Normalizing based on an invalid baseline could produce difficult to interpret results. The present analyses are therefore offered for descriptive purposes only.

Table1. 1 Mean (SE) Baseline, pre-cTBS and Post-cTBS Flanker Interference Scores Across Exercise Conditions

Moderate Intensity			Minimum Intensity		
Baseline	Pre-cTBS	Post-cTBS	Baseline	Pre-cTBS	Post-cTBS
15.221 (4.253)	12.153 (2.345	15.827 (2.348)	25.388 (4.298)	23.963 (3.035)	19.221 (3.374)

Figure 1.2 Mean (SE) square root transformed pre- stimulation and post-stimulation Flanker interference scores (in milliseconds) across exercise conditions.

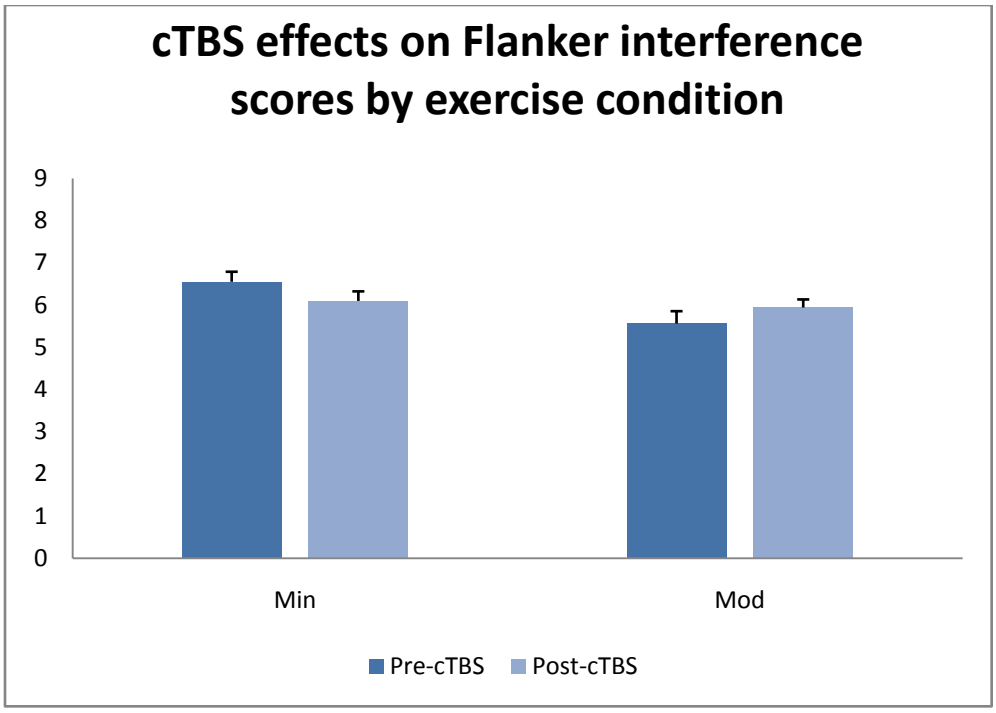
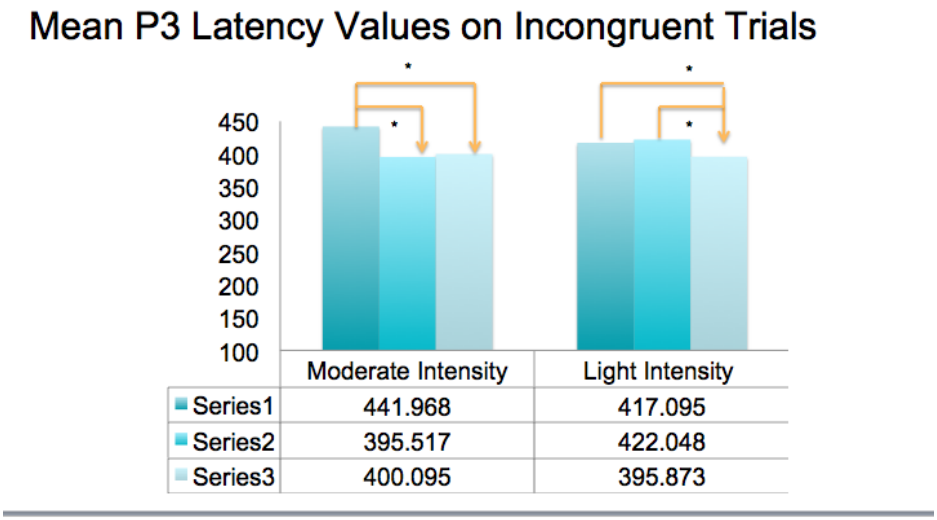

