Effects of Cerebral Blood Flow and Temperature on Executive Function During Moderate Hyperthermia

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Abstract

This thesis tested whether executive function using five different cognitive tests (Groton Maze Learning Test, 2-Back Test, Detection Test, Set Shifting and Groton Maze Learning Test recall) during passive heat stress may be affected by changes in cerebral blood flow (CBF) as opposed to thermal perception changes. An end-tidal forcing system was used to maintain eucapnia and baseline CBF in the isocapnic trial during the hypocapnia-induced CBF reduction. Repeated measures analysis of variance indicated that an increase of 5°C in mean skin temperature impaired working memory regardless of rectal temperature. The results also indicated that an increase of 1.5°C in rectal temperature increases the amount of errors by 38% when compared to baseline regardless of mean skin temperature. Although eucapnia was maintained during hyperthermia, it did not preserve baseline levels of mean middle cerebral artery velocity, indicating that changes in CBF are not the main hyperthermia-induced impairment factor for EF. In conclusion, increased skin temperature impaired working memory and increased rectal temperature impaired cognitive flexibility. In addition, as EF impairments were seen before any changes in CBF, it indicates that a decrease in CBF is not the main hyperthermia-induced impairment factor for EF.
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<th>Description</th>
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<tbody>
<tr>
<td>ACA</td>
<td>Anterior cerebral artery</td>
</tr>
<tr>
<td>BF</td>
<td>Body fat</td>
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<td>Ć</td>
<td>Convection</td>
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<tr>
<td>CBF</td>
<td>Cerebral blood flow</td>
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<tr>
<td>C-H</td>
<td>Cold core; hot skin</td>
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<tr>
<td>CO₂</td>
<td>Carbon dioxide</td>
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<tr>
<td>CRF</td>
<td>Cardiorespiratory fitness</td>
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<tr>
<td>Db</td>
<td>Body density</td>
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<tr>
<td>DLPFC</td>
<td>Dorsolateral prefrontal cortex</td>
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<tr>
<td>Ė</td>
<td>Evaporation</td>
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<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
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<tr>
<td>EF</td>
<td>Executive function</td>
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<tr>
<td>EFTB</td>
<td>Executive function testing battery</td>
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<tr>
<td>fMRI</td>
<td>Functional magnetic resonance image</td>
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<tr>
<td>GMLT</td>
<td>Groton maze learning task</td>
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<tr>
<td>GWT</td>
<td>Global workspace theory</td>
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<tr>
<td>H-C</td>
<td>Hot core; cold skin</td>
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<tr>
<td>H-H</td>
<td>Hot core; hot skin</td>
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<tr>
<td>ICA</td>
<td>Internal carotid artery</td>
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<tr>
<td>IZOF</td>
<td>Individual zone of optimal functioning</td>
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<tr>
<td>K</td>
<td>Conduction</td>
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<tr>
<td>Abbreviation</td>
<td>Full Form</td>
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<tr>
<td>LCG</td>
<td>Liquid conditioning garment</td>
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<tr>
<td>$\dot{M}$</td>
<td>Metabolic heat production</td>
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<tr>
<td>MAM</td>
<td>Maximal adaptability model</td>
</tr>
<tr>
<td>MAP</td>
<td>Mean arterial pressure</td>
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<tr>
<td>MCA</td>
<td>Middle cerebral artery</td>
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<tr>
<td>MCA\textsubscript{v}</td>
<td>Middle cerebral artery velocity</td>
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<tr>
<td>$O_2$</td>
<td>Oxygen</td>
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<tr>
<td>$P_{a\text{CO}_2}$</td>
<td>Arterial partial pressure of carbon dioxide</td>
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<tr>
<td>$P_{a\text{O}_2}$</td>
<td>Arterial partial pressure of oxygen</td>
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<tr>
<td>PCA</td>
<td>Posterior cerebral artery</td>
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<tr>
<td>$P_{e\text{CO}_2}$</td>
<td>End-tidal partial pressure of carbon dioxide</td>
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<tr>
<td>$\dot{R}$</td>
<td>Radiation</td>
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<tr>
<td>$\dot{S}$</td>
<td>Heat storage</td>
</tr>
<tr>
<td>SNA</td>
<td>Sympathetic nervous activity</td>
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<tr>
<td>TC</td>
<td>Thermal comfort</td>
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<tr>
<td>TCD</td>
<td>Transcranial doppler ultrasound</td>
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<tr>
<td>$T_{\text{core}}$</td>
<td>Core temperature</td>
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<tr>
<td>$T_{\text{re}}$</td>
<td>Rectal temperature</td>
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<tr>
<td>TS</td>
<td>Thermal sensation</td>
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<tr>
<td>$T_{\text{skin}}$</td>
<td>Skin temperature</td>
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<tr>
<td>$T_{\text{mean\ skin}}$</td>
<td>Mean skin temperature</td>
</tr>
<tr>
<td>VA</td>
<td>Vertebral artery</td>
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<tr>
<td>VE</td>
<td>Ventilation</td>
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\( \dot{W}_k \) Mechanical work
1. Introduction

Heat stress is a widely accepted as an occupational hazard because it is often associated with impaired cognitive functioning (1). Ramsey and colleagues (2) reported that unsafe behaviour increases when ambient temperature is above 23°C. This relationship between ambient temperature and cognitive functioning is critical because heat-induced impairments in cognitive functioning may cause errors in judgments and decision making which can have serious health and safety consequences among workers (3). In fact, Tawatsupa and colleagues (4) reported that approximately 20% of Taiwanese workers experienced occupational heat stress which was strongly associated with the workplace accident rates. Therefore, it is essential to understand how elevated temperature may affect cognitive function as there are many occupations that are exposed to elevated temperatures such as construction workers, police, firefighters and infantry soldiers.

The impacts of hyperthermia on human physiology and exercise performance are well documented; however, the thermal impact on cognitive performance remains contradictory and inconsistent (5, 6). Some of these inconsistencies are due to the variety of cognitive measures and tests used (e.g., task complexity, type, and duration) (6), the different modalities to induce hyperthermia (e.g., active, passive, liquid garment suit, water immersion), and magnitudes and durations of heat stress which hinders comparison of findings and development of a clear model (3).

Hyperthermia-induced impairments in cognition might have different causes. The alliesthesial effect, which is linked to a displeasure state under heat strain (7, 8), and psychological theories (e.g., arousal theory and maximum adaptability theory) suggest that
cognition operates within an optimal range and that heat strain might shift cognition beyond this range impairing its functioning (9–11). Physiological hypotheses (e.g., changes in functional networks and reduction in cerebral blood flow) propose that hyperthermia might create a non-optimal condition for cerebral functioning (12, 13). The alliesthesial effect hypothesizes that changes in ambient temperature and, consequently, skin temperature can result in pleasant or unpleasant feelings depending on the current state of the body (14). For example, going inside a warm room during the winter may cause a subjective pleasant feeling whereas going inside a warm room during the summer may cause a subjective unpleasant feeling. According to Cabanac (14) a pleasant or unpleasant feeling can either restore or disrupt the body's internal homeostasis due to thermoregulation. In contrast, Baars (15) suggested that consciousness has a limited capacity to operate as well as to coordinate the neuronal resources for the unconscious (i.e., basic physiological functions). According to Baars, if a thermal stimulus is perceived as an unpleasant feeling, it will disrupt the body's homeostasis by using some of the available neural resources for thermoregulation, thus reducing the amount of remaining resources for cognitive functioning (16). For example, Gaoua and colleagues (9) reported that participants took longer to find a correct solution on a planning task with a 3°C increase in mean skin temperature (T$_{\text{skin}}$) with no changes in core temperature (T$_{\text{core}}$) significantly increasing thermal sensation and discomfort when compared to thermoneutral. The authors concluded that this heat stress-induced perceptual changes appeared to be sufficient to cause cognitive impairments (9). Similarly, Malcolm and colleagues (8) reported impaired complex cognitive functions after 1-hour of passive heat exposure. According to the authors, the exposure to 42°C and an increase in $T_{\text{skin}}$ may have
sacrificed neural resources from complex cognitive functions (i.e., perception and executive function) so simple cognitive functions (i.e., attention) are preserved (8).

In addition to the alliesthesial effect theory for cognitive impairments due to heat stress, thermo-physiological changes may contribute to cognitive impairments (5). For example, an increase in $T_{\text{core}}$ produces a hyperventilatory response (17) which causes hypocapnia and, consequently, a decrease in cerebral blood flow (CBF) (18). Under thermoneutral conditions, neural activation (e.g., executive functioning) results in an increase in CBF – also known as neurovascular coupling (18). However, the capacity for neurovascular coupling may be disrupted by hyperthermia (19). In fact, temporary reductions in CBF due to pharmacological manipulation (e.g., indomethacin) (20) or cardiovascular conditions (e.g., chronic heart failure) are linked to impairments in cognitive tasks such as executive functioning, ability to sustain attention, processing speed and learning (21). Therefore, it is plausible that hyperthermia-induced impairments in cognitive performance are, perhaps, related to a decrease in CBF and a consequent disruption of the close control of cerebral metabolic demand and supply.

Overall, hyperthermia impairs cognitive function (i.e., executive function). Therefore, the primary purpose of this thesis is to examine the separate and combined effect of $T_{\text{skin}}$ and $T_{\text{core}}$ on executive function; the secondary purpose of this thesis is to examine the role of hyperthermia-induced decrease in CBF on executive function during hyperthermia. Based on previous research, two hypotheses were made. First, it is hypothesized that an increase of $T_{\text{core}}$ will impair executive function regardless of $T_{\text{skin}}$. Second, it is hypothesized that the
maintenance of CBF in the isocapnic condition will restore executive function due to a steady neurovascular coupling.
2. Review of the Literature

2.1. Executive Function

Executive function (EF) has been described as a set of general purpose control mechanisms that govern human cognition and action (22) and is closely related to the function of the prefrontal cortex (23). However, the specific concept of EF is broad (22), as 68 different nomenclatures have been proposed for EF and its domains, as well as 98 different tests have been designed to assess EF (24). The first definition of EF was proposed by Shallice and Burgess (25) which described EF as a supervisory executive system for planning and decision making, error correction, generating action, judgement and inhibition. Similarly, Baddeley and Sala (26) described EF as an adaptable system responsible for coordinating the simultaneous operation of multiple cognitive processes such as working memory, task shifting, selective attention, inhibitory control, and the integration of information. However, Rabbitt (27) proposed a broader EF definition where it has a role in learning novel tasks, interpreting the past and projecting the future, behavioural control and inhibition, task switching, error identification and correction, and sustained attention. On the other hand, Perner and Lang (28) described EF as a high-level process responsible for maintaining focus and for completing a specific task despite distraction. Finally, Smith and Jonides (29) described EF as having a role on focused attention and inhibition, task management, planning, monitoring and coding. However, for the purpose of this literature review, all further reference to EF will follow the definition proposed by Lehto and colleagues (30) and by Miyaki and colleagues (31) which describes EF with three core processes: inhibitory control, working memory and cognitive flexibility. This description of EF help develop a framework that appears to conform to reported effects of hyperthermia.
(5, 16, 32, 33), have simple and valid assessment methodologies (34, 35) and are typically required in more complex cognitive tasks (31, 36).

2.1.1 Inhibitory Control

Inhibitory control allows an individual to control impulsive response, actions and thoughts, suppressing inappropriate automatic responses for a more appropriate ones (36). Bari and Robbins (37) classified inhibitory control into two main categories: cognitive inhibition and behavioural inhibition. As this thesis focuses on hyperthermia-induced changes in physiology and behaviour, cognitive inhibition (related to memories, thoughts and emotions) falls outside of the literature review’s scope. Further categorization divides behavioural inhibition into two different subcategories: response inhibition (impulsive action) and deferred gratification (impulse choice) (38). In the response inhibition, one’s response must wait for a “go” stimulus (action waiting), withhold with a “no-go” stimulus or cancel with a “stop” stimulus (39).

Therefore, inhibitory control allows humans to self-control and present an appropriate behaviour to a specific situation/task (36). However, impaired inhibitory control is often characterized by impulsivity (40) which is represented by an inability to focus on a specific goal/task in the presence of other stimulus (31), inability to make a correct response due to the lack of deliberation, to withhold a response when appropriate (41), and increased likelihood of engaging in risky behaviours (37). Based on findings from brain imaging studies, behavioural inhibition appears to depends on the integrity of the frontal lobe such as the medial section (37) and right inferior frontal gyrus of the pre-frontal cortex (42). For example, impulsive symptoms are part of the diagnostic criteria for attention
deficit hyperactivity disorder and imaging studies showed that the activation in the right inferior frontal gyrus is abnormally reduced when compared to healthy individuals (42). Furthermore, alcohol-induced neurodegeneration of the frontal lobe, as seen among chronic heavy alcohol drinkers, leads to an impaired impulse control and loss of executive function (43).

2.1.2 Working Memory

Even though there are various models describing working memory, it is generally agreed that working memory permits individuals to remember and process information for a limited amount of time (44–46). According to Baddeley (47), working memory is a multicomponent model with three different units (phonological loop, visuospatial sketchpad and episodic buffer) and a supervisory unit (central executive). The phonological loop is responsible for temporary storage and manipulation of the short-term verbal memory and consists of two subunits: the phonological store and the rehearsal system (45). The verbal information in the phonological store decays after approximately 2 seconds but it can be maintained through vocal or sub-vocal rehearsing (46). The visuospatial sketchpad is responsible for the temporary storage and manipulation of visuospatial information, spatial orientation and solution for visuospatial problems (48). Together, these two units are responsible for intake, temporary storage and processing of verbal and visual information. The episodic buffer, however, is responsible for integrating the inputs from the phonological loop and visuospatial sketchpad and assessing information stored in long term memory (46). The last element for Baddeley’s model of working memory is executive control, which coordinates and controls goal-directed behaviours (49) such as how the three components of working memory will be used to perform a specific task (48). This executive control is
responsible for the sustained attention towards relevant information and for the inhibition of irrelevant information (50). Awh and colleagues (51) describe the role of sustained attention as the gatekeeper for working memory as it determines which information will be stored in the limited working memory capacity. Therefore, any impairment in one’s sustained attention may lead to impaired working memory. Supporting this view, Gooding and colleagues (52) reported that impairments in the executive attention network is a common finding among schizophrenia-spectrum patients which leads to an overload of information stored in the working memory. Moreover, working memory capacity is a good predictor of long-term memory (53) as working memory functions as a bridge between the information being processed and the long-term memory (54). The opposite also occurs as the information stored in the long-term memory can be retrieved by the working memory at any time to assist in the information processing (54). Consequently, it is possible that impairments in working memory lead to poor storage and retrieval of information from the long-term memory. In fact, a source of cognitive error occurs when a person loses his or her situation awareness (e.g., conscious of what is happening, perception of the environment, and anticipation of the near future) (55) as one of the sources of limitations for working memory is the inability of disregard sources of extraneous cognitive loads (54) causing the task demand to exceed the working memory capacity: decreasing performance (56). Consequently, it is possible that heat strain impairs working memory by acting as an significant extraneous cognitive load increasing the task demand beyond the working memory capacity to process information.

