EFFECTS OF THERMAL STIMULI DURING SIMULATED HEMORRHAGING ON ASPECTS OF COGNITIVE PERFORMANCE

BY

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DISSERTATION

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ABSTRACT

Warming a hemorrhaging victim is the standard of care due to the adverse effects of combined hemorrhage and hypothermia on survival. However, it has been found that heating can be detrimental to the maintenance of arterial pressure, cerebral perfusion, and may also impact cognitive function. **PURPOSE:** To test the hypothesis that mildly heating an otherwise normothermic individual can be detrimental to cognitive function during a simulated mild hemorrhagic insult. **METHODS:** Nine men (mean ± SD: age, 29.9 ± 8.4 y; body mass, 79.4 ± 15.2 kg) underwent a randomized, crossover experimental design. Following 15 min of supine rest, 10 min of 30 mmHg of lower body negative pressure (LBNP) was applied to simulate a mild hemorrhagic challenge while subjects were normothermic. With LBNP continuing, subjects were exposed to mild whole-body heating (mean skin temperature (T_{sk}): 36.7 ± 0.5°C), skin surface cooling (T_{sk}: 29.6 ± 1.0°C), or remained thermoneutral (T_{sk}: 33.5 ± 0.6°C) for an additional 40 min via a water-perfused suit. A modified Erikson Flanker task was used as a measure of cognitive function. Affective valence and thermal sensations were also assessed. Upon completion of trials, subjects remained supine for 15 min for T_{sk} to return to baseline temperatures. **RESULTS:** Interaction between thermal perturbations and LBNP time did not reveal changes in cognitive function, as reflected in response accuracy (P = 0.19), reaction time (P = 0.09) or performance variability (P = 0.16) on the Flanker task. This suggests that LBNP with and without thermal perturbations had little influence on cognitive function. **CONCLUSIONS:** For the applied level of simulated hemorrhage (30 mmHg LBNP), these data suggest that mild heating of a hemorrhaging victim does not compromise cognitive function, while

cooling is not beneficial. It remains unknown whether mild heating would be detrimental during a more profound simulated hemorrhagic challenge.

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LIST OF ABBREVIATIONS

Abbreviation	Term
CBFV	Cerebral blood flow velocity
COOL	Skin cooling stimulus
FS	Feeling Scale
HEAT	Mild heating stimulus
LBNP	Lower body negative pressure
LBNP+thermal early	5 min into LBNP and thermal stimulus
LBNP+thermal later	20 min into LBNP and thermal stimulus
MAP	Mean arterial pressure
NEUT	Thermoneutral/normothermia stimulus
RT	Reaction time
TS	Thermal Sensations scale
T_{sk}	Skin temperature

CHAPTER 1

INTRODUCTION

One in 10 deaths worldwide is caused by traumatic injury, with 30-40% of trauma-related deaths due to hemorrhage (Hoyt et al., 2008). Additionally, hemorrhage from major trauma is the predominant mechanism of death in potentially survivable casualties, based on each wounds potential for survivability (Eastridge et al., 2011). It is also responsible for deaths on the battlefield (BAA 11-1, October 2010). Among the trauma patients who do not die immediately, hemorrhage-induced hypotension (systolic blood pressure ≤ 90 mmHg) often occurs (Heckbert et al., 1998).

This decrease in arterial pressure may compromise blood flow through the primary blood vessels in the brain (i.e., carotid, vertebral arteries), one result of which may be cognitive impairment. Consequently, the ability to accurately make rapid decisions or allocate attention to pertinent tasks (e.g., battalion commander, incident commander, firefighter in a dangerous situation) while severely injured may be compromised. Currently, trauma patients are passively heated due to severe unintentional hypothermia (core body temperature < 35°C) that can accompany trauma (Martin et al., 2005; Peng & Bongard, 1999). However, if the patient does not present with hypothermia (e.g., normothermic), it may not be conducive, and may even be disadvantageous to heat them. Thus, development of countermeasures to prevent or attenuate decrements in arterial pressure and possibly cognitive function during traumatic injury (e.g., hemorrhage) is an important undertaking.

Aerobic exercise and fitness has been associated with better cognitive vitality (e.g., enhanced executive function, visuospatial processing, speeded processing) and improvements in aerobic fitness, from both acute and chronic exercise, have been shown to influence cognitive functioning (Colcombe & Kramer, 2003; Hillman, Erickson & Kramer, 2008; Themanson & Hillman, 2006). Certain populations, notably military soldiers and firefighters, are routinely challenged to perform tasks and operations that are both physically and cognitively demanding. Further, high levels of stress (i.e., physical, environmental, cognitive) are generated during battlefield combat and firefighting and the risk for developing psychiatric symptoms and compromised neurocognitive functioning increases (van Wingen et al., 2012). Battlefield combat and firefighting often involve long (> 60 min) and arduous work that can lead to dehydration and fatigue, which may further compromise information processing and memory functions (Tomporowski, 2003).

Ultimately, the combination of extreme environmental temperatures, physical exertion, heavy equipment, and body armor or personal protective equipment, results in body temperatures that often exceed 38°C (Horn, Blevins, Fernhall, & Smith, 2013; Welles et al., 2013). As the body experiences elevated temperatures, such as during exercise or in a hot environment, the rectal to skin temperature gradient is reduced, causing vasodilatation and an increase in skin blood flow to the periphery to dissipate heat. The increase in skin blood flow then causes peripheral pooling of the blood, leading to a drop in central pressure, and thus hypoperfusion to the brain and decrements in cognitive function (Castellani 2003; Sawka & Wenger 1988). Additionally, Lieberman et al. (2005a) have also shown decrements in both simple and higher cognitive functions as a result of such multiple stressors. Thus, through the course of their activities, either on the battleground

or fire ground, a soldier or firefighter may have compromised cognitive function even before experiencing a hemorrhagic injury.

Clearly research is needed to identify whether, or to what extent, such combined stressors lead to adverse effects on cognitive function. Thus, the primary research question to be addressed in the present study is whether in normothermic hemorrhaging individuals, mild heating or skin surface cooling alters cognitive function? A secondary question is the extent to which aerobic fitness might modify that effect. As a result, the purpose of this study is to evaluate the effects of different thermal stimuli during simulated hemorrhaging on various aspects of cognitive performance. The following research hypotheses are generated:

1. Mildly heating an otherwise normothermic individual experiencing a simulated hemorrhagic insult will be detrimental to cognitive function. Specifically, (a) response accuracy will decrease; (b) reaction time will increase (i.e., slow); and (c) variability in response times will increase for the cognitive task. Such responses will be related to aerobic fitness such that more fit individuals will show proportionately less decrement than less fit individuals, as well as compared to their baseline scores.
2. Skin surface cooling an otherwise normothermic individual experiencing a simulated hemorrhagic insult will be beneficial to cognitive function. Specifically, (a) response accuracy will increase; (b) reaction time will decrease (i.e., become faster); and (c) variability in response times will decrease for the cognitive task. Such responses will be related to aerobic fitness such that more fit individuals will

show proportionally more benefit than less fit individuals, as well as compared to their baseline scores.

CHAPTER 2

REVIEW OF LITERATURE

This review of literature describes various factors that influence cognitive function. The first section presents an overview of physical activity and its association with the cognitive function. Next, the relationship between multiple stressors (including exercise), experienced by military and firefighting personnel, and cognitive performance will be evaluated. Subsequently, because hypothermia is a frequent occurrence for both military and firefighting personnel, the influence of hyperthermia on cognition will also be reviewed. Alternative treatments, such as body-cooling techniques, have shown favorable effects on cognitive function (as described), which may also benefit cognitive performance in trauma patients (i.e., those experiencing hemorrhage). Lastly, an overall summary and the statement of the problem are given.

2.1 PHYSICAL ACTIVITY AND COGNITIVE FUNCTION

Participation in physical activity has been associated with fewer physical and mental disorders (Hillman et al., 2008). As a result, the relationship between physical activity and improvements in brain function and cognition has been explored. According to Nehlig (2010), cognitive function is defined as the capacity for information processing, as well as applying knowledge and changing preferences. All of these aspects of cognitive function involve memory, attention, executive function, perception, language and psychomotor functions. Colcombe and Kramer (2003) noted that while the largest positive effect of exercise on cognitive function occurred for executive function tasks (effect size =

0.68), visuospatial and speeded processing (i.e., reaction time) was also influenced (effect size = 0.426 and 0.274, respectively). Executive control is a particular aspect of cognition responsible for the management of cognitive processes of perception, memory and action. An oft-used cognitive task that taps these various aspects of executive functioning is the Flanker task (Eriksen & Eriksen, 1974; Themanson & Hillman, 2006). Ultimately, 20-60 min of submaximal aerobic exercise has been shown to facilitate multiple cognitive processes that are critical to optimal performance and adaptive behavior (e.g., reaction time, speed of information processing). Acute moderate intensity exercise has also been shown to improve performance on higher-order cognitive processes, aspects of executive functioning such as planning and working memory (Ratey & Loehr, 2011).

