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LBNP reduces cerebral perfusion but does not impact executive function

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Abstract

A growing body of literature has demonstrated that a single bout of aerobic exercise and/or hypercapnic manipulations increase cerebral blood flow (CBF) and are linked to a transient (i.e., <60 min) post-intervention executive function (EF) benefit. However, there are no direct studies examining whether a transient decrease in CBF elicits a post-intervention EF decrement. Accordingly, my thesis employed 10-min single bout manipulations of -30 mmHg and -50 mmHg lower-body negative pressure (LBNP) to determine whether a transient reduction in CBF impacts EF. LBNP was applied as it renders sub-atmospheric pressure to the lower limbs and redistributes blood from the upper to lower compartments of the body. Results demonstrated that a reduction in CBF at both LBNP magnitudes; however, this did not result in a post-intervention EF decrement. Accordingly, my thesis demonstrates that an acute reduction in CBF does not negatively influence EF.

Keywords

Exercise

Cerebral blood flow

Transcranial Doppler ultrasound

Lower body negative pressure

Antipointing

Summary for Lay Audience

Executive function is a component of cognition and supports our ability to plan and implement actions essential to activities of daily living (e.g., making a pot of coffee). A single bout of aerobic or resistance exercise for as little as 10-min benefits executive function. One candidate mechanism for this benefit is an exercise-mediated increase in blood flow to the brain (i.e., cerebral blood flow). Although there is some evidence demonstrating that an increase in cerebral blood flow in healthy young adults is linked to an executive function benefit, it is unclear whether a brief reduction in cerebral blood imparts a post-intervention executive function impairment. The goal of my thesis was to address this issue via the use of a technique known as lower body negative pressure (LBNP). LBNP utilizes vacuum pressure (or negative pressure) applied to the lower limbs and results in an accumulation of blood in the lower extremities and thus reduces blood flow other regions of the body; that is, LBNP provides a safe and reliable means to decrease cerebral blood flow. The results from my study demonstrated that blood flow to the brain decreased during LBNP; however, this change did not impact a post-intervention assessment of executive function. Accordingly, my results suggest that a brief (i.e., 10-min) reduction in brain blood flow does not result in post-intervention executive function impairment.

Co-Authorship Statement

The author, under the supervision and mentorship of Dr. Matthew Heath, conducted the work in this master's thesis. With the guidance of Dr. Matthew Heath, I designed the experiments, recruited participants, collected, analyzed and interpreted data, and prepared the manuscripts. I received support from fellow lab members in recruiting participants and collection of data for Chapter Two. For this manuscript, James Van Riesen was the first author, and Mustafa Shirzad, Chloe Edgar, Dr. Benjamin Tari, and Dr. Matthew Heath served as co-authors in the manuscript version of the work.

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Chapter 1

1 Literature Review

The goal of my thesis was to determine whether an acute reduction in cerebral blood flow (CBF) transiently impairs executive function (EF). To address this issue, I employed lower body negative pressure (LBNP) to safely and reliably decrease CBF and examined EF prior to and immediately following the LBNP protocol via an EF countermanding task (i.e., antipointing). In developing my thesis, the below Literature Review outlines: (1) the distinct components and neural correlates of EF, (2) the antisaccade and antipointing tasks, (3) the relationship between exercise and EF (4) the mechanisms supporting a postexercise EF benefit, and (5) a general overview of the LBNP protocol. In turn, Chapter 2 provides the manuscript version of my thesis document.

1.1 Distinct Components and Neural Correlates of Executive Function

EF entails a constellation of higher-order cognitive processes supporting problem solving, future planning, reacting to stimuli and making informed decisions, and includes the core components of inhibitory control, working memory and cognitive flexibility (Diamond, 2013). Inhibitory control serves to suppress internal biases and other external environmental stimuli that interfere with goal-directed behaviors. In the absence of inhibitory control, behaviour is guided based on conditioned responses and without the ability to select a response based on an appropriate environmental context. If, for example, a hiker is bitten by a mosquito, the prepotent response would be to itch the bite to provide relief instead of focusing on their footing while walking. Failure to inhibit this automatic response may cause the hiker to look towards and subsequently scratch the mosquito bite, leading to attention being drawn away from the trail and the hiker potentially tripping. In turn, working memory supports the ability to manipulate and modify information (Diamond, 2013). For example, working memory is essential for a student completing mental arithmetic. The student must be able to remember the numbers provided while simultaneously manipulating those numbers to complete the final calculation. Last, cognitive flexibility supports set-shifting and “switching” between

tasks and supports the maintenance of multiple thoughts, ideas, and tasks and the ability to redirect our attentional resources between them (Diamond, 2013). For example, when working in a fast-food restaurant an employee must be able to switch between discrete tasks such as taking and order from a customer, entering that order into a cash register, and then preparing the meal.

An extensive body of lesion and neuroimaging work has reported that EF is supported by prefrontal cortical structures that include: (1) the dorsolateral prefrontal cortex (DLPFC), (2) orbitofrontal cortex (OFC), (3) ventromedial prefrontal cortex (vmPFC), and (4) anterior cingulate cortex (ACC) (Delgado et al., 2016; Royall et al., 2002). The DLPFC supports attention, planning, emotional regulation, sequencing, and effortful cognitive decisions (Forbes et al., 2014). The OFC is involved in motivational behaviour such as eating/drinking, and abstract behavioral reinforcers such as pain, taste, and smell (Rolls, 2004). In turn, the vmPFC supports emotional regulation and suppresses negative affect through amygdalar inhibition (Myers-Schulz & Koenigs, 2012). Last, the ACC supports conflict monitoring/resolution and modulates activity in downstream brain regions to adapt to incorrect behaviors (Bush et al., 2000). Notably, the DLPFC supports the top-down processes associated with each core component of EF (Diamond, 2013), and as such, my literature review below focuses on its role supporting inhibitory control, working memory and cognitive flexibility.

The Stroop task (Stroop 1935) is an exemplar paradigm used evaluate the inhibitory control component of EF and involves the presentation of a word wherein the meaning of the word and the colour in which the word is printed is congruent (standard task: i.e., the word "RED" printed in red ink) or incongruent (non-standard task: i.e., the word "RED" printed in blue ink). An extensive body of evidence has shown that reaction time (RT) and response errors are increased during incongruent compared to congruent Stroop trials (i.e., Stroop Interference Effect) and is a result attributed to the time-consuming EF demands of inhibiting a standard word-naming response in favour of a non-standard colour-naming response (for meta-analysis, see Macleod 1992). Neuroimaging and lesions studies have highlighted the DLPFC's role in facilitating response inhibition during the Stroop task. For example, Vendrell and colleagues (1995) recruited 32 patients

with prefrontal lesions as well as 32 age-, sex-, and education-matched controls and reported that individuals in the former group produced longer RTs and more errors during incongruent Stroop trials. Moreover, Milham and colleagues (2002) used functional magnetic resonance imaging (fMRI) to assess neural activity while young (i.e., age 21-27) and older (i.e., 60-75) adults completed the Stroop task. An age-related decrease in task-based DLPFC activity was observed in older adults and this was linked to longer RTs and increased errors during incongruent trials. Further, a recent meta-analysis investigating DLPFC activation during the Stroop task found that the task elicits "vast" increases in neuronal clusters housed within DLPFC (Huang et al., 2020). Accordingly, results evince the role the DLPFC plays in response inhibition, and more broadly EF.

Another task used to assess inhibitory control is the Flanker task (Eriksen & Eriksen, 1974). The task includes a central target surrounded by non-targets (i.e., flankers). A common central target for this task includes a directional arrow with flanking arrows that are directionally congruent (e.g., <<<<<) or incongruent (e.g., << > <<). The task requires participants to respond to the central target while ignoring the flankers. Extensive evidence has shown that incongruent trials produce longer RTs and less accurate responses than their congruent trial counterparts (for review see Riddrerinkof et al., 2021). It is thought that the incongruent stimuli interfere with participants' ability to process the goal-directed behavior (i.e., correctly indicating the direction of the target stimulus) and thus lengthens RT. Neuroimaging studies have demonstrated the involvement of the DLPFC during the Flanker task. For example, Zhu et al., (2009) investigated neural activity via fMRI in young (i.e., 20±3 years) and older (i.e., 74±6 years) adults and showed decreased DLPFC task-based activity in the latter group was linked to increased incongruent trial RTs. Moreover, lesion studies Geddes et al.'s (2014) lesion work reported that incongruent Flanker trial performance resulted in longer RTs for persons with unilateral DLPFC lesions compared to healthy controls. As such, convergent evidence demonstrates the DLPFC supports Flanker task performance, and thus, inhibitory control.

The n-back task (Kirchner, 1958) is an exemplar measure of the working memory component of EF (Jaeggi et al., 2010) and entails that a performer report whether a

current stimulus within a sequence matches a target from *n* steps earlier in the sequence. In this task, '*n*' represents the number of items from earlier in a sequence that is to be recalled and serves to manipulate task complexity. For example, a 3-back task requires that a participant recall whether a current stimulus matches one presented three items earlier in the sequence and results in longer RTs and less accurate responses than comparator 1- and 2-back tasks (Kirchner, 1958). Thus, the n-back task requires maintenance of the appropriate task goal in working memory. Yeung et al.'s (2021) functional near infrared spectroscopy (fNIRS) work examined changes in prefrontal cortex (PFC) activity between different n-back tasks. Thirty-nine healthy young adults completed a 0-back (i.e., a control condition wherein participants respond each time when a predetermined stimulus appeared) and 3-back task. Results showed that there were no changes to DLPFC activity during a 0-back task when compared to a resting control, whereas a task-dependent increase in DLPFC activity was observed during the 3-back condition and this was linked to increased RT. As well, Owen et al.'s (2004) meta-analysis reported that prefrontal cortex activity is heightened as a function of increasing n-back task complexity (i.e., increased prefrontal activation during the 3-back task than during the during the 2-back task). In the context of lesion work, Tsuchida and Fellows (2009) had a corpus of individuals with bilateral DLPFC lesions and healthy age-matched controls complete 1, 2, and 3-back tasks and observed longer RTs and increased errors in the former group and reported that between-group differences increased in relation to task complexity. Accordingly, evidence demonstrates that n-back task performance, and thus working memory, is supported – in part – via the DLPFC.

Cognitive flexibility employs inhibitory control and working memory and reflects the ability to adapt cognitive processes to novel stimuli based on present task-relevant goals (Cañas, 2006). One task used to assess cognitive flexibility is the Wisconsin Card Sorting Task (WCST) (Milner, 1964). In this task, participants are presented with cards displaying geometric shapes that vary in colour, shape and quantity. The goal of the task is to sort the cards based on colour, shape or quantity in relation to current task goals (e.g., sort all cards as a function of colour) with the sorting rule changed to reflect task difficultly (i.e., task difficulty increases in relation to the frequency of a "switch" in the sorting rule). As such, performance is determined via completion time and the total

number of errors with a higher number of errors reflecting diminished cognitive flexibility. In one study investigating the neural correlates of the WCST, Li et al. (2006) used fMRI to demonstrate an increase in task-based DLPFC activity in relation to the frequency of task-switching instructions; that is, when the task-switching frequency increased DLPFC was increased. Further, work by Arnett and colleagues (1994) assessed WCST performance between individuals with frontal lobe lesions (e.g., DLPFC) relative to individuals with non-frontal lesions and found that the former group produced longer completion times and more errors.