One of the main limitations of the working memory is the limited amount of storage for information (57) which affects other high order cognitive processes that depend on this
relevant information (58). For example, while reading a sentence, the reader requires the
capacity (working memory) to maintain the information in the reader’s mind so that its
comprehension is possible. However, there are differences between a good and a poor
reader. The first difference is related to storing capacity where a good reader is able to store
more information during reading than a poor reader (50). The second difference is due to
the fact that EF has a role in supervising, coordinating, and controlling goal-oriented
behaviour (49) by selecting relevant information and inhibiting irrelevant information from
working memory (50). Therefore, it is plausible that impairments in working memory may
impair other EF domains. For example, a meta-analysis by Berryman and colleagues (59)
reported impaired working memory among patients with chronic pain. According to the
authors, pain sensation diverts attention away from the task due to an impaired inhibitory
control (59).

Similar to inhibitory control, working memory is also linked to a rich neuronal
network located mainly in the frontal lobe (60). A meta-analysis by Wager and Smith (61)
reported that left and right frontal cortex are responsible for verbal and spatial working
memory respectively. A review by Christophel and colleagues (62), however, reported that
working memory has a more distributed nature using multiple areas from sensory and
parietal cortex. The contributions of cerebral regions other than the frontal cortex for
working memory represent the multifactorial nature of working memory (62). Therefore,
neural activity from various cerebral regions (e.g., parietal cortex, basal ganglia and sensory
cortex) is functionally necessary for maintenance and integration of information in working
memory. As a result, disruption in any neural activity in cerebral regions associated with
working memory may lead to impairments.
2.1.3 Cognitive Flexibility

Cognitive flexibility is a key trait of adaptive human behaviour (63) to adapt to a constant changing environment (64). Cognitive flexibility has different definitions (65) but it often refers to one's ability to shift back and forth between behaviours, thoughts and actions (66) in order to identify, process and respond to a given situation in different ways (63). The flexibility component is described by Davidson and colleagues (67) as the ability to shift from one mental set to another, which may be incompatible with the previous mental set. However, this shifting involves two phases. First, a mental set (i.e., behaviour, thoughts, action, etc.) is formed between a stimulus and a response allowing attentional focus to be placed on the stimulus and ignore distractions (68). Second, there is a shift to a different mental set that may conflict to the initial set, making cognitive flexibility essential in overcoming conflicting circumstances (68). The Wisconsin Card Sort Test is an example of cognitive flexibility, which provides a sorting rule to the participant to match cards based on color, number or shape. However, the sorting rule unpredictably changes throughout the test forcing the participant to identify such change and to create a new mental set that may be conflicting to the previous one (69). The time needed to identify the error/change, reconfigure a new mental set, to resolve the interference from a previous mental set and act is known as switch cost and is the main measure of cognitive flexibility tests (65).

Impairments in cognitive flexibility are better represented by pathological behaviour (65). For example, participants with obsessive-compulsive disorder showed significantly higher errors in a task-switching paradigm test than healthy participants (70). The results indicate that cognitive inflexibility is a trait among obsessive-compulsive disorder patients, which is portrayed as an impaired ability to switch between tasks (70). Similarly, Steinglass
and colleagues (69) reported impaired cognitive flexibility as a trait of anorexia nervosa. Patients with anorexia nervosa develop specific rules around starvation which lead to an inflexible eating behaviour regardless of any explicit desire to change (69). Therefore, both obsessive-compulsive disorder and anorexia nervosa patients are unable to shift between one behaviour/thought to another, demonstrating how cognitive flexibility can be impaired.

The core processes of cognitive flexibility are generally linked to the frontoparietal network such as the posterior parietal cortex and the inferior frontal junction of the brain (64). Eslinger and Grattan (63) assessed cognitive flexibility in patients with damage to the frontal lobe, basal ganglia and posterior cortices and reported impaired cognitive flexibility when the damage was in the frontal cortex and basal ganglia. In addition to the frontoparietal network, other parts of the prefrontal cortex such as anterior, mid and posterior regions (64) as well as the basal ganglia and the caudate nucleus may also be active as supplementary areas for cognitive flexibility (70).

2.1.4 The Effects of Cardiorespiratory Fitness on Cerebral Morphology and Executive Function

High levels of cardiorespiratory fitness (CRF) and physical activity are associated with prevention of physical comorbidities and diseases such as diabetes, hypertension and obesity. However, the benefits of an active lifestyle and high CRF are not only restricted to physical health – higher levels of CRF are associated with higher levels of cognitive performance (71).

Indeed, there is an increasing amount of research advocating the beneficial effects of exercise and high CRF on cerebral morphology. For example, chronic aerobic exercise and CRF are linked to a superior cerebral vascular function (72) and enhanced regulation of CBF
Pereira and colleagues (74) reported better cognitive performance on learning and memory tasks after a three month aerobic exercise program. According to the authors, the improvements in cognition seen with an improvement in CRF are linked to an increase in CBF (74). The relationship between CRF and CBF was also reported by Ainslie and colleagues (75) which examined the association between CRF and CBF in a total of 307 healthy men aged from 18 to 79 years old. The authors reported a consistent increase of ~17% (9.1 ± 3.3cm/s) in the middle cerebral artery velocity (MCAv) in fit individuals when compared to sedentary subjects (75). Supporting these findings, Braz and colleagues (76) assessed the effects of age and CRF on CBF using a bilateral measurement of blood flow in the internal carotid artery (ICA). It was found that the higher CRF group had a 31% greater ICA blood flow when compared to the lower CRF group. The authors concluded that high CRF was linked to a greater CBF due to an exercise-induced microvasculogenesis, improvement in endothelial and cardiac function (76).

In addition to differences in CBF, imaging studies showed global changes in cerebral structure due to chronic aerobic exercise (77) and high CRF (78, 79). For example, 1 year of aerobic training among older adults led to a high gray matter volume in the dorsolateral prefrontal cortex (DLPFC) which was associated with better cognitive performance on a Stroop test and a Spatial Working Memory assessment (80). In addition to the effects of aerobic exercise and higher levels of CRF on gray matter volume, high levels of CRF are also associated with an increase in white matter integrity and functional cortical connectivity (77). A study by Voss and colleagues (78) examined if an increase in CRF would lead to an increase in functional cortical connectivity and if such increases would improve working memory and task switching. It was also found an increase in functional cortical connectivity
as a function of an increase in CRF. In addition, a better performance was found in the spatial memory task and a decrease in switch cost (78). The authors concluded that the cognitive improvements seen after an increase in CRF were mediated by an increase in functional connectivity (78). The opposite relationship between CRF and cerebral structure is also true. According to Zhu and colleagues (73), low levels of CRF lead to structural cerebral changes such as white matter lesions, brain atrophy and decrease in CBF, which are related to impaired cognitive function later in life.

Given the evidence supporting the effects of high levels of CRF and aerobic exercise on cerebral structure, it is likely that CRF and aerobic exercise also affect EF. Indeed, there is some evidence that high CRF and chronic aerobic exercise are associated with a better EF – especially on tasks that require cognitive flexibility, selective attention, inhibitory control and working memory (72). Smiley-Oyen and colleagues (81) compared the separate effects of 10-months of aerobic training and strength training on Go/No-Go tasks. The authors reported that, even though both groups improved their CRF after 10-months of exercise intervention, only the aerobic training group showed a significant decrease in reaction time and number of errors (81). Similarly, Colcombe and colleagues (82) assessed the effects of CRF on spatial selection and inhibitory functioning during a flanker paradigm. The authors reported that high CRF individuals were better at dealing with conflicts than the low CRF. It was also reported that high CRF was associated with a higher activation of areas associated with selective attention and inhibitory response when compared to low CRF (82). Supporting these findings on CRF and inhibitory control, Martin and colleagues (83) compared inhibitory control between professional cyclists (peak power output: 414 ± 48 watts) and recreational cyclists (peak power output: 261 ± 28 watts) using a Stroop task. It
was found that professional cyclists showed superior Stroop task performance than their recreational counterparts. The authors hypothesized that the differences in cognitive performance were related to the superior aerobic training and lifestyle of professional cyclists (83).

In addition to inhibitory control, there is some evidence of beneficial effects of high CRF on working memory. A study by Hansen and colleagues (84) assessed the effects of an 8-week aerobic training and detraining program on prefrontal cognitive function. The authors found that the training group had faster reaction times and better performance on a working memory test when compared to the detraining group. It was concluded that an increase in CRF levels are related to an increase performance on tasks that involves working memory (84). Similarly, Kamijo and Takeda (85) assessed the effects of CRF on a Sternberg Working Memory Task on 72 undergraduate students. Although no differences in performance were seen between the high CRF and low CRF, there was a smaller amplitude in the event-related brain potentials in the high CRF group. The authors concluded that the high CRF group had a more efficient cognitive process than the low CRF group (85).

Overall, the research on the effects of aerobic exercise and CRF on cerebral structure and EF showed beneficial effects on CBF, functional cerebral connectivity, and gray and white matter volume. Ultimately, these morphological changes appear to enhance cerebral functioning and may be associated with a better EF.

2.2 Neurovascular Coupling

Despite its small relative mass (2-3% of body weight) the human brain consumes more than 20% and 25% of oxygen and glucose, respectively, at rest for aerobic energy
production. To match this significant need for oxygen and glucose, the human brain is highly vascularized with a complex regulation of blood flow (86, 87). The extracranial arteries, internal carotid artery (ICA) and the vertebral arteries (VA), are responsible for the blood supply to the cerebral vasculature. The ICA delivers blood to the frontal, parietal and temporal lobes and are responsible for approximately 70% of cerebral blood supply whereas the VA delivers blood to the brainstem, cerebellum and occipital lobe and is responsible for approximately 30% of the cerebral blood supply (18). Both ICA and VA supply blood to the Circle of Willis (Figure 2.1), which is a circulatory anastomosis that maintains cerebral perfusion if supply becomes disrupted in one or more arteries. In the Circle of Willis, blood flow is mainly distributed throughout the brain through three main arteries – the anterior cerebral artery (ACA), middle cerebral artery (MCA), and the posterior cerebral artery (PCA) – before it becomes segmented and wraps around the cerebral tissue (18, 88). This continuous anatomy is critical because if the blood supply becomes reduced/ceased from one of the extracranial arteries, cerebral blood supply is minimally affected, as there is a compensatory flow from adjacent arteries.

The Circle of Willis ensures a continuous supply of glucose and oxygen from the CBF as the brain has limited substrate storage and a high metabolic rate (19, 90). This close link between CBF and cerebral metabolism is also known as neurovascular coupling (18, 19, 91, 92). For example, Willie and colleagues (90) reported an increase of approximately 25% in blood flow velocity (an indirect measure of CBF) in the PCA with an activation of the occipital lobe through visual stimuli. Similarly, Lin and colleagues (93) reported that an increase of 8% in brain metabolism led to an increase of 65% in CBF. This disproportionate CBF response is twofold: first, it is believed to create a safety margin ensuring sufficient delivery
of oxygen and glucose; and, second, it ensures blood supply to the most distant neuronal structure (92). As a result, brain activation caused by a cognitive process will lead to a disproportionate increase in CBF to ensure that the active area and its surrounding structures are provided with enough oxygen and glucose.

![Figure 2.1 Structure of Circle of Willis.](image)

Neurovascular coupling is a vital physiological factor for normal cerebral function and, therefore, it is plausible to hypothesize that any disruptions in the neurovascular coupling can lead to brain dysfunction, such as cognitive impairments. Indeed, Zuccala and colleagues (94) reported cognitive impairments among patients with chronic heart failure due to a decrease in CBF. In addition, it was reported that cardiac transplantation, and consequently, restoration of CBF, led to some recovery of cognitive function (94). Supporting this connection between disrupted neurovascular coupling and impaired cognitive function, a review by Ogoh (19) concluded that cerebral vascular dysfunction (i.e., impaired CBF) precedes the onset of cognitive impairments and dementia. Therefore, a disruption in the
neurovascular coupling may lead to an abnormal brain function such as impaired cognitive function.

2.3 Hyperthermia

Under normothermic and resting conditions humans can dissipate heat at the same rate of heat production and, consequently, any disruptions in this equilibrium can lead to an increase or a decrease in body temperature (95). Hyperthermia is defined as an increase in core temperature \( T_{\text{core}} \) above the \( \sim 37^\circ \text{C} \) normal state of humans (96). It can be classified as mild, moderate and severe as \( T_{\text{core}} \) increases by \( \leq 1.0 \), \( 1.0 \) to 1.5 and \( \geq 1.5^\circ \text{C} \) respectively (89). The body's heat balance can be expressed by following equation:

\[
\dot{S} = \dot{M} \pm \dot{W}_k \pm \dot{R} \pm \dot{C} \pm \dot{K} \pm \dot{E}
\]

Where \( \dot{S} \) is body heat storage, \( \dot{M} \) is metabolic rate, \( \dot{W}_k \) is mechanical work, and \( \dot{R}, \dot{C}, \dot{K} \) and \( \dot{E} \) represent radiation, convection, conduction and evaporation respectively (97). A positive, zero and negative \( \dot{S} \) represent heat gain, thermal homeostasis and heat loss respectively. Therefore, exposure to high ambient temperature exceeds the body's capacity to lose heat, eventually leading to hyperthermia.