Following a 3-month aerobic exercise regimen (40 min cycling, running, stair climbing, or elliptical trainer), Pereira et al. (2007) noted a significant relationship between changes (i.e., improvements; $\beta = 0.70$) in VO_{2max} and improved cognitive function, specifically declarative memory (as assessed by a modified Rey Auditory Verbal Learning Test). Essentially, as aerobic fitness increased due to exercise, first-trial learning of new declarative memories improved (pre-exercise = ~8 correct responses; post-exercise = ~12 correct responses). Chapman et al. (2013) also utilized a 3-month aerobic exercise intervention (3, 60 min sessions per week of cycling or walking) and evaluated neurocognitive measures of executive function, memory and complex attention. Cognitive gains were manifested in the exercise group in terms of memory function (as assessed via the Wechsler Memory Scale, 4th Edition). Specifically, immediate and delayed memory improved from pre-training, or baseline, to post-training (immediate memory raw score:

exercise Δ mean = 1.6, control Δ mean = -2.3, $P = 0.003$; delayed memory raw score: exercise Δ mean = 2.0, control Δ mean = -0.3, $P = 0.03$).

Although significant cognitive benefits have been shown as a result of exercise training, short exercise periods (i.e., acute exercise) may also enhance cognitive function. Voluntary wheel running for 1 week was shown to improve learning acquisition in rats (i.e., shorter latency), as assessed by the time it took to find an escape platform in the hidden water maze compared to their sedentary counterparts (Vaynam, Ying, & Gomez-Pinilla, 2004). Further, memory retention in exercise rats exceeded control rats. That is, water maze trials were performed 2 days later still showed an advantage for the exercised rats. They swam toward the escape platform quadrant and spent a significantly ($P < 0.05$) greater percentage of time in this quadrant than the control sedentary group (48.27 ± 3.14% vs. 33.95 ± 4.64%; Vaynam et al., 2004). Improvements in cognitive function have also been shown in exercising humans.

Higher scores of executive functioning, as measured by performance on the Stroop test, were found following acute bouts of exercise (e.g., graded exercise test, 30 min low intensity cycling at ~56% VO_{2max}, and 30 min high intensity cycling at ~75% VO_{2max}; Ferris, Williams, & Shen, 2007). Similarly, Murray and Russoniello (2012) reported significant improvements in visual attention, task switching and reaction time following a 30 min bout of cycling at a self-determined intensity (average 65% VO_{2max}) in regular exercisers and non-exercisers. Specifically, time to complete complex tasks was reduced and faster reaction times were noted after an acute bout of moderate intensity cycling (Murray & Russoniello, 2012). Overall, both long-term and short-term exercise can selectively benefit

multiple aspects of cognitive performance, but can also be influenced by various factors (e.g., dehydration).

Exercise-induced (40 min walking, 5.6 $km \cdot h^{-1}$, 5% grade) dehydration (1.59% loss of body mass) produced significantly altered premature errors on the psychomotor vigilance test task, a test of simple visual reaction time in which participants must respond as rapidly as possible when a stimulus appears (Ganio et al., 2011). Minor dehydration affected sustained attention to the stimulus resulting in more incorrect responses. This decrement would be expected to continually worsen as dehydration continues (e.g., combat, fire suppression).

Imposition of a greater level of dehydration (~4% body mass loss), generated by 3 h of work-rest cycles and passive heating of 10, 20, 30 and 40°C, had no significant effect on reaction time to the same psychomotor vigilance test in comparison to the euhydrated group (Ely, Sollanek, Cheuvront, Lieberman, & Kenefick, 2013). Similarly, Adam et al. (2008) reported that moderate levels of dehydration (~3% body mass loss via 3 h of passive heating) had no significant effect on any measure of cognitive function. However, after 60 min of cycling (60% VO_2peak), while dehydrated, increased accuracy was shown in sentry duty friend-foe discrimination on a marksmanship simulator and improved total response latency (i.e., faster) to a visual vigilance task (Adam et al., 2008). Since both studies elicited dehydration over an extended period of time, it is possible that participants may have gradually acclimated to their hydration levels, allowing them to maintain cognitive performance.

Without question, military and firefighting operations require some form of physical activity that is also coupled with conditions that can negatively influence cognitive

performance (e.g., hyperthermia, dehydration). As such, in the presence of multiple stressors that are regularly encountered by military and firefighting individuals (e.g., extreme temperatures, traumatic injury), it is reasonable to ask whether the benefits of physical activity would preserve or attenuate cognitive function decline.

2.2 COMBAT AND FIREFIGHTING CONDITIONS INFLUENCING COGNITIVE FUNCTION

Various factors, including mood, level of arousal (reflecting alertness and energy), physical well-being, and motivation can influence cognitive function (Nehlig, 2010). Additional external stressors and risk factors that are continually present (e.g., exposure to extreme environments, heavy workload, inadequate sleep, dehydration, impaired nutritional state, fear, uncertainty and information overload), may further challenge or hinder cognitive performance, especially among military and firefighting personnel. These individuals are routinely challenged to perform tasks that are both physically and cognitively taxing, which increases the risk for developing psychiatric symptoms and compromised neurocognitive functioning (van Wingen et al., 2012). Even well trained, seasoned leaders are not immune to cognitive impairments during these high multi-stress environments.

Effects on Attention (Vigilance), Reaction Time, and Memory

Dismounted soldiers, as opposed to soldiers who fight from mobile platforms, perform a combination of complex tasks that require both physical and cognitive resources. As such, the combination of 30 min of walking around obstacles (rubber cones, plastic hurdles) while carrying a heavy load (40 kg) in simulating dismounted soldiers and its

effect on cognitive performance were observed (Mahoney, Hirsch, Hasselquist, Lesher, & Lieberman, 2007). Since substantial resources were needed to guide movement over and around the obstacles presented, performance on the vigilance task was worse than walking trials without obstacles, which theoretically required minimal attentional resources. With the addition of physical exertion (40 kg load) and the effort required for guided movement (obstacle walking), fewer signals on the vigilance task were detected, resulting in decreased accuracy (Mahoney et al., 2007). Since cognition was affected during simulated conditions, the ability to perform tasks accurately may be compromised further with the added stress of experiencing work operations or training simulations.

van Wingen and colleagues (2012) found that combat stress (e.g., exposure to enemy fire and improvised explosive devises, armed combat, combat patrols, witnessing injured and dead soldiers and civilians) adversely affected sustained attention in deployed soldiers. Further, attention decrements were related to functional and structural changes within the midbrain as observed by reduced fractional anisotropy and increased mean diffusivity seen with magnetic resonance imaging and diffusion tensor imaging. Consistent with this observation, soldiers exposed to combat performed worse on the sustained attention task following deployment relative to their non-deployed counterparts (van Wingen et al., 2012). At follow-up (1.5 y), midbrain changes reverted to baseline levels; however, it remains to be seen how constant significant alterations to the brain influence cognitive performance.

Cognitive impairments (i.e., decrements in vigilance, perception, reaction time, learning, memory and logical reasoning) were also reported during stressful combat-like training in elite U.S. Army Rangers and U.S. Navy SEALs that had served, on average, 9 and

3 y, respectively (Lieberman et al., 2005b). The extent of this impairment is highlighted by the fact that the four-choice reaction time latency was far greater (i.e., slower; Rangers, 20% degradation; SEALs, ~16% degradation) than those typically produced by alcohol intoxication (~7% degradation) or clinical hypoglycemia (~13% degradation; Lieberman et al., 2005b). During exposure to a multi-stressor environment (i.e., sleep deprivation, extreme temperatures, physical activities, verbal confrontations), significant decrements in both simple and higher cognitive functions were also observed in these military officers (Lieberman et al., 2005b). Greater incidence of errors was coupled with increased reaction time, both of which could have a costly impact on a soldier's survival and that of his or her comrades.

Similar negative alterations in cognitive functioning (via a continuous performance test; CPT) were observed in firefighters performing repeated strenuous live-fire drills (Smith, Manning, & Petruzzello, 2001). The CPT measured reaction times and response accuracy. Although reaction times did not drastically change over time, accuracy of responses to the digit stimuli decreased across experimental trials; the latter was evidenced by participants having 12% greater error by the final trial (Smith et al., 2001). While firefighting conditions may negatively influence response accuracy, it can also affect other areas of cognitive performance. As the stress reaction to a search and rescue operation in firefighters increased (i.e., evidenced as a change in heart rate compared to maximum heart rate), the index of controlled task-focused thinking varied between the firefighters from 5-46% (Kivimaki & Lusa, 1994). Since environmental stressors (e.g., ambient temperature, firefighting activities) were tightly controlled and similar for each subject, heightened stress could have lowered cognitive performance.

