The Effects of Heat and Cold on Cognitive Function and Endurance Capacity

Phillip J. Wallace, M.Sc.

Applied Health Sciences

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Faculty of Applied Health Sciences, Brock University
St. Catharines, ON
Canada

Dedication

For my daughter, Claire, may you be able to pursue your passions and interests in life.

Abstract

The maintenance of mental and physical function in hot and cold environments is more challenging compared to thermoneutral environments due to increases systemic physiological and psychological strain. The mechanism for impairments in both cognitive and physical function may be due to early perturbations in whole-body heat balance where the change in skin temperature (even before measurable changes in core temperature) impair performance, followed by greater impairments with changes in core temperature. However, the separate and combined effects of changes in skin and core temperature over a range of cognitive functions and exercise require further elucidation. Therefore, this dissertation tested cognitive function (psychomotor processing, working memory, and executive function) and endurance capacity (at 70% of peak power output) over a range of skin and core temperatures and thermal conditions. Chapter 4 investigates the effects of whole-body skin and core warming (hyperthermia) on cognitive function. In addition, the pharmacological drug, methylphenidate (20 mg, dopamine re-uptake inhibitor) was used as it may improve physiological and psychological strain during heat stress. Chapter 5 built upon Chapter 4 by testing the effects of whole-body skin and core cooling (mild hypothermia) on cognitive function. Chapter 6 extended the findings of Chapter 5 by testing the effects of whole-body skin and core cooling on endurance capacity, to potentially see a cognitive-physical performance interaction. Collectively, we found that neither changes in skin temperature (Range: Δ-6 to +4.5°C), without changes in core temperature, nor manipulation of core temperature (Range: Δ-0.8 to +1.5°C) significantly impaired cognitive function in hot or cold environments (Chapters 4 & 5). Furthermore, methylphenidate did not enhance cognitive function. Whereas, endurance capacity was significantly influenced by cold stress, where cooling the skin/outer shell impaired performance by 32%, while core cooling of Δ-0.5C and Δ-1.0C from baseline

temperature further impaired performance by 61% and 71% respectively. There were no differences between the two core cooling conditions. Collectively, this research program demonstrates the capacity to maintain cognitive function, but not physical capacity under thermal strain. From a practical standpoint, interventions should focus to minimize cold strain to prevent declines in physical capacity under cold conditions.

Keywords: Hyperthermia, Hypothermia, Cognitive Function, Endurance Capacity, Skin Temperature

Acknowledgments

I am not one for reflection, but as I reach the end of this academic milestone, I am reminiscent of how lucky I have been to be able to pursue a doctoral degree and the many people who have provided pivotal help and support along the way.

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ACC	=	anterior cingulate cortex
ACE	=	acute cold exposure
A_D	=	body surface area
AIC	=	anterior insula cortex
ANOVA	=	analysis of variance
BASE	=	baseline
CO_2	=	carbon dioxide
CS	=	cold shell/skin
C-0.3°C	=	cold with -0.3°C change in core temperature
C-0.8°C	=	cold with -0.3°C change in core temperature
$\dot{C}_{resp}$	=	convection from respiratory tract
$\dot{C}_{skin}$	=	convection of skin
CTB	=	cognitive test battery
DalCAB	=	Dalhoussie cognitive assessment battery
DBP	=	diastolic blood pressure
DOPAC	=	3,4-Dihydroxyphenylacetic acid
dt	=	exposure time
$\dot{E}_{resp}$	=	evaporation from respiratory tract
$\dot{E}_{skin}$	=	evaporation from skin
GMLT	=	Groton maze learning task

h_c	=	convective heat transfer coefficient
HC-CS	=	hot core – cooled skin
HC-HS	=	hot core – hot skin
HD	=	heat debt
h_e	=	heat transfer coefficient for evaporative heat loss
HYPO-0.5°C	=	mild hypothermia of Δ-0.5°C
HYPO-1.0°C	=	mild hypothermia of Δ-1.0°C
HVA	=	Homovanillic acid
IZOF	=	individual zone for optimal functioning
$\dot{K}$	=	conduction
$\dot{M}$	=	metabolic heat production
M1	=	motor cortex
MAM	=	maximal adaptability model
MAP	=	Mean arterial pressure
MCAv	=	middle cerebral artery velocity
MPH	=	methylphendate
η^2	=	partial eta squared
NC-HS	=	neutral core – hot skin
Ø	=	fractional relative humidity
OFC	=	orbitofrontal cortex
$P_{et}CO_2$	=	partial pressure of end tidal carbon dioxide
PLA	=	placebo

PFC	=	prefrontal cortex
PPO	=	peak power output
P_a	=	partial vapor pressure of the air
P_{sa}	=	saturated vapor pressure of water
P_{skin}	=	saturated vapor pressure of the skin
$\dot{R}$	=	radiation
RER	=	respiratory exchange ratio
RH	=	relative humidity
RPE	=	ratings of perceived exertion
RPM	=	revolutions per minute
$\dot{S}$	=	heat storage
SBP	=	systolic blood pressure
SMA	=	supplementrary motor area
T_{amb}	=	ambient air temperature
$T_{amb\ skin}$	=	air temperature at the skin surface
T_{core}	=	core temperature
TN	=	thermoneutral
T_{re}	=	rectal temperature
$\overline{T}_{skin}$	=	mean skin temperature
TC	=	thermal comfort
TN	=	thermoneutral
TS	=	thermal sensation

TT	=	time trial
TTE	=	Time To Exhaustion
USG	=	Urine specific gravity
V_b	=	ventral caudal part of the medial dorsal nucleus
$\dot{V}_E$	=	ventilation
$\dot{V}CO_2$	=	volume of carbon dioxide
$\dot{V}O_2$	=	volume of oxygen
$\dot{V}O_{2peak}$	=	peak oxygen consumption
VM_{po}	=	ventral medial nucleus
W	=	watts
$\dot{W}_K$	=	energy used for work
ω	=	skin wittedness of participant

1 - Introduction

Occupational workers, military personnel, and athletes are often required to work, perform military duties, and compete in hot and cold environments where maintenance of mental and physical function is important to maintain safe behaviors, prevent accidents, and determine strategies to minimize further thermal strain (1–4). Both hot and cold environments increase physiological strain through changes in cardiovascular, cerebral, and neuromuscular function as well as changes in energy metabolism and hormonal release (For reviews see: (1, 2)). Furthermore, both environments increase psychological strain (i.e., increased thermal discomfort) that can lead to changes in motivation, mood, and arousal (For reviews: (2–4)). Psychological perceptions of thermal stress are more vulnerable in the heat and cold and are proposed to impair cognitive function due to the sensory displeasure from hot or cold skin before changes in core temperature (5). For example, with heat stress, increased skin temperature led to more errors (6) and slower reaction times (7), while in the cold, cold water immersion leading to cold skin led to more variability in reaction times (8), compared to thermoneutral environments and no differences in core temperature. However, this response is not uniform as both increases (i.e., hyperthermia) and decreases (i.e., hypothermia) in core temperature have led to no impairment in cognitive function (8–12). The overall lack of consensus may be due to methodological differences and the lack of control of skin and core temperature (which also influences thermal comfort). Therefore, to address some of the potential issues related to methodological inconsistency, the overarching theme of this dissertation is to manipulate skin and core temperature to isolate their relative contribution to cognitive function under environmental stress. Furthermore, it is unknown if there is a relationship between changes in cognitive function and physical performance (e.g., endurance capacity) under environmental stress.

Alterations in brain neurochemistry including the alteration of dopamine levels may influence cognitive function in hot environments (13). Methylphenidate is a dopamine re-uptake inhibitor that increases dopamine levels in the brain, where acute doses (20-40 mg) improve cognitive function in healthy adults in thermoneutral environments (14–17). The effect of methylphenidate on cognitive performance in the heat is currently unknown. However, methylphenidate improved cycling time trial performance in 30°C by ~16% and potentially improved thermal perception as a ~0.3°C higher final core temperature was obtained despite similar perceptions of thermal comfort and effort as the placebo condition (18). These performance enhancements do not occur in thermoneutral environments, potentially indicating an interactive effect of dopamine and hyperthermia (19, 20). If cognitive performance is impaired due to sensory displeasure of hot skin (6), methylphenidate may work to counter performance decrements through reducing the psychological strain of heat stress (19). However, the separate and combined roles of methylphenidate and thermal perception on cognitive performance has yet to be determined.

The purpose of this research program is to examine the individual and synergistic effects of skin and core temperature on cognitive function under environmental stress. A secondary purpose is to test the effects of dopamine, skin, and core temperature and cognitive function under heat stress with increased dopamine levels in the brain with the drug, methylphenidate (a dopamine re-uptake inhibitor), as it may also influence arousal and motivation, and thermal perception. A tertiary purpose is to delineate between changes in cognitive function and endurance capacity in cold air. The research program consisted of 2 research projects. Chapter 4 will investigate the acute effects of 20 mg of methylphenidate (dopamine re-uptake inhibitor) compared to a placebo (lactose) on cognitive function during passive hyperthermia. In order to separate the roles of thermal displeasure, methylphenidate, and hyperthermia we tested cognitive function in four

distinct conditions: Baseline (no thermal manipulation), Neutral Core – Hot Skin, Hyperthermic Core – Hot Skin, and Hyperthermic Core – Cooled Skin. Chapter 5 describes the testing that was completed to explore the effects of cold air exposure (cooling skin temperature to two levels of core cooling) on cognitive function in order to identify the effects of cold skin compared to changes in core temperature. We tested cognitive function in four randomized conditions: i) a 30-min exposure to 22°C thermoneutral air, ii) an acute cold exposure to 0°C cold air, iii) a 0°C cold air exposure causing core cooling of Δ-0.3°C from baseline core temperature, and iv) a 0°C cold air exposure causing core cooling of Δ-0.8°C from baseline core temperature. Chapter 6 outlines the testing of cold air (0°C) exposure on endurance capacity to different levels of cold strain ranging from skin cooling through to significant core cooling. We measured time to exhaustion (TTE) at 70% of peak power output in four randomized conditions: i) a 30-min exposure to 22°C thermoneutral air, ii) an acute ~30-min exposure to 0°C cold air leading to a cold shell and neutral core, iii) a 0°C cold air exposure causing mild hypothermia of Δ-0.5°C from baseline core temperature, and iv) a 0°C cold air exposure causing mild hypothermia of Δ-1.0°C from baseline core temperature.

1.1 Introduction References

1. Cheung SS, Sleivert GG. Multiple triggers for hyperthermic fatigue and exhaustion. *Exercise and sport sciences reviews*. 2004;32(3):100–6.

2. Castellani JW, Tipton MJ. Cold stress effects on exposure tolerance and exercise performance. *Compr Physiol*. 2016;6(1):443–69.

3. Cheung SS. Interconnections between thermal perception and exercise capacity in the heat: Thermal perception and exercise capacity. *Scandinavian Journal of Medicine & Science in Sports*. 2010;20:53–9.

4. Stevens CJ, Mauger AR, Hassmèn P, Taylor L. Endurance Performance is Influenced by Perceptions of Pain and Temperature: Theory, Applications and Safety Considerations. *Sports Medicine* [Internet]. 2017 [cited 2018 Jan 3]; Available from: http://link.springer.com/10.1007/s40279-017-0852-6. doi:10.1007/s40279-017-0852-6.

5. Hocking C, Silberstein RB, Lau WM, Stough C, Roberts W. Evaluation of cognitive performance in the heat by functional brain imaging and psychometric testing. *Comp Biochem Physiol, Part A Mol Integr Physiol*. 2001;128(4):719–34.

6. Gaoua N, Grantham J, Racinais S, El Massioui F. Sensory displeasure reduces complex cognitive performance in the heat. *Journal of Environmental Psychology*. 2012;32(2):158–63.

7. Malcolm RA, Cooper S, Folland JP, Tyler CJ, Sunderland C. Passive Heat Exposure Alters Perception and Executive Function. *Frontiers in Physiology* [Internet]. 2018 [cited 2018 May 28];9 Available from: https://www.frontiersin.org/article/10.3389/fphys.2018.00585/full. doi:10.3389/fphys.2018.00585.

8. Cheung SS, Westwood DA, Knox MK. Mild body cooling impairs attention via distraction from skin cooling. *Ergonomics*. 2007;50(2):275–88.

9. van den Heuvel AMJ, Haberley BJ, Hoyle DJR, Taylor NAS, Croft RJ. The independent influences of heat strain and dehydration upon cognition. *European Journal of Applied Physiology*. 2017;117(5):1025–37.

10. Wallace PJ, Mckinlay BJ, Coletta NA, et al. Effects of motivational self-talk on endurance and cognitive performance in the heat. *Med Sci Sports Exerc*. 2017;49(1):191–9.

11. Taber MJ, Hartley GL, McGarr GW, et al. Cognitive Performance during a 24-Hour Cold Exposure Survival Simulation. *BioMed Research International*. 2016;2016:1–11.

12. Schlader ZJ, Lucas RAI, Pearson J, Crandall CG. Hyperthermia does not alter the increase in cerebral perfusion during cognitive activation: Cerebral perfusion during cognitive activation. *Experimental Physiology*. 2013;98(11):1597–607.

13. Kishore K, Ray K, Anand JP, Thakur L, Kumar S, Panjwani U. Tyrosine ameliorates heat induced delay in event related potential P300 and contingent negative variation. *Brain and Cognition*. 2013;83(3):324–9.

14. Mehta MA, Owen AM, Sahakian BJ, Mavaddat N, Pickard JD, Robbins TW. Methylphenidate Enhances Working Memory by Modulating Discrete Frontal and Parietal Lobe Regions in the Human Brain. *The Journal of Neuroscience*. 2000;20(6):RC65–RC65.

15. Elliott R, Sahakian BJ, Matthews K, Bannerjea A, Rimmer J, Robbins TW. Effects of methylphenidate on spatial working memory and planning in healthy young adults. *Psychopharmacology*. 1997;131(2):196–206.

16. Costa A, Riedel M, Pogarell O, et al. Methylphenidate Effects on Neural Activity During Response Inhibition in Healthy Humans. *Cerebral Cortex*. 2013;23(5):1179–89.

17. Ramasubbu R, Singh H, Zhu H, Dunn JF. Methylphenidate-mediated reduction in prefrontal hemodynamic responses to working memory task: a functional near-infrared spectroscopy study: METHYLPHENIDATE-MEDIATED REDUCTION IN HB RESPONSES. *Human Psychopharmacology: Clinical and Experimental*. 2012;27(6):615–21.

18. Roelands B, Hasegawa H, Watson P, et al. The Effects of Acute Dopamine Reuptake Inhibition on Performance: *Medicine & Science in Sports & Exercise*. 2008;40(5):879–85.

19. Roelands B, Hasegawa H, Watson P, et al. The Effects of Acute Dopamine Reuptake Inhibition on Performance: *Medicine & Science in Sports & Exercise*. 2008;40(5):879–85.

20. Roelands B, Meeusen R. Alterations in central fatigue by pharmacological manipulations of neurotransmitters in normal and high ambient temperature. *Sports Medicine*. 2010;40(3):229–46.

2 - Literature Review

2.1 Cognitive Function

Cognitive function defines performance in objective tasks that require conscious mental effort (1). Cognitive functions are either named after the type of task that measures that component or is based off the neural networks that it innervates (2). Cognitive functions are further categorized into simple and complex tasks based on the task's demands or the neural regions that they activate (For an example of simple and complex cognitive tasks see Table 2-1). Simple tasks (such as reaction time or psychomotor processing) require encoding of the task in the primary visual cortex followed by a motor response (2). Complex tasks (e.g., executive function, working memory) often require greater effort, attention, and neural resources, and tend to activate the frontal lobes to perform the tasks (2–5). The focus of this thesis will be on complex tasks such as executive function, working memory, attention and vigilance, and psychomotor processing which will be discussed in more detail below.

Simple Cognitive Tasks	Complex Cognitive Tasks
• Monitoring • Memory Recall • Numerical Vigilance • Choice Reaction Time • Psychomotor Processing • Short-Term Memory • Simple Arithmetic • Simple Visual Orientation	• Arithmetic Efficiency • Attention • Complex Motor Coordination • Mental Rotation • Recall Capacity • Vigilance • Executive Function • Working Memory Tasks

Table 2-1 - An example of categorization of types of simple and cognitive tasks reproduced from (1). It should be noted that this is not an exhaustive list of all cognitive functions and tasks but are the ones commonly tested in environmental physiology research.

2.1.1 Executive Function

Executive function is a umbrella term for a collection of higher-order cognitive processes and is defined as the ability to plan and execute behavior while being able to dynamically update goals, store and acquire information in working memory, switch among tasks, inhibit behaviors, process errors and being able to perform these behaviors in changing environments (2, 3, 6–10). Executive function is also used synonymously with frontal lobe functions, where executive function performance can be influenced by motivation, impulse control, and emotional regulation (2, 11, 12) Anatomically, executive functions occur within the executive attention network which includes: the anterior cingulate cortex (ACC), prefrontal cortex (PFC), hippocampal gyrus, thalamus, parietal lobe, pre-supplementary motor area, insula, and primary sensorimotor area (3, 13–20). There is no one pure task to measure executive function, however there are specific tasks to measure components of executive functioning including inhibitory control (e.g., Go/NoGo, Stroop Test), filtering (Attention Network Task, Flanker), visual-spatial working memory (e.g., Groton Maze Learning, Task, Trial Making Test), and cognitive flexibility (Wisconsin Card Sorting Task) (6).

2.1.2 Working Memory

Working memory is a cognitive process commonly studied in the cognitive science literature, and is typically defined as the ability to store information in the brain and access it ‘online’ (2, 21–26). Working memory allows for the continuous coherent representation of the external world, which would otherwise be interrupted by factors such as object occlusion or eye movement, and aids in storing available relevant visual information needed to support goal-directed behavior (27). High working memory capacity is associated with scholastic success / achievement and general fluid intelligence, while its subsequent decline is associated with chronic

neurological conditions such as Alzheimer's disease (3, 23, 28–30). Zimmer (26) proposes that working memory involves five key aspects: the storage of information, the ability to access stored information, the ability to imagine the information in semantic memory, transform the perceived stimuli, and the ability to reason and problem solve. Typically, working memory capacity is tested by measuring how many items can be 'stored' in working memory, which can be limited by factors such as the quality/resolution of the information stored, the hierarchy of bundled information, and ensemble statistics (22, 23). The time-course to test short-term working memory is displaying an item ≤ 300 ms, where longer presentation times ≥ 1000 ms enable processes such a verbal encoding and long-term memory to aid in performance (24). Xu (31) proposes that working memory occurs in the PFC, where it interacts via top-down regulation with sensory regions and the posterior parietal cortex to ensure task relevant information is properly encoded by sensory regions. Working memory is stored in the posterior parietal cortex and the prefrontal cortex and is not stored in the occipital lobes or visual sensory areas (information is only encoded in these regions) (31). The PFC is used to compare current information with what is stored in the posterior parietal cortex (31). The type of working memory task will play a role in which neural structures are used as visual and spatial stimuli are processed separately, where visual / object information is processed along the dorsal pathway ending in the parietal cortex, and spatial information is processed in the ventral pathway ending in the inferior temporal lobe. Working memory can be influenced by catecholamine neurotransmitters where dopamine and norepinephrine levels demonstrate an inverted U-shaped influence on working memory, spatial awareness, attention, arousal, posture and balance (32, 33), where high levels of dopamine and norepinephrine in alert, non-stress states enhances working memory, while depletion of dopamine and norepinephrine impairs working memory (32–34).

2.1.3 Attention and Vigilance

Attention and vigilance are the ability to keep one's mind continuously focused on a particular task and resist distractions (35). Both attention and vigilance differ from executive function and working memory as it is the ability to consciously process and detect stimuli on tasks lasting longer than 10 s, and this ability excludes executive functions such as spatial orienting, response inhibition, flexibility or the storage of information (36). Attention and vigilance can be influenced by multiple factors including: task-complexity, focus of attention, wakefulness, motivation, stress, and neurotransmitter concentrations (for review see (37)). Using a meta-analytic approach on neuro-imaging studies, Langner & Eickhoff (35) provide evidence that vigilance and attention are mediated by a right-lateralized network comprising of the prefrontal cortex, anterior insula, parietal areas, thalamus, basal ganglia, and midbrain.

2.1.4 Executive Attention

Executive function, working memory, attention and vigilance are interrelated constructs that share similar neural structures and pathways within the executive attention network. McCabe et al. (2) compared conventional executive function paradigms (Wisconsin card sorting task, verbal fluency, mental arithmetic, mental control, episodic memory) and working memory paradigms (reading span, computation span, letter rotation, match span) across the lifespan using factor analytic modelling and determined a strong common variance (r = 0.97) between executive function and working memory performance. Machizawa & Driver (3) extended these findings by determining the relationship between components of working memory (precision, filtering, and capacity) and aspects of attention and executive function using the attention network test (alerting, orienting, and executive control) through a principal component analysis (determines underlying relationship between variables to account for variance by determining similarities between

components). Their results demonstrated that each individual measure of working memory correlated to one measure on the attention network test such that there was a strong relationship between capacity and alerting, precision and orienting, and filtering and executive function (3). Due to the underlying similarity of attention, the shared cognitive ability of working memory and executive function is referred to as *executive attention* (2, 4, 38) and is anatomically distributed in the brain through the executive attention network . The most common similarities between the cognitive functions (executive function, working memory, attention and vigiliance) is the attentional ability, the ability to maintain a goal in an active state during a task and the ability to resolve interference and filter out distractions (Figure 2-1) (2). Both measures of executive function and working memory should be included in research design to determine if the executive attention network as a whole is impaired or if it is task-dependent cognitive functions that are impaired with thermal stress.

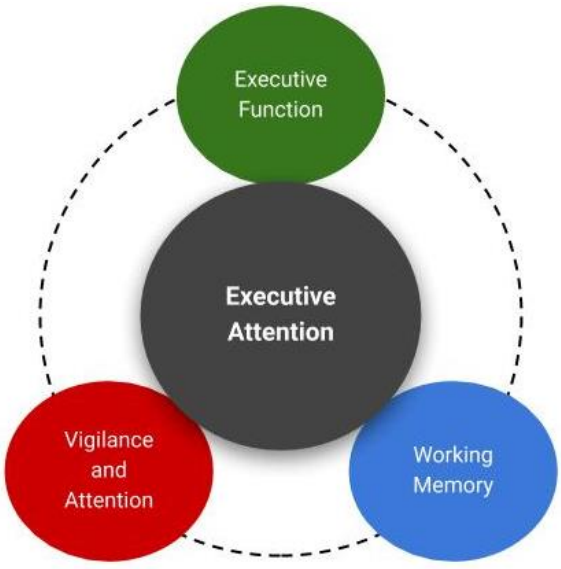

Figure 2-1– A conceptualization of relationship between executive function, working memory, attention and vigilance and how they combine to form executive attention. In this conceptualization, each cognition is a distinct function, though they are interrelated (dotted line) and can influence each other.

2.1.5 Psychomotor Processing

Psychomotor processing speed is a simple cognitive measure of reaction time and an indirect measure of encoding. The speed with which an individual can process information can constrain performance on all cognitive tasks and can be considered a general processing resource related to higher level cognitive tasks (39). For example, age-related decline in working memory is associated with declines in processing speed (40). This may occur through slower processing limiting the amount of information that will be simultaneously available for processing and/or limit the time available to make paired associations or retrieval of information during tasks. Psychomotor processing involves the left thalamus, right inferior lobule, and frontal and parietal lobes (41). Psychomotor processing is an important variable to measure in conjunction with higher-order cognitive tasks under environmental stress, as changes in executive function and working may be a result at the earlier stages of encoding information as opposed to impaired storage or control of information.

2.2 Models of Cognition and Environmental Stress

This section provides a discussion of how multiple models of the interrelationship between environment stressor, psychological responses, and physiological responses can influence cognitive function or brain structure to influence neurological function.

2.2.1 Distraction and Arousal Theory

From a psychological perspective, distraction theory and arousal theory have been prominently used to describe how temperature influences cognition. Distraction theory purports

that the sensory displeasure and sensation of hot/cold skin interrupts attention and directs focus away from a cognitive task towards the hot/cold stimuli (See Figure 2-2 for simplified example model) (42). For example, Shurtleff et al. (43) demonstrated that 60-min exposure to 4˚C cold air that reduced mean skin temperature ($\overline{T}_{skin}$) - but not core temperature (T_{core}) - reduced working memory performance. Additionally, work from our lab demonstrates an impairment in attention with cooling of skin temperature causing thermal discomfort, with no additional decrements with T_{core} cooling of 1.0˚C (44). As an alternative to distraction theory, the arousal theory argues that an inverted U-relationship (known as the Yerkes-Dodson law) exists between cognitive performance and arousal regulation (45). As ambient temperature, T_{core}, and $\overline{T}_{skin}$ increases or decreases, an individual's arousal level will either increase until there is an optimal state of arousal or performance will gradually decline as arousal levels increase or decrease further from the optimal arousal level (46). This model is supported by Spitznagel et al. (47) where 53 hour sleep deprivation reduced working memory performance during 2-hour cold air exposure (10˚C) on working memory and psychomotor processing compared to no sleep deprivation. An extension to this theory is the individual zone for optimal functioning (IZOF), which states that an optimal performance state is one with the best internal conditions (e.g., emotions, arousal) (48). This optimal zone of functioning will lead to a complete involvement in a task and result in the best possible performance. For example, an individual may perform optimally while having positive emotions and low arousal, while another individual can use negative emotions and a high state of arousal to perform optimally (48). Furthermore, an extension of arousal theory is the parallel processing model (49), where both perception (such as temperature and fatigue) and emotional-distress components are processed in a parallel fashion (as opposed to an additive process). In this model, perception is considered an active process, and the preconscious processing of sensory

information (e.g., temperature, heart rate, exertion), is processed before it is consciously available or made aware (49). This can lead to changes in perceptual measures (e.g., thermal comfort, sensation) and can be variable between individuals depending on motivational/ emotional regulation (49). This model also indicates the increased sensory and mental demands placed by changes in skin temperature alone as this information is required to be preconsciously and consciously process which can take away neural resources from a cognitive task (49). The arousal theory and IZOF are difficult to apply to hyperthermia, hypothermia and cognition research, as there are limited studies measuring arousal, or psychophysiological factors that may alter cognitive performance. Additionally, these approaches are highly descriptive and are difficult to experimentally quantify (50, 51).

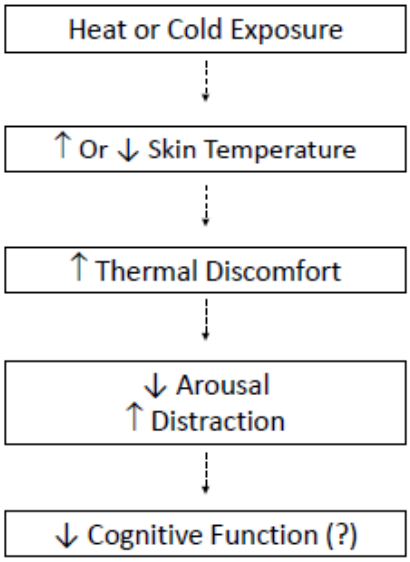

Figure 2-2 – Simplified model for how sensory displeasure (distraction and arousal theories) influences cognitive function under thermal stress.

2.2.2 Maximal Adaptability Model

Hancock & Warm (50) proposed the maximal adaptability model (MAM) to extend arousal theory to include both physiological and psychological stress and how they can influence cognitive

performance (Figure 2-3). The MAM model provides a normative zone where performance is near optimal because cognitive adjustments and task demands are easily accomplished, where performance degrades with extreme ends of stressors from hyperstress (e.g., hyperthermia, hypothermia) to hypostress (e.g., boredom) (51). In the normative zone, minor levels of stress inputs are readily adapted to, and do not disturb steady-state functioning or reflect any changes in behavior or cognitive performance (50). However, as the environmental stress becomes more adverse or the complexity of the task increases, arousal levels need to increase or cognitive resources need to efficiently shift to maintain optimal cognitive performance (51). In the MAM model, there exists a maximal zone of adaptability where performance is unaffected, however, eventually the increased level of stress will extend past this zone and deplete neural resources, which will cause decrements in cognitive performance (50, 51). The strength of this model is that there are both psychological and physiological maximal zones of adaptability when exposed to environmental stressors. Potentially, if an intervention (e.g., altering neurotransmitter levels) is successful in countering the decrements in cognitive performance in the heat, it can do so by extending both the physiological and psychological zones of adaptability. Or this model can be used in experimental designs by isolating and combining changes in skin and core temperature which can influence both physiological and psychological function.

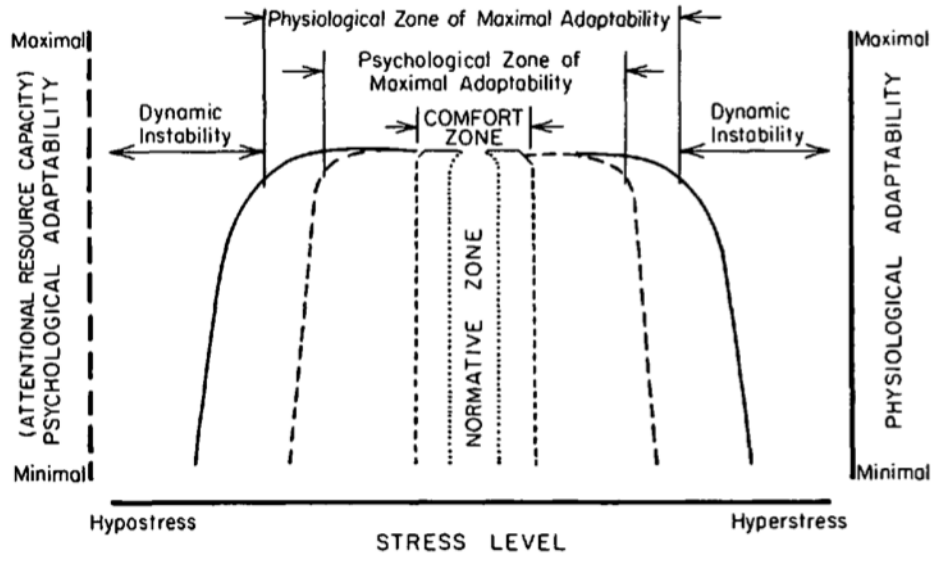

Figure 2-3 - The maximal adaptability model which indicates a normative zone where environmental stress is insufficient to cause degradation in performance and includes both physiological (solid lines) and psychological (dashed lines) adaptive capability zones. Outside of these zones is dynamic instability that will eventually lead to functional failure. Figure is from Hancock & Warm **(50)**.

2.2.3 Neurological Model of Exercise Capacity

Exercise is both physiologically and psychologically demanding in adverse environments (see below for psychophysiological responses to heat and cold) where exercise capacity and self-paced exercise performance is reduced (52–55). The decrements in exercise performance may be interrelated to changes in cognitive function under environmental stress due to shared neural regions with executive attention. The brain provides top-down regulation of exercise performance through altering behavior/pacing strategy to successfully complete a set duration of exercise or to prevent catastrophic failure (e.g., collapsing) and cease exercise in endurance capacity tests (56, 57). Recently multiple models have been proposed as to how changes in the brain and cognition may be related to physical fatigue and exercise (58–60). Robertson & Marino (58) have proposed a neurological model (Figure 2-4) where the prefrontal cortex (PFC), lateral PFC, orbitofrontal cortex (OFC), the premotor area, anterior insular cortex (AIC), and the anterior cingulate cortex

(ACC) integrate afferent feedback and determine a relevant motor response through the pre-motor area and basal ganglia to regulate voluntary exercise performance. These neural structures also play a role in motivation, reward, planning, projecting future states, and emotional regulation (11). Bottom-up afferent feedback (e.g., cardiovascular, respiratory, temperature) is integrated in the lateral PFC along with motivational and emotional context from the AIC, ACC, and OFC (58). The PFC is well known for its role in executive attention, where cognitive control coordinates thought and actions related to the achievement of internally derived goals (58). The AIC and the ACC appraise afferent homeostatic signals to determine the perception of the bodily state (including thermal perception and fatigue) and emotions, predicting future perturbations in homeostasis to determine behavior (61–64). The OFC processes both emotional and motivational responses to stimuli in an ongoing manner in order to continuously update information about the current situation and interpretation of how rewarding a task is to make continuous decisions about motor output (56). Ultimately, the bottom-up afferent signals and top-down psychological drive will be continuously integrated to create a task relevant response (via the basal ganglia and premotor area) and a motor response to modify pace (e.g., speed up, slow down, maintain pace) or to terminate exercise (58). Evidence for this model is that there are decreases in PFC oxygenation before exhaustion during incremental exercise testing (65), potentially indicating that the PFC and cerebral autoregulation play an important role in the regulation of performance.

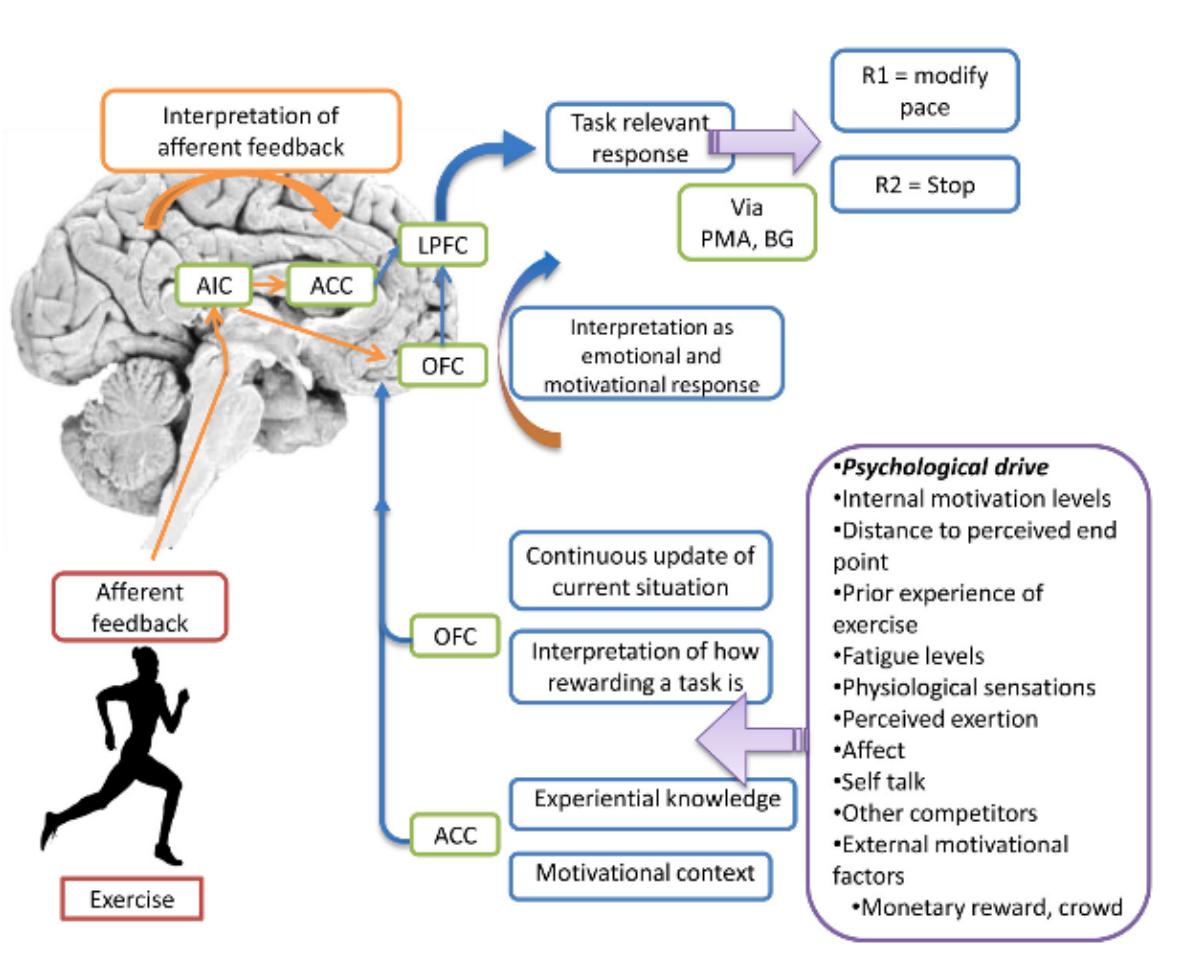

Figure 2-4 - Robertson & Marino **(58)** model on how neurological structures and psychological drive can influence the decision to modify pacing strategies or terminate exercise.

2.2.4 Interoception Model

Recently, McMorris et al. (59) have proposed moving towards an interoceptive model towards understanding physical fatigue during endurance based exercise (See (59) for review). Interoception is the conscious and unconscious perception of the internal physiological condition of the entire body that includes sensory information regarding homeostasis, muscular activity, emotion and motivation (59). In this model, the decision to continue or terminate exercise exists based on top-down processes in the brain (PFC) and bottom-up feedback from the entire body, as opposed to just the working muscle itself (59). The dorsolateral PFC is used to control top down

strategies to achieve the goal and creates a feed-forward loop to create predictions of the expected sensory feedback from the insular cortex (see neural pathway below) that will determine whether to stop or continue exercise (59–61). This process involves multiple factors to determine predictions of future states and will depend on the individual's: past experiences of similar physical activity, perception of their current fitness level (i.e., can they accomplish this exercise task), subjective interpretation of importance of the activity, and whether they feel their actions will be evaluated or if they are competing with others (59) (See Figure 2-5 below on factors influencing interoceptive predictions). These interceptive predictions are continuous and on-going and will also be influenced by a variety of chronic processes including long-term goals (e.g., push harder to achieve fitness goal), personality, and physical and social development (59). The individual will make continuous and ongoing interoceptive predictions during the task. Individuals can make errors in these interoceptive predictions that can be altered overtime. For example, Paterson and Marino (66), had 21 endurance trained cyclists complete a 30-km cycling time trail. Following the 1st 30 km time trial, these individuals were asked to perform a second 30-km time trail, however, in this trial, individuals were deceived and either completed a 24 km time trial (shorter distance), a 30 km time trial (identical distance), or a 36 km time trial (longer distance). They were then tasked to perform a 3rd 30 km time trial, where individuals' performance and pacing strategy changed based on the 2nd time trial they performed, where the individuals who performed the 30 km time trial performed similarly, while the shorter distance group were faster (increased power output) and the longer distance group were slower (decreased power output) where pacing strategies (and interceptive predictions) were matched based on the distance they performed in the second time trial. These results indicates that predictions are continuously updated and routed in past experiences and available information (59). These prediction errors also occur in adverse

environments as deceiving individuals of the environmental temperature (telling individuals the ambient temperature is 26°C as opposed to true temperature of 30°C) can ameliorate the heat-related declines in cycling performance (67). Ultimately, these studies support the basis of a top-down mechanism for altering exercise performance.

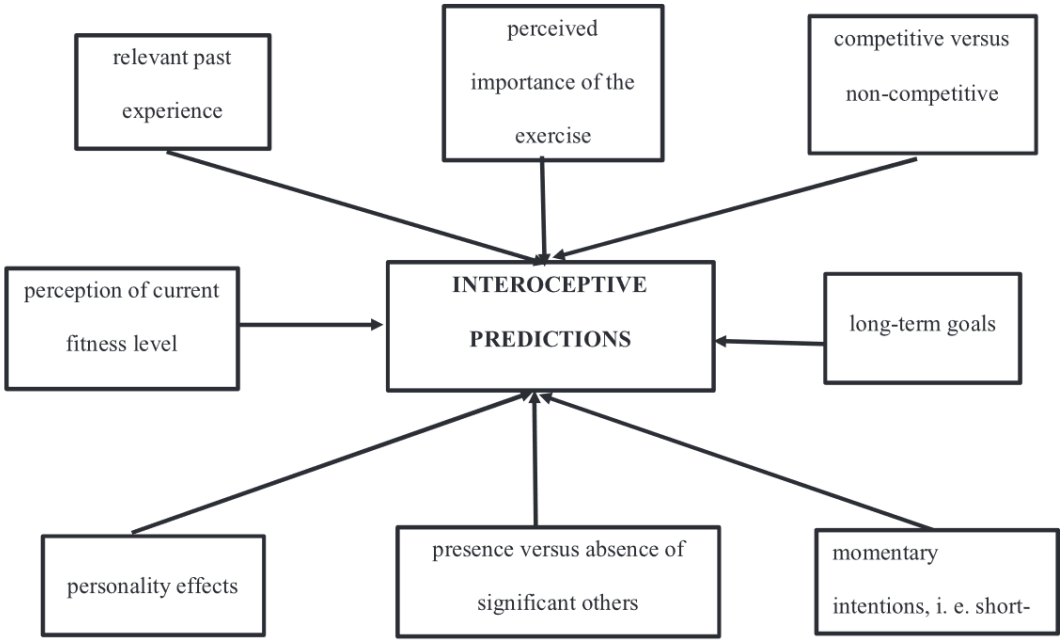

Figure 2-5 – Factors influencing interoceptive predictions from McMorris et al. **(59)**

The underlying pathway for interoception is that interoceptive signals are projected to the brain via multiple neural pathways including the lamina I- spinothalamocortical pathway, nucleus of the solitary tract (NTS), and somatosensory pathway (Figure 2-6) (61, 68). Along the lamina I-spinothalamocortical pathway, afferent signals including thermal, mechanical, chemical, metabolic, and endocrine status of viscera, skin, muscle, joints and teeth, are conducted from small-diameter (Aδ and C) primary afferents to the lamina I of the spinal and trigeminal dorsal horns and relay the afferent information along the lateral spinothalamic tract to the brainstem to provide information regarding homeostasis (59, 61). The NTS, which is a white bundle of nerve

fibers that receive parasympathetic afferent signals from the vagal and glossopharyngeal nerves (61). The NTS contributes significantly to autonomic function and receives input for taste, chemoreceptor and mechanoreceptor input from the cardio-respiratory system and gastrointestinal tract, where afferent signals are organized viscerotopically (61). The sympathetic lamina I and parasympathetic NTS pathways underlies perceived feelings such as cool, warm, itch, first (pricking) pain, second (burning) pain, muscle burn, hunger, joint pain, thirst and nausea (68). The ascending lamina I and the NTS axons terminate on the contralateral thalamus including the posterior part of the ventral medial nucleus (VM_{po}) and the ventral caudal part of the medial dorsal nucleus (VM_b). The VM_{po} and VM_b project to the insular cortex, then information is projected topographically to the contralateral AIC and then through the callosal pathway, is lateralized on the right AIC (59). This makes the interoceptive information consciously available, allowing the individual to create subjective feelings and awareness of one's self and their physical and emotional state (69). The insular cortex is activated during maximal exercise and increased activation is correlated with an increase in exercise intensity (70, 71). The insular cortex does not rely on mechanical and metabolic afferent feedback from the working limbs, as the insular cortex is not activated during passive cycling (tandem ergometer where one partner actively pedals so the other partners limbs are moving without active participation) (70). The AIC compares interoceptive feedback with top-down predictions of the interoceptive state and this information is forwarded to the ACC, lateral PFC, and ventro-lateral PFC. The ACC is the limbic sensory cortex that is responsible for numerous higher order cognitive processes such as: motivations, affective appraisal of stimuli, risk/reward determination, decision-making, and executive function (60, 61). Ultimately, interoceptive information (bottom-up afferent feedback) will be integrated in the AIC, ACC, and PFC and based on top-down decision making (based on current state, past experiences,

and motivational state) will lead to whether individuals will continue performing exercise or stop the action. Differing from the Robertson & Marino Model (58), in the interoceptive model, it is proposed that the ventrolateral PFC (and not the dorsolateral PFC) projects onto the pre-supplementary motor area (SMA), the SMA, and the pre-motor cortex (PMC) that initiates the stopping of a motor action by the primary motor cortex (M1) (59). Furthermore, neurotransmitters such as dopamine and norepinephrine are integrated in this model as they may influence the decision to terminate exercise, as dopamine plays and important role in the motivation/reward centers (ACC, PFC) and the basal ganglia, as well as norepinephrine synthesis which also influences motivation (59, 60). At exhaustive exercise, there is likely and increase in the concentrations and tonic firing of dopamine and norepinephrine which leads to the breakdown in the efficiency of the PFC (59). This process may lead to central fatigue, causing the PFC to terminate exercise (59). Ultimately, there is a complex and ongoing processes related to bottom up afferent information from the whole body, top down interpretation and regulation, and neurotransmitters influencing exercise tolerance and fatigue (59).

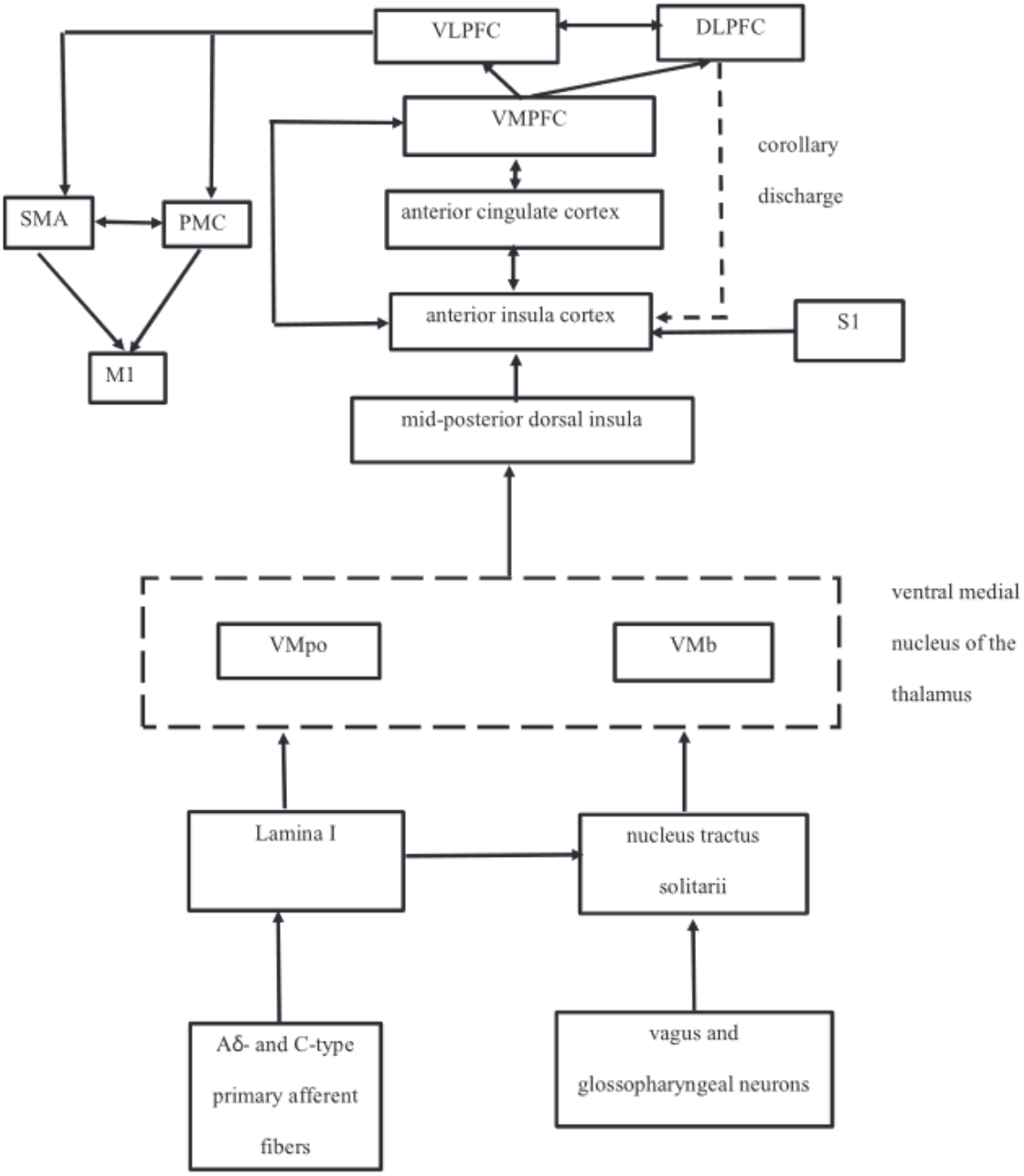

Figure 2-6 – Underlying neural pathway schematic for interoception from McMorris et al. **(59)**. DLPFC = dorsolateral prefrontal cortex, VLPFC = ventrolateral prefrontal cortex, SMA = supplementary motor area, PMC = pre-motor area, M1 = primary motor cortex, VMPFC = ventromedial prefrontal cortex, S1 = somatosensory cortex, VM_{po} = posterior ventral medial nucleus of the thalamus, VM_b = basal ventral medial nucleus of the thalamus.

Evidence for both these models can be made through indirect manipulations of the neural components of the PFC. For example, if the ACC is fatigued using the AX-Continuous

performance cognitive task, there is a decrease in time-to-exhaustion at 80% peak power output (PPO) by 16% (72). Meanwhile, previous work from our lab demonstrated that a two-week motivational self-talk intervention significantly improved time-to-exhaustion time at 80% PPO and executive function in the heat by improving psychological tolerance of high physiological strain (12). Motivational self-talk is a top-down regulation strategy requiring participants to continuously reappraise negative self-talk and bottom-up feedback with self-contextualized motivational statements which may have enhanced performance through altered neural activation in the PFC, AIC, ACC and OFC (12). However, these models are limited as it is difficult to measure neural activation within these structures during exercise and often indirect inferences have to be made (e.g., cognitive function testing, cerebral oxygenation). The Robertson & Marino (58) model and interoception can be used as a conceptual framework for testing cognitive function and exercise performance under environmental stress. Hypothetically, interventions (e.g., altering neurotransmitters) that improve exercise performance under environmental strain, may extend to executive attention network under similar levels of thermal stress. Whereas, impairments in executive attention and cognitive function may occur before (73) or at the same decline as cognitive function. Currently it is unknown if impairments of cognitive function occur concurrently or at different rates to physical performance, but based on the Robertson & Marino (58) model and interoception model (59, 60) these performance changes may be interrelated.

2.3 Psychophysiological and Cognitive Responses to Hot and Cold Environments

This section will breakdown of psychophysiological responses to hot and cold environments will be discussed. Next, how cognitive function changes under these environmental conditions will be discussed. The concepts of distraction and arousal theory in relation to sensory displeasure from changes in temperature, maximal adaptability model in relation to increase

psychological and physiological strain experiences, and the neurological model in relation to cold and exercise performance will be used to potentially explain changes in cognition under environmental stress.

2.4 Psychophysiological Responses to Hot Environments

Exposure to hot environments leading to elevations in core temperature (i.e., hyperthermia) increases physiological (i.e., cardiovascular, metabolic), psychological (i.e., thermal discomfort), and neurological (i.e., central processing, alterations in neurotransmitters) strain relative to thermoneutral environments (Figure 2-7). Passive hyperthermia increases cardiovascular strain through vasodilation leading to an increased blood flow to the skin to aid in dry heat loss and less venous return, decreases in plasma volume due to water loss from sweating and dehydration leading to higher heart rates (74–76). Although increased cardiovascular strain is a physical component of passive hyperthermia that contributes to overall strain, it does not appear to be the primary driver of impaired cognitive performance (68). Cardiovascular strain can be manipulated through fluid levels (as dehydration will lead to greater increases in heart rate), where increased cardiovascular strain from 3-5% dehydration of body mass coupled with moderate hyperthermia did not affect visual perception or working memory (77). However, the increased cardiovascular strain may contribute to psychological discomfort due to feeling of high heart rates while at rest, where the relief of cardiovascular strain while hot may reduce psychological strain and improve arousal (see below in ‘Psychological Responses to Hot Environments’).

2.4.1 Cerebral Function in Hot Environments

Multiple physiological changes occur with passive hyperthermia that influence cerebral function including alterations in neural processing, neurotransmitter concentrations, and cerebral

blood flow (Figure 2-7). Passive hyperthermia leads to alteration in brain activity where there are reduction in ß-band waves activity and increases in α-band activity in the frontal lobes (78). Brain activity normally shifts from high frequency β-band waves during periods of alertness to increased activity of α-band waves when drowsy, indicating that increases in T_{core} lead to decreased arousal (79). Furthermore, these changes in brain activity do not appear to be due to dehydration (3-5% of body mass) or cardiovascular strain, but rather due to changes in T_{core} (78). Changes in neural processing relative to thermoneutral conditions have been indexed with increases in nerve conduction velocity, decreases in neural network efficiency, and decreases in the amplitude in evoked-response potentials using electroencephalography (7, 80–82). These changes appear to be directly related to changes in T_{core}, as an increase in T_{core} by ~Δ1.2°C decrease P300 amplitude and increase latency during a Go-NoGo task, whereas whole-body cooling back to baseline T_{core} restored P300 amplitude (83).