A second paradigm commonly used to assess cognitive flexibility is an AABB task-switching paradigm wherein participants alternate between different task-types after every second trial. For example, Allport et al. (1994) had participants alternate between word- (i.e., standard task) and colour-naming (i.e., non-standard task) variants of the Stroop task every second trial (i.e., AABB) and reported that a colour- to word-naming switch increased RT, whereas the converse switch did not influence performance. The authors proposed that the non-standard stimulus-response (SR) mapping of colour-naming engenders an executive task-set that persists inertially and proactively interferes with a subsequent standard response (i.e., task-set inertia hypothesis). In turn, the task-set inertia hypothesis contends that alternating from a standard to a non-standard response does not produce a 'switch-cost' because the former is planned independent of an executive task-set (for review see Monsell 2003; see also Wylie and Allport 2000). In support of the hypothesis, neuroimaging studies have shown an increased signal change in frontal executive regions including the DLPFC for task-switch compared to task-repeat trials – a result taken to reflect the persistent activation of a non-standard task-set (for meta-analysis see Derrfuss, et al. 2005; Weiler and Heath 2014). Hence, the DLPFC has shown to play a salient role in the cognitive flexibility component of EF.

1.2 Antisaccade and Antipointing Tasks

The previous section of this Literature Review discussed tasks used to assess specific core components of EF (i.e., inhibitory control, working memory, and cognitive flexibility). Here, I outline the neural correlates of the antisaccade and antipointing tasks as alternatives to more traditional measures of EF. Indeed, I note the benefit of the

antisaccade/antipointing tasks because they provide a basis to identify subtle EF changes independent of the non-EF processes associated with more traditional EF task such as language and colour processing (i.e., Stroop and WCST), perception-based shape identification (i.e., Flanker task, WCST) and numerical processing (i.e., n-back). Moreover, the antipointing task serves as the EF measure employed in Chapter 2.

The antisaccade task requires a goal-directed eye movement mirror-symmetrical to an exogenously presented target and results in longer RTs (Hallett, 1978), more directional errors (Fischer and Weber 1992) and less accurate and more variable endpoints (Dafoe et al., 2007; Gillen & Heath, 2014) than their prosaccade counterparts (i.e., saccade to veridical target location). The antisaccade behavioral 'costs' have been attributed to the two-component EF demands of inhibiting of a prepotent prosaccade (i.e., inhibitory control) and the 180º spatial transposition of a target's coordinates (i.e., vector inversion) (for review see, Munoz & Everling, 2004). An extensive literature involving human and non-human primates have reported that the production of a directionally correct antisaccade is associated with increased activity within the DLPFC (Desouza et al., 2003). Additionally, human neuroimaging and lesion studies, as well as non-human primate single-cell recording and transient cooling studies, demonstrate that directionally correct antisaccades are supported by a malleable task-set that maintains behavioral rules moment-by-moment (Everling & Johnston, 2013). As such, antisaccades are a top-down and EF task, supported by each core component of EF.

Antipointing is the limb-based corollary to the antisaccade task and requires that an individual point mirror-symmetrical to an exogenously presented target. A number of studies have shown that antipointing produces longer RTs, increased directional errors and endpoint variability than their propointing (i.e., point to veridical target location) counterparts (Heath et al., 2009; Maraj & Heath., 2010) and these costs have been attributed to the time-consuming and EF demands of the antipointing task. Moreover, neuroimaging and electroencephalographic work has shown that antipointing engages DLPFC regions that overlap with the antisaccade task (Connolly et al. 2000; Heath et al. 2011). In other words, antipointing engages the same EF networks as antisaccades. Moreover, the benefit of the antipointing task is that it can be employed without the need

for the expensive and often non-portable eye-tracking equipment requirements of the antisaccade task. For example, Tari and Heath (2019) examined whether an iPad® based antipointing paradigm is feasible for detecting subtle changes to EF following a single 20-min session of moderate intensity aerobic exercise. Results showed a reliable postexercise reduction in antipointing RTs and thus evince that antipoining provides the requisite resolution to detect exercise-based changes in EF.

1.3 Exercise and Executive Function

An extensive literature has reported that chronic aerobic and/or resistance exercise interventions benefit brain health and EF (for meta-analyses, see Colcombe & Kramer, 2003). Indeed, Colcombe et al.'s (2004) seminal investigation found that high-fit older adults showed improved Flanker task behavioural performance compared to low-fit older adults and that this benefit was linked to increased prefrontal cortex activity. Moreover, Colcombe et al. included an intervention study contrasting participants that completed a six-month progressive walking study (i.e., aerobic exercise group) with a stretching and toning group (i.e., control group). Results showed that the aerobic exercise group had improved post-intervention Flanker task performance that was linked to increased task-based activity in the prefrontal cortex. In turn, Ludyga et al (2018) examined Stroop task performance and event-related cortical activity via electroencephalography (EEG) before and after an exercise intervention (8/wk for 20-min). Results showed that chronic exercise enhanced inhibitory control as evidenced by improved Stroop task performance and was linked to an increased amplitude P300 waveform (i.e., a measure of context-updating and EF). In addition, Heath et al (2017) had participants in the prodromal stages of Alzheimer's disease complete a six-month exercise intervention that entailed group-based aerobic exercise classes (4/wk for 60-min) and evaluated pre- and post-intervention changes in EF via the antisaccade task. Results showed a marked post-intervention reduction in antisaccade RTs and a subsequent study showed that this benefit persisted at a six-month follow-up (Shellington et al. 2017).

In addition to chronic exercise, work has shown that a single bout of aerobic/resistance exercise benefits each core component of EF. In one example, (Sibley et al., 2006) had participants complete 20-min of self-paced moderate intensity exercise (i.e., between

'fairly light' and 'somewhat hard' on the Borg Rating of Perceived Exertion) and reported improved postexercise Stroop task performance in comparison to a non-exercise control group. In other words, results showed a postexercise benefit to the inhibitory control component of EF. Additionally, Kao and colleagues (2020) had 23 healthy young adults complete the n-back task following 20-min of aerobic exercise at 60-70% of maximum predicted heart rate (HR_{max}: i.e., 220 minus participant age) and following a non-exercise control condition. The authors observed that the exercise condition was associated with reduced RT variability and an increased amplitude P300 compared to the control condition and was a result interpreted to reflect improved working memory efficiency. Moreover, Bae and Masaki (2019) used a task-switching paradigm to examine the impact of a single bout of exercise on cognitive flexibility. Twenty-nine healthy young adults completed 30-min of aerobic exercise (i.e., treadmill exercise at 70% HR_{max}) and a same duration non-exercise control condition. Results showed improved postexercise task-switching RTs and this benefit was linked to decreased latency P300 waveforms. Accordingly, results above demonstrate that a single bout of exercise positively benefits each core component of EF.

Although single bouts of aerobic exercise facilitate postexercise EF benefits, the literature is equivocal with regards to whether exercise intensity and duration are primary moderators of this benefit. Chang et al.'s (2012) meta-analysis reported that a single bout of moderate intensity exercise (i.e., 64-76% of HR_{max}) for 20-min results in the largest and most reliable postexercise EF benefit. In turn, work by my lab group – and others – has shown that exercise benefits EF across a continuum of metabolically sustainable intensities (Heath et al. 2018; Petrella et al. 2019; Tari et al. 2021) and for durations as brief as 10-min (Johnston et al. 2016; Samani & Heath, 2018). For example, Petrella et al (2019) had older adults complete 10-min of treadmill running at moderate (i.e., power output at 80% of participant's estimated lactate threshold), heavy (i.e., 15% of the difference between estimated lactate threshold and VO_{2peak}) and very-heavy intensity (i.e., 50% of the difference between estimated lactate threshold and VO_{2peak}) and assessed EF via the antisaccade task prior to and immediately postexercise. Results showed a postexercise reduction in antisaccade RTs across each intensity that did not vary in magnitude, and is a result replicated in a 20-min cycle ergometry protocol involving

healthy young adults (Heath et al. 2018). What is more, work by my group had healthy young adults complete 20-min single bout aerobic exercise sessions via cycle ergometer at light intensity (i.e., 25 W), moderate (i.e., 80% of estimated lactate threshold), and heavy-intensity (i.e., 15% of the difference between participant-specific estimated lactate threshold and VO_{2peak}) and examined pre- to postexercise changes in EF via the antisaccade task. Results showed that each intensity produced a reliable decrease in antisaccade RTs, with null hypothesis, equivalence and Bayesian statistics demonstrating that this benefit did not vary in magnitude as a function of intensity. Accordingly, a single bout of exercise across a continuum of metabolically sustainable intensities for durations as brief as 10 min elicits a postexercise EF benefit.

1.4 Mechanisms Supporting a Postexercise Executive Function Benefit

The chronic exercise literature has reported that hippocampal neurogenesis is a primary moderator associated with an EF benefit. For example, van Praag et al. (2005) found that mice provided *ad libitum* access to exercise over 45 days showed improved memory and spatial learning (via the Morris water maze task) compared to sedentary controls and that improved memory performance was linked to hippocampal neurogenesis. In humans, Erickson et al (2011) used fMRI to assess hippocampal volume changes in older adults that completed a year-long exercise program (i.e., walking three times weekly at 60-75% of HR reserve) and an age-matched sedentary control group. At 12 months, results demonstrated that the exercise group produced a 2% increase in hippocampal volume, whereas over the same duration a 1.4% reduction in hippocampal volume was observed in the sedentary controls. Hence, compelling evidence suggests that chronic exercise supports neurogenesis, prevents neural death and supports improved EF.

Although chronic exercise supports hippocampal neurogenesis, it is unlikely that such a change would support improved EF following a single bout of exercise (Ming & Song, 2011). Accordingly, it has been proposed that a single bout of exercise improves EF via: (1) increased biomolecule concentrations (i.e., brain-derived neurotrophic factor and catecholamines) (for review, see Knaepen et al., 2010; Zouhal et al., 2008) (2) increased resting state functional connectivity (Schmitt et al., 2019) and (3) increased cerebral

blood flow (CBF) (Tari et al., 2020), that improve the efficiency and effectiveness of EF networks.

BDNF is a neuroprotective hormone that aids neuronal and glial survival and growth, modulates neurotransmitter levels/binding and is essential for promoting neuronal plasticity (Bathina & Das, 2015). Some work has proposed that BDNF supports a single bout postexercise EF benefit. For example, Hwang et al. (2016) investigated the impact that 20-min of high-intensity aerobic exercise (i.e., 85-90% of VO_{2max}) had on Stroop task performance and serum BDNF. Results showed the expected postexercise reduction in Stroop task RTs and this benefit was linked to increase serum BDNF levels. In contrast, Ferris et al. (2007) had participants perform the Stroop task prior to and following 30-min of aerobic exercise at 10% above ventilatory threshold (i.e., point when ventilation increases faster than the rate of VO_2). Results showed that Stroop task performance was not related to serum BDNF levels and thus demonstrate that the role of BDNF as a mechanism for a postexercise EF benefit remains equivocal.