Although decrements in cognition to varying degrees have been noted, Vincent and colleagues (2012) observed minimal effects in active duty service members following deployment. This was due in part to the large sample sizes (N = 8002) used and over-powered statistics performed. A selection of cognitive tests believed to be especially sensitive to mild traumatic brain injury (TBI) within military and sports concussion research was administered the 6th day after returning home from deployment. Specifically, these cognitive tests were derived from Automated Neuropsychological Assessment Metrics (version 4; ANAM4), which measured attention, processing speed, and general cognitive efficiency. Vincent et al. (2012) also acknowledged that differences in study design and analyses may have attributed to the conflicting results. For example, the ANAM4 test battery could have been administered immediately upon return from deployment. Additionally, a regression analysis could have helped ascertain declines in cognitive function with varying durations of deployment, as demonstrated by Vasterling and others (2006).

Vasterling et al. (2006) utilized the ANAM and Neurobehavioral Evaluation System (3rd edition; NES3), test batteries to evaluate sustained attention, working memory/executive functioning, fine motor speed, verbal and visual learning and memory, reaction time, and cognitive efficiency in soldiers deploying to Iraq. They compared those responses to soldiers not deployed (those preparing for extended intensive desert training within the US). Results revealed that deployment was associated with neuropsychological compromise on tasks of sustained attention, verbal learning, and visual-spatial memory (Vasterling et al., 2006). Ultimately, it would appear that neuropsychological compromise is a possible negative health consequence of war-zone deployment.

While typical computer test batteries tend to isolate aspects of cognitive performance, they may not represent the dynamism and complexity found in combat environments (Wong, 2005), although it may induce unnecessary stress on the individual. Composite scores, from a multiple-task battery (SynWin), assessed working memory, arithmetic computation, and visual and auditory monitoring declined (1500 to 1000) in enlisted Navy and Marine Corps personnel as sleep deprivation increased from 18 to 63 h (Elsmore, 1994). Similarly, composite scores prior to and following 12 and 24 h shifts in flight crewmembers decreased (Braude, Goldsmith, & Weiss, 2011). Furthermore, significant albeit small relationships between the multi-task battery and irritability were observed before (r = -0.25) and after (r = -0.34) a shift. Essentially, higher reported states of irritability corresponded to poorer multi-tasking performance. Overall, decrements in cognitive performance (e.g., memory, computation, visual and auditory vigilance) due to sleep deprivation stress were observed during flight operations (Braude et al., 2011; Elsmore, 1994).

2.3 THERMAL STRESS AND COGNITIVE FUNCTION

The combination of stressors experienced during combat and firefighting (e.g., extreme environmental temperatures, physical exertion, heavy equipment, and body armor) may result in internal temperatures that often exceed 38°C (Horn et al., 2013; Welles et al., 2013). Additionally, brain temperature can exceed core body temperature by 0.2°C (Morley et al., 2012). As the body experiences elevated temperatures, such as during physical activity or in a hot environment, the rectal to skin temperature gradient is reduced. This causes vasodilatation and an increase in skin blood flow to the periphery. In

addition to sweating, this helps to dissipate heat to the environment (i.e., non-sweating). The increase in skin blood flow then causes peripheral pooling of the blood, leading to a drop in central pressure, and thus hypoperfusion to the brain and decrements in cognitive function (Castellani, 2003; Sawka & Wenger, 1988).

It has been suggested that cognitive performance is essentially unaffected unless thermal stress is sufficient enough to change core body temperature away from normal or steady state conditions. Perceptions of thermal stress (e.g., comfort, sensation) however, are more sensitive to changes in skin temperature (Simmons, Saxby, McGlone, & Jones, 2008). According to the maximal adaptability model, thermal stress exerts its detrimental effects on cognitive performance by competing for and eventually draining attentional resources (Hancock & Vasmatzidis, 2003). Additionally, the level of performance deterioration is dependent on the severity of heat strain and the complexity of the task.

As core or ambient temperatures persist (either in duration or intensity of exposure or both), attentional resources are progressively drained, and thus a decline in performance. During heat exposure of 26.67°C and above, Pilcher, Nadler and Busch (2002) observed the most negative effect on attentional and perceptual type tasks (e.g., vigilance), and mathematical processing tasks. As temperature conditions became hotter, performance on these tasks worsened. Under the hottest conditions (≥ 32.22°C), a 14.88% average decrement in cognitive performance was reported, while 26.67-32.17°C created a 7.5% average decrement (Pilcher et al., 2002). Overall, simple tasks such as reaction time are less vulnerable to the effects of heat; alternatively, more complex tasks such as vigilance and monitoring performance have shown to be the more sensitive to extreme temperatures.

Heat stress poses a significant problem among individuals wearing protective clothing (e.g., military pilots, firefighters, athletes) since it provides extra insulation, which prevents evaporative heat loss. Volunteers (dressed in flight gear) have reported feeling "slightly uncomfortable" on a thermal comfort scale 15 min into heat exposure (40°C, 19% relative humidity), while thermoneutral conditions (0°C and 23°C) remained at "comfortable" (Faerevick & Reinersten, 2003). Eventually, thermal comfort escalated (i.e., worsened) and remained at "uncomfortable" and "very uncomfortable" for the remainder of the heating condition (3 h). As a result of heat exposure, decrements in vigilance were observed, as indexed by the increased number of incorrect responses to the test stimulus (Faerevick & Reinersten, 2003). Further, a strong positive correlation (r = 0.907) was detected between changes in core temperature from baseline and the number of incorrect reactions. Since sustained attention over long periods of time is required, increased pilot error may occur as a result of increased core temperature from wearing protective clothing in hot ambient conditions.

Combat body armor, involving clothing and personal protective equipment, could also potentially impede heat loss mechanisms (e.g., sweating and skin blood flow), which can negatively influence cognitive performance. Long duration (2.5 h), low intensity walking in the heat (36°C, 60% relative humidity) with full armor increased core temperature at a faster rate (0.51°C·h^{-1}, 38% faster than no armor trial) than wearing partial armor (0.41°C·h^{-1}, 10.8% faster than no armor trial) or no armor at all (0.37°C·h^{-1}; Caldwell, Engelen, van der Henst, Patterson, & Taylor, 2011). Although core temperature increased to ~38.3°C (minute 150) in the full armor trial (a 1.3°C rise from baseline, minute 0), no decrements in cognitive function (assessed by vigilance, reasoning, filtering, verbal

working memory, divided attention and perceived reaction time) were demonstrated. Caldwell et al. (2011) speculated that it would certainly be possible that with more severe conditions of hyperthermia (or dehydration, sleep loss, physical exertion, etc., alone or in combination), neurocognitive indices of cognitive performance would be more sensitive to changes in performance.

Similarly, increases in core and skin temperature and cognitive deficits were observed in firefighters who exercised while wearing thermal protective clothing and a self-contained breathing apparatus (SCBA) in a hot environment (33-35°C; Morley et al., 2012). While decrements in neurocognition did not appear immediately following exercise (~50 min), impairments in recall and psychomotor vigilance were noted more than an hour following exercise. Impaired short-term memory may place a firefighter at risk during fire suppression operations (e.g., exit location recall, details of unstable structures, errors in SCBA calculations); while delays in reaction time could result in injury from rapidly deteriorating structures (Morley et al., 2012). Furthermore, if these decrements are not adequately addressed, subsequent emergency operations may place firefighters and victims at increased risk of injury or death.

In an effort to develop more efficient protective gear that reduces thermal stress and subsequent elevations in core temperature, Smith and Petruzzello (1998) evaluated cognitive performance of response accuracy and response time in different firefighting gear configurations. Gear 1 was the standard 1987 National Fire Protection Agency (NFPA) gear (bunker boots and pants, turnout coat, Nomex hood, Cairns helmet, and Fire Grip gloves), while Gear 2 was the gear typically worn prior to the adoption of the Gear 1 (Servus ¾ hip boots, full-length turnout coat, Cairns helmet, and Fire Grip gloves). Participants

performed three trials of firefighting related tasks (e.g., dummy drag, heavy load carrying, hose hoisting, wood chopping) within a burning building (53.6-78.7°C) separated by 10 min of rest/recovery. While thermal sensation was reported higher with Gear 1 (1987 NPFA), there was little difference in response accuracy to stimulus continuous performance test (CPT) between the gear configurations and across firefighting trials (Smith & Petruzzello, 1998). Reaction time variability however, increased with Gear 1 across all trials (pre-trial = 124.95 ms, post-trial 1 = 128.91 ms, post-trial 2 = 145.17 ms, post-trial 3 = 158.40), resulting in an inconsistent performance.

Aside from developing more efficient protective clothing, to reduce thermal stress and potentially associated cognitive impairments, cooling interventions have also been employed to combat the negative effects of heat stress.