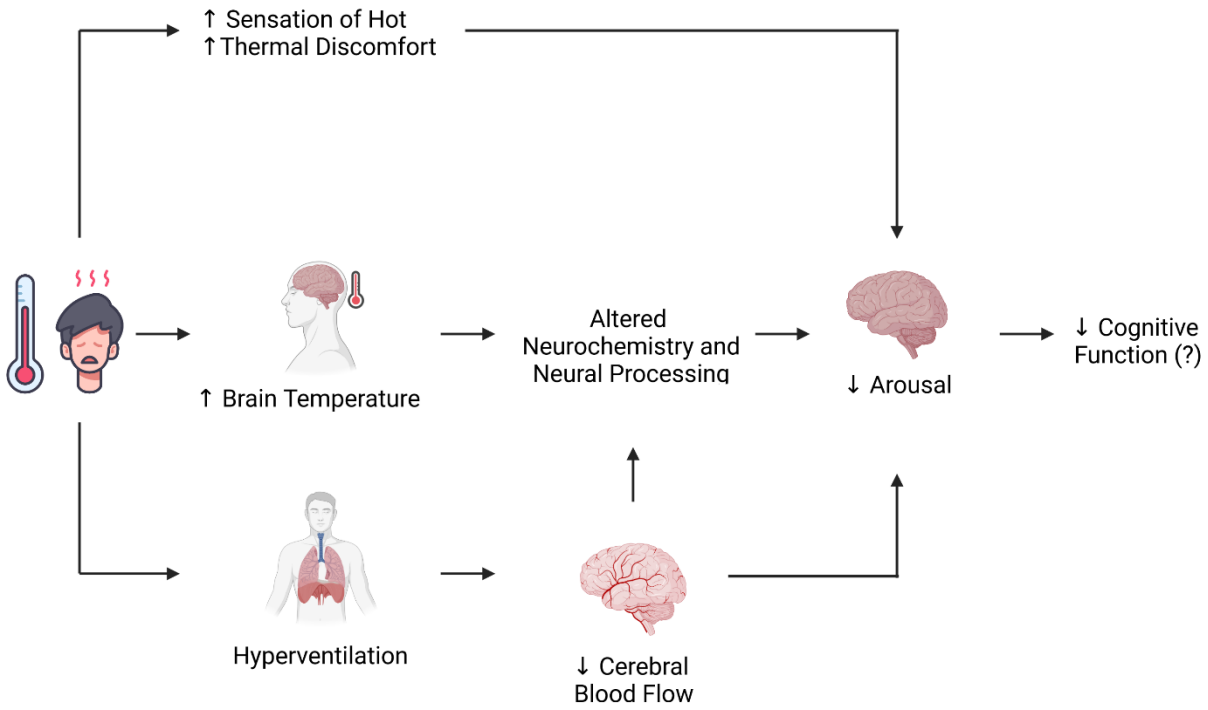

Figure 2-7 – The cerebral changes that occur with passive hyperthermia that may independently or combine to decrease cognitive function.

Along with changes in neural processing, mental function relies on neurotransmitter activity and sensitivity. For example, both dopamine and norepinephrine are important neurotransmitters for cognitive performance and each demonstrate an inverted-U response during working memory tasks, where either too little or too much of the neurotransmitters impair prefrontal cortex function and task performance (32–34). The study of altered neurochemistry in the heat has primarily focused on exercise performance. In animal models, there is a decrease of dopamine levels at physical fatigue in hot environments but not thermoneutral environments (84). Furthermore, the injection of bupropion, which is a dual norepinephrine and dopamine re-uptake inhibitor, improved exercise tolerance in the heat (84). Changes in performance also occur in

humans, as ingestion of bupropion improved cycling time-trial performance by ~9%, as well as ingestion of methylphenidate (dopamine re-uptake inhibitor) improved performance by ~16% in a hot environment (30°C) but not a thermoneutral environment (85, 86). It is currently unknown if alterations in dopamine neurotransmitters through the ingestion of pharmacological drugs (e.g., dopamine reuptake inhibitor) influences cognitive function in the heat.

The cerebral vasculature is highly sensitive to changes in arterial partial pressure of carbon dioxide (CO_2), where reductions (i.e., hypocapnia) lead to a decrease in cerebral blood flow (87–89). Passive hyperthermia causes a hyperventilatory hypocapnia response that leads to reductions in cerebral blood flow (90–94) and increased cerebral metabolism (95). For example, Fan et al. (2008) demonstrated increases in core temperature of 1.0°C and 1.5°C caused an increase of 14% and 57% in ventilation, a decrease of 13% and 29% in $P_{et}CO_2$, and a consequent decrease in middle cerebral artery velocity (MCAv, index of cerebral blood flow) by 14% and 24%, respectively. Along with decreases in cerebral blood flow, there is an increase in cerebral metabolism and metabolic rate in the cerebellum and hypothalamus (thermoregulatory center of the brain) and decreases in other regions of the brain, which may occur in order to maintain cerebral function under hyperthermia (90, 95). The maintenance of $P_{et}CO_2$ may be a potential countermeasure to hyperthermia-induced cognitive decrements or enhance cognitive function during thermal stress. In thermoneutral environments, hyperventilation-induced hypocapnia impaired executive function (stroop task) as indexed by longer reaction times and an increased error rate (97). These finding extend to hypoxic environments, as hypocapnia induced through hypoxic hyperventilation significantly impaired psychomotor processing as indexed by slower reaction times, but did not affect working memory performance (98). However, clamping $P_{et}CO_2$ to eucapnia levels during isocapnic hypoxia, countered the impairments in psychomotor processing (98). Therefore, based

on these findings, it is possible that reductions in CO_2 from hyperthermia-induced ventilation may contribute to alterations in cognitive performance under thermal strain. It is currently unknown if clamping $P_{et}CO_2$ to eucapnic levels throughout heat exposure can influence cognitive function.

2.4.2 Psychological Responses in Hot Environments

There is increased psychological strain in hot environments that occurs before measurable changes in T_{core} leading to increases in thermal displeasure, decreases in arousal, motivation, and decreases in vigor relative to thermoneutral environments causes by hot skin and core temperatures (12, 99–102). The perception of temperature is separated into two related but distinct measures; one is the perception of temperature (known as thermal sensation (TS)) while the other is the perceived satisfaction/indifference of that temperature measured as thermal comfort (TC) (103–105). Heating leads to the sensation of feeling hot, while thermal comfort can vary as heat can be perceived as comfortable (i.e., sitting in hot tub or sauna) or uncomfortable. The sensory displeasure from the heat is partially derived from skin temperature as regional cooling of the face, neck, and head or whole body skin cooling without a reduction in T_{core} improved TC and can lead to increases in exercise performance and cognitive function in the heat when cooling stimulus is applied (106–109). With heat stress, thermal discomfort from hot skin impairs visual spatial awareness and planning, as well as inhibitory control despite no changes in T_{core} (102, 110). These results have confounding variables, whereas as individuals experience thermal discomfort, they may demonstrate a speed-accuracy trade-off where reaction times are slower in order to maintain accuracy (110). However, few studies have independently manipulated the effects of skin and core temperature on cognitive function making it difficult to isolate the effects of thermal discomfort.

2.5 Cognitive Function, Heat Stress, and Hyperthermia

The reporting of alterations in cognitive function under heat stress are not new, where observations of mineworkers working in extreme hot conditions report higher instances of occupational accidents and mental errors in the heat (111). Alterations in cognitive function are proposed to be influenced by both the magnitude of thermal strain and task complexity, such that simple cognitive tasks (such as psychomotor processing reaction time) are less vulnerable and in some cases improved with passive heat stress, while higher-order complex cognitive tasks (such as executive function, vigilance, working memory) are more vulnerable to thermal strain as they require greater effort and neural regions to perform the tasks (112–115). Subjective perceptions of thermal stress may alter cognitive function prior to major changes in physiological status (116, 117). Elevations in $\overline{T}_{skin}$ leads to thermal displeasure which can limit the amount of resources that can be allocated to complete the task at hand (51). For example, Gaoua et al. (2012) found that an increase in $\overline{T}_{skin}$ by ~3.0˚C in a hot environment (50˚C, 30% relative humidity) led to a speed-accuracy trade-off where participants responded faster but made more errors on a complex executive function (spatial planning) task compared to a thermoneutral (24˚C, ~30% relative humidity) environment, with no difference in a simpler executive function task or psychomotor function task performance. Similarly, Malcolm et al. (2018) found a speed-accuracy trade-off, where participants had slower reaction times for perception and executive function based tasks, with no changes in accuracy during 1 hour passive exposure in a hot (~40˚C, 50% relative humidity) compared to a thermoneutral environment (~21˚C, ~42% relative humidity). However, a limitation of these studies was not standardizing the level of $\overline{T}_{skin}$ changes between the participants, where increasing $\overline{T}_{skin}$ by ~4 ˚C with no changes in T_{core} did not change somatosensory processing (82). One way to tease out the effects of sensory displeasure of warm skin versus core temperature *per se*, is to remove the sensory displeasure of hot skin while hyperthermic. If

cognitive performance is impaired due to sensory displeasure caused by elevated skin temperature, cooling the skin may mitigate the effects of hyperthermia-induced impairments in cognitive function (118). However, the evidence is mixed where studies using electroencephalography during whole-body cooling or head cooling while hyperthermic demonstrated that cooling did not alter central processing (82) or event-related potential amplitude (119) compared to hyperthermia with elevated skin temperature.

The thermal strain required to impair higher-order cognitive tasks (i.e., working memory and executive function) is variable, where studies demonstrate impairment relative to thermoneutral conditions with rises in T_{core} from 1-2°C (73, 81, 114, 120) , while others demonstrate little to no impairment in errors in executive function, working memory, or visual perception within a similar T_{core} range (77, 121, 122). Recently, it has been proposed that a threshold of $\geq$ 39°C in T_{core} is needed before cognitive impairments occur under heat stress (115). However, obtaining this high level of absolute T_{core} may also be influenced by thermal tolerance which may confound changes in cognitive function per say. Furthermore, thermal tolerance at this level of hyperthermia is variable between individuals and is influenced by a variety of factors such as aerobic fitness and heat acclimation status (54), body composition (123), neurotransmitter concentrations (e.g., dopamine) (84), and thermal perception (107). Future work is needed to determine the T_{core} threshold for hyperthermic impairment and underlying mechanisms influencing cognitive function under thermal strain. Furthermore, future research should aim to delineate the roles of core and skin temperature as well as sensory displeasure from cognitive function in the heat.

2.6 Dopamine as an Underlying Mechanism for Cognitive Function Impairments in the Heat

Activity of catecholamine neurotransmitters such as dopamine within the brain may affect physiological, cognitive, and psychological capacity in the heat and with hyperthermia that may be beneficial for cognitive function. Dopamine levels are an important physiological factor and ergogenic aid during cognitive and exercise performance in thermoneutral environments, improving prefrontal cortex function (33); increasing arousal, reward, and motivation (124); improving motor control, and through dampening overriding inhibitory signals from the central nervous system (86, 125–128). Dopamine is a monoamine catecholamine neurotransmitter produced in the brain and participates in two main ascending pathways i) the nigrostriatal system (the substantia nigra pars compacta to the striatum), and, ii) the mesolimbic and mesocortical pathways (the ventral tegmental area which extends to the arcuate nucleus of the hypothalamus and cortical sites such as the prefrontal cortex) (129, 130). Dopamine is synthesized through the catecholamine synthesis pathway, which includes the following steps:

- the amino acid tyrosine is converted into L-DOPA by the enzyme tyrosine hydroxylase (131)
- L-DOPA is converted into dopamine by the enzyme aromatic L-amino acid decarboxylase in the cytoplasm
- dopamine can be converted into norepinephrine by dopamine-ß-hydroxylase in the synaptic vesicles (132)
- norepinephrine can be methylated to form epinephrine by phenylethanolamine N-methyl transferase

The rate of synthesis is controlled through feedback inhibition of the rate limiting step, where tyrosine hydroxylase is inhibited through the accumulation of primarily norepinephrine, dopamine, and epinephrine (132, 133). Extracellular brain dopamine levels can be increased

pharmacologically with methylphenidate (MPH, common drug name Ritalin) which is most commonly used to treat attention deficit hyperactivity disorder (134). Methylphenidate is a dopamine reuptake inhibitor that binds to the dopamine transporter and has a fivefold-higher affinity for the dopamine transporter than for the norepinephrine transporter (134–138), thereby increasing extracellular dopamine levels (139). As MPH directly increases dopamine in the brain through dopamine re-uptake inhibition, the next sections will primarily focus on the use of MPH on cognitive function. In addition, to the use of MPH and other methods to increase neurotransmitters under environmental stress along the dopamine-norepinephrine pathway on exercise performance will be discussed.

In healthy adults, acute doses (20-40 mg) of MPH demonstrate a neuroenhancement for cognitive tasks such as spatial working memory and planning (140, 141), simple working memory (142, 143), and executive function through improved response inhibition (144–146) and mathematical operations (147). However, MPH does not improve all levels of cognition as it does not enhance vigilance and may disrupt attentional control (143, 148). This occurs as dopamine reduces background firing rate of neuronal cells, which decreases non-task related activity and improves the signal-to-noise ratio of mental operations leading to less distractibility (149). Methylphenidate influences the executive attention network through increasing dopamine in the prefrontal cortex (150) and altering the dorsolateral prefrontal cortex, thalamus, cingulate gyrus, posterior parietal cortex, and the supplementary motor area during cognitive tasks compared to placebos (138, 139, 141, 142, 147, 149, 151, 152). Additionally, MPH may work to improve cognitive performance through an alteration of cerebral hemodynamics leading to less cognitive load as there are regional reductions in CBF in the frontal and temporal lobes (141, 153), decreased oxy-hemoglobin in the right prefrontal cortex (142), and reduced cerebral glucose metabolism

(147) with improved performance on working memory and executive function tasks. These effects are sensitive to cognitive stimuli, where increases in extracellular dopamine only occur while performing cognitive tasks and not during neutral tasks (154). There are individual differences in these responses as some individuals may be responders and non-responders to MPH (134, 137, 154, 155), where individuals who have a low level of brain metabolism at baseline and show a large increase in brain metabolism with MPH, also show the largest improvements in cognitive performance (147). It is unknown if there are differences in the role of MPH on cognitive function and cerebral metabolism between healthy males and females. Currently, there are no published research studies testing the efficacy of MPH on cognitive performance on healthy adults in the heat.

2.6.1 Manipulation of Dopamine Levels on Performance in the Heat

Manipulation of dopamine levels may be beneficial for cognitive performance in the heat due to the effects of MPH on physical performance, alterations in thermal perception, or through a psychostimulant effect. Increasing baseline dopamine levels with MPH has been demonstrated to affect exercise performance in thermoneutral and hot environments (Table 2). Acute doses (20 mg) of MPH improved cycling time-trial performance in trained cyclists by 16% in the heat (30˚C) while finishing the trial with a higher terminating T_{core} (~0.3˚C) without any changes in perceived exertion or thermal discomfort (86). Performance enhancements do not appear to extend to thermoneutral environments as acute doses of MPH (20-40 mg) have not been demonstrated to significantly improve self-paced cycling performance (86, 156). However, MPH (10 mg) has been demonstrated to increase power output during cycling at a clamped perceived exertion of 16 (‘hard to very hard’) with a 32% increase in time to exhaustion (157). Methylphenidate (20 mg) also increases right-handed isometric force production by ~5-6% in thermoneutral environments (158).

With this improvement, there was an increase in coupling between left insular cortex and left motor cortex indicating enhanced flow of information (158). Additionally, MPH induced a negative connectivity between the insular cortex and orbitofrontal cortex (typically there is a positive connectivity with physical fatigue) indicating MPH may reduce the perception of fatigue (158). Furthermore, MPH has a psychostimulant effect, where MPH lead to increases in heart rate, blood pressure, and plasma epinephrine through sympatho-adrenal stimulation (139, 155, 159) that may increase arousal. Collectively, these results indicate that higher levels of dopamine may work to improve performance by dampening inhibitory signals to terminate activity (86), reducing perceptual thermal strain of the heat (86, 157, 158), or offsetting decreases in motivation or arousal (101, 124, 130). Importantly, the manipulation of catecholamine neurotransmitters along other avenues of the dopamine-norepinephrine pathway such as tyrosine (160, 161), L-DOPA (162) or norepinephrine re-uptake inhibitors (85, 163) do not have a positive effect in thermoneutral or in hot environments (Table 2). Overall, this indicates that it is the manipulation of dopamine directly, rather than the manipulation of other catecholamine neurotransmitters in the dopamine-norepinephrine pathways, that influences physical performance in the heat. Therefore, the use of dopamine re-uptake inhibitors as opposed to catecholamine precursors or norepinephrine are better suited to test the role of dopamine on cognitive performance in the heat. Theoretically, by increasing brain dopamine levels, cognitive decrements may be attenuated by maintaining prefrontal cortex function, motivation, or dampening thermal perception to maintain performance for executive function, attention and vigilance, and working memory tasks in the heat.

Study	Subjects	Drug, Dose	Protocol	Ambient Temperature	Main Results
King et al. (158)	9 males, 6 females	MPH, 20 mg, 90-min wash in	Maximal handgrip to fatigue (right hand)	Thermoneutral, not stated	↑ force production 5.4%. ↑ 194% left insular cortex and left motor cortex coupling ↓ connectivity of orbitofrontal cortex and left insular cortex
Klass et al. (156)	10 males	MPH, 40 mg	30-min of cycling at 55% of peak power output followed by cycling time-trial	Thermoneutral, not stated	→ time-trial time ↑ heart rate and T_{core} → RPE
Roelands et al. (86)	8 males	MPH, 20 mg, 60- min wash-in	60-min of cycling at 55% of peak power output followed by cycling time-trial	18˚C	→ time trial performance → RPE
Roelands et al. (86)	8 males	MPH, 20 mg, 60-min wash-in	30-min of cycling at 55% of peak power output followed by cycling time-trial	30˚C	↓ time-trial time by ~16% ↑ heart rate, power output, and T_{core} with MPH → RPE or thermal perception despite faster time and higher power output
Swart et al. (157)	16 men	MPH, 10 mg, 90-min wash in	Time to exhaustion cycling task at RPE of 16	Thermoneutral, not stated	↑ time to exhaustion by ~32% with MPD ↑ heart rate, ventilation, oxygen consumption, power output, and blood lactate at fatigue with MPD Participants cycled ~20 watts higher with MPH and held the intensity for longer while perceiving intensity at an RPE of 16
Cordery et al. (162)	10 males	2 x 100 mg of L-DOPA	Precursor to dopamine and norepinephrine	60-min of cycling at 60% $\dot{V}O_{2\,peak}$, followed by a time-trial	30˚C → time-trial time → RPE, thermal stress

O'Brien et al. (164)	14 males, 1 female	Tyrosine, 150 mg/kg	Amino acid, cross blood brain barrier, converts to dopamine and norepinephrine	2 x 90-min, cold-water immersions to reduce T_{core} 2˚C, followed by cycling time-trial	19˚C	→ time-trial time
Piacentini et al. (163)	7 males	4 mg, reboxetine	Norepinephrine reuptake inhibitor	time-trial	Thermoneutral	→ time-trial time
Roelands et al. (165)	9 males	2 x 4 mg, reboxetine	Norepinephrine reuptake inhibitor	60-min of cycling at 55% of peak power output followed by cycling time-trial	18˚C	↑ time-trial time by 10% → heart rate
Roelands et al. (165)	9 males	2 x 4 mg, reboxetine	Norepinephrine reuptake inhibitor	-60-min of cycling at 55% of peak power output followed by cycling time-trial	30˚C	↑ time-trial time by 20% → heart rate
Tumilty et al. (161)	7 males	Tyrosine, 150 mg/kg	Amino acid, cross blood brain barrier, converts to dopamine and norepinephrine	60-min of cycling at 60% $\dot{V}O_{2\,peak}$ followed by cycling time-trial	30˚C	→ time-trial time
Watson et al. (166)	7 males	2 x 300 mg, bupropion	Dopamine and norepinephrine reuptake inhibitor	60-min of cycling at 55% of peak power output followed by cycling time-trial	18˚C	→ time-trial time
Watson et al. (37)	7 males	2x 300 mg, bupropion	Dopamine and norepinephrine reuptake inhibitor	60-min of cycling at 55% of peak power output followed by cycling time-trial	30˚C	↓ time-trial time by ~9% ↑ T_{core}, power output → RPE

Table 2-2- Summary of studies using manipulations effecting the dopamine-norepinephrine pathway on exercise performance. ↑ = significant increase, ↓ = significant decrease, → = no significant change relative to placebo.

2.7 Psychophysiological Responses to Cold Environments

When humans are exposed to cold environments, cooling of the body can occur due to a combination of low temperature, wind, humidity and inadequate clothing, as well as insufficient heat production to offset the heat loss (167). When resting T_{core} decreases, the severity of hypothermia can range from mild (-0.5 to -2.0˚C), clinical (≤ -2.0˚C), to severe (≤ -7.0˚C) hypothermia (168). Mild hypothermia leads to systemic alterations in physiological, neurological, and psychological changes that may alter cognitive and physical performance (Figure 2-8). For cold exposure, this section will review will focus on the responses to acute cold exposure (ACE) and mild hypothermia as a majority of human research is performed within this ethical range.

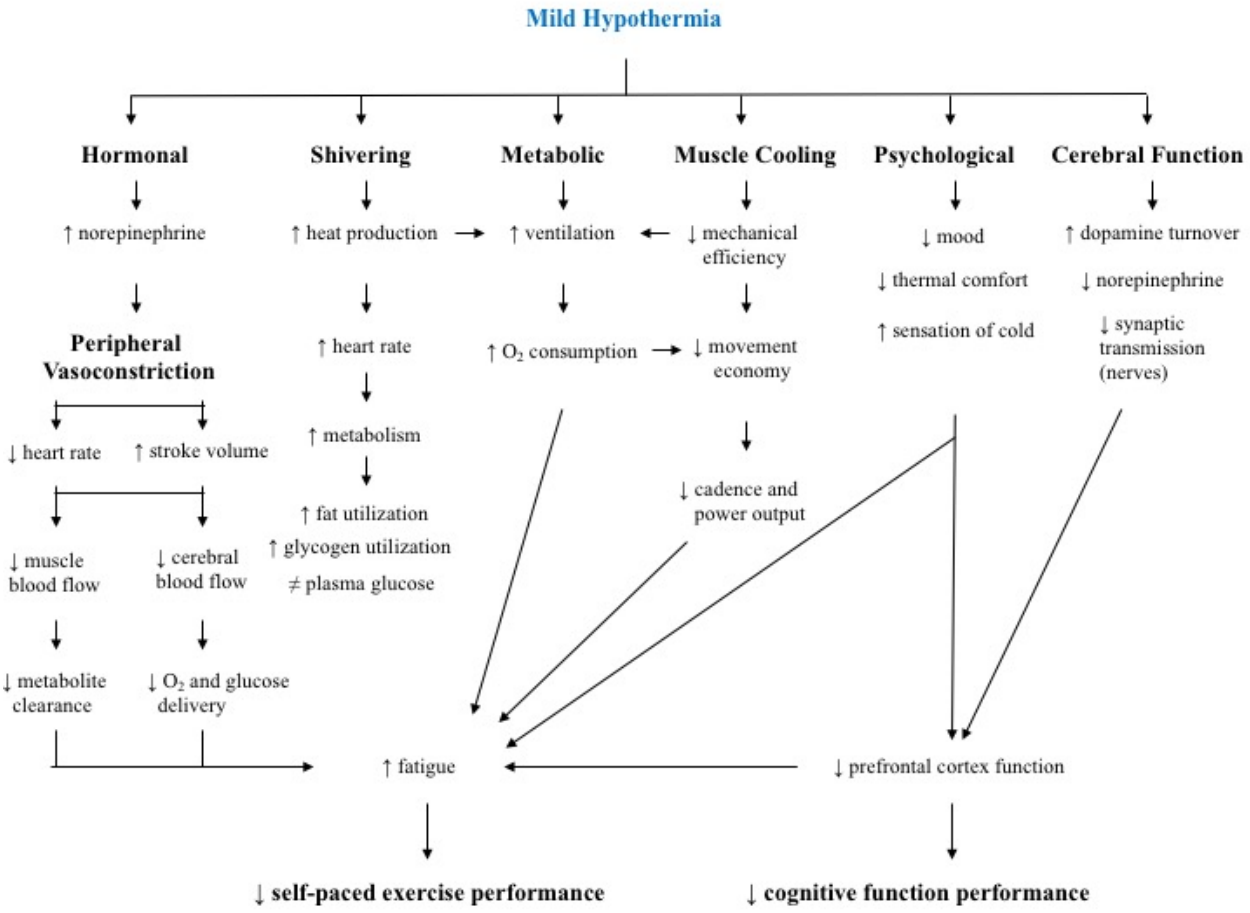

Figure 2-8 -The psychophysiological responses to acute cold stress and mild hypothermia on self-paced exercise and cognitive performance.

2.7.1 Hormonal and Heat Conservation Responses

The autonomic nervous system responds to cold stress through heat conservation and heat production strategies in order to prevent hypothermia. The initial response is peripheral vasoconstriction of blood vessels of the extremities (e.g., hands, feet) through the sympathetically driven release from post-ganglionic nerve fibres of norepinephrine, neuropeptide-Y, and RhoA-ROCK to shift blood from the periphery (i.e limbs) to the core (i.e torso) to decrease heat loss (169). The vasoconstrictory response is graded based on skin temperature, and is maximal at a mean skin temperature of 29.5-30˚C (169), The vasoconstriction response can affect heart rate as the increased venous return leads to an increase in filling time and left ventricular end diastolic volume, which increases stroke volume and decreases heart rate while cardiac output is maintained (170). Peripheral vasoconstriction leads to both a decrease in muscle blood flow (53) and cerebral blood flow (171, 172) which may limit exercise and cognitive performance in the cold through a reduction of both the delivery of oxygen and nutrients and the removal of metabolic byproducts such as lactate.

2.7.2 Shivering Thermogenesis and Metabolic Demands

The body's heat production response to cold stress can be quite effective in preventing hypothermia, as work from our laboratory has determined that it takes ~85-95 minutes to decrease T_{core} by -0.5˚C with passive exposure to 0˚C air while wearing light clothing (53, 173, 174). An increase in heat production occurs concurrently through shivering thermogenesis (involuntary low intensity muscular contractions) and non-shivering thermogenesis (e.g., increase in catecholamine release (e.g., epinephrine, norepinephrine), thyroid hormone concentrations, brown adipose tissue heat production) (1, 167, 175–179). Shivering is a low intensity (< 40% of peak oxygen

consumption ($\dot{V}O_{2\ peak}$)), < 20% maximal voluntary contraction) activity consisting of sporadic and asynchronous muscular contractions primarily in the torso and trunk muscles that increase heat production by up to 5x the resting metabolic rate (180–186). The bioenergetic response to fuel metabolism for shivering thermogenesis during acute passive cold stress is primarily fueled by fat oxidation (~50%) and muscle glycogen (~30%), with little change in plasma glucose levels (183, 184, 187). Despite the increased stroke volume from peripheral vasoconstriction, the increased sympathetic activity acting on the heart and metabolic production from shivering leads to a higher heart rate in the cold (0˚C) compared to resting in neutral temperatures (~22˚C) (173, 188). There is individual variability in the shivering response (182) where more research is needed to determine factors such as % fat mass, aerobic fitness, muscle mass, sex, and body surface area on the shivering response.

The conflicting metabolic and muscular demands from both exercise and shivering contributes to impaired exercise performance in the cold. During high intensity exercise, both ventilation ($\dot{V}_E$) and oxygen consumption ($\dot{V}O_2$) are significantly reduced relative to thermoneutral environments (189, 190). However, work performed at a constant absolute workload is more demanding, with $\dot{V}_E$ and $\dot{V}O_2$ significantly higher in the cold (-20 to 0°C air) compared in thermoneutral environments (189, 191). Additionally, it may be more difficult to consume oxygen in the cold because breathing cold air may induce constriction of the bronchioles which can diminish the amount of air that can be ventilated during maximal activities (192). Overall, these results indicate that the metabolic costs to produce work in the cold is greater than thermoneutral environments at the same relative intensity which may limit exercise performance in the cold.

2.7.3 Local Muscle Cooling, Hypothermia and Neuromuscular Function

The cooling of muscles can both impair and improve components of isometric and dynamic exercise performance (See Oska (193) for review) even without alterations in T_{core}. With cooling of muscle temperature, there is a decrease in nerve conduction velocity, altered motor unit recruitment patterns, and increased duration of motor unit action potentials (189, 194–199). The rate of muscular contractions is slower within cold muscles, which leads to less mechanical power that can be produced (200). Additional motor units need to be recruited to complete the same amount of work in cooler muscles (201) compared to thermoneutral environments, which can lead to an increase in amplitude of electromyography potentials due to temporal summation from the reduced conduction velocity and lengthened action potential (189, 195). These changes are estimated to decrease performance 2-10% per ˚C decrease in muscle temperature (193). However, not all performance measures decline with local cooling, as isometric muscular endurance demonstrates a strong negative relationship with muscle temperature, such that colder muscles demonstrate greater endurance (202). There is additional metabolic cost to performing work in the cold, as there is an increase in the $\dot{V}O_2$ requirements to produce the same work relative to thermoneutral conditions, leading to reduced movement economy during submaximal exercise (203).

With mild hypothermia, there are significant alterations to the central nervous system including decreased nerve conduction velocity (peripherally and centrally) along with increased time to peak tension and half-relaxation of the muscle and force production (204–207). Mild hypothermia (T_{core} = Δ-0.5-2.0˚C from baseline) induced through cold water immersion reduces both fine (204) and gross (204–208) motor task performance. Maximal voluntary activation, torque, and force production of the biceps brachii and gastrocnemius are significantly reduced

compared to thermoneutral conditions (205, 206); however the rate of physical fatigue is lower during 2-minute sustained maximal voluntary isometric contractions (205). These isometric changes do not appear to be due to central activation or a failure of the motor cortex to activate the motor nerve (205, 206). Overall neuromuscular function and components of the central nervous system are impaired with hypothermia. However, it is unknown if central fatigue occurs with whole body exercise in the cold. Future research is needed to determine if improving neuromuscular function through an intervention affecting the central nervous system can improve exercise performance when mildly hypothermic.

2.7.4 Cerebral Function

Hypothermia has a significant influence on the brain and includes alterations in neural activity, neurotransmitter function, and cerebral hemodynamics (For review see (168)). Surgical studies on patients undergoing cardiac surgery with reductions in T_{core} to 19-20˚C (209) demonstrate a progressive reduction in nerve conduction velocity, slowed latency of action potentials, decreased amplitude, and a depression in synaptic transmission through impaired neurotransmitter release (168, 209, 210). These changes are correlated with every -1.0˚C of T_{core} and return to baseline when normal T_{core} is restored (209). Therefore, hypothermia has typically been used as a clinical treatment during severe trauma to maintain neural function by minimizing neural metabolism (153, 211, 212). In one of the few studies to measure brain activity in healthy adults, reducing T_{core} to 33-33.5˚C using cold-water immersion in 7˚C water led to a significant 34% decrease in α-band activity and a 17% increase in theta-band and ß-band activity in the occipital and parietal lobes using electroencephalography (213) indicating changes in arousal. Recently, Jones et al. (214), measured neural activity using electroencephalography during repeated 90-minute water immersions in 10˚C water which led to mild hypothermia (T_{core} =

~36.1˚C, ~1.5˚C reduction) and found no differences in the N100 or P300 amplitude and latency with hypothermia (214). Despite the limited changes in neural activity, there were significant impairments in cognitive performance indexed by a slowing of reaction time on a psychomotor vigilance task (basic reaction time task) (214). These results would indicate that there are small alterations in neural activity with mild hypothermia that may not be the causal factor for reduced cognitive performance on simple tasks, and more research is needed to determine the underlying mechanisms leading to impaired cognitive performance with hypothermia.

Hypothermia inhibits the biosynthesis, release and uptake of neurotransmitters such as dopamine, epinephrine and norepinephrine (212, 215–218). In mice, hypothermia leads to small changes in dopamine levels in the brain; however there is a greater level of dopamine catabolites, 3,4-Dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA), indicating an accelerated level of dopamine turnover (217, 219). This response is different from norepinephrine, where plasma levels increase with acute cold stress (175, 176, 179, 191) and mild hypothermia (177, 186) to aid in the vasoconstrictor response. Dopamine is a precursor to the synthesis of norepinephrine and epinephrine neurotransmitters, and the increased turnover of dopamine may contribute to the reduction in norepinephrine levels (217, 220). To the best of our knowledge, only one study exists testing the effects of manipulating neurotransmitters on exercise performance in the cold. O'Brien et al. (221) tested the effects of tyrosine supplementation (150 mg/kg body mass) on self-paced cycling time trial performance (fixed work of 3 kJ per kg body weight) in cool air (19˚C) following two, back to back 90-min immersions in cold water (~10˚C) that reduced T_{core} from 37˚C to 35˚C, with a rewarming period to baseline T_{core} between immersions. Tyrosine is an amino acid which circulates freely in the blood stream that binds to receptors that allow it to cross the blood brain barrier. Under stressful conditions, tyrosine hydroxylase is released which

catalyzes the conversion the conversion of tyrosine to L-DOPA, leading to the synthesis of dopamine and/or norepinephrine (43). Therefore, artificially increasing tyrosine in the blood stream, potentially the more dopamine and norepinephrine neurotransmitters can be produced in the brain. O'Brien et al. (221) demonstrated a significant ~4% reduction in time trial performance after repeated cold-water immersions compared to a control trial, with no effects of tyrosine supplementation on performance (221).

A proposed mechanism of physical fatigue is a decrease in cerebral blood flow during exercise because it will lead to less oxygen delivery and metabolite clearance (e.g., lactate) which would favor anaerobic metabolism and limit exercise performance (222). Cerebral hemodynamics are tightly regulated so that there is an adequate supply of oxygen and nutrients (e.g., glucose) to and metabolite removal (e.g., lactate) from the cerebral tissue without excessive perfusion. The cerebral vasculature is highly sensitive and is regulated primarily through changes in arterial blood gases such as the arterial pressures of carbon dioxide and oxygen as well as secondary mechanisms such as sympathetic activity (223), thermoafferent signals from the peripheral cold receptors, and cerebral metabolic and pharmacological supplementation that influence cardiovascular and respiratory centres (224–227). Increases in exercise intensity up to 60% $\dot{V}O_{2\ peak}$ lead to increases in cerebral blood flow, whereas exercise at higher intensities leads to reductions in CBF despite further increases in exercise intensity and cerebral metabolism due to hyperventilation-induced hypocapnia (222, 228). With heat stress, cycling at a steady rate at ~60% $\dot{V}O_{2\ peak}$ led to a ~26% decline in middle cerebral artery velocity (MCAv) and premature physical fatigue in a hot environment (40˚C) compared to no changes in MCAv or without reaching physical fatigue in a thermoneutral (18˚C) environment (229). In the cold, cold water immersion studies have demonstrated that mild hypothermia of -1.0°C leads to an increase in $\dot{V}_E$ compared to baseline,

increasing expiration of carbon dioxide and decreasing arterial carbon dioxide level, leading to decreases in cerebral blood flow (172). There is minimal evidence available on CBF during exercise in the cold in healthy individuals, as most relevant cold studies are in clinical populations using therapeutic hypothermia as a medical intervention. These demonstrate a consistent decline in CBF with severe hypothermia through cerebral vasoconstriction (230–233). As reductions in brain blood flow are associated with reduced exercise performance in adverse environments, it is important to consider how these variables may influence performance.

With cold stress and mild hypothermia, there are alterations in cerebral oxygenation due to decreased CBF. In thermoneutral environments, during mild to moderate intensity exercise (≤ 60% $\dot{V}O_{2\,peak}$), cerebral oxygen uptake remains unchanged, whereas at higher intensities cerebral oxygen uptake increases despite reductions in CBF in order to maintain cerebral metabolism. In cold environments, decreases in blood temperature reduces the ability to extract oxygen during exercise due to a temperature-dependent leftward shift in the oxygen-disassociation curve (234). Combined with the reduction in the ability to uptake oxygen, there are increased oxygen demands in the cold due to the increased $\dot{V}O_2$ consumption required due to shivering and reduced movement economy during exercise. Using near-infrared spectroscopy (NIRS), cold-exposure of 0˚C air and mild hypothermia (-0.5˚C) led to a significant decrease in cerebral tissue oxygenation index from ~60% to ~50% from baseline (188) as well as a decrease in skin blood flow to the forehead (174). Recently, our lab has determined that the use of supplemental hyperoxia (~40% oxygen) can counter the impairments in time-trial performance through an increased oxygen saturation from a maintenance in cerebral tissue oxygenation similar to thermoneutral levels (188). Overall, this evidence would indicate that cerebral oxygenation is an important variable to monitor as it contributes to reduced cycling performance in the cold.

2.7.5 Psychological Function

There is increased psychological strain with cold stress even before any measurable change in T_{core}, where performance may be impaired due to alterations in thermal perception. At its mildest effect, cold exposure causes thermal discomfort and cold thermal sensations (168, 235). These perceptions have neural correlates as exposure to 20 minutes of cold (8˚C) air significantly activates the right and left amygdala (measured with functional magnetic resonance imaging) and demonstrate a significant negative linear relationship ($r^2 = 0.63$) to TC compared to neutral (28˚C) and warm (32˚C) air (236). This may indicate that exposure to cold temperature may lead to a heightened anxiety or fear response (236); however it is unknown how this response would change with mild hypothermia. Little is known about how these alterations in thermal perception influence cognitive or exercise performance in the cold. However, distraction theory (42) proposes that cold stress provides additional sensory stimuli to the brain which interrupts focus that would otherwise be fixed or utilized for the cognitive or exercise task at hand. There is weak evidence to suggest that distraction has a causal effect, as an individual's thermal discomfort increases their cognitive performance becomes impaired (153). It is difficult to isolate and prove the distraction theory as the causal factor for changes in cognitive function or endurance capacity. Primarily, previous studies have not controlled for the amount of cold strain as they've implemented time-based approaches as opposed to normalizing the physiological strain between individuals. However, a central issue in the cold literature is whether or not performance is decreased by the sensory displeasure of cold skin or whether cooling of T_{core} is the causal factor for decreased performance.

2.7.6 Summary of Psychophysiological Responses

Overall, the effects of hypothermia cause a systemic response resulting in alterations in multiple systems which include; hormonal, cardiovascular, metabolic, neuromuscular,

psychological, and neurological alterations compared to thermoneutral environments (Figure 2-8). Due to the sensory displeasure from cold skin and cold stress as well as the systemic effects of hypothermia, it is difficult to isolate a single system that leads to a reduction in cognitive and/or exercise performance in the cold. Therefore, research is needed to determine how both cognitive function and exercise capacity changes under cold strain. The next sections will discuss cognitive function and exercise performance and how they are affected by acute cold stress and mild hypothermia. The concept of how cognitive function and exercise performance may be linked in the brain will also be discussed.

2.8 Cognitive Function, Cold Stress, and Hypothermia

Occupational workers, military personnel, and athletes are often required to work, perform military duties, and compete in cold environments that can impact cognitive function and decision making. For example, Alaskan fisherman are consistently exposed to cold air and water lasting several hours, and this is proposed to cause numerous occupational injuries and fatalities each year (237). Meta-analysis data determined that there is a ~14% reduction in cognitive task performance for temperatures ≤ 10˚C, where higher order executive function tasks that require sustained vigilance or working memory are most vulnerable to ACE (238, 239). This finding is supported by studies demonstrating that ACE (-20 to 10˚C) decreases simple task performance (such as reaction time) and complex task performance such as working memory, vigilance, and attention (44, 168, 240–244). However, these results are not uniform, where short-term cold-water (2 to 8˚C) immersion improves performance on psychomotor processing and executive function tasks, potentially through increased arousal (245). Additionally, there were no decreases in executive function with passive acute air exposure (5-10˚C) of 60-90 minutes (243, 244). Previously, our lab has attempted to isolate the effects of cold skin temperature (causing thermal displeasure) from

mild hypothermia of -0.5°C and -1.0°C in cold water, which demonstrated an increase in the variability in reaction time (but not impairment) during a prolonged vigilance task with skin cooling and no further changes with mild hypothermia (44). However, this experiment did not include additional measures of cognitive function (e.g., working memory, executive function), making it difficult to determine if there are task-dependent changes in cognitive function with either skin or core cooling.

Less is known regarding the cognitive responses that occur with mild hypothermia in cold air (reduction in T_{core} 0.5-2˚C) which can occur from prolonged exposure to cold environments, combined with inadequate clothing and/or insufficient heat production. In these scenarios, the maintenance of cognitive function can be a vital aspect of human survival. For example, the maintenance of executive function (inhibiting behavior, filtering distractions, planning and executing behavior) can aid in maintaining safe behaviors, preventing accidents, or determining strategies to minimize further thermal strain (44, 50). Recent reviews (1, 246) have concluded that cold stress has an adverse effect on cognitive function; however it is currently unclear what the task-dependent changes in cognitive function are, and the physiological strain in which performance degrades is also unclear. A consistent finding is that higher-order cognitive tasks that require executive function are impaired indexed by slower reaction times and more errors with ~1 to 4˚C reductions in T_{core} with cold water immersion (247–250). There may be a T_{core} threshold for this response, as work from our lab demonstrated that a -0.5˚C reduction in T_{core} did not impair executive function during a 24-hour exposure to cold air (7.5˚C) (251). Evidence for changes in working memory, vigilance and attention, and psychomotor processing are less consistent. Working memory performance demonstrates a mixed response, where some studies find no change in performance with -0.5 to -2˚C in T_{core} (164, 248, 251), while others demonstrate decrements in

working memory performance (247, 252). Vigilance and attention also demonstrate a mixed response, where some studies demonstrate no changes in attention or vigilance with ~1 to 4˚C reductions in T_{core} (164, 247), while previous work from our lab demonstrate an increase in response time on a vigilance task with -0.5˚C reduction in T_{core}, and reductions in spatial attention indexed through more variable responses starting with reductions in skin temperature, with no continued reductions with T_{core} cooling to -1.0˚C (44). Simple task performance such as psychomotor processing is demonstrated to be impaired with ~1 to 4˚C reductions in T_{core} (246, 247, 250, 253) with also no changes demonstrated with reductions in T_{core} up to ~ 2.0˚C (164). Overall, these results indicate that both higher order cognitive functions such as executive function and in some cases attention and working memory, as well as psychomotor processing are impaired with hypothermia. However, additional evidence is needed to tease out the task-dependent changes that occur with hypothermia and the underlying mechanisms that cause these changes.

2.9 Is There a Relationship Between Cognitive Function and Endurance Capacity in the Cold Stress

Currently, there is no consensus on the role of cold stress and mild hypothermia on aerobic exercise performance or endurance capacity due to the performance tests used and lack of standardization of cold stress (e.g., duration, actual decreases in T_{core}) (254). The evidence for the effects of ACE on exercise performance is mixed, where cycling time-to-exhaustion (TTE) at ~70% maximal aerobic capacity has shown both no difference in 4°C (52) and a 40% improvement in performance at 3°C (255) compared to thermoneutral conditions. Furthermore, 30-minute self-paced cycling performance in 2°C remained unchanged compared to thermoneutral conditions (256). Very few studies have tested the effects of actual mild hypothermia on exercise performance; however it appears to have a negative effect. Recent work from our lab has

determined that 15-km cycling time trial performance was reduced by ~2% (+ ~30 seconds) through a lowered power output and potentially cerebral and muscular oxygenation in the cold (0˚C air) with mild hypothermia (-0.5˚C) compared to thermoneutral trials (23˚C) (188). Furthermore, a reduction in T_{core} of 2.0˚C decreased self-paced cycling performance in a thermoneutral (19˚C) environment by ~4-5% (164). The underlying mechanisms of performance impairments may be limited by a variety of physiological factors including cardiovascular strain due to a strong peripheral vasoconstriction reducing cerebral and muscle blood flow and oxygenation (174, 188), reduced neuromuscular capacity (193, 257), increased metabolic costs (181, 258), shifts in fuel oxidation (176, 177, 183, 187, 259) or potentially from alterations in cerebral function (128, 164). Currently, it is unknown if the level of cold strain (from ACE to mild hypothermia) influences performance. Hypothetically, ACE can decrease (due to cold strain) or improve endurance capacity (help with heat dissipation), while mild hypothermia should decrease endurance capacity. Furthermore, it is unknown if the level of mild hypothermia (e.g., -0.5˚C or -1.0˚C in T_{core}) affects endurance capacity. Hypothetically, increased mild hypothermia (-1.0˚C in T_{core}) should lead to significantly greater reductions in endurance capacity compared to milder hypothermia ranges (-0-5˚C in T_{core}) because of greater cold strain and potentially greater psychophysiological stress.

The Robertson & Marino (58) model and the McMorris et al. interoception model (59) can be used as a conceptual framework for testing endurance capacity in the cold. Mild hypothermia leads to central changes in the brain that can affect the psychological drive to perform exercise from alterations in neurotransmitters, discomfort from cold skin and core temperature, mood disturbances, and decreased motivation. Additionally, hypothermia decreases executive function and psychomotor processing, as well as impairing working memory, attention, and vigilance.

These psychophysiological and cognitive alterations are interrelated as there is considerable neural overlap between the Robertson & Marino (58) model, interoception model (59) and executive attention network (Figure 2-4, Section: Cognitive Function), including the PFC, ACC, and AIC. Paulus et al. (64, 260) proposed a hypothesis that interventions working directly on the PFC, ACC, and AIC can improve or decrease performance in adverse environments due to these structures regulating afferent feedback to maintain homeostasis. Evidence for this hypothesis is that endurance capacity is reduced by pre-exercise hyperthermia (~26%) and is further reduced with pre-exercise hyperthermia combined with mentally fatiguing the PFC (~46.3%) compared to thermoneutral cycling. Currently it is unknown what the relationship is between changes in cognitive function and exercise performance in the cold (Figure 2-9). Theoretically, according the Robertson & Marino (58) model, if there are decrements in executive attention performance with ACE or hypothermia, then these changes will occur with endurance capacity through impairment of the top-down regulation of performance. In order to determine the role of dopamine on performance in the cold, future research studies are needed that include measures of cognitive function and self-paced exercise and also include components of executive attention as these tasks are interrelated with proposed brain regions that may optimize performance in adverse environments.

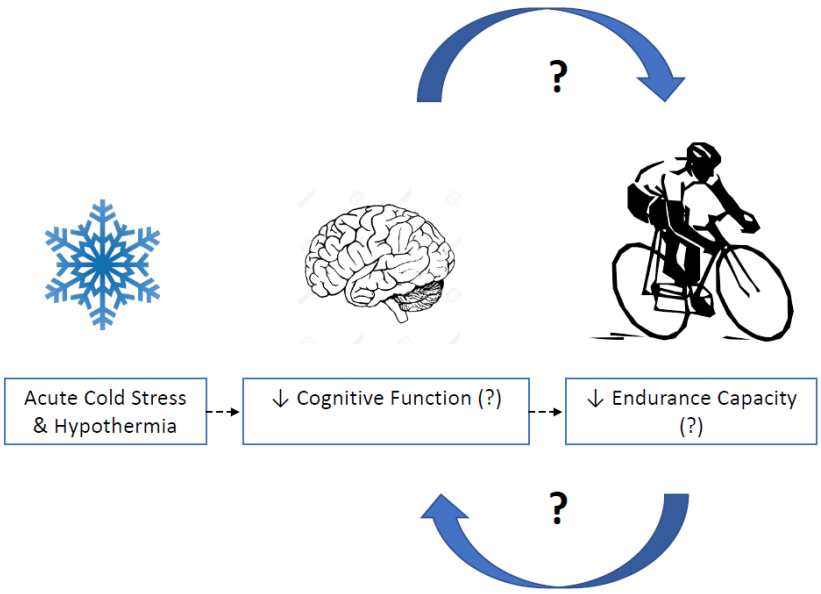

Figure 2-9 - A conceptualization of the responses in cognitive function and endurance capacity with cold stress. It is unknown if there is a relationship between the alterations in cognitive function (e.g., executive function) and endurance capacity. ? indicates unknown relationship.

2.10 Gaps in the Literature and Future Directions

Currently one of the primary limitations in cognitive function research in both hot and cold environments is delineating the separate and combined roles of skin temperature and core temperature. Changes in skin temperature may alter cognitive function before any major changes in core temperature due to an alteration of arousal or increased distraction from the sensory displeasure of warm or cold skin, or increase the workload of cognitive tasks through increasing the effort of monitoring the thermal state and performing a task (102, 113, 261). Either hyperthermia and hypothermia can lead to increased psychophysiological strain that may further reduce performance (1). However, the limitations of previous studies are that they do not control for the degree of thermal strain (skin temperature or T_{core} or both) experienced by participants,

making it difficult to determine the separate and combined roles of thermal discomfort and changes in core temperature on cognitive performance in adverse environments. Future studies are needed to address these methodological concerns in order to determine the underlying mechanisms for the decrements in cognitive function. An overarching theme in the studies presented in this dissertation is to isolate the effects of skin and core temperature on cognitive performance. In study one, we attempted to isolate the temperature and combined effects of skin and core temperature and thermal displeasure on cognitive function with 4 distinct conditions: baseline (no thermal manipulation), neutral core-hot skin, hyperthermic core-hot skin, and hyperthermic core- cooled skin. In study 2, we compared the 4 conditions of various degrees of cold strain: thermoneutral (22°C air), ACE (0°C cold exposure of ~20 minutes), mild hypothermia with -0.5°C in baseline T_{core}, and mild hypothermia of -1.0° C in baseline $T_{core.}$ This approach can determine if the initial sensory displeasure of cold skin impairs cognitive function (ACE), while the two hypothermic conditions can determine the reduction in T_{core} needed to impair performance.

In hot environments, performance in the heat is physically and mentally demanding, where cognitive function is reduced relative to thermoneutral environments(1, 113). The underlying mechanisms for the decrements in performance are currently unknown, however one potential physiological mechanism may alteration in neurotransmitters such as dopamine seen with hyperthermia. In study 1, we propose that methylphenidate (MPH, dopamine re-uptake inhibitor) will counter the decrements in cognitive performance induced by passive hyperthermia through improving prefrontal cortex function and potentially through reducing psychological strain through increasing motivation or reducing the sensory displeasure and distraction of cold skin (Figure 2-10). These findings will help determine the underlying mechanisms and role of dopamine in impaired cognitive performance in the heat.

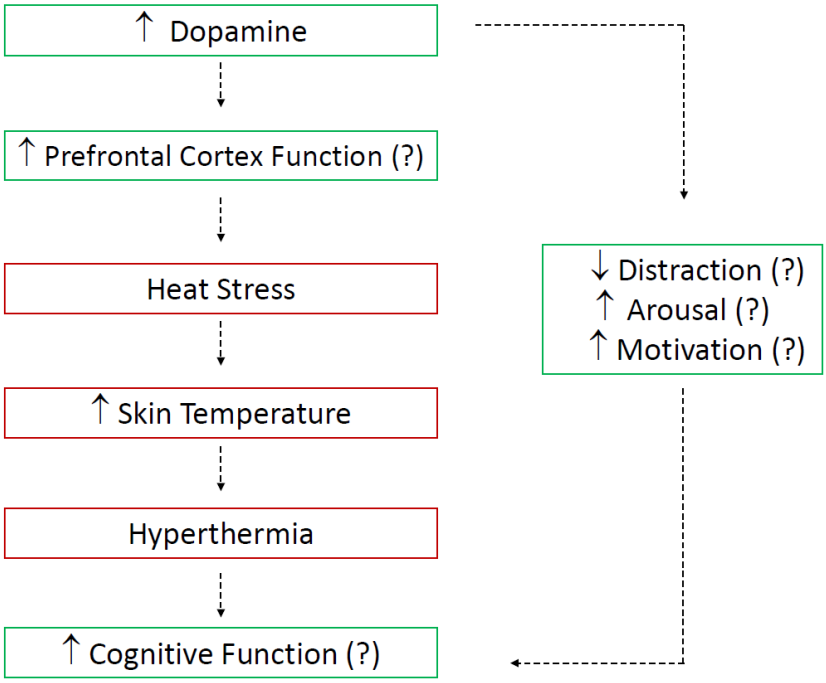

Figure 2-10 – Conceptualization of the role of dopamine on cognitive performance in the heat. We propose that MPH will increase baseline dopamine levels and prefrontal cortex function that will counter or improve cognitive performance. A secondary mechanism may be through improving motivation, improving arousal, reducing distraction from discomfort of hot skin. Future studies are needed to isolate the roles of thermal discomfort, hyperthermia, and dopamine on cognitive function in the heat. ? indicates currently unknown response under heat stress.

Currently it is unknown if there is a relationship between changes in cognitive and endurance capacity in the cold. According to the Robertson & Marino (58) model, if there are decrements in executive attention performance with ACE or hypothermia, then there should be decrements in endurance capacity through negatively impacting the top-down regulation of performance. Based on this model, if there are decrements in executive attention-based tasks such as working memory and executive function, there should be subsequent decrements in exercise performance. Determining the relationship between both cognitive and endurance capacity will help determine if counter measures in future studies need to be focused to improving cognitive function, physical function, or both. In study 2, we test endurance capacity immediately following

testing cognitive function to also isolate the effects of core and skin temperature on performance in the cold.