Catecholamines are monoamines derivatives foundational to the production of epinephrine and norepinephrine that some work has linked to improved EF. For example, McMorris et al.'s (2011) meta-analysis states that an acute bout of moderate intensity exercise (i.e., 50-75% VO_{2max}) improves working memory when compared to light- or heavy-intensity exercise and that this improvement is linked to increased catecholamine metabolites concentrations in the brain (i.e., increased norepinephrine and dopamine). In contrast, Ando et al (2022) had participants complete a single bout of aerobic and resistance exercise for 30-min (53-58% of HR_{max}) and observed that a postexercise inhibitory control benefit was not linked to a pre- to postexercise change in catecholamine levels. Taken together, the literature does not demonstrate that changes in catecholamines are the sole mechanism by which postexercise EF is influenced.

Another mechanism proposed to modulate postexercise EF benefits is increased functional connectivity in DLPFC networks (Verburgh et al., 2014). Functional connectivity is a measure of how regions in the brain interact with each other and is quantified via non-invasive imaging (i.e., fMRI). Schmitt and colleagues (2019) had

participants complete 30-min single bouts of aerobic exercise at low- (i.e., 35% below lactate threshold) and high-intensities (i.e., 20% above lactate threshold) and showed improved connectivity within DLPFC regions for both intensities. In contrast, Voss et al. (2020) showed that a 20-min single bout of moderate intensity exercise (i.e., 65% of HR_{max}) improved n-back task performance but did not alter functional connectivity with frontoparietal EF networks. The literature investigating changes in DLPFC functional connectivity does not provide consistent results demonstrating its role as a primary moderator of a postexercise EF benefit.

The fourth candidate mechanism related to a postexercise EF benefit is an exercise-mediated increase in CBF. Notably, exercise engenders a rapid increase in CO_2 (i.e., a by-product of cellular metabolism), HR, and systolic blood pressure, all of which facilitate a systemic increase in perfusion (Smith & Ainslie, 2017). Indeed, Byun et al. (2014) showed that a 10-min single bout of light intensity exercise (i.e., 30% VO_{2peak}) improved Stroop task performance and demonstrated this benefit was linked to increased cerebral oxygenation in the DLPFC as assessed via functional near-infrared spectroscopy (fNIRS). As well, Tari et al. (2020) compared EF in separate conditions requiring: (1) 10-min of moderate- to heavy-intensity aerobic exercise (i.e., wattage determined via participant-specific incremental ramp test to volitional exhaustion), and (2) 10-min of hypercapnia (5% CO_2: i.e., higher-than-atmospheric concentration of CO_2). The hypercapnic condition was used because it provides a reliable basis to increase CBF independent of the metabolic costs of exercise via chemoreceptor reflex-induced vasodilation (O'Regan & Majcherczyk, 1982) Results showed that exercise and hypercapnic conditions provided an equivalent magnitude improvement in EF and was a result the authors attributed to an exercise-based improvement in CBF. Additionally, disease states and age-related impairments to EF have been linked to cerebral hypoperfusion. Indeed, Bertsch and colleagues (2009) demonstrated that healthy young adults show increased resting-state CBF and improved cognitive performance compared to a healthy cohort of older adults (i.e., > 55 years of age). As such, the bidirectional relationship between CBF and EF suggests that CBF provides a strong candidate mechanism for a single bout postexercise EF benefit.

1.5 Lower Body Negative Pressure

Lower body negative pressure (LBNP) is a non-invasive, safe, and reliable means to stimulate physiological changes associated with blood volume shifts from the upper body (i.e., above the iliac crest) to lower body compartments (i.e., leg and pelvic regions) without involving changes in body position (i.e., seated to supine etc.) (Hirsch et al. 1989). This blood-volume redistribution is enacted by applying vacuum (i.e., sub-atmospheric pressure) to the lower limbs that creates a negative pressure environment that pulls, and subsequently pools, blood in the venous system (Petersen et al., 2019). The resultant caudal shift in blood volume reduces venous return to the heart as a result of the lower body sequestered blood (Akselrod et al., 2001). In particular, upon LBNP onset there is an immediate reduction in peripheral vascular resistance leading to systemic hypotension. When this hypotension persists, there is a reduction in mean arterial pressure along with the onset of bradycardia (i.e., reduction in heartrate) leading to decreased cerebral perfusion (Little et al., 1995). Following LBNP initiation, the aforementioned hypotension stimulates aortic and carotid body baroreceptors that inhibit parasympathetic vagal nerve response to increase heart rate (Mancia & Mark, 2011). Moreover, mechano- and chemoreceptors initiate efferent sympathetic output to cardiac tissue in concert with the muting of vagal parasympathetic innervation (Carter et al., 2015). In tandem, these autonomic mechanisms work to induce elevations in heartrate to attenuate hypotension. Additionally, LBNP-induced hypotension causes sympathetic activation of the smooth musculature surrounding veins and arteries lead to systemic vasoconstriction (Furlan et al., 2001). Furthermore, hormonal mechanisms act to maintain systemic perfusion upon prolonged hypotension. For example, Convertino and Sather (2000) assessed vasopressin (i.e., antidiuretic hormone), plasma renin-angiotensin, and noradrenaline (i.e., hormones essential for regulating blood pressure, volume, and peripheral vasoconstriction) in participants following exposure to LBNP up to pre-syncopal physiological limits. Results demonstrated that there were increased levels of vasopressin, renin-angiotensin, and noradrenaline. Although these hormones are elevated during LBNP, this can take upwards of 20-min to take effect, suggesting that the initial homeostatic response of increasing heart rate and promoting peripheral vasoconstriction is autonomically mediated (Geelen et al., 2002). Although autonomic and endocrine

mechanisms work to counteract the central hypotension resulting from LBNP, cerebral perfusion is not adequately maintained as demonstrated via numerous studies showing a LBNP-based decrease in middle cerebral artery blood velocity (MCAv) (Samora et al., 2020).

A number of studies have demonstrated that a reduction of in CBF that scales in relation to LBNP magnitude (Bondar et al., 1994; Durocher et al., 2015). For example, Bondar et al (1994) had participants undergo successive increases in LBNP magnitudes until the onset of presyncope and showed proportional decrease in CBF corresponding to increasing LBNP magnitudes. Moreover, reductions in CBF have been implicated with reduced cerebral tissue oxygenation and some work has reported that this may contribute to an information processing impairment (Guo et al., 2006). For example, Han et al (2009) had participants complete 5-min -30 mmHg and -50 mmHg LBNP protocols and assessed information processing via EEG recording of an oddball task (i.e., attentional assessment of stimulus novelty). In addition, Han et al. measured MCAv via transcranial Doppler ultrasound (TCD) to provide an estimate of CBF. Results showed that MCAv decreased in relation to the magnitude of the LBNP protocol and also produced a decreased amplitude, and increased latency, P300 waveform. The authors proposed that the change in P300 waveform reflects impaired information processing attributed to an LBNP-induced reduction in CBF. Although Han et al (2009) demonstrated reduced amplitude and increased P300 latency, it is important to note that the oddball paradigm employed by the authors does not provide a measure of EF (García-Larrea et al., 1992). Hence, it is unclear as to whether a transient reduction in CBF negatively impacts EF.

My thesis sought to expand on the work done by Han et al (2009) by investigating the relationship between a LBNP-based reduction in CBF and post-intervention EF. In particular, my thesis employed the antipointing paradigm prior to and immediately following LBNP exposure to examine the impact of reduced CBF on EF efficiency and effectiveness. In my thesis work, participants completed a 10-min control condition as well as 10-min -30 mmHg and -50 mmHg LBNP protocols and an estimate of CBF was obtained via TCD based measure of MCAv. In terms of research predictions, if an LBNP reduction in CBF elicits a transient impairment in the efficiency and effectiveness of EF,

then post-intervention antipointing RTs should be longer than their pre-intervention counterparts and the magnitude of this reduction should scale with the magnitude of the LBNP protocol. In turn, if the reduction in LBNP does not reliably impair EF, then post-intervention LBNP antipointing RTs will not reliably differ from pre-intervention.

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Chapter 2

2 Introduction »

Executive function (EF) is a high-level cognitive construct that includes the core components of inhibitory control, working memory and cognitive flexibility (for reviews see, Diamond, 2013; Miyake et al., 2000). Extensive literature has demonstrated that a single bout of exercise provides a postexercise EF benefit (Barella et al., 2010; Chang et al., 2012; Heath et al., 2018; Tari et al., 2020) that has been linked to an exercise-mediated increase in cerebral blood flow (CBF) (Kleinloog et al., 2019; Poels et al., 2008; Tari et al. 2020). In particular, an exercise-mediated increase in CBF is thought to produce mechanical- and temperature-based changes to the brain's glial and neural circuits that improve information processing efficiency and effectiveness (i.e., the hemo-neural hypothesis) (Moore & Cao, 2008).

In demonstrating the role of CBF in mediating a postexercise EF benefit, Tari et al. (2020) used transcranial Doppler ultrasound (TCD) to measure middle cerebral artery velocity (MCAv) to estimate CBF in healthy young adults in separate conditions involving: (1) a 10 min single bout of moderate to heavy intensity aerobic exercise (via cycle ergometer) and, (2) a 10 min non-exercise condition involving the inhalation of a higher-than-atmospheric concentration of CO_2 (i.e., hypercapnic environment). The hypercapnic condition was used because it involves a well-documented increase in CBF to frontoparietal EF networks (Mehren et al., 2019) in response to elevated CO_2 and reduced serum pH (Ainsle and Duffin, 2009; Hoiland, 2019). As expected, exercise and hypercapnic conditions produced an average 19% increase in MCAv, and both conditions produced a pre- to post-intervention reduction in antisaccade reaction times (RT) (see details of antisaccade task below). In other words, an exercise- and hypercapnic-based increase in CBF was associated with an EF benefit. Moreover, Shirzad et al. (2022) contrasted MCAv and postexercise EF benefits in healthy young adults in separate single bout conditions involving a traditional "active" exercise intervention (i.e., volitional pedalling of cycle ergometer at a light intensity) and a "passive" exercise condition wherein the cycle ergometer flywheel was mechanically driven and did not require

volitional muscle activation. The passive exercise condition was used because the protocol is known to increase CBF via the stimulation of type *III* mechanoreceptive feedback to the primary sensory and motor cortices that increases cardiac output and stroke volume (Nóbrega & Araujo, 1993). Results showed that active and passive exercise increased MCAv – albeit the magnitude was larger in the former condition – and both conditions produced an equivalent magnitude reduction in antisaccade RTs. Accordingly, Tari et al. and Shirzad et al. demonstrate that an increase in CBF independent of the metabolic costs and intensity demands of active exercise is related to an EF benefit that persists for up to 60 min (Tari et al., 2023). In contrast, chronic hypoperfusion to cortical structures resulting from age- and disease-related states (e.g., atherosclerosis) has been shown to impair EF (Bertsch et al., 2009). For example, Jefferson et al. (2007) stratified a group of older adults based on low (i.e., <4.0 L/min) and normal (i.e., ≥ 4.0 L/min) cardiac output and reported that the former showed an impairment across each core component of EF. Thus, evidence suggests a bidirectional relationship between CBF and EF.