Cooling Interventions to Preserve Cognitive Performance

Following ~2.5 h of passive heating (45°C, 50% relative humidity) inside a climatic chamber, both skin and core temperature increased along with subsequent decrements in cognitive performance, assessed by simple reaction time, digit vigilance, choice reaction time and rapid visual information processing (Simmons et al., 2008). Power of attention (composite score measure of reaction time) and continuity of attention (composite score measure of accuracy were calculated from the battery of cognitive tasks. As core temperature increased, power of attention increased, representing quicker reaction times, while continuity of attention decreased, representing a loss of accuracy. Additionally, decreased perceptions of thermal comfort, and increased "hot" thermal sensations also occurred with increasing skin and core temperatures (Simmons et al., 2008). When skin

cooling was employed via cold water (~3-8°C) perfused through a helmet encapsulating the head and neck, participants reported feeling less uncomfortable and less hot. However, cooling had no significant effect on cognitive performance, as shown by increased reaction time and decreased response accuracy, since core temperature was unchanged (Simmons et al., 2008). Since decrements in cognitive performance occur when increases in core body temperature is beyond thermal steady state (~37°C) that can be compensated for (e.g., sweating; Hancock, 1986), isolating cooling strictly to the head and neck may not be sufficient enough to quickly reduce core temperature, and thus cognitive performance.

Liquid-cooling garments have been used to extract significant amounts of thermal energy (i.e., heat) from the body. In particular, Caldwell, Patterson and Taylor (2012) utilized such a garment (15°C water) in conjunction with a standard military combat uniform and protective ensemble (e.g., face mask, boots, gloves). Participants performed 8, 13 min bouts of low intensity exercise (30 W, simulating flying a helicopter) on a semi-recumbent cycle ergometer in dry heat conditions (48°C, 30% relative humidity) with and without garment cooling. As expected, both skin and core temperature decreased during the cooling condition, and consequently, improved perceptions of thermal sensation and thermal comfort (Caldwell et al., 2012). However, no significant changes in cognition on the MiniCog Rapid Assessment Battery (assesses attention, verbal working memory, problem solving, and perceptual reaction time) were detected between dry heat conditions with and without auxiliary cooling. Caldwell et al. (2012) speculated that thermal strain in the absence of dehydration (water deficits kept < 1% via ad libitum drinking) had minimal impact on cognitive function.

Cold-water immersion has also been investigated as a method of decreasing core and skin temperature. Giesbrecht, Jamieson, and Cahill (2007) performed cold water immersion cooling of the hands and forearms in hyperthermic firefighters. While donning firefighter "turn-out gear" (e.g., jacket, pants, rubber boots, helmet, self-contained breathing apparatus), participants performed three 20 min of stair stepping in the heat (40°C, 40% relative humidity) separated by 20 min of either rest (no active cooling) or different cold-water immersion conditions. Forearm immersion in both 20°C and 10°C water resulted in lower core body temperature during each stair stepping trial than hand immersion alone or no active cooling (Giesbrecht, et al., 2007). Since the forearms have a greater proportion of total body surface area than the hands (~7% and ~5%, respectively), immersion of the entire lower arm increased heat loss, and thus decreased core temperature. Although cognitive performance was not measured, based on the association between core temperature and cognitive performance (Hancock, 1986), it would be expected that cognitive function improved.

When applying cold-water immersion, body temperature should be monitored so that core temperature does not fall below normothermic levels (hypothermia), which may cause cognitive decrements. Volunteers equipped with a personal flotation device that submerged the back of the head and the entire body in cold water (10°C) resulted in 60% greater core cooling than when the head and upper chest were supported out of the water (Lockhart, Jamieson, Steinman, & Giesbrecht, 2005). When core temperature dropped to 34-35°C, mental performance deficits were observed in increased time required to correctly complete the Stroop color-word test, and decreased number of correct responses for attention short-term memory tasks (Lockhart et al., 2005). Cooling interventions

should be monitored closely to prevent deficits in cognitive performance as a result of hypothermia.

During soccer games (with no cooling intervention) in the summer months of July and August, increased core temperature of the players (37.21- 40.05°C) had significant negative effects on speed for all cognitive tests assessed (visual sensitivity, finger-tapping test, visual/auditory working memory, and visuo-spatial working memory; Bandelow et al., 2010). Specifically, increases were observed for fine motor speed, visuo-motor reaction time, and serial working memory scanning function. It appeared that significantly elevated core temperatures during play exerted a global, non-specific slowing effect on psychomotor response speed (Bandelow et al., 2010). While at a different game, a tent equipped with misting cold water (air temperature ~25°C) was pitched next to the field; players sat under the tent for 15 min prior to the start of the game, and for 10 min during half-time. Although elevated core temperature was unchanged, visuo-motor reaction times were faster, which the authors (Bandelow et al., 2010) attributed to increased perceived comfort (i.e., more comfortable) in the cooling tent.

Cooling interventions, resulting in decreased skin and core temperature, in addition to improved cognitive function and perceptions of stress, have also shown increased control of arterial blood pressure and cerebral perfusion. Skin-surface cooling (15°C), through a water perfused suit, 1 min prior to a 10 min head-up tilting manipulation proved to be effective in preventing the decrease in cerebral blood flow velocity (CBFV) in both normothermic (~37°C) and heat-stressed individuals (~38°C; Wilson, Cui, Zhang, Witkowski, & Crandall, 2002). Adequate cerebral perfusion was indicated by the lack of presyncopal symptoms (i.e., dizziness, headache, nausea; Durand, Cui, Williams, & Crandall,

2004). As such, skin surface cooling prior to the orthostatic challenge did not result in any reports of presyncopal symptoms (Wilson et al., 2004), which would imply better cognitive performance since these symptoms would be a hindrance.

Preservation of CBFV was also observed during progressive decreases in lower body negative pressure (LBNP) while undergoing skin surface cooling (16°C, water perfused suit; Durand et al., 2004). Prior to the start of the LBNP challenge, skin-surface cooling caused significant increases in CBFV. This resulted in statistically greater CBFV protection during LBNP stages of -40 and -50 mmHg (i.e., greater orthostatic tolerance) in comparison to non-skin surface cooling (34°C, normothermia control group). Although cognitive function was not measured, improvements in performance may arise since cerebral perfusion to the brain was protected. Since cognitive impairments manifest during traumatic injury, such as hemorrhage, it would be important to more carefully investigate the effectiveness of cooling interventions.

2.4 HEMORRHAGE AND COGNITIVE FUNCTION

Hemostasis is a process that causes bleeding to stop through the mechanisms of coagulation, or blood clotting, and fibrinolysis, or breakdown of blood clots (Tanaka, Key, & Levy, 2009). Specifically, blood coagulation plays an important role in containing blood loss and repairing the vascular injury (wound). However, during traumatic injury, 28% of patients have coagulation dysfunction (coagulopathy) due in part to progressive dilution of coagulation factors from resuscitation products (MacLeod, Lynn, McKenney, Cohn, & Murtha, 2003; Tanaka et al., 2009). As a result of coagulopathy, mortality increases 3-5 times higher compared to a patient with normal coagulation (MacLeod et al., 2003).

Consequently, hemorrhage from major trauma is the leading cause of death in both civilian and battlefield settings (Eastridge et al., 2011; Soreide et al., 2007). Among the trauma patients who do not die immediately, hemorrhage-induced hypotension (i.e., systolic blood pressure ≤ 90 mmHg), a phenomenon comparable to orthostasis, often occurs (Heckbert et al., 1998). While several physiological responses occur in order to maintain vital organ perfusion during a hemorrhagic insult (e.g., tachycardia, vasoconstriction, respiration), the severity of the trauma experienced may negate these compensatory responses. Decreases in arterial pressure may compromise perfusion through the primary blood vessels in the brain (i.e., carotid, vertebral arteries), similar to hypoxia or decreased oxygenation, which may cause cognitive impairment. Further reductions in blood pressure and accompanying cerebral hypoperfusion are also accompanied by presyncopal symptoms, such as headache and dizziness, which may lead to irreversible brain damage if left unattended (Duschek & Schandry, 2007).

Cognitive Impairments of Attention and Memory

Several hypotheses have been developed to help explain the relationship between hypotension and cognitive impairment among several clinical populations (e.g., elderly, dementia syndromes, movement disorders). However, the most applicable explanation to hemorrhagic injury is cerebral hypoperfusion, which can develop due to hypotension and/or impaired autoregulation (Novak & Hajjar, 2010; Sambati, Calandra-Buonaura, Poda, Guaraldi, & Cortelli, 2014). Hypotension influences neurovascular coupling (i.e., redistribution of cerebral blood flow to areas of increased activity and metabolic demand),

causing decreased perfusion, oxygenation, and vascular reserve capacity, which is associated with decline in cognitive function (Novak & Hajjar, 2010).