2.3.1 Hyperthermia and Cerebral Hemodynamics

Cerebral hemodynamics is closely regulated so that an adequate supply of oxygen and nutrients are provided to the cerebral tissue without excessive perfusion (18). Cerebral vasculature is highly sensitive and is primarily regulated by changes in partial pressure of carbon dioxide \( \left( P_{\text{aCO}_2} \right) \) (98). Additionally, a drop below 60 mmHg in partial pressure of oxygen \( \left( P_{\text{aO}_2} \right) \), an increase in sympathetic nervous activity (SNA) (99) and changes in cardiovascular function and hemodynamics can also modulate CBF (89). However, even mild
heat strain can cause changes in cerebral hemodynamics due to cardiovascular and respiratory adjustments to the heat (89, 100).

Hyperthermia elicits changes in the respiratory and cardiovascular systems, which may disrupt neurovascular coupling. For example, an increase in $T_{\text{core}}$ leads to a hyperventilatory reflex and, consequently, a decrease in $P_{\text{aCO}_2}$ (100). For example, Bain and colleagues (101) reported a reduction of approximately 15 mmHg in end-tidal partial pressure of carbon dioxide ($P_{\text{etCO}_2}$) due to the hyperventilatory reflex when $T_{\text{core}}$ was increased by 2°C. Similarly, Nelson and colleagues (44) reported that mild and severe hyperthermia increased ventilation by 17% and 54%, respectively. Therefore, hyperventilatory-induced decreases in $P_{\text{etCO}_2}$ appear to be an important CBF modulator (44, 89, 98, 102). In fact, Fan and colleagues (103) reported that hyperthermia-induced hyperventilation is the main determinant in reducing $P_{\text{etCO}_2}$ (Table 1).

More specifically, each mmHg change in $P_{\text{aCO}_2}$ above or below eucapnia (~ 40 mmHg) causes a 4% increase and 2% decrease in CBF, respectively (104). This shows that CBF is highly sensitive to changes in $P_{\text{aCO}_2}$ because it has a vital homeostatic role regulating central pH through ventilation (102). A hypercapnic state (increase in $P_{\text{aCO}_2}$) causes the smooth muscle of cerebral vessels to relax, leading to a dilatation of the cerebrovascular bed and an increase of CBF to wash out CO$_2$ from brain tissue (102). The opposite response is seen during hypocapnic state (decrease in $P_{\text{aCO}_2}$), which leads to a decrease in CBF through vasoconstriction of the cerebral vascular bed. Ito and colleagues (105) reported a decrease of 37.5% and 10.6% in CBF and cerebral blood volume respectively with a decrease of 10 mmHg in $P_{\text{aCO}_2}$. This relationship between the ability of cerebral vasculature to change blood flow in responses to changes in $P_{\text{aCO}_2}$ is known as cerebrovascular reactivity (106). In
addition to changes in $P_aCO_2$, CBF can also change in response to a drop in partial pressure of oxygen ($P_aO_2$). However, CBF is less sensitive to changes in $P_aO_2$ when compared to $P_aCO_2$ because it requires a drop of ~ 40 mmHg from baseline (~100 mmHg) for CBF to increase (102).

### Table 2.1 Impact of ventilation on arterial partial pressure of carbon dioxide and middle cerebral artery velocity (103).

<table>
<thead>
<tr>
<th>$T_{core}$</th>
<th>+0.5°C</th>
<th>+1.0°C</th>
<th>+1.5°C</th>
<th>+2.0°C</th>
</tr>
</thead>
<tbody>
<tr>
<td>VE (%)</td>
<td>+14%</td>
<td>+14%</td>
<td>+57%</td>
<td>+114%</td>
</tr>
<tr>
<td>$P_{et}CO_2$ (%)</td>
<td>- 8%</td>
<td>- 13%</td>
<td>- 29%</td>
<td>- 44%</td>
</tr>
<tr>
<td>MCAv (%)</td>
<td>- 6%</td>
<td>- 14%</td>
<td>- 24%</td>
<td>- 32%</td>
</tr>
</tbody>
</table>

Values are expressed as percentage differences from baseline. $T_{core}$ = core temperature; °C = degrees Celsius; VE = ventilation; $P_{et}CO_2$ = end-tidal carbon dioxide; MCAv = middle cerebral artery velocity.

In addition to the hyperthermia-induced hyperventilation and hypocapnia, a decrease in CBF has been speculated to be a result of thermoregulation. For example, a decrease in the middle cerebral artery velocity (MCAv), an indirect indicator of CBF (107), has been suggested to develop as a result of thermoregulation by shifting the blood flow from the ICA, which supplies blood to the MCA, to the external carotid artery, which supplies blood to the cutaneous vasculature (108). However, this hypothesis is unclear as Bain and colleagues (101) reported that, despite an increase of 250% in the external carotid artery blood flow during severe passive hyperthermia, it is unlikely to compromise blood flow to the ICA.

Moreover, hyperthermia may decrease CBF due to changes in the cardiovascular and nervous systems. Hyperthermia causes blood to be redistributed to the skin for thermoregulation, decreasing venous return and stroke volume (109). In fact, a study by Nelson and colleagues (44) reported a decrease of 9% in stroke volume caused by an
increase in cutaneous blood flow during passive hyperthermia led to a decrease of 26% in CBF. One of the cardiovascular consequence of elevated sympathetic nervous activity (SNA) during hyperthermia (100) is the redistribution of blood volume from the internal organs towards the cutaneous vasculature for thermoregulation (110).

Increased SNA, as seen during hyperthermia, is also speculated to play a role on cerebral vascular tone due to the dense adrenergic innervation of the cerebral arteries suggesting a potential neurological regulation of CBF (100). Although, the role of SNA on cerebral circulation and CBF during heat stress remains hypothetical, animal and human studies show that SNA has the potential to regulate CBF and cerebrovasculature at normothermia (89). For example, the role of SNA on CBF regulation is supported by pharmacological studies which showed an increase in CBF due to sympathetic ganglia blockage (90). In fact, data from animal studies (111, 112) reported that sympathectomy increased CBF by approximately 26.5%, demonstrating that SNA withdrawal contributes to CBF regulation. Similarly, Sadoshima and colleagues (113) assessed the effects of an increase in intracranial pressure (ICP) on cerebral sympathetic nerves on rabbits. The authors found that an increase in ICP by 40 mmHg led to a 3-5 times increase in cerebral sympathetic activity, causing a 49% reduction in CBF (from 55 ml·min⁻¹·100g⁻¹ to 27 ml·min⁻¹·100g⁻¹) despite no changes in P_aCO2. It was concluded that the increase in cerebral sympathetic activity was a protective reflex to prevent excessive perfusion in the brain (113) and reduce the risk for blood-brain barrier breakdown (114). Although most studies assessing the role of SNA on CBF regulation were performed on animals, human studies have similar findings. Umeyama and colleagues (115) examined the sympathetic control of cerebral vasculature using an unilateral pharmacological blockage of the stellate ganglion in healthy males. The
authors found an increase of CBF in the blocked hemisphere following the pharmacological blockage with no changes in the non-affected side (115). Similarly, Fernandes and colleagues (116) assessed the role of SNA on ICA blood flow through a pharmacological blockade of adrenergic receptors during a static handgrip hold. The adrenergic receptor blockage led to a different increase in ICA blood flow (contralateral = from 348 ml·min⁻¹ to 406 ml·min⁻¹; ipsilateral = 355 ml·min⁻¹ to 410 ml·min⁻¹) when compared to the control group (contralateral = from 362 ml·min⁻¹ to 443 ml·min⁻¹; ipsilateral = 375 ml·min⁻¹ to 365 ml·min⁻¹). Since static handgrip hold is a potent sympathetic stimulus, the authors concluded that the adrenergic receptor blockage and therefore a block in the SNA led to impairments in the cerebral autoregulation during an increase of blood pressure (116). Collectively, pharmacological studies showed that SNA may play a role in cerebral autoregulation (117).

In addition to the pharmacological studies, the effects of SNA on CBF are also seen in studies using the Valsalva maneuver – a breathing technique that can be used to stimulate SNA. Zhang and colleagues (118) assessed the effects of the Valsalva maneuver and an increase in SNA on cerebral hemodynamics in humans. The authors found that a pharmacological SNA blockage doubled CBF increase during the Valsalva maneuver suggesting the presence of a neurogenic component in the cerebral autoregulatory responses. Therefore, if increased SNA is associated with a cerebral vasoconstriction and hyperthermia increases SNA, it is plausible to speculate that sympathetic-mediated vasoconstriction during hyperthermia contributes to a decrease in CBF. However, the exact role of SNA on CBF regulation is inconclusive and instead of being a direct regulator of CBF, SNA may have a protective role against sudden increases in blood pressure (119) and excessive perfusion of cerebral circulation (112). Similar to the Valsalva maneuver, lower
body negative pressure (LBNP) is also known to stimulate SNA. Kaur and colleagues (120) assessed the effects of graded sympathetic activation via LBNP on regional CBF in healthy men. It was found that when subjects were exposed to -50 mmHg, ICA and VA blood flow were reduced by 12.4% and 12% respectively and MCAv was reduced by 13%. Moreover, when exposed to -70 mmHg, ICA and VA blood flow were reduced by 21% and 27.6% and MCAv was reduced by 23% (120). In addition to the reduction in blood flow, both ICA and VA suffered a 6% and 7% reduction in vessel diameter. It was concluded that an increase in SNA via LBNP led to vasoconstriction in the ICA and VA vessels and, although MCA diameter was not assessed, it was hypothesized the vasoconstriction in the MCA was due to a 14% decrease in MCA conductance (120).

Lastly, hyperthermia-induced changes in cardiovascular factors such as mean arterial pressure (MAP – a result of cardiac output and total peripheral resistance) can impact CBF. Cerebral perfusion pressure is the net pressure gradient that drives cerebral perfusion, and is a product of MAP and intracranial pressure (89). However, one consequence of hyperthermia is an increase in cutaneous vascular conductance (121) which has a negative effect on cardiac output (89). Therefore, to prevent drops in MAP during hyperthermia there is an increase in cardiac output via an increase in heart rate (121) even though in certain cases (e.g., orthostatic challenge and dehydration), the increase in cardiac output is insufficient to maintain MAP and cerebral perfusion (89). Indeed, a review by Ogoh and Ainslie (106) pointed to cardiac output as an important factor for CBF maintenance. For example, one way to test the connection between cardiac output and CBF is by manipulating central blood volume. Ogoh and colleagues (122) tested the connection between cardiac output and MCAv by both an increase and decrease in central blood volume. The authors
reported that a negative pressure of 16 mmHg via LBNP decreased cardiac output and MCAv by 18% and 6% respectively due to a decrease in central blood volume. In addition, infusion of albumin increased central blood volume leading to an increase in cardiac output and MCAv by 30% and 11% respectively. The authors concluded that cardiac output and MCAv have a positive linear relationship during normothermic conditions without changes in MAP and $P_aCO_2$ (122). Although these findings support the relationship between cardiac output and CBF at normothermic conditions, this might not be valid during hyperthermia. As internal temperature increases, approximately 50% of the cardiac output goes to cutaneous circulation leading to a decrease in central blood volume (121). To prevent abrupt decreases in arterial blood pressure, the baroreceptor reflex increases heart rate and total peripheral resistance leading to an increase in cardiac output (121). However, in contrast to what occurs under normothermia conditions, during hyperthermia, changes in cardiac output have minimal effects on CBF. In fact, an increase of 1.4°C in $T_{core}$ increased cardiac output by 58% with a concomitant decrease of 25% in MCAv (123). This difference between normothermia and hyperthermia is due to the fact that most of the increase in cardiac output is distributed to the cutaneous circulation (i.e., extracranial circulation) due to a lower vascular resistance (123). This is supported by Schlader and colleagues (124) who assessed if an acute plasma expansion could reverse the hyperthermia-induced decrease in CBF. The authors reported that an increase of ~1.1°C in pulmonary artery blood temperature reduced MCAv by 12% and that an increase of 3 L·min⁻¹ in cardiac output through saline infusion did not restore MCAv to normothermic levels. Despite the fact that an acute volume expansion restored central blood volume to baseline values, the extra volume increased blood flow in low resistance vascular beds (i.e., cutaneous circulation) whereas blood flow in high
resistance vascular beds (i.e., cerebral vasculature) remained constant (124). Based on the reviewed findings, cardiac output does not appear to affect CBF during hyperthermia.

2.4 Proposed Theories on Cognitive Performance and Thermal Strain

The reviewed literature reports impairments in cognitive processes – such as EF – during thermal strain (16). It has been proposed that impairments in cognitive processes during heat exposure are related to a number of potential mechanisms ranging from changes in arousal to a depletion of neural resources (1, 5). Therefore, this section will focus on proposed theories that aim to explain changes in cognitive processes during hyperthermia.

2.4.1 Arousal Theory and the Individual Zone of Optimal Functioning

The Arousal Theory is based on the concept that performance efficiency is a function of arousal (125) – a state of general drive (126) which involves non-specific physiological and psychological components of alertness (127). The Arousal Theory has an inverted U-shape (Figure 2.2) going from low to high levels of arousal with the extremes being considered inhibitive and disruptive, respectively, with an “optimal facilitation” zone in the middle (127). Therefore, this theory proposes that performance efficiency and arousal levels increase simultaneously until it reaches a threshold or peak performance and that performance decreases with a further increase in arousal – this relationship constitutes the principle of the Yerkes-Dodson Law (126).

This inverted U-shape relationship between mental performance and arousal level is a way to interpret the effects of temperature on cognitive performance (125). A study by Åkerstedt and colleagues (128) reported that $T_{\text{core}}$ and alertness have a direct relationship as both reach their peaks at the same time and that further increases in $T_{\text{core}}$ impairs
alertness. Similarly, as $T_{core}$ increases, the arousal level also increase, leading to an improvement in cognitive performance up to an “optimal arousal level” (128). Once arousal pass the optimal arousal level, further increases in $T_{core}$ and arousal will lead to a decrease in performance (125).

![Figure 2. 2 The inverted U-shape relationship between arousal and performance (99).](image)

However, the Yerkes-Dodson Law has been criticized due to four reasons: it fails to precisely predict performance, does not offer a theoretical explanation, does not take into consideration interindividual differences for the relationship between arousal and performance, and does not consider the multidimensional nature of arousal (129). While the Yerkes-Dodson Law uses an inverted-U relationship between arousal and performance, the Individual Zone of Optimal Functioning (IZOF) proposed by Hanin (130) highlights the fact that each individual has a zone of optimal range of arousal for best performance. The IZOF differs from the inverted U-shape because the zone for best performance may be low, medium or high based on both exogenous and endogenous factors that might influence performance (131), which deteriorates if the arousal level is outside of the zone for best
performance (132). This way, according to the IZOF it is possible to have an optimal performance even when arousal is at minimal levels if that is the individual’s optimal zone. In this case, hyperthermia could impair cognitive performance once arousal increases from minimal levels whereas for some other people with a high IZOF arousal, hyperthermia could, theoretically, improve cognitive performance.