2.11 Literature Review References

1. Taylor L, Watkins SL, Marshall H, Dascombe BJ, Foster J. The Impact of Different Environmental Conditions on Cognitive Function: A Focused Review. *Front Physiol* [Internet]. 2016 [cited 2017 Feb 9];6 Available from: http://journal.frontiersin.org/Article/10.3389/fphys.2015.00372/abstract. doi:10.3389/fphys.2015.00372.

2. McCabe DP, Roediger HL, McDaniel MA, Balota DA, Hambrick DZ. The relationship between working memory capacity and executive functioning: Evidence for a common executive attention construct. *Neuropsychology*. 2010;24(2):222–43.

3. Machizawa MG, Driver J. Principal component analysis of behavioural individual differences suggests that particular aspects of visual working memory may relate to specific aspects of attention. *Neuropsychologia*. 2011;49(6):1518–26.

4. Engle RW, Kane MJ. Executive Attention, Working Memory Capacity, and a Two-Factor Theory of Cognitive Control. *Psychology of Learning and Motivation*. Elsevier; 2003. p. 145–99. [cited 2019 May 17] Available from: https://linkinghub.elsevier.com/retrieve/pii/S007974210344005X.

5. Sibley BA, Beilock SL. Exercise and Working Memory: An Individual Differences Investigation. *J Sport Exerc Psychol*. 2007;29(6):783–91.

6. Etnier JL, Chang Y-K. The Effect of Physical Activity on Executive Function: A Brief Commentary on Definitions, Measurement Issues, and the Current State of the Literature. *J Sport Exerc Psychol*. 2009;31(4):469–83.

7. Shibasaki M, Namba M, Oshiro M, Kakigi R, Nakata H. Suppression of cognitive function in hyperthermia; From the viewpoint of executive and inhibitive cognitive processing. *Sci Rep* [Internet]. 2017 [cited 2017 Oct 18];7 Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5353598/. doi:10.1038/srep43528.

8. Alvarez JA, Emory E. Executive Function and the Frontal Lobes: A Meta-Analytic Review. *Neuropsychol Rev*. 2006;16(1):17–42.

9. Segalowitz SJ, Dywan J. Individual differences and developmental change in the ERN response: implications for models of ACC function. *Psychol Res Psychol Forsch*. 2009;73(6):857–70.

10. Cavanagh JF, Zambrano-Vazquez L, Allen JJB. Theta lingua franca: A common mid-frontal substrate for action monitoring processes: Omnipresent theta. *Psychophysiology*. 2012;49(2):220–38.

11. Oliveira L, Mocaiber I, David IA, Erthal F, Volchan E, Pereira MG. Emotion and attention interaction: a trade-off between stimuli relevance, motivation and individual differences. *Front Hum Neurosci* [Internet]. 2013 [cited 2019 Apr 26];7 Available from:

http://journal.frontiersin.org/article/10.3389/fnhum.2013.00364/abstract. doi:10.3389/fnhum.2013.00364.

12. Wallace PJ, Mckinlay BJ, Coletta NA, et al. Effects of motivational self-talk on endurance and cognitive performance in the heat. *Med Sci Sports Exerc*. 2017;49(1):191–9.

13. Simmonds DJ, Pekar JJ, Mostofsky SH. Meta-analysis of Go/No-go tasks demonstrating that fMRI activation associated with response inhibition is task-dependent. *Neuropsychologia*. 2008;46(1):224–32.

14. Kok A. Effects of degradation of visual stimuli on components of the event-related potential (ERP) in go/nogo reaction tasks. *Biol Psychol*. 1986;23(1):21–38.

15. Nakata H, Sakamoto K, Ferretti A, et al. Executive functions with different motor outputs in somatosensory Go/Nogo tasks: An event-related functional MRI study. *Brain Res Bull*. 2008;77(4):197–205.

16. Konishi S, Nakajima K, Uchida I, Kikyo H, Kameyama M, Miyashita Y. Common inhibitory mechanism in human inferior prefrontal cortex revealed by event-related functional MRI. *Brain*. 1999;122(5):981–91.

17. Casey BJ, Trainor RJ, Orendi JL, et al. A Developmental Functional MRI Study of Prefrontal Activation during Performance of a Go-No-Go Task. *J Cogn Neurosci*. 1997;9(6):835–47.

18. van Noordt SJR, Desjardins JA, Segalowitz SJ. Watch out! Medial frontal cortex is activated by cues signaling potential changes in response demands. *NeuroImage*. 2015;114:356–70.

19. Van Noordt SJR, Campopiano A, Segalowitz SJ. A functional classification of medial frontal negativity ERPs: Theta oscillations and single subject effects: Medial frontal negativities and theta power. *Psychophysiology*. 2016;53(9):1317–34.

20. Gajewski PD, Falkenstein M. Effects of task complexity on ERP components in Go/Nogo tasks. *Int J Psychophysiol*. 2013;87(3):273–8.

21. Awh E, Barton B, Vogel EK. Visual Working Memory Represents a Fixed Number of Items Regardless of Complexity. [date unknown];18(7):7.

22. Brady TF, Alvarez GA. No evidence for a fixed object limit in working memory: Spatial ensemble representations inflate estimates of working memory capacity for complex objects. *J Exp Psychol Learn Mem Cogn*. 2015;41(3):921–9.

23. Brady TF, Konkle T, Alvarez GA. A review of visual memory capacity: Beyond individual items and toward structured representations. *J Vis*. 2011;11(5):4–4.

24. Ramaty A, Luria R. Visual Working Memory Cannot Trade Quantity for Quality. *Front Psychol* [Internet]. 2018 [cited 2019 Apr 26];9 Available from:

https://www.frontiersin.org/article/10.3389/fpsyg.2018.00719/full. doi:10.3389/fpsyg.2018.00719.

25. Schurgin MW. Visual memory, the long and the short of it: A review of visual working memory and long-term memory. *Atten Percept Psychophys*. 2018;80(5):1035–56.

26. Zimmer H. Visual and spatial working memory: From boxes to networks. *Neurosci Biobehav Rev*. 2008;32(8):1373–95.

27. Serences JT. Neural mechanisms of information storage in visual short-term memory. *Vision Res*. 2016;128:53–67.

28. Conway ARA, Kane MJ, Engle RW. Working memory capacity and its relation to general intelligence. *Trends Cogn Sci*. 2003;7(12):547–52.

29. de Jong PF. Working Memory Deficits of Reading Disabled Children. *J Exp Child Psychol*. 1998;70(2):75–96.

30. Cowan N, Elliott EM, Scott Saults J, et al. On the capacity of attention: Its estimation and its role in working memory and cognitive aptitudes. *Cognit Psychol*. 2005;51(1):42–100.

31. Xu Y. Reevaluating the Sensory Account of Visual Working Memory Storage. *Trends Cogn Sci*. 2017;21(10):794–815.

32. Shackman AJ, Maxwell JS, McMenamin BW, Greischar LL, Davidson RJ. Stress Potentiates Early and Attenuates Late Stages of Visual Processing. *J Neurosci*. 2011;31(3):1156–61.

33. Arnsten AFT. Stress signalling pathways that impair prefrontal cortex structure and function. *Nat Rev Neurosci*. 2009;10(6):410–22.

34. Birnbaum S, Gobeske KT, Auerbach J, Taylor JR, Arnsten AFT. A Role for Norepinephrine in Stress-Induced Cognitive Deficits: ⎵-1-Adrenoceptor Mediation in the Prefrontal Cortex. *BIOL PSYCHIATRY*. [date unknown];9.

35. Langner R, Eickhoff SB. Sustaining attention to simple tasks: A meta-analytic review of the neural mechanisms of vigilant attention. *Psychol Bull*. 2013;139(4):870–900.

36. Robertson IH, Manly T, Andrade J, Baddeley BT, Yiend J. `Oops!': Performance correlates of everyday attentional failures in traumatic brain injured and normal subjects. *Neuropsychologia*. 1997;35(6):747–58.

37. Oken BS, Salinsky MC, Elsas SM. Vigilance, alertness, or sustained attention: physiological basis and measurement. *Clin Neurophysiol*. 2006;117(9):1885–901.

38. Kane MJ, Engle RW. The role of prefrontal cortex in working-memory capacity, executive attention, and general fluid intelligence: An individual-differences perspective. *Psychon Bull Rev*. 2002;9(4):637–71.

39. Salthouse TA. The Processing-Speed Theory of Adult Age Differences in Cognition. [date unknown];26.

40. Park DC, Smith AD, Lautenschlager G, Earles JL, et al. Mediators of long-term memory performance across the life span. *Psychol Aging*. 1996;11(4):621–37.

41. Xiao M, Ge H, Khundrakpam BS, et al. Attention Performance Measured by Attention Network Test Is Correlated with Global and Regional Efficiency of Structural Brain Networks. *Front Behav Neurosci* [Internet]. 2016 [cited 2019 Apr 26];10 Available from: http://journal.frontiersin.org/article/10.3389/fnbeh.2016.00194/full. doi:10.3389/fnbeh.2016.00194.

42. Teichner WH. Reaction time in the cold. *J Appl Psychol*. 1958;42(1):54–9.

43. Shurtleff D, Thomas JR, Schrot J, Kowalski K, Harford R. Tyrosine reverses a cold-induced working memory deficit in humans. *Pharmacol Biochem Behav*. 1994;47(4):935–41.

44. Cheung SS, Westwood DA, Knox MK. Mild body cooling impairs attention via distraction from skin cooling. *Ergonomics*. 2007;50(2):275–88.

45. Yerkes RM, Dodson JD. The relation of strength of stimulus to rapidity of habit-formation. *J Comp Neurol Psychol*. 1908;18(5):459–82.

46. Arent SM, Landers DM. Arousal, Anxiety, and Performance: A Reexamination of the Inverted-U Hypothesis. *Res Q Exerc Sport*. 2003;74(4):436–44.

47. Spitznagel MB, Updegraff J, Pierce K, et al. Cognitive Function During Acute Cold Exposure With or Without Sleep Deprivation Lasting 53 Hours. *Aviat Space Environ Med*. 2009;80(8):703–8.

48. Tenenbaum G, Edmonds WA, Eccles DW. Emotions, Coping Strategies, and Performance: A Conceptual Framework for Defining Affect-Related Performance Zones. *Mil Psychol*. 2008;20(sup1):S11–37.

49. Rejeski WJ. Perceived Exertion: An Active or Passive Process? *J Sport Psychol*. 1985;7(4):371–8.

50. Hancock PA, Vasmatzidis I. Human occupational and performance limits under stress: the thermal environment as a prototypical example. *Ergonomics*. 1998;41(8):1169–91.

51. Hancock PA, Vasmatzidis I. Effects of heat stress on cognitive performance: the current state of knowledge. *Int J Hyperthermia*. 2003;19(3):355–72.

52. Galloway SD, Maughan RJ. Effects of ambient temperature on the capacity to perform prolonged cycle exercise in man. *Med Sci Sports Exerc*. 1997;29(9):1240–9.

53. Ferguson SAH, Eves ND, Roy BD, Hodges GJ, Cheung SS. Effects of mild whole body hypothermia on self-paced exercise performance. *J Appl Physiol*. 2018;125(2):479–85.

54. Cheung SS, McLellan TM. Heat acclimation, aerobic fitness, and hydration effects on tolerance during uncompensable heat stress. *J Appl Physiol*. 1998;84(5):1731–9.

55. González-Alonso J, Teller C, Andersen SL, Jensen FB, Hyldig T, Nielsen B. Influence of body temperature on the development of fatigue during prolonged exercise in the heat. *J Appl Physiol Bethesda Md 1985*. 1999;86(3):1032–9.

56. St Clair Gibson A, De Koning JJ, Thompson KG, et al. Crawling to the Finish Line: Why do Endurance Runners Collapse?: Implications for Understanding of Mechanisms Underlying Pacing and Fatigue. *Sports Med*. 2013;43(6):413–24.

57. Noakes TD. Fatigue is a Brain-Derived Emotion that Regulates the Exercise Behavior to Ensure the Protection of Whole Body Homeostasis. *Front Physiol* [Internet]. 2012 [cited 2019 May 3];3 Available from: http://journal.frontiersin.org/article/10.3389/fphys.2012.00082/abstract. doi:10.3389/fphys.2012.00082.

58. Robertson CV, Marino FE. A role for the prefrontal cortex in exercise tolerance and termination. *J Appl Physiol*. 2016;120(4):464–6.

59. McMorris T, Barwood M, Corbett J. Central fatigue theory and endurance exercise: Toward an interoceptive model. *Neurosci Biobehav Rev* [Internet]. 2018 [cited 2018 Aug 8]; Available from: https://linkinghub.elsevier.com/retrieve/pii/S0149763417308527. doi:10.1016/j.neubiorev.2018.03.024.

60. McMorris T. The acute exercise-cognition interaction: From the catecholamines hypothesis to an interoception model. *Int J Psychophysiol*. 2021;170:75–88.

61. Craig AD. How do you feel? Interoception: the sense of the physiological condition of the body. *Nat Rev Neurosci*. 2002;3(8):655–66.

62. Critchley HD, Wiens S, Rotshtein P, Öhman A, Dolan RJ. Neural systems supporting interoceptive awareness. *Nat Neurosci*. 2004;7(2):189–95.

63. Hilty L, Langer N, Pascual-Marqui R, Boutellier U, Lutz K. Fatigue-induced increase in intracortical communication between mid/anterior insular and motor cortex during cycling exercise: Muscle fatigue-induced intracortical communication. *Eur J Neurosci*. 2011;34(12):2035–42.

64. Paulus MP, Potterat EG, Taylor MK, et al. A Neuroscience Approach to Optimizing Brain Resources for Human Performance in Extreme Environments. *Neurosci Biobehav Rev*. 2009;33(7):1080–8.

65. Robertson CV, Marino FE. Prefrontal and motor cortex EEG responses and their relationship to ventilatory thresholds during exhaustive incremental exercise. *Eur J Appl Physiol*. 2015;115(9):1939–48.

66. Paterson S, Marino FE. Effect of Deception of Distance on Prolonged Cycling Performance. *Percept Mot Skills*. 2004;98(3):1017–26.

67. Castle PC, Maxwell N, Allchorn A, Mauger AR, White DK. Deception of ambient and body core temperature improves self paced cycling in hot, humid conditions. *Eur J Appl Physiol*. 2012;112(1):377–85.

68. (Bud) Craig AD. How do you feel — now? The anterior insula and human awareness. *Nat Rev Neurosci*. 2009;10(1):59–70.

69. Singer T, Seymour B, O'Doherty J, Kaube H, Dolan RJ, Frith CD. Empathy for Pain Involves the Affective but not Sensory Components of Pain. *Science*. 2004;303(5661):1157–62.

70. Williamson JW, Nobrega ACL, McColl R, et al. Activation of the Insular Cortex During Dynamic Exercise in Humans. *J Physiol*. 1997;503(2):277–83.

71. Williamson JW, McColl R, Mathews D, Ginsburg M, Mitchell JH. Activation of the insular cortex is affected by the intensity of exercise. *J Appl Physiol*. 1999;87(3):1213–9.

72. Marcora SM, Staiano W, Manning V. Mental fatigue impairs physical performance in humans. *J Appl Physiol*. 2009;106(3):857–64.

73. Hocking C, Silberstein RB, Lau WM, Stough C, Roberts W. Evaluation of cognitive performance in the heat by functional brain imaging and psychometric testing. *Comp Biochem Physiol A Mol Integr Physiol*. 2001;128(4):719–34.

74. Crandall CG, González-Alonso J. Cardiovascular function in the heat-stressed human: Heat stress and the cardiovascular system. *Acta Physiol*. 2010;199(4):407–23.

75. Crandall CG, Wilson TE. Human Cardiovascular Responses to Passive Heat Stress. In: Terjung R, editor. *Comprehensive Physiology*. Hoboken, NJ, USA: John Wiley & Sons, Inc.; 2014. p. 17–43. [cited 2018 Sep 12] Available from: http://doi.wiley.com/10.1002/cphy.c140015.

76. Rowell LB, Brengelmann GL, Murray JA. Cardiovascular responses to sustained high skin temperature in resting man. *J Appl Physiol*. 1969;27(5):673–80.

77. van den Heuvel AMJ, Haberley BJ, Hoyle DJR, Taylor NAS, Croft RJ. The independent influences of heat strain and dehydration upon cognition. *Eur J Appl Physiol*. 2017;117(5):1025–37.

78. van den Heuvel AMJ, Haberley BJ, Hoyle DJR, Taylor NAS, Croft RJ. Hyperthermia, but not dehydration, alters the electrical activity of the brain. *Eur J Appl Physiol*. 2020;120(12):2797–811.

79. Nielsen B, Hyldig T, Bidstrup F, González-Alonso J, Christoffersen GRJ. Brain activity and fatigue during prolonged exercise in the heat. *Pflüg Arch*. 2001;442(1):41–8.

80. Qian S, Sun G, Jiang Q, et al. Altered topological patterns of large-scale brain functional networks during passive hyperthermia. *Brain Cogn*. 2013;83(1):121–31.

81. Liu K, Sun G, Li B, et al. The impact of passive hyperthermia on human attention networks: An fMRI study. *Behav Brain Res*. 2013;243:220–30.

82. Nakata H, Oshiro M, Namba M, Shibasaki M. Effects of passive heat stress on human somatosensory processing. *Am J Physiol - Regul Integr Comp Physiol*. 2015;309(11):R1387–96.

83. Nakata H, Kakigi R, Shibasaki M. Effects of passive heat stress and recovery on human cognitive function: An ERP study. *PLOS ONE*. 2021;16(7):e0254769.

84. Hasegawa H, Piacentini MF, Sarre S, Michotte Y, Ishiwata T, Meeusen R. Influence of brain catecholamines on the development of fatigue in exercising rats in the heat: Effect of bupropion on thermoregulation and exercise performance. *J Physiol*. 2008;586(1):141–9.

85. Watson P, Hasegawa H, Roelands B, Piacentini MF, Looverie R, Meeusen R. Acute dopamine/noradrenaline reuptake inhibition enhances human exercise performance in warm, but not temperate conditions: Dopamine and noradrenaline reuptake and exercise. *J Physiol*. 2005;565(3):873–83.

86. Roelands B, Hasegawa H, Watson P, et al. The Effects of Acute Dopamine Reuptake Inhibition on Performance: *Med Sci Sports Exerc*. 2008;40(5):879–85.

87. Al-Khazraji BK, Shoemaker LN, Gati JS, Szekeres T, Shoemaker JK. Reactivity of larger intracranial arteries using 7 T MRI in young adults. *J Cereb Blood Flow Metab*. 2019;39(7):1204–14.

88. Nattie E. CO2, brainstem chemoreceptors and breathing. *Prog Neurobiol*. 1999;59(4):299–331.

89. Szabo K, Lako E, Juhasz T, Rosengarten B, Csiba L, Olah L. Hypocapnia induced vasoconstriction significantly inhibits the neurovascular coupling in humans. *J Neurol Sci*. 2011;309(1–2):58–62.

90. Nunneley SA, Martin CC, Slauson JW, Hearon CM, Nickerson LDH, Mason PA. Changes in regional cerebral metabolism during systemic hyperthermia in humans. *J Appl Physiol*. 2002;92(2):846–51.

91. Fujii N, Honda Y, Hayashi K, Kondo N, Koga S, Nishiyasu T. Effects of chemoreflexes on hyperthermic hyperventilation and cerebral blood velocity in resting heated humans: Hyperthermic hyperpnoea and chemoreflex drive, cerebral circulation. *Exp Physiol*. 2008;93(8):994–1001.

92. Brothers RM, Wingo JE, Hubing KA, Crandall CG. The effects of reduced end-tidal carbon dioxide tension on cerebral blood flow during heat stress: Cerebrovascular blood flow during heat stress. *J Physiol*. 2009;587(15):3921–7.

93. Brothers RM, Ganio MS, Hubing KA, Hastings JL, Crandall CG. End-tidal carbon dioxide tension reflects arterial carbon dioxide tension in the heat-stressed human with and without simulated hemorrhage. *Am J Physiol-Regul Integr Comp Physiol*. 2011;300(4):R978–83.

94. Ross EZ, Cotter JD, Wilson L, Fan J-L, Lucas SJE, Ainslie PN. Cerebrovascular and corticomotor function during progressive passive hyperthermia in humans. *J Appl Physiol*. 2012;112(5):748–58.

95. Bain AR, Hoiland RL, Donnelly J, et al. Cerebral metabolism, oxidation and inflammation in severe passive hyperthermia with and without respiratory alkalosis. *J Physiol*. 2020;12.

96. Fan J-L, Cotter JD, Lucas RAI, Thomas K, Wilson L, Ainslie PN. Human cardiorespiratory and cerebrovascular function during severe passive hyperthermia: effects of mild hypohydration. *J Appl Physiol*. 2008;105(2):433–45.

97. Van Diest I, Stegen K, Van de Woestijne KP, Schippers N, Van den Bergh O. Hyperventilation and attention: effects of hypocapnia on performance in a Stroop task. *Biol Psychol*. 2000;53(2–3):233–52.

98. Friend AT, Balanos GM, Lucas SJE. Isolating the independent effects of hypoxia and hyperventilation-induced hypocapnia on cerebral haemodynamics and cognitive function. *Exp Physiol*. 2019;EP087602.

99. Wallace PJ, McKinlay BJ, Cheung SS. Comment on: "Endurance Performance is Influenced by Perceptions of Pain and Temperature: Theory, Applications and Safety Considerations." *Sports Med*. 2018;1–3.

100. Cheung SS. Interconnections between thermal perception and exercise capacity in the heat: Thermal perception and exercise capacity. *Scand J Med Sci Sports*. 2010;20:53–9.

101. Bridge MW, Weller AS, Rayson M, Jones DA. Responses to exercise in the heat related to measures of hypothalamic serotonergic and dopaminergic function. *Eur J Appl Physiol*. 2003;89(5):451–9.

102. Gaoua N, Grantham J, Racinais S, El Massioui F. Sensory displeasure reduces complex cognitive performance in the heat. *J Environ Psychol*. 2012;32(2):158–63.

103. Stevens CJ, Mauger AR, Hassmèn P, Taylor L. Endurance Performance is Influenced by Perceptions of Pain and Temperature: Theory, Applications and Safety Considerations. *Sports Med* [Internet]. 2017 [cited 2018 Jan 3]; Available from: http://link.springer.com/10.1007/s40279-017-0852-6. doi:10.1007/s40279-017-0852-6.

104. Gagge AP, Stolwijk JAJ, Hardy JD. Comfort and thermal sensations and associated physiological responses at various ambient temperatures. *Environ Res*. 1967;1(1):1–20.

105. IUPS Thermal Commission. Glossary of terms for thermal physiology: Third edition. *Jpn J Physiol*. 2001;51(2):245–80.

106. Simmons SE, Saxby BK, McGlone FP, Jones DA. The effect of passive heating and head cooling on perception, cardiovascular function and cognitive performance in the heat. *Eur J Appl Physiol*. 2008;104(2):271–80.

107. Tyler CJ, Sunderland C. Neck Cooling and Running Performance in the Heat: Single versus Repeated Application. *Med Sci Sports Exerc*. 2011;43(12):2388–95.

108. Tyler CJ, Wild P, Sunderland C. Practical neck cooling and time-trial running performance in a hot environment. *Eur J Appl Physiol*. 2010;110(5):1063–74.

109. Wallace PJ, Masbou AT, Petersen SR, Cheung SS. The effects of cranial cooling during recovery on subsequent uncompensable heat stress tolerance. *Appl Physiol Nutr Metab*. 2015;40(8):811–6.

110. Malcolm RA, Cooper S, Folland JP, Tyler CJ, Sunderland C. Passive Heat Exposure Alters Perception and Executive Function. *Front Physiol* [Internet]. 2018 [cited 2018 May 28];9 Available from: https://www.frontiersin.org/article/10.3389/fphys.2018.00585/full. doi:10.3389/fphys.2018.00585.

111. Vernon HM, Warner CG. The Influence of the Humidity of the Air on Capacity for Work at High Temperatures. *J Hyg (Lond)*. 1932;32(3):431–62.

112. Pilcher JJ, Nadler E, Busch C. Effects of hot and cold temperature exposure on performance: a meta-analytic review. *Ergonomics*. 2002;45(10):682–98.

113. Hancock PA, Ross JM, Szalma JL. A Meta-Analysis of Performance Response Under Thermal Stressors. *Hum Factors J Hum Factors Ergon Soc*. 2007;49(5):851–77.

114. Racinais S, Gaoua N, Grantham J. Hyperthermia impairs short-term memory and peripheral motor drive transmission. *J Physiol*. 2008;586(19):4751–62.

115. Schmit C, Hausswirth C, Le Meur Y, Duffield R. Cognitive Functioning and Heat Strain: Performance Responses and Protective Strategies. *Sports Med*. 2017;47(7):1289–302.

116. Gaoua N, Grantham J, Racinais S, El Massioui F. Sensory displeasure reduces complex cognitive performance in the heat. *J Environ Psychol*. 2012;32(2):158–63.

117. Malcolm RA, Cooper S, Folland JP, Tyler CJ, Sunderland C. Passive Heat Exposure Alters Perception and Executive Function. *Front Physiol* [Internet]. 2018 [cited 2018 May 28];9 Available from: https://www.frontiersin.org/article/10.3389/fphys.2018.00585/full. doi:10.3389/fphys.2018.00585.

118. Allnutt MF, Allan JR. The Effects of Core Temperature Elevation and Thermal Sensation on Performance. *Ergonomics*. 1973;16(2):189–96.

119. Shibasaki M, Namba M, Oshiro M, Kakigi R, Nakata H. Suppression of cognitive function in hyperthermia; From the viewpoint of executive and inhibitive cognitive processing. *Sci Rep* [Internet]. 2017;7 Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC5353598/. doi:10.1038/srep43528.

120. Gaoua N, Racinais S, Grantham J, Massioui FE. Alterations in cognitive performance during passive hyperthermia are task dependent. *Int J Hyperthermia*. 2011;27(1):1–9.

121. Schlader ZJ, Lucas RAI, Pearson J, Crandall CG. Hyperthermia does not alter the increase in cerebral perfusion during cognitive activation: Cerebral perfusion during cognitive activation. *Exp Physiol*. 2013;98(11):1597–607.

122. Wallace PJ, Mckinlay BJ, Coletta NA, et al. Effects of Motivational Self-Talk on Endurance and Cognitive Performance in the Heat: *Med Sci Sports Exerc*. 2017;49(1):191–9.

123. Selkirk GA, McLellan TM. Influence of aerobic fitness and body fatness on tolerance to uncompensable heat stress. *J Appl Physiol*. 2001;91(5):2055–63.

124. Meeusen R, Watson P, Dvorak J. The brain and fatigue: New opportunities for nutritional interventions? *J Sports Sci*. 2006;24(7):773–82.

125. Balthazar CH, Leite LHR, Ribeiro RMM, Soares DD, Coimbra CC. Effects of blockade of central dopamine D1 and D2 receptors on thermoregulation, metabolic rate and running performance. *Pharmacol Rep*. 2010;62(1):54–61.

126. Balthazar CH, Leite LHR, Rodrigues AG, Coimbra CC. Performance-enhancing and thermoregulatory effects of intracerebroventricular dopamine in running rats. *Pharmacol Biochem Behav*. 2009;93(4):465–9.

127. Hasegawa H, Piacentini MF, Sarre S, Michotte Y, Ishiwata T, Meeusen R. Influence of brain catecholamines on the development of fatigue in exercising rats in the heat: Effect of bupropion on thermoregulation and exercise performance. *J Physiol*. 2008;586(1):141–9.

128. Roelands B, Meeusen R. Alterations in central fatigue by pharmacological manipulations of neurotransmitters in normal and high ambient temperature. *Sports Med*. 2010;40(3):229–46.

129. Solanto MV. Neuropsychopharmacological mechanisms of stimulant drug action in attention-deficit hyperactivity disorder: a review and integration. *Behav Brain Res*. 1998;94(1):127–52.

130. Zheng X, Hasegawa H. Central dopaminergic neurotransmission plays an important role in thermoregulation and performance during endurance exercise. *Eur J Sport Sci*. 2016;16(7):818–28.

131. Daubner SC, Le T, Wang S. Tyrosine hydroxylase and regulation of dopamine synthesis. *Arch Biochem Biophys*. 2011;508(1):1–12.

132. Jongkees BJ, Hommel B, Kühn S, Colzato LS. Effect of tyrosine supplementation on clinical and healthy populations under stress or cognitive demands—A review. *J Psychiatr Res*. 2015;70:50–7.

133. Tam S-Y, Elsworth JD, Bradberry CW, Roth RH. Mesocortical dopamine neurons: High basal firing frequency predicts tyrosine dependence of dopamine synthesis. *J Neural Transm*. 1990;81(2):97–110.

134. Leonard BE, McCartan D, White J, King DJ. Methylphenidate: a review of its neuropharmacological, neuropsychological and adverse clinical effects. *Hum Psychopharmacol Clin Exp*. 2004;19(3):151–80.

135. Pan D, Gatley SJ, Dewey SL, et al. Binding of bromine-substituted analogs of methylphenidate to monoamine transporters. [date unknown];6.

136. Ihalainen JA, Tanila H, Scheinin M, Jr PR. ⎵2C-Adrenoceptors modulate the effect of methylphenidate on response rate and discrimination accuracy in an operant test. [date unknown];5.

137. Volkow ND, Wang Gene-J, Fowler JS, et al. Dopamine Transporter Occupancies in the Human Brain Induced by Therapeutic Doses of Oral Methylphenidate. *Am J Psychiatry*. 1998;155(10):1325–31.

138. Volkow ND, Fowler JS, Wang G, Ding Y, Gatley SJ. Mechanism of action of methylphenidate: Insights from PET imaging studies. *J Atten Disord*. 2002;6(1_suppl):31–43.

139. Volkow ND, Wang G-J, Fowler JS, et al. Therapeutic Doses of Oral Methylphenidate Significantly Increase Extracellular Dopamine in the Human Brain. *J Neurosci*. 2001;21(2):RC121–RC121.

140. Elliott R, Sahakian BJ, Matthews K, Bannerjea A, Rimmer J, Robbins TW. Effects of methylphenidate on spatial working memory and planning in healthy young adults. *Psychopharmacology (Berl)*. 1997;131(2):196–206.

141. Mehta MA, Owen AM, Sahakian BJ, Mavaddat N, Pickard JD, Robbins TW. Methylphenidate Enhances Working Memory by Modulating Discrete Frontal and Parietal Lobe Regions in the Human Brain. *J Neurosci*. 2000;20(6):RC65–RC65.

142. Ramasubbu R, Singh H, Zhu H, Dunn JF. Methylphenidate-mediated reduction in prefrontal hemodynamic responses to working memory task: a functional near-infrared spectroscopy study: METHYLPHENIDATE-MEDIATED REDUCTION IN HB RESPONSES. *Hum Psychopharmacol Clin Exp*. 2012;27(6):615–21.

143. Agay N, Yechiam E, Carmel Z, Levkovitz Y. Non-specific effects of methylphenidate (Ritalin) on cognitive ability and decision-making of ADHD and healthy adults. *Psychopharmacology (Berl)*. 2010;210(4):511–9.

144. Nandam LS, Hester R, Wagner J, et al. Methylphenidate But Not Atomoxetine or Citalopram Modulates Inhibitory Control and Response Time Variability. *Biol Psychiatry*. 2011;69(9):902–4.

145. Costa A, Riedel M, Pogarell O, et al. Methylphenidate Effects on Neural Activity During Response Inhibition in Healthy Humans. *Cereb Cortex*. 2013;23(5):1179–89.

146. Ilieva IP, Hook CJ, Farah MJ. Prescription Stimulants' Effects on Healthy Inhibitory Control, Working Memory, and Episodic Memory: A Meta-analysis. *J Cogn Neurosci*. 2015;27(6):1069–89.

147. Volkow ND, Fowler JS, Wang G-J, et al. Methylphenidate Decreased the Amount of Glucose Needed by the Brain to Perform a Cognitive Task. *PLoS ONE*. 2008;3(4):e2017.

148. Rogers RD, Blackshaw AJ, Middleton HC, et al. Tryptophan depletion impairs stimulus-reward learning while methylphenidate disrupts attentional control in healthy young adults: implications for the monoaminergic basis of impulsive behaviour. *Psychopharmacology (Berl)*. 1999;146(4):482–91.

149. Volkow N, Wang G-J, Fowler J, et al. Evidence That Methylphenidate Enhances the Saliency of a Mathematical Task by Increasing Dopamine in the Human Brain. 2004;

150. Berridge CW, Devilbiss DM, Andrzejewski ME, et al. Methylphenidate Preferentially Increases Catecholamine Neurotransmission within the Prefrontal Cortex at Low Doses that Enhance Cognitive Function. *Biol Psychiatry*. 2006;60(10):1111–20.

151. Marquand AF, O'Daly OG, De Simoni S, et al. Dissociable effects of methylphenidate, atomoxetine and placebo on regional cerebral blood flow in healthy volunteers at rest: A multi-class pattern recognition approach. *NeuroImage*. 2012;60(2):1015–24.

152. Wang G-J, Volkow ND, Fowler JS, et al. Methylphenidate decreases regional cerebral blood flow in normal human subjects. *Life Sci*. 1994;54(9):PL143–6.

153. Wang H, Wang B, Normoyle KP, et al. Brain temperature and its fundamental properties: a review for clinical neuroscientists. *Front Neurosci* [Internet]. 2014 [cited 2018 Mar

13];8 Available from: http://journal.frontiersin.org/article/10.3389/fnins.2014.00307/abstract. doi:10.3389/fnins.2014.00307.

154. Volkow ND, Wang G-J, Fowler JS, Ding Y-S. Imaging the Effects of Methylphenidate on Brain Dopamine: New Model on Its Therapeutic Actions for Attention-Deficit/Hyperactivity Disorder. *Biol Psychiatry*. 2005;57(11):1410–5.

155. Volkow ND, Wang G-J, Fowler JS, et al. Cardiovascular effects of methylphenidate in humans are associated with increases of dopamine in brain and of epinephrine in plasma. *Psychopharmacology (Berl)*. 2003;166(3):264–70.

156. Klass M, Roelands B, Lévénez M, et al. Effects of Noradrenaline and Dopamine on Supraspinal Fatigue in Well-Trained Men: *Med Sci Sports Exerc*. 2012;44(12):2299–308.

157. Swart J, Lamberts RP, Lambert MI, et al. Exercising with reserve: evidence that the central nervous system regulates prolonged exercise performance. *Br J Sports Med*. 2009;43(10):782–8.

158. King M, Rauch LHG, Brooks SJ, Stein DJ, Lutz K. Methylphenidate Enhances Grip Force and Alters Brain Connectivity: *Med Sci Sports Exerc*. 2017;49(7):1443–51.

159. Volkow ND, Wang G-J, Gatley SJ, et al. Temporal relationships between the pharmacokinetics of methylphenidate in the human brain and its behavioral and cardiovascular effects. *Psychopharmacology (Berl)*. 1996;123(1):26–33.

160. Watson P, Enever S, Page A, Stockwell J, Maughan RJ. Tyrosine Supplementation Does Not Influence the Capacity to Perform Prolonged Exercise in a Warm Environment. *Int J Sport Nutr Exerc Metab*. 2012;22(5):363–73.

161. Tumilty L, Davison G, Beckmann M, Thatcher R. Failure of Oral Tyrosine Supplementation to Improve Exercise Performance in the Heat: *Med Sci Sports Exerc*. 2014;46(7):1417–25.

162. Cordery P, James LJ, Peirce N, Maughan RJ, Watson P. A Catecholamine Precursor Does Not Influence Exercise Performance in Warm Conditions: *Med Sci Sports Exerc*. 2016;48(3):536–42.

163. Francesca Piacentini M, Meeusen R, Buyse L, et al. No effect of a noradrenergic reuptake inhibitor on performance in trained cyclists: *Med Sci Sports Exerc*. 2002;34(7):1189–93.

164. O'Brien C, Mahoney C, Tharion WJ, Sils IV, Castellani JW. Dietary tyrosine benefits cognitive and psychomotor performance during body cooling. *Physiol Behav*. 2007;90(2–3):301–7.

165. Roelands B, Goekint M, Heyman E, et al. Acute norepinephrine reuptake inhibition decreases performance in normal and high ambient temperature. *J Appl Physiol*. 2008;105(1):206–12.

166. Watson P, Hasegawa H, Roelands B, Piacentini MF, Looverie R, Meeusen R. Acute dopamine/noradrenaline reuptake inhibition enhances human exercise performance in warm, but not temperate conditions. *J Physiol*. 2005;565(3):873–83.

167. Castellani JW, Young AJ. Human physiological responses to cold exposure: Acute responses and acclimatization to prolonged exposure. *Auton Neurosci*. 2016;196:63–74.

168. Hoffman RG. Human psychological performance in cold environments. *Med Asp Harsh Environ*. 2001;1:383–410.

169. Greaney JL, Alexander LM, Kenney WL. Sympathetic control of reflex cutaneous vasoconstriction in human aging. *J Appl Physiol*. 2015;119(7):771–82.

170. Doubt TJ. Physiology of Exercise in the Cold: *Sports Med*. 1991;11(6):367–81.

171. Rosomoff HL, Holaday DA. Cerebral Blood Flow and Cerebral Oxygen Consumption During Hypothermia. *Am J Physiol-Leg Content*. 1954;179(1):85–8.

172. Gibbons TD, Tymko MM, Thomas KN, et al. Global REACH 2018: The influence of acute and chronic hypoxia on cerebral haemodynamics and related functional outcomes during cold and heat stress. *J Physiol*. 2020;598(2):265–84.

173. Hodges GJ, Ferguson SAH, Cheung SS. Cardiac autonomic function during hypothermia and its measurement repeatability. *Appl Physiol Nutr Metab*. 2019;44(1):31–6.

174. Hodges GJ, Ferguson SAH, Cheung SS. Glabrous and non-glabrous vascular responses to mild hypothermia. *Microvasc Res*. 2019;121:82–6.

175. Castellani JW, Young AJ, Kain JE, Rouse A, Sawka MN. Thermoregulation during cold exposure: effects of prior exercise. *J Appl Physiol*. 1999;87(1):247–52.

176. Gagnon DD, Rintamäki H, Gagnon SS, et al. Cold exposure enhances fat utilization but not non-esterified fatty acids, glycerol or catecholamines availability during submaximal walking and running. *Front Physiol* [Internet]. 2013 [cited 2018 Feb 28];4 Available from: http://journal.frontiersin.org/article/10.3389/fphys.2013.00099/abstract. doi:10.3389/fphys.2013.00099.

177. Gagnon DD, Rintamäki H, Gagnon SS, et al. Fuel selection during short-term submaximal treadmill exercise in the cold is not affected by pre-exercise low-intensity shivering. *Appl Physiol Nutr Metab*. 2014;39(3):282–91.

178. Tipton MJ. Environmental extremes: origins, consequences and amelioration in humans: Extreme environments. *Exp Physiol*. 2016;101(1):1–14.

179. Thomas JR, Ahlers ST, House JF, et al. Adrenergic responses to cognitive activity in a cold environment. *J Appl Physiol*. 1990;68(3):962–6.

180. Vallerand AL, Jacobs I. Rates of energy substrates utilization during human cold exposure. *Eur J Appl Physiol*. 1989;58(8):873–8.

181. Gagnon DD, Rintamäki H, Gagnon SS, et al. Fuel selection during short-term submaximal treadmill exercise in the cold is not affected by pre-exercise low-intensity shivering. *Appl Physiol Nutr Metab*. 2014;39(3):282–91.

182. Bell DG, Tikuisis P, Jacobs I. Relative intensity of muscular contraction during shivering. *J Appl Physiol*. 1992;72(6):2336–42.

183. Haman F, Legault SR, Weber J-M. Fuel selection during intense shivering in humans: EMG pattern reflects carbohydrate oxidation: Fuel selection during shivering. *J Physiol*. 2004;556(1):305–13.

184. Haman F, Mantha OL, Cheung SS, et al. Oxidative fuel selection and shivering thermogenesis during a 12- and 24-h cold-survival simulation. *J Appl Physiol*. 2016;120(6):640–8.

185. Haman F, Péronnet F, Kenny GP, et al. Effects of carbohydrate availability on sustained shivering I. Oxidation of plasma glucose, muscle glycogen, and proteins. *J Appl Physiol*. 2004;96(1):32–40.

186. Frank SM, Higgins MS, Fleisher LA, Sitzmann JV, Raff H, Breslow MJ. Adrenergic, respiratory, and cardiovascular effects of core cooling in humans. *Am J Physiol-Regul Integr Comp Physiol*. 1997;272(2):R557–62.

187. Haman F, Péronnet F, Kenny GP, et al. Effect of cold exposure on fuel utilization in humans: plasma glucose, muscle glycogen, and lipids. *J Appl Physiol*. 2002;93(1):77–84.

188. Ferguson SAH, Eves ND, Roy BD, Hodges GJ, Cheung SS. Effects of mild whole body hypothermia on self-paced exercise performance. *J Appl Physiol*. 2018;125(2):479–85.

189. Oksa J, Kaikkonen H, Sorvisto P, Vaappo M, Martikkala V, Rintamäki H. Changes in maximal cardiorespiratory capacity and submaximal strain while exercising in cold. *J Therm Biol*. 2004;29(7–8):815–8.

190. Barbara Timmons, Araujo J, Thomas, Tom. Fat utilization enhanced by exercise in a cold environment. 1985;

191. Therminarias A, Flore P, Oddou-Chirpaz MF, Pellerei E, Quirion A. Influence of cold exposure on blood lactate response during incremental exercise. *Eur J Appl Physiol*. 1989;58(4):411–8.

192. Anderson SD, Daviskas E. The mechanism of exercise-induced asthma is …. *J Allergy Clin Immunol*. 2000;106(3):453–9.

193. Oksa J. Neuromuscular performance limitations in cold. *Int J Circumpolar Health*. 2002;61(2):154–62.

194. Chen W-L, Shih Y-C, Chi C-F. Hand and Finger Dexterity as a Function of Skin Temperature, EMG, and Ambient Condition. *Hum Factors*. 2010;52(3):426–40.

195. Racinais S, Oksa J. Temperature and neuromuscular function: Temperature and neuromuscular function. *Scand J Med Sci Sports*. 2010;20:1–18.

196. Todnem K, Knudsen G, Riise T, Nyland H, Aarli JA. The non-linear relationship between nerve conduction velocity and skin temperature. *J Neurol Neurosurg Psychiatry*. 1989;52(4):497–501.

197. De Ruiter CJ, De Haan A. Similar effects of cooling and fatigue on eccentric and concentric force-velocity relationships in human muscle. *J Appl Physiol*. 2001;90(6):2109–16.

198. Petrofsky JS, Lind AR. The influence of temperature on the amplitude and frequency components of the EMG during brief and sustained isometric contractions. *Eur J Appl Physiol*. 1980;44(2):189–200.

199. Thornley LJ, Maxwell NS, Cheung SS. Local tissue temperature effects on peak torque and muscular endurance during isometric knee extension. *Eur J Appl Physiol*. 2003;90(5–6):588–94.

200. Sargeant AJ. Effect of muscle temperature on leg extension force and short-term power output in humans. *Eur J Appl Physiol*. 1987;56(6):693–8.

201. Mallette MM, Green LA, Gabriel DA, Cheung SS. The effects of local forearm muscle cooling on motor unit properties. *Eur J Appl Physiol*. 2018;118(2):401–10.

202. Thornley LJ, Maxwell NS, Cheung SS. Local tissue temperature effects on peak torque and muscular endurance during isometric knee extension. *Eur J Appl Physiol*. 2003;90(5–6):588–94.

203. Oksa J, Ducharme MB, Rintamäki H. Combined effect of repetitive work and cold on muscle function and fatigue. *J Appl Physiol*. 2002;92(1):354–61.

204. Giesbrecht GG, Wu M, White MD, Johnston C, Bristow GK. Isolated effects of peripheral arm and central body cooling on arm performance. 1995;

205. Cahill F, Kalmar JM, Pretorius T, Gardiner PF, Giesbrecht GG. Whole-body hypothermia has central and peripheral influences on elbow flexor performance: Hypothermia and elbow flexor activation. *Exp Physiol*. 2011;96(5):528–38.

206. Brazaitis M, Paulauskas H, Skurvydas A, Budde H, Daniuseviciute L, Eimantas N. Brief Rewarming Blunts Hypothermia-Induced Alterations in Sensation, Motor Drive and Cognition. *Front Physiol* [Internet]. 2016 [cited 2019 Jul 9];7 Available from: http://journal.frontiersin.org/article/10.3389/fphys.2016.00592/full. doi:10.3389/fphys.2016.00592.

207. Solianik R, Skurvydas A, Pukėnas K, Brazaitis M. Comparison of the effects of whole-body cooling during fatiguing exercise in males and females. *Cryobiology*. 2015;71(1):112–8.

208. Brazaitis M, Skurvydas A, Pukėnas K, Daniusevičiūtė L, Mickevičienė D, Solianik R. The effect of temperature on amount and structure of motor variability during 2-minute maximum voluntary contraction. *Muscle Nerve*. 2012;46(5):799–809.

209. Markand ON, Warren C, Mallik GS, King RD, Brown JW, Mahomed Y. Effects of hypothermia on short latency somatosensory evoked potentials in humans. *Electroencephalogr Clin Neurophysiol Potentials Sect*. 1990;77(6):416–24.

210. Brooks VB. Study of brain function by local, reversible cooling. *Reviews of Physiology, Biochemistry and Pharmacology, Volume 95*. Springer; 1983. p. 1–109.

211. Wang H, Kim M, Normoyle KP, Llano D. Thermal Regulation of the Brain—An Anatomical and Physiological Review for Clinical Neuroscientists. *Front Neurosci* [Internet]. 2016 [cited 2018 Mar 12];9 Available from: http://journal.frontiersin.org/Article/10.3389/fnins.2015.00528/abstract. doi:10.3389/fnins.2015.00528.

212. Busto R, Globus MY, Dietrich WD, Martinez E, Valdés I, Ginsberg MD. Effect of mild hypothermia on ischemia-induced release of neurotransmitters and free fatty acids in rat brain. *Stroke*. 1989;20(7):904–10.

213. FitzGibbon T, Hayward JS, Walker D. EEG and visual evoked potentials of conscious man during moderate hypothermia. *Electroencephalogr Clin Neurophysiol*. 1984;58(1):48–54.

214. Jones DM, Bailey SP, De Pauw K, et al. Evaluation of cognitive performance and neurophysiological function during repeated immersion in cold water. *Brain Res*. 2019;1718:1–9.

215. Avakian EV, Horvath SM, Colburn RW. Influence of age and cold stress on plasma catecholamine levels in rats. *J Auton Nerv Syst*. 1984;10(2):127–33.

216. Lieberman HR, Georgelis JH, Maher TJ, Yeghiayan SK. Tyrosine prevents effects of hyperthermia on behavior and increases norepinephrine. *Physiol Behav*. 2005;84(1):33–8.

217. Chieko Okuda, Akiko Saito, Masao Miyazaki, Kinya Kuriyama. Alteration of the turnover of dopamine and 5-hydroxytryptamine in rat brain associated with hypothermia. *Pharmacol Biochem Behav*. 1986;24(1):79–83.

218. Quock RM, Gale CC. Hypothermia-mediating dopamine receptors in the preoptic anterior hypothalamus of the cat. *Naunyn Schmiedebergs Arch Pharmacol*. 1974;285(3):297–300.

219. Okuda C, Miyazaki M, Kuriyama K. Hypothalamic control of pituitary and adrenal hormones during hypothermia. *Psychoneuroendocrinology*. 1986;11(4):415–27.

220. Ebinger G, Michotte Y, Herregodts P. The Significance of Homovanillic Acid and 3,4-Dihydroxyphenylacetic Acid Concentrations in Human Lumbar Cerebrospinal Fluid. *J Neurochem*. 1987;48(6):1725–9.

221. O'Brien C, Mahoney C, Tharion WJ, Sils IV, Castellani JW. Dietary tyrosine benefits cognitive and psychomotor performance during body cooling. *Physiol Behav*. 2007;90(2–3):301–7.

222. Ogoh S, Ainslie PN. Cerebral blood flow during exercise: mechanisms of regulation. *J Appl Physiol*. 2009;107(5):1370–80.

223. Datta A, Tipton M. Respiratory responses to cold water immersion: neural pathways, interactions, and clinical consequences awake and asleep. *J Appl Physiol*. 2006;100(6):2057–64.

224. Secher NH, Seifert T, Van Lieshout JJ. Cerebral blood flow and metabolism during exercise: implications for fatigue. *J Appl Physiol*. 2008;104(1):306–14.

225. Ide K, Eliasziw M, Poulin MJ. Relationship between middle cerebral artery blood velocity and end-tidal PCO2 in the hypocapnic-hypercapnic range in humans. *J Appl Physiol*. 2003;95(1):129–37.

226. Ainslie PN, Duffin J. Integration of cerebrovascular CO_2 reactivity and chemoreflex control of breathing: mechanisms of regulation, measurement, and interpretation. *Am J Physiol-Regul Integr Comp Physiol*. 2009;296(5):R1473–95.

227. Willie CK, Cowan EC, Ainslie PN, et al. Neurovascular coupling and distribution of cerebral blood flow during exercise. *J Neurosci Methods*. 2011;198(2):270–3.

228. Hellstrom G, Fischer-Colbrie W, Wahlgren NG, Jogestrand T. Carotid artery blood flow and middle cerebral artery blood flow velocity during physical exercise. *J Appl Physiol*. 1996;81(1):413–8.

229. Nybo L, Nielsen B. Middle cerebral artery blood velocity is reduced with hyperthermia during prolonged exercise in humans. *J Physiol*. 2001;534(1):279–86.

230. McCullough JN, Zhang N, Reich DL, et al. Cerebral metabolic suppression during hypothermic circulatory arrest in humans. *Ann Thorac Surg*. 1999;67(6):1895–9.

231. Clifton GL, Jiang JY, Lyeth BG, Jenkins LW, Hamm RJ, Hayes RL. Marked Protection by Moderate Hypothermia after Experimental Traumatic Brain Injury. *J Cereb Blood Flow Metab*. 1991;11(1):114–21.

232. Schwab S, Schwarz S, Spranger M, Keller E, Bertram M, Hacke W. Moderate Hypothermia in the Treatment of Patients With Severe Middle Cerebral Artery Infarction. *Stroke*. 1998;29(12):2461–6.

233. Kawamura S, Suzuki A, Hadeishi H, Yasui N, Hatazawa J. Cerebral Blood Flow and Oxygen Metabolism During Mild Hypothermia in Patients with Subarachnoid Haemorrhage. *Acta Neurochir (Wien)*. 2000;142(10):1117–22.

234. Shiojiri T, Shibasaki M, Aoki K, Kondo N, Koga S. Effects of reduced muscle temperature on the oxygen uptake kinetics at the start of exercise. *Acta Physiol Scand*. 1997;159(4):327–33.

235. Ferguson S, Eves ND, Roy B, Hodges GJ, Cheung SS. Oxygen availability effects on exercise performance and tissue oxygenation during mild hypothermia. Kobe, Japan: 2017.

236. Kanosue K, Sadato N, Okada T, et al. Brain activation during whole body cooling in humans studied with functional magnetic resonance imaging. *Neurosci Lett*. 2002;329(2):157–60.

237. Lincoln JM, Conway GA. Preventing commercial fishing deaths in Alaska. *Occup Environ Med*. 1999;56(10):691–5.

238. Pilcher JJ, Nadler E, Busch C. Effects of hot and cold temperature exposure on performance: a meta-analytic review. *Ergonomics*. 2002;45(10):682–98.

239. Hancock PA, Ross JM, Szalma JL. A Meta-Analysis of Performance Response Under Thermal Stressors. *Hum Factors J Hum Factors Ergon Soc*. 2007;49(5):851–77.

240. Ellis HD. The Effects of Cold on the Performance of Serial Choice Reaction Time and Various Discrete Tasks. *Hum Factors J Hum Factors Ergon Soc*. 1982;24(5):589–98.

241. Flouris AD, Westwood DA, Cheung SS. Thermal Balance Effects on Vigilance During 2-Hour Exposures To ⁄20°C. 2007;78(7):7.

242. Makinen T, Palinkas L, Reeves D, et al. Effect of repeated exposures to cold on cognitive performance in humans. *Physiol Behav*. 2006;87(1):166–76.

243. Muller MD, Muller SM, Kim C-H, Ryan EJ, Gunstad J, Glickman EL. Mood and selective attention in the cold: the effect of interval versus continuous exercise. *Eur J Appl Physiol*. 2011;111(7):1321–8.