Neuropsychological testing has demonstrated reduced cognitive performance in individuals experiencing hypotension, primarily in domains of attention and memory, which seem to be a direct consequence of low blood pressure (Duschek & Schandry, 2007; Perlmuter, Sarda, Casavant, & Mosnaim, 2013). Comprehensive cognitive tests measuring domains of global function, executive function, processing speed, attention and memory were evaluated in older adults (≥ 50 y) participating in the Irish Longitudinal Study on Ageing (Frewen, Savva, Boyle, Finucane, & Kenny, 2014). Among individuals with orthostasis, global cognitive function (from mini-mental state exam and Montreal Cognitive Assessment) and memory (word recall and picture memory tests) performance were significantly less than their normotensive counterparts. Frewen et al. (2014) concluded that rapid changes in blood pressure, from orthostasis could substantially alter cerebral blood flow, and cerebral hypoperfusion, causing cognitive impairment.

In another group of older adults (≥ 55 y), Yap, Niti, Yap, and Ng (2008) evaluated cognitive decline and orthostasis 1-2 y following baseline evaluation. The mini-mental state exam (MMSE), a validated and widely used measure of global cognitive function in the domains of memory, attention, language, praxis, and visuospatial ability, was used. Individuals with baseline MMSE scores < 24 were classified as cognitively impaired. At follow-up (1-2 y) hypotensive adults were 4 times more likely to present with cognitive impairment, defined as at least a 1-point drop in baseline MMSE scores. The authors (Yap et al., 2008) suggested that decreased blood pressure might impair cerebral perfusion and aggravate dementia.

Since anatomical structures that degenerate in dementia are also involved in autonomic function, all forms of dementia are most likely due to impaired autonomic function (Perlmuter et al., 2013; Sambati et al., 2014). The composite autonomic symptom score, derived from the frequency of orthostatic intolerance and syncope, quantifies the severity of autonomic dysfunction (cardiovascular, urinary, gastrointestinal and sudomotor). Although Low et al. (1995) did not assess cognitive function they did observe cognitive impairments in patients (mean age = 63.6 y) with symptomatic orthostasis. Following an upright tilt table test, patients were unable to perform arithmetic calculations, became disoriented to time, place and persons, and had considerable slowing in thinking (Low et al., 1995).

In a more specific form of autonomic disorder, specifically patients (46-82 y) diagnosed with pure autonomic failure, a disorder involving peripheral denervation of the autonomic system, results in the inability to control blood pressure. Deficits in speed and attention (5 out of 6 participants), and frontal executive functioning (3 out of 6 participants) were observed (Heims et al., 2006). It was proposed that significantly impaired speed, attention and executive functioning among these patients were consequences of cerebral hypoperfusion via systemic hypotension (Heims et al., 2006; Perlmuter et al., 2013).

Hypotension is also common among Lewy body disorders, which may contribute to cognitive impairment (Allcock et al., 2006; Perlmuter et al., 2013). Parkinson's disease (PD) is considered to represent a Lewy body disease. Generally, the relationship between decreased cognitive function and hypotension in PD patients has been described as significant differences in single tasks, especially executive tasks (i.e., attention, memory;

Sambati et al., 2014). Since hypotensives experience attention and visual memory deficits, it would be expected that PD with normal orthostatic responses would have a different cognitive profile than PD with orthostatic intolerance. PD patients with hypotension, had greater impairments in sustained attention and visual episodic memory, compared to PD patients without hypotension. As such, after adjusting for age and medication, PD patients with accompanying hypotension were less accurate in the digit vigilance test (79 vs. 93) and visual episodic memory (0.48 vs. 0.59) than patients without hypotension (Allcock et al., 2006). Given these observations, hypotension may be a marker for disease progression and cognitive decline.

The aforementioned findings may not be consistent in all groups. For example, while young adults (mean age = 26.1 y) became slightly hypotensive (head-down tilt = 127 ± 17 mmHg; head-up tilt = 124 ± 13 mmHg) following an orthostatic tilt test after blood donation (350-400 mL) than at baseline (head-down tilt = 124 ± 11 mmHg; head-up tilt = 141 ± 20 mmHg), cognitive performance remained unchanged (Tuboly et al., 2012). EEG recordings, measured ~5 min following hemodynamic data, assessed cognitive processing of new information when attention was engaged (Tuboly et al., 2012). Images of distracters (natural scenes) and targets (animals) were used to elicit cognitive processing, and participants had to decide if the image was an "animal" or "non-animal". The ability to categorize incoming stimuli (i.e., suppress insignificant distracters, process significant targets) is very basic and vitally important. Tuboly and colleagues (2012) interpreted the lack of cognitive decline post-donation as an adaptive tendency that is resistant to challenges (e.g., minor blood loss). However, a hemorrhaging patient may be losing more blood (>400 mL), which may interfere with this paradigm.

Decreased blood oxygenation, which reduces the oxygen supply throughout the periphery and in the brain, has been reported immediately upon ascent to high altitudes (Ando et al., 2013; Shukitt-Hale, Banderet, & Lieberman, 1998). As a result, hypoxia impairs cognitive performance during altitude exposure (simulations of 4,200 and 4,700 m for 4.5 h), specifically in relatively simple tasks, such as simple and choice reaction time, as well as more complex tasks, such as the addition test (Shukitt-Hale et al., 1998). The rapid onset and severity of these observed decrements observed could interfere with safe military and firefighting operations, since alertness and vigilance are important for combat and fire suppression performance.

While hypoxia alone (simulations of 1,300 and 2,600 m for ~1 h) may be detrimental to cognitive function, when combined with an acute bout of moderate exercise (10 min at 60% peak VO_2) performance may be maintained (Ando et al., 2013). Responses in reaction time to a Go/No-Go task following aerobic exercise decreased (i.e., responded quicker) from rest while experiencing conditions of hypoxia (decreased levels of oxygen) and normoxic (normal levels of oxygen). As such, Ando et al. concluded that improvement in cognitive function was attributable to the exercise performed.

In addition to decreased arterial pressure, severe unintentional hypothermia (decrease in core body temperature below 35°C) accompanies trauma, perhaps secondary to reduced metabolism, and increases mortality rates (Martin et al., 2005; Peng & Bongard, 1999). Hypothermia can deplete energy stores, disrupt cellular homeostasis, and correlate with more severe injuries (Kheirbek, Kochanek, & Alam, 2009). Further, decreased body temperatures (in non-hemorrhaging individuals) result in cerebral changes, including decreases in cerebral perfusion, and are associated with reduced cognitive functioning,

especially on speeded cognitive tasks, visual vigilance, and mood disturbances (Muller et al., 2012; Lieberman, Castellani, & Young, 2009). As a result trauma patients are often passively heated (Martin et al.; Peng & Bongard, 1999). However, if the patient does not present with hypothermia (e.g., normothermic), it is reasonable to question whether heating would still be beneficial to the patient. Perhaps cooling techniques, as previously described (section III), would be a better solution for cognitive performance in hemorrhaging individuals.

Uncontrolled hemorrhage was induced in female swine by creating lacerations to the iliac artery and veins and keeping the animals in shock for 30 min (simulating transport time to hospital; Alam et al., 2005). Animals then underwent 60 min of normothermia (control) or profound hypothermia (10°C) via fluid infused into the aorta at varying rates of slow, medium or fast. Unfortunately, clinical brain death (e.g., fixed dilated pupils, absence of corneal and gag reflexes, no spontaneous respiratory activity) occurred in all of the animals in the normothermic group. Alternatively, none of the hypothermic animals displayed any cognitive impairment based on a training and memory task where the animal had to identify the box with food (Alam et al., 2005). The number of sessions required to learn the task, and the time taken to open the correct box were the same as normal animals (animals that did not undergo hemorrhage). Not only was this cooling technique able to increase survivability during hemorrhage, it also preserved cognitive function.

2.5 SUMMARY

It is well accepted that participation in physical activity provides an array of benefits for cognitive performance (Colcombe & Kramer, 2003; Hillman et al., 2008). However,

when coupled with negative stressors (e.g., extreme temperatures, traumatic injury) that are present among military and firefighting cohorts, cognitive performance is at risk of impairment (van Wingen et al., 2012). Subsequently, as a result of these factors, hyperthermia may develop (Horn et al., 2013; Welles et al., 2013), which may further degrade performance. Since various cooling interventions have shown favorable effects on cognitive function, it may also provide similar benefits to an individual suffering from a hemorrhagic trauma (which could be a likely scenario in both military and firefighting personnel).

Hemorrhage from major trauma is the leading cause of death in both civilian and battlefield settings (Eastridge et al., 2011; Soreide et al., 2007). Consequently, decreases in arterial pressure due to hemorrhage may compromise perfusion through the primary blood vessels in the brain (i.e., carotid, vertebral arteries). This may result in cognitive impairment, and the ability to continue making rapid decisions or allocating attention to pertinent tasks (e.g., battalion commander, incident commander, firefighter in a dangerous situation) may be impacted negatively.

The current medical practice with hemorrhagic patients is to passively warm them, via blanket, since severe unintentional hypothermia (core body temperature < 35°C) can accompany trauma and increase mortality rates (Martin et al., 2005; Peng & Bongard, 1999). However, if the patient does not present with hypothermia (e.g., normothermic), it may not be conducive, and can be detrimental, to heat or even warm them (Crandall & Gonzalez-Alonso, 2010; Wilson et al., 2006). Thus, development of countermeasures to prevent or attenuate decrements in arterial pressure and accompanying cognitive function during traumatic injury (e.g., hemorrhage) is an important undertaking.