Although a number of studies have shown that a chronic reduction in CBF impairs EF, to my knowledge no work has examined whether a transient reduction in CBF elicits a transient EF impairment in healthy young adults. This represents a salient question because acute reductions in LBNP are common occupational environments in military and space flight/exploration. A technique for evoking a transient CBF reduction is lower body negative pressure (LBNP). LBNP entails positioning participants supine in an airtight bore sealed at the level of the iliac crest (i.e., waist-level) and exerting sub-atmospheric pressure to the lower-limbs to produce a caudal fluid shift by sequestering blood in the venous system of the lower limbs (see Akselrod et al., 2001). As a result, venous return to the heart is decreased coupled with an immediate hypotension and reductions in peripheral vascular resistance and cerebral perfusion (Little et al., 1995). LBNP has been continuously employed since the 1950's and is a simple, non-invasive and safe method for decreasing CBF (Crystal and Salem, 2015). Notably, although there has been extensive research examining the physiological and hemodynamic response to LBNP, a paucity of work has examined the influence of LBNP on cognition and EF. Indeed, Han et al. (2009) provide the only study to examine the putative link between a

LBNP-based reduction in CBF and information processing. In their study, participants were exposed to 5 min -30 mmHg and -50 mmHg LBNP protocols and the authors concurrently measured MCAv. During the LBNP protocols, event-related brain potentials (ERP) were measured in response to an oddball paradigm to provide a stimulus-based measure of stimulus detection (i.e., the P300). Results showed that a decrease in MCAv scaled in relation to LBNP magnitude and that P300 ERP amplitude and latency decreased and increased, respectively, in the LBNP conditions. In other words, LBNP decreased CBF and diminished the attentional system's reactivity to a novel stimulus. It is, however, unclear whether the P300 response is directly associated with reductions in CBF or is an epiphenomenon attributed to LBNP symptomology that adversely impacted attentional control. This is salient consideration given that the LBNP protocol can elicit nausea, syncope and produce shortness of breath (Zaslansky et al., 1996). Moreover, the oddball paradigm employed by Han et al. did not provide a measure of EF and thus it remains unclear as to whether an LBNP-based reduction in CBF adversely impacts EF.

The goal of my thesis project was to determine whether a 10-min bout of LBNP-based CBF reduction renders a post-intervention impairment in EF. As such, participants completed separate 10-min conditions of -30 mmHg and -50 mmHg LBNP as well as a 10-min non-LBNP control condition. During all conditions, CBF was estimated via a TCD-based measure of MCAv and pre- and post-intervention EF was assessed via the pro- and antipointing task. Propointing requires a goal-directed limb response to the veridical location of an exogenously presented target, whereas antipointing requires a response mirror-symmetrical to the target. Notably, antipointing results in longer reaction times (RT) and less accurate and more variable endpoints than their propointing counterparts (Chua et al.,1992; Carey et al., 1996; Heath et al., 2009; Maraj and Heath 2010). The behavioural 'costs' of antipointing has been linked to the two-component EF demands of response inhibition and vector inversion (Heath et al., 2011). Moreover, neuroimaging and electroencephalographic work has shown that antipointing engages DLPFC regions that overlap with the antisaccade task (Connolly et al., 2000; Heath et al., 2011). Accordingly, antipointing engages the same EF networks as the more extensively evaluated antisaccade task (for extensive review see, Munoz and Everling 2004). In

terms of research predictions, if a transient reduction in CBF adversely impacts EF then -30 mmHg and -50 mmHg LBNP post-intervention antipointing RTs should be longer than their pre-intervention counterparts and the magnitude of this increase should scale in relation to the magnitude of the LBNP reduction in CBF. In turn, if a transient reduction in CBF does not negatively impact EF then post-intervention antipointing RTs should not be different than pre-intervention RTs. As well, by including propointing response, the current study provides a framework to determine whether a LBNP-based reduction in CBF provides a general information processing deficit (i.e., a post-intervention increase in pro- and antipointing RTs) or renders a selective EF deficit (i.e., a selective post-intervention reduction in antipointing RTs).

2.1 Methods

2.1.1 Participants

Seventeen participants aged 19-26 years (6 females, 11 males) were recruited from the University of Western Ontario community. Sample size was determined *a priori* via an effect size from previous work examining pre- to postexercise changes in antipointing RTs ($\alpha = 0.05$, power = 0.90, $d_z = 1.30$) (Tari et al., 2020). All participants were naïve to the purpose of this study and were self-reported right-hand dominant (i.e., What hand do you write with?) with normal/corrected to normal vision. Participants self-reported that they were free of metabolic, neurological (including concussion), psychiatric, and musculoskeletal conditions and did not have a history of smoking or cardiorespiratory problems. Further, participants indicated they did not consume prescription or nonprescription medications that alter metabolic, cardiovascular, respiratory, hemodynamic or neuropsychological states. It was requested that participants abstain from caffeine and alcohol 12 hours prior to starting the study and that they get eight hours of sleep the night before the data collection session. Participants reported adhering to these recommendations. Prior to all data collection, participants read a letter of information approved by the Health Sciences Research Ethics Board, University of Western Ontario (HSREB #119772) and provided informed written consent. This study was conducted according to the most recent iteration of the Declaration of Helsinki with the exception that participants were not registered within a database.

All participants obtained a full score on the 2020 Physical Activity Readiness Questionnaire (PAR - Q+). In addition, participants completed the Godin Leisure-Time Exercise Questionnaire (GLTEQ) to determine participant-specific fitness levels. The average GLTEQ score was 69 (SD=19; range: 39-111) and thus indicated that all participants were recreationally active. The GLETQ was used given some work has reported that fitness level influences the relationship between CBF and EF (Chang et al. 2012)

2.2 Apparatus and Procedure

Participants completed three experimental conditions: -30 mmHg and -50 mmHg LBNP conditions and a non-LBNP control condition. The conditions were ordered randomly and performed in a single session with each condition requiring approximately 30 min to complete with 10 min provided between successive conditions. Prior to the intervention an ECG monitor (ADInstruments Bio Amp FE132) was affixed to participants chest to record heart rate (HR), while systolic and diastolic blood pressure (BP) were recorded via finometer (FMS Finometer Model 1 Non Invasive Blood Pressure Monitor). For each condition a TCD probe (Neurovision 500M, Neurovision TOC2M; Multigon Industries, Elmsford, CA) was coated with an aqueous ultrasound gel (Aquasonic Clear, Parker Laboratories Inc., Farifield, NJ) and secured via headset to the participant's left anterior temporal window to assess MCAv. TCD has been shown to be a valid proxy for direct measures of CBF (e.g., Xenon 133 tracing) (see Bishop et al., 1986). LBNP was achieved by having participants lie supine in the LBNP bore with their feet placed flat on an adjustable footrest. The footrest was adjusted according to the participant's height as to ensure that the entrance to the bore was at the level of the participant's iliac crest. Once inside the bore, an adjustable nylon skirt was placed around the participant's waist and secured to the bore in an airtight fashion. Negative atmospheric pressure in the LBNP bore was achieved via vacuum.

For the duration of the protocol, participants lay supine with their lower body (i.e., below the iliac crest) placed in an airtight LBNP bore (**Figure 1)**. All conditions consisted of three assessment timepoints (see **Figure 2** for timeline of experimental events). The first was a 10 min pre-intervention wherein HR and BP were recorded for the last 2 min of

this timepoint, and during which an EF assessment was completed (see EF function task details below). The second timepoint consisted of a 10-min application of -30 mmHg or -50 mmHg LBNP protocols, or the non-LNBP control condition (i.e., intervention). As per the pre-intervention timepoint, HR and BP were recorded during the last 2 min of the intervention timepoint. In addition, at the 5- and 10-min intervals of this timepoint, a checklist (see **Table 3**) was provided to participants to allow them to indicate the intensity of any symptom(s) (i.e., lightheadedness, nausea, etc.) that have been associated with the LBNP protocol. Participants verbally reported LBNP symptom intensity on a Likert scale ranging from 0-5 (i.e., "0" indicating an absence of symptomology and "5" indicating severe intensity and termination of the LBNP protocol). The symptomology checklist was delivered to determine whether possible changes in post-intervention EF was related to the adverse consequence of LBNP-induced symptomology. An assessment of EF was not completed during the intervention timepoint. To my knowledge no studies have directly investigated whether an LBNP-induced reduction in CBF impacts EF, and as such, I the current study elected to not measure EF during a time period that may be associated with LBNP-induced symptomology. The third timepoint (i.e., post-intervention) employed the same procedures as the pre-intervention timepoint; that is, a 10-min session wherein HR and BP were collected for the last 2 min of the postintervention timepoint following the EF task assessment. Assessment of middle cerebral artery blood velocity (MCAv) via transcranial Doppler ultrasound was continuous. Hence, the current study sought to evaluate whether 10-min exposure to LBNP elicits a post-, and not concurrent, protocol EF impairment.

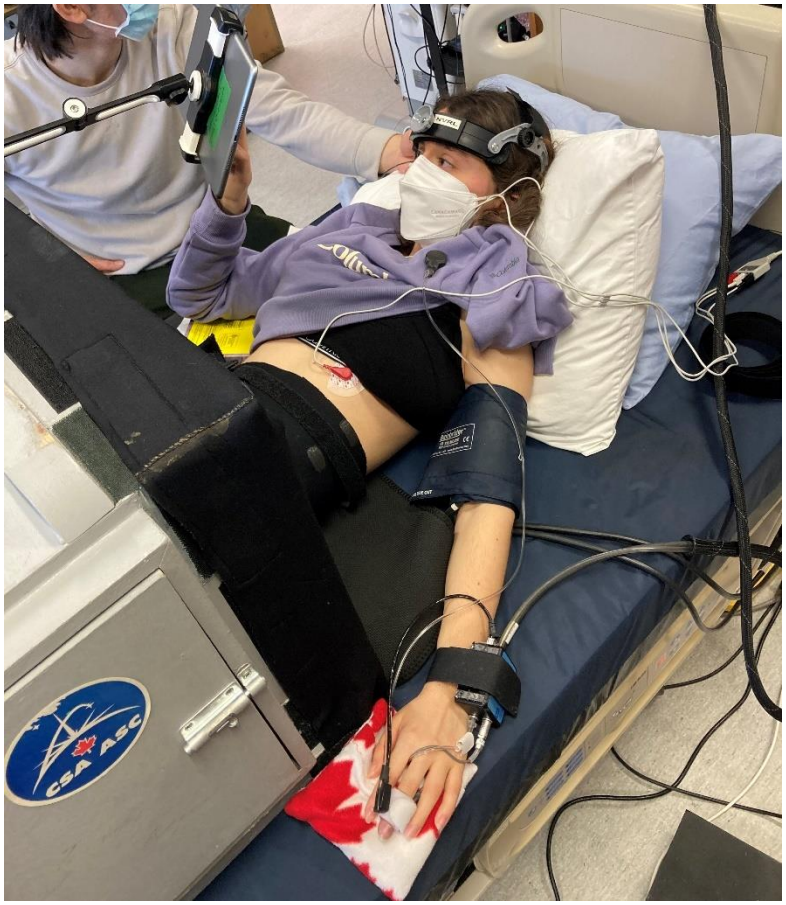


Figure 1. *Image of participant placed in the lower body negative pressure (LBNP) bore while concurrently competing the executive function task.*