cTBS effects on Flanker interference scores by exercise condition
9
8
7
6
5
4
3
2
1
0
Min
Mod
Pre-cTBS
Post-cTBS

Figure 1.3Mean P3 latency values on Incongruent Trials



1.92 ERP Results

Table 1.2 Mean Amplitude and Latency Values (SE) for P3 ERP Component

	Moderate Intensity			Minimum Intensity		
	Baseline	Pre-cTBS	Post-cTBS	Baseline	Pre-cTBS	Post-cTBS
P3 Congruent Amplitude	5.514 (3.576)	5.941 (3.626)	6.509 (4.391)	6.613 (4.822)	7.290 (4.537)	6.482 (4.720)
P3 Congruent Latency	413.302 (51.150)	393.143 (50.995)	414.270 (71.878)	402.587 (48.509)	392.825 (59.705)	381.444 (47.005)
P3 Incongruent Amplitude	5.860 (3.453)	6.122 (4.433)	6.392 (3.841)	5.889 (3.984)	6.736 (3.819)	6.436 (4.289)
P3 Incongruent Latency	441.968 (67.072)	395.517 (53.302)	400.095 (71.878)	417.095 (50.394)	422.048 (72.020)	395.873 (59.342)

Table 1.3 Mean Amplitude and Latency Values (SE) for N2 ERP Component

	Moderate Intensity			Minimum Intensity		
	Baseline	Pre-cTBS	Post-cTBS	Baseline	Pre-cTBS	Post-cTBS
N2 Congruent Amplitude	-1.321 (1.638)	-2.156 (2.257)	-1.860 (2.321)	-2.329 (2.205)	-3.145 (1.826)	-2.002 (1.471)
N2 Congruent Latency	158.746 (63.469)	158.222 (54.928)	160.810 (69.818)	162.000 (69.139)	168.556 (63.495)	111.459 (45.088)
N2 Incongruent Amplitude	-2.1081 (1.920)	-2.056 (1.530)	-1.913 (1.478)	-2.417 (1.859)	-3.089 (2.261)	2.548 (21.956)
N2 Incongruent Latency	179.492 (71.064)	175.571 (60.985)	164.603 (75.045)	170.413 (64.187)	185.667 (73.052)	168.476 (69.419)

Overall P3 amplitude effects

Examination into the amplitude effects of the P3 ERP component indicated that the main effects of time ($F(2,40)=.417$, $p=.662$), exercise condition ($F(1,20)=.295$, $p=.593$), and congruency ($F(1,20)=.310$, $p=.584$) were not significant. In addition, the time by exercise interaction ($F(2,40)= .789$, p=.461), time by congruency ($F(2, 40)=0.31$, $p=.970$) and exercise by congruency ($F(1,20)=1.78$, $p=.544$) interactions were not significant. Further, the 3 way interaction of time, exercise and congruency ($F(2,40)=.618$, $p=.544$) was not significant.

Moderate Intensity condition P3 amplitude effects

Results from the moderate intensity exercise condition indicated that the main effect of time ($F(2,30)=.468$, $p=.630$), and congruency ($F(1,20)=1.34$, $p=.718$) were not significant. Further, no significant interaction of time and congruency ($F(2,40)$, $p=.872$) was apparent.