CHAPTER 3

METHODOLOGY

This study specifically focused on whether, in otherwise normothermic hemorrhaging individuals, mild heating or skin surface cooling influenced cognitive function, and the extent to which aerobic fitness might modify that effect.

PARTICIPANTS

Nine healthy, non-obese, men from the Dallas-Fort Worth area were recruited to participate in this investigation. The descriptive characteristics of these men (mean ± SD) were: age, 29.9 ± 8.4 y; height, 176.7 ± 10.7 cm; body mass, 79.4 ± 15.2 kg; VO_{2max}, 40.4 ± 6.3 $ml \cdot kg^{-1} \cdot min^{-1}$. Due to the difficulty of controlling hormonal and temperature changes and potentially varying dosages of birth control, coupled with 4 laboratory visits being necessary, women were excluded from the study. Potential participants with cardiovascular, neurological, and/or metabolic illnesses were excluded, as these conditions may affect the physiology of the systems targeted in the investigation. Participants who met the aforementioned inclusion criteria were invited to participate.

All procedures and the written consent were approved by the following Institutional Review Boards for Human Subjects: US Department of Defense, University of Texas Southwestern Medical Center, Texas Health Presbyterian Hospital of Dallas, and the University of Illinois at Urbana-Champaign. Participants gave their written informed consent (see Appendix A) after being completely informed as to the nature of the investigation.

FAMILIARIZATION DAY

On familiarization testing day (Table 1), participants completed an extensive health history form and the International Physical Activity Questionnaire (see Appendix B and C), had body mass assessed on an electronic scale, and were measured for height. The participant was then familiarized with the cognitive function test, perceptual scales and overall testing procedures. Participants were encouraged to ask questions. Next, aerobic fitness, as measured by maximal oxygen consumption, was determined via open circuit spirometry during a graded exercise test using a cycle ergometer.

Participants sat quietly for 2 min (baseline data collection) while equipped with the mouthpiece and headgear (for metabolic analysis). After the 2 min baseline metabolic data had been collected, participants began cycling at a self-selected pace between 60-80 revolutions per minute (rpm) at a workload of 80 watts for 2 min (warm-up period). Following the 2 min warm-up, resistance on the cycle ergometer increased 20 watts every minute thereafter, with the pace remaining between 60-80 rpm, until the participant reached volitional exhaustion. Heart rate was recorded at every stage, while blood pressure and ratings of perceived exertion were taken at every other stage. Not including warm-up time, total test duration was approximately 10 min. The following criteria verified attainment of VO_{2max}: an increase of oxygen consumption less than 150 ml·min^{-1} despite an increase in workload, a respiratory exchange ratio (V_{CO2}/V_{O2}) > 1.10, or achieving predicted maximum heart rate (i.e., 220-age).

INSTRUMENTATION FOR EVALUATION DAYS

Following the familiarization day, participants visited the laboratory on three additional occasions to undergo a randomized, crossover experimental design (Table 1). Instrumentation and procedures for each visit were identical, with the exception that participants were exposed to the following thermal conditions: cooling (COOL), mild heating (HEAT), or thermoneutral (NEUT) during key periods of data collection (see below).

Upon arrival to the laboratory on each of the subsequent test days, participants ingested a telemetric temperature-sensing pill (HQ Inc. CorTemp) to monitor intestinal temperature throughout the experimental trials. Participants then provided a urine sample, to ensure adequate hydration (urine specific gravity < 1.028), and a nude body weight. Six thermocouples interfaced with Sable Systems TC-2000 thermocouple meter were attached to the participant's skin (upper chest, upper back, abdomen, lower back, thigh and calf) to obtain and monitor mean skin temperature throughout the trials. Participants were also instrumented with a 5-lead ECG and arterial blood pressure cuffs (both auscultation of the brachial artery and finger-derived blood pressures).

Participants then donned a full body tube-lined suit (Allen Vanguard) and lay in the supine position with the lower half of their body in a lower body negative pressure (LBNP) box, sealed at the level of the iliac crest. The LBNP device is an airtight chamber that seals at the level of the iliac crest, resulting in central hypovolemia, i.e., a redistribution of blood away from the upper body (inclusive of the brain and chest) to the lower extremities. While in the LBNP box, an intravenous catheter was placed in an antecubital vein to collect blood samples at the end of each experimental stage. Next, cerebral perfusion was

evaluated via transcranial Doppler (DWL DopBox) of the middle cerebral artery as previously performed (Durand et al., 2004; Wilson et al., 2002). Data collected from these variables, with the exception of blood pressure and cerebral perfusion, were used for separate analyses discussed elsewhere.

Familiarization (1 Day)	Evaluation (3 Days)
• Health history, physical activity questionnaire • Height, weight, VO_{2max} test • Explained testing procedures (i.e., cognitive and perceptual measures)	• COOL (15-17°C), HEAT (40-44°C) and NEUT (34°C) • Superimposed with simulated moderate hemorrhagic challenge (30 mmHg) • Randomized order, performed on separate days

Table 1: Experimental design overview. *Participants visited the laboratory on 4 separate occasions. The first day was to collect descriptive data and familiarize with testing procedures. The following 3 days were to evaluate the effects of thermal stimuli during simulated hemorrhaging on cognitive performance.*

PROCEDURES

Figure 1 provides a graphical illustration of the experimental procedures. Upon completion of instrumentation and LBNP set-up, and prior to the start of data collection, participants were reacquainted with the same cognitive test (i.e., Flanker task) performed during familiarization day (denoted by grey arrow). Following the practice cognitive test, a 15 min baseline of quiet rest began, where participants remained in the supine position within the LBNP box, while normothermic water (33-34°C) perfused the tube-lined suit. Participants performed the cognitive test 2 min into baseline data collection (denoted by the first black arrow).

Immediately following baseline rest period (15 min), 10 min of LBNP chamber decompression at 30 mmHg was applied to simulate a mild hemorrhagic challenge, but not

a sufficient challenge to cause arterial hypotension (reduction > 10 mmHg in mean arterial blood pressure) while subjects remained normothermic. This approach has previously been verified to simulate central hypovolemia accompanying actual hemorrhage (Cooke, Ryan, & Convertino, 2004). The level of LBNP chosen (30 mmHg) equates to approximately 400-450 mL of blood loss, which is approximately the amount of a routine blood donation (~470 mL). This was chosen to simulate a sustained hemorrhagic injury, and to ensure that all participants would complete the entire protocol without syncope. To avoid interfering with hemodynamic data and blood draws, participants performed the cognitive test 2 min into the LBNP only stage.

With 30 mmHg LBNP continuing, participants were then exposed to 40 min of the following thermal perturbations via the water-perfusing suit:

1. COOL— 15-17°C water perfused through the tube-lined suit to decrease mean skin temperature from normothermia (~34°C) to as low as possible, without causing shiver. Water bath temperature was adjusted if the participant began to shiver, or if a 0.5°C decrease in core temperature was observed. This condition was used to evaluate any potential benefit from cooling that would not occur with heating.
2. HEAT— 40-44°C water perfused through the tube-lined suit to elevate mean skin temperature from ~34°C (normothermia) to ~37°C, and cause no more than a 0.5°C increase in intestinal temperature. Water bath temperature was adjusted if the participant's intestinal temperature surpassed a 0.5°C increase. This condition was used to simulate a blanket placed on a hemorrhaging victim (i.e., the current medical standard of care).

3. NEUT— 33-34°C water continued to perfuse the tube-lined suit in order to maintain a mean skin temperature at normothermia (~34°C). Since the water bath was kept at thermoneutral, core temperature was not expected to change. This condition was used as a control condition to compare with heating and cooling.

The order for thermal challenges was randomized with each performed on separate days (at least 24 h between each trial). Cognitive test was administered at 5 min (LBNP+thermal early) and 20 min (LBNP+thermal later) into the 40 min of LBNP and thermal condition stage. This frequency insured in-task assessment in the event that the participant might be unable to complete the entire stage (i.e., low tolerance).

Upon termination of LBNP and the thermal provocation, participants remained in the supine position within the LBNP box (device not engaged), while normothermic water (33-34°C) perfused the tube-lined suit for 15 min (post-test) to allow mean skin temperature to return to baseline (normothermic) levels. At the end of the post-test period, the cognitive test was administered a final time.

For all trials, the Feeling Scale (Hardy & Rejeski, 1989) and the Thermal Sensations Scale (Toner, Drolet, & Pandolf, 1986; Young, Sawka, Epstein, Decristofano, & Pandolf, 1987) were used to assess affective valence (good versus bad) and perceptions of thermal sensations. Participants responded to both scales every 10 min beginning at the start of experimentation (minute 0).