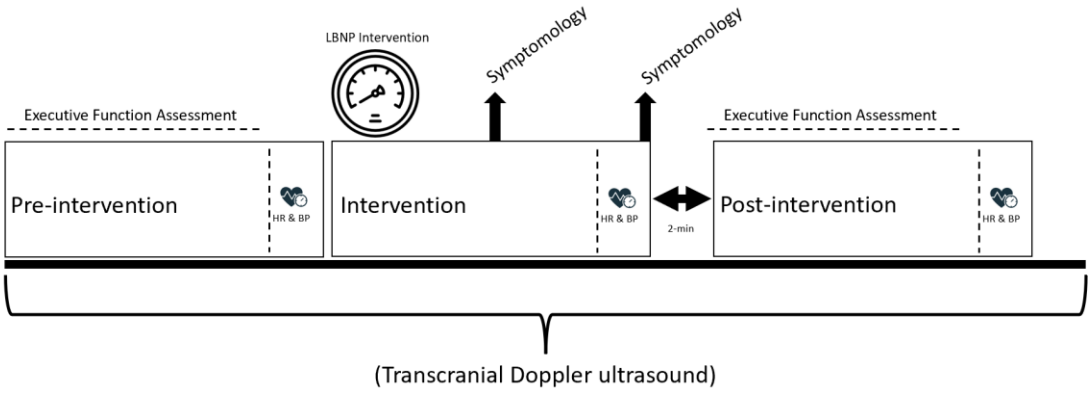


Figure 2. *Schematic depicting the timeline for experimental events in each of the control, -30 mmHg LBNP, and -50 mmHg LBNP conditions. The control condition followed the same timing as the LBNP conditions with the exception that participants were*

continuously exposed to atmospheric barometric pressure. The schematic shows that heart rate (HR) and blood pressure (BP) were measured during the last 2 min of each assessment timepoint (i.e., pre-intervention, intervention, post-intervention) and that EF assessment was administered at the onset of the pre-intervention and post-intervention timepoints. Transcranial Doppler ultrasound was continuously measured throughout each condition to provide an estimate of middle cerebral artery velocity. Vertical black arrows at the 5- and 10-min mark indicate when participants verbally reported LBNP-induced symptom intensity.

2.2.1 Executive Function Assessment

Pre- and post-intervention EF assessments were completed via pro- and antipointing trials completed on a custom-built iPad® app (XCode developed via Swift; v. 5.3 Apple Inc, Cupertino CA) operating at a native screen and touch resolution of 60 Hz (Tari and Heath 2022). Prior to data collection, participants were familiarized with the pro- and antipointing task via in-app tutorials. For all assessments, participants completed the task while supine in the LBNP bore with the iPad® (10.9" screen) equipped with the iOS v.15.0 operating system (Apple Inc., Cupertino, CA) and secured above body midline (see **Figure 1**). Visual stimuli were presented on a grey (RGB code: 125, 125, 125) background and included a centrally located white (RGB code: 255, 255, 255) home location cross (i.e., 1 by 1 cm) and targets (i.e., open white circle; 1 cm in diameter) presented 6 cm (i.e., proximal target) and 9 cm (i.e., distal target) to the left and right of the home location and on the same horizontal plane. The onset of a trial was initiated by presentation of the home location which indicated where participants were to place their right index finger. Following contact with the home location, a uniformly distributed randomized foreperiod between 1000 and 2000 ms was introduced after which a target appeared for 50 ms in one of four locations (i.e., left 6 cm or 9 cm; right 6 cm or 9 cm) and cued participants to either pro- (i.e., point to veridical target location) or antipoint (i.e., point mirror-symmetrical to target location) "as quickly and accurately as possible". Additionally, participants were instructed to not slide their finger from the home location to the target; rather, the instruction was to lift and point to the target. Pro- and antipointing trials were completed in separate and randomly ordered blocks with 80 trials

pseudo randomly presented at each target location (i.e., left and right field) and eccentricity (i.e., proximal or distal to screen's midline). Prior to a block of trials an instruction screen was provided that indicated that nature of the upcoming trial-type (i.e., pro- vs. antipointing). Upon completion of the pre-intervention EF task, the associated "intervention" timepoint was initiated. Post-intervention pro- and antipointing trials were completed ~2 minutes upon LBNP cessation to allow HR, BP and MCAv to return to pre-intervention values. Each EF assessment required approximately 8-min to complete.

2.2.2 Data Reduction

TCD data corrupted by signal aliasing or loss (e.g., sudden head shift) were omitted (Terslev et al., 2017) and peak systolic MCAv were analyzed given Rosengarten and Kaps' (2002) demonstration that they provide a valid measure for TCD-based measure of CBF. As in previous pro- and antipointing work (e.g., Maraj & Heath, 2010), RTs less than 150 ms or greater than 2.5 standard deviations of a participant- and task-specific mean were excluded from data analysis (< 3% of trials). Further, movement times (MT) less than 100 ms or greater than 2.5 standard deviations of a participant- and task-specific mean were removed from analysis (<2 % of trials). Pro- and antipointing trials resulting in a directional error (i.e., propointing instead of antipointing and vice versa) were excluded from RT and MT analyses (<1 % of trials). The low error rate is attributed to the completion of pro- and antipointing trials in separate blocks (Heath et al., 2011).

2.2.3 Dependent Variables and Statistical Analyses

MCAv, HR and systolic and diastolic BP were analyzed via 3 (condition: control, -30mmHg LBNP, -50mmHg LBNP) by 3 (time: pre-intervention, intervention, post-intervention fully repeated measures ANOVA ($\alpha = 0.05$). Dependent variables for the pro- and antipointing tasks included RT (i.e., time from target onset to release of pressure from the iPad screen [i.e., movement onset]), movement time (MT) (i.e., time from movement onset to subsequent contact with the iPad screen), and gain (i.e., saccade amplitude/veridical target location). RT, MT, and gain were analyzed via 3 (condition: control, -30 mmHg LBNP, and -50 mmHg LBNP) by 2 (time: pre-intervention, post-intervention) by 2 (task: propointing, antipointing) fully repeated measures ANOVA

(alpha = 0.05). Where appropriate, the two one-sided test (TOST) statistic is reported to determine whether results were within an equivalence boundary (Lakens et al., 2016). The effect size used to compute the TOST statistic (d_z =0.62) was derived from previous work contrasting pre- and postexercise changes in antipointing RTs (Tari & Heath, 2022). In addition, **Table 2** presents Bayesian single-samples t-test contrasts of pro- and antipointing RT difference scores (i.e., post-intervention minus pre-intervention) across control, -30 mmHg and -50 mmHg LBNP conditions and are included to demonstrate unified behavioural conclusions drawn from frequentist and Bayesian statistical approaches.

2.3 Results

2.3.1 Heart rate (HR) and Blood Pressure (BP)

HR produced main effects of condition, $F(2,32) = 27.13$ $p < 0.001$, $\eta_p^2 = 0.63$, time, $F(2,32) = 87.56$, $p< 0.001$, $\eta_p^2 = 0.85$, and their interaction, $F(4,64) = 75.36$, $p <0.001$, $\eta_p^2 = 0.83$. To decompose the interaction, I computed HR difference scores (intervention minus pre-intervention, post-intervention minus pre-intervention) separately for each condition and contrasted results to a value of zero via single-samples t-tests. **Figure 3** shows that control condition intervention and post-intervention HR did not differ from pre-intervention ($ts(16) = 1.43$ and 1.17, $ps = 0.17$ and 0.26, $d_z = 0.35$ and 0.28). In turn, for the -30 mmHg and -50 mmHg LBNP conditions, HR during the intervention timepoint was greater than pre-intervention ($ts(16) = 7.62$ and 10.84, $ps < 0.001$, d_z = 1.85 and 2.63); however, at post-intervention HR for both conditions did not reliably differ from pre-intervention ($ts(16) = 0.37$ and 1.01, $ps = 0.72$ and 0.33, $d_z = 0.09$ and 0.25).

Table 1. *Means and standard deviations for pre-intervention (PR-I), intervention (I), and post-intervention (PS-I) physiological variables as a function of control, -30 mmHg and -50 mmHg LBNP conditions.*

Control			-30mmHg			-50mmHg		
PR-I	I	PS-I	PR-I	I	PS-I	PR-I	I	PS-I

HR (BMP)	72±9	71±9	71±9	73±11	81±11	72±11	71±9	91±12	70±10
BP_{sys} (mmHg)	116±7	115±8	116±8	116±8	109±11	115±9	116±9	100±13	115±9
BP_{dia} (mmHg)	74±7	73±7	72±7	75±8	74±8	74±8	73±8	72±11	74±10
MCAv (cm/s)	113±14	113±14	113±15	114±14	101±17	113±21	115±12	101±12	118± 16

Note: Heart rate (HR), systolic blood pressure (BP_{sys}), diastolic blood pressure (Bp_{dia}) and peak systolic middle cerebral artery velocity (MCAv).

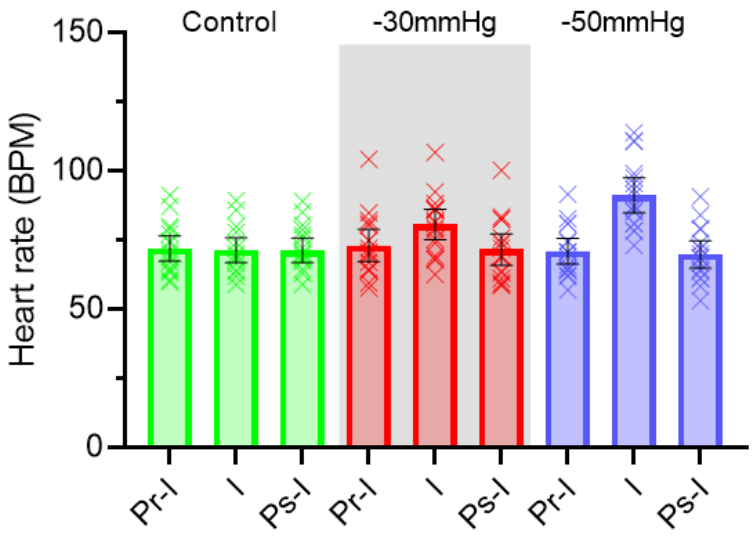


Figure 3*. Participant-specific (i.e., symbols) and group mean (i.e., bars) heart rate for control, -30 mmHg and -50 mmHg LBNP conditions at pre-intervention (Pr-I), intervention (I) and post-intervention (Ps-I) assessments. Error bars represent 95% between-participant confidence intervals.*

Systolic BP (BP_{sys}) produced a main effect of condition, $F(2,32) = 6.75$, $p < 0.05$, $\eta_p^2 = 0.29$, time, $F(2,32) = 79.47$, $p < 0.001$, $\eta_p^2 = 0.83$, and their interaction, $F(2,32) = 17.73$, p

< 0.001, $\eta_p^2 = 0.53$. As per HR, the interaction was decomposed via HR difference scores (intervention minus pre-intervention, post-intervention minus pre-intervention) computed separately for each condition with results contrasted to a value of zero via single-samples t-test. For the control condition, BP_{sys} did not vary between pre-intervention and intervention ($t(16) = 2.01$, $p > 0.06$, $d_z = 0.49$) or pre-intervention and post-intervention ($t(16) = 1.00$, $p = 0.33$, $d_z = 0.24$). In contrast, for the -30 mmHg LBNP and -50 mmHg LBNP conditions, BP_{sys} at pre-intervention was larger than intervention ($ts(16) = 3.84$ and 9.25 for -30 mmHg LBNP and -50 mmHg LBNP, respectively, $ps < 0.001$, $d_z = 0.93$ and 2.24); however, for both conditions post-intervention values did not reliably differ from pre-intervention ($ts(16) = 0.60$ and 0.29, $ps = 0.56$ and 0.77, $d_z = 0.15$ and 0.07) (see **Table 1 and Figure 4**). In addition, I contrasted BP_{sys} difference score (i.e., intervention minus pre-intervention) between -30 and -50 mmHg LBNP conditions and observed that the magnitude of a pre-intervention to intervention change in BP_{sys} was larger in the -50 mmHg than -30 mmHg LBNP condition ($t(16) = 3.50$, $p = 0.003$, $d_z = 0.85$).