Light Intensity condition P3 amplitude effects

Results from the light intensity exercise condition indicated that the main effects of time ($F(2,40)=.562$, $p=.574$) and congruency ($F(1,20)=1.834$, $p=.191$) were not significant. The interaction of time and congruency was also not significant ($F(2,40)=1.02$, $p=.370$).

Overall P3 latency effects

Examination into the latency effects revealed a significant main effect of time ($F(2,40)=3.825$, $p=.031$). The main effects of exercise condition ($F(1,20)=.589$, $p=.452$) and congruency were not significant ($F(1,20)=.2.104$, $p=.162$). This was qualified by a significant time by exercise condition interaction ($F(2,40)=4.313$, $p=.020$). The time by congruency ($F(2,40)=1.414$, $p=.255$) and exercise by congruency ($F(1,20)=1.014$, $p=.326$) were not significant. In addition

the three way (time by exercise condition by congruency) interaction was not significant ($F(2,40)=2.375$, $p=.106$).

Moderate intensity condition P3 latency effects

Follow up 2 by 2 (time by congruency) ANOVAs revealed a significant main effect of time ($F(2,40)=3.510$, $p=.039$) in the moderate exercise condition. The main effect of congruency ($F(1, 20)=.251$, $p=.622$) and the time by congruency interaction ($F(2,40)=2.270$, $p=.116$) were not significant. Across congruency condition (congruent and incongruent trials), the latency of the P3 component significantly decreased ($p=.018$) from baseline ($M=427.635$; $SE=10.363$) following moderate intensity exercise ($M=.394.57$; $SE=8.616$). There was no change in the latency ($p=.307$) from pre-cTBS to post-cTBS ($M=407.183$; $SE=10.694$). In addition, the post-cTBS latency was not significantly different from baseline levels ($p=.126$).

Light intensity condition P3 latency effects

Similar effects are apparent in the light intensity exercise condition, such that a significant main effect of time was observed ($F(2,40)=5.667$, $p=.007$). Across congruency, no significant differences in the latency of the P3 component between baseline ($M=409.841$; $SE=8.652$) and post-exercise ($M=407.437$; SE=12.434) was observed ($p=.704$). However, the post-cTBS latency ($M=388.659$) was significantly faster than post-exercise ($p=.013$) and baseline ($p=.010$). In addition, a trend towards significance was apparent for the main effect of congruency ($F(1,20)=3.258$, $p=.086$), indicating that across time points the latency for congruent trials ($M=392.286$; $SE=9.428$) was faster than incongruent trials ($M=411.672$; $SE=12.390$). The congruency by time interaction was not significant ($F(2,40)=.788$, $p=.462$).

Overall N2 amplitude effects

Examination into the amplitude effects of the N2 ERP component indicated that the main effects of time ($F(2,40)=.1.467$, $p=.243$), exercise condition ($F(1,20)=.026$, $p=.874$), and congruency ($F(1,20)=.583$, $p=.454$) were not significant. In addition, the time by exercise interaction ($F(2,40)= 1.819$, $p=.175$), time by congruency ($F(2,40)=1. 063$, $p=.355$) and exercise by congruency ($F(1,20)=1.433$, $p=.207$) were not significant. Further, the 3 way interaction of time, exercise and congruency ($F(2,40)=.774$, $p=.468$) was not significant

Moderate intensity condition N2 amplitude effects

Results from the moderate intensity exercise condition indicated that the main effect of time ($F(2,30)=.451$, $p=.640$), and congruency ($F(1,20)=.804$, $p=.381$) were not significant. Further, there was no significant interaction of time and congruency ($F(2,40)=1.037$ $p=.364$).

Light intensity condition N2 amplitude effects

Results from the light intensity exercise condition indicated that the main effects of time ($F(2,40)=1.666$, $p=.202$) and congruency ($F(1,20)=.962$, $p=.338$) were not significant. The interaction of time and congruency was also not significant ($F(2,40)=.911$, $p=.410$).