2.4.2 Maximal Adaptability Model

The Maximal Adaptability Model (MAM) was first proposed by Hancock (133), integrating both physiological and psychological functioning in response to a stressor (134). In this model, a stressor is considered a force that degrades performance capacity due to a limited amount of coping mechanisms (135) leading to a competition for cognitive resources (125) and is often considered as part of the environment (e.g., temperature, vibration, noise, etc.) (133).

Figure 2.3 The Maximal Adaptability Model (136).
In addition, the MAM describes a specific stressor as an input which may or may not cause an adaptive or compensatory response, which may lead to an output that reflects changes in physical function or behaviour towards a specific goal (135). In the MAM framework (Figure 3), stress level ranges from hypostress (underload) to hyperstress (overload) and has two dynamic instability regions on its extremes and a dynamic stability zone in the middle – which is further divided in four zones (133). At the center of this framework lies the “normative zone” where the stressor is not strong enough to cause compensation and performance is not affected. Surrounding the normative zone, lies the “comfort zone” where the stressor causes some compensatory responses but performance remains close to its best level (134). As the stressor falls beyond the comfort zone towards the “psychological zone of maximal adaptability”, there is a progressive depletion of available neural resources due to its use by the compensatory mechanism. When the stressor falls in the psychological zone of maximal adaptability cognitive performance starts to decline due to the lack of available neural resources (135). However, if a stressor is powerful enough to fall in the “physiological zone of maximal adaptation”, the body's homeostasis will be disrupted provoking physiological responses to restore homeostasis (133). If stressor's intensity continues to increase (by either increasing its duration and/or intensity) it will lead to the life-threatening aspects of stress exposure – also known as the region of dynamic instability (134). For example, an exposure to mild heat stress may not impact cognitive performance negatively and may even increase performance. It happens because the compensatory mechanism (thermoregulation) does not deplete enough neural resources and heat stress can add extra stress towards the comfort zone, however, if prolonged, hyperthermia may use more neural resources for thermoregulation. This would impair
cognitive performance due to the lack of available resources and, if heat exposure is continued beyond the physiological capacity to dissipate heat, life-threatening conditions may arise such as heat stroke.

### 2.5 Effects of Thermal Strain on Executive Function

Heat stress is considered an occupational hazard because it is often associated with impairments in EF. Mazloumi and colleagues (137) investigated EF in two different groups of workers: one group worked under heat stress (~33°C) conditions while another group worked in a cool (~17°C) environment for three hours. The authors found an increase in test duration, reaction time and errors in the incongruent part of the Stroop Colored-Word Test. Similarly, a recent study by Saini and colleagues (138) assessed EF and reaction time among soldiers in conditions sufficient to cause heat stress and reported a decrease in EF. According to the authors, heat stress impaired working memory and cognitive flexibility, whereas reaction time was unchanged, suggesting that complex tasks are more sensitive to heat stress (138). Supporting the findings from these occupational studies, a meta-analysis by Pilcher and colleagues (11) described the relationship between ambient temperature and cognitive performance as an inverted U-shape with significant decrease in cognitive performance with exposures to ambient temperature below 10°C and above 32°C. In addition, the authors reported that ambient temperature between 21°C and 26°C results in little to no effect on cognitive performance (11). Although a limitation of these studies was the absence of physiological and perceptual measurements, it supports the detrimental effects of elevated ambient temperature on cognitive functioning.

According to Cheung (3) it is critical to understand how elevations in $T_{core}$ impact cognitive function, since different cognitive processes such as executive function, attention,
and planning may have different thresholds for impairments. In addition, the magnitude of cognitive impairments depends on the intensity of heat strain and the complexity of the cognitive tasks (139) in which complex cognitive tasks are more sensitive to thermal strain than simple cognitive tasks (16). This difference between complex and simple tasks is related to the difference in cognitive effort and the amount of neural resources used by these processes (2). Therefore, simple tasks require low cognitive effort and few neural resources, whereas complex cognitive tasks require a greater cognitive effort and more neural resources (1, 2, 16). Because of the variety of cognitive processes and the focus of this literature review, the remainder of this section will concentrate on the effects of hyperthermia on EF, as impairments in EF are well documented and are seen even during mild hyperthermia (32, 33).

A functional magnetic resonance image (fMRI) study by Liu and colleagues (13) assessed the effects of passive hyperthermia (50°C and 40% relative humidity) on attention networks and reported an impairment in executive function at $T_{\text{core}}$ of 38.4°C despite an increased activity in the prefrontal cortex (13). In a follow-up study, Liu and colleagues (140) reported a positive linear relationship between $T_{\text{core}}$ and impairments in EF, indicating that EF was not only impaired by reaching a specific threshold but throughout the development of hyperthermia. Indeed, impairments in EF are seen at early stages of mild hyperthermia and severe hyperthermia led to significant impairments (141).

Hyperthermia is also linked to an increase in impulsivity. Gaoua and colleagues (16) reported a significantly higher amount of false alarms in the rapid visual information processing test during severe hyperthermia. The authors concluded that severe hyperthermia impairs inhibitory control, where participants were unable to withhold a
response leading to impulsivity (16). Furthermore, impairments in inhibitory control are also seen in moderate hyperthermia. Shibasaki and colleagues (142) examined the effects of moderate hyperthermia on inhibitory control and reported that error rate in the Go/No-go test in the hyperthermic condition was twice as higher as at thermoneutral (142). These findings are in agreement with Sun and colleagues (32), who reported an impaired ability to inhibit responding and a deficit in conflict resolution after an increase of 1.1°C in T<sub>core</sub>. Although the comparison between different magnitude of hyperthermia on inhibitory control are not possible due to different tests used, there is evidence that hyperthermia impairs inhibitory control. This way, hyperthermic people might engage in risky behaviours due to an impaired executive control.

Similarly to what happens to inhibitory control, working memory is also impaired by hyperthermia. A study by Gaoua and colleagues (16) reported that visuospatial component of working memory was significantly impaired during severe hyperthermia when compared to thermoneutral (16). These findings are in agreement with Racinais and colleagues (10) who reported that spatial span and the percentage of correct answers in the pattern recognition memory were significantly lower during severe hyperthermia. Furthermore, working memory shows the same pattern as cognitive flexibility where impairments occur even with mild hyperthermia. A study by Bandelow and colleagues (143) assessed working memory during mild hyperthermia and reported impairments on speed and accuracy in the Corsi block-tapping test and the Sternberg test. Once again, although comparison between different studies are not possible due to different tests, there is evidence that hyperthermia impairs working memory.
Research on hyperthermia and cognitive function have focused mainly on measuring physiological variables (e.g., $T_{\text{core}}$ and $T_{\text{skin}}$, heart rate, etc.) during cognitive tests, but the literature lacks assessment of the separate and combined effects of $T_{\text{core}}$ and $T_{\text{skin}}$ along with manipulation of CBF (3). According to Gaoua (6) impaired cognitive function during hyperthermia could be partially explained by the alliesthesial effect, in which $T_{\text{skin}}$ may induce either feelings of pleasure (positive alliesthesia) or displeasure (negative alliesthesia) given the body’s thermal status. The role of the alliesthesial effect on cognitive function is important because a displeasure feeling may be seen as a cognitive load leading to distraction and reduced available neural resources for cognitive functioning (6). Gaoua and colleagues (9) assessed the effects of displeasure feelings through an elevated $T_{\text{skin}}$ and no changes in $T_{\text{core}}$ on cognitive functioning and reported impairments in cognitive function when $T_{\text{skin}}$ was increased by 3°C. The authors concluded that an increase in $T_{\text{skin}}$ may be a sufficient thermal stimulus to impair cognition (9). However, findings about the alliesthesial effect on cognition are inconsistent. A study by Simmons and colleagues (139) tested the combined and separated effects of elevated $T_{\text{skin}}$ and $T_{\text{core}}$ on cognition and reported cognitive impairments only when both $T_{\text{skin}}$ and $T_{\text{core}}$ were elevated. In addition, head and neck cooling to decrease thermal perception, cardiovascular strain, and thermal discomfort failed to reduce the hyperthermia-induced impairments on cognition (139). The authors suggested that head and neck cooling might have been insufficient to restore cognition and recommended future studies to assess the effects of whole-body cooling instead.

In addition to the alliesthesial effect, hyperthermia may cause impairments due to changes in brain physiology, as hyperthermia disrupts functional neural connections throughout the brain. A fMRI study by Qian and colleagues (144) assessed 4005 functional
connections throughout the entire brain during passive hyperthermia and reported 67 inter-regional connections were altered with hyperthermia. A total of 54 inter-regional correlations (mainly in the frontal, parietal, temporal and occipital lobe) were decreased and 13 inter-regional correlations (mainly in the insula, basal ganglia, and thalamus) were increased when compared to the control (144). A similar fMRI study was performed by Sun (145) and reported that hyperthermia-induced reductions in functional connectivity were mainly located in the prefrontal cortex, temporal lobe, and occipital lobe. Therefore, it is possible that hyperthermia alters normal functional connectivity pattern within the brain, which may be another possible explanation for the impairments in cognitive performance.

2.5.1 Possible Effects of Cerebral Blood Flow and $P_{\text{etCO}_2}$ on Executive Function

Previous research showed that a close spatial and temporal relationship between cerebral blood flow and neural activity is required for normal cognitive function (19) and that cerebral hypoperfusion is linked to impairments in cognitive function (146). Therefore, if normal cognitive functioning requires adequate blood supply, it is possible that impairments in cognitive function may be related to a hyperthermia-induced decrease in CBF. The combination of results from different studies suggests that decreases in $P_{\text{etCO}_2}$ and CBF may cause impairments in cognitive tasks such as EF. A study by Schlader and colleagues (12) appears to be the only study that attempted to assess cerebral perfusion during cognitive activation during moderate hyperthermia, reporting that hyperthermia does not disrupt the neurovascular coupling mechanism.
2.6 Gaps in the Literature

Despite current research on the effects of hyperthermia on cognitive functioning, there is limited evidence available on the relationship between CBF and cognitive performance under passive hyperthermia. Schlader and colleagues (12) that has attempted to assess this relationship, and reported that hyperthermia did not alter cerebral perfusion during cognitive activation. However, the authors assessed only one component of EF (working memory) and reported a decline in CBF far less than other studies (44, 98, 103) reported under similar conditions. Therefore, a decrease in CBF due to respiratory hypocapnia may have a role in the hyperthermia-induced impairments in executive function.

In addition, the available literature on the effects of hyperthermia on cognitive functioning lacks a systematic assessment of physiological and perceptual thermal strain throughout the cognitive performance (3). For example, no study attempted to assess cognitive function while clamping P$_{et}$CO$_2$ and CBF during hyperthermia. This way, it is not possible to assess how the separate variables (T$_{skin}$, T$_{core}$, CBF, thermal sensation and thermal comfort) play a role in EF impairments during hyperthermia.
3. 3. Study Objectives and Hypotheses

3.1 Objectives

The objectives of this study are:

1. The primary objective of this study is to examine the combined and separate effects of changes in thermal sensation/discomfort caused by an increase in mean skin temperature and central temperature (core temperature) on executive function impairments.

2. The secondary objective of this study is to examine the effects of a reduced cerebral blood flow due to a hyperthermia-induced hypocapnia on executive function impairments.

3.2 Hypothesis

It is hypothesized that core temperature will be the main factor in executive function impairments as it leads to an increased brain temperature, disruptions on functional cerebral connectivity.

It is also hypothesized that maintenance of cerebral blood flow during the isocapnic conditions will restore executive function as it preserves the coupling between cerebral metabolism and nutrients delivery.
4. Methods

4.1 Participants

The experimental protocol and procedures were approved by the Bioscience Research Ethics Board at Brock University (REB #17-385) and conformed to the Declaration of Helsinki. Ten males (n = 12) participants from Brock University volunteered to participate in this study. The mean ± SD age, height, body mass, body fat %, cerebrovascular reactivity to CO₂, maximal aerobic capacity and cognitive failure questionnaire were 24 ± 1.8 years, 180.0 ± 4.9 cm, 77.5 ± 9.7 kg, 10.2 ± 5.6 %, 1.32 ± 0.3 cm·s⁻¹·mmHg⁻¹, 45.1 ± 8.1 ml·kg⁻¹·min⁻¹ and 23.2 ± 6.8 respectively. Female participants were not recruited (excluded) for this study due to known sex-related differences in cerebrovascular reactivity to CO₂ (147, 148), thermal perception (149) and thermoregulatory responses (150). Participants were also excluded if they had a diagnosed cardiovascular, respiratory and/or neurological condition.

4.2 Experimental Design

Each participant visited the Environmental Ergonomics Laboratory on four different occasions. The first visit was used as a screening session (described in the ‘4.2.1 Screening’ section), wherein a physician performed a health screening. The participant returned to the lab for a familiarization trial (described in the ‘4.2.2 Familiarization Trial’ section), then were scheduled for two randomized experimental sessions (described in the ‘4.2.3 Experimental Trial’ section) consisting of a poikilocapnic (no intervention on PetCO₂) and an isocapnic (PetCO₂ was maintained throughout the heat stress) condition, with at least 7 days apart to reduce the potential effects of fatigue or heat acclimation. Both trials started at the same time of the day to minimize the influence of the circadian rhythm on Tcore. The participant was
blinded to the order of the experimental trials, which were randomly selected (www.random.org).

4.2.1 Screening Session

The participant filled out a modified 2018 Physical Activity Readiness Questionnaire (151) which detailed the participant’s current health status, use of medication, and health history. Participants were excluded from the study if they had a diagnosed cardiovascular, respiratory, or neurological condition. The participant was also screened using the Cognitive Failure Questionnaire which is a self-evaluative questionnaire with 25 items that measures spatial orientation failures, memory lapses, motor functioning and is related to four factors of absentmindedness such as memory, distractibility, blunders, and names (152). Items were scored on a 5-point Likert scale (0 = never and 4 = very often) and scores can range from 0 to 100. The participant was excluded from this study if the score was >45 as it indicates considerable difficulties in completing tasks that require vigilance.