Diastolic BP (BPd_{ys}) did not produce main effects of condition, $F(2,32) = 1.10$, $p = 0.35$, $\eta_p^2 = 0.06$), time, $F(2,32) = 3.09$, $p = 0.07$, $\eta_p^2 = 0.16$) nor their interaction, $F(2,32) = 1.81$, $p = 0.139$, $\eta_p^2 = 0.10$) (**Table 1 and Figure 4**).

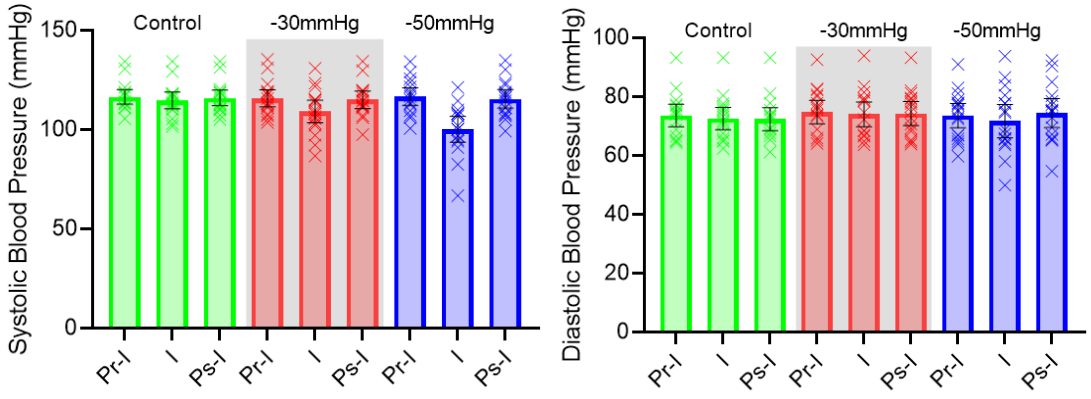


Figure 4*. Participant-specific (i.e., symbols) and group mean (i.e., bars) systolic (left) and diastolic (right) blood pressure for control, -30 mmHg and -50 mmHg LBNP conditions at pre-intervention (Pr-I), intervention (I) and post-intervention (Ps-I) assessments. Error bars represent 95% between-participant confidence intervals.*

2.3.2 Middle Cerebral Artery Velocity (MCAv)

Figure 5 presents an exemplar participant's MCAv at pre-intervention, intervention and post-intervention timepoints for control, -30 mmHg and -50 mmHg conditions. The figure provides a clear demonstration that MCAv in the -30mmHg and -50mmHg LBNP – but not the control – conditions decreased at LBNP onset and then increased to pre-intervention levels following LBNP cessation. In terms of quantitative results, MCAv produced a main effect for time, $F(1,16)= 57.42$, $p< 0.001$, $\eta_p^2 = 0.76$, and a condition by time interaction, $F(1,16) = 26.56$, $p< 0.001$, $\eta_p^2 = 0.59$. The same post hoc technique used for HR and BP_{sys} was used here and **Figure 6** shows that MCAv in the control condition did not reliably differ between pre-intervention and intervention ($t(16) = 0.19$, $p = 0.85$, $d_z = 0.05$) or between intervention and post-intervention ($t(16) = -0.67$, $p = 0.51$, $d_z = -0.16$. In contrast, -30 mmHg and -50 mmHg LBNP conditions produced a pre-intervention to intervention decrease in MCAv ($ts(16) = 4.16$ and 4.69, $ps < 0.001$, $d_z = 1.02$ and 1.14). In contrast, at post-intervention -30 mmHg and -50 mmHg condition MCAv values did not reliably differ from their pre-intervention counterparts ($ts(16) = 0.90$ and -0.46, $ps = 0.38$ and 0.65, $d_z = 0.22$ and -0.11). As well, -30 mmHg and -50 mmHg LBNP difference scores (i.e., pre-intervention minus intervention) were contrasted via paired-samples t-tests with results showing a larger magnitude change in latter condition (**Figure 6**). In other words, the decrease in MCAv scaled in relation to LBNP magnitude.

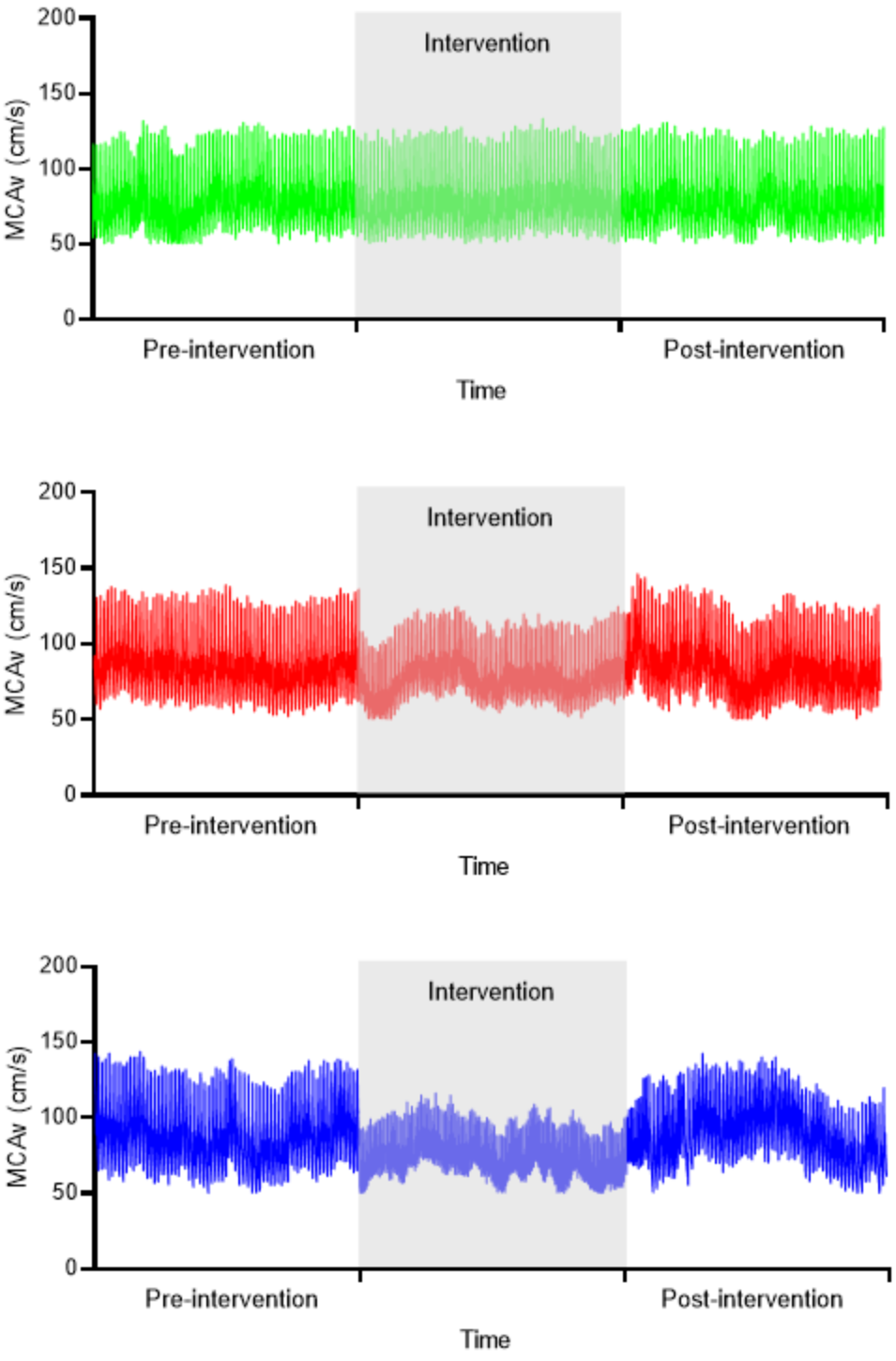


Figure 5*. Middle cerebral artery velocity (MCAv) for an exemplar participant as a function of control, -30 mmHg, -50 mmHg LBNP conditions at pre-intervention, intervention, and post-intervention assessment timepoints. For this figure note that data*

are not presented continuously. Hence, for the pre-intervention and intervention timepoints, MCAv is depicted for the last 2-min of each assessment period, whereas for the post-intervention timepoint MCAv is shown for the first 2-min of this assessment period.