244. Muller MD, Gunstad J, Alosco ML, et al. Acute cold exposure and cognitive function: evidence for sustained impairment. *Ergonomics*. 2012;55(7):792–8.

245. Patil P. Effects of a cold-water stressor on psychomotor and cognitive functioning in humans. *Physiol Behav*. 1995;58(6):1281–6.

246. Jones DM, Bailey SP, Roelands B, Buono MJ, Meeusen R. Cold acclimation and cognitive performance: A review. *Auton Neurosci*. 2017;208:36–42.

247. Giesbrecht GG, Arnett JL, Vela E, Bristow GK. Effect of task complexity on mental performance during immersion hypothermia. *Aviat Space Environ Med*. 1993;64(3, Sect 1):206–11.

248. Solianik R, Skurvydas A, Mickevičienė D, Brazaitis M. Intermittent whole-body cold immersion induces similar thermal stress but different motor and cognitive responses between males and females. *Cryobiology*. 2014;69(2):323–32.

249. O'Brien C, Tharion WJ, Sils IV, Castellani JW. Cognitive, Psychomotor, and Physical Performance in Cold Air After Cooling by Exercise in Cold Water. 2007;78(6):7.

250. Mahoney CR, Castellani J, Kramer FM, Young A, Lieberman HR. Tyrosine supplementation mitigates working memory decrements during cold exposure. *Physiol Behav*. 2007;92(4):575–82.

251. Taber MJ, Hartley GL, McGarr GW, et al. Cognitive Performance during a 24-Hour Cold Exposure Survival Simulation. *BioMed Res Int*. 2016;2016:1–11.

252. Solianik R, Skurvydas A, Urboniene D, Eimantas N, Daniuseviciute L, Brazaitis M. SIMILAR COLD STRESS INDUCES SEX-SPECIFIC NEUROENDOCRINE AND WORKING MEMORY RESPONSES. [date unknown];9.

253. Ellis HD. The Effects of Cold on the Performance of Serial Choice Reaction Time and Various Discrete Tasks. *Hum Factors J Hum Factors Ergon Soc*. 1982;24(5):589–98.

254. Castellani JW, Tipton MJ. Cold stress effects on exposure tolerance and exercise performance. *Compr Physiol*. 2016;6(1):443–69.

255. Parkin JM, Carey MF, Zhao S, Febbraio MA. Effect of ambient temperature on human skeletal muscle metabolism during fatiguing submaximal exercise. *J Appl Physiol*. 1999;86(3):902–8.

256. Cheuvront SN, Iii RC, Castellani JW, Sawka MN. Hypohydration impairs endurance exercise performance in temperate but not cold air. *J Appl Physiol*. 2005;99:6.

257. Oksa J. Neuromuscular performance limitations in cold. *Int J Circumpolar Health*. 2002;61(2):154–62.

258. Gagnon DD, Rintamäki H, Gagnon SS, et al. Cold exposure enhances fat utilization but not non-esterified fatty acids, glycerol or catecholamines availability during submaximal walking and running. *Front Physiol* [Internet]. 2013 [cited 2019 Feb 26];4 Available from: http://journal.frontiersin.org/article/10.3389/fphys.2013.00099/abstract. doi:10.3389/fphys.2013.00099.

259. Fink WJ, Costill DL, Van Handel PJ. Leg muscle metabolism during exercise in the heat and cold. *Eur J Appl Physiol*. 1975;34(1):183–90.

260. Paulus MP, Flagan T, Simmons AN, et al. Subjecting Elite Athletes to Inspiratory Breathing Load Reveals Behavioral and Neural Signatures of Optimal Performers in Extreme Environments. *PLoS ONE* [Internet]. 2012 [cited 2017 Feb 9];7(1) Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3261851/. doi:10.1371/journal.pone.0029394.

261. Gaoua N. Cognitive function in hot environments: a question of methodology: Cognitive function in hot environments. *Scand J Med Sci Sports*. 2010;20:60–70.

3 - Objectives and Hypotheses

The main objectives of this thesis are to examine the separate and combined roles of skin and core temperature on cognitive function during passive heat and cold stress. Two specific projects were designed to assess this idea and are detailed in Chapters 4-5. Specific objectives and hypothesises (predictions as opposed to statistical hypotheses) for these projects are listed below.

3.1 Objectives and Hypotheses – Chapter 4

Primary Objective: To examine the effect of skin and core temperature on cognitive function during passive heat stress.

Secondary Objective: To test the effects of methylphenidate a dopamine reuptake inhibitor, on cognitive performance due to its potential psychophysiological effects on thermal tolerance, thermal perception, and cardiovascular function.

Hypotheses: It was predicted that i) Hyperthermia will reduce higher order cognitive function (e.g., executive function, working memory) as they are more vulnerable to heat stress, ii) methylphenidate will counter the declines in higher order cognitive function, and iii) methylphenidate will improve thermal perceptions during passive heat stress and will counter any cognitive decrements caused by thermal displeasure of hot skin.

3.2 Objectives and Hypotheses – Chapter 5

Objective: To examine the effect of skin and core temperature on cognitive function during passive cold stress.

Hypothesis: It was predicted that i) both cold skin and both core cooling conditions will lead to a reduction in cognitive performance in both errors made and longer reaction times for all cognitive domains compared to thermoneutral conditions, and ii) core cooling would impair cognitive function greater than cooling the skin alone.

3.3 Objectives and Hypotheses – Chapter 6

Primary Objective: To examine the effect of skin and core temperature on endurance capacity (time to exhaustion at 70% peak power output) in the cold.

Hypotheses: It was predicted that i) endurance capacity would be impaired with cold shell cooling compared with thermoneutral; ii) both core cooling conditions will decrease endurance capacity more than skin cooling alone; and iii) core cooling to Δ-1.0°C will lead to greater impairments in endurance capacity compared to Δ-0.5°C in core temperature due to increased cold strain.

4 – The Effects of Acute Dopamine Reuptake Inhibition on Cognitive Function During Passive Heat Stress

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4.1 Abstract

Dopamine activity can modulate physical performance in the heat, but less is known about its effects on cognition during thermal stress. Twelves males completed a randomized, double-blinded protocol consisting of oral ingestion of 20 mg of methylphenidate (MPH) or placebo (lactose pill) during passive heating using a water-perfused suit (water temperature ~49°C). To identify the impact of peripheral versus central thermal strain, a cognitive test battery was completed at four different thermal states: baseline (BASE; 37.2±0.6˚C core, 32.9±0.7˚C skin), neutral core-hot skin (NC-HS; 37.2±0.3˚C, 37.4±0.3˚C), hyperthermic core-hot skin (HC-HS; 38.7±0.4˚C, 38.7±0.2˚C), and hyperthermic core-cooled skin (HC-CS; 38.5±0.4˚C, 35.1±0.8˚C). The cognitive test battery consisted of the 2-back task (i.e. ,working memory), set-shifting (i.e., executive function), Groton Maze Learning Task (i.e., executive function) and detection task (i.e., psychomotor processing). MPH led to significantly higher heart rates (~5-15 b·min^{-1}) at BASE, NC-HS, and HC-HS (all p<0.05). There were no significant differences in the number of errors made on each task (all p<0.05). Participants were significantly faster (p<0.05) on the set-shifting task in the HC-HS timepoint, irrespective of drug condition (p>0.05). In summary, we demonstrated that 20 mg of MPH did not significantly alter cognitive function during either normothermia or moderate hyperthermia.

4.1.1 Novelty:

20 mg of MPH did not significantly alter cognitive function during passive heat stress

MPH led to significant higher heart rates (~5-15 $b \cdot min^{-1}$) in thermoneutral and during passive heat stress

Future studies are needed to determine the mechanisms of why MPH improves physical but not cognitive performance during heat stress

Keywords: passive hyperthermia, cognitive function, methylphenidate, dopamine, thermal perception, executive function, working memory

4.2 Introduction

Heat stress and hyperthermia increase physiological and psychological strain relative to thermoneutral environments that can lead to decrements in cognitive function and decision making (Pilcher et al. 2002; Hancock et al. 2007; Schmit et al. 2017). Heat stress induces an inverted-U response where mild heat stress may improve performance due to increased attentional focus, however as hyperthermia develops there is a decrease in attentional resources to maintain task performance (Hancock and Vasmatzidis 1998; Liu et al. 2013). Task-dependent changes in cognitive function exist, where higher order functions such as executive function, vigilance, working memory and planning decrease with the passive raising of core temperature ≥ 1.0˚C, while lower order cognitive tasks such as psychomotor processing reaction time are less vulnerable (Gaoua et al. 2011; Liu et al. 2013). However, the threshold for impairment of working memory and executive function is variable with others demonstrating minimal impairment with rises in core temperature of 1.3-2.0°C (Schlader et al. 2013; Wallace et al. 2017; van den Heuvel et al. 2017). Several mechanisms have been proposed to explain how hyperthermia impairs cognitive performance, including thermal sensory displeasure from skin heating (Gaoua et al. 2012), altered neural activity (Liu et al. 2013; Qian et al. 2013; Gaoua et al. 2018), decreases in cerebral blood flow from hyperventilatory hypocapnia (Bain et al. 2015), or alterations in brain neurochemistry (Kishore et al. 2013).

Dopamine is a brain neurotransmitter that may affect physiological, cognitive, and psychological responses during hyperthermia. Methylphenidate (MPH) increases dopamine levels within the brain by binding to the dopamine transporter and thereby inhibiting its re-uptake, with a fivefold-higher affinity for the dopamine transporter than for the norepinephrine transporter (Volkow et al. 1998, 2001, 2002; Berridge et al. 2006). In a thermoneutral environments, acute

doses (20-40 mg) of MPH in healthy adults improves cognitive tasks such as spatial working memory and planning (Elliott et al. 1997a; Mehta et al. 2000), simple working memory (Agay et al. 2010; Ramasubbu et al. 2012), and executive function through improved response inhibition (Nandam et al. 2011; Costa et al. 2013). MPH improves neurological function and neurovascular uncoupling as improvements in working memory and executive function occur despite regional reductions in cerebral blood flow in the frontal and temporal lobes (Wang et al. 1994; Costa et al. 2013), as well as reduced cerebral glucose metabolism (Volkow et al. 2008). Acute doses of MPH also improves exercise capacity and reduces thermal discomfort in the heat, with ~16% improvement in cycling time trial performance in 30°C and a ~0.3°C higher final core temperature despite similar perceptions of thermal discomfort and effort as the placebo condition (Roelands et al. 2008). However, the effects of MPH cognitive performance in the heat is currently unknown.

Psychological perceptions of thermal stress are more vulnerable in the heat and have been proposed to alter cognitive function even before significant physiological change. Executive function and working memory performance were impaired with elevated skin temperatures despite core temperature remaining unchanged (Racinais et al. 2008; Gaoua et al. 2012; Malcolm et al. 2018), possibly due to the sensory displeasure of hot skin increasing cognitive load and limiting neural resources available for both cognitive tasks and monitoring of thermal state (Gaoua et al. 2012) or else through a speed-accuracy trade-off (Malcolm et al. 2018). In thermoneutral environments, MPH may improve cognitive performance through increased feelings of arousal and motivation (Volkow et al. 2011), decreased cognitive load (Mehta et al. 2000), and reduced perception of physical fatigue (King et al. 2017). If cognitive performance is impaired due to sensory displeasure of hot skin, MPH may work to counter performance decrements through reducing the psychological strain of heat stress (Roelands et al. 2008). However, the separate and

combined roles of MPH and thermal perception on cognitive performance has yet to be determined.

Therefore, the purpose of this study was to investigate the acute effects of 20 mg of MPH (dopamine re-uptake inhibitor) compared to a placebo (lactose) on cognitive performance (i.e. executive function, working memory, psychomotor processing) during passive hyperthermia. In order to separate the roles of thermal displeasure, MPH, and hyperthermia we tested cognitive function in four distinct timepoints: Baseline (no thermal manipulation), Neutral Core – Hot Skin, Hyperthermic Core – Hot Skin, and Hyperthermic Core – Cooled Skin. We hypothesize that i) hyperthermia will reduce higher order cognitive function (e.g., executive function, working memory) as they are more vulnerable to heat stress, ii) MPH will counter the declines in higher order cognitive function, and iii) MPH improves thermal perceptions during passive heat stress to counter any cognitive decrements caused by thermal displeasure of hot skin.

4.3 Methods

4.3.1 Participants

The experimental protocol and procedures were approved by the Bioscience Research Ethics Board at Brock University (REB #17-385) and conformed to the latest revision of the *Declaration of Helsinki*. Twelve males (age: 24.0 ± 1.9 years, body mass: 76.5 ± 9.2 kg, % body fat: 11.6 ± 6.2%, peak oxygen consumption ($\dot{V}O_{2\,peak}$): 44.4 ± 7.5 ml·kg·min^{-1}, and Cognitive Failure Questionnaire score: 25.0 ± 7.9) were screened by a physician and provided informed consent prior to study participation. All participants were free from cardiovascular, respiratory, and neurological disorders, have not been diagnosed with attention hyperactivity disorder, nor taken methylphenidate or stimulant drugs within the last 12 months.

4.3.2 Experimental Design

The experiment was a randomized, double-blinded study consisting of a familiarization session and two experimental trials. The familiarization session consisted of collecting anthropometric data, practicing the cognitive tasks, and determining $\dot{V}O_{2\,peak}$. The two experimental sessions were identical, only differing by drug manipulation and were separated by one week to allow for drug wash-out, reduce the potential for heat acclimation, and performed at the same time of day to control for circadian fluctuation in core temperature. Participants were instructed to avoid vigorous exercise and alcohol consumption 24 hours and caffeine (stimulant) 12 hours prior to each experimental session.

4.3.3 Preliminary Assessment

Upon arrival, anthropometric measurements (height, mass) and % body fat calculated using the 7-site skinfold technique (Jackson and Pollock 1978) were recorded. Participants then

completed the Cognitive Failure Questionnaire (CFQ), which is a 25-item questionnaire that is a self-evaluative measure of general fluid intelligence and is related to four factors of absentmindedness (memory, distractibility, blunders, and names) (Broadbent et al. 1982). Items were scored on a 5-point Likert scale where 0 equals "never" and 4 equals "very often". CFQ scores can range from 0 to 100, where average CFQ scores are between 19 and 45. Participants were excluded from the study if CFQ score is > 45, as this score indicates considerable difficulties in completing tasks that require vigilance. Ultimately, no participants were excluded based on this threshold. Next, participants practiced the Cognitive Test Battery (CTB, see below for details) three times in order to minimize the learning effect for each task (Wallace et al. 2017). An incremental test to exhaustion was performed in a thermoneutral environment (~22°C, 30% RH) on a cycle ergometer (Velotron, RacerMate Inc, USA) to determine $\dot{V}O_{2peak}$. The test began with a standardized 5-min warm-up at 100 W, followed by workload increase of 25 W each minute until exhaustion. $\dot{V}O_{2peak}$ was defined as the highest 30 s value measured breath by breath from expired gases collected through a soft silicone facemask connected to an online gas collection system (Gas Analyzer, ADInstruments, USA).

4.3.4 Experimental Protocol

Upon arrival, participants voided their bladder to measure urine specific gravity (USG; PAL-10S, Atago, Japan) to determine hydration status and nude body mass (kg) was recorded. Participants were considered euhydrated if USG was ≤1.020, or else the test was rescheduled. Participants were then given either 20 mg of i) MPH (2 x 10 mg tablets, methylphenidate hydrocholaride (pms-methylphenidate, Pharmascience Inc., Canada) or ii) a placebo (PLA, lactose) crushed and mixed into a container of apple sauce (113 g, 50 calories, 14 g carbohydrates, 0 g fat, 0.3 g protein) to be indistinguishable for participants. 20 mg of MPH was chosen as this

dosage has demonstrated improvement of physical performance and behavioral changes in hot environments (Roelands et al. 2008). Participants were then instrumented (see below for details) and fitted with a two-piece liquid conditioning garment (BCS 4 Cooling System, Med Eng, Canada) consisting of 1/8" diameter Tygon tubing sewn into a stretchable jacket and pant; with the head, hands and feet uncovered. After a 60-minute wash-in period, participants performed a baseline (BASE) measure of the CTB (see below for details) with no temperature manipulation. Next participants were fitted with a polyvinyl rain suit and thermal blanket over the liquid conditioning garment with the hands and head uncovered to minimize evaporative heat loss.

Four timepoints were tested manipulating both physiological and perceptual thermal strain. The first testing period was BASE which took place in a thermoneutral environment. Next, in order to manipulate the separate and combined effects of core temperature and sensory displeasure of hot skin, ~49.0˚C water was circulated at 2.5 $L \cdot min^{-1}$ through the liquid cooling garment and the next CTB was performed once a mean skin temperature ($\overline{T}_{sk}$) of ~37.0˚C was achieved, creating a neutral core – hot skin (NC-HS) timepoint. To test the effects of hyperthermia on cognition, passive heat stress was continued until there was a rise in core temperature by ~Δ1.5˚C creating a hyperthermic core – hot skin (HC-HS) timepoint. Lastly, upon completion of the CTB, to test the effects of hyperthermia without sensory displeasure of hot skin, ~15-20˚C water was circulated through the liquid conditioning garment until $\overline{T}_{sk}$ of 35.5˚C while minimizing changes in core temperature, creating a hyperthermic core – cooled skin (HC-CS) timepoint.

4.3.5 Cognitive Test Battery

To measure progressive changes in cognitive function, a ~15-min CTB (CogState, New Haven, USA) was performed at BASE, NC-HS, HC-HS, and HC-CS, which consisted of a Groton Maze Learning Task (GMLT), detection task, 2-back task, set-shifting task, and GMLT- Recall.

Three practice trials were performed at the preliminary assessment to increase familiarity and to minimize the learning effect of multiple exposures to tasks (Wallace et al. 2017). Additionally, a shortened version of each task was performed at the beginning of each task for further familiarization. All participants were told to perform the tasks as quickly and as accurately as they could.

The GMLT is a self-paced touchscreen based cognitive task that measures executive function through error detection and spatial memory. The test consists of a 10 x 10 grid of squares that cover a hidden 28-step pathway that includes 11 turns. A blue tile on the top left corner of the screen indicates the starting position and a red circle on the bottom right corner indicates the finish location. Participants are provided with correct feedback (green checkmark), or error feedback (red circle) based on square selected to reveal the hidden pathway. Overall goal is to focus on overall task of maze completion, as opposed to focusing on immediate next move or reacting to stimuli presented on screen (which is goal of subsequent tasks). The GMLT was performed six times (initial test sequence and five block trials) per test. The GMLT test sequence required approximately 5 to 10 minutes to complete. Each maze is randomized and has an equal level of difficulty, in order to minimize a learning effect due to repeated exposure. Performance was measured for the total duration (s) and total number of errors measured during the five-block period as well as the final block (GMLT-5). A GMLT-Recall test was performed at the end of each CTB, which required the participant to find the same hidden pathway from the initial five-block period in the current CTB.

The detection task was used to test psychomotor function and reaction time. A playing card was presented on the screen flipped over, and participants were tasked with pressing a key when the card was turned over presenting the front of the card. This process continues until the task is

completed. There was an inter-stimulus interval of 2 seconds between each presentation of 35 cards and continues until the task is complete. Performance was measured for speed (mean of the $\log_{10}$ transformed reaction times for correct responses) where a lower score represents a better performance. The task took approximately 2 minutes to complete.

The 2-back task is a measure of attention and visual working memory. Participants were tasked with determining if the card presented is identical to the card presented two cards ago. There was a total of 48 cards presented and participants could either answer 'Yes' or 'No' for the card presented. Performance for this task was measured for speed (mean of the $\log_{10}$ transformed reaction times for correct responses) and total # of errors made. The test took approximately 2 minutes to complete.

The set-shifting task is a measure of cognitive flexibility and response inhibition. Participants were asked to answer the question "is this the target card?". Participants were presented with either the category "number" or "colour" above a playing card in the center of the screen. Participants had to answer if the target was with a "yes" or "no" response based on the category. The target card suddenly changes throughout the test which could be either from one colour to the other (i.e., from a red target card to a black target card or intra-dimensional shift) or from "colour" to "number" (i.e., from a red target card to a number two target card or extra-dimensional shift). Participants were not told when these changes occurred and needed to re-learn the new target card to continue with the test. The task is performed until the participant has achieved 120 correct trials. The only feedback presented to the participant was that the next card would not be displayed until the correct response is made. Performance was measured based on speed of processing (mean of the $\log_{10}$ transformed reaction times for correct responses) and total number of errors.

4.4 Instrumentation

Before the commencement of BASE, participants were instrumented with a flexible thermistor (Mon-A-Therm Core, Mallinkrodt Medical, USA) self-inserted 15 cm beyond the anal sphincter to measure rectal temperature (T_{re}) sampled at 4 Hz. Four thermocouples (VC-T-24-190, Omega Environmental Inc., Canada) were used to determine weighted $\bar{T}_{sk}$ at four sites defined as $\bar{T}_{sk} = 0.3_{arm} + 0.3_{chest} + 0.2_{thigh} + 0.2_{calf}$ (Ramanathan 1964) on the right side of the body sampled at 4 Hz. Heart rate was calculated using R-R intervals using a standard three-lead electrocardiogram (MLA2340, AD Instruments; USA). Systolic blood pressure (SBP) and diastolic blood pressure (DBP) was taken from a manual sphygmomanometer (Aneroid Sphygmomanometer, Welch Allyn Hillrom, USA) on their left arm by the same and experienced researcher before the CTB at each timepoint. Mean arterial pressure (MAP) was calculated as: $MAP = \frac{((2*DP)+SBP)}{3}$. A silicone facemask connected to an online gas collection system (Gas Analyzer, AD Instruments; USA) was used to measure ventilation ($\dot{V}_E$, L·min^{-1}) and to determine the end tidal partial pressure of carbon dioxide ($P_{et}CO_2$, mmHg) sampled continuously at 1 kHz. These data were used to quantify additional markers of moderate hyperthermia and demonstrate that hyperthermia-induced hypocapnia occurred, which leads to reductions in cerebral blood flow (Fujii et al. 2008; Brothers et al. 2011; Ross et al. 2012). All physiological data were continuously sampled throughout the experiment and is the average over the course of the entire CTB. Thermal perceptions were assessed using a 1-4 scale to measure thermal comfort and a 1-7 scale for thermal sensation (Gagge et al. 1967) and was collected upon the completion of the CTB at BASE, NC-HS, HC-HS, and HC-CS.

4.5 Data analyses

All continuous variable data are presented as the mean ± SD. All continuous variables were analyzed using separate Drug (PLA vs. MPH) x Timepoints (BASE, NC-HS, HC-HS, HC-CS) repeated measures ANOVAs. If a significant timepoint effect was found using 2 x 4 repeated measures ANOVA, individual drug (MPH or PLA) x timepoints repeated measure ANOVAs (1 x 4) followed by Bonferroni pairwise comparisons were used to compare significant timepoint effects for each drug. This was used to determine the independent timepoint effects of MPH or PLA drug conditions. Paired sample *t* tests were performed to test significant main effects at specific timepoint if there was a significant drug effect.

All ordinal data (TC, TS) is presented as the median (quartiles 1 and 3) and was analyzed using separate Drug (PLA vs. MPH) x Timepoints (BASE, NC-HS, HC-HS, HC-CS) repeated measures ANOVAs, with a Wilcoxon signed-rank test used to compare at specific time points. Friedman's ANOVAs were used to analyze and confirm timepoint effects. Statistical significance was set at $p < 0.05$. All analyses were performed using IBM SPSS Statistics for Windows (version 26.0; IBM Corp., USA).

4.6 Results

4.6.1 Experimental Design

The experimental design was successful in creating four distinct temperature-perceptual timepoints (Figure 4-1). T_{re} demonstrated a timepoint effect ($F_{(3,33)} = 223.0$, $p \leq 0.001$), where T_{re} was significantly higher in HC-HS and HC-CS compared to BASE (both ≤ 0.001) and NC-HS (both ≤ 0.001). Pairwise comparisons demonstrated no differences in T_{re} between BASE and NC-HS ($p = 1.00$), nor with HC-HS compared to HC-CS ($p > 0.05$). There was a timepoint effect for $\bar{T}_{sk}$ ($F_{(3,33)} = 562.6$, $p \leq 0.001$) which was different at all timepoints (all $p < 0.05$). Thermal Comfort ($F_{(3,33)} = 153.2$, $p \leq 0.001$, Friedman's ANOVA: $p \leq 0.001$) increased (was worse) in NC-HS and HC-HS (both $p \leq 0.001$), but not HC-CS ($p = 0.401$) compared to BASE. Thermal Sensation ($F_{(3,33)} = 68.2$, $p < 0.001$, Friedman's ANOVA: $p \leq 0.001$) increased (was hotter) in NC-HS and HC-HS (all $p \leq 0.01$) but not HC-CS ($p = 0.401$) compared to BASE, with no difference ($p = 0.118$) between NC-HS and HC-CS. In a debriefing questionnaire, $n = 6$ (50%) of participants correctly guessed the MPH trials.

4.6.2 Physiological Variables

4.6.3 Hydration and body mass responses

Urine specific gravity approached significance ($p = 0.056$) before and after the trial in both MPH (Pre: 1.013 ± 0.006, Post: 1.018 ± 0.007), and PLA (Pre: 1.012 ± 0.006, Post: 1.016 ± 0.008) with no drug ($p = 0.609$) or drug x timepoint interaction (0.557). Body mass (*ad libitum* water volume corrected) decreased similarly in MPH (Pre: 76.9 ± 9.2, Post: 76.0 ± 9.5 kg), and PLA (Pre: 76.7 ± 9.1, Post: 75.6 ± 9.7 kg) ($p = 0.973$) with no timepoint ($p = 0.572$), drug ($p = 0.876$), or drug x timepoint interaction ($p = 0.973$).

4.6.4 Cardiovascular responses

Due to technical issues, data for HR is reduced with $n = 11$. There was a significant drug ($F_{(1,10)} = 6.873$, $p = 0.026$) and timepoint ($F_{(3,30)} = 88.127$, $p \leq 0.001$) effect for heart rate, with no drug x timepoint interaction ($F_{(3,30)} = 34.518$, $p = 0.420$) (Figure 4-2, Panel A). In both drug conditions, pairwise comparisons revealed heart rate significantly increased from BASE at all timepoints (all $p \leq 0.001$), with HC-HS significantly higher than NC-HS ($p < 0.001$), but not HC-CS ($p = 0.308$). There were significantly higher heart rates with MPH at BASE (MPH: 79.0 ± 12.8 PLA: 74.0 ± 8.0 b·min^{-1}, $p = 0.036$), NC-HS (MPH: 95.0 ± 12.5 PLA: 85.0 ± 7.8 b·min^{-1}, $p = 0.002$), and HC-HS (MPH: 135.0 ± 15.2 PLA: 124.0 ± 15.0 b·min^{-1}, $p = 0.004$), but not HC-CS ($p = 0.129$). There was a significant drug ($F_{(1,11)} = 18.07$, $p = 0.001$) and timepoint effect ($F_{(3,33)} = 15.471$, $p \leq 0.001$) for SBP (Figure 4-2, Panel B) with no drug x timepoint interaction ($F_{(3,33)} = 0.571$, $p = 0.638$). Specifically, SBP was significantly higher in HC-HS compared to all other timepoints (all $p \leq 0.05$). Paired samples *t*-tests indicated that SBP was significantly higher at timepoints NC-HS (MPH: 124.0 ± 9.6 PLA: 116.0 ± 7.3 mmHg, $p = 0.007$) and HC-HS (MPH: 131.0 ± 9.7 PLA: 126.0 ± 8.2 mmHg $p = 0.033$) but not at BASE (MPH: 120.0 ± 9.0 PLA: 117.0 ± 6.0 mmHg $p = 0.08$) and not HC-CS (MPH: 122.0 ± 10.1 PLA: 115.0 ± 11.5 mmHg, $p = 0.055$). There was no drug, timepoint, or drug x time interaction (all $p > 0.05$) for DBP (Figure 4-2, Panel C). There was a significant drug ($F_{(1,11)} = 5.903$, $p = 0.033$) effect with no timepoint ($F_{(3,33)} = 17.933$, $p = 0.326$) or drug x timepoint interaction ($F_{(3,33)} = 6.039$, $p = 0.340$) for MAP (Figure 4-2, Panel D). Paired samples *t*-tests indicated that there was significantly higher MAP with MPH at HC-HS (MPH: 91.0 ± 5.5 PLA: 87.0 ± 5.0 mmHg, $p = 0.008$), with no differences at BASE (MPH: 89.0 ± 6.5 PLA: 87.0 ± 5.1 mmHg, $p = 0.170$), NC-HS (MPH: 90.0 ± 5.9 PLA: 87.0 ± 4.7 mmHg, $p = 0.085$), or HC-CS (MPH: 88.0 ± 6.5 PLA: 86.0 ± 6.7 mmHg, $p = 0.356$).

4.6.5 Respiratory responses

Due to technical issues, the $\dot{V}_E$ data was reduced to $n = 11$. There was a significant timepoint effect for $\dot{V}_E$ ($F_{(3,30)} = 14.917$, $p \leq 0.001$), with no drug ($p = 0.137$) or drug x timepoint interaction ($p = 0.498$). Hyperthermia led to a hyperventilatory response, where $\dot{V}_E$ was significantly higher at HC-HS compared to all other timepoints (all $p < 0.05$), with no other differences between timepoints (all $p > 0.05$) (Figure 4-3, Panel A). In conjunction, there was a significant timepoint effect with $P_{et}CO_2$ ($F_{(3,33)} = 19.266$, $p \leq 0.001$), with no drug or drug x time point interaction (both $p > 0.05$) (Figure 4-3, Panel B). Pairwise comparisons revealed a significant reduction from BASE at all timepoints (all $p < 0.05$). Additionally, NC-HS was significantly different than both HS-HC ($p = 0.004$) and HC-CS ($p = 0.003$), with no different between HC-HS and HC-CS ($p = 0.104$).

4.6.6 Cognitive variables

GMLT – There were no significant drug or drug x timepoint interactions (all $p > 0.05$) for the GMLT, GMLT-5, or GMLT-Recall # of errors or completion duration (Table 4-1). There was a significant timepoint effect for GMLT duration ($F_{(3,33)} = 3.904$, $p = 0.017$) and GMLT-5 duration ($F_{(3,33)} = 4.082$, $p = 0.014$), however pairwise comparisons show no significant differences between any timepoints (all $p > 0.05$) for either variable. There was a non-significant timepoint effect for GMLT errors ($F_{(3,33)} = 0.905$, $p = 0.905$). There were no timepoint effects (all $p > 0.05$) for GMLT-5 errors, GMLT-Recall duration or errors made.

Detection Task – There were no drug or drug x timepoint (both $p > 0.05$) for speed on the detection task, with a significant overall timepoint effect ($F_{(3,33)} = 13.069$, $p \leq 0.001$) (Table 4-1). Pairwise comparisons revealed no significant differences for speed in MPH (all $p > 0.05$), however participants were significantly faster in PLA at HC-HS compared to BASE ($p = 0.026$) and NC-

HS (p = 0.002). There were no drug, timepoint, or drug x timepoint interactions (all $p > 0.05$) for # of errors made.

2-Back Task – There were no drug, timepoint, or drug x timepoint interactions (all $p > 0.05$) for both # of errors and speed for the 2-back task (Table 4-1).

Set-Shifting Task – There were no drug or drug x timepoint interactions for both speed and # of errors made (all $p > 0.05$) on the set-shifting tasks. There were significant timepoint effects for both speed ($F_{(3,33)} = 14.181$, $p \leq 0.001$) and # of errors ($F_{(3,33)} = 3.361$, $p = 0.030$) (Table 4-1). Follow up for specific timepoint effects based on drug, 1 x 4 repeated measures ANOVAs pairwise comparisons revealed that in MPH, speed was significantly faster in NC-HS (p = 0.035), HC-HS (p = 0.001), and HC-CS (p = 0.002) compared to BASE. While in PLA, speed was significantly faster in HC-HS compared to HC-CS (p = 0.003) with no differences between any other timepoints. Paired samples t-test revealed that, at BASE, MPH was significantly slower than PLA (p = 0.013). Follow up for specific timepoint effects based on drug, 1 x 4 repeated measures ANOVA pairwise comparisons revealed no significant differences between timepoints with either drug (all $p > 0.05$).

4.7 Discussion

This study tested the effects of acute oral administration of 20 mg of MPH (a dopamine reuptake inhibitor) on executive function, working memory, and psychomotor processing during passive heat stress. Despite the moderate hyperthermic change in T_{re} (Δ+1.5°C) coupled with increased cardiovascular strain and a hyperventilatory hypocapnia, we did not find an impairment in cognitive function. Furthermore, we found neither changes in skin temperature nor core temperature impaired accuracy on any measured cognitive variables. Instead, hyperthermia led to significantly faster reaction times for both the detection task (psychomotor processing) and set-shifting task (executive function, inhibitory control), without a speed accuracy trade off.

Physiologically, MPH demonstrated a sympatho-adrenal response through significantly higher cardiovascular strain during the heating protocol. Psychologically, we found no benefits of MPH on thermal perception compared with PLA. The use of MPH did not significantly alter cognitive performance. There was a significantly slower speed in thermoneutral temperatures at BASE during the set-shifting task, with no differences in errors made with MPH compared to PLA. However, speed on the set-shifting task was similar to PLA upon the commencement of heating, such that any effect was not maintained throughout thermal stress. Overall, it appears that acute oral administration of MPH does not enhance cognitive function during moderate passive hyperthermia.

Our findings indicated neither a slowing of response nor reduction in accuracy with any test performed within the CTB supports the general confusion surrounding whether hyperthermia impairs cognitive performance. One obvious explanation is that our level of hyperthermia could have been insufficiently stressful. We are confident that participants were thermally strained in the HC-HS timepoint (+1.5˚C T_{re}), as participants had a hyperthermia-induced hyperventilatory hypocapnia response, which is demonstrated to lead to significant reductions in cerebral blood flow (Brothers et al. 2011; Ross et al. 2012), along with a high perceptual thermal strain. It could be that this may still be insufficient thermal strain to overload cognitive resources, as Schlader et al. (2013) found no impairment in *n*-back (working memory) performance with Δ+1.3˚C core temperature, Similarly, van den Heuvel et al. (2017), found neither a Δ+2.0˚C in core temperature or dehydration of 3-5% impaired *n*-back (working memory) or visual-perception performance, however, participants demonstrated improved reaction time and were more liberal (i.e. response bias) with responses while hyperthermic. It may be possible that an absolute threshold in core temperature (≥ 39.0°C) may be necessary before decrements in complex cognitive function (e.g.,

spatial planning, visual motor tracking) occur or that cognitive resources are sufficiently strained (Schmit et al. 2017; Racinais et al. 2017; Piil et al. 2017; Gaoua et al. 2018). Arguing against this, higher order cognitive tasks (e.g., executive function) were impaired with a passive increase in core temperature by ≥ 1.0˚C (Hocking et al. 2001; Gaoua et al. 2011; Liu et al. 2013; Qian et al. 2013). Therefore, future research is needed to determine the core temperature threshold required before decrements in cognitive function occur during both passive and active hyperthermia.

Both the dopaminergic and norepinephrine systems project to the prefrontal cortex, and the level of these catecholamine neurotransmitters are proposed to affect cognitive function, motor performance, and motivation (Volkow et al. 2004; McMorris et al. 2006; Hasegawa et al. 2008; Kishore et al. 2013; Roelands et al. 2015). Both dopamine and norepinephrine demonstrate an inverted U response, where either too little or too much of each neurotransmitter can impair cognitive performance (Arnsten 2009). Methylphenidate directly increases extracellular brain dopamine levels in the prefrontal cortex (Volkow et al. 2001; Berridge et al. 2006), enhancing cognitive function in thermoneutral environments (Elliott et al. 1997a; Mehta et al. 2000; Agay et al. 2010; Costa et al. 2013). However, in the current study we found minimal effects of MPH on cognitive function during passive hyperthermia. We found a significantly slower speed of processing on the set-shifting task (i.e., inhibitory control, cognitive flexibility) with MPH, which returned to PLA levels upon the commencement of heating. Additionally, MPH did not lead to significant difference in errors on any of the cognitive tasks. These results are in line with other studies attempting to manipulate central catecholamines through tyrosine (amino acid precursor to dopamine and norepinephrine synthesis) showing no effect on vigilance or psychomotor task performance after exercise in the heat (40°C, 30% relative humidity) (Coull et al. 2016). Overall, these results demonstrate that manipulating central dopamine with MPH was not beneficial at

enhancing cognitive performance during normothermia nor moderate passive hyperthermia (+1.5˚C in T_{re}).

The acute 20 mg dose of MPH used in this study was the same dose that improved cycling time-trial performance by 16% in the heat (30˚C) while finishing the trial with a higher terminating core temperature (~0.3˚C) without any changes in perceived exertion or thermal discomfort (Roelands et al., 2008). Therefore, we hypothesized that this dosing strategy would be effective in altering cognitive function during passive hyperthermia. In adults, the average dose is between 20 to 30 mg administered in 2 to 3 doses daily, for a maximal daily dose of 60 mg (Pharmascience Inc, 2018). It is plausible that both a larger dosage or chronic use of MPH may have a different effect compared to the 20 mg used in the current study. Peak plasma concentration and peak dopamine transport receptor occupancy within the striatum of oral MPH is reached at ~2 hours (Volkow et al., 1998, Spencer et al., 2006) with the half-life in adults ~2.1 hours (Pharmascience Inc, 2018). Despite the minimal changes in cognitive function, MPH led to some physiological changes compared to PLA during thermal stress. Similar to both thermoneutral (Elliott et al. 1997b; Volkow et al. 2003) and hot environments (Roelands et al. 2008), we demonstrated sympatho-adrenal stimulation with increased heart rates (~5-15 $b \cdot min^{-1}$) and systolic blood pressure (~4-8 mmHg) with MPH throughout the experimental protocol. Indirectly, this response would point to MPH being present during our study testing points. However, a limitation of our study is not including plasma measures of MPH, catecholamines, or pituitary hormones (e.g., prolactin) to confirm circulating plasma concentrations. Future studies are needed to determine if there is a dose-response relationship with MPH on cognitive function in the heat to fully elucidate the role of dopamine on cognitive function during hyperthermia.

One of the potential mechanism for dopamine to enhance performance under thermal stress may be throughout dampening perceptual thermal strain (Roelands et al. 2008). In order to isolate this effect, we attempted control for changes in thermal displeasure by manipulating $\bar{T}_{skin}$ to test the independent effects of hot skin without changes in core temperature (NC-HS), and the effects of hyperthermia without the sensory displeasure of hot skin (HC-CS) (Nakata et al. 2015). As expected, with heating there was a worsening of thermal comfort and thermal sensation (NC-HS, HC-HS), that was significantly improved upon cooling the skin (HC-CS). However, there was no effect of MPH on thermal perception. The differences in lack of thermal perception changes may be due to our study design using clamped thermal conditions compared to Roelands et al (2008), which used behavioral thermoregulation through self-paced exercise in the heat to regulate core and skin thermal states. Potentially, dopamine may work to extend the tolerance of unpleasant thermal perceptions, as opposed to acutely modifying the comfort/sensation of the thermal stressor. For example, rat models demonstrate that use of a dual dopamine/norepinephrine reuptake inhibitor (bupropion) led to significantly longer running times in the heat (30˚C) leading to higher core and brain temperatures that were correlated with increases in dopamine and norepinephrine in the brain (Hasegawa et al. 2008). Furthermore, variability in heat tolerance has been demonstrated to be correlated to non-serotonergic (likely dopaminergic) prolactin release in recreationally active male's cycling time to exhaustion (r = 0.661 and end-core temperature (r = 0.623) in the heat (35 ˚C) (Bridge et al. 2003). Additionally, previous evidence has demonstrated that MPH (20 mg, slow release) significantly extended the tolerance time of a cold pressor test in adults with ADHD (Pud et al. 2017). Combined, this evidence points to dopamine playing a potential role in thermal tolerance as opposed to affecting instantaneous thermal perception per se.

However, future research is needed to determine the influence of dopamine on behavioral thermoregulation, thermal tolerance, and thermal perceptions.

Similar to previous investigations (Nakata et al. 2015) a strength of our research design was controlling both skin and core temperature between participants in order to determine the separate and combined effects of temperature on cognitive function. An additional strength of our protocol was the use of a CTB that tested multiple components of executive function (visual spatial memory, inhibitory control, cognitive flexibility, and working memory) in order to determine which components of cognitive function may change with thermal stress and with MPH. A limitation of our experiment is that we cannot determine if there is a dose-response relationship for MPH on cognitive function in the heat. Additionally, although there were minimal changes in core temperature in the HC-CS timepoint, this may have occurred due to our use of rectal temperature, which is slower to respond to rapid changes in temperature compared to esophageal temperature. Additionally, we cannot account for changes in central nervous system electrical activity in the executive attention network and prefrontal cortex, which are important neural regions for the executive function and working memory during passive hyperthermia (Liu et al. 2013; Qian et al. 2013). We cannot determine if the increased heart rate and SBP with MPH influenced cerebrovascular function. Cerebral blood flow is tightly regulated by arterial CO_2, MAP, cerebral metabolism and autonomic nervous system function (For review see: Willie et al. 2014). Cerebral vasculature is highly sensitive to changes in atrial CO_2 where the ~18% decrease in $P_{et}CO_2$ (regardless of drug condition) likely led to a decrease in cerebral blood flow (Fujii et al. 2008; Brothers et al. 2011; Ross et al. 2012). Currently, it is unknown if clamping $P_{et}CO_2$ during passive hyperthermia can influence cognitive function. MAP was ~3-4 mmHg greater during heating with MPH, and we cannot rule out if this change influenced cerebral perfusion pressure or

global or regional cerebral blood flow. Lastly, the results of this study are limited to males as no females were tested in the current study to account for fluctuation in resting core temperature due to the menstrual cycle. Currently it is unknown if there are sex-related differences in cognitive function under thermal stress or with acute doses of MPH. Future research is needed to determine if sex-related differences in responsiveness to MPH during thermal stress occurs.

In summary, we demonstrated that 20 mg of MPH did not significantly alter cognitive function during either normothermia or moderate levels of passive heat stress. The use of MPH led to higher a higher cardiovascular strain of ~10-15 $b \cdot min^{-1}$ during passive heat stress compared to the PLA without altering other physiological or perceptions of thermal strain during the skin and core temperature manipulations. Future studies are needed to determine the mechanisms of why MPH improves physical but not cognitive performance during heat stress. One avenue may be determining the role of dopamine and MPH on thermal tolerance.

4.7.1 Conflict of interest statement

The authors declare that there are no financial or other conflicts of interest to disclose.

4.7.2 Acknowledgements

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4.7.3 References

Agay, N., Yechiam, E., Carmel, Z., and Levkovitz, Y. 2010. Non-specific effects of methylphenidate (Ritalin) on cognitive ability and decision-making of ADHD and healthy adults. Psychopharmacology (Berl.) 210(4): 511–519. doi:10.1007/s00213-010-1853-4.

Arnsten, A.F.T. 2009. Stress signalling pathways that impair prefrontal cortex structure and function. Nat. Rev. Neurosci. 10(6): 410–422. doi:10.1038/nrn2648.

Bain, A.R., Nybo, L., and Ainslie, P.N. 2015. Cerebral Vascular Control and Metabolism in Heat Stress. *In* Comprehensive Physiology. *Edited by* R. Terjung. John Wiley & Sons, Inc., Hoboken, NJ, USA. pp. 1345–1380. doi:10.1002/cphy.c140066.

Berridge, C.W., Devilbiss, D.M., Andrzejewski, M.E., Arnsten, A.F.T., Kelley, A.E., Schmeichel, B., Hamilton, C., and Spencer, R.C. 2006. Methylphenidate Preferentially Increases Catecholamine Neurotransmission within the Prefrontal Cortex at Low Doses that Enhance Cognitive Function. Biol. Psychiatry 60(10): 1111–1120. doi:10.1016/j.biopsych.2006.04.022.

Bridge, M.W., Weller, A.S., Rayson, M., and Jones, D.A. 2003. Responses to exercise in the heat related to measures of hypothalamic serotonergic and dopaminergic function. Eur. J. Appl. Physiol. 89(5): 451–459. doi:10.1007/s00421-003-0800-z.

Broadbent, D.E., Cooper, P.F., FitzGerald, P., and Parkes, K.R. 1982. The Cognitive Failures Questionnaire (CFQ) and its correlates. Br. J. Clin. Psychol. 21(1): 1–16. doi:10.1111/j.2044-8260.1982.tb01421.x.

Brothers, R.M., Ganio, M.S., Hubing, K.A., Hastings, J.L., and Crandall, C.G. 2011. End-tidal carbon dioxide tension reflects arterial carbon dioxide tension in the heat-stressed human with and without simulated hemorrhage. Am. J. Physiol.-Regul. Integr. Comp. Physiol. 300(4): R978–R983. doi:10.1152/ajpregu.00784.2010.

Costa, A., Riedel, M., Pogarell, O., Menzel-Zelnitschek, F., Schwarz, M., Reiser, M., Möller, H.-J., Rubia, K., Meindl, T., and Ettinger, U. 2013. Methylphenidate Effects on Neural Activity During Response Inhibition in Healthy Humans. Cereb. Cortex 23(5): 1179–1189. doi:10.1093/cercor/bhs107.

Coull, N., Chrismas, B., Watson, P., Horsfall, R., and Taylor, L. 2016. Tyrosine Ingestion and Its Effects on Cognitive and Physical Performance in the Heat: Med. Sci. Sports Exerc. 48(2): 277–286. doi:10.1249/MSS.0000000000000757.

Elliott, R., Sahakian, B.J., Matthews, K., Bannerjea, A., Rimmer, J., and Robbins, T.W. 1997a. Effects of methylphenidate on spatial working memory and planning in healthy young adults. Psychopharmacology (Berl.) 131(2): 196–206.

Elliott, R., Sahakian, B.J., Matthews, K., Bannerjea, A., Rimmer, J., and Robbins, T.W. 1997b. Effects of methylphenidate on spatial working memory and planning in healthy young adults. Psychopharmacology (Berl.) 131(2): 196–206.

Fujii, N., Honda, Y., Hayashi, K., Kondo, N., Koga, S., and Nishiyasu, T. 2008. Effects of chemoreflexes on hyperthermic hyperventilation and cerebral blood velocity in resting heated humans: Hyperthermic hyperpnoea and chemoreflex drive, cerebral circulation. Exp. Physiol. 93(8): 994–1001. doi:10.1113/expphysiol.2008.042143.

Gagge, A.P., Stolwijk, J.A.J., and Hardy, J.D. 1967. Comfort and thermal sensations and associated physiological responses at various ambient temperatures. Environ. Res. 1(1): 1–20. doi:10.1016/0013-9351(67)90002-3.

Gaoua, N., Grantham, J., Racinais, S., and El Massioui, F. 2012. Sensory displeasure reduces complex cognitive performance in the heat. J. Environ. Psychol. 32(2): 158–163. doi:10.1016/j.jenvp.2012.01.002.

Gaoua, N., Herrera, C.P., Périard, J.D., El Massioui, F., and Racinais, S. 2018. Effect of Passive Hyperthermia on Working Memory Resources during Simple and Complex Cognitive Tasks. Front. Psychol. 8. doi:10.3389/fpsyg.2017.02290.

Gaoua, N., Racinais, S., Grantham, J., and Massioui, F.E. 2011. Alterations in cognitive performance during passive hyperthermia are task dependent. Int. J. Hyperthermia 27(1): 1–9. doi:10.3109/02656736.2010.516305.

Hancock, P.A., Ross, J.M., and Szalma, J.L. 2007. A Meta-Analysis of Performance Response Under Thermal Stressors. Hum. Factors J. Hum. Factors Ergon. Soc. 49(5): 851–877. doi:10.1518/001872007X230226.

Hancock, P.A., and Vasmatzidis, I. 1998. Human occupational and performance limits under stress: the thermal environment as a prototypical example. Ergonomics 41(8): 1169–1191. doi:10.1080/001401398186469.

Hasegawa, H., Piacentini, M.F., Sarre, S., Michotte, Y., Ishiwata, T., and Meeusen, R. 2008. Influence of brain catecholamines on the development of fatigue in exercising rats in the heat: Effect of bupropion on thermoregulation and exercise performance. J. Physiol. 586(1): 141–149. doi:10.1113/jphysiol.2007.142190.

van den Heuvel, A.M.J., Haberley, B.J., Hoyle, D.J.R., Taylor, N.A.S., and Croft, R.J. 2017. The independent influences of heat strain and dehydration upon cognition. Eur. J. Appl. Physiol. 117(5): 1025–1037. doi:10.1007/s00421-017-3592-2.

Hocking, C., Silberstein, R.B., Lau, W.M., Stough, C., and Roberts, W. 2001. Evaluation of cognitive performance in the heat by functional brain imaging and psychometric testing. Comp. Biochem. Physiol. A. Mol. Integr. Physiol. 128(4): 719–734. doi:10.1016/s1095-6433(01)00278-1.

Jackson, A.S., and Pollock, M.L. 1978. Generalized equations for predicting body density of men. Br. J. Nutr. 40(03): 497. doi:10.1079/BJN19780152.

King, M., Rauch, L.H.G., Brooks, S.J., Stein, D.J., and Lutz, K. 2017. Methylphenidate Enhances Grip Force and Alters Brain Connectivity: Med. Sci. Sports Exerc. 49(7): 1443–1451. doi:10.1249/MSS.0000000000001252.

Kishore, K., Ray, K., Anand, J.P., Thakur, L., Kumar, S., and Panjwani, U. 2013. Tyrosine ameliorates heat induced delay in event related potential P300 and contingent negative variation. Brain Cogn. 83(3): 324–329. doi:10.1016/j.bandc.2013.09.005.

Liu, K., Sun, G., Li, B., Jiang, Q., Yang, X., Li, M., Li, L., Qian, S., Zhao, L., Zhou, Z., von Deneen, K.M., and Liu, Y. 2013. The impact of passive hyperthermia on human attention networks: An fMRI study. Behav. Brain Res. 243: 220–230. doi:10.1016/j.bbr.2013.01.013.

Malcolm, R.A., Cooper, S., Folland, J.P., Tyler, C.J., and Sunderland, C. 2018. Passive Heat Exposure Alters Perception and Executive Function. Front. Physiol. 9. doi:10.3389/fphys.2018.00585.

McMorris, T., Swain, J., Smith, M., Corbett, J., Delves, S., Sale, C., Harris, R.C., and Potter, J. 2006. Heat stress, plasma concentrations of adrenaline, noradrenaline, 5-hydroxytryptamine and cortisol, mood state and cognitive performance. Int. J. Psychophysiol. 61(2): 204–215. doi:10.1016/j.ijpsycho.2005.10.002.

Mehta, M.A., Owen, A.M., Sahakian, B.J., Mavaddat, N., Pickard, J.D., and Robbins, T.W. 2000. Methylphenidate Enhances Working Memory by Modulating Discrete Frontal and Parietal Lobe Regions in the Human Brain. J. Neurosci. 20(6): RC65–RC65. doi:10.1523/JNEUROSCI.20-06-j0004.2000.

Nakata, H., Oshiro, M., Namba, M., and Shibasaki, M. 2015. Effects of passive heat stress on human somatosensory processing. Am. J. Physiol. - Regul. Integr. Comp. Physiol. 309(11): R1387–R1396. doi:10.1152/ajpregu.00280.2015.

Nandam, L.S., Hester, R., Wagner, J., Cummins, T.D.R., Garner, K., Dean, A.J., Kim, B.N., Nathan, P.J., Mattingley, J.B., and Bellgrove, M.A. 2011. Methylphenidate But Not Atomoxetine or Citalopram Modulates Inhibitory Control and Response Time Variability. Biol. Psychiatry 69(9): 902–904. doi:10.1016/j.biopsych.2010.11.014.

Piil, J.F., Lundbye-Jensen, J., Trangmar, S.J., and Nybo, L. 2017. Performance in complex motor tasks deteriorates in hyperthermic humans. Temperature 4(4): 420–428. doi:10.1080/23328940.2017.1368877.

Pilcher, J.J., Nadler, E., and Busch, C. 2002. Effects of hot and cold temperature exposure on performance: a meta-analytic review. Ergonomics 45(10): 682–698. doi:10.1080/00140130210158419.

Pud, D., Broitman, E., Hameed, O., Suzan, E., Aviram, J., Haddad, M., Hadad, S., Shemesh, R., and Eisenberg, E. 2017. Methylphenidate attenuates the response to cold pain but not to aversive auditory stimuli in healthy human: a double-blind randomized controlled study. PAIN Rep. 2(3): e593. doi:10.1097/PR9.0000000000000593.

Qian, S., Sun, G., Jiang, Q., Liu, K., Li, B., Li, M., Yang, X., Yang, Z., and Zhao, L. 2013. Altered topological patterns of large-scale brain functional networks during passive hyperthermia. Brain Cogn. 83(1): 121–131. doi:10.1016/j.bandc.2013.07.013.