Overall N2 latency effects

Overall latency effects showed a significant main effect of time ($F(2,40)=4.993$, $p=.015$), and congruency ($F(1,20)=8.905$, $p=.007$). The main effects of exercise condition ($F(1,20)=.299$, $p=.591$) were not significant. This was qualified by a significant time by exercise condition interaction ($F(2,40)=3.698$, $p=.036$). The time by congruency ($F(2,40)=1.458$, $p=.245$) and exercise by congruency ($F(1,20)=1.505$, $p=.234$) were not significant. In addition, the three way

(time by exercise condition by congruency) interaction was significant (F(2,40)=3.628, p=.049).

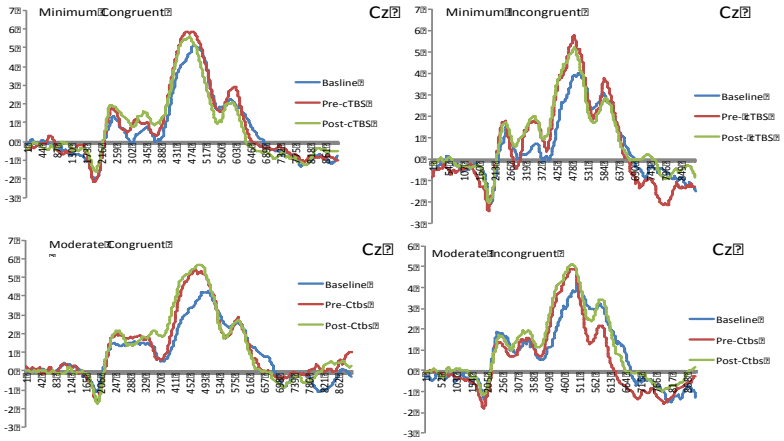
Moderate intensity condition N2 latency effects

Results from the moderate intensity condition revealed a non- significant main effect of time (F(2,40)=.243, p=.786) and congruency (F(1,20)=1.619, p=.218). The time by congruency interaction (F(2,40)=.658, p=.523) were not significant.

Light intensity condition N2 latency effects

Results from the minimum intensity condition revealed significant effects of time (F(2,40)=8.866, p=.002), and congruency (F(2,40)=20.350, p=.000). Further, the time by congruency interaction was significant (F(2,40)=4.665, p=.016). Results from incongruent trials were not significant across time (F(2,40)=.729, p=.489). However, there was a significant effect of time on congruent trials (F(2,40)=17.206, p=0.00). Pairwise comparisons reveal a significant change (p=0.00) from baseline (M=162.; SE= 69.139), to post cTBS (M=111.459; SE=45.088) and pre-cTBS (M=168.556; SE=63.495) to post-cTBS (p=0.00), however, there was no significant change from baseline to pre c-TBS (p= 0.600).

Figure 1.4 Waveforms depicting N2 and P3 ERP component latency and amplitude for incongruent and congruent trials across exercise conditions.



1.10 Discussion

The current study sought to assess the capacity of aerobic exercise to offset (i.e., act as a buffer against) the temporary attenuating effects of cTBS targeting the left dlPFC, an important brain region involved in the executive control network. The Flanker task was used to quantify inhibitory control prior to receiving cTBS, and possible buffering effects following cTBS. Based on findings from Lowe, Staines, & Hall, 2016, light intensity exercise served as the control condition and moderate intensity exercise as the experimental condition. A significant increase in flanker task performance was apparent following moderate intensity exercise. This finding is consistent with several other studies reporting improvements in executive functioning following an acute bout of aerobic activity (Tomporowski, 2003; Lowe, Staines, & Hall, 2016). Further, no changes in task performance were apparent following cTBS in both the moderate and light intensity exercise conditions. While this effect was unexpected, it may suggestthat both light and moderate intensity exercise may offset the temporary cTBS induced attenuation to cognitive control, assuming that cTBS was effective. Additionally, there were no apparent changes in N2 and P3 amplitude prior to and following cTBS. However, a latency effect was apparent in the P3 ERP component following cTBS in the light intensity exercise condition. Furthermore, a latency effect in the N2 ERP component was apparent following cTBS in the light exercise condition on congruent trials.