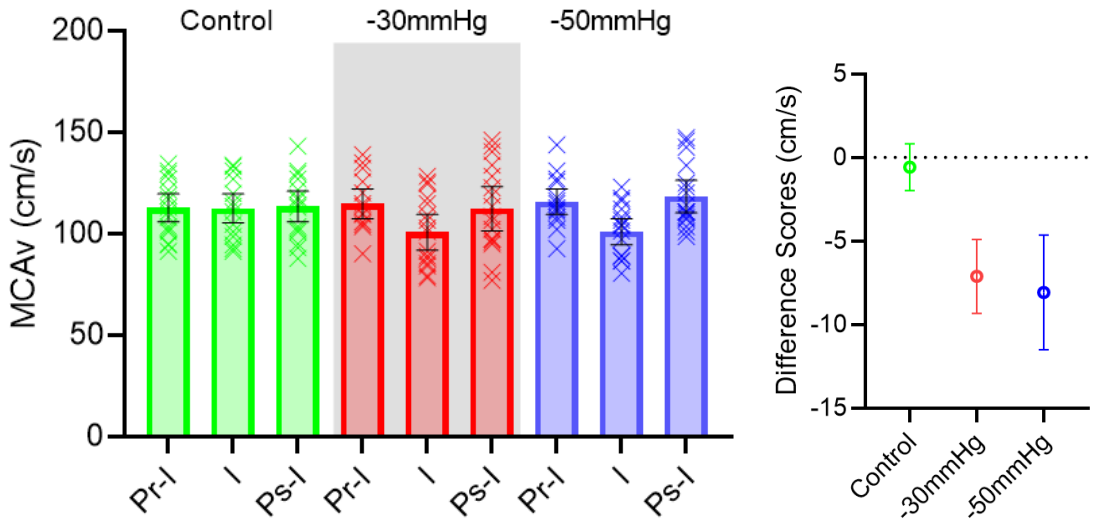


Figure 6. *The left panel depicts participant-specific (i.e., symbols) and group mean (i.e., bars) middle cerebral artery velocity (MCAv) as a function of control, -30 mmHg and -50 mmHg LBNP conditions at pre-intervention (Pr-I), intervention (I) and post-intervention (Ps-I) assessments. Error bars represent 95% between-participant confidence intervals. The right panel shows group mean MCAv difference scores (i.e., pre- minus post-intervention). Error bars in all panels represent 95% between-participant confidence intervals.*

2.3.3 Assessment of Executive Function (EF)

RT produced a main effect of task, $F(1,16) = 34.07$, $p < 0.001$, $\eta_p^2 = 0.68$. As expected, values for propointing (296 ms, SD=39) were less than antipointing (335 ms, SD=55) – a finding independent of condition and time of assessment. RT did not produce main effects for condition, $F(1,16) = 1.61$, $p = 0.22$, $\eta_p^2 = 0.08$, time, $F(1,16) = 1.37$, $p = 0.26$, $\eta_p^2 = 0.07$, nor any higher-order interactions, $Fs(1,16) < 0.52$, $ps > 0.61$, $\eta_p^2 < 0.03$

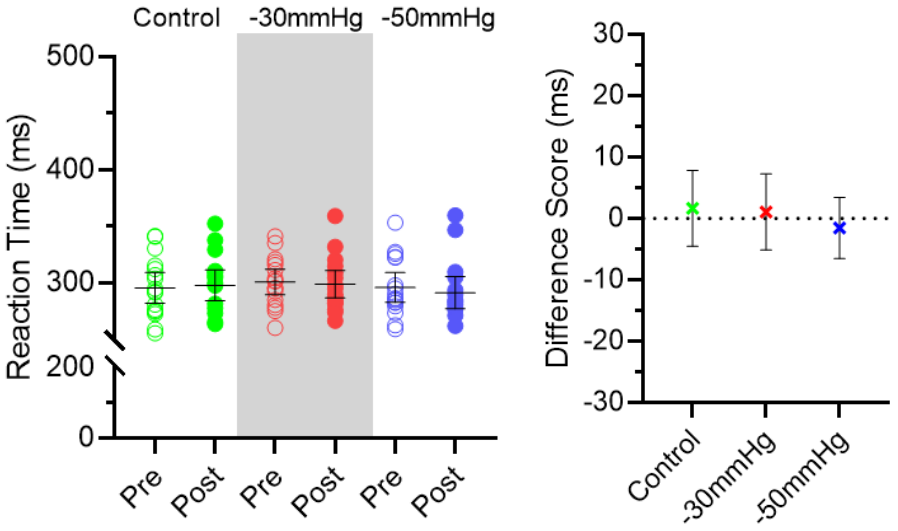
(**Figure 7**). Moreover, and given the nature of the research hypothesis examined here, I computed participant-specific RT differences scores (pre- minus post-intervention) separately for pro- and antipointing across control, -30 mmHg LBNP and -50 mmHg LBNP conditions. Pro- and antipointing difference scores for each condition were subsequently contrasted to a value of zero via single-sample TOST statistics. Results indicated that values for all conditions were within an equivalence boundary ($ts(16) > 2.56$, $ps < 0.01$). In other words, null hypothesis and equivalence testing showed that the LBNP manipulations did not influence pro- or antipointing RTs. As well, **Table 2** provides results for Bayesian single-sample t-tests contrasts of pro- and antipointing RT difference scores and results for all contrasts demonstrated anecdotal to moderate support for the null hypothesis.

Table 2*. BF_{10} and BF_{01} differences scores (i.e., post- minus pre-intervention) for pro- and antipointing performance as a function of control, -30mmHg LBNP, and -50mmHg LBNP.*

	Propointing		Antipointing	
	BF_{10}	BF_{01}	BF_{10}	BF_{01}
RT_{con}	0.33	3.08	0.25	4.01
RT_{-30}	0.29	3.44	0.25	4.00
RT_{-50}	1.01	0.99	0.28	3.56
MT_{con}	0.90	1.11	0.26	3.84
MT_{-30}	0.34	2.94	0.29	3.39
MT_{-50}	0.25	4.01	0.26	3.92
$Gain_{con}$	0.26	3.87	0.26	3.89
$Gain_{-30}$	0.46	2.16	0.26	3.91
$Gain_{-50}$	0.27	3.76	1.15	0.87

Note: Reaction time (RT), movement time (MT), con (control), -30 (-30mmHg LBNP), and -50 (-50mmHg LBNP) is reported. Van Doorn et al.'s (2021) nomenclature of BF_{10} (i.e., Bayes factor in favour of the alternative over the null hypothesis) and BF_{01} (i.e., Bayes factors in favour of the null hypothesis) are used here. BF_{10} values are categorized as "anecdotal" (i.e., 1 to <3), "moderate" (i.e., 2 to <10), "strong" (i.e., 10 to <100) and "very strong" (i.e., >100) and are used to categorize the robustness of the Bayes factor.

MT and gain produced main effects of task, *Fs*(1,16) = 11.26 and 6.88, for MT and gain, respectively , ps = 0.01 and = 0.02, η_p^2 = 0.41 and 0.31) such that propointing response has shorter durations (213 ms, SD=69) and amplitudes were closer to veridical (0.90, SD=0.37) than antipointing (MT: 227 ms, SD=77; gain: 0.86, SD=0.35)



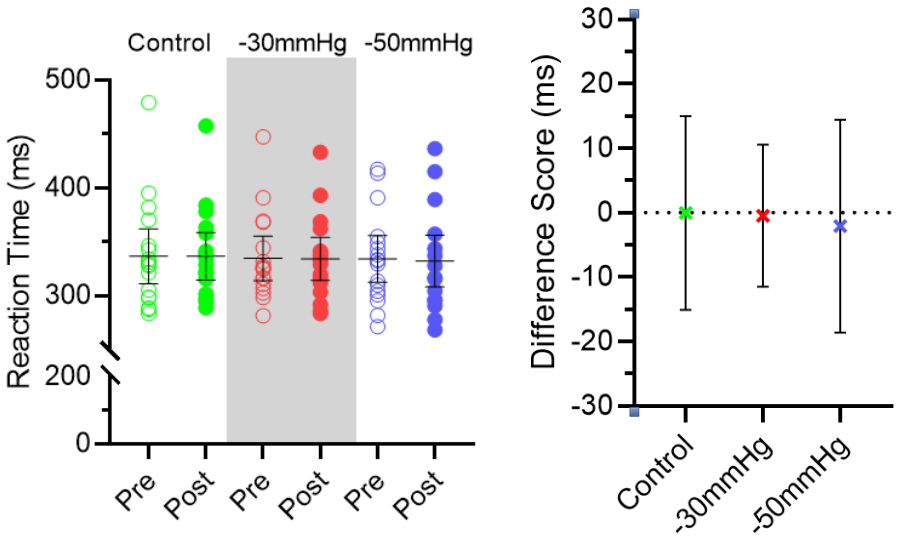


Figure 7. *The left panels show participant-specific (i.e., symbols) and group mean (i.e., black lines) propointing (top) and antipointing (bottom) reaction times at pre- and post-intervention. The right panels shows group mean pro- and antipointing reaction time difference scores (i.e., pre- minus post-intervention). Error bars in all panels represent 95% between-participant confidence intervals.*

2.3.4 Relationship Between MCAv Difference Scores and Antipointing RT Difference Scores

To determine whether the magnitude of a MCAv reduction was associated with a change in antipointing RTs, Pearson r correlation coefficients relating MCAv difference scores (i.e., pre-intervention minus intervention) and antipointing RT difference scores (i.e., pre-intervention minus post-intervention) were computed separately for -30 mmHg and -50 mmHg conditions. Results indicated that the variables were not reliably related across any condition (ps>0.08).

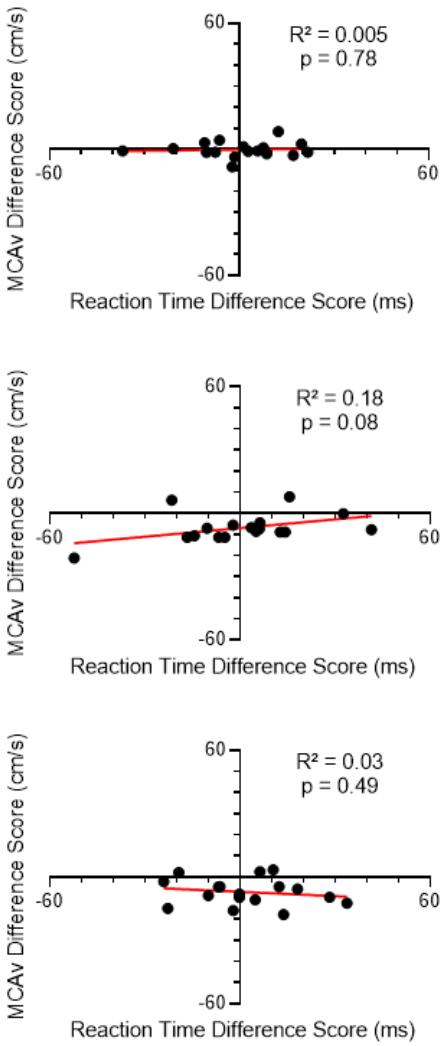


Figure 8. *Participant-specific middle cerebral artery blood velocity (MCAv) difference scores (i.e., pre-intervention minus intervention) plotted as function of participant-specific antipointing reaction time difference scores (i.e., post- minus pre-intervention) across control (top), -30 mmHg LBNP (middle), and -50 mmHg LBNP (bottom) conditions. Linear regression lines are denoted in red, and each panel provides associated* R^2 *and p-values.*

2.3.5 LBNP Symptomology Measures

Participant-specific symptomology was reported at the 5- and 10-min marks during the intervention timepoints for all conditions (i.e., control, -30 mmHg LBNP and -50 mmHg

LBNP) (**Table 3**). All symptomology reported during the control intervention produced Likert ratings of "0" at 5- and 10-min. For the -30 mmHg and -50 mmHg LBNP conditions, the total Likert score (i.e., summed across all participants) is presented in Table 3 and indicates that symptomology was largely absent during the manipulation. For example, Table 3 shows that "General Discomfort" produced the largest symptomology score at the 10 min mark of the -50 mmHg LBNP condition with a value of "4".