4.2.2 Familiarization Session

During the familiarization, all participants were given the opportunity to practice experimental protocols and acquaint themselves with the experimental equipment in the following order: first, height, weight, and body fat (described in the ‘4.3.1 Body Fat Assessment’ section) were assessed; second, each participant performed a cerebrovascular reactivity test to CO₂; third, each participant practiced the executive function testing battery (EFTB; described in the ‘4.4 Executive Function Testing Battery’ section) three times with a 10-minute break in between; lastly, the participant performed a maximal aerobic capacity test (VO₂peak; described in the ‘4.3.10 Maximal Aerobic Capacity’ section).
The cerebrovascular reactivity to CO₂ test exposed the participant to different CO₂ manipulations to familiarize the participant with the end-tidal forcing system and the data from this test were used to quantify the participant’s cerebrovascular reactivity to CO₂ (cm·s⁻¹·mmHg⁻¹). The participant was exposed to three stages with different concentrations of CO₂ for four minutes each. First, the participant breathed normal air (eucapnia) and baseline $P_{etCO2}$ was measured. Following the baseline, hypercapnia was induced by the end-tidal forcing system by increasing the amount of inspired CO₂ until $P_{etCO2}$ was 10 mmHg above baseline level. Lastly, hypocapnia was induced through hyperventilation until $P_{etCO2}$ decreased by 10 mmHg from baseline level. In addition to the end-tidal forcing system, middle cerebral artery velocity was measured using a transcranial doppler ultrasound (described in the ‘4.3.6 Middle Cerebral Artery Velocity’ section).

4.2.3 Experimental Sessions

Upon arriving to the laboratory, participants were asked to change into exercise shorts and to provide a urine sample for hydration assessment (described in the ‘4.3.2 Hydration Status’ section). If euhydrated, the participant’s nude body mass was taken, and the participant proceeded with the experiment (Figure 4.1).

To measure real-time body rectal temperature, the participant inserted a rectal thermistor (described in ‘4.3.3 Temperature Measurement’ section) in a private washroom. Instrumentation began by dressing the participant with the liquid conditioning garment (LCG) and placing the $\overline{T}_{skin}$ thermistors, electrocardiogram electrodes, silicone mask for the end-tidal forcing system, the finger blood pressure cuff, and the transcranial doppler system.
An impermeable polyvinyl rain suit was used by the participant over the LCG to eliminate evaporative heat loss creating an uncompressible heat stress environment.

During the passive heating protocol, the LCG was perfused with 49°C water and 10°C during the passive cooling protocol, at a flow rate of approximately 2.5 L·min⁻¹. The target water temperature was achieved by adding hot or cold water and was maintained by an immersion circulator (VWR MX Immersion Circulators, VWR International, PA, USA).

During each experimental session, participants performed the EFTB four different times: baseline (BASE); cold core and hot skin (C-H); hot core and hot skin (H-H); and, hot core and cold skin (H-C). BASE testing point consisted of the participant already
instrumented, sitting in a supine position without water perfusion. The C-H testing point was identified when $T_{\text{skin}}$ increased by approximately 4.5°C above baseline. The test at this time point assessed the effects of elevated $T_{\text{skin}}$ on EF despite no changes in rectal temperature ($T_{\text{re}}$). The H-H testing point started when $T_{\text{re}}$ increased by 1.5°C above baseline or when the participant achieved the thermal intolerance point – the point where the participant asked the heating protocol to be stopped. The test at this time point assessed the combination of both elevated $T_{\text{skin}}$ and $T_{\text{re}}$ on EF. The H-C testing point started when $T_{\text{skin}}$ dropped approximately 4°C from the H-H condition as it restores thermal comfort (153, 154). The test at this timepoint assessed the effects of elevated $T_{\text{re}}$ on EF.

Each testing point (baseline, C-H, H-H and H-C) consisted of an EFTB, thermal comfort, and thermal perception as well as manual blood pressure test before and after. The EFTB (described in the ‘4.4 Executive Function Test Battery’ section) consisted of four different tests (the Groton Maze Learning Task, Detection Task, Two-Back Task, Set-shifting Task and the Groton Maze Learning Recall) which assessed the three components of EF (inhibitory control, working memory and cognitive flexibility). The manual blood pressure test was used to normalize the blood pressure readings from the photoplethysmography.
Once the participants completed the assessment in the H-C time point, they were de-instrumented followed by a nude body weight measurement and were monitored for 30 minutes to ensure that there were no side-effects caused by the experimental protocol.

4.3 Equipment/Assessments

4.3.1 Body Fat Assessment

Body fat was assessed using the 7-site (chest, mid-axilla, triceps, subscapular, abdomen, supra-iliac crest and thigh) skinfold protocol as described by Jackson and Pollock (155). Body density (Db) was calculated from the sum of skinfolds (ΣSKF) using the following equation:

\[
Db \text{ (kg} \cdot \text{m}^3) = 1.1120 - 0.00043499 \times (\Sigma SKF) + 0.00000055 \times (\Sigma SKF^2) - 0.00028826 \times \text{age}.
\]

Once Db was calculated, body fat (BF) was calculated using the following equation:

\[
BF \% = \left[\frac{4.95}{Db} - 4.5\right] \times 100 \quad (156).
\]

4.3.2 Hydration Status

Hydration status was assessed before and after each experimental trial using a refractometer (PAL-10S, Atago, USA) to measure the urine specific gravity, with \( \leq 1.02 \) used as a cut-off value for euhydration (157). If this threshold was exceeded, 0.5 L of water was consumed, and urine specific gravity was reassessed 30 minutes later. If euhydration was confirmed, the participant proceeded with the trial.
4.3.3 Temperature Measurement

During each trial, $T_{re}$ was continuously measured using a thin and flexible rectal thermistor (Mon-A-Therm Core, Mallinkrodt Medical) inserted by the participant 15 centimeters beyond the anal sphincter.

Mean skin temperature ($\bar{T}_{\text{skin}}$) was continuously measured using flexible thermocouple (PVC-T-24-190, Omega Environmental Inc.) taped to four different skin sites (chest = $T_{\text{chest}}$; arm = $T_{\text{arm}}$; thigh = $T_{\text{thigh}}$; and calf = $T_{\text{calf}}$) and was converted to $\bar{T}_{\text{skin}}$ using the following equation:

$$\bar{T}_{\text{skin}} (^\circ C) = 0.3 \times (T_{\text{chest}}) + 0.3 \times (T_{\text{thigh}}) + 0.2 \times (T_{\text{arm}}) + 0.2 \times (T_{\text{calf}}) \ (158).$$

4.3.4 Blood Pressure Measurement

Beat by beat blood pressure was assessed using a photoplethysmography (Nexfin, BMEYE B.V., Amsterdam, Netherlands) with the finger cuff placed on the medial phalanx of the middle finger on the left hand. The physiological calibration (Physiocal) with a threshold interval of 50 beats was used to improve the quality of the continuous blood pressure measurement from the finger. In addition, manual blood pressure was taken on the left arm before and after each executive function test to normalize the finger cuff blood pressure measurements.

4.3.5 Electrocardiogram

A 3-lead electrocardiogram (ECG; BioAmp, ADInstruments, Colorado Springs, USA) was used to measure heart rate. The ‘right arm’ and ‘left arm’ leads were placed under the right and left clavicle close to the shoulders. The ‘left leg’ lead was placed on the left side of the rib cage below the pectoralis muscle. Heart rate was continuously measured from R-R
intervals from the 3-lead ECG signal and was calculated using Lab Chart (Version 8, ADInstruments, Colorado Springs, USA).

Exercise electrodes (PerformancePlus, Vermed, Buffalo, USA) were used to ensure proper adherence to the skin and quality readings. The lead sites were shaved and cleaned with rubbing alcohol prior the electrodes placement.

4.3.6 Middle Cerebral Artery Velocity Measurement

Cerebral blood velocity was measured through a bi-lateral assessment of the middle cerebral artery velocity (MCAv) using a 2 MHz Transcranial Doppler (TCD) Ultrasound system (Doppler-Box, Compumedics DWL, San Juan Capistrano, USA). The ultrasound probes were positioned over the temporal window and were secured in place using a head frame (M600 Headframe, Spencer Technologies, Seattle, USA). The TCD signals were identified and optimized following techniques described by Willie and colleagues (107).

MCA was selected for this study as it is the primary blood supplier (159) to the cerebral areas associated with EF (160, 161) and because previous research revealed similar changes in blood velocity from ACA and MCA during cognitive activation (162).

4.3.7 End-Tidal Gas Measurement

Participants breathed through a silicone face mask (7450 Series Silicone V2 Oro-Nasal Mask, Hans Rudolph, Shawnee, USA), which was attached to a dynamic end-tidal forcing system. Inspired flow rate was measured using a pneumotach (3813, Hans Rudolph, Shawnee, USA) while expired fractions of O₂ and CO₂ were sampled and analyzed in real time using a gas analyzer (ML206, AD Instruments, Colorado Springs, USA). The PₑCO₂ was
measured and controlled using a custom end-tidal forcing system described by Hartley and colleagues (163).

This study had two experimental trials: a poikilocapnic (in which $P_{et}CO_2$ values were measured but not controlled) and an isocapnic (in which the end-tidal forcing system maintained $P_{et}CO_2$ at baseline levels). Since the end-tidal forcing system analyzes every breath, participants wore the mask throughout the entire experimental trial though they were allowed to momentarily remove the mask for hydration in between the EFTB periods.

Figure 4.3 – Setup of the transcranial doppler ultrasound with the end-tidal forcing system.

4.3.8 Liquid Conditioning Garment

A close-fitting liquid conditioning garment (LCG; BCS 4 Cooling System, Med-Eng, Ottawa, Canada) was worn by the participants throughout the experimental trial. The LCG contains Tygon tubing throughout the garment, which was perfused by water, with only the
participant’s face, hands and feet left uncovered. To promote maximum heat exchange between the LCG and the participant’s skin, the participant wore only shorts during the experiment trials. In addition, an impermeable polyvinyl rain suit was worn over the LCG to minimize evaporative heat loss.

4.3.9 Thermal Comfort/Thermal Sensation

To examine any potential effects of changes in perception and sensation on EF, thermal comfort (TC) and thermal sensation (TS) values were assessed at each experimental time point (baseline, C-H, H-H, H-C and post). TC is a 4-point scale (153) (1 – comfortable; 2 – slightly comfortable; 3 – uncomfortable; and 4 – very uncomfortable) and assessed how temperature was rated by the participant. TS (TS) is a 7-point scale (153) (1 – cold; 2 – cool; 3 – slightly cool; 4 – neutral; 5 – slightly warm; 6 – warm; and 7 – hot) and assessed the participant’s subjective rate of comfort for the thermal impulse.

4.3.10 Maximal Aerobic Capacity

Peak oxygen consumption (VO$_2$peak) was measured in a thermoneutral environment (~22°C, 30% relative humidity) on a cycle ergometer (Velotron, RacerMate Inc., Seattle, WA). Prior to the test, the participant completed a 5-minute rest period followed by a 5-minute warm-up period at 100 watts followed by an incremental workload of 25 watts every minute until volitional exhaustion. The participant wore a soft silicone mask connected to a gas analyser system (ML206, AD Instruments, Colorado Springs, USA). VO$_2$peak was defined as the highest 30s value of oxygen consumption. Once volitional fatigue was achieved, the participant performed a 5-minute cool down period at 75 watts followed by a 5-minute rest period.
4.4 Executive Function Test Battery

4.4.1 Groton Maze Learning Task

The Groton Maze Learning Task (GMLT) (CogState, New Haven, CT) is a touch screen-based test which assesses spatial working memory, information processing and error monitoring (34, 164). The GMLT is a 10x10 grid of tiles with the task to find a hidden pathway (28 moves, 11 turns) from a blue tile on the top left corner to the red circle on the bottom right corner. If a correct move is made, a green check mark appears on the selected tile and the participant moves to the next tile. If a wrong move is made, a red ‘x’ appears on the selected tile and the participant was required to go back to the last correct tile and try a different tile.

The GMLT was performed seven times with an initial sequence followed by five trials and one delayed recall trial at the end of the EFTB. Each maze was randomized from 20 different versions of the task to minimize learning from the repeated exposure. The GMLT performance was measured for speed (ms) and for total errors made during the five-block period and recall. A lower score for speed and for total amount of errors represents a better performance.

4.4.2 Detection Task

The Detection Task was used to assess psychomotor function and reaction time (CogState, New Haven, USA). A turned card was presented in the middle of the screen and the participant was asked to select ‘YES’ (Letter ‘D’ on the keyboard) as soon as possible once the card flipped. The Detection Task presented 35 cards, and performance was measured for
speed of correct responses and for total amount of errors (premature response). A lower score for speed and for total amount of errors represents a better performance.

4.4.3 Two-Back Task

The Two-Back Task assessed attention and visual working memory span (165). A sequence of cards was presented in the middle of the screen and the participant continuously maintain a mental image of the last two items in the sequence while updating this memory set with each new card and dropping out the least recent one (if different from the stored card in memory). If the card presented on the screen was the same as two cards ago, participants were required to press “YES” (letter ‘D’ on the keyboard) whereas if the card was not the same as two cards ago, participants were required to press “NO” (letter ‘K’ on the keyboard). Therefore, the first two answers were always a “NO”. Performance in the Two-Back Task was measured for the accuracy of performance for correct answers and for the total amount of errors. A higher number for accuracy and lower total amount of errors represents a better performance.

4.4.4 Set-Shifting Task

The Set-Shifting Task assessed cognitive flexibility (66). In this test, the participant was presented with a playing card in the center of the screen with the word “number” or “color” above it. The only instruction provided was the question “is this a target card?”. The participant then guessed whether a card being presented on the screen was the target card. The only feedback provided was that the next card was not displayed until the correct response is made. The target card suddenly changed 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). The participant was not told when these changes occurred and needed to re-learn the new target card to continue with the test. Performance was measured based on the average time taken to identify the changes in the target card and the total amount of errors where a lower score indicates a better performance.

4.5 Data Collection and Analysis

$T_{re}$ and $\bar{T}_{\text{skin}}$ data were collected at 4 Hz, middle cerebral artery velocity data were collected at 400 Hz, and blood pressure, ECG, gases analyses data were collected at 1 kHz (LabChart, ADInstruments, Colorado Springs, USA) and were stored for offline analysis.