Racinais, S., Gaoua, N., and Grantham, J. 2008. Hyperthermia impairs short-term memory and peripheral motor drive transmission. J. Physiol. 586(19): 4751–4762. doi:10.1113/jphysiol.2008.157420.

Racinais, S., Wilson, M.G., Gaoua, N., and Périard, J.D. 2017. Heat acclimation has a protective effect on the central but not peripheral nervous system. J. Appl. Physiol. 123(4): 816–824. doi:10.1152/japplphysiol.00430.2017.

Ramanathan, N.L. 1964. A new weighting system for mean surface temperature of the human body. J. Appl. Physiol. 19: 531–533.

Ramasubbu, R., Singh, H., Zhu, H., and Dunn, J.F. 2012. Methylphenidate-mediated reduction in prefrontal hemodynamic responses to working memory task: a functional near-infrared spectroscopy study: METHYLPHENIDATE-MEDIATED REDUCTION IN HB RESPONSES. Hum. Psychopharmacol. Clin. Exp. 27(6): 615–621. doi:10.1002/hup.2258.

Roelands, B., De Pauw, K., and Meeusen, R. 2015. Neurophysiological effects of exercise in the heat: Exercise and the brain. Scand. J. Med. Sci. Sports 25: 65–78. doi:10.1111/sms.12350.

Roelands, B., Hasegawa, H., Watson, P., Piacentini, M.F., Buyse, L., De Schutter, G., and Meeusen, R.R. 2008. The Effects of Acute Dopamine Reuptake Inhibition on Performance: Med. Sci. Sports Exerc. 40(5): 879–885. doi:10.1249/MSS.0b013e3181659c4d.

Ross, E.Z., Cotter, J.D., Wilson, L., Fan, J.-L., Lucas, S.J.E., and Ainslie, P.N. 2012. Cerebrovascular and corticomotor function during progressive passive hyperthermia in humans. J. Appl. Physiol. 112(5): 748–758. doi:10.1152/japplphysiol.00988.2011.

Schlader, Z.J., Lucas, R.A.I., Pearson, J., and Crandall, C.G. 2013. Hyperthermia does not alter the increase in cerebral perfusion during cognitive activation: Cerebral perfusion during cognitive activation. Exp. Physiol. 98(11): 1597–1607. doi:10.1113/expphysiol.2013.074104.

Schmit, C., Hausswirth, C., Le Meur, Y., and Duffield, R. 2017. Cognitive Functioning and Heat Strain: Performance Responses and Protective Strategies. Sports Med. 47(7): 1289–1302. doi:10.1007/s40279-016-0657-z.

Volkow, N., Wang, G.-J., Fowler, J., Talang, F., Maynard, L., Logan, J., Gatley, S., Pappas, N., Wong, C., Vaska, P., Zhu, W., and Swanson, J. 2004. Evidence That Methylphenidate Enhances the Saliency of a Mathematical Task by Increasing Dopamine in the Human Brain. Am J Psychiatry 161(7).

Volkow, N.D., Fowler, J.S., Wang, G., Ding, Y., and Gatley, S.J. 2002. Mechanism of action of methylphenidate: Insights from PET imaging studies. J. Atten. Disord. 6(1_suppl): 31–43. doi:10.1177/070674370200601S05.

Volkow, N.D., Fowler, J.S., Wang, G.-J., Telang, F., Logan, J., Wong, C., Ma, J., Pradhan, K., Benveniste, H., and Swanson, J.M. 2008. Methylphenidate Decreased the Amount of Glucose Needed by the Brain to Perform a Cognitive Task. PLoS ONE 3(4): e2017. doi:10.1371/journal.pone.0002017.

Volkow, N.D., Wang, Gene.-J., Fowler, J.S., Gatley, S.J., Logan, J., Ding, Y.-S., Hitzemann, R., and Pappas, N. 1998. Dopamine Transporter Occupancies in the Human Brain Induced by Therapeutic Doses of Oral Methylphenidate. Am. J. Psychiatry 155(10): 1325–1331. doi:10.1176/ajp.155.10.1325.

Volkow, N.D., Wang, G.-J., Fowler, J.S., Logan, J., Gerasimov, M., Maynard, L., Ding, Y.-S., Gatley, S.J., Gifford, A., and Franceschi, D. 2001. Therapeutic Doses of Oral Methylphenidate Significantly Increase Extracellular Dopamine in the Human Brain. J. Neurosci. 21(2): RC121–RC121. doi:10.1523/JNEUROSCI.21-02-j0001.2001.

Volkow, N.D., Wang, G.-J., Fowler, J.S., Molina, P.E., Logan, J., Gatley, S.J., Gifford, A., Ding, Y.-S., Wong, C., Pappas, N.R., Zhu, W., and Swanson, J.M. 2003. Cardiovascular effects of methylphenidate in humans are associated with increases of dopamine in brain and of epinephrine in plasma. Psychopharmacology (Berl.) 166(3): 264–270. doi:10.1007/s00213-002-1340-7.

Volkow, N.D., Wang, G.-J., Newcorn, J.H., Kollins, S.H., Wigal, T.L., Telang, F., Fowler, J.S., Goldstein, R.Z., Klein, N., Logan, J., Wong, C., and Swanson, J.M. 2011. Motivation deficit in ADHD is associated with dysfunction of the dopamine reward pathway. Mol. Psychiatry 16(11): 1147–1154. doi:10.1038/mp.2010.97.

Wallace, P.J., Mckinlay, B.J., Coletta, N.A., Vlaar, J.I., Taber, M.J., Wilson, P.M., and Cheung, S.S. 2017. Effects of Motivational Self-Talk on Endurance and Cognitive Performance in the Heat: Med. Sci. Sports Exerc. 49(1): 191–199. doi:10.1249/MSS.0000000000001087.

Wang, G.-J., Volkow, N.D., Fowler, J.S., Ferrieri, R., Schlyer, D.J., Alexoff, D., Pappas, N., Lieberman, J., King, P., Warner, D., Wong, C., Hitzemann, R.J., and Wolf, A.P. 1994. Methylphenidate decreases regional cerebral blood flow in normal human subjects. Life Sci. 54(9): PL143–PL146. doi:10.1016/0024-3205(94)00873-6.

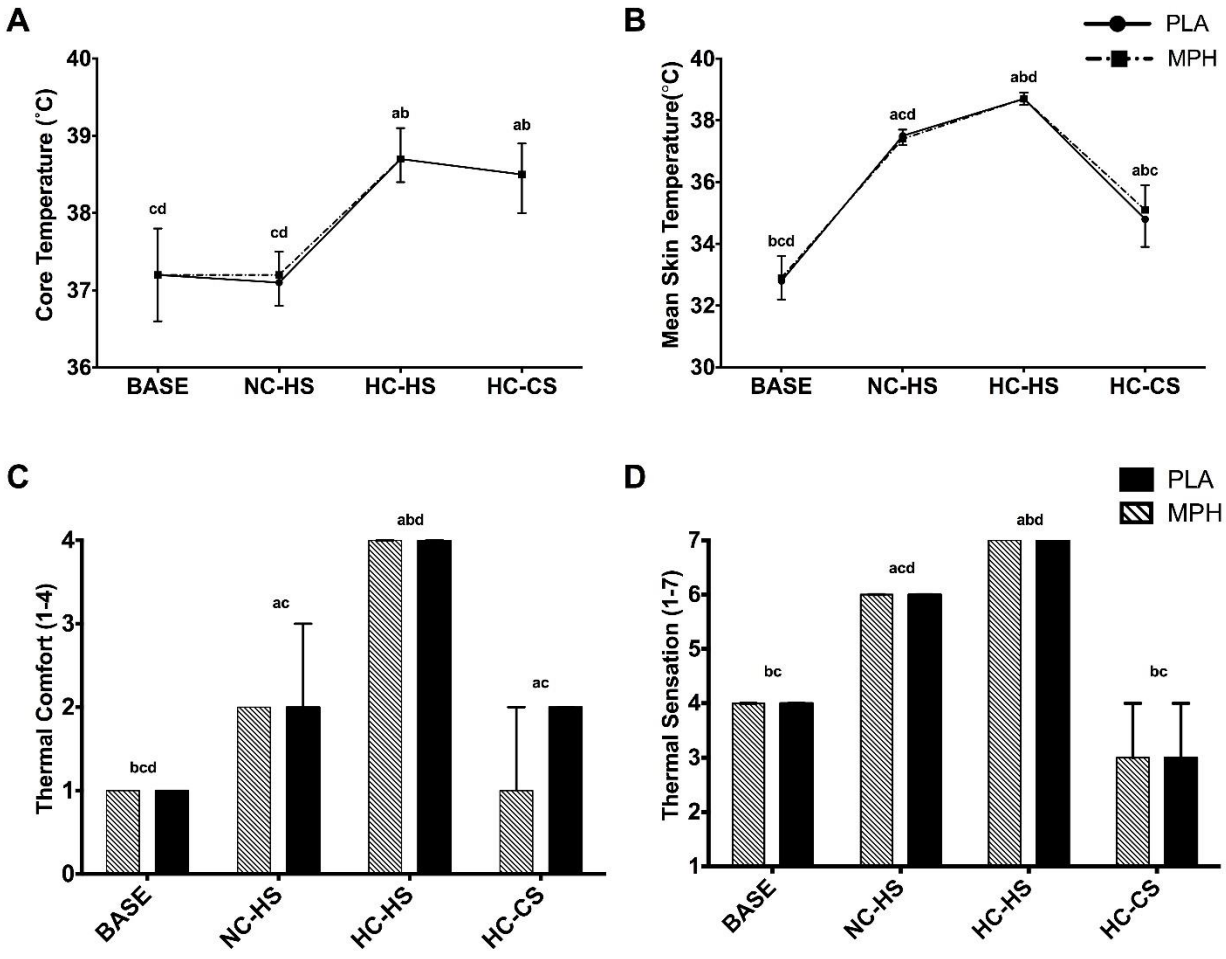
Willie, C.K., Tzeng, Y.-C., Fisher, J.A., and Ainslie, P.N. 2014. Integrative regulation of human brain blood flow: Integrative regulation of human brain blood flow. J. Physiol. 592(5): 841–859. doi:10.1113/jphysiol.2013.268953.

Variable	BASE	NC-HS	HC-HS	HC-CS
GMLT Errors Made (#)				
MPH	30.0 ± 8.6	30.0 ± 8.6	30.0 ± 8.0	26.0 ± 7.3
PLA	27.0 ± 8.4	27.0 ± 8.2	27.0 ± 10.0	26.0 ± 5.5
GMLT Duration (s)				
MPH	128.7 ± 20.9	122.0 ± 22.0	120.5 ± 19.5	116.4 ± 19.9
PLA	123.9 ± 19.6	123.9 ± 23.0	110.0 ± 17.5	113.2 ± 13.1
GMLT-5 Errors Made (#)				
MPH	3.0 ± 1.6	3.0 ± 1.7	3.0 ± 1.7	2.0 ± 2.0
PLA	2.0 ± 1.4	3.0 ± 1.2	3.0 ± 2.2	2.0 ± 1.4
GMLT-5 Duration (s)				
MPH	18.8 ± 5.1	18.8 ± 4.1	17.0 ± 2.6	15.8 ± 3.6
PLA	18.0 ± 3.1	17.1 ± 3.3	15.8 ± 3.3	15.5 ± 3.3
GMLT-Recall Errors Made (#)				
MPH	3.0 ± 1.7	3.0 ± 1.7	3.0 ± 1.7	2.0 ± 1.9
PLA	2.0 ± 1.5	2.0 ± 1.2	2.0 ± 2.1	2.0 ± 1.3
GMLT-Recall Duration (s)				
MPH	20.8 ± 4.7	18.0 ± 3.6	17.0 ± 3.2	17.5 ± 4.3
PLA	16.6 ± 3.3	18.1 ± 3.8	16.3 ± 4.1	16.7 ± 1.8
Set-Shifting Task Errors Made (#)				
MPH †	19.0 ± 6.8	19.0 ± 9.6	21.0 ± 10.4	22.0 ± 7.5
PLA †	20.0 ± 7.8	20 ± 10.0	23.0 ± 7.6	23.0 ± 9.8
Set-Shifting Task Speed (log10)				

MPH †	2.41 ± 0.07 [bcd*]	2.34 ± 0.10 [ac]	2.30 ± 0.09 [ab]	2.31 ± 0.11 [a]
PLA †	2.33 ± 0.13[*]	2.35 ± 0.12 [c]	2.26 ± 0.14 [b]	2.30 ± 0.14
2-Back Task Errors Made (#)				
MPH	2.0 ± 1.9	2.0 ± 1.4	2.0 ± 1.9	2.0 ± 1.9
PLA	1.0 ± 1.2	2.0 ± 1.2	4.0 ± 2.6	1.0 ± 1.3
2-Back Task Speed (log10)				
MPH	2.80 ± 0.11	2.82 ± 0.07	2.79 ± 0.06	2.76 ± 0.05
PLA	2.82 ± 0.07	2.81 ± 0.06	2.81 ± 0.08	2.79 ± 0.08
Detection Task Errors Made (#)				
MPH	0.0 ± 0.5	1.0 ± 0.7	1.0 ± 0.7	0.0 ± 0.9
PLA	1.0 ± 0.8	1.0 ± 1.1	1.0 ± 1.1	1.0 ± 1.0
Detection Task Speed (log10)				
MPH †	2.52 ± 0.07	2.50 ± 0.05	2.48 ± 0.06	2.50 ± 0.07
PLA †	2.52 ± 0.05[c]	2.52 ± 0.06[c]	2.48 ± 0.05[ab]	2.49 ± 0.04

Table 4-1 – Cognitive responses (presented as mean ± SD) for the four experimental timepoints. * indicates significant ($p \leq 0.05$) timepoint effect between PLA and MPH. † indicates a significant timepoint effect ($p < 0.05$) where pairwise comparisons can be interpreted as: a significantly different from BASE, b significantly different from NC-HS, c significantly different from HC-HS, d significantly different from HC-CS.

4.8 List of Figures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HC-CS

Figure 4-1

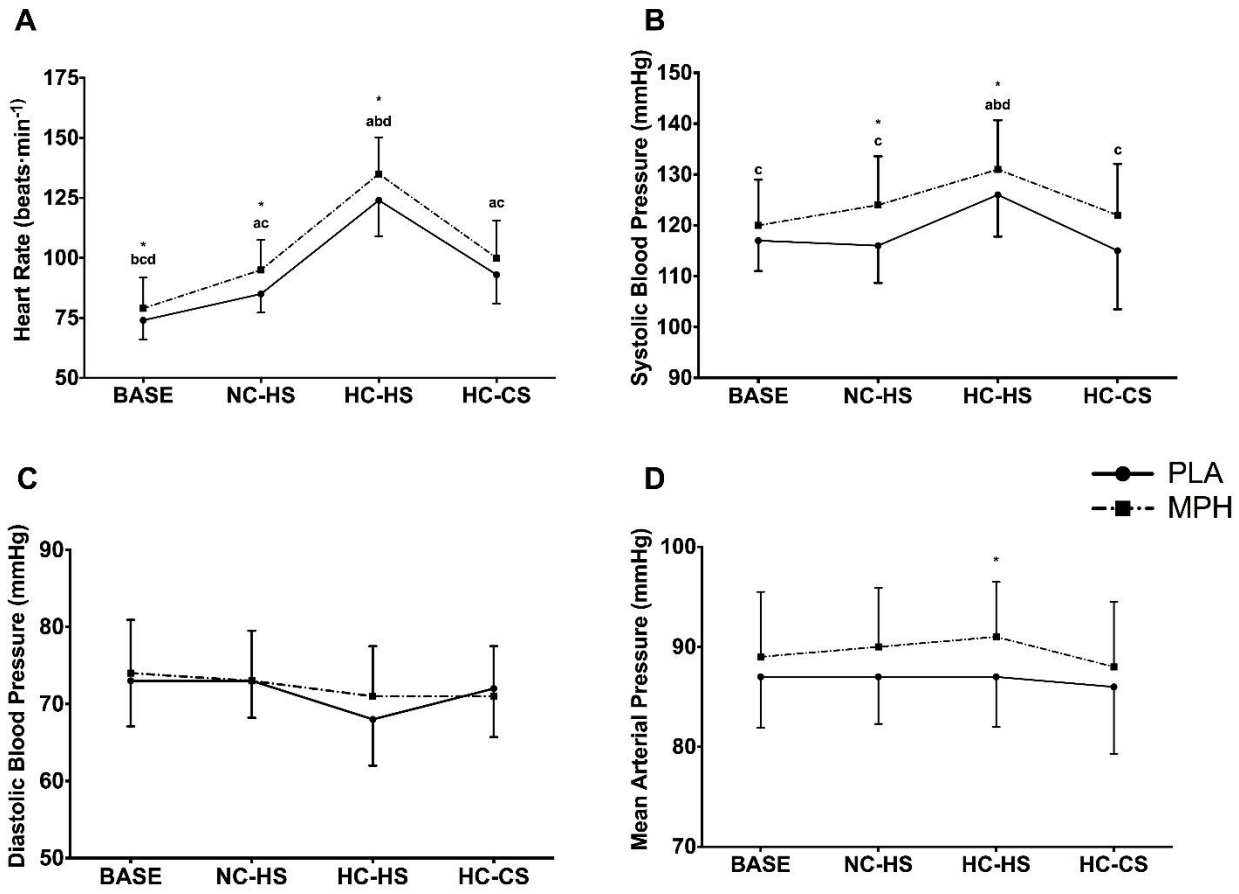
A
Heart Rate (beats·min-1)
175
150
125
100
75
50
*
bcd
*
ac
*
abd
ac
BASE
NC-HS
HC-HS
HC-CS
B
Systolic Blood Pressure (mmHg)
150
140
130
120
110
100
90
c
*
c
*
abd
c
BASE
NC-HS
HC-HS
HC-CS
C
Diastolic Blood Pressure (mmHg)
90
80
70
60
50
BASE
NC-HS
HC-HS
HC-CS
D
PLA
MPH
Mean Arterial Pressure (mmHg)
100
90
80
70
*
BASE
NC-HS
HC-HS
HC-CS

Figure 4-2

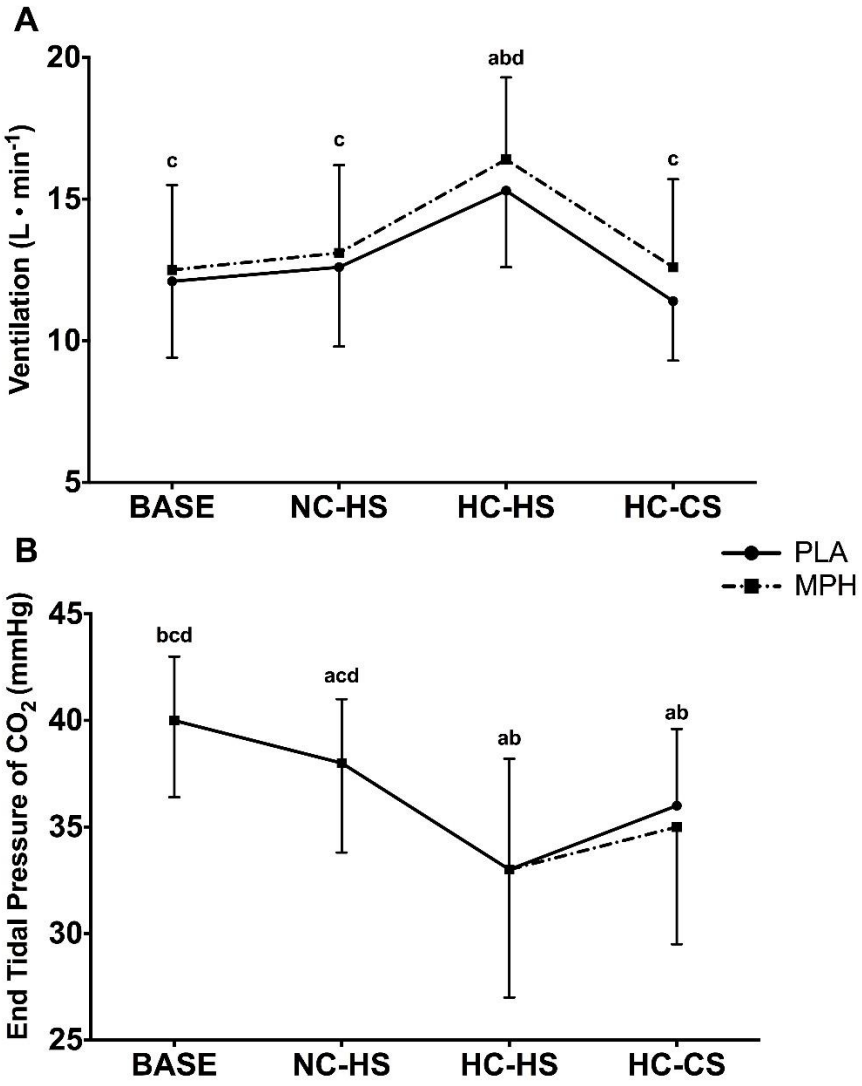
A
20
15
10
5
Ventilation (L • min-1)
c
c
abd
c
BASE
NC-HS
HC-HS
HC-CS
B
PLA
MPH
45
40
35
30
25
End Tidal Pressure of CO2 (mmHg)
bcd
acd
ab
ab
BASE
NC-HS
HC-HS
HC-CS

Figure 4-3

4.9 Research Program Progression

In Chapter 4, we found that neither skin nor core temperature, or thermal comfort, significantly affected cognitive function during passive hyperthermia. Furthermore, we found that an acute 20 mg dose of MPH was not different from the PLA in influencing cognitive function or thermal perception. However, MPH had a significant effect on cardiovascular function including higher heart rates and higher systolic blood pressure likely caused by a sympatho-adrenal effect. Based on these results we decided to explore these responses in a few different ways:

1. We first wanted to extend the findings from Chapter 4, by using the same research model of manipulating skin and core temperature and use of MPH on cognitive function in the cold. However, one of the methodological concerns was the 20 mg dose of MPH used in Chapter 4 was not a sufficient dose to influence cognitive function (as there were no differences at Baseline). Therefore, we aimed to increase the dosage to 40 mg which is the maximal acute dose that can be consumed. We also wanted to keep the four experimental timepoints but re-arranged for cold (baseline (thermoneutral), cold skin – neutral core, cold skin – hypothermia core, and warmed skin – hypothermia core), however in pilot testing the logistics (from equipment implementation) and participant risk (warming of the skin while hypothermic leads to after drop of core temperature increasing risk of clinical hypothermia), therefore we removed the fourth warmed skin – hypothermic core condition. For this project, we obtained Health Canada clearance (Phase IV Clinical Trial), institutional research ethic board clearance, piloted the cooling protocol, and officially started data collection March 5th 2020. Due to the COVID-19 Pandemic, our research lab was shut down for 18 months. In this time, we lost our medical oversight for the project and

Health Canada clearance was not renewed. Therefore, we were unable to continue to investigate the use of MPH during thermal stress.

2. One of the key insights from Chapter 4, was that 20 mg of MPH was not able to enhance cognitive function during passive hyperthermia, however previous research has shown it enhanced exercise performance in hot environments but not neutral environments. In chapter 4, MPH led to a significant sympatho-adrenal response with higher heart rates and higher systolic blood pressure. This response may work to increase exercise performance through improved thermal tolerance or increased sympathetic activity. Therefore, MPH may be better suited to improve exercise performance under thermal strain as opposed to cognitive function *per se*. However, it is unknown if there is a differential effect between the effects of MPH on cognition and exercise performance in the same design. We were originally going to test the effects of MPH on exercise performance in the cold following mild hypothermia to tease out the effects on cognition and exercise performance, however this project was also cancelled due to the COVID-19 Pandemic.

3. As neither skin or core temperature impaired cognitive function during passive heat exposure, and the general mixed findings of thermal stress on cognition, we decided to determine if the null findings in Chapter 4 would apply to changes in skin and core temperature in cold environments and hypothermia. The psychophysiological responses differ greatly between hot and cold environments such that the cognitive response may vary. We also sought to determine if the changes in cognitive function occur in a similar pattern as physical performance. Based on the neurological model of exercise performance, impairments or strain of the attentional network should lead to changes in exercise performance as well. Lastly, in survival scenarios in the cold both the maintenance of cognitive and physical function is vital, so having an understanding of

how these factors intertwine can provide important information and interventions to maintain overall function to increase survival rates.

5 – The manipulation of skin and core temperature on cognitive function in cold air (0°C)

5.1 Abstract

This study tested the effects of 0°C cold air exposure on cognitive function to determine if impairments occur due to skin or core cooling. 10 males completed a randomized, repeated measures study consisting of four environmental conditions: i) 30-min of exposure to 22°C thermoneutral air (TN), ii) 15-minutes to 0°C cold air to reduce skin temperature to ~27°C (CS), iii) 0°C cold air exposure causing mild core cooling of -0.3°C from baseline core temperature (C-0.3°C) and iv) 0°C cold air exposure causing mild core cooling of -0.8°C from baseline core temperature (C-0.8°C). Cognitive function (reaction time (ms) and errors made (#)) was tested using a simple reaction test to test psychomotor function, a 2-6 item working memory capacity task, and vertical flanker to assess executive function using the Dalhousie Cognitive Assessment Battery. There were no significant condition effects for # of errors made for any task (all $p > 0.05$). There were no significant differences in reaction time relative to TN for any of the tasks. However, there was a significant condition effect ($p \leq 0.001$) demonstrating a slowing of psychomotor processing in C-0.3°C (297±33 ms) and C-0.8°C (296±41 ms) compared to CS (267±26 ms) but not TN (274±38). Despite small changes in psychomotor processing (~30 ms), executive function and working memory appears to be maintained in 0°C cold air with up to -0.8°C reduction in core temperature.

5.2 Introduction

Occupational workers, military personnel, and athletes may often perform in cold environments, where maintaining cognitive and physical function is critical to prevent accidents and minimize further thermal strain (1–3). Maintaining cognitive function is more demanding in cold compared to thermoneutral environments (~22˚C) due to strong peripheral vasoconstriction reducing cerebral and muscle blood flow and oxygenation (4–6), altered energy metabolism due to shivering (7), and decreased manual function and coordination due to cooled muscles and joints (8, 9). Furthermore, psychological strain increases, with higher thermal discomfort (10) and alterations in mood (11). Collectively, these changes can lead to decrements in cognitive task performance in ambient air ≤ 10°C (12–14). Specific decrements have been reported to include impaired executive function (15), working memory (16, 17), attention/vigilance (18) and psychomotor processing (19) with acute (30-120 minutes) passive cold air (range: -10 to 10°C) exposure.

Impaired cognitive performance in the cold is not a universal finding, as no effects on executive function (20–22), working memory (21–23), attention/vigilance (22), or psychomotor processing (22, 23) have also been reported with cold air exposure. Differences in performance outcomes may be due to a variety of factors including the speed of cooling, intensity of cold environment, duration of exposure, and the cognitive test being performed (12–14). However, a majority of the studies in cold air primarily reduce mean skin temperature as opposed to reducing deep core body temperature (14). This raises a fundamental question of whether significant or sufficient deep core body cooling was achieved, leaving largely unanswered, the question of whether core cooling impairs cognitive function in cold air. Cooling skin temperature alone (without reductions in core temperature) causes vasoconstriction, mild shivering, and thermal

discomfort (16). Under these conditions, cognition is proposed to be impaired due increased distraction and decreased arousal from thermal discomfort leading to fewer attentional resources available to complete cognitive tasks (19). Whereas whole-body cooling sufficient to induce mild hypothermia (decrease in core temperature by 0.5-2.0°C) further increases cold strain (increased shivering, thermal discomfort, heart rate, vasoconstriction) (6, 24) while likely decreasing brain temperature and increased neural strain affects prefrontal cortex function and subsequently cognitive function (4, 25).

Based on previous findings, it could be reasonably suggested that there may be a core temperature threshold for impairment in cognitive function in cold air. For example, Ellis (26) determined that 150 minutes of -12°C cold air exposure – leading to a Δ-0.8°C reduction in core temperature – impaired speed and accuracy on a serial choice reaction test (mathematical discrimination task) but did not impair executive function (Stroop test) or verbal reasoning. These impairments first started to occur within the first 30 minutes as skin temperature decreased, without changes in core temperature (26). However, Taber et al. (2) found no impairment to executive attention, executive function, working memory, psychomotor processing, or mental rotation throughout 24 hours of cold exposure (7.5°C air) despite a sustained ~Δ-0.5°C reduction in core temperature. Similarly, Mäkinen et al. (22) found no impairments in executive function, working memory, or psychomotor processing following single exposure of 100 minutes of cold air exposure (10°C) leading to ~Δ-0.4°C in core temperature. Collectively, this limited data may indicate a potential core temperature threshold for impairment in cognitive function in cold air (12). However, a key limitation of both these studies is that cold exposure was based on time, which fails to acknowledge the large individual responses and thus variations in cold strain among participants (3). In order to tease out if there is a cold air exposure-response on cognitive function,

we manipulated thermal strain based on changes in core temperature to incorporate individual differences in thermoregulatory capacity and normalized cold strain between participants (8). Furthermore, we tested multiple levels of core temperature cooling to determine if there is a threshold for cognitive task impairment.

The purpose of this study was to investigate a dose response to cold air exposure – ranging from skin/peripheral cooling through to two levels of core temperature decrease – on cognitive performance using executive function, working memory, and psychomotor processing tasks. To achieve these thermal states, we tested cognitive function in 4 distinct randomized conditions: thermoneutral (TN, 22°C), cold skin (CS) where skin temperature was lowered but not core temperature in cold air (0°C); and cold air exposures where core temperature decreased by either Δ-0.3°C (C-0.3°C) or Δ-0.8°C (C-0.8°C). We hypothesize that: i) cognitive performance (speed and accuracy) will be impaired with CS compared to thermoneutral conditions, and ii) cognitive performance will be further impaired with progressively greater levels of core cooling.

5.3 Methods

Participants - The experimental protocol was approved by the Research Ethics Board at Brock University (REB# 19-026) and conformed to the latest revision of the Declaration of Helsinki. 10 healthy male volunteers (Age: 27.0 ± 9.8 years, Mass: 77.9 ± 10.6 kg, Height: 178.6 ± 3.7 cm, Body Fat: 13.3 ± 5.0, Body Surface Area: 1.93 ± 0.12 m^2), who were free from cardiovascular, respiratory, neurological, and cold disorders were recruited from the university and community population. All participants were informed of experimental protocol and associated risks before participating in this experiment and provided both verbal and informed written consent.

Experimental Design – The experiment was a randomized repeated measures design consisting of two familiarization sessions and 4 experimental sessions. The first experimental session involved collecting anthropometric measures and practicing the cognitive test battery (CTB). The second familiarization was designed to reduce the possibility of a learning effect through two further complete practices of the CTB. The 4 experimental conditions were separated by 3-7 days to minimize the potential of cold acclimation and performed at the same time of day to control for circadian fluctuations in core temperature. Participants were instructed to avoid vigorous exercise and alcohol consumption 24 hours and caffeine 6 h prior to each experimental session.

Familiarization Trials – Upon arrival for the 1st familiarization trial, anthropometric measurements (height (cm), mass (kg)), body surface area (m^2) (27), and % body fat was calculated using the 7-site skinfold technique (28). Participants then performed a familiarization of the CTB (see description below) in a thermoneutral environment (22°C). Upon arrival for the 2nd familiarization trial, participants practiced the CTB twice more (separated by ~45 minutes) for a total of 3 times (29). Familiarization was performed on multiple days as the selected CTB has demonstrated to have better familiarization when memory consolidation is allowed to occur (30). During all practice trials, participants wore winter gloves and a soft-silicone mask that were identical to equipment used during the experimental trials.

Experimental Trials –Upon arrival, participants voided their bladder and nude body mass (kg) was recorded. A urine sample was tested for urine specific gravity (PAL-10S, Atago, Japan) to determine hydration status. Participants were considered euhydrated if USG was ≤1.020, or else the test was rescheduled (no trials were ultimately rescheduled from hypohydration). Participants were then instrumented (see below), entered an environmental chamber, and were seated on a chair and were provided with ear plugs. Participants then completed a 5-min baseline sitting quietly with

eyes closed in thermoneutral conditions (~22.0°C, ~50% relative humidity). Next, participants completed testing in one of the following 4 experimental conditions:

Thermoneutral (TN) – Participants remained seated in the chamber for 25 minutes (30-minute total) before being fitted with the winter gloves prior to commencing the CTB.

Cold Skin (CS) – Participants remained seated in the environmental chamber as the ambient temperature was incrementally decreased to 0°C (~15-16 minutes) and wind speed was increased to 0.8-1.2 m/s using a fan. Once the chamber temperature reached 0°C, the fan was turned off and participants performed the CTB. This design allowed for the core temperature to remain neutral while skin temperature was reduced to approximately 27°C. This level of skin temperature change was used as the vasoconstrictory response is maximal at a mean skin temperature of 29.5-30˚C (31) and thus would lead to increased thermal discomfort.

C-0.3°C – Participants remained seated in the environmental chamber as ambient temperature was decreased to 0°C and wind speed was increased to 0.8-1.2 m/s until their rectal core temperature (T_{re}) dropped by Δ-0.3°C before performing the CTB.

C-0.8°C – Participants remained seated in the environmental chamber as ambient temperature was decreased to 0°C and wind speed was increased to 0.8-1.2 m/s until the participants T_{re} dropped by Δ-0.8°C before performing the CTB.

For all cold trials, participants remained in the chamber and performed the CTB in cold air (0°C) which allowed for further cooling and continuous shivering to occur. For all cold trials, there was an institutional ethical cutoff of core temperature ≤ 35.0°C and an exposure limit of 150 minutes following chamber air temperature reaching 0°C. Three participants (30%) did not reach the

desired Δ-0.8°C T_{re} within the 150 minutes cutoff limit. Therefore, they started the CTB at the cutoff time with a Δ-0.7°C T_{re}.

Clothing – During TN trials, participants wore a cotton t-shirt or cycling jersey, cycling bib shorts, socks, and athletic shoes (~0.26 clo ensemble) and participants were provided with winter gloves before commencing the CTB. In all three cold trials, participants wore the same clothing as TN plus a pair of track pants throughout the experimental trial. Following baseline, participants were fitted with earmuffs, gloves, and a fleece blanket around their shoes (~0.63 clo). Based on pilot testing, this additional equipment was deemed necessary to offset extreme discomfort of the extremities during cooling and minimize the risk of participant dropout.

Physiological Measurements – Prior to baseline, participants were instrumented with a flexible thermocouple thermistor (RET-1, Physitemp Instruments, USA), self-inserted 15 cm beyond the anal sphincter to measure T_{re} (°C) sampled at 4 Hz. Weighted mean skin temperature ($\overline{T}_{skin}$, °C) were measured using thermistors (Concept Engineering, Old Saybrook, USA) sampled at 100 Hz at seven sites (32):

$$\overline{T}_{skin} = 0.07_{forehead} + 0.14_{forearm} + 0.05_{hand} + 0.35_{abdomen} + 0.19_{thigh} + 0.13_{shin} + 0.07_{foot}$$

Forearm temperature ($T_{forearm}$) and hand temperature (T_{hand}) were analyzed to quantify the local cooling response as these sites were likely to influence the ability to respond during the CTB. Heart rate was calculated using R-R intervals using a standard three-lead electrocardiogram (MLA2340, AD Instruments; USA). Participants were fitted with a soft silicone facemask (7450 V2, Hans Rudolph, USA) connected to an inline gas collection system (ML206 Gas Analyzer, AD Instruments; USA). Expired gases were collected to continuously measure oxygen consumption ($\dot{V}O_2$, $L \cdot min^{-1}$), carbon dioxide expiration ($\dot{V}CO_2$, $L \cdot min^{-1}$), respiratory exchange ratio (RER,

$\dot{V}CO_2/\dot{V}O_2$) to determine metabolic heat production ($\dot{M}$) to quantify the shivering response. If RER was < 1.00 the following equation (33) **normalized to body surface area (**A_D) was used to calculate $\dot{M}$:

$$\dot{M} = \left(\dot{V}O_2 \cdot \frac{\left[\left(\left(\frac{RER - 0.7}{0.3}\right) \cdot 21.13\right) + \left(\left(\frac{1.0 - RER}{0.3}\right) \cdot 19.62\right)\right]}{60} \cdot 1000 \right) / A_D \ [W \cdot m^2]$$

If RER ≥ 1, the following equation was used to account for the energy equivalent for carbohydrates only (33)**:**

$$\dot{M}\ (RER \geq 1.0) = \left(\dot{V}O_2 \cdot \frac{21.13}{60} \cdot 1000\right) / A_D \ [W \cdot m^2]$$

All physiological data were averaged over the 5-minute baseline and while performing the tasks during the CTB.

Perceptual Measures – Subjective assessments of the environmental conditions were assessed using a 1-4 scale to measure thermal comfort and a 1-7 scale for thermal sensation (34) and a 0-10 scale (0 = rest, 3 = moderate, 5 = hard, 7 = very hard, 10 = maximal effort) to measure perceived mental exertion of the cognitive tests and were collected upon the completion of the CTB.

Cognitive Test Battery - To measure progressive changes in cognitive function, participants performed an ~15-min cognitive function test battery using the Dalhousie Cognitive Assessment Battery (DalCAB) (30, 35). The DalCAB is a validated assessment tool to measure executive attention (30, 35) and is susceptible to impairment in learning with sleep deprivation (36). The chosen tasks consisted of a simple reaction time task, vertical flanker task, and item working memory task. These tasks were selected as they have been shown to measure a part of the executive control of attention referred to as executive attention, which is comprised of several different cognitive processes including executive function, working memory, attention, and vigilance and

share similar neural structures and pathways within the executive attention network (30, 35, 37). The most common similarities between the cognitive functions is attentional ability, maintaining a goal in an active state during a task and to resolve interference and filter out distractions (37). Due to the shared nature of these cognitive processes, we aimed to test multiple executive attention functions (e.g., working memory, attention, filtering, executive function) and simple task performance (e.g., psychomotor processing speed) to determine if task-dependent changes in cognition occur in cold air exposure.

To ensure similar manual dexterity requirements between trials, participants wore winter gloves for all cognitive testing. Furthermore, in pilot testing, it was determined that the glove thickness caused difficulty responding (using keyboard keys) causing false misses and errors. In order to minimize these errors, we affixed an analogue thumbstick (1 cm diameter) to the "caps lock" and "enter" keys creating a raised platform (2.5 cm in height) for easier responding and minimizing the manual dexterity required to respond (i.e., the entire hand could be used to respond if needed). For all tests, the reaction time was averaged only using correct trials.

Simple Reaction Time Task: The simple reaction time task assessed psychomotor processing and vigilance. For this test, a turned playing card (French deck) was presented in the middle of the screen and the participant was asked to respond as soon as the card flipped over. Participants used their dominant hand to respond. A total of 60 stimuli were presented with a maximal response time of 1000 ms. Response-stimulus intervals (RSI) were randomly set at 500, 1000, and 1500 ms to minimize anticipatory responses. Furthermore, the varied response-stimulus intervals provide an index of vigilance through a temporal preparation effect, where healthy individuals respond faster when given a longer RSI (i.e. 1500 ms) compared with a shorter RSI (i.e., 500 ms) due to a longer preparation time (30, 35). Performance was measured as reaction time (ms) and accuracy (%) on

all trials. Reaction time was also quantified for each RSI. Furthermore, a preparation effect was calculated as the difference between 1500 ms and 500 ms RSI.

Vertical Flanker Task: The flanker task is used as a measure of executive function based on selective attention, filtering, and/or conflict resolution. In this task, a central target stimulus is presented with two flanking stimuli (flankers) above and below that are either the same as (congruent) or different than (incongruent) the central target stimulus. The participant had to decide and respond regarding a feature of the central stimulus (e.g., red heart or red diamond) while ignoring/filtering the flanking stimuli. This creates a flanker effect where participants respond faster with fewer errors on congruent compared to incongruent stimuli (30, 35). The array was slightly offset vertically for each stimulus display in order to reduce attentionally spotlighting on the central stimulus, while also allowing flankers to remain visible throughout the task. A total of 100 stimuli were presented with a maximal response time of 1500 ms. The variables measured were the reaction time (ms),# of errors, and accuracy on congruent, incongruent, and all trials. Furthermore, an interference effect was calculated as difference in response times between incongruent and congruent stimuli.

Item Working Memory Task: The item working memory task (Identity Sternberg task) is a measure of working memory capacity where participants are presented with a series of memory sets of stimuli to be measured. The stimulus set is followed after a delay by a single probe stimulus. There were 3 set sizes (2, 4, 6 items) where participants were presented with a series of non-repeating stimuli (playing cards) and had to respond if the probe stimulus was present or absent in the previously viewed stimulus set. Set presentation were randomized where a total of 30 series were presented (10 of each set size) with a maximum reaction time allowed of 3,000 ms. In healthy individuals, as the number of items in the set increases, the number of errors increase, and the

reaction time required to decide about the probe stimulus also increases (30). The variables measured were reaction time (ms),# of errors, and accuracy (%) for the 2, 4, and 6 item and total sets.

Statistical Analysis – All physiological and cognitive data are presented as mean ± SD. Data were normally distributed as assessed by Kolmogorov-Smirnov Test. Simple reaction time task reaction time was assessed with a 3 RSI (500 vs 1000 vs 1500) X 4 condition (TN vs CS vs C-0.3°C C-0.8°C) repeated measures ANOVA. Vertical flanker reaction time, errors, and accuracy were assessed using a 2 flanker type (congruent vs incongruent) X 4 condition repeated measures ANOVA. Item working memory reaction time, errors, and accuracy were assessed with a 3 set size (2 items vs. 4 items vs. 6 items) X 4 condition repeated measures ANOVA. Furthermore, the preparation effect of the simple reaction time task, accuracy for the simple reaction time task, and interference effect from the vertical flanker were assessed using a 1 x 4 (condition) repeated measures ANOVA. Physiological variables were assessed using a 4 x 2 repeated measures ANOVA for condition X experimental timepoint (Baseline vs CTB). If sphericity was violated ($p < 0.05$), the Greenhouse Geisser correction was used. A Bonferroni *post hoc* analysis corrected for multiple comparisons were used to test for specific main effects between task sets (e.g., RSI), conditions or between conditions and timepoints. Significance was assumed with a $p < 0.05$.

All perceptual responses (ordinal data) are presented as median (quartile 1 – quartile 3). Perceptual data were assessed using a 1 x 4 (condition) Friedman's ANOVA with a Wilcoxon-Signed Rank test for post-hoc analysis to compare between conditions. To reduce the likelihood of Type 1 error due to multiple comparisons, α value was revised based on number of comparisons (6), therefore p=0.008. All statistical analyses were performed using SPSS statistics for Windows (SPPS Statistics for Windows, version 28; IBM Corp. USA).

5.4 Results

Experimental Design – Cooling times before commencing the CTB were CS: 19.0 ± 2.3 min, C-0.3°C: 103.0 ± 37.2 min (Range: 20-146 min), C-0.8°C: 149.3 ± 32.2 min (Range: 89-173 min). We were successful in creating 4 distinct experimental conditions. There was a significant condition ($p = 0.04$), experimental timepoint ($p < 0.001$), and interaction ($p < 0.001$) for absolute T_{re} (Figure 1A) with no differences at Baseline, however all conditions were different from each other during the CTB, except TN vs CS ($p = 1.00$) and TN vs. C-0.3°C ($p = 0.284$). When analyzed based on ΔT_{re} from Baseline, there was a significant difference between TN and C-0.3°C ($p < 0.001$) (Figure 1B). There was a condition, experimental timepoint, and interaction (all $p < 0.001$) for $\overline{T}_{skin}$ (Figure 1C), with no differences at Baseline, while all experimental conditions were different from each other during the CTB except C-0.3°C and C-0.8°C ($p = 0.057$). For local temperature responses, forearm temperature and hand temperature all demonstrated a significant condition, experimental timepoint, and interaction effect (all $p < 0.0001$). Pairwise comparisons determined no differences in baseline forearm temperature (TN: 31.8 ± 0.8°C, CS: 31.8 ± 1.2°C, C-0.3°C: 32.9 ± 1.4°C, C-0.8°C: 32.0 ± 0.9°C), while forearm temperature was significantly lower (all $p < 0.0001$) during the CTB in CS (20.9 ± 3.1°C), C-0.3°C (18.8 ± 6.3°C), and C-0.8°C (15.8 ± 4.1°C) compared to TN (30.7 ± 1.0°C). There were no differences during the CTB between CS and C-0.3°C ($p = 0.6874$) or C-0.3°C and C-0.8°C ($p = 0.176$), with lower forearm temperature in C-0.8°C compared to CS ($p = 0.002$). For hand temperature, there were no differences at baseline (all $p = 1.00$) (TN: 30.7 ± 1.5°C, CS: 30.4 ± 2.3°C, C-0.3°C: 30.0 ± 3.1°C, C-0.8°C: 30.4 ± 1.9°C), while during the CTB there were significant differences between all conditions (TN: 30.3 ± 1.8°C,

CS: 29.5 ± 2.4°C, C-0.3°C: 22.4 ± 2.5°C, C-0.8°C: 19.1 ± 2.7°C, all $p < 0.01$) except TN compared to CS ($p = 1.00$).

Perceptual Responses – Perceptual measures are presented in Table 1 where all variables demonstrated a significant condition effect (all $p \leq 0.001$). Overall, there was no significant difference in thermal comfort between TN and CS ($p = 0.018$) with significantly greater discomfort in C-0.3°C and C-0.8°C (both $p = 0.004$) relative to TN. Both C-0.3°C ($p = 0.004$) and C-0.8°C ($p = 0.007$) had greater discomfort compared to CS, with no difference between the two conditions ($p = 0.317$). Thermal sensation was perceived as significantly cooler relative to TN in all cold conditions (all $p \leq 0.007$). There were no differences between the 3 cold conditions (all $p \geq 0.015$). Despite significant condition effect for perceived mental exertion, there were no differences between the conditions (all $p \geq 0.010$).

Cardiorespiratory Responses – There was a condition, experimental timepoint, and interaction effect (all $p \leq 0.03$) for heart rate (Figure 2A) and $\dot{M}$ (Figure 2B) with no differences at Baseline (all $p > 0.05$). Heart rate increased and was significantly higher for both C-0.3°C ($p = 0.012$) and C-0.8°C ($p = 0.017$) compared to TN with no differences between the two conditions ($p = 1.00$). Additionally, C-0.8°C was significantly higher than CS ($p = 0.029$). $\dot{M}$ increased in all cold conditions, however, it was significantly higher in both C-0.3°C and C-0.8°C compared to both TN and CS (all $p < 0.0001$), with no differences in $\dot{M}$ between C-0.3°C and C-0.8°C ($p = 1.00$).

Cognitive Performance - Cognitive performance for the simple reaction task, vertical flanker, and item working memory for all four experimental conditions are presented in Table 2. For simple reaction time, there was a significant effect for RSI ($p \leq 0.001$, $\eta_p^2 = 0.784$, ß = 1.00), condition ($p \leq 0.001$, $\eta_p^2 = 0.467$, ß = 0.977), but no interaction ($p = 0.169$, $\eta_p^2 = 0.150$, ß = 0.560). Pairwise comparisons demonstrated that reaction time was significantly longer for 500 ms RSI (304 ± 40

ms) compared to 1000 ms RSI (274 ± 36 ms, $p \leq 0.001$) and 1500 ms RSI (271 ± 36 ms, $p \leq 0.001$). There was no difference between 1000 ms and 1500 ms RSIs ($p = 1.000$). Pairwise comparisons for the condition effect demonstrated slower reaction times (~29 ms) in C-0.3°C ($p = 0.035$) and C-0.8°C ($p = 0.008$) compared to CS. There was no significant condition effect for a preparation effect ($p = 0.088$) or accuracy ($p = 0.493$) for simple reaction time.

Vertical flanker reaction time demonstrated a significant effect for flanker type ($p \leq 0.001$, $\eta_p^2 = 0.969$, ß = 1.00), however no effect for condition ($p = 0.097$, $\eta_p^2 = 0.284$, ß = 0.410) or interaction ($p = 0.578$, $\eta_p^2 = 0.074$, ß = 0.163). Pairwise comparisons revealed participants had a longer reaction time in incongruent trials (576 ± 54 ms) compared to congruent trials (511 ± 55 ms)**.** For errors made on the vertical flanker, there was a significant flanker type effect ($p = 0.005$, $\eta_p^2 = 0.655$, ß = 0.925), with no condition ($p = 0.238$, $\eta_p^2 = 0.158$, ß = 0.346) or interaction ($p = 0.496$, $\eta_p^2 = 0.093$, ß = 0.200). Pairwise comparisons revealed participants committed more errors on incongruent trials (2 ± 2) compared to congruent trials (1 ± 1, $p = 0.005$)**.** For accuracy, there was a significant effect for congruency ($p = 0.014$, $\eta_p^2 = 0.551$, ß = 0.784) with no condition ($p = 0.580$, $\eta_p^2 = 0.077$, ß = 0.169), nor interaction ($p = 0.708$, $\eta_p^2 = 0.055$, ß = 0.130). Participants were more accurate in congruent trials (98 ± 2%) compared to incongruent trials (95 ± 4%, $p = 0.014$). There was no condition effect for the interference effect (all $p > 0.05$).

Item working reaction time had a significant effect for set size ($p = 0.006$, $\eta_p^2 = 0.569$, ß = 0.883) with no condition ($p = 0.175$, $\eta_p^2 = 0.165$, ß = 0.382) or interaction ($p = 0.231$, $\eta_p^2 = 0.148$, ß = 0.325). Overall, pairwise comparisons revealed the reaction time for 2 items (715 ± 148 ms) was significantly faster compared to 4 items (900 ± 234 ms, $p = 0.016$) and 6 items (976 ± 279 ms, $p = 0.021$). 4 items reaction time were not significantly different from 6 items ($p = 0.082$) despite the ~76 ms difference. For errors made on the item working memory, there was a significant set-

size effect ($p \leq 0.0001$, $\eta_p^2 = 0.634$, ß = 0.997), but no condition ($p = 0.799$, $\eta_p^2 = 0.036$, ß = 0.188) or interaction ($p = 0.801$, $\eta_p^2 = 0.053$, ß = 0.188). For accuracy, there was a significant set-size effect ($p \leq 0.0001$, $\eta_p^2 = 0.613$, ß = 0.995), but no condition ($p = 0.893$, $\eta_p^2 = 0.022$, ß = 0.083) or interaction ($p = 0.670$, $\eta_p^2 = 0.070$, ß = 0.245). Pairwise comparisons revealed participants committed more errors with reduced accuracy on 6 items (2 ± 2 errors, 78 ± 16%) compared to 2 items (1 ± 1 errors, $p = 0.003$, 94 ± 10%, $p = 0.004$) and 4 items (1 ± 1 errors, $p = 0.028$, 89 ± 11%, $p = 0.033$). The # of errors made ($p = 0.054$) approach significance and was not significant for accuracy ($p = 0.113$) for 2 items approached significance compared to 4 items.

5.5 Discussion

This study tested the effects of cold air exposure leading to skin and core temperature decreases on executive function, working memory and psychomotor processing. We hypothesized that cognitive performance would be impaired with decreases in skin temperature due to increased thermal discomfort (19), with further reductions in performance with progressively greater core cooling (26). We found that neither reductions in skin temperature nor core temperature of Δ-0.3°C and Δ-0.8°C significantly impacted executive attention based cognitive process (i.e., temporal preparation effect (simple react time task), flanker effect (vertical flanker), set-size effect (item working memory)). Furthermore, there was no significant slowing of reaction time, nor more errors made in any of the cold conditions compared to TN. There were slower reaction times (~30 ms) on the simple reaction test in both core cooling conditions compared to CS however, from a practical standpoint, the difference would not be expected to effect overall performance for a young healthy males in the short-term. Combined, these data demonstrate that that executive

function, working memory, and psychomotor processing are generally well maintained during cold air exposure at magnitudes of up to Δ-0.8°C core temperature decrease from baseline temperature.