Table 3. *Total symptom score of all participants (n=17) during -30 mmHg and -50 mmHg LBNP conditions at the 5-, and 10-min timepoints. Verbal symptomology reporting was conducted during the intervention timepoint of control, -30 mmHg, and -50 mmHg conditions.*

	-30 mmHg		-50 mmHg	
	5 min	10 min	5 min	10 min
Nausea	1	0	1	1
Sweating	1	0	2	1
Light-headedness	0	0	0	0
Shortness of Breath	2	2	2	3
Chest Stiffness	1	1	1	0
Stomach-ache	0	1	2	2
General Discomfort	2	2	4	4

Note: Numbers indicate total symptom score for all participants (n=17). Participants indicate symptom score from on a Likert scale ranging from 0-5. (i.e., if all participants indicate 5 for a symptom then total score is of 95, if all participants indicate 0 for a symptom then total score would be 0). Symptomology severity scores ranged from 0-2, with no individuals reporting symptom severity above 2 on the Likert scale.

3 Discussion

3.1 HR, BP, MCAv, and Symptomology Changes in Response to Lower Body Negative Pressure

As expected, the control condition did not produce any changes in HR, BP_{sys}, BP_{dia}, or MCAv across the pre-intervention, intervention and post-intervention timepoints. In contrast, -30 mmHg and the -50 mmHg LBNP conditions produced an intervention-based increase in HR, BP_{sys}, and a decrease in MCAv. These findings are well-documented and reflect a compensatory effort to maintain BP and cerebral perfusion while experiencing hypovolemia (Bennett, 1987; Blomqvist & Stone, 1991). In particular, LBNP onset reduces peripheral vascular resistance and fosters a systemic hypotensive state that leads to aortic and carotid body baroreceptors to increase HR via parasympathetic vagal nerve inhibition. As such, both mechanoreceptors and chemoreceptors activate efferent sympathetic nervous system output to cardiac tissues. Indeed, these autonomic responses work to counteract the LBNP-induced hypotension through increased cardiac output via increases in heart rate and stroke volume. Moreover, while autonomic mechanisms work to counteract the central hypotension resulting from LBNP, cerebral perfusion is not adequately maintained in relation to homeostatic baselines, and as such LBNP results in a decrease in MCAv (Guo et al., 2006, Han et al., 2009, Kay & Rickards, 2016). At the post-intervention timepoint, HR, BP_{sys}, and MCAv in the -30 mmHg and -50 mmHg conditions rapidly returned to pre-intervention values. The return to pre-intervention values is an expected finding and relates to the immediate return to baseline blood volume levels. This return in blood volume leads to reflex-mediated reductions in efferent sympathetic activity and vasodilation of peripheral venous systems and tissue. As such, HR, BP, and MCAv return to pre-intervention values rapidly.

The LBNP intensities used here (i.e., -30 mmHg and -50 mmHg) are considered to be “mild” (for review see Goswami et al., 2019) and results for self-reported measures of symptomology provide a clear demonstration that most participants did not experience any concurrent LBNP-induced symptoms . That being said, LBNP magnitudes at -30 mmHg and -50 mmHg were selected based on a review by Goswami et al., 2019 indicating that such magnitudes elicit reductions in MCAv. Importantly, the largely

absent symptomology associated with the LBNP condition provided a framework by which to exclude attentional-distracting effects on putative deleterious post-LBNP EF changes.

3.2 Executive Function Assessment in Response to Lower Body Negative Pressure

As expected, antipointing produced longer RTs and MTs as well as decreased endpoint accuracy as compared to propointing. These results were consistent across each condition (i.e., control, -30 mmHg, and -50 mmHg LBNP) and assessment (i.e., pre-intervention and post-intervention). The longer antipointing RTs relate to the time-consuming and EF demands required to suppress a prepotent propointing response (i.e., inhibitory control) and compute the 180° spatial transformation of the target's coordinates (i.e., vector inversion) (Chua et al., 1992; Heath et al., 2009). Moreover, that antipointing produced longer MTs and were associated with decreased endpoint accuracy has been linked to increased uncertainty related to visuomotor control (Edelman & Goldberg, 2001) and a decrease in motor excitability due to the high-level EF demands of inhibiting a prepotent response (Heath et al., 2012).

The primary goal of my thesis was to examine whether LBNP provides a post-intervention detriment to EF as assessed via the pro- and antipointing task. Previous work has shown that the pro- and antipointing paradigm provides the resolution to detect subtle changes in EF. For example, Tari and Heath (2019) examined whether an iPad® based pro- and antipointing EF task was able to detect subtle changes in EF following a single 20-min session of moderate intensity exercise. Results from this investigation demonstrated a reliable postexercise reduction in antipointing RTs – a result the authors attributed to a task-based resolution sufficient to detect subtle EF changes. In the present work, the control condition produced an expected null pre- to post-intervention change in pro- and antipointing metrics. This is a salient finding because it demonstrates that the task was immune to practice-related performance benefits. In terms of the -30mmHg and -50 mmHg LBNP conditions, results similarly showed that pro- and antipointing metrics

did not vary from pre- to post-intervention – a conclusion supported by frequentist null hypothesis and equivalence tests as well as Bayesian contrasts. Indeed, my statistical approach demonstrates that the equivalent pre- and post-intervention antipointing RTs are not the result of an inadequate sample size (Lakens et al., 2018). Additionally, that pre- and post-intervention MT and gain did not vary across LBNP and control conditions indicates that participants did not adopt an explicit or implicit strategy designed to decrease movement planning times at the cost of reduced movement accuracy (i.e., a speed-accuracy trade-off) (Fitts 1954). As such, results suggest that LBNP, and an associated intervention-based decrease in CBF, did not influence post-intervention performance of a non-EF (i.e., propointing) and EF (i.e., antipointing) task.

The fact that pro- and antipointing metrics for -30 mmHg and -50 mmHg LBNP did not vary from pre- to post-intervention may relate to a compensatory mechanism(s) designed to optimize the extraction of oxygen under reduced CBF. For example, Lewis and colleagues (2014) employed a pharmaceutical intervention through oral administration of indomethacin to reduced CBF and demonstrated that cortical tissues were able to extract oxygen from the blood more efficiently when experiencing hypoperfusion. As well, McHenry et al., (1961) observed cerebral oxygen extraction capacity was significantly elevated during profound hypotension (i.e., presyncopal levels of hypotension) and proposed that such a finding evinces a compensatory measure to preserve information processing capacity (Lewis et al., 2014). Moreover, it is important to recognize that the decrease in MCAv reported during the -30 mmHg and -50 mmHg LBNP conditions immediately returned to pre-intervention values upon LBNP termination. As such, rapid post-intervention restoration of CBF may have provided a sufficient environment and timeframe to maintain/restore normative information processing and EF.

3.2.1 Limitations and Future Directions

I recognize that my work is limited by several methodological constraints. First, I did not assess EF during the LBNP interventions, and it is therefore unclear whether a concurrent reduction in CBF would elicit an impairment in EF. My *a priori* rationale for not investigating EF during LBNP was due to reports that presyncopal and other LBNP symptomology may adversely impact concurrent EF independent of any reduction in

CBF. Of course, given that my work showed that the LBNP protocol used here did not increase in symptomology it is recommended that future work employ a EF assessment concurrent with the LBNP protocol. Second, the TCD-based used here does not quantify vessel diameter and thus does not provide an absolute measure of CBF. That said, to my knowledge vessel size changes have not been reported to impact the validity of TCD in LBNP protocols. Third, I employed only a 10-min LBNP protocol and as such it is unknown whether a longer duration reduction in CBF would adversely impact a post-intervention assessment of EF. Last, I recruited healthy young adults and as such it is unclear whether older adults, individuals with limited mobility, or persons with chronic reductions in CBF (i.e., hypoperfusion) would show a similar persistent of high-level EF following a transient LBNP protocol.

4 Conclusion

The present study demonstrates that 10-min of 30 mmHg and -50 mmHg LBNP protocol reliably decrease CBF; however, this physiological change did not result in impact a post-intervention measure of general information processing (i.e., propointing) and EF (i.e., antipointing).

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Appendix

Appendix A: Health Science Research Board Approvals

Western Research

Date: 14 December 2021

To: Dr. Matthew Heath

Project ID: 119772

Study Title: Effect of Reduced Cerebral Perfusion on Executive Function

Application Type: HSREB Initial Application

Review Type: Delegated

Meeting Date / Full Board Reporting Date: 11/Jan/2022

Date Approval Issued: 14/Dec/2021

REB Approval Expiry Date: 14/Dec/2022

Dear Dr. Matthew Heath

The Western University Health Science Research Ethics Board (HSREB) has reviewed and approved the above mentioned study as described in the WREM application form, as of the HSREB Initial Approval Date noted above. This research study is to be conducted by the investigator noted above. **All other required institutional approvals and mandated training must also be obtained prior to the conduct of the study.**

Documents Approved:

Document Name	Document Type	Document Date	Document Version
GLTEQ	Online Survey	08/Nov/2021	1
PARQPlus 2020	Online Survey	08/Nov/2021	1
Research Protocol LBNP REB Edit	Protocol	09/Dec/2021	2
NeuroBehavioural Lab COVI19 REB Edit	Paper Survey	09/Dec/2021	2
Symptom Checklist LBNP REB Edit	Other Data Collection Instruments	09/Dec/2021	2
Finometer Info LBNP REB Edit	Other Data Collection Instruments	09/Dec/2021	2
Respiration Transducer Info LBNP REB Edit	Other Data Collection Instruments	09/Dec/2021	2
TCD Info LBNP REB Edit	Other Data Collection Instruments	09/Dec/2021	2
Vacuum Info LBNP REB Edit	Other Data Collection Instruments	09/Dec/2021	2
Voltage Transformer Info LBNP REB Edit	Other Data Collection Instruments	09/Dec/2021	2
NIRS Tool REB Edit	Other Data Collection Instruments	09/Dec/2021	2
ECG info REB Edit	Other Data Collection Instruments	09/Dec/2021	2
Executive Function Assessment Tool REB Edit	Other Data Collection Instruments	09/Dec/2021	2
Email script LBNP REB Edit	Email Script	09/Dec/2021	2
CLEAN LBNP Recruitment REB Edit	Recruitment Materials	13/Dec/2021	3
CLEAN Letter of Information LBNP REB Edit	Written Consent/Assent	13/Dec/2021	3

Documents Acknowledged:

Document Name	Document Type	Document Date	Document Version
Citations LBNP	References	16/Sep/2021	1
Itemized Study Budget LBNP	Study budget	22/Sep/2021	1
Flow Diagram LBNP REB Edit	Flow Diagram	09/Dec/2021	2

No deviations from, or changes to, the protocol or WREM application should be initiated without prior written approval of an appropriate amendment from Western

Curriculum Vitae

Name: James Van Riesen

Post-secondary Education and Degrees:
The University of Western Ontario
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Publications:

Shirzad, M., Tari, B., Dalton, C., **Van Riesen, J**., Marsala, M. J., & Heath, M. (2022). Passive exercise increases cerebral blood flow velocity and supports a postexercise executive function benefit. Psychophysiology, e14132. Advance online publication. https://doi.org/10.1111/psyp.14132

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Presentations:

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