4.6 Statistical Analysis

Data are presented as the mean ± SD. Normal distribution was assessed using the Kolmogorov-Smirnov Test for Normality. Sphericity was assessed using the Mauchly’s test and if the assumption was not met ($p ≤ 0.05$), the Greenhouse-Geisser correction was used. Changes in respiratory, cardiovascular, cerebral hemodynamics, and cognitive responses among the 4-time points (baseline, C-H, H-H and H-C) across both poikilocapnic and isocapnic conditions were analyzed using a two-way repeated measures ANOVA. Bonferroni Post Hoc test was used to identify main effect. Paired sample t-tests were performed to test significant main effects at specific time points within-group effects. Statistical significance was set at $p < 0.05$. All ordinal data (TS and TC) was analyzed using a Friedman’s ANOVA. A post-hoc Wilcoxon signed-rank tests was used with a Bonferroni correction resulting in a significance level of $p < 0.008$. All statistical analysis was performed on IBM SPSS (Version 25, IBM Corp., Armonk, NY, USA).
5. Results

All participants arrived at the laboratory (PRE) in a euhydrated state (Isocapnic, ISO, baseline USG = 1.011 ± 0.006; Poikilocapnic, POIKI, baseline USG = 1.011 ± 0.007). USG following the trial (POST) was slightly, but not significant, higher (ISO PRE USG= 1.016 ± 0.006; POIKI POSTUSG = 1.015 ± 0.008). Body mass was significantly reduced from baseline to post: ISO from 77.5 ± 10.4 to 75.7 ± 10.5 kgs; POIKI from 77.6 ± 9.6 to 75.9 ± 9.6 kgs. Average heating time in the ISO condition was 141 ± 47 minutes and 136 ± 38 minutes in the POIKI condition. Cooling time in the ISO condition was 12 ± 5 minutes and 11 ± 3 minutes in the POIKI condition. There were no differences in USG, body mass, heating or cooling time between conditions at any time point.

5.1 Thermal and Perceptual Responses

5.1.1 Core and Skin Temperature

A t-test was used to assess mean differences between conditions at baseline. There was no difference ($p = 0.48$) in $T_{re}$ at baseline between POIKI ($37.1 ± 0.4 ^\circ C$) and ISO ($37.0 ± 0.4 ^\circ C$). There was no difference in $T_{\text{skin}}$ ($p = 0.07$) at baseline between POIKI ($32.7 ± 0.5 ^\circ C$) and Iso ($32.4 ± 0.5 ^\circ C$).

Given that the data was normally distributed, a repeated measures ANOVA was used to test the $T_{re}$ data (Figure 5.1) for changes across the experimental conditions and time points. The results indicated that there was a significant main effect for time ($F(1.52, 14.33)$ = 440.16, $p < 0.001$, $\eta_p^2 = 0.98$). No significant main effect for conditions was observed ($F(1,9)$ = 0.175, $p > 0.05$, $\eta_p^2 = 0.02$). No significant interactions were observed $F(3, 27) = 2.47, p > 0.05$, $\eta_p^2 = 0.22$. The results represented as changes from baseline indicate that $T_{re}$ increased for both groups across the different time points. Post-hoc T-tests were performed, and baseline
did not differ from C-H ($\Delta -0.1 \pm 0.2^\circ C, p = 1.00$) but was significantly lower than H-H ($\Delta +1.6 \pm 0.1^\circ C, p = 0.00$) and H-C ($\Delta +1.4 \pm 0.3^\circ C, p = 0.00$); C-H was significantly lower than H-H ($p = 0.00$) and H-C ($p = 0.00$); H-H did not differ from H-C ($p = 0.18$).

![Figure 5.1](image)

Figure 5.1 Changes from baseline in $T_{re}$ across all four time points. Note: $^\circ C$ = Celsius; POIKI = poikilocapnic; ISO = isocapnic; C-H = cold core and hot skin; H-H = hot core and hot skin; H-C = hot core and cold skin; * = main effect for condition ($p < 0.05$); a = different from baseline ($p < 0.05$); b = different from C-H ($p < 0.05$).

Given that the data was normally distributed, a repeated measures ANOVA was used to test the $\overline{T_{skin}}$ data (Figure 5.2) for changes across the experimental conditions and time points. The results indicated that there was a significant main effect for time ($F(3,27) = 990.5, p < 0.001, \eta^2_p = 0.99$). The results indicated a non-significant main effect for condition ($F(1,9) = 5.47, p > 0.05, \eta^2_p = 0.18$). No significant interactions were observed $F(3, 27) = 0.66, p > 0.05, \eta^2_p = 0.07$. The results indicate that $\overline{T_{skin}}$ increased for both groups across from baseline to H-H and decreased from H-H to H-C. Post-hoc T-tests were performed, and baseline was significantly lower than C-H ($37.4 \pm 0.2^\circ C, p = 0.00$), H-H ($38.6 \pm 0.3^\circ C, p = 0.00$) and H-C ($34.6 \pm 0.5^\circ C, p = 0.00$); C-H was
significantly lower than H-H ($p = 0.00$) and H-C ($p = 0.00$); H-H was significantly higher than H-C ($p = 0.00$).

Figure 5.2 $T_{\text{skin}}$ across all four time points. Note: °C = Celsius; POIKI = poikilocapnic; ISO = isocapnic; C-H = cold core and hot skin; H-H = hot core and hot skin; H-C = hot core and cold skin; a = different from baseline ($p < 0.05$); b = different from C-H ($p < 0.05$); c = different from H-H ($p < 0.05$); d = different from H-C ($p < 0.05$).

5.1.2 Thermal Sensation and Thermal Comfort

Given that the data from TS were Likert scales, a Friedman's test was used followed by a Wilcoxon signed-rank test Post-Hoc with a Bonferroni correction with a significance level set at $p < 0.008$. The analysis showed a statistically significant change in TS (Figure 5.3) in the ISO condition: $\chi^2(3) = 30.089, p < 0.001$; and in the POIKI condition: $\chi^2(3) = 34.500, p < 0.001$. Median (IQR) TS levels for ISO baseline, C-H, H-H and H-C were 4 (4 to 4), 6 (5.25 to 6), 7 (6 to 7) and 3.5 (3 to 4) respectively. Median (IQR) TS levels for POIKI baseline, C-H, H-H and H-C were 4 (3 to 4), 6 (5 to 6), 7 (7 to 7) and 2.25 (2.25 to 4) respectively. ISO baseline was statistically different from C-H ($Z = -2.994, p = 0.003$), H-H ($Z = -3.105, p = 0.002$), but not from H-C ($Z = -1.897, p = 0.058$). C-H was statistically different from H-H ($Z = -2.2887, p = 0.004$) and H-C ($Z = -2.979, p = 0.003$).
H-H was statistically different from H-C (Z = -3.095, p = 0.002). POIKI baseline was statistically
different from C-H (Z = -3.100, p = 0.002), H-H (Z = -3.140, p = 0.002), but not from H-C (Z = -
2.333, p = 0.02). C-H was statistically different from H-H (Z = -2.997, p = 0.008) and H-C (Z = -
3.078, p = 0.002). H-H was statistically different from H-C (Z = -3.089, p = 0.002).

![Figure 5.3 TS across all four time points. Note: POIKI = poikilocapnic; ISO = isocapnic; C-H =
cold core and hot skin; H-H = hot core and hot skin; H-C = hot core and cold skin; a = different from
baseline (p < 0.05); b = different from C-H (p < 0.05); c = different from H-H (p < 0.05); d = different
from H-C (p < 0.05).](image)

Given that the data from TC were Likert scales, a Friedman’s test was used followed by a
Wilcoxon signed-rank test Post-Hoc with a Bonferroni correction with a significance level set at p <
0.008. The analysis showed a statistically significant change in TC (Figure 5.4) in the ISO condition:
χ²(3) = 30.089, p < 0.001; and for POIKI condition: χ²(3) = 25.252, p < 0.001. Median (IQR) TC levels
for ISO baseline, C-H, H-H and H-C were 1 (1 to 1), 2 (1.25 to 2), 4 (3 to 4) and 1 (1 to 2) respectively.
Median (IQR) TC levels for POIKI baseline, C-H, H-H and H-C were 1 (1 to 1), 2 (2 to 2), 4 (3 to 4) and
1.5 (1 to 2) respectively. ISO baseline was statistically different from C-H (Z = -2.810, p = 0.005), H-H
(Z = -3.169, p = 0.002), but not from H-C (Z = -2.121, p = 0.034). C-H was statistically different from
H-H (Z = -3.025, p = 0.002) but not from H-C (Z = -1.667, p = 0.096). H-H was statistically different
from H-C (Z = -3.100, p = 0.002). POIKI baseline was statistically different from C-H (Z = -2.889, p = 0.004), H-H (Z = -3.025, p = 0.002), but not from H-C (Z = -2.449, p = 0.014). C-H was statistically different from H-H (Z = -3.025, p = 0.002) but not from H-C (Z = -1.667, p = 0.096). H-H was statistically different from H-C (Z = -2.852, p = 0.004).

Figure 5.4 TC across all four time points. Note: POIKI = poikilocapnic; ISO = isocapnic; C-H = cold core and hot skin; H-H = hot core and hot skin; H-C = hot core and cold skin; a = different from baseline (p < 0.05); b = different from C-H (p < 0.05); c = different from H-H (p < 0.05); d = different from H-C (p < 0.05).

5.2 Physiological Responses

5.2.1 Respiratory Responses

A t-test was used to compare mean differences in $P_{\text{etCO}_2}$ and $V_e$ at baseline between conditions. No significant differences were observed for $P_{\text{etCO}_2}$ (p = 0.93) and $V_e$ (p = 0.19) at baseline between POIKI (40.8 ± 1.1 mmHg; 15.4 ± 3.7 L·min⁻¹) and ISO (40.9 ± 1.9 mmHg; 13.8 ± 3.0 L·min⁻¹) respectively.

Given that the data was normally distributed, a repeated measures ANOVA was used to test the $P_{\text{etCO}_2}$ data (Figure 5.5) for changes across the experimental conditions and time points. The results indicated that there was a significant interaction ($F_{(1,47,13.3)} = 15.87, p < 0.001, \eta_p^2 = 0.64$). At C-
H, there was no difference \( (p = 0.45) \) between ISO \( (39.8 \pm 2.3 \text{ mmHg}) \) and POIKI \( (39.3 \pm 1.2 \text{ mmHg}) \). The results indicate that \( P_{\text{etCO2}} \) differed between ISO and POIKI groups at two time points. At H-H, ISO was significantly higher \( (41.8 \pm 2.1 \text{ mmHg}, p = 0.003) \) than POIKI \( (32.9 \pm 5.5 \text{ mmHg}) \). At H-C, ISO remained significantly higher \( (41.2 \pm 2.4 \text{ mmHg}, p = 0.005) \) than POIKI \( (36.3 \pm 3.1 \text{ mmHg}) \).

Given that the data was normally distributed, a repeated measures ANOVA was used to test the \( V_e \) data (Figure 5.6) for changes across the experimental conditions and time points. The results indicated that there was a significant interaction \( (F_{(1,32,14.6)} = 5.47, p < 0.05, \eta^2_p = 0.33) \). However, further t-tests analysis showed no differences between conditions across the time points. The results also indicated a significant main effect for time \( (F_{(1,76,19.4)} = 23.81, p < 0.001, \eta^2_p = 0.68) \). No significant main effect for condition \( (F_{(1,11)} = 0.51, p > 0.05, \eta^2_p = 0.10) \) was observed. The results indicate that \( V_e \) increased from baseline to H-H and decreased from H-H to H-C. Post-hoc T-tests were performed, and baseline \( (15.3 \pm 2.8 \text{ L/min}) \) was significantly lower than C-H \( (16.5 \pm 2.6 \text{ L/min}, p = 0.02) \), H-H \( (21.8 \pm 5.3 \text{ L/min}, p = 0.001) \) and H-C \( (17.3 \pm 3.3 \text{ L/min}, p = 0.008) \); C-H was significantly lower than H-H \( (p = 0.001) \) but did not differ from H-C \( (p = 0.53) \); H-H was significantly higher than H-C \( (p = 0.01) \).

![Figure 5.5 P_{etCO2} across all four time points. Note: mmHg = millimetre of mercury; POIKI = poikilocapnic; ISO = isocapnic; C-H = cold core and hot skin; H-H = hot core and hot skin; H-C = hot core and cold skin; * = difference between conditions (p < 0.05).](image-url)
5.2.2 Cerebral Hemodynamics Responses

A t-test was used to compare mean differences in mean MCAv at baseline between conditions. A significant difference ($p = 0.03$) was observed for mean MCAv at baseline between POIKI ($61.5 \pm 10.4 \text{ cm} \cdot \text{s}^{-1}$) and ISO ($59.1 \pm 9.2 \text{ cm} \cdot \text{s}^{-1}$).

Given that the data was normally distributed, a repeated measures ANOVA was used to test the mean MCAv data (Figure 5.7) for changes across the experimental conditions and time points. The results indicated that there was a significant interaction ($F_{(3, 27)} = 4.83$, $p < 0.01$, $\eta^2_p = 0.35$). Further analysis using t-test showed that mean MCAv at both baseline ($61.5 \pm 10.4 \text{ cm} \cdot \text{s}^{-1}$; $p = 0.03$) and C-H ($57.9 \pm 9.6 \text{ cm} \cdot \text{s}^{-1}$) were higher than ISO (Baseline = $59.1 \pm 9.2 \text{ cm} \cdot \text{s}^{-1}$; C-H $55.2 \pm 8.8 \text{ cm} \cdot \text{s}^{-1}$). POIKI and ISO did not differ at H-H ($p = 0.11$) and H-C ($p = 0.90$). The analysis also indicated a significant main effect for time ($F_{(1.23, 11.11)} = 13.91$, $p < 0.01$, $\eta^2_p = 0.61$). The main effect for condition was not significant ($F_{(1, 9)} = 0.012$, $p > 0.05$).
Post-hoc t-tests were performed, and mean MCAv at baseline (60.3 ± 9.7 cm s⁻¹) was significantly higher than C-H (56.5 ± 9.1 cm s⁻¹, \( p = 0.003 \)) and H-H (49.0 ± 8.0 cm s⁻¹, \( p = 0.002 \)) but not different from H-C (54.5 ± 6.6 cm s⁻¹, \( p = 0.18 \)); C-H was significantly higher than H-H (\( p = 0.03 \)) but did not differ from H-C (\( p = 1.00 \)); H-H was significantly lower than H-C (\( p = 0.001 \)).