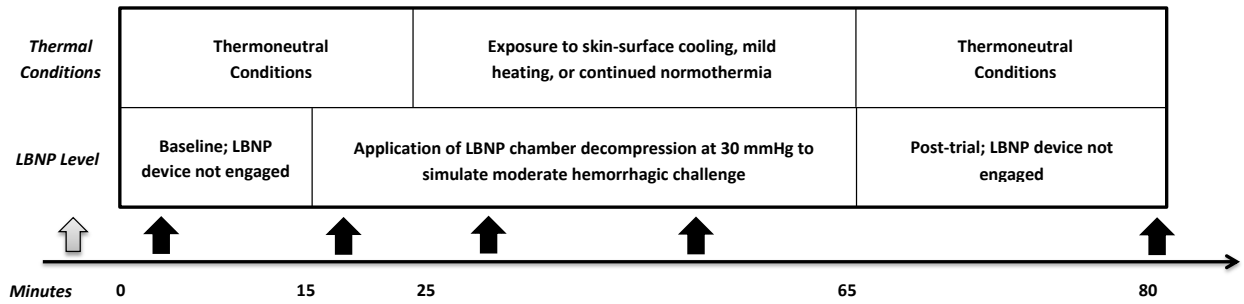


Figure 1: Graphical illustration of experimental procedures. *Participants were supine within the lower-body negative pressure (LBNP) device under thermoneutral conditions but without LBNP for 15 min (baseline). Participants were then exposed to 10 min of sub-hypotensive LBNP (30 mmHg) while remaining in a thermoneutral condition (LBNP only). Next, for the ensuing 40 min and with LBNP continuing, participants remained thermoneutral, underwent mild heating, or underwent skin surface cooling (each on a different day and randomized; LBNP + thermal). Upon completion of trials, participants remained in the supine position within the LBNP device under thermoneutral conditions without the LBNP for 15 min (post-trial). Thermal and hemodynamic variables were continuously obtained, and perceptions of feeling and thermal comfort were obtained every 10 min throughout. Arrows denote when cognitive performance was assessed; gray arrow denotes practice cognitive test (data was not used in analyses). Numbers across the bottom are approximate time points in minutes.*

ASPECTS OF COGNITIVE PERFORMANCE

A measure of cognitive function, specifically cognitive inhibition, was measured with a modified Eriksen Flanker task test (Colcombe et al., 2004; Eriksen & Eriksen, 1974). This task requires the participant to ignore irrelevant stimuli surrounding a relevant stimulus, thus it provides a measure of inhibitory control. Specifically, the Flanker task targets selective response inhibition, which is a subset of executive control function. In this task, five arrows appear on a computer screen, and participants are to respond to the orientation of the central arrow by pressing a button with their left index finger if the central arrow in the array is pointing to the left, or pressing a button with their right index finger if the central arrow in the array is pointing to the right. Flanking arrows are either oriented in the same direction (Congruent trials) as the central arrow (e.g., >>>>> or <<<<<), or oriented in the opposite direction (Incongruent trials) as the central arrow (e.g., <<><< or >><>>). The percentages of Congruent and Incongruent trials were evenly

divided (i.e., 50% each). Participants responded to 132 total trials as rapidly as they could while also trying to minimize incorrect responses. Each trial lasted 80-100 ms, and the inter-trial interval was between 1200-1300 ms. In addition to response accuracy (% correct responses) and reaction time, variability in reaction times (standard deviation) was calculated. Trials were counterbalanced and randomly ordered, and the entire set of 132 trials was completed in 3 min. As shown in Figure 1, there were a total of 5 blocks of 132 trials during each thermal condition.

During simulated hemorrhage and thermal conditions, it was expected that participants would experience changes in affect and thermal sensations. Additionally, affective states and perceptions were expected to fluctuate within and across trials. As such, affective state was assessed with the Feeling Scale (FS; Hardy & Rejeski, 1989; see Appendix D). This is an 11-point scale with anchors provided at 0 (neutral) and at odd integers, ranging from -5 (very bad) to +5 (very good) in response to the prompt "how do you feel right now?" Perception of thermal sensation (Toner et al., 1986; Young et al., 1987; see Appendix E) was measured via the Thermal Sensations Scale (TS). This is a rating scale ranging from 0.0 (unbearably cold) to 4.0 (comfortable) to 8.0 (unbearably hot) in response to the prompt "rate your perception of how hot or cold you are right now". Participants gave verbal responses to each prompt, which were recorded by the experimenter.

STATISTICAL ANALYSES

All statistical analyses were carried out with the SigmaPlot 13.0 statistical software package. Data was input into a SigmaPlot spreadsheet with proper variable coding for time

and condition. Appropriate pair-wise multiple comparison procedures were performed to identify any significant interactions of cognitive performance during LBNP and the thermal provocations. The criterion of significance was established at an alpha level of $P < 0.05$.

A power analysis for estimating the sample size necessary for a within-participants design that would include treatment and control conditions was conducted using G*Power 3.1 (Faul, Erdfelder, Lang, & Buchner, 2007). Since arterial blood pressure and cerebral perfusion were primary variables of interest (cognitive function as an accompanying variable influenced by these two), these variables were used in the power analysis. Using arterial blood pressure as the variable of interest from previous data (Wilson et al., 2002), alpha = 0.05, beta = 0.80, effect size f = 1.20, resulted in an estimated sample size of 9 participants. When cerebral perfusion was used as the variable of interest, the results yielded a similar sample size. Thus, 9 participants were recruited for this investigation.

A two-way repeated measures analysis of variance (RM ANOVA) was executed on the two primary variables of interest: arterial blood pressure via continuous non-invasive finger pressure monitoring, and cerebral perfusion via transcranial Doppler of the middle cerebral artery. The two main factors were time (i.e., baseline, LBNP only, LBNP+thermal early, LBNP+thermal late, post-trial) and the superimposed thermal stimulus (i.e., COOL, HEAT, NEUT).

To delineate whether, mild heating or skin surface cooling altered cognitive function in normothermic hemorrhaging individuals, the following analyses were carried out with the Flanker task data. Response accuracy (% correct), reaction time (ms), and reaction time variability (ms) for Congruent trials, Incongruent trials and for overall trials combined were computed for each experimental stage at which the cognitive test was administered

(5 total: baseline, LBNP only, LBNP+thermal early, LBNP+thermal later, post-trial). Data were then statistically analyzed using a two-way RM ANOVA with main factors of the superimposed thermal stimulus (i.e., COOL, HEAT, NEUT) and time (i.e., baseline, LBNP only, LBNP+thermal early, LBNP+thermal later, post-trial). Thus a 3 x 5 Condition x Time RM ANOVA was used as the primary analytic strategy. To address individual variability, the change (Δ) in cognitive performance from baseline to later stages was calculated for each Flanker outcome (e.g., response accuracy, reaction time, reaction time variability). A one-way RM ANOVA with the main factor of thermal condition was executed on these data.

Perceptual data was analyzed with a two-way (3 x 8) RM ANOVA with main thermal conditions and time (i.e., every 10 min from minute 0 to post-trial) to detect changes in affective valence and thermal sensations. To address individual variability, the change (Δ) in Feeling Scale and Thermal Sensations (TS) from baseline to the last 10 min of LBNP+thermal stage (minute 60) was calculated. Data was analyzed using a one way RM ANOVA with the main factor of thermal condition. Pearson correlations were performed to compare TS scores and skin temperature.

To determine the extent to which aerobic fitness might modify alterations in cognitive function (should they exist), a one-way analysis of covariance (ANCOVA), with the main factor of thermal condition and covariate of VO_{2max} was carried out. Given the homogeneity of the group, with respect to VO_{2max}, further statistical analyses, aside from the ANCOVA, would not have provided further information.

CHAPTER 4

RESULTS

Mean Arterial Pressure and Cerebral Perfusion

The two-way RM ANOVA for arterial pressure revealed a significant interaction between thermal perturbations and LBNP time [$F(8, 64) = 4.7$, $P < 0.001$], suggesting that changes in blood pressure were affected by the thermal provocation (see Figure 2). Effect size (η^2_p) measures the degree of association between the interaction and dependent variable. The effect size for the interaction between condition and time was $\eta^2_p = 0.08$, indicating that 8% of the variance was accounted for by this interaction. Within the LBNP+thermal early stage, mean arterial pressure (MAP) was significantly greater in COOL (95.4 mmHg) than in the NEUT ($P = 0.008$; 87.0 mmHg) and HEAT ($P = 0.009$; 87.5 mmHg) conditions. Similarly, at the LBNP+thermal later stage, COOL trials had statistically greater MAP (95.1 mmHg) than NEUT ($P = 0.03$; 88.5 mmHg) and HEAT ($P = 0.01$; 87.3 mmHg) conditions.