While many studies report an impairment in cognitive function with cold air exposure, this finding is not universal. In the current study, the general pattern of response was slowing of reaction time ~24-78 ms in C-0.3°C and ~24-56 ms in C-0.8°C from TN depending on the task, however we did not demonstrate any statistically significant changes in the two core cooling conditions compared to TN. We attempted to control for individual differences in thermoregulatory capacity by normalizing cold strain based on changes in skin temperature as well as normalizing the relative core temperature decrease from baseline as opposed to using a time-based approach. One obvious explanation for the lack of impairment found in the present study could be that the level of core cooling was not sufficiently thermally stressful to impair cognitive performance. However, we are confident that in both core cooling conditions participants demonstrated significant relative cold strain as compared to baseline in thermoneutral conditions, as there were large decreases in $\overline{T}_{skin}$ (~Δ-9.5 to 11.4°C), moderate level of shivering (indicated by ≥~2x increase in $\dot{M}$ and higher heart rates by ~10-15 $b \cdot min^{-1}$), and high perceptual thermal strain in the C-0.3°C and C-0.8°C conditions. Overall, these findings are in line with previous studies in cold air causing core cooling where decreases in core temperature did not impair executive function, working memory, or simple reaction time in cold air (-12 to 7.5°C) over 100 minutes to 24 hours (2, 22, 23, 26). However, these are in contrast to impaired reaction time and increased errors made on a serial choice reaction time test on a mathematical based task (26). Potentially, the null findings could be explained by the fact that the absolute core temperature (~36.5°C in C-0.8°C) was not sufficient to impair cognitive function as no participants experienced clinical hypothermia (core temperature < 35°C). Giesbrecht et al. (38) determined that cold water

immersion reducing core temperature to 33-35°C impaired executive function and working memory performance, but not simple task performance, indicating a lower absolute core temperature may be necessary for impairment. Future work is necessary to more finely delineate core temperature thresholds on impairments of cognitive functions, however, this may not be feasible in practice as ethical core temperature cutoffs are typically ≤ 35.0°C.

A confounding variable for testing reaction time in the cold is the well-documented decrease in manual dexterity (3), which can occur with both local temperature changes to forearm and hand temperature (9) as well as with reductions in core temperature (8). For computerized cognitive assessments, the hands and fingers are required to respond and therefore can directly influence reaction time and errors made. The large decreases in forearm and hand temperature noted in our study would likely impair manual dexterity, which we did not directly test but attempted to minimize. In pilot testing, we first attempted to normalize the manual dexterity requirements by having individuals wear the same winter gloves for testing while responding using a standard computer keyboard. However, participant feedback indicated that regardless of thermoneutral or cold conditions, participants perceived false errors were occurring through missing the response buttons due to the bulkiness of the gloves, or in the cold condition due to cold hands and fingers. Therefore, we manipulated the keyboard to include two raised analogue thumbsticks in order to create an easier platform for responses. This is an unvalidated tool and we did not control for participants using a single finger (e.g., 2nd digit) or multiple fingers to respond, but did instruct for their approach to be consistent during familiarization and experimental trials. This may have potentially contributed to the null effect in cognitive function, as the dexterity requirements were minimized. However, despite the altered manual dexterity requirement and environmental manipulations, each task were valid measures of the cognitive function tested as we

demonstrated common task performance including the temporal preparation effect (simple reaction time), flanker effect (vertical flanker), and set-size effect (item working memory) for reaction time, errors, and accuracy (30, 35). Future studies in the cold may benefit from different button configurations to minimize the dexterity requirements, however research is needed to see how different configuration affect reaction time and errors made. Furthermore, as manual dexterity is considered a major performance problem experienced in the cold (3), future studies should include information regarding hand conditions (e.g., wearing gloves, uncovered), local temperature, as well as method used to respond to cognitive tasks (e.g., keyboard, touch screen, button configuration). This may aid in clarifying confounding variables for the mixed results in cognitive function between studies.

Thermal displeasure from decreases in $\overline{T}_{skin}$ has been shown to impair cognitive function before changes in core temperature through decreases in arousal and increases in distraction requiring multi-tasking to focus on the task and monitor thermal state (8, 19). Furthermore, it has been reported that cooling $\overline{T}_{skin}$ to ~30°C can slow neuronal conduction velocity and central processing (39). In the current study, we found cooling $\overline{T}_{skin}$ to ~ 27°C increased discomfort and perception of feeling cold; however, we found no differences compared to TN for reaction time or errors made on any of the cognitive tasks. Overall, these results indicate that increased discomfort and distraction did not significantly influence cognitive performance relative to TN. We did see a significantly slower reaction time on the simple reaction time task (~30 ms) compared to both C-0.3°C and C-0.8°C.From a real-world application standpoint, the statistically significant changes in reaction time are not considered practically significant for relatively young healthy individuals working in environments where there is an opportunity to prepare (i.e., don weather appropriate clothing) in advance and prevent high degrees of shivering and mild core cooling. This suggestion

is supported by the changes found in this study were relatively small given the increased physiological and psychological strain in the core cooling conditions. Furthermore, there was a significant level of whole-body shivering (Figure 2B) and local cooling of the forearm and hand, which may have increased the motor demands, influenced coordination for responding, or influenced manual dexterity leading to small differences in reaction time. Most importantly, from a practical standpoint, these changes did not influence the number of errors made or accuracy, and did not extend to more complex vertical flanker and item working memory tasks However, given the changes that were identified, future research is needed to better isolate (e.g., identification of a specific $\overline{T}_{skin}$ threshold at which impairment begins) the effects of skin versus core cooling on reaction time. Based on the current results of the CS condition cooling $\overline{T}_{skin\ to} \sim 27°C$ in 0°C did not significantly impair cognitive function relative to TN conditions.

A strength of the research design was controlling for both changes in skin temperature as well as relative changes in core temperature to determine the separate and combined effects of cold on cognitive function. A limitation of the current study is that the task complexity may not have been high enough to induce impairments, as the median ratings of perceived mental exertion was 3-5 out of 10 (“moderate” to “hard”), and participants may have retained sufficient neural resources in order to complete the tasks. Previous studies have found impairment in working memory with increased task complexity (16, 40). We demonstrated that individuals made more errors and were slower to respond as the set number increased from 2 to 6 items, however we found no impairments in performance at collectively or at each level of difficulty due to cold. Furthermore, we cannot account for any central changes in neural function including cerebral blood flow (4) and electrical activity (using electroencephalography) (25) limiting our understanding of neural changes during cognitive tasks. Recently, Jones et al. (25) determined core

cooling by ~1.5°C with cold water immersion increased the requirement for pre-attention (N100) and processing effort (P300) using electroencephalography on a psychomotor vigilance task indicating higher cognitive load with mild hypothermia. Previously, Qian et al. (41) found passive heat stress increases the onset of mental fatigue, and currently it is unknown if the increased cognitive load leads to a faster onset of mental fatigue in the cold.

In summary, we demonstrated that a decrease in both skin and core temperature combined with increased perceptual thermal strain and shivering after cold exposure in air did not impair executive function, working memory or psychomotor processing compared to thermoneutral conditions. Future research is needed to determine the threshold for impairment in these functions as well as determining task dependent changes that occur in cold air environments. Furthermore, future research is needed to determine how longer exposures and/or different modes of cold stress may affect cognition.

Variable	TN	CS	C-0.3°C	C-0.8°C
Thermal Comfort (1-4)*	1 (1-2)[cd]	3 (2-3.25)[cd]	4 (3-4)[ab]	4 (4-4)[ab]
Thermal Sensation (1-7)*	4 (3-4)[acd]	2 (1-3)[a]	1 (1-1)[a]	1 (1-1)[a]
Mental Exertion (0-10)*	3 (2-3.25)	4 (2-4.25)	4 (3-5.5)	5 (3-6.25)

Table 5-1 - Perceptual responses collected following completion of the CTB presented as median (Quartile 1 – Quartile 3) for the four experimental conditions. * indicates a significant effect ($p < 0.05$) using a Friedmans ANOVA where post-hoc comparisons using Wilcoxon signed rank tests can be interpreted as: a significantly different ($p < 0.008$) from TN, b significantly different from CS, c significantly different from C-0.3°C, d significantly different from C-0.8°C.

Variable	TN	CS	C-0.3°C	C-0.8°C
Simple Reaction Time Task – All				
Reaction time (ms)* †	273 ± 38	267 ± 26[cd]	297 ± 33[b]	296 ± 41[b]
Accuracy (%)	98 ± 2	98 ± 2	97 ± 3	97 ± 4
Simple Reaction Time Task – RSI				
500 RSI reaction time (ms)	292 ± 45	284 ± 24	323 ± 38	321 ± 47
1000 RSI reaction time (ms)	263 ± 36	258 ± 26	290 ± 35[b]	283 ± 40
1500 RSI reaction time (ms)	264 ± 38	260 ± 60	277 ± 35	282 ± 41
Simple Reaction Time Task – Preparation Effect				
Reaction time (ms)	-28 ± 22	-25 ± 16	-40 ± 20	-37 ± 25
Vertical Flanker - All				
Reaction time (ms) †	536 ± 67	527 ± 46	565 ± 54	573 ± 100
Errors (#)†	3 ± 3	3 ± 2	4 ± 3	3 ± 2
Accuracy (%)†	97 ± 4	96 ± 2	96 ± 3	96 ± 3
Vertical Flanker - Congruent Stimuli				
Reaction time (ms)	504 ± 69	494 ± 47	530 ± 54	542 ± 94
Errors (#)	1 ± 1	1 ± 1	1 ± 1	0 ± 1
Accuracy (%)	98 ± 2	98 ± 2	97 ± 3	98 ± 3
Vertical Flanker - Incongruent Stimuli				
Reaction time (ms)	568 ± 66	561 ± 47	601 ± 54	606 ± 107
Errors (#)	2 ± 3	2 ± 2	3 ± 3	3 ± 2
Accuracy (%)	96 ± 6	94 ± 3	94 ± 5	94 ± 3
Vertical Flanker Interference Effect				
Reaction time (ms)	64 ± 20	66 ± 16	71 ± 21	60 ± 15
Item Working Memory - All				
Reaction time (ms)* †	844 ± 186	827 ± 198	922 ± 223	900 ± 235
Errors (#)†	4 ± 3	4 ± 2	4 ± 2	4 ± 3
Accuracy (%)†	87 ± 11	86 ± 8	88 ± 5	86 ± 10
Item Working Memory – 2 Items				
Reaction time (ms)	673 ± 104	674 ± 115	762 ± 139	751 ± 210
Errors (#)	1.0 ± 1.2	1.0 ± 0.7	1.0 ± 1.0	1.0 ± 0.5
Accuracy (%)	93 ± 12	95 ± 7	93 ± 10	93 ± 13

Item Working Memory – 4 Items				
Reaction time (ms)	843 ± 171	884 ± 219	904 ± 194	969 ± 305
Errors (#)	1 ± 1	1 ± 1	1 ± 1	1 ± 1
Accuracy (%)	89 ± 12	87 ± 12	93 ± 7	85 ± 11
Item Working Memory – 6 Items				
Reaction time (ms)	987 ± 249	931 ± 297	1048 ± 346	947 ± 244
Errors (#)	2 ± 1	3 ± 1	2 ± 1	2 ± 2
Accuracy (%)	79 ± 15	74 ± 16	77 ± 12	80 ± 23

Table 5-2– Cognitive Performance responses (presented as mean ± SD) for the four experimental conditions. π indicates a significant response-stimulus interval effect for detection task or flanker effect for vertical flanker task, or set-size effect for item working memory task. * indicates a significant condition effect where pairwise comparisons can be interpreted as: [a] significantly different from TN, [b] significantly different from CS, [c] significantly different from C-0.3°C, [d] significantly different from C-0.8°C.

5.6 List of Figures

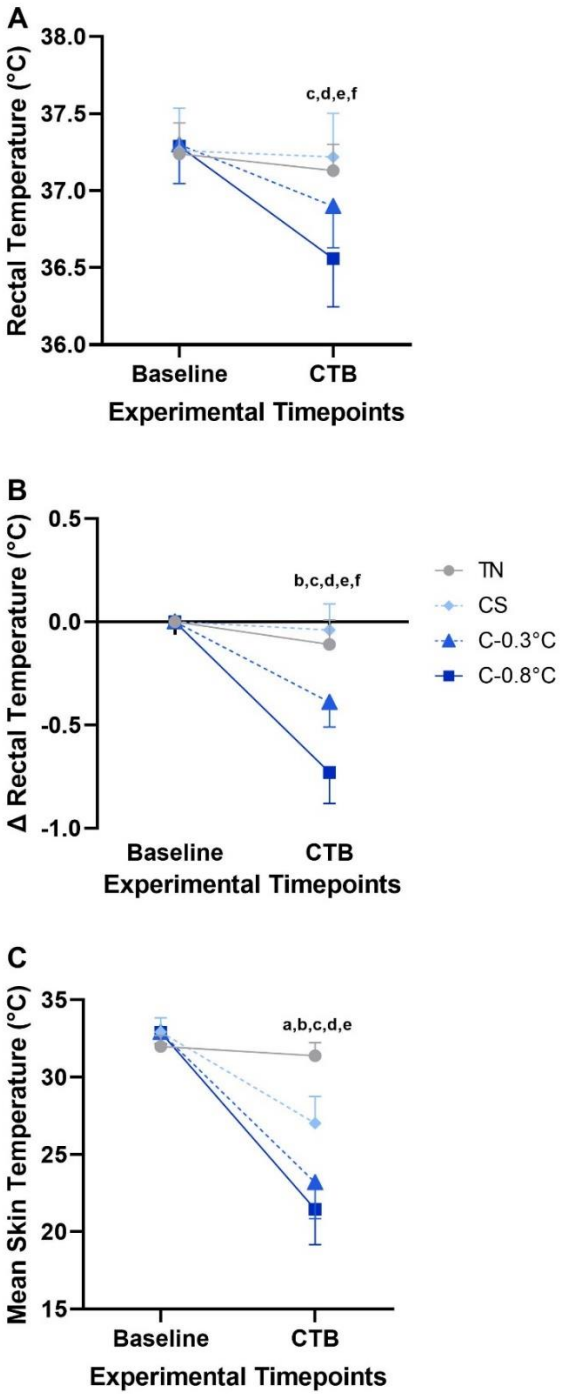
A
38.0
37.5
37.0
36.5
36.0
Rectal Temperature (°C)
c,d,e,f
Baseline
CTB
Experimental Timepoints
B
0.5
0.0
-0.5
-1.0
Δ Rectal Temperature (°C)
b,c,d,e,f
TN
CS
C-0.3°C
C-0.8°C
Baseline
CTB
Experimental Timepoints
C
35
30
25
20
15
Mean Skin Temperature (°C)
a,b,c,d,e
Baseline
CTB
Experimental Timepoints

Figure 5-1

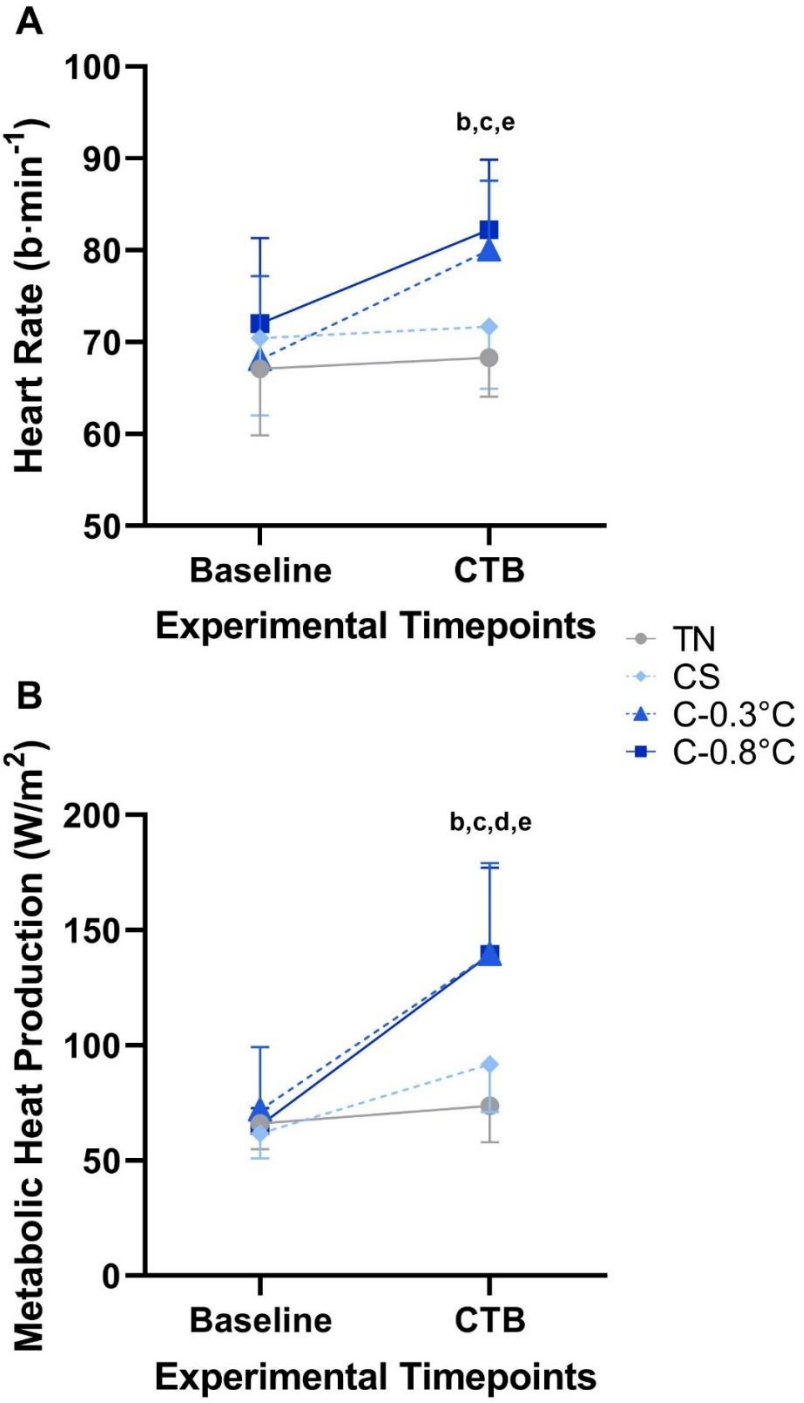
A
100
90
80
70
60
50
Heart Rate (b·min-1)
b,c,e
Baseline
CTB
Experimental Timepoints
TN
CS
C-0.3°C
C-0.8°C
B
200
150
100
50
0
Metabolic Heat Production (W/m2)
b,c,d,e
Baseline
CTB
Experimental Timepoints

Figure 5-2

5.7 References

1. **Palinkas LA**. Mental and Cognitive Performance in the Cold. *International Journal of Circumpolar Health* 60: 430–439, 2001. doi: 10.1080/22423982.2001.12113048.

2. **Taber MJ**, **Hartley GL**, **McGarr GW**, **Zaharieva D**, **Basset FA**, **Hynes Z**, **Haman F**, **Pinet BM**, **DuCharme MB**, **Cheung SS**. Cognitive Performance during a 24-Hour Cold Exposure Survival Simulation. *BioMed Research International* 2016: 1–11, 2016. doi: 10.1155/2016/8130731.

3. **Castellani JW**, **Tipton MJ**. Cold stress effects on exposure tolerance and exercise performance. *Compr Physiol* 6: 443–469, 2016. doi: 10.1002/cphy.c140081.

4. **Gibbons TD**, **Tymko MM**, **Thomas KN**, **Wilson LC**, **Stembridge M**, **Caldwell HG**, **Howe CA**, **Hoiland RL**, **Akerman AP**, **Dawkins TG**, **Patrician A**, **Coombs GB**, **Gasho C**, **Stacey BS**, **Ainslie PN**, **Cotter JD**. Global REACH 2018: The influence of acute and chronic hypoxia on cerebral haemodynamics and related functional outcomes during cold and heat stress. *The Journal of Physiology* 598: 265–284, 2020. doi: 10.1113/JP278917.

5. **Ferguson SAH**, **Eves ND**, **Roy BD**, **Hodges GJ**, **Cheung SS**. Effects of mild whole body hypothermia on self-paced exercise performance. *Journal of Applied Physiology* 125: 479–485, 2018. doi: 10.1152/japplphysiol.01134.2017.

6. **Hodges GJ**, **Ferguson SAH**, **Cheung SS**. Glabrous and non-glabrous vascular responses to mild hypothermia. *Microvascular Research* 121: 82–86, 2019. doi: 10.1016/j.mvr.2018.10.006.

7. **Haman F**, **Mantha OL**, **Cheung SS**, **DuCharme MB**, **Taber M**, **Blondin DP**, **McGarr GW**, **Hartley GL**, **Hynes Z**, **Basset FA**. Oxidative fuel selection and shivering thermogenesis during a 12- and 24-h cold-survival simulation. *Journal of Applied Physiology* 120: 640–648, 2016. doi: 10.1152/japplphysiol.00540.2015.

8. **Cheung SS**, **Westwood DA**, **Knox MK**. Mild body cooling impairs attention via distraction from skin cooling. *Ergonomics* 50: 275–288, 2007. doi: 10.1080/00140130601068683.

9. **Castellani JW**, **Yurkevicius BR**, **Jones ML**, **Driscoll TJ**, **Cowell CM**, **Smith L**, **Xu X**, **O'Brien C**. Effect of localized microclimate heating on peripheral skin temperatures and manual dexterity during cold exposure. *Journal of Applied Physiology* 125: 1498–1510, 2018. doi: 10.1152/japplphysiol.00513.2018.

10. **Hoffman RG**. Human psychological performance in cold environments. *Medical aspects of harsh environments* 1: 383–410, 2001.

11. **Muller MD**, **Muller SM**, **Kim C-H**, **Ryan EJ**, **Gunstad J**, **Glickman EL**. Mood and selective attention in the cold: the effect of interval versus continuous exercise. *European Journal of Applied Physiology* 111: 1321–1328, 2011. doi: 10.1007/s00421-010-1759-1.

12. **Pilcher JJ**, **Nadler E**, **Busch C**. Effects of hot and cold temperature exposure on performance: a meta-analytic review. *Ergonomics* 45: 682–698, 2002. doi: 10.1080/00140130210158419.

13. **Hancock PA**, **Ross JM**, **Szalma JL**. A Meta-Analysis of Performance Response Under Thermal Stressors. *Human Factors: The Journal of the Human Factors and Ergonomics Society* 49: 851–877, 2007. doi: 10.1518/001872007X230226.

14. **Falla M**, **Micarelli A**, **Hüfner K**, **Strapazzon G**. The Effect of Cold Exposure on Cognitive Performance in Healthy Adults: A Systematic Review. *IJERPH* 18: 9725, 2021. doi: 10.3390/ijerph18189725.

15. **Racinais S**, **Gaoua N**, **Mtibaa K**, **Whiteley R**, **Hautier C**, **Alhammoud M**. Effect of Cold on Proprioception and Cognitive Function in Elite Alpine Skiers. *International Journal of Sports Physiology and Performance* 12: 69–74, 2017. doi: 10.1123/ijspp.2016-0002.

16. **Shurtleff D**, **Thomas JR**, **Schrot J**, **Kowalski K**, **Harford R**. Tyrosine reverses a cold-induced working memory deficit in humans. *Pharmacology Biochemistry and Behavior* 47: 935–941, 1994. doi: 10.1016/0091-3057(94)90299-2.

17. **Thomas JR**, **Ahlers ST**, **House JF**, **Schrot J**. Repeated exposure to moderate cold impairs matching-to-sample performance. *Aviat Space Environ Med* 60: 1063–1067, 1989.

18. **Watkins SL**, **Castle P**, **Mauger AR**, **Sculthorpe N**, **Fitch N**, **Aldous J**, **Brewer J**, **Midgley AW**, **Taylor L**. The Effect of Different Environmental Conditions on the Decision-making Performance of Soccer Goal Line Officials. *Research in Sports Medicine* 22: 425–437, 2014. doi: 10.1080/15438627.2014.948624.

19. **Teichner WH**. Reaction time in the cold. *Journal of Applied Psychology* 42: 54–59, 1958. doi: 10.1037/h0049145.

20. **Yang L**, **Wu J**, **Hu Z**, **Gao F**, **Hu X**. Effects of workload on human cognitive performance of exposure to extremely cold environment. *Physiology & Behavior* 230: 113296, 2021. doi: 10.1016/j.physbeh.2020.113296.

21. **Muller MD**, **Gunstad J**, **Alosco ML**, **Miller LA**, **Updegraff J**, **Spitznagel MB**, **L. Glickman E**. Acute cold exposure and cognitive function: evidence for sustained impairment. *Ergonomics* 55: 792–798, 2012. doi: 10.1080/00140139.2012.665497.

22. **Makinen T**, **Palinkas L**, **Reeves D**, **Paakkonen T**, **Rintamaki H**, **Leppaluoto J**, **Hassi J**. Effect of repeated exposures to cold on cognitive performance in humans. *Physiology & Behavior* 87: 166–176, 2006. doi: 10.1016/j.physbeh.2005.09.015.

23. **Færevik H**, **Hansen JH**, **Wiggen Ø**, **Sandsund M**. Cognitive Performance During Night Work in the Cold. *Front Physiol* 12: 768517, 2021. doi: 10.3389/fphys.2021.768517.

24. **Bittel JH**, **Nonotte-Varly C**, **Livecchi-Gonnot GH**, **Savourey GL**, **Hanniquet AM**. Physical fitness and thermoregulatory reactions in a cold environment in men. *Journal of Applied Physiology* 65: 1984–1989, 1988. doi: 10.1152/jappl.1988.65.5.1984.

25. **Jones DM**, **Bailey SP**, **De Pauw K**, **Folger S**, **Roelands B**, **Buono MJ**, **Meeusen R**. Evaluation of cognitive performance and neurophysiological function during repeated immersion in cold water. *Brain Research* 1718: 1–9, 2019. doi: 10.1016/j.brainres.2019.04.032.

26. **Ellis HD**. The Effects of Cold on the Performance of Serial Choice Reaction Time and Various Discrete Tasks. *Human Factors: The Journal of the Human Factors and Ergonomics Society* 24: 589–598, 1982. doi: 10.1177/001872088202400509.

27. **Du Bois, D**, **Du Bois, EF**. A Formular to Estimate Surface Area if Height and Weight are Known. *Arch Intern Med* 17: 863–871, 1916.

28. **Jackson AS**, **Pollock ML**. Generalized equations for predicting body density of men. *Br J Nutr* 40: 497–504, 1978.

29. **Wallace PJ**, **Mckinlay BJ**, **Coletta NA**, **Vlaar JI**, **Taber MJ**, **Wilson PM**, **Cheung SS**. Effects of motivational self-talk on endurance and cognitive performance in the heat. *Med Sci Sports Exerc* 49: 191–199, 2017. doi: 10.1249/MSS.0000000000001087.

30. **Jones SAH**, **Butler BC**, **Kintzel F**, **Johnson A**, **Klein RM**, **Eskes GA**. Measuring the Performance of Attention Networks with the Dalhousie Computerized Attention Battery (DalCAB): Methodology and Reliability in Healthy Adults. *Frontiers in Psychology* 7, 2016. doi: 10.3389/fpsyg.2016.00823.

31. **Greaney JL**, **Alexander LM**, **Kenney WL**. Sympathetic control of reflex cutaneous vasoconstriction in human aging. *Journal of Applied Physiology* 119: 771–782, 2015. doi: 10.1152/japplphysiol.00527.2015.

32. **Hardy JD**, **Du Bois, EF**, **Soderstrom, GF**. The Technic of Measuring of Radiation and convection. *J Nutr* : 461–475, 1938. doi: 10.1093/jn/15.5. 461.

33. **Cramer MN**, **Jay O**. Partitional calorimetry. *Journal of Applied Physiology* 126: 267–277, 2019. doi: 10.1152/japplphysiol.00191.2018.

34. **Gagge AP**, **Stolwijk JAJ**, **Hardy JD**. Comfort and thermal sensations and associated physiological responses at various ambient temperatures. *Environmental Research* 1: 1–20, 1967. doi: 10.1016/0013-9351(67)90002-3.

35. **Jones SAH**, **Butler B**, **Kintzel F**, **Salmon JP**, **Klein RM**, **Eskes GA**. Measuring the components of attention using the Dalhousie Computerized Attention Battery (DalCAB). *Psychological Assessment* 27: 1286–1300, 2015. doi: 10.1037/pas0000148.

36. **Cunningham JEA**, **Jones SAH**, **Eskes GA**, **Rusak B**. Acute Sleep Restriction Has Differential Effects on Components of Attention. *Front Psychiatry* 9: 499, 2018. doi: 10.3389/fpsyt.2018.00499.

37. **McCabe DP**, **Roediger HL**, **McDaniel MA**, **Balota DA**, **Hambrick DZ**. The relationship between working memory capacity and executive functioning: Evidence for a common executive attention construct. *Neuropsychology* 24: 222–243, 2010. doi: 10.1037/a0017619.

38. **Giesbrecht GG**, **Arnett JL**, **Vela E**, **Bristow GK**. Effect of task complexity on mental performance during immersion hypothermia. *Aviation, Space, and Environmental Medicine* 64: 206–211, 1993.

39. **Nakata H**, **Kobayashi F**, **Lawley JS**, **Kakigi R**, **Shibasaki M**. Effects of whole body skin cooling on human cognitive processing: a study using SEPs and ERPs. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology* 317: R432–R441, 2019. doi: 10.1152/ajpregu.00087.2019.

40. **Mahoney CR**, **Castellani J**, **Kramer FM**, **Young A**, **Lieberman HR**. Tyrosine supplementation mitigates working memory decrements during cold exposure. *Physiology & Behavior* 92: 575–582, 2007. doi: 10.1016/j.physbeh.2007.05.003.

41. **Qian S**, **Li M**, **Li G**, **Liu K**, **Li B**, **Jiang Q**, **Li L**, **Yang Z**, **Sun G**. Environmental heat stress enhances mental fatigue during sustained attention task performing: Evidence from an ASL perfusion study. *Behavioral Brain Research* 280: 6–15, 2015. doi: 10.1016/j.bbr.2014.11.036.

5.8 Appendix

Variable	Famil 1	Famil 2	Famil 3	TN	Condition Effect
Detection Task					
Reaction time (ms)*	274.9 ± 24.6	277.9 ± 27.2	282.0 ± 25.1	273.5 ± 37.6	≤ 0.509
Vertical Flanker - All					
Reaction time (ms)	558.4 ± 51.1	564.4 ± 47.1	540.1 ± 59.8	535.9 ± 67.1	0.073
Errors (#)	3.0 ± 3.1	3.0 ± 1.6	4.0 ± 3.3	3.0 ± 3.1	0.412
Item Working Memory - All					
Reaction time (ms)	993.1 ± 236.4	990.8 ± 269.5	883.2 ± 198.7	843.6 ± 186.4	0.074
Errors (#)	4.0 ± 1.7	3.0 ± 1.8	3.0 ± 1.9	4.0 ± 3.2	0.516

Table 5-3-Appendix Table of Learning Effect Data presented as mean ± SD. Data was analyzed with a 1 x 4 repeated measured ANOVA from Famil 1 to TN. There were no significant learning effects.

5.9 Research Program Progression

In Chapter 5, we found that neither skin nor core temperature, or thermal comfort, significantly affected cognitive function during passive hypothermia of core temperature of Δ-0.3°C and Δ-0.8°C. We induced a significant degree of 'cold strain' in both core cooling conditions as indexed by low levels of mean skin temperature, local forearm and hand temperature, increased metabolic heat production (index of shivering thermogenesis), and thermal displeasure. This was an unexpected finding as the impairment of cognitive function is well-documented to be impaired with milder levels of cold strain (index by minimal changes in core temperature and higher skin temperature). However, this finding is not universal, which adds to the complexity of determining threshold for cognitive impairment in the cold. One key difference in our study is that we attempted to minimize the manual dexterity requirements for responding during the cognitive tasks (within the confines of a cold environment). This included wearing gloves during all testing (including familiarization and thermoneutral conditions) and creating a raised platform on the keyboard for responding. This may have aided in the null responses.

In Chapter 6, we wanted to extend our research model to include an aspect of physical capacity. Based on the neurological model of exercise performance, impairments or strain of the attentional network should lead to changes in exercise performance or endurance capacity. If this model holds true for cold environments, based on the results of Chapter 5, there should be no impairment exercise capacity. However, it has been well documented that cold impairs exercise performance, so this result is unlikely. Using a model of reducing skin versus core temperature in cold air will allow the ability isolate and potentially determine the threshold for endurance capacity in the cold. Understanding of how these factors intertwine can provide important information and interventions to maintain overall function to increase survival rates.

6 – The effects of cold air exposure ranging from cooling of the outer shell to mild hypothermia on endurance capacity in cold air (0°C)

6.1 Abstract

We tested the effects of cold air (0°C) exposure on endurance capacity to different levels of cold strain ranging from skin cooling through to significant core cooling. 10 males completed cycling test-to-exhaustion (TTE) at 70% of their peak power output following: i) 30-min of exposure to 22°C thermoneutral air (TN), ii) 30-min exposure to 0°C cold air leading to a cold shell (CS), iii) 0°C cold air exposure causing mild hypothermia of -0.5°C from baseline rectal temperature (T_{re}) (HYPO-0.5°C), and iv) 0°C cold air exposure causing mild T_{re} hypothermia of -1.0°C from baseline (HYPO-1.0°C). Absolute T_{re} and ΔT_{re} from baseline at the start of the TTE were TN (37.0±0.2°C), CS (37.1±0.3°C, Δ-0.2±0.2°C), HYPO-0.5°C (36.6±0.4°C, Δ-0.7±0.3°C), HYPO-1.0°C (36.4±0.5°C, Δ-1.0±0.4°C). There was a significant condition effect ($p \leq 0.001$) for TTE, where median (quatile1-quartile3) TTE declined from TN (21.7 (12.8-31.1) min) in CS (14.0 (7.8-24.3 min), HYPO-0.5°C (7.0 (3.5-12.8) min), and HYPO-1.0°C (4.2 (2.9-8.1) min). Furthermore, participants had a greater endurance capacity in CS compared to HYPO-0.5°C (p = 0.005), and HYPO-1.0°C (p = 0.005), with no differences between HYPO-0.5°C and HYPO-1.0°C (p = 0.444). Endurance capacity impairment at 70% peak power output occurs early in cold exposure CS, with significantly larger impairments with mild hypothermia up to Δ-1.0°C.

6.2 Introduction

Exercise in cold air is physiologically more demanding compared to thermoneutral environments due to changes in cardiorespiratory function (i.e., vasoconstriction, shifts in oxygen dissociation, reduced peak oxygen consumption) (1, 2), increased metabolic demands due to shivering (3, 4), and reduced neuromuscular function, coordination, and contractility (5–7). Despite these physiological changes with cold exposure, data concerning performance changes are equivocal, with time-to-exhaustion (TTE) at ~70% of maximal aerobic capacity either similar between 4°C and 21°C air (8) or even improved by ~40% in 3°C (9) compared to 20°C. One potential cause of these disparate findings may be the lack of significant cooling to the body, as these were acute exposure protocols where exercise commenced almost immediately upon entry to the cold environment, resulting in little to no change in core or muscle temperature. Recently, studies inducing actual mild hypothermia pre-exercise demonstrate a performance decrement, with ~Δ1.5°C in core temperature via cold-water immersion (10°C) reducing the work completed by ~11% during a 20-min self-paced cycling time trial in a thermoneutral environment (23°C) (10). Similarly, an ~Δ-0.5°C in core temperature via cold-air exposure impaired 15-km time trial performance in trained cyclists in cold air (0°C) (1). The ~5% lower average power output in the latter study suggests a voluntary downregulation of workload in the face of elevated thermal discomfort, as ratings of perceived exertion remained similar across hypothermia and thermoneutral conditions.

Whether a cold exposure dose response exists for exercise capacity is currently unknown. This is true for whether differences exist between peripheral versus deep core cooling, and also for the magnitude of core cooling. Cooling skin or outer shell temperature alone increases peripheral vasoconstriction, which may impair muscular capacity by reducing temperature and oxygen

availability at the muscles (11). Exercise impairment may be caused directly from a cold shell, as using a heated jacket to maintain whole-body skin temperature improved 2-km rowing time-trial performance following 25-min of passive cold air exposure (8°C) (12). Greater cold strain from further core cooling to mild hypothermia elicits shivering and further increases heart rate, thermal discomfort, and vasoconstriction (1–3, 13), leading to greater potential impairments in endurance capacity. Peak aerobic capacity during combined arm/leg ergometry is demonstrated to decline ~5-6% per °C decrease in core temperature (14). However, the separate and combined effects of cooling skin/shell and core temperature on endurance capacity are unknown.

One of the inherent methodological challenges in cold physiology research is normalizing the cold strain between individuals. A set duration protocol (e.g., 120 mins) can lead to wide individual variability in actual core cooling, due to by such factors as anthropometrics (body mass, surface-area to mass ratio, fat insulation), age, and sex (For review see (11)). An alternative approach is to cool individuals to a set decrease in baseline core temperature (e.g., Δ-0.5°C) (1, 2, 13) to normalize cold strain. However, this approach can lead to inter-individual variability in cooling times, as recently we demonstrated that cooling core temperature by Δ-0.8°C from baseline in cold air (0°C) ranged from 89-173 minutes across participants (Wallace et al. Chapter 5). The differences in cold exposure/cooling times prior to exercise may introduce additional confounding variables related to cooling that may influence performance. For example, cooling leads to an increase in shivering to increase metabolic heat production to offset heat loss, which leads to more energy expended prior to and during exercise. Furthermore, from a biophysical perspective, changes in core temperature are determined by the cumulative imbalance between metabolic heat production and net heat loss (i.e., body heat storage), body mass (i.e. internal heat sink) and body composition (i.e. specific heat capacity of body tissues) (15). In cold environments, partitional

calorimetry is used to calculate the rate of heat storage (Ṡ, where positive values indicate heat gain, negative values indicate heat loss), and can be used to estimate heat debt (HD), which represents the cumulative change in whole- body heat content and provides an indication of cold strain (16–18). The use of HD as physiological measure has primarily been used to assess the thermoregulatory response to cold air following repeated cold-water immersion (18, 19) or high intensity interval training (20). This tool can be used to provide an index of cold strain between participants and differentiate between different levels of core cooling. Therefore, the inclusion of the cooling response prior to exercise may provide insight as to how cold affects performance beyond thermometric changes in core and skin temperature alone.

The purpose of this study was to test the effects of cold air (0°C) exposure, ranging from initial cooling of the shell to two levels of mild hypothermia, on endurance capacity. We tested time to exhaustion (TTE) at 70% of peak power output in four randomized conditions: i) a 30-min exposure to 22°C thermoneutral air (TN), ii) an acute ~30-min exposure to 0°C cold air leading to a cold shell (CS) and neutral core, iii) a 0°C cold air exposure causing mild hypothermia of Δ-0.5°C from baseline rectal temperature (T_{re}) (HYPO-0.5°C), and iv) a 0°C cold air exposure causing mild hypothermia of Δ-1.0°C from baseline T_{re} (HYPO-1.0°C). We predict that: i) endurance capacity would be impaired with CS compared with thermoneutral; ii) both core cooling conditions will decrease endurance capacity more than skin cooling alone; and iii) HYPO-1.0°C will lead to greater impairments in endurance capacity compared to HYPO-0.5°C due to increased cold strain.

6.3 Methods

Participants - The experimental protocol was approved by the Research Ethics Board at Brock University (REB# 19-026) and conformed to the latest revision of the Declaration of Helsinki. 10

healthy male volunteers (See Table 6-1 for characteristics), who were free from cardiovascular, respiratory, neurological, and cold disorders were recruited from the university and community population. All participants were informed of the experimental protocol and associated risks before participating in this experiment and provided both verbal and written consent.

Experimental Design – The experiment was a randomized repeated measures design consisting of two familiarization sessions and 4 experimental sessions. The first experimental session involved collecting anthropometric measures, determining peak oxygen consumption, peak power output, and practicing the TTE. The second familiarization provided two further practices of the TTE. The 4 experimental conditions were separated by 3-7 days to minimize the potential of cold acclimation and performed at the same time of day to control for circadian fluctuations in core temperature. Participants were instructed to avoid vigorous exercise and alcohol consumption 24 hours and caffeine 6 hours prior to each experimental session.

Familiarization Trials – Upon arrival for the 1st familiarization trial, anthropometric measurements of height (cm), mass (kg), body surface area (m^2) (21), and % body fat from 7-site skinfold (22) were obtained. An incremental test to exhaustion was performed on a cycle ergometer (Velotron, RacerMate Inc, USA) to determine peak oxygen consumption and peak power output (PPO). The test began with a standardized 5-min warm-up at 100 W, followed by workload increase of 25 W each minute until exhaustion. Peak oxygen consumption was defined as the highest continuous 30-s value measured breath-by-breath from expired gases collected through a soft silicone facemask connected to an inline gas collection system. The final stage completed was considered PPO (W). Following warm down and ~30-min passive recovery, participants then performed a TTE consisting of a standardized 5-min warm up at 100 W followed by the TTE at 70% of PPO (see

details below). Upon arrival for the 2nd familiarization trial, participants practiced the TTE a total of two times, separated by 25-30 minutes.

Experimental Trials **–** Upon arrival participants voided their bladder and nude body mass (kg) was recorded. A sample of the urine was tested for urine specific gravity (PAL-10S, Atago, Japan) to determine hydration status. Participants were considered euhydrated if urine specific gravity was ≤1.020, or else the test was rescheduled (no trials were rescheduled from hypohydration). Participants were then instrumented (see below) and entered an environmental chamber and were seated on a chair. Participants then performed a 5-min baseline in thermoneutral conditions (~22.0°C, ~50% relative humidity) sitting quietly with their eyes closed. Next, participants performed one of the following 4 experimental conditions before commencing the TTE:

Thermoneutral (TN) – Participants remained seated in the chamber (~22.0°C, ~50% relative humidity) for 25 minutes (30 minutes total) before commencing TTE.

Cold Shell (CS) – Participants remained seated in the environmental chamber as the ambient temperature was incrementally decreased to 0°C (~15-16 minutes) and wind speed was increased to 0.8-1.2 m/s using a fan. Participants remained seated for an additional ~15 minutes such that cold exposure was ~30-min in duration prior to commencing the TTE. This design allowed for the core temperature to remain neutral while skin/shell temperature was reduced.

HYPO-0.5°C – Participants remained seated in the environmental chamber as ambient temperature was decreased to 0°C and wind speed was increased to 0.8-1.2 m/s until the participants' rectal temperature (T_{re}) dropped by Δ-0.3°C from baseline. This design was implemented in order to target a T_{re} decrease of Δ-0.5°C at the start of the TTE with the additional time for transfer to the ergometer along with postural shifts.

HYPO-1.0°C – Participants remained seated in the environmental chamber as ambient temperature was decreased to 0°C and wind speed was increased to 0.8-1.2 m/s until the participants T_{re} dropped by Δ-0.8°C from baseline before transferring to the ergometer and performing the TTE. This design was implemented in order to target a T_{re} decrease of Δ-1.0°C for the TTE.

For all cold trials, there was an institutional ethical cutoff of core temperature ≤ 35.0°C and an exposure limit of 150-min following chamber air temperature reaching 0°C in cold trials. Three participants reached the 150-min cutoff limit in the HYPO-1.0°C trials.

Time to Exhaustion **–** The TTE started with a standardized 'warmup' of 5-min at 100 W followed by the TTE at 70% of PPO. Participants could freely choose their cadence, and the test was performed to volitional fatigue or when cadence dropped below 60 rpm for 5 consecutive seconds. No feedback or verbal motivation was provided except for one verbal warning if cadence dropped below 60 rpm. Due to differences in completion times between participants and trials, comparison of physiological responses were averaged over 30-s at normalized percentages of 0%, 25%, 50%, 75%, and 100% of total TTE.

Clothing **–** During TN trials, participants wore a cotton t-shirt or cycling jersey, cycling bib shorts, socks, athletic/ cycling shoes, and metabolic mask (~ 0.26 clo ensemble). In all cold trials, participants wore the same ensemble as TN at baseline with the inclusion of track pants (~0.48 clo ensemble). Upon commencement of cooling the chamber, participants were fitted with earmuffs, winter gloves, and a fleece blanket around their shoes (~0.63 clo ensemble). Prior to the TTE, the blanket was removed (~0.57 clo ensemble). The additional clothing during the cold trials was deemed necessary during pilot testing to offset extreme discomfort of extremities during cooling and minimize the risk of participant dropout.

Perceptual Measurements – Prior to performing the TTE, motivation was taken using a 0-4 scale (23)**.** Subjective assessments of the environmental conditions were assessed using a 1-4 scale to measure thermal comfort and a 1-7 scale for thermal sensation (24), and ratings of perceived exertion (6-20) (25) at ISO0% and ISO100%.

Physiological Measurements – Prior to baseline, participants self-instrumented with a flexible thermocouple thermistor (RET-1, Physitemp Instruments, USA) 15 cm beyond the anal sphincter to measure T_{re} (°C) sampled at 4 Hz. Weighted mean skin temperature ($\overline{T}_{skin}$, °C) and mean heat flux (HF, $W \cdot m^{-2}$) were measured using heat flux sensors with an integrated thermistor (Concept Engineering, Old Saybrook, USA) sampled at 100 Hz at seven sites (26):

$$\overline{T}_{skin} \text{ or } HF = 0.07_{forehead} + 0.14_{forearm} + 0.05_{hand} + 0.35_{abdomen} + 0.19_{thigh} + 0.13_{shin} + 0.07_{foot}$$

Water vapor pressure of the skin was measured using a temperature and humidity sensor (HMP60-L, Vaisala, FN) sampled at 100 Hz at four sites: upper arm, chest, thigh, and calf. Heart rate was calculated using R-R intervals using a standard three-lead electrocardiogram (MLA2340, AD Instruments; USA). Participants were fitted with a soft silicone facemask (Hans Rudolph, USA) connected to a 4.7L gas mixing chamber where gas volume was measures using a pneumotach (MTL 1000L, AD Instruments; USA) and gas concentrations with a gas analyzer (ML206 Gas Analyzer, AD Instruments, USA). Measures of expired ventilation ($\dot{V}_E$, $L \cdot min^{-1}$), oxygen consumption ($\dot{V}O_2$, $L \cdot min^{-1}$), carbon dioxide expiration ($\dot{V}CO_2$, $L \cdot min^{-1}$), and respiratory exchange ratio (RER, $\dot{V}CO_2/\dot{V}O_2$) were used to calculate metabolic heat production. Calculations were adjusted based on barometric pressure (mmHg) and mixing chamber air temperature (°C, sampled at 1 kHz) to account for changes in body temperature on gas volumes.

Partitional Calorimetry Calculations – Heat storage using partitional calorimetry was calculated each minute and normalized to body surface area using the following equation during pre-TTE cooling periods (27):

$$\dot{S} = \dot{M} - \dot{W}_K \pm \dot{R} \pm \dot{C}_{skin} \pm \dot{K} - \dot{E}_{skin} - (\dot{E}_{resp} + \dot{C}_{resp}) \, [W \cdot m^{-2}]$$

Where: $\dot{S}$= heat storage, $\dot{M}$ = metabolic heat production, $\dot{W}_K$= energy used for work, $\dot{R}$ = Radiation,$\dot{C}_{skin}$ = convection of skin, $\dot{K}$= conduction, $\dot{E}_{skin}$= evaporation from skin, $\dot{E}_{resp}$= evaporation from respiratory tract, and $\dot{C}_{resp}$ = convection from respiratory tract. $\dot{W}_K$ is considered 0 in this study as participants were at rest. $\dot{K}$ is assumed to be at 0 in this experiment. Combined $\dot{R} \pm \dot{C}_{skin}$ was determined through weighted HF. The average of each component was taken from baseline and over the course of the environmental condition prior to performing the TTE.

Metabolic Heat Production – Heat production was calculated using indirect calorimetry of expired gases using the following equation if RER was < 1.00 (27)**:**

$$\dot{M} = \left(\dot{V}O_2 \cdot \frac{\left[\left(\left(\frac{RER - 0.7}{0.3} \right) \cdot 21.13 \right) + \left(\left(\frac{1.0 - RER}{0.3} \right) \cdot 19.62 \right) \right]}{60} \cdot 1000 \right) / \, A_D \, [W \cdot m^{-2}]$$

Where, $\dot{V}O_2$ is in L·min^{-1}, RER is the respiratory exchange ratio, and is normalized to A_D is body surface area calculated using the following equation (21):

$$A_D = 0.202 \cdot (Height)^{0.425} \cdot (mass)^{0.725} \, [m^2]$$

Where, height is in m and mass is in kg.

Indirect calorimetry assumes that metabolic heat production is due to oxidative, rather than non-oxidative (anerobic) energy sources (27), however during passive cold exposure, RER has the potential to ≥ 1 due to increased reliance on glycogen and carbohydrates to fuel shivering thermogenesis (28) and/or through hyperventilation leading to increase carbon dioxide expired

(29). If RER ≥ 1, the following equation was used to account for the energy equivalent for carbohydrates only (27)**:**

$$\dot{M}\ (\text{RER}\ \geq 1.0) = \left(\dot{V}O_2\ \cdot \frac{21.13}{60} \cdot 1000\right) /\ A_D\ [W \cdot m^{-2}]$$

Energy expenditure was calculated as Kcals expended from the start of baseline until the commencement of the TTE by taking the integral of $\dot{M}$ in W divided by 70 (16).

Evaporative heat loss from the skin surface –The following equation was used to determine $\dot{E}_{skin}$ from the relative humidity sensors and environmental factors (27, 30)**:**

$$\dot{E}_{skin} = h_e \cdot \omega \cdot (P_{skin} - P_a)\ [W \cdot m^{-2} \cdot °C]$$

Where, h_e = heat transfer coefficient for evaporative heat loss, ω = skin wittedness of participant, assumed to be minimal at 0.06 due to no regulatory sweating, P_{skin} = saturated vapor pressure of the skin, P_a = partial vapor pressure of the air.

The heat transfer coefficient for evaporative heat loss is calculated by re-arranging the Lewis relation equation:

$$\text{Lewis Relation} = \frac{h_c}{h_e}$$

Where, the Lewis relation is assumed to be 16.5 °C·kpa^{-1} (31), h_c = convective heat transfer coefficient (see equation above), and h_e = heat transfer coefficient for evaporative heat loss.

Saturated vapor pressure of the skin was calculated using Antoine's equation by using mean skin temperature:

$$P_{skin} = \frac{\exp\left(18.956 - \frac{4030.18}{\overline{T}_{skin} + 235}\right)}{10}\ [\text{kpa}]$$

Where, $\overline{T}_{skin}$ = mean skin temperature (°C), division by 10 is to convert P_{skin} from mb to kPa.

The partial vapor pressure in the air (P_a) and saturated vapor pressure of water (P_{sa}) were derived based on their relationship with relative humidity (Ø, fractional %) using temperature and humidity measurements from sensors with the following equations:

$$P_a = ØP_{sa}\ [kPa]$$

$$P_{sa} = \frac{\exp\left(18.956 - \frac{4030.18}{T_{amb\ skin} + 235}\right)}{10}\ [kpa]$$

$T_{amb\ skin}$ is the air temperature (°C) at the skin surface, division by 10 is to convert P_{sa} from mb to kPa. Each measurement was calculated for each site, then weighted using the following equation which was originally derived for mean skin temperature (32):

$$\text{Weighted Relative Humidity or } T_{amb\ skin} = 0.3_{arm} + 0.3_{chest} + 0.2_{thigh} + 0.2_{calf}$$

Respiratory Heat Loss – Combined convective and evaporative heat loss from the respiratory tract was the summation of the following equations (27)**:**

$$\dot{C}_{resp} = \frac{\left(0.001516 \cdot \dot{M}\left(28.56 + (0.641 \cdot P_a) - (0.885 \cdot T_{amb})\right)\right)}{A_D}\ [W \cdot m^2]$$

$$\dot{E}_{resp} = \frac{\left(0.00127 \cdot \dot{M}\left(59.34 + (0.53 \cdot P_a) - (11.63 \cdot T_{amb})\right)\right)}{A_D}\ [W \cdot m^2]$$

Where $\dot{M}$ is in W, P_a is the vapor pressure of inspired air in kPa, and T_{amb} is ambient temperature of inspired air in °C. Ambient temperature (T_{amb}, °C) and relative humidity (%) were measured using a hand-held hygrometer and thermometer (Pocket DewPoint, VWR, USA) for respiratory heat loss at the level of xyphoid process of the participants at baseline and every 15-min.

Heat Debt - The change in body heat content over time or HD was obtained by taking the integral of heat storage and converting to kJ with the following equation (6, 9)**:**

$$\Delta HD = \int_{t=0}^{t} \dot{S} * A_D * dt/1000\ [kJ]$$

Where, the rate of heat storage is converted to W by multiplying by A_D, then multiplied by exposure time (dt) in seconds (s) and divided by 1000 to convert W to kJ. HD was calculated every minute from when cooling the chamber started until prior to commencing the TTE.

Statistical Analysis – All physiological data are presented as mean ± SD. Data was assessed for normal distribution using the Kolmogorov-Smirnov Test (SPPS Statistics for Windows, version 28, IBM Corp., USA). Prior to analysis, a Mauchly's test of sphericity was performed, if violated ($p < 0.05$), the Greenhouse Geisser correction was used. To compare conditions, a 1 x 4 condition (TN vs CS vs HYPO-0.5°C HYPO-1.0°C) repeated measures ANOVAs were performed. All continuous variables collected over time were analyzed using condition (TN vs CS vs HYPO-0.5°C HYPO-1.0°C) X experimental timepoint (Baseline vs ISO0% vs ISO25% vs ISO50% vs ISO75% vs ISO100%) repeated-measures ANOVAs. If there was a significant effect, a Bonforroni post-hoc correct for multiple comparisons was performed. The α level was set at $p \leq 0.05$. These statistical analyses were performed with GrahPad Pism (v. 8.3, GraphPad Software, USA).