Figure 5.7 Mean MCAv across all four time points. Note: cm s⁻¹ = centimetres per second; POIKI = poikilocapnic; ISO = isocapnic; C-H = cold core and hot skin; H-H = hot core and hot skin; H-C = hot core and cold skin; a = different from baseline (\( p < 0.05 \)); b = different from C-H (\( p < 0.05 \)); c = different from H-H (\( p < 0.05 \)).

5.2.3 Cardiovascular Responses

T-tests were used to assess mean differences between conditions at baseline. No significant differences were observed for HR (\( p = 0.08 \)), MAP prior the executive function testing battery (PRE; \( p = 0.34 \)) and MAP following the executive function testing battery (POST; \( p = 0.41 \)) at baseline between POIKI (74.5 ± 8.8 beats min⁻¹; 62.4 ± 41.2 mmHg; 63.1 ± 41.6 mmHg) and ISO (70.5 ± 7.1 beats min⁻¹; 68.6 ± 37.6 mmHg; 68.5 ± 37.5 mmHg).
Given that the data was normally distributed, a repeated measures ANOVA was used to test the HR data (Figure 5.8) for changes across the experimental conditions and time points. The results indicated that there was a significant main effect for time ($F_{(3, 24)} = 91.02$, $p < 0.001, \eta_p^2 = 0.92$). No significant main effect for conditions was observed ($F_{(1,8)} = 0.21$, $p > 0.05, \eta_p^2 = 0.03$). No significant interactions were observed ($F(1.59, 12.8) = 1.20, p > 0.05, \eta_p^2 = 0.13$). The results are represented as changes from baseline indicate that HR increased for both groups from baseline to H-H followed by a decrease at H-C. Post-hoc T-tests were performed, and baseline (70.8 ± 8 beats·min⁻¹) was lower than C-H (85.8 ± 9.1 beats·min⁻¹, $p = 0.003$), H-H (125.5 ± 15.0 beats·min⁻¹, $p = 0.00$) and H-C (94.6 ± 12.5 beats·min⁻¹, $p = 0.001$); C-H was significantly lower than H-H ($p = 0.001$) but did not differ from H-C ($p = 0.07$); H-H was significantly higher than H-C ($p = 0.001$).

Figure 5.8 Mean heart rate across all four time points. Note: beats·min⁻¹ = beats per minute; POIKI = poikilocapnic; ISO = isocapnic; C-H = cold core and hot skin; H-H = hot core and hot skin; H-C = hot core and cold skin; a = different from baseline ($p < 0.05$); b = different from C-H ($p < 0.05$); c = different from H-H ($p < 0.05$); d = different from H-C ($p < 0.05$).
Given that the data was normally distributed, a repeated measures ANOVA was used to test the MAP pre (prior to the EFTB) data (Figure 5.9) and MAP post (following the EFTB) data (Figure 5.10) for changes across the experimental conditions and time points. The analysis for MAP pre indicated that there was not a significant main effect for time ($F_{(1.01, 12.1)} = 0.93, p > 0.05, \eta^2_p = 0.07$). No significant main effect for conditions was observed ($F_{(1,13)} = 2.11, p > 0.05, \eta^2_p = 0.14$). No significant interactions were observed $F(1.02, 12.2) = 0.93, p > 0.05, \eta^2_p = 0.07$. The analysis for MAP post indicated that there was not a significant main effect for time ($F_{(3,36)} = 0.36, p > 0.05, \eta^2_p = 0.03$). No significant main effect for conditions was observed ($F_{(1,12)} = 2.69, p > 0.05, \eta^2_p = 0.18$). No significant interactions were observed $F_{(3,36)} = 0.12, p > 0.05, \eta^2_p = 0.01$.

Figure 5.9 Mean MAP prior to the EFTB across all four time points. Note: mmHg = millimetres of mercury; POIKI = poikilocapnic; ISO = isocapnic; C-H = cold core and hot skin; H-H = hot core and hot skin; H-C = hot core and cold skin.
Figure 5.10 Mean MAP post to the EFTB across all four time points. Note: mmHg = millimetres of mercury; POIKI = poikilocapnic; ISO = isocapnic; C-H = cold core and hot skin; H-H = hot core and hot skin; H-C = hot core and cold skin.

5.3 Executive Function Responses

5.3.1 Groton Maze Learning Test/Recall Test

T-tests were used to assess mean differences between conditions at baseline. No significant differences were observed for GMLT total duration ($p = 0.89$), GMLT total errors ($p = 0.36$), GMLT 5 duration ($p = 0.67$), GMLT 5 total errors ($p = 0.22$), GMLT recall duration ($p = 0.32$), and GMLT recall total errors ($p = 0.76$).

Given that the data was normally distributed, a repeated measures ANOVA was used to test the GMLT total duration data (Figure 5.11) and GMLT total errors data (Figure 5.12) for changes across the experimental conditions and time points. The analysis for GMLT total duration indicated that there were no significant interactions ($F(3,27) = 0.03, p > 0.05, \eta^2_p = 0.06$). No significant main effect for conditions was observed ($F(1,9) = 2.11, p > 0.05, \eta^2_p = 0.05$). A significant main effect for time was observed $F(3, 27) = 3.57, p < 0.05, \eta^2_p = 0.28$. However, further t-tests analysis showed no differences between conditions across the time points. The analysis for GMLT total errors indicated that there were no significant interactions ($F(3,27) = 1.12, p > 0.05, \eta^2_p =$
No significant main effect for conditions was observed ($F_{(1,9)} = 0.17, p > 0.05, \eta^2_p = 0.01$). There was also no significant main effect for time ($F_{(3, 27)} = 2.20, p < 0.05, \eta^2_p = 0.20$).

Figure 5.11 Mean GMLT Duration across all four time points. Note: (s) = seconds; POIKI = poikilocapnic; ISO = isocapnic; C-H = cold core and hot skin; H-H = hot core and hot skin; H-C = hot core and cold skin.

Figure 5.12 Mean GMLT number of errors across all four time points. Note: POIKI = poikilocapnic; ISO = isocapnic; C-H = cold core and hot skin; H-H = hot core and hot skin; H-C = hot core and cold skin.
Given that the data was normally distributed, a repeated measures ANOVA was used to test the GMLT 5 total duration data (Figure 5.13) and GMLT 5 total errors data (Figure 5.14) for changes across the experimental conditions and time points. The analysis for GMLT 5 total duration indicated that there were no significant interactions \(F(1.08, 11.91) = 1.97, p > 0.05, \eta^2_p = 0.15\). No significant main effect for condition was observed \(F(1, 11) = 0.66, p > 0.05, \eta^2_p = 0.06\). In addition, no significant main effect for time was observed \(F(1.06, 11.66) = 1.46, p > 0.05, \eta^2_p = 0.12\). The analysis for GMLT 5 total errors indicated that there were no significant interactions \(F(3, 33) = 0.24, p > 0.05, \eta^2_p = 0.02\). No significant main effect for condition was observed \(F(1, 11) = 2.98, p > 0.05, \eta^2_p = 0.21\). In addition, no significant main effect for time was observed \(F(3, 33) = 2.35, p > 0.05, \eta^2_p = 0.18\).

![Figure 5.13 Mean GMLT 5 Duration across all four time points. Note: (ms) = milliseconds; POIKI = poikilocapnic; ISO = isocapnic; C-H = cold core and hot skin; H-H = hot core and hot skin; H-C = hot core and cold skin.](image-url)
Given that the data was normally distributed, a repeated measures ANOVA was used to test the GMLT recall duration data (Figure 5.15) and GMLT recall total errors data (Figure 5.16) for changes across the experimental conditions and time points. The analysis for GMLT recall duration indicated that there were no significant interactions ($F_{(3, 27)} = 0.04, p > 0.05, \eta^2_p = 0.00$). No significant main effect for conditions was observed ($F_{(1, 9)} = 0.54, p > 0.05, \eta^2_p = 0.06$). Also, a non significant main effect for time was observed $F_{(3, 27)} = 0.97, p < 0.05, \eta^2_p = 0.10$. The analysis for GMLT recall total errors indicated that there were no significant interactions ($F_{(3, 27)} = 0.26, p > 0.05, \eta^2_p = 0.03$). No significant main effect for conditions was observed ($F_{(1, 9)} = 0.62, p > 0.05, \eta^2_p = 0.06$). A significant main effect for time ($F_{(3, 27)} = 10.78, p < 0.001, \eta^2_p = 0.54$) was observed. Post-hoc $t$-test were performed to test mean differences across all time points. Total errors at baseline ($1.8 \pm 1$ errors) was significantly lower than C-H ($3.0 \pm 2$ errors, $p = 0.01$), H-H ($3.8 \pm 2$ errors, $p = 0.001$), and H-C ($3.8 \pm 2$ errors, $p = 0.001$).
errors \( p = 0.004 \) and H-C (2.9 ± 1.7 errors, \( p = 0.012 \)). Total errors at C-H did not differ from H-H (\( p = 0.54 \)) and H-C (\( p = 1.00 \)); and, H-H did not differ from H-C (\( p = 0.16 \)).

Figure 5.15 Mean GMLT Recall Duration across all four time points. Note: (ms) = milliseconds; POIKI = poikilocapnic; ISO = isocapnic; C-H = cold core and hot skin; H-H = hot core and hot skin; H-C = hot core and cold skin.

Figure 5.16 Mean GMLT recall errors across all four time points. Note: POIKI = poikilocapnic; ISO = isocapnic; C-H = cold core and hot skin; H-H = hot core and hot skin; H-C = hot core and cold skin; a = different from baseline (\( p < 0.05 \)).
Figure 5.17 Mean GMLT errors per maze in the isocapnic condition. Note: ISO = isocapnic; BASE = baseline; C-H = cold core and hot skin; H-H = hot core and hot skin; H-C = hot core and cold skin; M1 = maze 1; M2 = maze 2; M3 = maze 3; M4 = maze 4; M5 = maze 5; RE = recall

Figure 5.18 Mean GMLT errors per maze in the poikilocapnic condition. Note: POIKI = poikilocapnic; BASE = baseline; C-H = cold core and hot skin; H-H = hot core and hot skin; H-C = hot core and cold skin; M1 = maze 1; M2 = maze 2; M3 = maze 3; M4 = maze 4; M5 = maze 5; RE = recall
5.3.2 Detection Test

T-tests were used to assess mean differences between conditions at baseline. No significant differences were observed for speed ($p = 0.52$) and total errors ($p = 0.43$). Given that the data was normally distributed, a repeated measures ANOVA was used to test the speed data (Figure 5.17) and total errors data (Figure 5.18) for changes across the experimental conditions and time points. The analysis for Detection Test speed indicated that there were no significant interactions ($F_{(1.47, 13.27)} = 0.12, p > 0.05, \eta^2_p = 0.01$). No significant main effect for conditions was observed ($F_{(1.9)} = 0.02, p > 0.05, \eta^2_p = 0.02$). A significant main effect for time was observed $F_{(3, 27)} = 9.90, p < 0.001, \eta^2_p = 0.52$. Post-hoc t-tests were performed, and mean speed at baseline ($2.52 \pm 0.05$) did not differ from C-H ($2.52 \pm 0.06, p = 1.00$), but was significantly higher than H-H ($2.49 \pm 0.05, p = 0.03$) and H-C ($2.49 \pm 0.05, p = 0.04$); C-H was significantly higher than H-H ($p = 0.02$) and H-C ($p = 0.02$); H-H did not differ from H-C ($p = 1.00$). The analysis for Detection Test total errors indicated that there were no significant interactions ($F_{(3, 27)} = 0.51, p > 0.05, \eta^2_p = 0.05$). No significant main effect for conditions was observed ($F_{(1.9)} = 0.69, p > 0.05, \eta^2_p = 0.07$). Also, a non significant ($F_{(3, 27)} = 0.87, p > 0.05, \eta^2_p = 0.09$) main effect for time was observed.

![Detection Test Speed Graph](image)

Figure 5.19 Mean Detection test speed across all four time points. Note: POIKI = poikilocapnic; ISO = isocapnic; C-H = cold core and hot skin; H-H = hot core and hot skin; H-C = hot core and cold skin.
Figure 5.20 Mean Detection errors across all four time points. Note: POIKI = poikilocapnic; ISO = isocapnic; C-H = cold core and hot skin; H-H = hot core and hot skin; H-C = hot core and cold skin;

5.3.3 2-Back Test

T-tests were used to assess mean differences between conditions at baseline. No significant differences were observed for speed ($p = 0.58$) and total errors ($p = 0.31$). Given that the data was normally distributed, a repeated measures ANOVA was used to test the speed data (Figure 5.19) and total errors data (Figure 5.20) for changes across the experimental conditions and time points. The analysis for 2-Back Test speed indicated that there were no significant interactions ($F(3, 27) = 0.72$, $p > 0.05$, $\eta^2 = 0.07$). No significant main effect for condition was observed ($F(1,9) = 0.01$, $p > 0.05$, $\eta^2 = 0.01$). A non significant ($F(3, 27) = 1.34$, $p > 0.05$, $\eta^2 = 0.13$) main effect for time was also observed. The analysis for 2-Back Test total errors indicated that there were no significant interactions ($F(3, 27) = 2.62$, $p > 0.05$, $\eta^2 = 0.23$). No significant main effect for condition was observed ($F(1,9) = 0.81$, $p > 0.05$, $\eta^2 = 0.01$). A significant ($F(1.62, 14.7) = 5.12$, $p < 0.05$, $\eta^2 = 0.36$) main effect for time was observed. However, post-hoc t-tests showed no differences in errors across all time points.
5.3.4 Set Shifting Test

T-tests were used to assess mean differences between conditions at baseline. No significant differences were observed for speed ($p = 0.58$) and total errors ($p = 0.07$).
Given that the data was normally distributed, a repeated measures ANOVA was used to test the speed data (Figure 5.21) and total errors data (Figure 5.22) for changes across the experimental conditions and time points. The analysis for Set Shifting speed indicated that there were no significant interactions ($F_{(3,27)}=1.75, p > 0.05, \eta^2_p=0.16$). No significant main effect for condition was observed ($F_{(1,9)}=0.05, p > 0.05, \eta^2_p=0.01$). However, a significant ($F_{(1.63, 14.69)}=14.3, p < 0.001, \eta^2_p=0.61$) main effect for time was observed. Post-hoc t-tests were performed, and mean speed at baseline ($2.36 \pm 0.1$) did not differ from C-H ($2.35 \pm 0.1, p = 0.65$), but was significantly higher than H-H ($2.28 \pm 0.1, p = 0.005$) and H-C ($2.30 \pm 0.1, p = 0.01$); C-H was significantly higher than H-H ($p = 0.03$) but did not differ from H-C ($p = 0.11$); H-H did not differ from H-C ($p = 0.43$).