The results from the current study add to the existing literature by suggesting that an acute bout of moderate and light intensity exercise can act as a buffer against temporary fluctuations in executive control in response to perturbations. This expands on the findings by Lowe, Staines & Hall (2016), which demonstrate that exercise following perturbation can speed recovery. Although the current study employed an experimental perturbation (specifically,

cTBS), there are many naturally occurring perturbations in everyday life, including lack ofsleep, mood fluctuations, and acute stress (Porcelli& Delgado, 2009; Shields et al, 2016; Fossati, et al, 2002; Nillson, et al, 2005; Tucker, et al, 2010). If generalizable to these types of everyday perturbations, the current findings suggest the possibility that exercise may serve to provide protection against momentary cognitive perturbations in everyday living. Such findings may have implications for clinical intervention strategies as well. For instance, engagement with acute bouts of exercise may provide an optimal intervention or preventative strategy for people who are chronically subject to exposure to lifestyle perturbations mentioned previously (e.g., shift workers, hospital employees). Additionally, given that buffering effects appear to manifest in relation to both moderate and light intensity exercise, the effects of this intervention could extend to individuals who may not be physically able to perform moderate intensity exercise, such as older adults.

Other candidate explanations for the current results involve the theory of boredom and its impact on performance on tasks involving attentional control. Studies have suggested that boredom may lead to negative effects on cognition as well as affect (Hill, Perkins, 1985). Tasks that involve attentional control rely on the employment of the executive control network as these tasks require mental effort and sustained attention (Eastwood,Frischen, Fenske, Smilek, 2012; Thackray, Bailey, Touchstone,1997; Scerbo, 1998). Furthermore, elevated levels of boredom and fatigue are correlated with increased variability on performance speed on repetitive computer tasks, lower levels of effectiveness, and significantly lower grade point averages(Pan, Shell, Schleifer, 2009; Drory, 1982; Mann, Robinson, 2009).

Flanker interference scores in the light intensity condition were considerably higher compared with the moderate intensity condition at both baseline and following light intensity

exercise. Following cTBS, interference scores in the minimum intensity condition appeared to improve, which could be explained due to the novelty of the cTBS experience. Studies have indicated that novel stimuli elicit elevated cerebral blood flow to regions that support executive control, including the prefrontal cortex and the hippocampus (Tulving, Markowitsch, Kapur, Habib, et al, 1994). Further, it seems that neurons of the dlPFC display greater response to novel stimuli compared with familiar stimuli (Duzel, Habib, Guderie, Heinze, 2004). This may present the possibility of a novel cTBS experience to have washed away the boredom effects experienced during the lengthy and non- stimulating light intensity protocol. Further studies would be required in order to more fully investigate this possibility however.

Neuroelectric indices of cognitive processes have been shown to be more sensitive to fluctuations in cognitive control than behavioral measures (i.e., cognitive task performance; see Hillman, et al, 2003 for an example). The P3 latency is thought to represent the stimulus evaluation time, and classification speed (Duncan- Johnson, 1981; Polich, 2007), whereas the P3 amplitude tends to represent the amount of attentional resources allocated to a particular task (Wickens, 1983). Consistent with the current findings, P3 latencies in both young and older adults have been shown to be shorter following both light and moderate intensity exercise (Kamijo, 2009, Kamijo, 2007). The current study found that P3 latency was significantly shorter following moderate intensity exercise, and did not change following cTBS. Results from the light intensity condition suggest no changes to P3 latency following exercise, however shorter latencies were observed following cTBS, potentially indicating a beneficial role of light intensity exercise on processing speed. Furthermore, both light and moderate intensity exercise did not incur changes to P3 and N2 amplitudes. Following cTBS, P3 and N2 amplitudes were not affected in either exercise condition. The N2 ERP component is associated with response

inhibition and tasks involving conflicting stimuli (i.e, Flanker task, Jodo, Kayama, 1991). The current N2 ERP results revealed shorter latencies only on congruent trials in the light intensity condition, which may suggest possible practice effects (McEvoy, Smith, Gevins, 1998). The current findings add to the well-documented effects of exercise by demonstrating that both light and moderate intensity exercise may reduce the experimentally modulated perturbation induced in the laboratory (Chang, Labban, Gapin&Etnier, 2012; Hillman, Erikson & Kramer, 2008; Lowe, Staines & Hall, 2017)**.** The buffering effects of exercise have been largely unexplored, and may differ from other proposed mechanisms.