The TTE data was not normally distributed based on Kolmogorov-Smirnov Test in the HYPO-1.0°C condition ($p = 0.006$). Thus, TTE data were assessed using a non-parametric 1 x 4 (condition) Friedman's ANOVA with a Wilcoxon-Signed Rank test for post-hoc analysis to compare between conditions. Perceptual data (RPE, TC, TS) were analyzed using 4 (condition) x 2 ISO-timepoint (ISO0%, ISO100%) repeated measures ANOVAs. As data was not normally distributed and ordinal data, post hoc comparisons between conditions were also performed using a Wilcoxon-Signed Rank test at ISO0% and ISO100%. Motivation was assessed using a 1 x 4 (condition) Friedman's ANOVA with a Wilcoxon-Signed Rank test for post-hoc analysis to compare between conditions. To reduce the likelihood of Type 1 error due to multiple comparisons, α value was revised based on number of comparisons (total 6), therefore $p \leq 0.008$

was set for significance. All perceptual analyses and TTE data (unless stated otherwise) is expressed as Median (Quartile 1 – Quartile 3) were performed using SPSS statistics for Windows.

6.4 Results

Thermal Manipulations **–** Cooling times prior to performing the TTE were as follows: CS (30.0 ± 1.1), HYPO-0.5°C (116.0 ± 39.2 min) and HYPO-1.0°C (160.3 ± 32.3 min). We were successful at creating an CS group (neutral core, cooled skin/shell) and two mild hypothermia groups (reduced T_{re} and cold skin) compared to TN. There was a condition, experimental timepoint, and interaction effect (all $p < 0.001$) for absolute T_{re} (Figure 6-1A), relative ΔT_{re} (Figure, 6-1B) and $\overline{T}_{skin}$ (Figure 6-1C) where pairwise comparisons demonstrated no difference at Baseline for each variable (all $p > 0.05$). For absolute T_{re}, at ISO0%, both TN and CS were significantly different (all $p < 0.05$) from HYPO-1.0°C that was maintained throughout the TTE. There were significant differences (all $p < 0.05$) between TN and CS compared to HYPO-0.5°C from ISO50% to the end of the TTE. Relative ΔT_{re} was significantly lower in HYPO-0.5°C and HYPO-1.0°C than TN (all $p \leq 0.003$) and CS (all $p \leq 0.001$) at all ISO timepoints of the TTE. Mean skin temperature was significantly lower than TN at all ISO timepoints in CS, HYPO-0.5°C, and HYPO-1.0°C (all $p \leq 0.001$). Furthermore, HYPO-0.5°C, and HYPO-1.0°C was significantly lower (all $p \leq 0.01$) compared to CS at all ISO timepoints with no difference between HYPO-0.5°C, and HYPO-1.0°C (all $p \geq 0.05$).

Partitional Calorimetry – There was a significant condition effect (all $p \leq 0.018$) for $\dot{M}$ (Figure 6-2A), $\dot{R} \pm \dot{C}_{skin}$ (Figure 6-2B), $\dot{E}_{resp} + \dot{C}_{resp}$ (Figure 6-2C), $\dot{E}_{skin}$ (Figure 6-2D), $\dot{S}$ (Figure 6-2E), and HD (Figure 6-2F). Metabolic heat production and $\dot{E}_{resp} + \dot{C}_{resp}$ (all $p \leq 0.035$) were significantly higher in all cooling conditions compared to TN, with both variables significantly

greater in HYPO-0.5°C and HYPO-1.0°C compared to CS. Radiative and convective heat loss from the skin was significantly (all $p \leq 0.001$) greater in all cold conditions compared to TN, with no differences (all $p \geq 0.999$) between the cold conditions. Evaporative heat loss was only significantly different ($p = 0.007$) between TN and CS only. Heat storage was significantly (all $p \leq 0.036$) reduced compared to TN in all cooling conditions. Heat storage was significantly (both $p \leq 0.002$) lower in CS (-87.0 ± 13.6 $W \cdot m^2$) compared to HYPO-0.5°C (-54.0 ± 17.9 $W \cdot m^2$) and HYPO-1.0°C (-41.0 ± 12.6 $W \cdot m^2$). Heat Debt was greater in HYPO-1.0°C (-808.0 ± 371.0 kJ), HYPO-0.5°C (-734.0 ± 294.1 kJ), and CS (-328.0 ± 65.2 kJ) compared to TN (-129.0 ± 71.2 kJ, all $p < 0.001$). Both HYPO-0.5°C ($p = 0.005$) and HYPO-1.0°C ($p = 0.009$) were lower compared to CS with no difference between the core cooling conditions. There were no differences between HYPO-0.5°C and HYPO-1.0°C for any variable used to calculate Ṡ and HD. For Kcals expended, there was a significant condition effects ($p \leq 0.001$), with the number of Kcals expended different (all $p \leq 0.024$) between all conditions (TN (87.0 ± 4.8 kcals), CS (72.4 ± 6.2 kcals), HYPO-0.5°C (387.0 ± 153.9 kcals), HYPO-1.0°C (576.0 ± 151.0 kcals)).

Cardiorespiratory Responses – There were no differences at Baseline and all cardiorespiratory variables increased from Baseline during the TTE. There was a significant experimental timepoint (all $p < 0.001$), experimental timepoint x condition interaction (all $p \leq 0.003$) with no condition effect (all $p > 0.05$) for all cardiorespiratory variables (Figure 6-3) except for RER (Figure 6-3E) which demonstrated a condition effect ($p = 0.01$). Pairwise comparisons demonstrated a non-uniform difference of responses between conditions, where significant differences ($p < 0.05$) are displayed in Figure 3.

Perceptual Variables – There was a significant condition, and interaction (all $p < 0.05$) for RPE, TS, and TC (Table 6-2). There was a significant iso-timepoint effect (both $p < 0.05$), where RPE

and TS increased over the course of the TTE. However, there was no condition effect for TC (p = 0.399). Post-hoc comparisons are displayed in Table 2. RPE was significantly higher at ISO0% in HYPO-1.0°C compared to TN, with no differences at ISO100% between conditions. Thermal sensation was lower in all cold conditions compared to TN at ISO0% (all $p < 0.007$), while TS remained lower at ISO100% in both core cooling conditions compared to TN and CS (all $p <$ 0.007). Thermal comfort was higher (i.e., more uncomfortable) in both core cooling conditions compared to TN (both $p = 0.004$) at ISO0%. Thermal comfort approach significance between TN and CS ($p = 0.013$) and CS and HYPO-0.05°C ($p = 0.020$) at ISO0%, with no differences between (all $p > 0.007$) at ISO100%. There was a significant condition effect ($p \leq 0.001$) for motivation to perform TTE, however post-hoc comparisons determined there were no difference between conditions (all $p \geq 0.011$) (Table 6-2).

Endurance Capacity - There was a significant condition effect ($p \leq 0.001$) for TTE time where post-hoc comparisons using Wilcoxon-Signed Rank test demonstrated that endurance capacity was reduced (all $p \leq 0.007$) from TN (21.7 (12.8-31.1) min), in CS (14.0 (7.8-24.3 min), HYPO-0.5°C (7.0 (3.5-12.8) min), and HYPO-1.0°C (4.2 (2.9-8.1) min) (Figure 6-4A). Furthermore, participants had a greater endurance capacity in CS compared to HYPO-0.5°C ($p = 0.005$), and HYPO-1.0°C ($p = 0.005$), with no differences between HYPO-0.5°C and HYPO-1.0°C ($p =$ 0.444). The average % change in TTE from TN was Δ-30.9 ± 21.5% in CS, Δ-61.4 ± 19.7 in HYPO-0.5°C and Δ-71.6 ± 16.4% in HYPO-1.0°C. There was a significant timepoint effect ($p <$ 0.001), but no condition ($p = 0.978$) or interaction ($p = 0.934$) for cadence, where cadence was lower in ISO75% and ISO100% (all $p < 0.05$) compared to all other iso timepoints (Figure 6-4B). The average peak afterdrop in T_{re} over the course of the TTE were: TN (0.0 ± 0.1°C), CS (0.1 ± 0.1°C), HYPO-0.5°C (0.2 ± 0.2°C), HYPO-1.0°C (0.3 ± 0.2°C).

6.5 Discussion

In real-life scenarios such as acute exposure or survival situations in the cold, the first experience faced by an individual is a reduction in skin temperature, occurring well before significant changes to core temperature. If cold exposure continues, eventually core temperature drops along with further skin cooling. Therefore, we aimed to determine if there was a dose-response of cold exposure on endurance capacity in cold (0°C) air; this was done by separating and isolating the effects of a cold outer shell - without changes in core temperature - compared to two levels of core cooling. Cooling just the shell by itself without any core cooling was sufficient to increase physiological strain and reduce physical performance by ~30% compared to thermoneutral. Mild cooling of the core led to a further ~30-40% impairment in performance compared to skin cooling alone. While we attempted to have two distinct doses of core cooling, the drop in core temperature and actual heat debt incurred were similar, and this may have contributed to the similar endurance capacity. Notably, the colder of the two core cooling conditions elicited greater net metabolic energy expenditure, suggesting that endurance capacity across this range of core cooling could be maintained despite sustained shivering over a longer time period.

Consensus for whether cold air by itself impairs exercise capacity is equivocal (11), as most studies initiate exercise directly upon cold exposure. Thus, actual skin cooling and heat debt is minimized and offset by the large and immediate endogenous metabolic heat production from exercise. In the CS condition of the current study, participants were exposed to cold air for ~30 minutes before performing the TTE, allowing for significant reductions in $\overline{T}_{skin}$ and likely superficial muscle temperature. Even though core temperature did not significantly decrease, heat debt decreased ~200 kJ more than thermoneutral, demonstrating that significant cooling did occur.

Furthermore, the rate of heat storage ($\dot{S}$) was the lowest of all three cooling conditions, as there was a large decrease in $\overline{T}_{skin}$ (due to vasoconstriction and $\dot{R} \pm \dot{C}_{skin}$ heat loss) compared to a relatively minor increase in shivering thermogenesis ($\dot{M}$) (33). However, impairment was not uniform, with a wide range of responses from -64% to one participant actually improving performance by +6%. There was strong vasoconstriction with our average $\overline{T}_{skin}$ of ~25.2˚C at ISO0%, as maximal vasoconstriction occurs at $\overline{T}_{skin}$ of ~29.5-30˚C $\overline{T}_{skin}$ (32). This likely impaired performance through both superficial muscle cooling and decreased blood flow to working muscles. For example, 15 minutes of 12°C cold-water leg immersion decreased maximal power (13.7%) and average power (9.5%) during a 30-s cycling sprint in thermoneutral conditions (34). Our data thus highlight the importance of preventing shell cooling, supported by observations that the wearing of a heated vest for 25-min of rest in cold air (8°C) prevented core and skin temperature decreases compared to wearing a tracksuit, eliciting a ~1.1% improvement in subsequent rowing time trial performance (12). Overall, these results indicate that shell cooling by itself can impair endurance capacity in cold air, though the magnitude of this response may vary widely across individuals.

With continued cold exposure, core cooling itself can occur, eliciting a host of physiological responses that may further negatively impact exercise capacity. In the current study, core cooling significant impaired endurance capacity beyond just cooling the shell alone. Relative to TN and CS, both core cooling conditions induced significant reductions in $\overline{T}_{skin}$, T_{re}, and thermal discomfort, along with greater negative heat storage and heat debt prior to exercise. Pre-exercise shivering – measured as $\dot{M}$ in the partitional calorimetry calculations – was greater in both core cooling conditions than in TN or CS. Thus, one potential mechanism for impairment may be reduced motor coordination or altered motor unit recruitment strategies within the musculature

from the asynchronous shivering contractions. Shivering primarily occurs in trunk and thigh muscles where continuous low intensity shivering (~2-5% maximal voluntary contraction) recruit primarily Type I muscle fibres, while high intensity bursts (~7-15% of maximal voluntary contraction) recruit Type II muscle fibres (For review see: (35)) and these shivering muscle groups were very likely similar muscles that were required for our submaximal test workload. Further, local cooling of the muscle decreases maximal voluntary force while altering motor unit contractile characteristics and recruitment patterns (7). Collectively, the pre-exercise shivering may have impaired endurance capacity through a direct influence on muscle capacity. Beyond colder muscles alone or changes in motor coordination from shivering, another mechanism of impairment may be a competition between the metabolic demands of exercise itself versus that from shivering. Comparing pre-cooling to a sustained 40% of peak shivering versus no pre-cooling, Gagnon et al. (3) reported a reduction in treadmill speed in order to maintain a constant metabolic demand of either light or moderate exercise intensities of 50 or 70% peak oxygen uptake, respectively. In both Gagnon et al. (3) and the current study, the endogenous heat production from exercise appears insufficient to compensate for the large heat debt and shivering throughout subsequent exercise likely contributed to the further decrease in exercise capacity in the two cooling conditions compared to the cold shell condition.

Our previous study reported an approximate 6% reduction in average wattage in 15 km cycling time trial performance with a 0.5°C decrease in core temperature (1), and we aimed to extend this range with a dose response of core cooling. Across a range of core cooling, Bergh and Ekblom (15) reported a $20\%\cdot°C^{-1}$ linear reduction in maximal work time below a threshold esophageal and muscle temperatures of 37.5°C and 38°C, respectively, up to absolute core temperature reductions to ~35°C. Despite our pre-experimental target of a 0.5°C T_{re} difference between the two core

cooling conditions, there were no statistically significantly differences in HD at the end of cooling, nor in core temperature or skin temperature at ISO0%. The lack of HD differences may be due to continued core cooling increasing shivering drive, as $\dot{M}$ progressively increases and is near maximal at a core temperature of ~35°C (36)), while reductions in $\overline{T}_{skin}$ decrease the thermal gradient between the skin and environment reducing convective heat loss (30). Though these individual partitional calorimetry components were non-significant in our calculations, they may still have been sufficient to moderate any heat storage differences and slow down the further accumulation of HD between the two core cooling conditions. The HYPO-1.0°C condition had a total cooling time 38% longer than the HYPO-0.5°C condition, and this longer cooling time resulted in greater total energy expenditure from shivering but no further impairment in endurance capacity. This suggests that the longer cold exposure time did not reduce fuel stores to a level where it impaired exercise capacity. Indeed, moderate shivering appears sustainable over at least 24 hours, aided by a shift in fuel reliance from carbohydrates to lipids (4).

There are several considerations and limitations in the current study limiting the understanding of cold on performance. A TTE was used to measure endurance capacity to determine if a mechanism for impairment was the inability to sustain an absolute submaximal workload in the cold. However, although the signal-to-noise and sensitivity are similar between TTEs and time-trials in trained cyclists (37), TTEs are less ecologically valid, and more variable compared to time-trials in untrained populations (38). Participants performed a total of 3 TTEs in thermoneutral conditions to minimize this variability. Furthermore, data collection was performed over the winter and spring months (November to May), where potential cold acclimation may have influenced the cooling responses. However, this may not have directly influenced TTE, as recently, Jones et al. (10) found that cold acclimation following 7 days of cold-water immersion did not mitigate the

decrements in 20-min self-paced time-trial performance in thermoneutral conditions induced by a reduction in core temperature by ~Δ-1.5°C. We demonstrated an average T_{re} afterdrop of Δ-0.2-0.3°C during the TTEs in the core cooling conditions likely caused from the skeletal muscle pump moving cooler blood from the periphery to the core and warmer blood from the core towards the working muscle (11, 30). The cardiovascular fluid shift is challenging to model (30), and we cannot account if this fluid shift caused an independent effect on TTE performance (e.g., through systemic vasoconstriction, decreased brain temperature). Lastly, this study is limited to males as no females were used in the current study to control against fluctuations in resting core temperature during the menstrual cycle. On average, females have a lower body mass, height, body surface area, and greater body fat percentage compared to males (39) and have a higher core temperature during the luteal phase that may influence cutaneous vasoconstriction, shivering and non-shivering thermogenesis (40) leading to potential sex-related differences in cooling times. However, based on the current study, regardless of cooling time or starting core temperature, core cooling impaired endurance capacity, potentially indicating that these sex-related differences may not influence endurance impairment. However, future research is needed to determine sex-related differences and if the menstrual cycle influences whole-body cooling and endurance capacity in the cold.

In summary, we determined that cooling of the shell reduced mean endurance capacity by ~30% compared to the thermoneutral condition, and core cooling further reduced capacity by and additional ~30-40%. From a practical perspective, these data give insight into the magnitude of impairment from cold that may be useful for modeling work capacity or survival and indicate that individuals should prevent declines in shell or core temperature prior to performing sustained work in the cold. Future research is needed to investigate the high inter-individual variability in both cooling response and exercise tolerance, along with whether these responses are similar in females.

Overall, this will aid in understanding exercise response in the cold and to develop effective countermeasures to improve capacity in the cold.

Variable	Mean ± SD
Age (years)	27 ± 9.8
Mass (kg)	77.9 ± 10.6
Height (cm)	178.6 ± 3.7
Body Surface Area (m^2)	1.93 ± 0.12
Body Fat (%)	13.3 ± 5.0
Peak oxygen consumption ($mL \cdot kg \cdot min^{-1}$)	47.6 ± 6.6
Absolute Peak Power Output (W)	283.0 ± 20.6
Relative Peak Power Output (W/kg)	3.7 ± 0.66

Table 6-1 - Participant characteristics presented as mean ± SD.

Variable	TN	CS	HYPO-0.5°C	HYPO-1.0°C
Ratings of Perceived Exertion (6-20)*				
ISO0%	9.5 (8-11)[d]	10.5 (8.5-11)	12 (9.75-13)	12.5 (11-14.25)[a]
ISO100%	20 (18.5-20)	20 (17-20)	20 (19.25-20)	20 (19-20)
Thermal Comfort (1-4)*				
ISO0%	1 (1-1.25)[cd]	2 (2-3.25)[d]	4 (3-4)[a]	4 (4-4)[ab]
ISO100%	2 (1.75-3)	2 (2-3)	3.5 (2.75-4)	4 (2.75-4)
Thermal Sensation (1-7)*				
ISO0%	4 (3.75-4.5)[bcd]	2 (1-3)[a]	1 (1-1.25)[a]	1 (1-1)[a]
ISO100%	6 (4-6)[cd]	4.5 (3-6)[cd]	1 (1-2.25)[ab]	1 (1-2)[ab]
Motivation (0-4)*				
Pre-TTE	3(2-4)	3.5 (2-4)	2.5 (1-3)	2 (0-4)

Table 6-2 – Perceptual responses collected during the TTE at ISO0% and ISO100% presented as median (Quartile 1 – Quartile 3) for the four experimental conditions. * indicates a significant condition effect ($p < 0.05$). Post-hoc comparisons using Wilcoxon signed rank tests at iso-timepoints can be interpreted as: a significantly different ($p < 0.008$) from TN, b significantly different from CS, c significantly different from HYPO-0.5°C, d significantly different from HYPO-1.0°C.

6.6 List of Figures

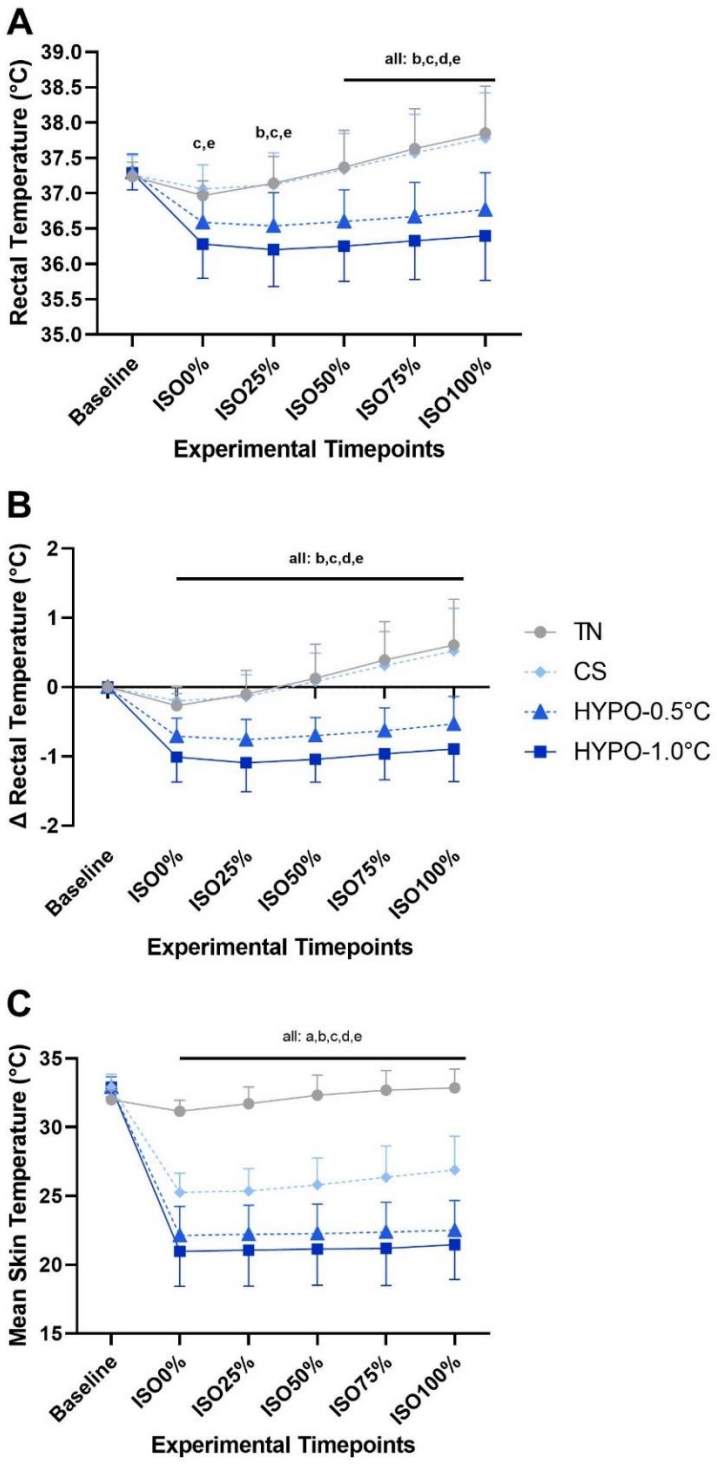
A
Rectal Temperature (°C)
39.0
38.5
38.0
37.5
37.0
36.5
36.0
35.5
35.0
all: b,c,d,e
c,e
b,c,e
Baseline
ISO0%
ISO25%
ISO50%
ISO75%
ISO100%
Experimental Timepoints
B
Δ Rectal Temperature (°C)
2
1
0
-1
-2
all: b,c,d,e
Baseline
ISO0%
ISO25%
ISO50%
ISO75%
ISO100%
Experimental Timepoints
TN
CS
HYPO-0.5°C
HYPO-1.0°C
C
Mean Skin Temperature (°C)
35
30
25
20
15
all: a,b,c,d,e
Baseline
ISO0%
ISO25%
ISO50%
ISO75%
ISO100%
Experimental Timepoints

Figure 6-1

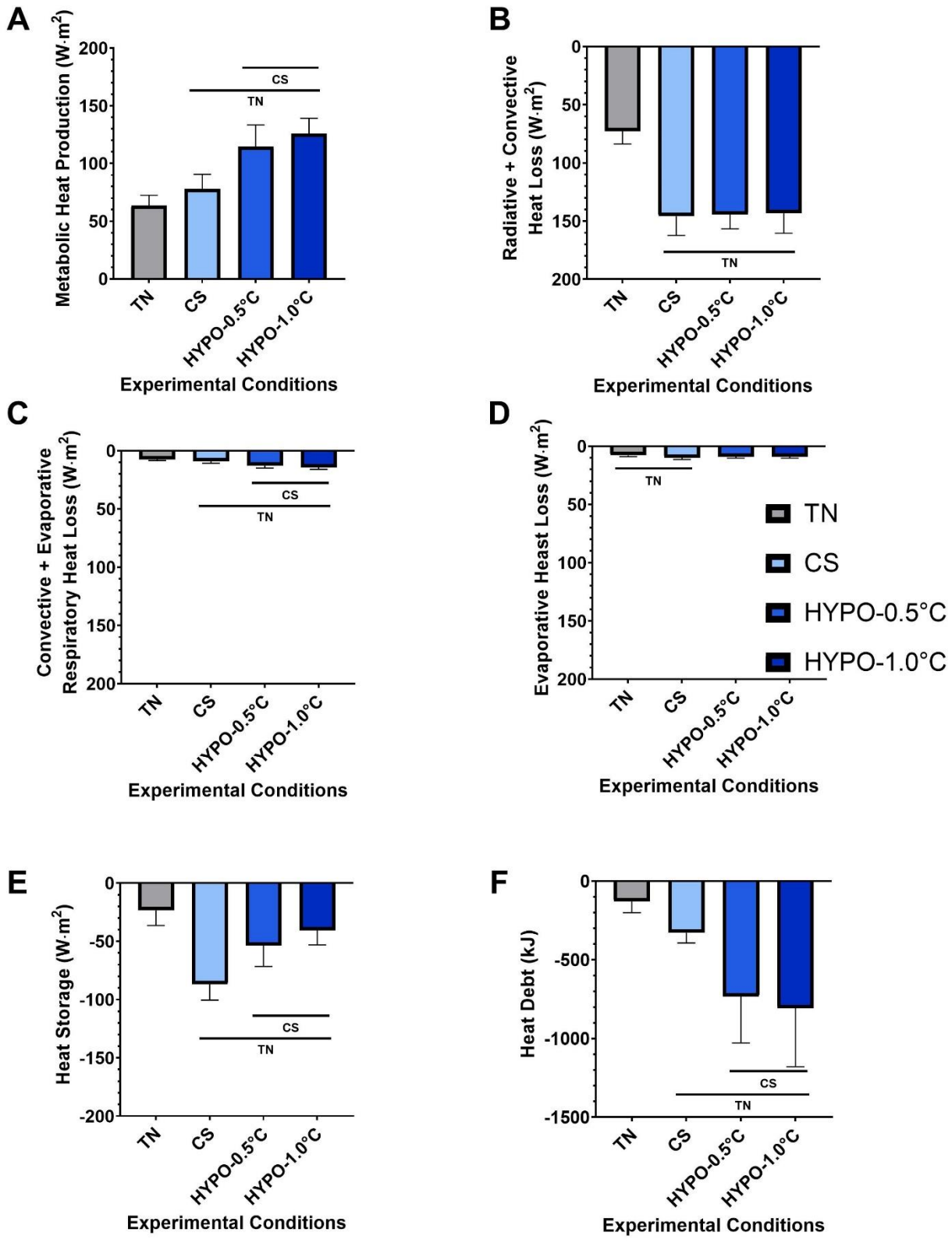
A
Metabolic Heat Production (W·m²)
200
150
100
50
0
CS
TN
TN
CS
HYPO-0.5°C
HYPO-1.0°C
Experimental Conditions
B
Radiative + Convective Heat Loss (W·m²)
0
50
100
150
200
TN
TN
CS
HYPO-0.5°C
HYPO-1.0°C
Experimental Conditions
C
Convective + Evaporative Respiratory Heat Loss (W·m²)
0
50
100
150
200
CS
TN
TN
CS
HYPO-0.5°C
HYPO-1.0°C
Experimental Conditions
D
Evaporative Heast Loss (W·m²)
0
50
100
150
200
TN
TN
CS
HYPO-0.5°C
HYPO-1.0°C
Experimental Conditions
E
Heat Storage (W·m²)
0
-50
-100
-150
-200
CS
TN
TN
CS
HYPO-0.5°C
HYPO-1.0°C
Experimental Conditions
F
Heat Debt (kJ)
0
-500
-1000
-1500
CS
TN
TN
CS
HYPO-0.5°C
HYPO-1.0°C
Experimental Conditions

Figure 6-2

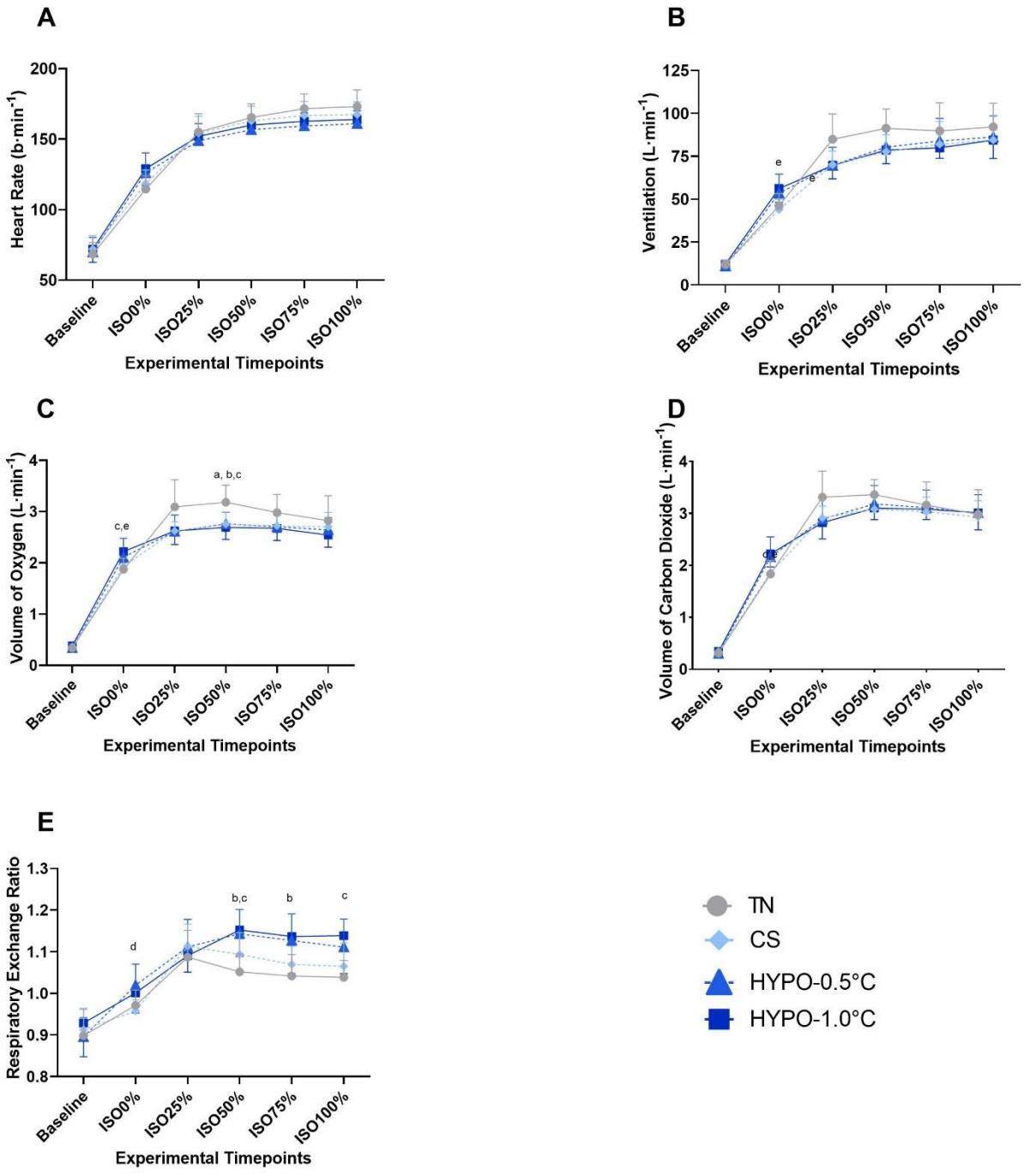
A
Heart Rate (b·min-1)
200
150
100
50
Baseline
ISO0%
ISO25%
ISO50%
ISO75%
ISO100%
Experimental Timepoints
B
Ventilation (L·min-1)
125
100
75
50
25
0
e
e
Baseline
ISO0%
ISO25%
ISO50%
ISO75%
ISO100%
Experimental Timepoints
C
Volume of Oxygen (L·min-1)
4
3
2
1
0
a, b,c
c,e
Baseline
ISO0%
ISO25%
ISO50%
ISO75%
ISO100%
Experimental Timepoints
D
Volume of Carbon Dioxide (L·min-1)
4
3
2
1
0
Baseline
ISO0%
ISO25%
ISO50%
ISO75%
ISO100%
Experimental Timepoints
E
Respiratory Exchange Ratio
1.3
1.2
1.1
1.0
0.9
0.8
d
b,c
b
c
Baseline
ISO0%
ISO25%
ISO50%
ISO75%
ISO100%
Experimental Timepoints
TN
CS
HYPO-0.5°C
HYPO-1.0°C

Figure 6-3

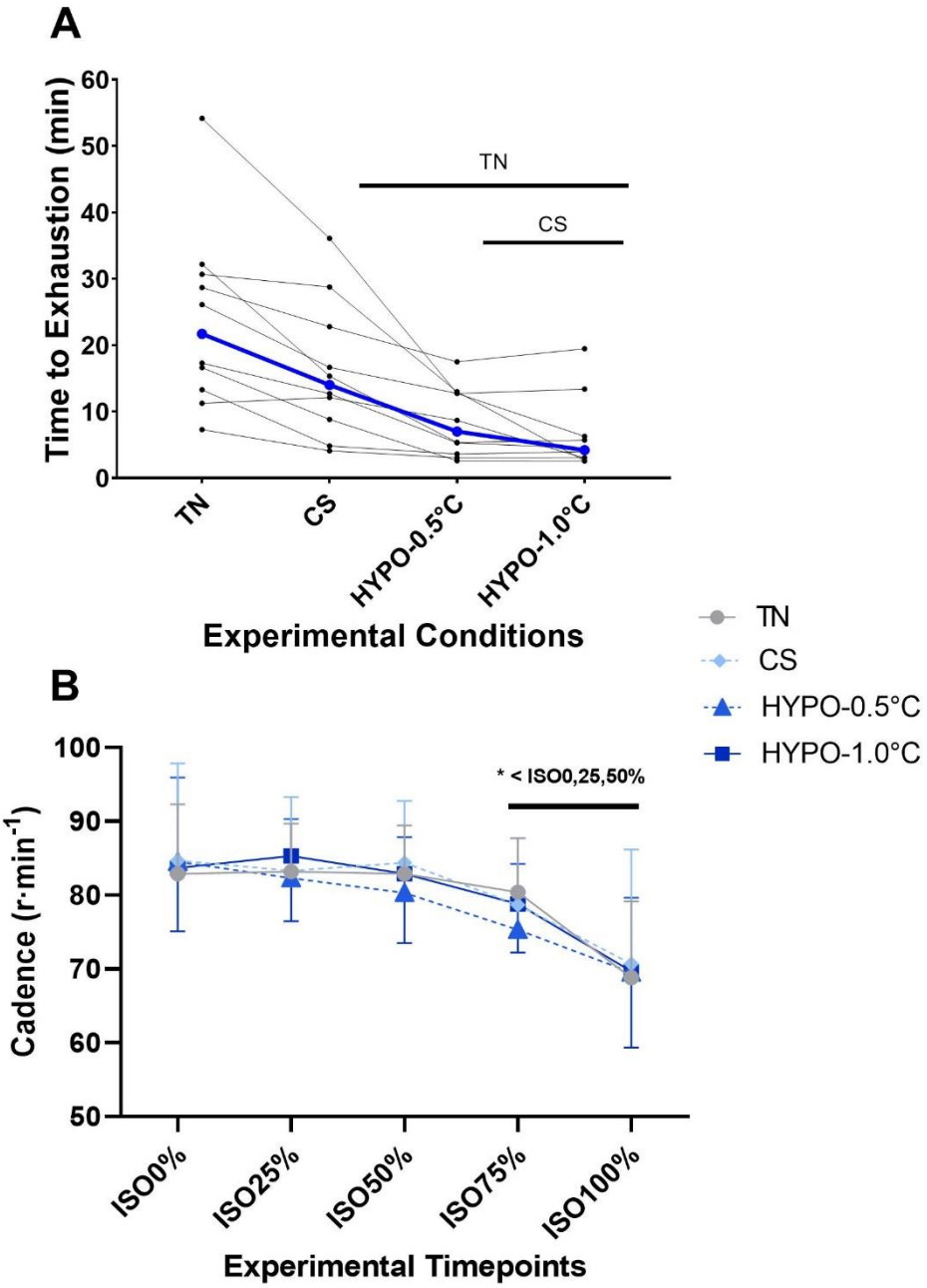
A
Time to Exhaustion (min)
60
50
40
30
20
10
0
TN
CS
TN
CS
HYPO-0.5°C
HYPO-1.0°C
Experimental Conditions
B
Cadence (r·min-1)
100
90
80
70
60
50
* < ISO0,25,50%
ISO0%
ISO25%
ISO50%
ISO75%
ISO100%
Experimental Timepoints
TN
CS
HYPO-0.5°C
HYPO-1.0°C

Figure 6-4

6.7 References

1. **Ferguson SAH**, **Eves ND**, **Roy BD**, **Hodges GJ**, **Cheung SS**. Effects of mild whole body hypothermia on self-paced exercise performance. *Journal of Applied Physiology* 125: 479–485, 2018. doi: 10.1152/japplphysiol.01134.2017.

2. **Hodges GJ**, **Ferguson SAH**, **Cheung SS**. Glabrous and non-glabrous vascular responses to mild hypothermia. *Microvascular Research* 121: 82–86, 2019. doi: 10.1016/j.mvr.2018.10.006.

3. **Gagnon DD**, **Rintamäki H**, **Gagnon SS**, **Oksa J**, **Porvari K**, **Cheung SS**, **Herzig K-H**, **Kyröläinen H**. Fuel selection during short-term submaximal treadmill exercise in the cold is not affected by pre-exercise low-intensity shivering. *Applied Physiology, Nutrition, and Metabolism* 39: 282–291, 2014. doi: 10.1139/apnm-2013-0061.

4. **Haman F**, **Mantha OL**, **Cheung SS**, **DuCharme MB**, **Taber M**, **Blondin DP**, **McGarr GW**, **Hartley GL**, **Hynes Z**, **Basset FA**. Oxidative fuel selection and shivering thermogenesis during a 12- and 24-h cold-survival simulation. *Journal of Applied Physiology* 120: 640–648, 2016. doi: 10.1152/japplphysiol.00540.2015.

5. **Oksa J**, **Rintamäki H**, **Rissanen S**. Muscle performance and electromyogram activity of the lower leg muscles with different levels of cold exposure. *Eur J Appl Physiol Occup Physiol* 75: 484–490, 1997. doi: 10.1007/s004210050193.

6. **Oksa J**, **Ducharme MB**, **Rintamäki H**. Combined effect of repetitive work and cold on muscle function and fatigue. *Journal of Applied Physiology* 92: 354–361, 2002.

7. **Mallette MM**, **Cheung SS**, **Kumar RI**, **Hodges GJ**, **Holmes MWR**, **Gabriel DA**. The effects of local forearm heating and cooling on motor unit properties during submaximal contractions. *Experimental Physiology* 106: 200–211, 2021. doi: https://doi.org/10.1113/EP088256.

8. **Galloway SD**, **Maughan RJ**. Effects of ambient temperature on the capacity to perform prolonged cycle exercise in man. *Med Sci Sports Exerc* 29: 1240–1249, 1997.

9. **Parkin JM**, **Carey MF**, **Zhao S**, **Febbraio MA**. Effect of ambient temperature on human skeletal muscle metabolism during fatiguing submaximal exercise. *Journal of Applied Physiology* 86: 902–908, 1999. doi: 10.1152/jappl.1999.86.3.902.

10. **Jones DM**, **Roelands B**, **Bailey SP**, **Buono MJ**, **Meeusen R**. Impairment of exercise performance following cold water immersion is not attenuated after 7 days of cold acclimation. *Eur J Appl Physiol* 118: 1189–1197, 2018. doi: 10.1007/s00421-018-3848-5.

11. **Castellani JW**, **Tipton MJ**. Cold stress effects on exposure tolerance and exercise performance. *Compr Physiol* 6: 443–469, 2016. doi: 10.1002/cphy.c140081.

12. **Cowper G**, **Barwood M**, **Goodall S**. Improved 2000-m Rowing Performance in a Cool Environment With an External Heating Garment. *International Journal of Sports Physiology and Performance* 16: 103–109, 2020. doi: 10.1123/ijspp.2019-0923.

13. **Hodges GJ**, **Ferguson SAH**, **Cheung SS**. Cardiac autonomic function during hypothermia and its measurement repeatability. *Applied Physiology, Nutrition, and Metabolism* 44: 31–36, 2019. doi: 10.1139/apnm-2018-0248.

14. **Bergh U**, **Ekblom B**. Physical performance and peak aerobic power at different body temperatures. *J Appl Physiol Respir Environ Exerc Physiol* 46: 885–889, 1979.

15. **Cramer MN**, **Jay O**. Selecting the correct exercise intensity for unbiased comparisons of thermoregulatory responses between groups of different mass and surface area. *Journal of Applied Physiology* 116: 1123–1132, 2014. doi: 10.1152/japplphysiol.01312.2013.

16. **Cramer MN**, **Jay O**. Biophysical aspects of human thermoregulation during heat stress. *Autonomic Neuroscience* 196: 3–13, 2016. doi: 10.1016/j.autneu.2016.03.001.

17. **Vallerand AL**, **Savourey G**, **Bittel JH**. Determination of heat debt in the cold: partitional calorimetry vs. conventional methods. *Journal of Applied Physiology* 72: 1380–1385, 1992. doi: 10.1152/jappl.1992.72.4.1380.

18. **Bittel JH**. Heat debt as an index for cold adaptation in men. *Journal of Applied Physiology* 62: 1627–1634, 1987. doi: 10.1152/jappl.1987.62.4.1627.

19. **Tikuisis P**, **McCracken DH**, **Radomski MW**. Heat debt during cold air exposure before and after cold water immersions. *Journal of Applied Physiology* 71: 60–68, 1991. doi: 10.1152/jappl.1991.71.1.60.

20. **Savourey G**, **Bittel J**. Thermoregulatory changes in the cold induced by physical training in humans. *European Journal of Applied Physiology* 78: 379–384, 1998. doi: 10.1007/s004210050434.

21. **Du Bois D**, **Du Bois EF**. A formula to estimate the approximate surface area if height and weight be known. 1916. *Nutrition* 5: 303–311; discussion 312-313, 1989.

22. **Jackson AS**, **Pollock ML**. Generalized equations for predicting body density of men. *Br J Nutr* 40: 497–504, 1978.

23. **Matthews G**, **Campbell SE**, **Falconer S**. Assessment of Motivational States in Performance Environments. *Proceedings of the Human Factors and Ergonomics Society Annual Meeting* 45: 906–910, 2001. doi: 10.1177/154193120104501302.

24. **Gagge AP**, **Stolwijk JAJ**, **Hardy JD**. Comfort and thermal sensations and associated physiological responses at various ambient temperatures. *Environmental Research* 1: 1–20, 1967. doi: 10.1016/0013-9351(67)90002-3.

25. **Borg GA**. Psychophysical bases of perceived exertion. *Med Sci Sports Exerc* 14: 377–381, 1982.

26. **Hardy JD**, **Du Bois, EF**, **Soderstrom, GF**. The Technic of Measuring of Radiation and convection. *J Nutr* : 461–475, 1938. doi: 10.1093/jn/15.5. 461.

27. **Cramer MN**, **Jay O**. Partitional calorimetry. *Journal of Applied Physiology* 126: 267–277, 2019. doi: 10.1152/japplphysiol.00191.2018.

28. **Haman F**, **Péronnet F**, **Kenny GP**, **Massicotte D**, **Lavoie C**, **Weber J-M**. Partitioning oxidative fuels during cold exposure in humans: muscle glycogen becomes dominant as shivering intensifies: Fuel selection and shivering intensity. *The Journal of Physiology* 566: 247–256, 2005. doi: 10.1113/jphysiol.2005.086272.

29. **Gibbons TD**, **Tymko MM**, **Thomas KN**, **Wilson LC**, **Stembridge M**, **Caldwell HG**, **Howe CA**, **Hoiland RL**, **Akerman AP**, **Dawkins TG**, **Patrician A**, **Coombs GB**, **Gasho C**, **Stacey BS**, **Ainslie PN**, **Cotter JD**. Global REACH 2018: The influence of acute and chronic hypoxia on cerebral haemodynamics and related functional outcomes during cold and heat stress. *The Journal of Physiology* 598: 265–284, 2020. doi: 10.1113/JP278917.

30. **Xu X**, **Tikuisis P**. Thermoregulatory Modeling for Cold Stress. *Comprehensive Physiology* 4: 25, 2014.

31. **Gagge AP**, **Gonzalez RR**. Mechanisms of Heat Exchange: Biophysics and Physiology. In: *Comprehensive Physiology*, edited by Terjung R. John Wiley & Sons, Inc.

32. **Ramanathan NL**. A new weighting system for mean surface temperature of the human body. *J Appl Physiol* 19: 531–533, 1964.

33. **Greaney JL**, **Alexander LM**, **Kenney WL**. Sympathetic control of reflex cutaneous vasoconstriction in human aging. *Journal of Applied Physiology* 119: 771–782, 2015. doi: 10.1152/japplphysiol.00527.2015.

34. **Schniepp J**, **Campbell TS**, **Powell KL**, **Pincivero DM**. The Effects of Cold-Water Immersion on Power Output and Heart Rate in Elite Cyclists: *Journal of Strength and Conditioning Research* 16: 561–566, 2002. doi: 10.1519/00124278-200211000-00012.

35. **Haman F**, **Blondin DP**. Shivering thermogenesis in humans: Origin, contribution and metabolic requirement. *Temperature* 4: 217–226, 2017. doi: 10.1080/23328940.2017.1328999.

36. **Eyolfson DA**, **Tikuisis P**, **Xu X**, **Weseen G**, **Giesbrecht GG**. Measurement and prediction of peak shivering intensity in humans. *European Journal of Applied Physiology* 84: 100–106, 2001. doi: 10.1007/s004210000329.

37. **Amann M**, **Hopkins WG**, **Marcora SM**. Similar Sensitivity of Time to Exhaustion and Time-Trial Time to Changes in Endurance: *Medicine & Science in Sports & Exercise* 40: 574–578, 2008. doi: 10.1249/MSS.0b013e31815e728f.

38. **McLellan TM**, **Cheung SS**, **Jacobs I**. Variability of time to exhaustion during submaximal exercise. *Canadian Journal of Applied Physiology* 20: 39–51, 1995.

39. **Wickham KA**, **Wallace PJ**, **Cheung SS**. Sex differences in the physiological adaptations to heat acclimation: a state-of-the-art review. *Eur J Appl Physiol* 121: 353–367, 2021. doi: 10.1007/s00421-020-04550-y.

40. **Greenfield AM**, **Charkoudian N**, **Alba BK**. Influences of ovarian hormones on physiological responses to cold in women. *Temperature* 9: 23–45, 2021. doi: 10.1080/23328940.2021.1953688.

7 - General Discussion

7.1 Skin Versus Core Temperature on Cognitive Function

The overarching theme of this thesis was to isolate the separate and combined effects of skin and core temperature on cognitive function in hot and cold environments. Collectively, changes in skin temperature (Range: Δ-6 to +4.5°C), with or without changes in core temperature, and the manipulation of core temperature (Range: Δ-0.8 to +1.5°C) all failed to significantly impair cognitive function performance in hot or cold environments. Changes in skin temperature have previously been proposed to affect cognitive function by increasing thermal discomfort leading to a decrease in arousal, as well as increasing distraction and increasing the overall mental workload due to multitasking between focusing on the task at hand and monitoring thermal strain (1–3). We attempted to test the effects of thermal discomfort caused by changes in skin temperature in three ways. The first two approaches were to simply increase thermal discomfort by increasing skin temperature to ~37.5°C with NC-HS (Chapter 4) or decreasing skin temperature with CS (Chapter 5, ~27°C), but neither manipulation demonstrated any significant changes in the cognitive tasks tested. Furthermore, we attempted to isolate the role of thermal discomfort caused by hot skin versus hyperthermia in the HC-CS condition in Chapter 4, which despite leading to improved thermal comfort (HC-HS: 4 to HC-CS: 1-2), and reduced physiological strain (e.g., ~-3.6°C in $\overline{T}_{skin}$, ~-35 b·min^{-1} in heart rate, ~-3 L·min^{-1} in ventilation compared to HC-HS) failed to elicit impairments in cognitive function. During the piloting phase of Chapter 5, there were attempts to warm skin temperature following core cooling of Δ-1.0°C using a liquid cooling garment circulating warm water, however, this led to significant after drops in core temperature that increased the risk of clinical hypothermia (≤ 35°C). For safety and ethical reasons, we removed this condition. Therefore, we cannot fully isolate the effects of skin versus core temperature in cold

environments. However, the collective results indicate that the independent manipulation of skin temperature did not significantly impair cognitive function in either hot or cold environments.

Overall, cognitive function was maintained with both moderate hyperthermia (Δ+1.5°C in T_{core}) and mild hypothermia (up to Δ-0.7 to -0.8°C in T_{core}). Our collective findings of neither a slowing nor an increase in errors performed with any of the executive attention tasks used supports the general confusion as to whether changes in T_{core} under thermal stress impair cognitive function. One explanation is that the level of thermal stress was not sufficient to impair cognitive function. However, in Chapter 4, participants demonstrated a high thermal strain (T_{core} = 38.7°C), high cardiovascular strain (~125-135 b·min^{-1}), a hyperventilatory response, as well as high perceptual strain. While in Chapter 5; participants performed two trials of different levels of core cooling, with high amounts of shivering, perceptual strain, and a hyperventilatory response (this was not included in Chapter 5; however, the results were: C-0.3°C: 19.0 L·min^{-1} and C-0.8°C: 21.4 L·min^{-1} compared to TN: 12.9 L·min^{-1}). This thermal strain still may not be sufficient as recent studies in the heat demonstrate that passive or active hyperthermia to Δ+1.3-2.0°C in core temperature did not lead to decrements in errors for executive function, working memory, or visual perception performance (4–7). Meanwhile, previous work from our lab demonstrated that neither 24 hours of cold air exposure (10°C) sustaining a mild hypothermia of Δ-0.5°C (8), nor cold water immersion to reduce T_{core} by as much as Δ-1.0°C did not impair executive function and attention (9, 10). Collectively, this indicates that a thermal strain of up to Δ-0.8°C to +1.5°C may not impair cognitive function under thermal stress.

There are potentially confounding variables in learning effects, task complexity, and cognitive capacity in our studies. In both studies, participants were familiarized with the cognitive tasks a total of 3 times in familiarization trials to stabilize performance and task familiarity. To the

best of our knowledge, there are no studies directly testing the learning effect on cognitive performance in hot and cold environments. However, high levels of expertise may offset impairment in cognitive function as a military simulation of vigilance did not report any decrements over nearly 3 h of cold exposure (0°C air with 5°C water circulating through a water-perfused suit) compared to thermoneutral (22°C air) in trained soldiers (11). Potentially, initial familiarization led to a ceiling effect or plateau of performance leading to no impairment in cognitive function under thermal strain. Furthermore, the task complexity of the tasks may not have been sufficient to impair performance. For example, Shurtleff et al. (12), found significant impairments to 60-min exposure to cold (4˚C) compared to thermoneutral (22˚C) air on a delayed match-to-sample test, which consists of a presentation of an 8 x 8 array (64 cell matrix) composed of 32 red and green squares for 4-s, followed by a delay of 2, 8, and 16-s after 30 minutes of exposure. Performance was maintained throughout the cold exposure for the 2-s and 8-s intervals (~80% accuracy), but significantly decreased with the 16-s delay intervals (~70% accuracy in thermoneutral versus ~55% accuracy in cold) (12). These results indicated that the more difficult version task was impaired more with thermal stress, indicating task complexity may influence cognitive functions under thermal stress. In Chapter 5, we used a test battery that is a valid measure of executive attention (13, 14) and used the item working memory tasks with different levels of difficultly (2-6 items) to potentially tease out the effects of task capacity and mental workload where we found no impairments in performance. Lastly, although performance was maintained, it is unknown if participants required additional mental resources or effort to complete the task under thermal stress as the same level as thermoneutral environments (15, 16). If participants required additional mental resources to maintain tasks performance, potentially participants could have less overall capacity or fatigue quicker under thermal stress. This may have significant practical

applications as it could indicate that individuals are able to perform mental work under thermal stress, but whether they are able to sustain the same mental workload over time is unknown. Previous research has demonstrated that inducing mental fatigue prior to exercise (17–19) and marksmanship tasks (20) impairs performance in thermoneutral and hot environments. Furthermore, there is greater physical fatigue in cold air while performing repetitive low intensity work (~10% of maximal voluntary contraction wrist flexion) (21), which may extend towards cognitive function. Collectively, fatigue may occur more rapidly under thermal stress, however future research is needed to determine the effects of environmental stress on mental fatigue.