The analysis for Set Shifting total errors indicated that there were significant interactions ($F_{(3, 27)}=5.56, p < 0.01, \eta^2_p=0.38$). However, further post-hoc t-tests showed no differences between conditions across the time points. No significant main effect for condition was observed ($F_{(1,9)}=0.73, p > 0.05, \eta^2_p=0.08$). A significant ($F_{(3, 27)}=7.50, p < 0.01, \eta^2_p=0.45$) main effect for time was observed. Post-hoc t-tests were performed, and the total errors at baseline ($17.4 \pm 1.8$ errors) did not differ from C-H ($20.3 \pm 2.4, p = 0.12$), but was significantly lower than H-H ($22.9 \pm 2.5, p = 0.01$) and H-C ($23.8 \pm 2.6, p = 0.039$); C-H did not differ from H-H ($p = 0.51$) but did not differ from H-C ($p = 1.00$); H-H did not differ from H-C ($p = 1.00$).
Figure 5.23 Mean Set Shifting speed across all four time points. Note: POIKI = poikilocapnic; ISO = isocapnic; C-H = cold core and hot skin; H-H = hot core and hot skin; H-C = hot core and cold skin; a = different from baseline (p < 0.05); b = different from C-H (p < 0.05); c = different from H-H (p < 0.05).

Figure 5.24 Mean Set Shifting errors across all four time points. Note: POIKI = poikilocapnic; ISO = isocapnic; C-H = cold core and hot skin; H-H = hot core and hot skin; H-C = hot core and cold skin; a = different from baseline (p < 0.05);
6. Discussion

This thesis studied the mechanisms underlying hyperthermic induced impairments in working memory (WM) and cognitive flexibility (two components of EF). An end-tidal forcing system created conditions of either poikilocapnia or isocapnia to manipulate cerebral blood flow. Testing was also performed at four distinct thermal states to study the relative contribution of core versus skin temperature changes. Overall, data suggests that the nature of thermal strain had differential impairments across various components of EF: elevated thermal discomfort impaired WM whereas elevated $T_r$ impaired cognitive flexibility; and that means MCAv was not the primary impairing factor.

Previous research reported that an increase in $T_{\text{skin}}$, and consequently thermal discomfort, might impair working memory as it redirects some of the neural resources used for cognition towards thermoregulation. Indeed, an increase of 5°C in $T_{\text{skin}}$ from baseline to C-H and a change from thermally comfortable to uncomfortable were enough to almost double the amount of errors in the GMLT recall test. Moreover, a further 1°C increase in $T_{\text{skin}}$ and thermally uncomfortable to very uncomfortable from C-H to H-H increased the amount of errors by 25%. This is in accordance to Gaoua and colleagues, who reported that an elevated $T_{\text{skin}}$ imposes a cognitive load that competes for resources with working memory leading to an increase in errors (9). Similarly, the initiation of rapid skin heating caused an increase in heart rate, and this cardiovascular strain might increase the participant’s stress level beyond the comfort zone where there is a progressive depletion of neural resources as compensatory mechanisms to try to restore homeostasis (134). In this study, a 5°C increase of $T_{\text{skin}}$ from baseline to C-H increased heart rate by 15 beats·min⁻¹. When $T_r$ was also elevated by 1.5°C, heart rate was 79% higher than baseline. Taken together, it is possible
that the temperature exposure depleted available neural resources towards thermoregulation instead of cognition.

In addition, the increase in thermal discomfort and thermal perception at C-H, H-H and H-C might have also played a role in the WM impairment as thermal discomfort and elevated thermal perception are also associated with cognitive impairments as negative alliesthesia also disrupts homeostasis (7). Negative alliesthesia might disrupt homeostasis as the nervous system senses, interprets and integrates signals across the body – also called interoception – which creates the adaptive responses towards the maintenance of body homeostasis (166). Therefore, it is possible that the increase in $T_{\text{skin}}$ and $T_{\text{re}}$ were sensed by the thermal monitoring system increasing information processing, which might have used the available neural resources, to generate a thermoregulatory response. Therefore, the increase in WM errors might be a consequence of the overload of brain processing and not due to changes in information transmission, which might explain why speed response did not differ across all time points.

Differently than the impairment in WM, cognitive flexibility was only impaired when $T_{\text{core}}$ was increased by 1.5°C. A possible mechanism that explain this impairment pattern was explained by McIlvoy (167) who investigated the effects of cerebral temperature and structural integrity. According to the author, an increase in cerebral temperature changes the cerebral architecture which may lead to impaired cerebral function (167). This is particularly important as cerebral temperature can be up to 2.5°C higher than $T_{\text{core}}$ due to a high cerebral metabolism (167). More specifically, an increase in cerebral temperature is associated with disruptions in functional connectivity (33) mainly in the frontal, temporal
and parietal lobes (144) which might explain the 38% increase in the total amount of errors in the Set Shifting test. In addition, it is possible that the increase in the total information being processed caused by the Set Shifting test and thermoregulation caused the decrease in the speed of response in this cognitive test. Our findings showed significantly slower Set Shifting responses when \( T_{re} \) was increased by 1.5°C which is defined by the literature as the switching cost – the time that it took the participant to identify a new rule and respond accordingly (65). Therefore, it is possible that the increase in errors and switching cost seen in the Set Shifting test were caused by changes in cerebral connectivity. The relationship between changes in functional connectivity in these cerebral lobes and impairment in cognitive flexibility is supported by MRI studies which reported the frontoparietal region of the brain as the main processing location for this cognitive domain (23, 64). Therefore, it is possible that impairments in cognitive flexibility during hyperthermia are due to changes in cerebral functional connectivity and abnormal information processing (168). The fact the change in speed were only seen in the Set Shifting test supports the mechanism of disrupted functional connectivity. For example, the Detection test is a simple reaction test where information processing does not play a big role in performance. In the Set Shifting test, however, the participant had to identify the rule change (e.g., from black to red or from the card number 2 to number 3), modify the mental response and react towards the answer.

The different pattern seen in this study between impairments in WM (driven by the increase in \( T_{\text{skin}} \) and thermal displeasure) and cognitive flexibility (driven by the increase in \( T_{re} \)) might be related to the different nature of the mental tasks used in this thesis. First, WM and sustained attention are closely connected as WM depends on it to maintain relevant information input and suppressing exogenous distractions (169). However, thermal stress
is known to overload the information processing with a significant exogenous stimulus. According to Chase and colleagues (170), thermal stress is linked to an inability to sustain attention towards the task. Indeed, our results showed that WM became impaired after a 5°C increase in $T_{\text{skin}}$ leading to an increase in TS and a decrease in TC. This way, it is possible that the increase in the subjective feeling of the thermal impulse decreased the sustained attention towards the task and increased the attention towards the “feeling hot”. Cognitive flexibility, however, has the function to allocate attention (171) to the switching sources of information – such as seen in a task switching task (172). Differently than WM, cognitive flexibility is less susceptible to changes in sustained attention and more vulnerable to changes in cerebral structure (173). If elevated cerebral temperature causes functional connectivity disruptions (145), then it is possible that the 38% increase in total amount of errors and larger switching cost are related to hyperthermia-induced changes in cerebral structure.

The second objective of this study was to determine the potential role of cerebral blood flow (CBF) on hyperthermia-induced EF impairments. We were unable to directly address this as, despite systematically creating a POIKI and ISO conditions as shown by the significantly differences in $P_{\text{etCO}_2}$ at H-H and H-C between conditions, we were unable to maintain baseline levels of mean MCAv in the ISO condition. However, although we were unable to maintain baseline mean MCAv in the isocapnic condition, the increase in errors in the GMLT Recall (baseline: 1.8 ± 1; C-H: 3.0 ± 2; H-H: 3.8 ± 2.3; and, H-C: 2.9 ± 1.8) and cognitive flexibility (baseline: 17.6 ± 5.8; C-H: 20.3 ± 8.3; H-H: 23.9 ± 7.7; and, H-C: 21.5 ± 8.4) show that a hyperthermia-induced decrease in CBF is not the main driver and that temperature itself plays a role in the executive function impairment. Although previous
research reported that $P_{etCO2}$ is the main modulator of CBF (103), our data suggests that $P_{etCO2}$ is not the only CBF modulator as mean MCAv was reduced regardless of maintenance of $P_{etCO2}$ at baseline levels during hyperthermia. The increase in $T_re$ led to an increase of $\sim 42\%$ in ventilation and a decrease of $\sim 20\%$ in $P_{etCO2}$ in the POIKI reducing mean MCAv by $\sim 25\%$. These results are in agreement with Fan and colleagues (103) who reported an increase of $\sim 50\%$ in ventilation, a decrease of $\sim 25\%$ and $\sim 24\%$ in $P_{etCO2}$ and mean MCAv during hyperthermia, respectively. However, our data suggests that $T_re$ is not the only driving factor for the hyperthermia-induced hyperventilation as a decrease in $T_{skin}$ by $\sim 4^\circ C$ decreased ventilation to baseline levels and partially restored mean MCAv and $P_{etCO2}$. Therefore, it is possible that both $T_re$ and $T_{skin}$ might have a role in hyperthermia-induced hyperventilation and a decrease in mean MCAv. Brothers and colleagues (98) reported a decrease of $18\%$ in MCAv regardless of the maintenance of normothermic levels of $P_{etCO2}$ when $T_re$ was increased by $1.5^\circ C$. The authors concluded that an increased sympathetic nervous activity is also involved in mediating this response (98). Therefore, our findings support that sympathetic nervous activity might have an effect on CBF regulation as MCAv was reduced by $15\%$ and $10\%$ at H-H and H-C respectively despite a maintenance of eucapnia.

In addition to the partial maintenance of mean MCAv caused by maintenance of eucapnia during hyperthermia, the skin cooling protocol used at H-C partially restored mean MCAv. To the best of our knowledge, however, there is only one study that assessed the effects of skin cooling during hyperthermia on CBF. Wilson and colleagues (175) reported that skin cooling during hyperthermia (increase of $1.0^\circ C$ in $T_{re}$) partially restored MCAv due to an elevation of mean arterial pressure. However, in the present study, MAP remained constant throughout all four time points. The partial restoration of mean MCAv might be due
to a decrease in cardiac strain as skin cooling decreased heart rate. In addition, skin cooling during hyperthermia has also been linked to an increase in venous return which increases cardiac output (176). In fact, a decrease in central blood volume – as seen during hyperthermia – decreases cardiac output and MCAv whereas an increase in central blood volume increased cardiac output and MCAv (122). Therefore, it is possible that the skin cooling during hyperthermia was responsible for the increase in mean MCAv from H-H to H-C respectively.

6.3 Technological Considerations/Limitations

The first limitation of the study was the use of the transcranial doppler ultrasound to assess mean MCAv and not absolute volumetric flow. This method assumes that the diameter of the insonated vessel remains constant throughout the experiment (107). Although this study used CO₂ – a potent vasoactive agent – the changes in mean MCAv did not differ between the isocapnic and poikilocapnic conditions.

The second limitation was that this study used only college-aged males as participants. Previous research showed that females have different cerebrovascular reactivity to CO₂ and thermal sensation than males. Therefore, the findings from this study might differ among females. In addition, as age plays a factor in cognition, CBF, cerebral reactivity to CO₂ (177) and thermal sensation/comfort (178), it is possible that the findings from this study might differ among younger/older cohorts.

Another limitation of this study is related to the development of hyperthermia used. One of the objectives of this study was to assess the effects of thermal discomfort/displeasure on executive function by increasing $\bar{T}_{\text{skin}}$ by $\sim 4^\circ \text{C}$. Therefore, it is
possible that impairments in WM might happen prior to this thermal stage. In addition, once we have achieved each testing point, we were unable to clamp thermal status as thermal impulse was kept constant.

6.4 Perspective and Future Directions

The primary objective of this study was to investigate the manipulation of skin and rectal temperature on hyperthermia-induced impairments in working memory, inhibitory control and cognitive flexibility – three components of executive function. The secondary objective of this study was to investigate the effects of the hyperthermia-induced decrease of mean MCAv on executive function. Our findings suggest that: first, temperature impairs the domains of EF as $T_{\text{skin}}$ impairs WM and $T_{\text{core}}$ impairs cognitive flexibility; second, MCAv is not the driving factor for such impairments. Previous research reported hyperthermia-induced changes in cortical connectivity and changes in brain waves that might further explain the cause for the executive function impairments. Therefore, future research should assess changes in cortical connectivity and brain waves during performance of executive tasks with an elevated core temperature.

In addition, this study used a passive heating protocol to induce hyperthermia. Future studies should assess cognitive function using an active heating protocol, as acute bouts of exercise have been shown to positively benefited cognitive performance (79). Likewise, the use of an active heating protocol would have greater ecological validity by mimicking a daily situation for those who suffer from heat stress and its cognitive impairments such as firefighters and construction workers.
6.5 Conclusions

This study explored the effects of manipulating rectal and skin temperature on EF and assessed the effects of $P_{et}CO_2$ and CBF on EF during an increase of 1.5°C in $T_{re}$. The results showed that an increase of 5°C in $T_{skin}$ without changes in $T_{re}$ impaired WM regardless of mean MCAv or $P_{et}CO_2$. It was also found that working memory was not restored once $T_{skin}$ was cooled down, suggesting that its recovery might take longer than the time allowed in the current testing protocol. The results also showed that cognitive flexibility was only impaired when $T_{re}$ was increased by 1.5°C regardless of $T_{skin}$. Altogether, the results indicated that hyperthermia-induced impairments in EF are far more complex than manipulations of $T_{skin}$, $T_{re}$ and mean MCAv. In addition, although we were unable to directly assess the effects of CBF on EF, this study found that a maintenance of eucapnic $P_{et}CO_2$ levels were not enough to maintain baseline MCAv levels. Moreover, the skin cooling protocol used at H-C time point was able to partially restore MCAv. Therefore, it is possible that cardiac function and sympathetic nervous system also play a role in CBF regulation during hyperthermia.
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