Although the present study may not fully explain the mechanisms underlying the effects of exercise on cTBS, alterations in neuronal activity through increased cerebral blood oxygenation may be a potential mediator. The inhibitory effects of cTBS have been attributed to reduced prefrontal oxygenation at the ipsilateral (Cho, et al, 2012) and contralateral sites of stimulation (Mochizuki, et al, 2007) and reduced synaptic activity in the specific brain regions of interest (Butler, 2007). Additionally, previous literature has demonstrated that cTBS attenuation may be associated with inhibited nerve transmission through elevated levels of GABA (Stagg, et al, 2009). Given that exercise has been demonstrated to increase cerebral blood oxygenation, it is possible that both light and moderate intensity exercise were sufficient to offset cTBS- induced attenuation to the dlPFC. Previous studies have indicated that light intensity walking does indeed increase cerebral blood oxygenation to the PFC (Holtzer, et al, 2011; Suzuki, et al, 2004). It is also possible that elevated levels of certain neurotransmitters such as norepinephrine, epinephrine, serotonin, and dopamine induced a buffering effect, as they have been demonstrated to be elevated following acute bouts of exercise. Further research is warranted to better determine the neurophysiological processes underlying cortical buffering.

Strengths in the present study include the use of a within-subject study design in an effort to minimize any inter-individual variability. Additionally, the use of cTBS as our neuromodulation protocol provided a safe and reliable method by which to investigate the buffering effects of exercise (Ko, Monchi, Ptito, et al, 2010; Tupak, Dresler, Badewien, et al, 2011) . Limitations of the present study include sampling a healthy university student population, who may not be as receptive to the effects of cTBS and/or exercise compared to an older adult sample (Dayan, et al, 2013; Kamijo, et al, 2009). It is also possible that experiences of natural modulators of executive functioning such as acute stress, sleep deprivation and alcohol consumption may have altered the observed effect size through impairment to inhibitory control (Verdejo-Garcia, Bechara, 2006; Shields, et al, 2016; Nilsson, et al, 2005). Finally, the lack of a non-exercise control group served as a limitation. Although both light and moderate intensity exercise appeared to demonstrate a potential buffering effect, this cannot be known definitively in the absence of a no-movement control condition. Without this, an alternative interpretation of the findings is that no cTBS effect emerged in either condition, which is possible given that not all studies show significant perturbation effects on executive function following cTBS (Lowe, Manocchio, Safati, Hall, 2018;Tupak, Dresler, Badewien, 2011). Future studies should aim to disentangle this issue.

The beneficial effects of acute exercise on cognitive functioning have been previously investigated, however, the current study was, to the best of our knowledge, the first to examine the buffering potential of acute exercise to attenuation of cognitive control. As such, further research examining the buffering effects of exercise is warranted to build on the current findings. Investigating the capacity of exercise to offset attenuation could be beneficial in alternate samples and target groups (e.g., older adults, shift workers). Additional research on the

buffering effect of exercise using natural modulators previously mentioned (sleep deprivation, alcohol consumption, acute stress) could provide a deeper understanding into how exercise could impact everyday stressors. Finally, subsequent studies using a no-movement control group could reveal important information regarding the role light intensity exercise plays in reducing attenuation to key areas involved in executive control.

1.11 Conclusion

The current study employed a cTBS protocol to temporarily down-regulate the dlPFC, involved in EF. Findings suggested that acute bouts of both light and moderate intensity exercise may provide a buffer to impairments in cognitive control. Specifically, no significant decrements to performance on the Flanker task were apparent through both behavioural and EEG measures,demonstrated through P3 and N2 ERP components. Findings from this study are noteworthy as it provides theoretical and experimental implications for the therapeutic potential of acute exercise to maintain and support optimal EF.

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