7.2 The Effects of Dopamine on Cognitive Function Under Environmental Stress

The acute 20 mg dose of MPH used in this study was the same dose that improved cycling time-trial performance by 16% in the heat (30˚C) while finishing the trial with a higher terminating core temperature (~0.3˚C) without any changes in perceived exertion or thermal discomfort (22). Therefore, we hypothesized that the ingestion of MPH (a dopamine re-uptake inhibitor) would prevent impairments in cognitive function under thermal strain potentially through an alteration in thermal perception or from increased arousal from a sympatho-adrenal response. We demonstrated sympatho-adrenal stimulation with increased heart rates (~5-15 $b \cdot min^{-1}$) and systolic blood pressure (~4-8 mmHg) with MPH throughout the experimental protocol which is in line with previous work in thermoneutral and hot environments (22–24), however we saw no difference in thermal perception. The differences in lack of thermal perception changes may be due to our study design using clamped thermal conditions compared to Roelands et al (22), who used self-paced exercise design that allowed for higher workloads and behavioral thermoregulation to regulate skin and core temperature and thermal perception. Potentially, MPH may be advantageous to extend thermal tolerance to uncomfortable stimuli as opposed to manipulation of thermal discomfort. For

example, rat models demonstrate that use of a dual dopamine/norepinephrine reuptake inhibitor (bupropion) led to significantly longer running times in the heat (30˚C) leading to higher core and brain temperatures that were correlated with increases in dopamine and norepinephrine in the brain (25). Overall, as cognitive function was not impaired, we cannot fully rule out if MPH can prevent cognitive impairments with passive hyperthermia; however, MPH was not different than the placebo on affecting cognitive function under thermal strain.

Currently it is unknown what the effects of MPH on cognitive performance in the cold are, as few studies that have attempted to manipulate neurotransmitters to influence cognitive performance during acute cold stress or mild hypothermia. Mahoney et al. (26) tested the effects of tyrosine supplementation on psychomotor processing, short- and long-term working memory (same delayed matched to sample test as above), and vigilance in room air following repeated 90-minute immersions in cold water (~10˚C) that reduced core temperature from 37˚C to 35˚C, with a rewarming period to baseline between immersions. Results found impairments after hypothermia for vigilance and psychomotor processing with no performance effects of tyrosine. Additionally, there were fewer correct responses in the placebo group compared to the tyrosine group on the 16-s delayed match to sample test. This study was followed that of O'Brien et al. (26), who used the same cooling protocol and tested the effects of tyrosine supplementation on psychomotor processing, short- and long-term working memory (same delayed matched to sample test as above), logical reasoning and vigilance, where the difference is that cognitive tests were performed in an environmental chamber set at 19˚C. Repeated hypothermia did not reduce performance for psychomotor processing, logical reasoning or vigilance. However, similar results were found with fewer correct responses in the placebo group compared to tyrosine group on the 16-s delayed match to sample test. These results indicate that tyrosine *only* appears to be effective in countering the

decrements in 16-s delayed match to sample performance, but on no other cognitive domains (i.e., executive function, short-term working memory, psychomotor processing, vigilance). The mechanism for this response is unclear, however these findings may be similar to those for exercise and cognitive performance in hot environments, where increasing dopamine levels through earlier precursors such as tyrosine in the dopamine pathway are not as beneficial for performance (27, 28). Based on the results of Chapter 4, it is unlikely that the acute use of MPH would have an enhancement on cognitive function using the design and cognitive tests in Chapter 5, as we demonstrated no impairment in cognitive performance. One potential future direction is testing the effects of MPH on endurance capacity in the cold, as MPH improved cycling time-trial performance by ~16% (22) and bupropion (a dual dopamine and norepinephrine reuptake inhibitor) improved performance by ~9% (29) in hot but not thermoneutral environments. This may indicate the role of dopamine on physical performance during thermal stress, as opposed to a direct effect on performance *per se*. As there were large decrements in endurance capacity with CS and mild hypothermia, MPH may work to reduce the decrements in capacity by improving the ability to maintain power output, improve thermal tolerance, or potentially motivation. A potential confounding variable is the peripheral effect of stimulants on cooling responses, as a mixture of ephedrine (1 mg/kg) and caffeine (2.5 mg/kg) led to less of a reduction in core temperature (Δ-0.4°C) compared to a placebo (Δ-0.7°C), through greater shivering thermogenesis over 180 minutes of passive cold exposure (10°C) (30). This would ultimately decrease the overall heat debt accumulated, creating potential differences in cold strain prior to performing exercise. It is unknown if a stimulant such as MPH can have an influence on thermoregulation in the cold, but the indexing of cold strain through heat debt may provide a potential mechanism for changes in

performance. A future avenue to explore is the effect of MPH on physical performance in the cold, with and without mild hypothermia.

7.3 Changes in Cerebral Blood Flow and Cognition

The cerebral vasculature is highly sensitive to changes in arterial CO_2, as hypercapnia (elevated CO_2) produces smooth muscle relaxation, vessel dilation and increased blood flow, while hypocapnia (reduced CO_2) increases cerebrovascular resistance and decreases cerebral blood flow (CBF) (31, 32). Both hyperthermia and hypothermia can lead to decreases in arterial CO_2, as both states lead to a hyperventilatory hypocapnic response ultimately decreasing cerebral blood flow (33–36). In Chapter 4, we demonstrated that passive hyperthermia led to a significant increase in ventilation with a significant decrease by ~7 mmHg in $P_{et}CO_2$. Furthermore, we found that heating and cooling of the skin may influence cerebrovascular function, as it was demonstrated that passively heating whole-body $\overline{T}_{skin}$ (~37°C) temperature without changes in T_{core} led to a decrease in $P_{et}CO_2$ by ~2 mmHg, while cooling $\overline{T}_{skin}$ when T_{core} was elevated (Δ+1.5°C) decreased hyperthermia-induced hyperventilation to thermoneutral levels and increased $P_{et}CO_2$ ~2-3 mmHg. A potential mechanism influencing cognitive function during heat stress may be due to changes in neurovascular function, as the human brain requires rich vascularization and an efficient regulation of blood flow to match its metabolism – also known as neurovascular coupling – without excessive perfusion (37). Therefore, we followed up Chapter 4 with an identical design manipulating core and skin temperature with an identical CTB, however we clamped $P_{et}CO_2$ (isocapnia) to baseline levels using an end-tidal forcing system compared to no CO_2 manipulation (poikilocapnia) (38). We found that passive hyperthermia of +1.5°C led to a hyperventilatory hypocapnia (~Δ -8 mmHg in $P_{et}CO_2$) and a ~26% decrease in middle cerebral artery velocity (an index of cerebral blood flow) and led to faster reaction times for psychomotor processing and the set-shifting task

(executive function) with no speed-accuracy trade-off (38). Furthermore, clamping $P_{et}CO_2$ to baseline levels led to a higher middle cerebral artery velocity compared to poikilocapnia at HC-HS, though it was still reduced 18% relative to BASE (38). When compared to poikilocapnia, the isocapnic cognitive performance results did not appear to be different, thereby suggesting that $P_{et}CO_2$ does not appear to influence the cognitive functions examined (executive function, working memory, and psychomotor processing) under heat stress. Recently it has been demonstrated that cold-water immersion to decrease T_{core} by -1.0°C led to decreases in cerebral blood flow (36). In Chapter 5, we did not quantify cerebral blood flow or $P_{et}CO_2$, but given that ventilation was higher in C-0.3°C (19.0 $L \cdot min^{-1}$) and C-0.8°C (21.4 $L \cdot min^{-1}$) compared to the HC-HS (16.6 $L \cdot min^{-1}$) condition in Chapter 4, a decrease in cerebral blood flow is likely. Currently it is unknown if the clamping of $P_{et}CO_2$ during passive mild hypothermia influences cognitive function. Given the results of Chapter 5 demonstrating no impairment in the cognitive functions tested, it is likely a similar non-effect would occur to clamping of $P_{et}CO_2$ during core cooling up to Δ-0.8°C in T_{core}.

7.4 Cognitive Test Batteries Under Environmental Stress

One of the key limitations in this research program (and the study of cognition and environmental stress in general) is whether or not the cognitive test batteries used are sensitive to detect changes in cognitive function under thermal stress. The first limitation that needs to be mentioned, is the cognitive tasks used were not designed to be environmental stress specific cognitive-based tasks, rather they are commonly used tasks to assess cognitive functions within the executive attention network. In Chapter 4, we used Cogstate Software and used the Groton maze learning task and set-shifting task (executive function), 2-back task (working memory), and detection task (psychomotor processing), primarily to test tasks within the executive attention network. However, our lab has tested this battery using exercise-induced hyperthermia to Δ+1.5°C

degrees in core temperature (5), passive hyperthermia to Δ+1.5°C degrees (6, 38), and 24 hours of cold air exposure leading to decrease in core temperature by ~Δ-0.5°C (8) without cognitive impairment, indicating that task performance within this cognitive test battery does not appear to be impaired with core temperature ranges of Δ-0.5 to + 1.5°C in core temperature. In Chapter 5, we used the DalCAB which is a validated assessment tool to measure executive attention (28, 33) and is susceptible to impairment in learning with sleep deprivation (34). However, this battery was not designed to be sensitive to thermal stress and we showed no impairment in task performance compared to thermoneutral conditions with core temperature reductions of Δ-0.8°C. Ultimately, more research is needed to determine what cognitive functions are impaired with thermal stress, what is the threshold for impairments (i.e., skin versus core temperature), and what interventions are able to counter these decrements (i.e., interventions manipulating core temperature such as cooling or acclimation, interventions manipulating psychological function such as psychological skills training or head/neck cooling). The research designs used in Chapters 4 and 5 hopefully provide a model in which skin and core temperature can be isolated and combined in hot and cold environments to tease out the thresholds for impairment.

7.5 Models of Cognition and Environmental Stress

In Chapter 2, multiple models for how environmental stress could influence cognitive function under environmental stress were provided including: distraction and arousal theory, individual zone of optimal functioning (IZOF), and the maximum adaptability model (MAM). The research designs used in Chapters 4 and 5 were used to separate the effects of thermal discomfort caused by changes in skin/shell temperature (causing distraction or decreased resources available for the task) to incorporate whether distraction and arousal theory played a role in impairments in

cognitive function under environmental stress. In Chapter 4, the NC-HS condition increased skin temperature (but not core) to increase thermal discomfort and the sensation of feeling 'warm/hot' and showed no impairment in performance. Additionally, the HC-CS, which lowered skin temperature (with minimal changes in core) leading to improved thermal comfort and sensations of 'neutral/cool' as well as reduced physiological strain (lower heart rates, ventilation) did not demonstrate an improvement in cognitive performance. Lastly, in Chapter 5, the CS condition reduced skin temperature and improved thermal comfort and sensations of 'cool/cold' but did not impair performance. Collectively, these results would indicate that the model of distraction and arousal theory was invalid for explaining the results on the cognitive functions tested (executive function, working memory, psychomotor processing) within skin temperature ranges of Δ-6 to +4.5°C and high levels of thermal discomfort. We are limited by not having any measures of arousal, however we are confident that our protocol influenced arousal as previous studies have demonstrated that increasing skin temperature to ~36.0°C (lower than ~37C in NC-HS condition) significantly increases negative affect (indicating a decrease in arousal) (39). Additionally, as we did not demonstrate an inverted 'U' response or impairments in cognitive function performance, we were unable to test if an individual zone of optimal function occurred for participants because technically all performance could be considered optimal as it was not different from baseline or thermoneutral conditions. Furthermore, if there were an optimal zone of functioning, the research designs used in Chapters 4 and 5 would not be sufficient to pinpoint optimal performance as the temperature manipulations were large.

The MAM model extends the arousal theory that includes both psychological and physiological stress and how they may influence performance under environmental stress (Figure 2-3). The MAM model provides a normative zone where performance is near optimal because

cognitive adjustments and task demands are easily accomplished, where performance degrades with extreme ends of stressors from hyperstress (e.g., hyperthermia, hypothermia) to hypostress (e.g., boredom) (40). In the normative zone, minor levels of stress inputs are readily adapted to, and do not disturb steady-state functioning or reflect any changes in behavior or cognitive performance (41). However, as the environmental stress becomes more adverse or the complexity of the task increases, arousal levels need to increase or cognitive resources need to efficiently shift to maintain optimal cognitive performance (40). In the MAM model, there exists a maximal zone of adaptability where improvements in psychological function (i.e., psychological skills training, pharmacological interventions) or physiological function (i.e., acclimation) can occur to maintain task performance, however, eventually the further increases in the level of stress will extend past this zone and deplete neural resources, which will cause decrements in cognitive performance (40, 41). Based on the results of Chapter 4 and Chapter 5, our results would indicate that for the executive function, working memory, and psychomotor processing, the maintenance of task performance extends well beyond the proposed 'normative zone' and 'comfort zones' based on the significant range of perturbations for both physiological strain (core temperature changes of Δ-0.8 to +1.5°C) and psychological strain (i.e., very uncomfortable on thermal comfort). These results would indicate that the MAM could be adjusted to incorporate a larger zone of optimal functioning for cognitive function. Future research is needed to determine the thresholds for where cognitive function impairment occurs for these executive attention-based tasks, in order to determine how to adjust the physiological and psychological zones of maximal adaptability. The MAM was a better fit to describe the endurance capacity responses (see below) in Chapter 6. Endurance capacity was impaired in the cold with perturbations outside of the normative zone as performance degraded with a relatively short cold exposure in the CS condition. Furthermore, as

the cold strain increased in the two core cooling conditions, there was greater impairment in endurance capacity. It is currently unknown how psychological factors or physiological factors could be used to determine the ranges of maximal adaptability. Based on the current results, future research is needed to determine how to counter the declines in endurance capacity and the logical first step would be to start with extending the physiological zone of maximal adaptability as endurance capacity is impaired prior to cognitive function. These interventions can include manipulation of clothing sets, warm up protocols prior to cold exposure, work-rest ratios, or reducing the exercise workload to extend endurance capacity.

7.6 Endurance Capacity in the Cold

The primary finding from Chapter 6 was that cold stress significantly impaired endurance capacity in the cold leading to premature fatigue relative the thermoneutral conditions. Cold air exposure for ~30 minutes was sufficient to decrease TTE by ~32%, however, this response was variable between participants (range: -63 to +7% change compared to TN). Whereas core cooling significantly impaired TTE in both HYPO-0.5°C (~-61%) and HYPO-1.0°C (~-71%) compared to TN. Both core cooling conditions were significantly impaired compared to CS. There was significantly greater cold strain in the two core cooling conditions as evidence by lower skin temperature, greater energy expenditure and heat debt prior to exercise, and well as higher levels of perceived exertion and lower levels of comfort. The lack of difference between the two core cooling conditions may have been because the level of cold strain was not significantly different between the two conditions as indexed HD prior to commencing the TTE and no statistical differences in thermal variables (T_{re}, $\overline{T}_{skin}$) throughout the TTE. Potentially the increased metabolic rate and energy expended with further core cooling in HYPO-1.0°C combined with low skin temperature helped offset heat storage losses to lead to similar HD between conditions despite

differences in core temperature. Overall, cold exposure combined with inadequate clothing leading to either reduced skin temperature or core cooling prior to exercise in 0°C cold air impairs endurance capacity. From a practical perspective, these data indicate that individuals should prevent declines in shell or core temperature prior to performing sustained work in the cold combined with inadequate clothing.

Although this was not directly analyzed in the Chapters 5 and Chapters 6, we used the Robertson & Marino (42) neurological model and the McMorris interoception model (43, 44) as a conceptual framework for the relationship cognitive function and endurance capacity under environmental stress. Under these models, interventions that improve prefrontal cortex function (and local structures such as the ACC, AIC, OFC, and cognitive functions such as those within the executive attention network) can lead to improvements in endurance capacity, while impairments to these areas would lead to an impairment in endurance capacity. For example, if the ACC is fatigued using the AX-Continuous performance cognitive task, there is a decrease in time-to-exhaustion time at 80% peak power output (PPO) by 16% (17). Furthermore, two-weeks of motivational self-talk training significantly improved time-to-exhaustion at 80% PPO and executive function in the heat by improving psychological tolerance of high physiological strain (45). Based on these results, we initially hypothesized that there would be impairments in cognitive function, followed by subsequent impairments in endurance capacity. However, this response did not occur, as we demonstrated no impairments in cognitive function in any cooling condition, while endurance capacity was impaired in all cooling conditions. These models have not been tested in cold environments prior to this research, but based on the current results, it does not appear that the neurological model extends to cold environments with or without core cooling based on the experimental approach using in Chapters 5 and 6. The interoception model may

potentially explain the results outside of changes in cognitive function, as the challenging conditions may have influenced interoception perceptions and interoceptive predictions (See Figure 2-5). For example, in both HYPO-0.5°C and HYPO-1.0°C conditions, interoceptive predictions would be difficult to predict. For example, at the start of the TTE, perceptions of RPE were higher (non-significantly statistically, however practically higher) and thermal sensations were colder compared to TN. Furthermore, the physiological state was in flux. The normal thermophysiological response to exercise is an increase in internal heat production (muscular work gives off 75-80% of energy as heat) leading to increased muscle, core, and blood temperature, combined with increased blood flow to working muscles, increased skin temperature to aid in convective heat loss and sweating (46). However, we demonstrated an average T_{re} afterdrop of Δ-0.2-0.3°C during the TTEs in the core cooling conditions likely caused from the skeletal muscle pump moving cooler blood from the periphery to the core and warmer blood from the core towards the working muscle (11, 30). Furthermore, this response was coupled with minimal sweating, cold skin temperatures, cold muscle temperatures, and likely cold blood circulating throughout the body causing systemic vasoconstriction and functional changes in the muscle (e.g., reduced force production, slower cross bridge contraction). Based on this afferent feedback differing from previous experiences performing the TTE during thermoneutral practice trials, interoceptive prediction errors were likely made and exercise was terminated to cease exercise as the body was drifting further away from homeostasis. In the TTEs, the average T_{re} change from the start of the TTE 'warmup' was +0.8 ± 0.7°C in TN, +0.6 ± 0.6°C in CS, +0.06 ± 0.4°C in HYPO-0.5°C, and -0.3 ± 0.4°C in HYPO-1.0°C. Potentially, if individuals had the capacity to maintain performance similar to CS, they had the capacity to generate enough metabolic heat production to get closer to their baseline core temperature (and thus move closer to homeostasis). However, as physical

function was reduced, combined with interoceptive feedback indicating further core cooling, this may have contributed to reduced endurance capacity. Furthermore, participants may have behaviorally terminated exercise to stop cold exposure and move into recovery into a thermoneutral environment to maintain homeostasis. However, these responses are speculative as we do not have data to measure interoception, nor its role in endurance capacity. We found null responses on cognitive function, it does not appear changes in executive function, working memory, or psychomotor processing indicating the executive attention network was not impaired which is a neural network important to both the neurological model and interoceptive model. We cannot fully rule out there are no central changes in the brain that influence endurance capacity in cold air following cooling. Future research is needed in testing different neural factors such as neural processing, cerebral blood flow, and cerebral oxygenation in order to determine their relationship to endurance capacity in the cold. From a practical perspective, countermeasures in the cold to increase survival should focus on maintaining physical function and capacity as there appears to be sufficient capacity for cognitive function in the initial stages of core cooling prior to clinical hypothermia.

There is a paucity of research on females in environmental exercise physiology research relative to males (47–50), and this trend is apparent in the cold literature as well (51). From a biophysical perspective, changes in core temperature are determined by the cumulative imbalance between metabolic heat production and net heat loss (i.e., body heat storage), body mass (i.e., internal heat sink) and body composition (i.e., specific heat capacity of body tissues) (52). On average, average, females have a lower body mass, height, body surface area, and greater body fat percentage compared to males (47). These differences can influence the rate of heat storage and accumulation of heat debt in several ways such as: i) a smaller overall body mass would require

less energy to cool ii) less muscle mass would lead to less metabolic heat that can be generated and less insulation from under-perfused muscle, iii) a higher surface area to mass ratio leads to more surface area available for convective heat loss from the skin surface, and iv) higher body fat percentage leading to more insulation. These net factors limit the maximal thermoregulatory capacity of females relative to males. Ultimately, these factors might lead to faster cooling rates in cold air in females relative to males. However, it is unknown if this is a clear disadvantage for women in relation to endurance capacity. Hypothetically, for exercise tasks, if an individual cools significantly faster to a set reduction in T_{core} (e.g., 45-min vs 90-min to -0.5°C) they will likely have less of a heat debt. Subsequently, these individuals will have less physiological strain to overcome during exercise and could potentially perform better (or have less of a decline in performance) compared to individuals with greater amounts of heat debt. Furthermore, it is quicker to heat core temperature in smaller individuals (in relation to body mass) compared to larger individuals at the same absolute workload (47, 53). Besides anthropometric differences, females have fluctuations in resting core temperature throughout the menstrual cycle with higher resting core temperatures (+0.1-0.7°C) in the luteal phase compared to the early follicular phase (47, 50, 51) that may influence cutaneous vasoconstriction, shivering, and non-shivering thermogenesis (51). This may lead to faster cooling times in the luteal phase as both skin and core temperature are higher, with a larger gradient from the ambient temperature promoting greater convective heat loss. However, as core temperature is higher there is a greater core temperature buffer before reaching clinical hypothermia. The logical next steps are to first compare both cooling responses and endurance capacity responses to set decreases in core temperature to determine if there is a sex-related difference uncontrolled for anthropometrics, and then sex-related differences when controlling for anthropometric factors (body mass, body fat percentage, lean body mass) and

fitness (note this is no easy task). Furthermore, a future direction would be comparing the cooling responses and endurance capacity changes over the course of the menstrual cycle to determine the effect of endogenous hormones. The use of partitional calorimetry is an important and necessary tool in this process to determine whether is differences in metabolic heat production or differences in heat loss. If this could be coupled with measures of peripheral vasoconstriction (such as skin blood flow with laser doppler flowmetry) an integrative understanding of female thermoregulation in the cold can be elucidated.

Fitness levels may also influence endurance capacity in the cold, as individuals who are more fit (indexed by higher peak aerobic capacity and peak power output) could influence endurance capacity by influencing the amount of heat generated during exercise. Hypothetically, if anthropometric variables were identical, a trained individual who could sustain a higher absolute workload in the cold compared to untrained individual, and thereby generate more metabolic heat production leading to faster increases in local muscle and whole-body core temperature compared to untrained individuals. This effect would be further influenced by body mass, such that those with a higher power output-to-mass ratio (W·kg ratio) could generate more heat to raise their core temperatures back to baseline temperature faster than individuals with a lower power output-to-mass ratio. An excellent example of this response can be seen in Ferguson et al. (54), where trained cyclists were able to sustain a power output of ~> 250W over a 15-km time trial where rectal temperature returned to baseline values despite pre-exercise cooling of Δ-0.5°C in 0°C cold air. The average peak W·kg ratio in that study was ~5.4 W·kg, which was greater than the average 3.7 W·kg ratio of the participants in Chapter 6 where the heat generation to body mass was much lower. A logical next step would be comparing groups of low and high training status and if it

influences endurance capacity, heat storage, and thermoregulation in the cold where the heat generation ability of the individual play an integral role in performance.

7.7 Future Directions:

The present research question has presented the following questions that warrant future investigation:

1. What is the role of dopamine in thermal tolerance? Previously, the pharmacological manipulation of dopamine (through re-uptake inhibitors) led to longer running times (25) and faster time trials concurrent with higher core temperatures and similar levels of thermal perception (22). In Chapter 4, we saw no effect of dopamine re-uptake inhibition on thermal perception, however the study design implemented clamped changes in skin and core temperature. Potentially dopamine plays a role in thermal tolerance as opposed to influencing thermal perception per say.

2. What is the threshold for cognitive impairment in the cold? In Chapter 5, there were no impairments in cognitive function despite reductions in mean skin temperature and core temperature by ~Δ-0.8°C. Potentially, the absolute core temperature was too high to lead to decrements in performance. Potentially, greater core cooling past clinical hypothermia (≤ 35°C) is necessary to see impairments (55). However, this level of cooling is typically greater than institutional ethical cutoffs, where the isolating of the threshold in cognitive impairment in the cold unfeasible.

3. What are the individual factors that influence endurance capacity following core cooling in the cold? In Chapter 6, a heterogenous group of males were tested where we demonstrated both reductions in skin and core temperature significantly impaired endurance capacity. Future studies would benefit from the comparing groups of different training levels, sexes, and anthropometric

(e.g., mass, % body fats) as each of these factors can influence heat storage and pre-exercise cooling that may extend towards endurance capacity.

4. What are the effects of combined stressors on endurance capacity and performance in cold air. Practically, environmental exposure is not experienced solely in isolation. For example, activities at high altitude (i.e., mountain climbing, ski touring) involve both cold and hypoxia (both influences oxygen availability). Furthermore, cold induces diuresis and dampens thirst (56) where cold exposure is coupled with dehydration. How these factors intertwine would further our understanding of environmental stress and physiological strain on endurance capacity.

7.8 Practical Recommendations

The findings from this research program have potential practical implications for activities in the cold. One key practical finding from pilot testing for Chapter 5, is the commonly known decrement in manual dexterity (57) and fine motor skill performance (9, 58, 59) with cold exposure, as well as the bulkiness of the gloves were influencing participants' ability to respond on a keyboard during computerized cognitive tasks. The practical implication of this finding is that tools and instruments used in the cold should be designed to reduce the manual dexterity requirement. For example, if individuals need to press a button, the button should be designed to be wider, larger, and allow for multiple fingers to aid in the pressing to make it more of a gross motor task. Furthermore, the general pattern of reaction time being slower in core cooling conditions compared to neutral (albeit non-significant) would indicate if electronics are being used and there is a certain time-duration required to response (i.e., inputting a password), then the program should be adjusted to have a longer duration required to respond to incorporate potential longer response latencies. Ultimately, tools and equipment in the cold need to be designed to incorporate the challenging environmental conditions, the gear (i.e., gloves) used by individuals,

the changes in manual dexterity, and psychophysiological strain of the individuals in those environments.

Based on the results of the study, physical performance demonstrates an earlier threshold (cold skin) and greater impairment in cold environments compared to cognitive function. For athletes, military personal, and occupational workers, these results would indicate that individuals should avoid precooling (skin or core) prior to performing moderate to high intensity exercise in cold air to avoid performance impairment. If a sustained moderate to high intensity workload is required (for sport, military operations, occupational demands), then the workload should be reduced (54) or work-to-rest ratios (21) should be incorporated in order to complete the activities based on the impairments in physical capacity in the cold. Furthermore, the average absolute core temperature in HYPO-1.0°C (36.3 ± 0.5°C) occurred well above clinical hypothermia of ≤ 35°C, indicating that countermeasures in the cold should aim to be performed before mild core cooling can occur. Other strategies that can be used to reduce precooling prior to exercise in the cold is wearing more or adequate clothing based on the environmental conditions and metabolic workload of the activity. For example, wearing of cross-country ski uniforms led to maximal running performance and TTE at cool temperatures of 1°C and -4°C, with performance lower at -14°C, 10°C, 20°C (60). However, more clothes in cold environments do not always indicate better performance, as heavy clothing can increase the energy demands of exercise caused by increased metabolic demands to support additional mass, resistance to movement, and increased sweat rate and heat production (which may cause hyperthermia despite the cold environment) (56). Therefore, individuals must dress based on the activity (and expected metabolic demands), the environmental conditions (temperature, wind speed), and expected duration. Generally, having available layers, and a collection of insulative layers and waterproof and wind resistant layers are

beneficial to adjust clothing throughout cold exposure. Lastly, individuals should aim to warm up muscles (actively or passively) prior to performing moderate to high intensity exercise in the cold. For example, using a heated jacket to maintain whole-body skin temperature improved 2-km rowing time-trial performance following 25-min of passive cold air exposure (8°C) (12). Overall, this indicates reducing overall cold strain (muscle, skin temperature) prior to exercise. The one caveat to this recommendation, is exercise prior to cold exposure leads to greater heat loss (through higher skin to air gradient, increased vasodilation from exercise) (61), indicating that individuals should minimize the gap between the warm up period and activity in order to prevent greater heat loss and negating the benefits of a warm up.

7.9 Sample Size and Experimental Design Considerations

A research consideration for Chapter 4 is that the experimental timepoints were not randomized, (i.e., the sequence was always BASE to NC-HS to HC-HS to HC-CS) which may have contributed to the null effect. This sequence was chosen as it matches the normal time course of passive heating and cooling (i.e., hot skin precedes hyperthermia). Furthermore, if cognition was impaired by hot skin, then that impairment should carry over throughout the experimental trial. Potentially, this created a confound, where there were no impairments with hyperthermia as individuals had multiple exposures of the CTB during heating contributing to a plateau in performance. Given the design and use of methylphenidate, from a practical standpoint, it would been logistically challenging to randomize the experimental timepoints (both for drug and experimental timepoint) as this would involve 8 experimental trials separated by a week, as opposed to two trials. Furthermore, this would consist of 4 drug trials as opposed to the one. Ultimately, this would also place unnecessary burden on participants through multiple exposures to the MPH and hyperthermia. Furthermore, it is unknown how well the learning effect for the

CTB can be maintained over this timeline. A potential solution to rectify this issue would be to have a time-matched thermoneutral control to see performance changes overtime in the absence of heat stress. In Chapters 5 and 6, we did try to account for this potential confound in experimental design confound by having 4 randomized experimental conditions. However, we did find a similar null effect on cognitive performance despite the trial randomization.

One of the inherent challenges in human-based physiology research is the over reliance on statistical significance (e.g., $p < 0.05$), and less focus on statistical power and power size calculations leading to potential Type II errors (false negatives) (62). For each of the studies in this dissertation, a post-hoc analysis of effect size and sample estimation was performed using G*Power version 3.1.9.7 software. Power analyses and sample size estimations were performed first for condition effects (within factors) for the repeated measures ANOVA with an α set at 0.05 (p value significance) and a ß = 0.80 (power), and correlation of 0.25 (to be conservative), and nonsphericity correction of 1.0. Effect size (f) was calculated from the partial eta^2 (η^2) value with the equation $f = (\frac{\eta^2}{1-\eta^2})$. Next, to determine sample size estimated to determine significant difference between two conditions (i.e., TN versus C-0.8°C), sample size estimations were performed based on mean differences between two specific experimental timepoints/ conditions based on a paired samples *t* test. For this measure Cohen' *d* was calculated for the effect size (63). In the following paragraphs, we will discuss the results from the power analysis and sample size estimations for each experiment in this dissertation.

For Chapter 4, the power analysis and sample size estimations were performed on the overall within group repeated measures experimental timepoint effect, as well as mean differences between experimental timepoints and mean difference between MPH and PLA at specific experimental timepoints. We first assessed GMLT total errors using a post-hoc 2 (MPH vs PLA)

x 4 (experimental timepoint) repeated measures ANOVA, where there was a $\eta^2 = 0.472$ and $f = 0.945$, where the estimated sample size required for an $\alpha = 0.05$ and ß = 0.80 would be 6 participants (actual ß = 0.973). Next, a comparison of means was performed on BASE compared to HC-HS (as this was the most strenuous condition), where there was a $d = 0.810$, where an estimated 15 participants are needed to determine a significant difference. Furthermore, we compared mean differences between MPH and PLA at the HC-HS experimental timepoint as this was hypothesized where MPH would have its highest effect. For this data, there was a $d = 0.327$ where it estimated that 76 participants would be needed to find a sufficiently powered significant difference. Based on these results, it indicates that the sample size used was likely powered enough for the experimental timepoints and environmental manipulations performed. However, there is not sufficient power for the use of MPH in the HC-HS condition. As discussed in the Discussion section of Chapter 4, the dosing strategy used was based on an exercise in the heat study that used 20 mg of MPH (22). Potentially, a greater effect size would be found with a higher dose of MPH. The results and effect sizes from this paper can be used to provide realistic effect sizes for MPH on cognitive function in the heat in order to provide estimates of sample size required for future studies.

Cold and cognition studies have typically included small samples sizes ranging from 6-12 participants typically due to the logistical demands of performing the study and the physiological and psychological strain induced (8–10, 12, 55, 64–68). In Chapter 5, we were in this range with a total of 10 participants. A post-hoc power analysis was performed on the item working memory task reaction time was for sample size estimations. For the 1 x 4 (condition) repeated measures ANOVA there was a $\eta^2 = 0.165$ and $f = 0.445$, where an estimate of 4 participants were needed to achieve a ß = 0.80 for the condition effect (actual ß = 0.569 for this measure, indicating low power

despite greater number of participants). Next, a sample size estimation was performed based on mean differences between TN and C-0.8°C as it was the most strenuous condition compared to TN. There was a small effect size of d = 0.26, where it is estimated that a sample size of 118 participants would be needed to achieve an $\alpha = 0.05$ and ß = 0.80. Logistically, it is unfeasible to perform the experimental design on such a large sample of participants (~118 participants) considering the challenging experimental design as well as the high amounts of physiological and psychological strains induced on the participants. Contributing to the low effect size and power for this measure is the individual variability in responses (See figure 7-1 below), where participant's performance was impaired, unchanged, and even improved(!) despite core cooling to -0.8°C. The sample is small, so no further analyses can be made based on responders and non-responders. However, these data highlight the limited effect size for changes in reaction time for the item working memory task. Ultimately, the item working memory reaction time data indicates that the data set is underpowered to find any statistically significant differences for item working memory reaction time. These results lead to a few potential conclusions: i) the effect size for cold stress on item working memory performance is small and therefore it is difficult to tease out significant differences without a large sample size, or ii) there is an increased probability of Type II error that may have contributed to the null finding, or iii) there are relatively little to no changes in cognitive function in the cold and therefore it is not possible to achieve an α less than 0.05 with sufficient statistical power. The other factor to consider is that there were practically and statistically no differences in errors or accuracy made for any of the task. These results would indicate that likely there is little to no impairment in cognitive function (executive attention) under the experimental conditions tested, even with individual variability with reaction time. However,

future experiments in cold and cognition need to consider the low effect size when designing future studies and the increased probability of Type II error occurring.

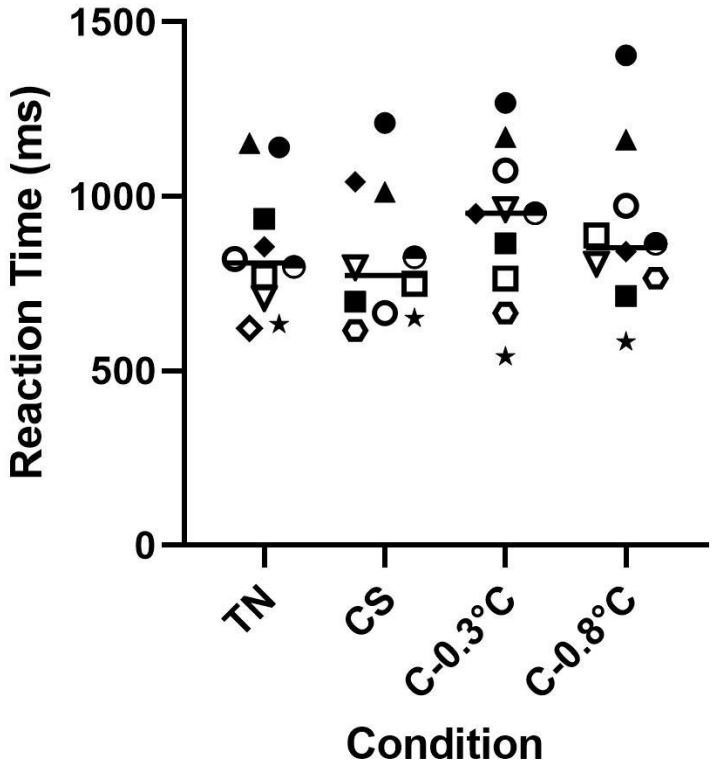

Figure 7-1 -Individual responses for reaction time on item working memory task. Horizontal lines represent the mean responses, and each icon represents a specific participant.

For Chapter 6, the TTE data was used to determine a post hoc analysis of statistical power and sample size estimations based on mean and standard deviations (due to tests available using G*Power). For the 1 X 4 repeated measures ANOVA there was a $\eta 2 = 0.765$, $f = 1.789$, where an estimate of 3 participants were needed to achieve a ß = 0.80 for the condition effect (actual ß = 0.858 for this measure). For mean differences between TN (23.75 ± 13.75 min) and HYPO-1.0°C (6.45 ± 5.59 min), there was a large effect size of d = 1.44, where it was estimated that a sample

size of 6 participants where needed to achieve a ß = 0.80. These results indicate that we were adequately powered for TTE in Chapter 6. These results also highlight the large differences in changes in cognition versus endurance capacity under cold stress.

7.10 General Conclusions

This research program demonstrated that neither manipulation of skin temperature, nor the manipulation of core temperature (Δ-0.8 to +1.5°C) elicited significant impairment of executive function, working memory, or psychomotor processing in hot or cold environments relative to thermoneutral conditions. Furthermore, the ingestion of a dopamine re-uptake inhibitor (20 mg, methylphenidate) did not enhance cognitive function in the heat. Overall, the collective results extend our findings of the overall capacity of the brain adverse environments. Lastly, we demonstrated large decrements in endurance capacity in the cold with both the reduction in skin temperature, as well as further impairments with two levels of core cooling (up to Δ-1.0°C) prior to starting the time to exhaustion test. These results indicate that physical performance is impaired prior to measurable decrements in executive function, working memory, or psychomotor processing under the environmental conditions tested. Interventions aiming to prevent decrements in performance should aim to prevent decreases in both skin and core temperature prior to performing sustained work in the cold. Future work is needed to isolate individual factors that may influence endurance capacity in the cold. Additionally, finding and developing tools for indexing cold strain can be beneficial in differentiating the mixed results demonstrated in cold environments.

7.11 Discussion References

1. Teichner WH. Reaction time in the cold. *Journal of Applied Psychology*. 1958;42(1):54–9.

2. Gaoua N, Grantham J, Racinais S, El Massioui F. Sensory displeasure reduces complex cognitive performance in the heat. *Journal of Environmental Psychology*. 2012;32(2):158–63.

3. Gaoua N. Cognitive function in hot environments: a question of methodology: Cognitive function in hot environments. *Scandinavian Journal of Medicine & Science in Sports*. 2010;20:60–70.

4. Schlader ZJ, Lucas RAI, Pearson J, Crandall CG. Hyperthermia does not alter the increase in cerebral perfusion during cognitive activation: Cerebral perfusion during cognitive activation. *Experimental Physiology*. 2013;98(11):1597–607.

5. Wallace PJ, Mckinlay BJ, Coletta NA, et al. Effects of Motivational Self-Talk on Endurance and Cognitive Performance in the Heat: *Medicine & Science in Sports & Exercise*. 2017;49(1):191–9.

6. Wallace PJ, Martins RS, Scott JS, Steele SW, Greenway M, Cheung SS. The effects of acute dopamine reuptake inhibition on cognitive function during passive hyperthermia. *Appl Physiol Nutr Metab*. 2020;apnm-2020-0869.

7. van den Heuvel AMJ, Haberley BJ, Hoyle DJR, Taylor NAS, Croft RJ. The independent influences of heat strain and dehydration upon cognition. *European Journal of Applied Physiology*. 2017;117(5):1025–37.

8. Taber MJ, Hartley GL, McGarr GW, et al. Cognitive Performance during a 24-Hour Cold Exposure Survival Simulation. *BioMed Research International*. 2016;2016:1–11.

9. Cheung SS, Westwood DA, Knox MK. Mild body cooling impairs attention via distraction from skin cooling. *Ergonomics*. 2007;50(2):275–88.

10. Payne J, Cheung SS. Isolated core vs. superficial cooling effects on virtual maze navigation. *Aviat Space Environ Med*. 2007;78(7):680–5.

11. Tikuisis P, Keefe AA. Effects of cold strain on simulated sentry duty and marksmanship. *Aviation, space, and environmental medicine*. 2007;78(4):399–407.

12. Shurtleff D, Thomas JR, Schrot J, Kowalski K, Harford R. Tyrosine reverses a cold-induced working memory deficit in humans. *Pharmacology Biochemistry and Behavior*. 1994;47(4):935–41.

13. Jones SAH, Butler BC, Kintzel F, Johnson A, Klein RM, Eskes GA. Measuring the Performance of Attention Networks with the Dalhousie Computerized Attention Battery (DalCAB): Methodology and Reliability in Healthy Adults. *Frontiers in Psychology* [Internet]. 2016 [cited 2019 Aug 19];7 Available from: http://journal.frontiersin.org/Article/10.3389/fpsyg.2016.00823/abstract. doi:10.3389/fpsyg.2016.00823.

14. Jones SAH, Butler B, Kintzel F, Salmon JP, Klein RM, Eskes GA. Measuring the components of attention using the Dalhousie Computerized Attention Battery (DalCAB). *Psychological Assessment*. 2015;27(4):1286–300.

15. Qian S, Sun G, Jiang Q, et al. Altered topological patterns of large-scale brain functional networks during passive hyperthermia. *Brain and Cognition*. 2013;83(1):121–31.

16. Liu K, Sun G, Li B, et al. The impact of passive hyperthermia on human attention networks: An fMRI study. *Behavioral Brain Research*. 2013;243:220–30.

17. Marcora SM, Staiano W, Manning V. Mental fatigue impairs physical performance in humans. *Journal of Applied Physiology*. 2009;106(3):857–64.

18. Franco-Alvarenga PE, Brietzke C, Canestri R, et al. Caffeine improved cycling trial performance in mentally fatigued cyclists, regardless of alterations in prefrontal cortex activation. *Physiology & Behavior*. 2019;204:41–8.

19. Otani H, Kaya M, Tamaki A, Watson P. Separate and combined effects of exposure to heat stress and mental fatigue on endurance exercise capacity in the heat. *European Journal of Applied Physiology*. 2017;117(1):119–29.

20. Head J, Tenan MS, Tweedell AJ, et al. Prior Mental Fatigue Impairs Marksmanship Decision Performance. *Frontiers in Physiology* [Internet]. 2017 [cited 2017 Sep 21];8 Available from: http://journal.frontiersin.org/article/10.3389/fphys.2017.00680/full. doi:10.3389/fphys.2017.00680.

21. Oksa J, Ducharme MB, Rintamäki H. Combined effect of repetitive work and cold on muscle function and fatigue. *Journal of Applied Physiology*. 2002;92(1):354–61.

22. Roelands B, Hasegawa H, Watson P, et al. The Effects of Acute Dopamine Reuptake Inhibition on Performance: *Medicine & Science in Sports & Exercise*. 2008;40(5):879–85.

23. Elliott R, Sahakian BJ, Matthews K, Bannerjea A, Rimmer J, Robbins TW. Effects of methylphenidate on spatial working memory and planning in healthy young adults. *Psychopharmacology*. 1997;131(2):196–206.

24. Volkow ND, Wang G-J, Fowler JS, et al. Cardiovascular effects of methylphenidate in humans are associated with increases of dopamine in brain and of epinephrine in plasma. *Psychopharmacology*. 2003;166(3):264–70.

25. Hasegawa H, Piacentini MF, Sarre S, Michotte Y, Ishiwata T, Meeusen R. Influence of brain catecholamines on the development of fatigue in exercising rats in the heat: Effect of bupropion on thermoregulation and exercise performance. *The Journal of Physiology*. 2008;586(1):141–9.

26. Mahoney CR, Castellani J, Kramer FM, Young A, Lieberman HR. Tyrosine supplementation mitigates working memory decrements during cold exposure. *Physiology & Behavior*. 2007;92(4):575–82.

27. Watson P, Enever S, Page A, Stockwell J, Maughan RJ. Tyrosine Supplementation Does Not Influence the Capacity to Perform Prolonged Exercise in a Warm Environment. *International Journal of Sport Nutrition and Exercise Metabolism*. 2012;22(5):363–73.

28. Cordery P, James LJ, Peirce N, Maughan RJ, Watson P. A Catecholamine Precursor Does Not Influence Exercise Performance in Warm Conditions: *Medicine & Science in Sports & Exercise*. 2016;48(3):536–42.

29. Watson P, Hasegawa H, Roelands B, Piacentini MF, Looverie R, Meeusen R. Acute dopamine/noradrenaline reuptake inhibition enhances human exercise performance in warm, but not temperate conditions: Dopamine and noradrenaline reuptake and exercise. *The Journal of Physiology*. 2005;565(3):873–83.

30. Vallerand AL, Jacobs I, Kavanagh MF. Mechanism of enhanced cold tolerance by an ephedrine-caffeine mixture in humans. *Journal of Applied Physiology*. 1989;67(1):438–44.

31. Ainslie PN, Ashmead JC, Ide K, Morgan BJ, Poulin MJ. Differential responses to CO_2 and sympathetic stimulation in the cerebral and femoral circulations in humans: Blood flow responses to sympathetic stimulation and CO_2 in humans. *The Journal of Physiology*. 2005;566(2):613–24.

32. Al-Khazraji BK, Shoemaker LN, Gati JS, Szekeres T, Shoemaker JK. Reactivity of larger intracranial arteries using 7 T MRI in young adults. *Journal of Cerebral Blood Flow & Metabolism*. 2019;39(7):1204–14.

33. Fujii N, Honda Y, Hayashi K, Kondo N, Koga S, Nishiyasu T. Effects of chemoreflexes on hyperthermic hyperventilation and cerebral blood velocity in resting heated humans: Hyperthermic hyperpnoea and chemoreflex drive, cerebral circulation. *Experimental Physiology*. 2008;93(8):994–1001.

34. Brothers RM, Wingo JE, Hubing KA, Crandall CG. The effects of reduced end-tidal carbon dioxide tension on cerebral blood flow during heat stress: Cerebrovascular blood flow during heat stress. *The Journal of Physiology*. 2009;587(15):3921–7.

35. Brothers RM, Ganio MS, Hubing KA, Hastings JL, Crandall CG. End-tidal carbon dioxide tension reflects arterial carbon dioxide tension in the heat-stressed human with and without simulated hemorrhage. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*. 2011;300(4):R978–83.

36. Gibbons TD, Tymko MM, Thomas KN, et al. Global REACH 2018: The influence of acute and chronic hypoxia on cerebral haemodynamics and related functional outcomes during cold and heat stress. *The Journal of Physiology*. 2020;598(2):265–84.

37. Willie CK, Tzeng Y-C, Fisher JA, Ainslie PN. Integrative regulation of human brain blood flow: Integrative regulation of human brain blood flow. *The Journal of Physiology*. 2014;592(5):841–59.

38. Schultz Martins R, Wallace PJ, Steele SW, et al. The Clamping of End-Tidal Carbon Dioxide Does Not Influence Cognitive Function Performance During Moderate Hyperthermia With or Without Skin Temperature Manipulation. *Front Psychol*. 2021;12:788027.

39. Gaoua N, Herrera CP, Périard JD, El Massioui F, Racinais S. Effect of Passive Hyperthermia on Working Memory Resources during Simple and Complex Cognitive Tasks. *Frontiers in Psychology* [Internet]. 2018 [cited 2018 Nov 30];8 Available from: http://journal.frontiersin.org/article/10.3389/fpsyg.2017.02290/full. doi:10.3389/fpsyg.2017.02290.

40. Hancock PA, Vasmatzidis I. Effects of heat stress on cognitive performance: the current state of knowledge. *International Journal of Hyperthermia*. 2003;19(3):355–72.

41. Hancock PA, Vasmatzidis I. Human occupational and performance limits under stress: the thermal environment as a prototypical example. *Ergonomics*. 1998;41(8):1169–91.

42. Robertson CV, Marino FE. A role for the prefrontal cortex in exercise tolerance and termination. *Journal of Applied Physiology*. 2016;120(4):464–6.

43. McMorris T. The acute exercise-cognition interaction: From the catecholamines hypothesis to an interoception model. *International Journal of Psychophysiology*. 2021;170:75–88.

44. McMorris T, Barwood M, Corbett J. Central fatigue theory and endurance exercise: Toward an interoceptive model. *Neuroscience & Biobehavioral Reviews*. 2018;93:93–107.

45. Wallace PJ, Mckinlay BJ, Coletta NA, et al. Effects of motivational self-talk on endurance and cognitive performance in the heat. *Med Sci Sports Exerc*. 2017;49(1):191–9.

46. Cheung SS, Ainslie PN. *Advanced environmental exercise physiology*. Second edition. Champaign, USA: Human Kinetics, Inc; 2022.

47. Wickham KA, Wallace PJ, Cheung SS. Sex differences in the physiological adaptations to heat acclimation: a state-of-the-art review. *Eur J Appl Physiol*. 2021;121(2):353–67.

48. Wickham KA, McCarthy DG, Spriet LL, Cheung SS. Sex differences in the physiological responses to exercise-induced dehydration: consequences and mechanisms. *Journal of Applied Physiology*. 2021;131(2):504–10.

49. Daanen HAM, Racinais S, Périard JD. Heat Acclimation Decay and Re-Induction: A Systematic Review and Meta-Analysis. *Sports Med*. 2018;48(2):409–30.

50. Giersch GEW, Morrissey MC, Katch RK, et al. Menstrual cycle and thermoregulation during exercise in the heat: A systematic review and meta-analysis. *Journal of Science and Medicine in Sport*. 2020;23(1134–1140):S144024402030058X.

51. Greenfield AM, Charkoudian N, Alba BK. Influences of ovarian hormones on physiological responses to cold in women. *Temperature*. 2021;9(1):23–45.

52. Cramer MN, Jay O. Selecting the correct exercise intensity for unbiased comparisons of thermoregulatory responses between groups of different mass and surface area. *Journal of Applied Physiology*. 2014;116(9):1123–32.

53. Notley SR, Akerman AP, Meade RD, McGarr GW, Kenny GP. Exercise Thermoregulation in Prepubertal Children: A Brief Methodological Review. *Medicine & Science in Sports & Exercise* [Internet]. 2020 [cited 2020 Jul 31];Publish Ahead of Print Available from: https://journals.lww.com/10.1249/MSS.0000000000002391. doi:10.1249/MSS.0000000000002391.

54. Ferguson SAH, Eves ND, Roy BD, Hodges GJ, Cheung SS. Effects of mild whole body hypothermia on self-paced exercise performance. *Journal of Applied Physiology*. 2018;125(2):479–85.

55. Giesbrecht GG, Arnett JL, Vela E, Bristow GK. Effect of task complexity on mental performance during immersion hypothermia. *Aviation, Space, and Environmental Medicine*. 1993;64(3, Sect 1):206–11.

56. Castellani JW, Eglin CM, Ikäheimo TM, Montgomery H, Paal P, Tipton MJ. ACSM Expert Consensus Statement: Injury Prevention and Exercise Performance during Cold-Weather Exercise. *Curr Sports Med Rep*. 2021;20(11):594–607.

57. Castellani JW, Tipton MJ. Cold stress effects on exposure tolerance and exercise performance. *Compr Physiol*. 2016;6(1):443–69.

58. Cheung SS, Montie DL, White MD, Behm D. Changes in Manual Dexterity Following Short-Term Hand and Forearm Immersion in 10°C Water. 2003;74(9):5.

59. Flouris AD, Cheung SS, Fowles JR, et al. Influence of body heat content on hand function during prolonged cold exposures. *J Appl Physiol*. 2006;101(3):802–8.

60. Sandsund M, Saursaunet V, Wiggen Ø, Renberg J, Færevik H, van Beekvelt MCP. Effect of ambient temperature on endurance performance while wearing cross-country skiing clothing. *European Journal of Applied Physiology*. 2012;112(12):3939–47.

61. Castellani JW, Young AJ, Kain JE, Rouse A, Sawka MN. Thermoregulation during cold exposure: effects of prior exercise. *Journal of Applied Physiology*. 1999;87(1):247–52.

62. Gemae MR, Akerman AP, McGarr GW, et al. Myths and methodologies: Reliability of forearm cutaneous vasodilatation measured using laser-Doppler flowmetry during whole-body passive heating. *Experimental Physiology*. 2021;106(3):634–52.

63. Cohen J. *Statistical power analysis for the behavioral sciences*. Hillsdale, NJ, USA: Lawrence Erlbaum; 1998.

64. Ellis HD. The Effects of Cold on the Performance of Serial Choice Reaction Time and Various Discrete Tasks. *Hum Factors*. 1982;24(5):589–98.

65. Ellis HD, Wilcock SE, Zaman SA. Cold and performance: the effects of information load, analgesics, and the rate of cooling. *Aviat Space Environ Med*. 1985;56(3):233–7.

66. Muller MD, Gunstad J, Alosco ML, et al. Acute cold exposure and cognitive function: evidence for sustained impairment. *Ergonomics*. 2012;55(7):792–8.

67. Færevik H, Hansen JH, Wiggen Ø, Sandsund M. Cognitive Performance During Night Work in the Cold. *Front Physiol*. 2021;12:768517.

68. Mäkinen TM, Palinkas LA, Reeves DL, et al. Effect of repeated exposures to cold on cognitive performance in humans. *Physiology & Behavior*. 2006;87(1):166–76.