Analysis from the two-way RM ANOVA for cerebral perfusion revealed an absence of an interaction between the thermal perturbation and LBNP time [$F(8, 53) = 0.7$, $P = 0.73$], suggesting that changes in brain blood flow were unaffected by the thermal provocation in combination with LBNP. The effect size for the interaction between condition and time was $\eta^2_p = 0.003$, indicating that 0.3% of the variance was accounted for by this interaction. However, there was a significant difference [$F(4, 53) = 4.9$, $P = 0.004$] between the mean values across LBNP time, regardless of condition (refer to Figure 3). Overall, cerebral

perfusion for LBNP+thermal early (51.0 cm·sec^{-1}; P = 0.004) and LBNP+thermal later stages (51.8 cm·sec^{-1}; P = 0.04) were significantly less than baseline values (54.7 cm·sec^{-1}).

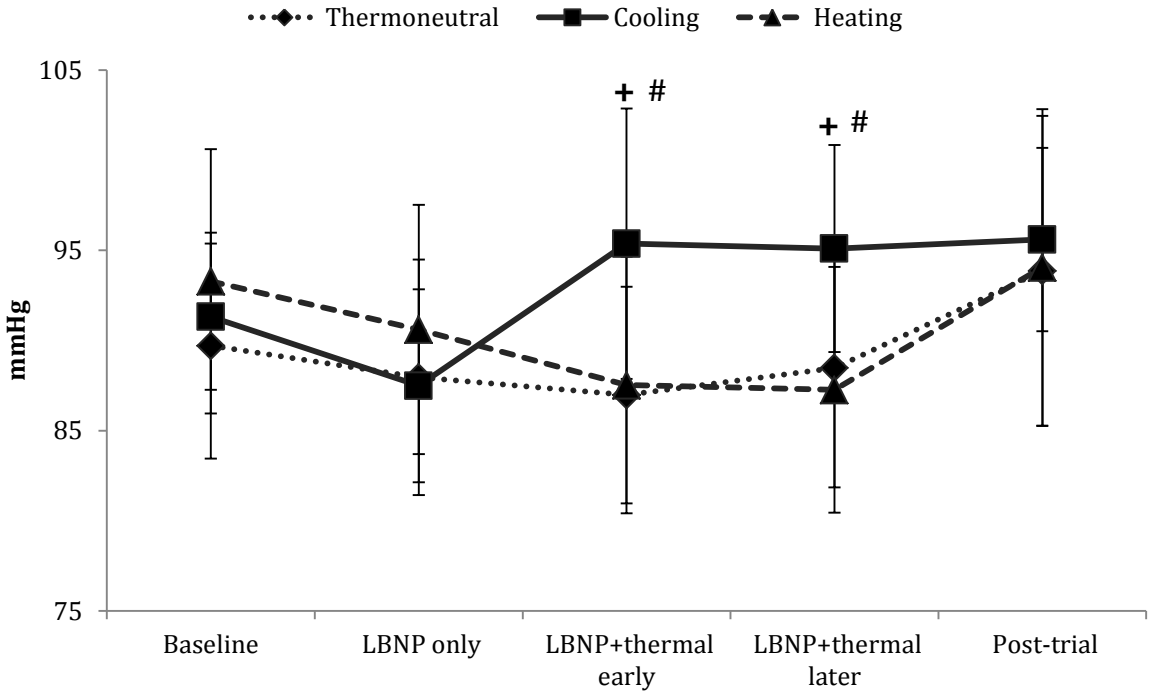


Figure 2: Mean arterial pressure. *Error bars represent + 1 standard deviation; +, significantly greater than thermoneutral condition; #, significantly greater than mild heating condition*

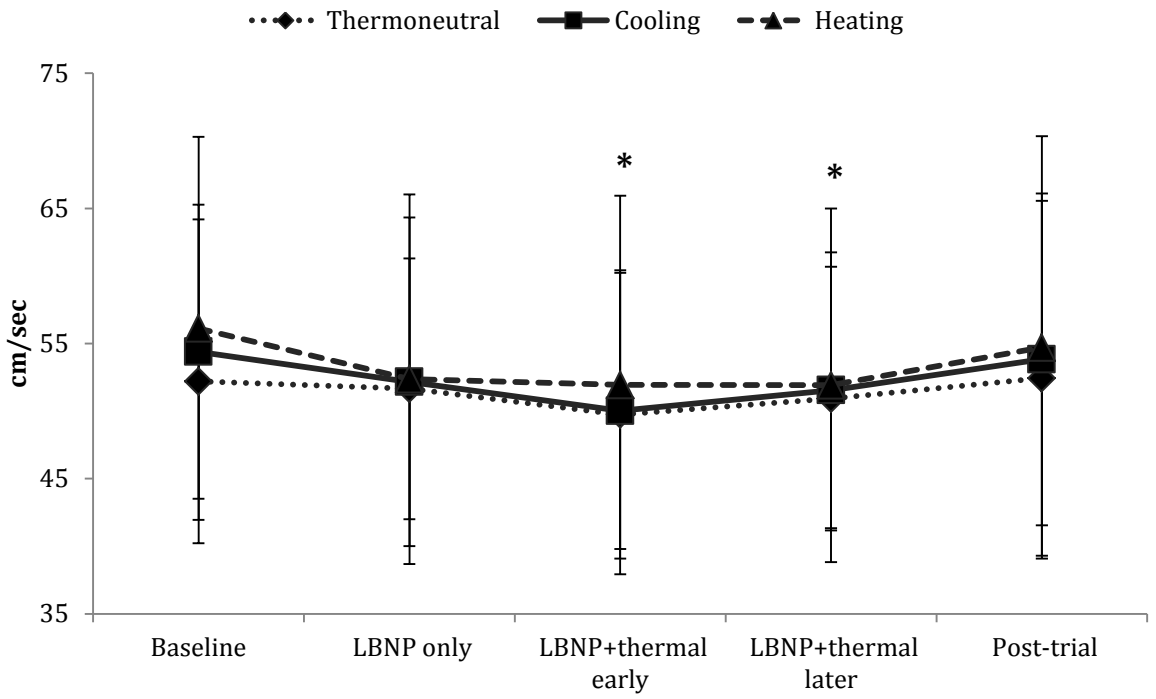


Figure 3: Cerebral perfusion. *Error bars represent + 1 standard deviation; significant difference with main effect of time (P = 0.004); *, significantly less than baseline*

Flanker Response Accuracy

Flanker response accuracy was calculated as the number of correctly identified responses out of all possible trials. If no response was provided, it was considered incorrect; values are reported as percentages.

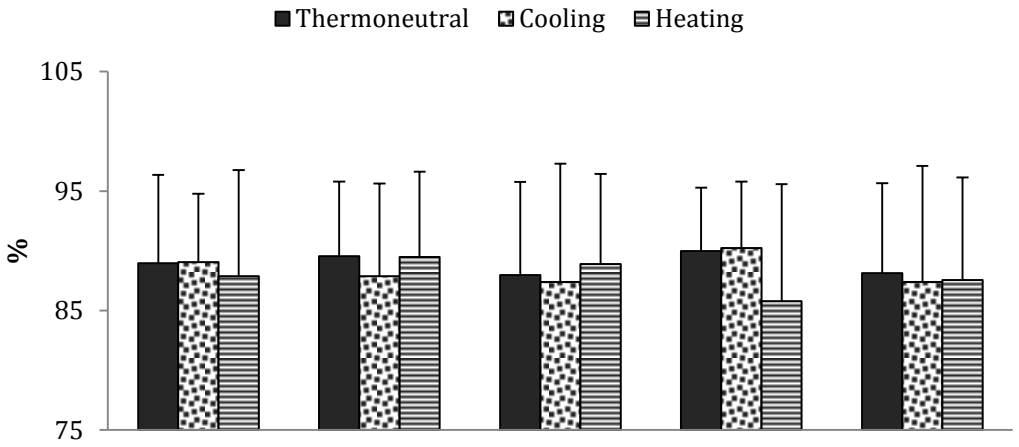
Analysis from the two-way RM ANOVA revealed an absence of an interaction between the thermal perturbation and LBNP time [$F(8, 64) = 1.47$, $P = 0.19$] for response accuracy to overall trials (see Figure 4A), suggesting that changes in overall response accuracy were unaffected by the thermal provocation/LBNP combination. The effect size for the interaction between condition and time was $\eta^2_p = 0.16$, indicating that 16% of the variance was accounted for by this interaction. There was no main effect of time [$F(4, 32) = 0.87$, $P = 0.49$], which indicated that LBNP duration alone did not affect these responses.

When analyzed separately, no significant interaction between thermal conditions and LBNP time were evident for either Congruent (P = 0.29; Figure 4B) or Incongruent trials (P = 0.50; Figure 4C). Calculated effect sizes were η^2_p = 0.08 and 0.01 for Congruent and Incongruent trials, respectively. The main effect of time was also not significant (Congruent, P = 0.90; Incongruent, P = 0.70), indicating no changes overtime for either type of stimulus. Despite the lack of significance, it appeared that participants performed better on Congruent trials (> 90% response accuracy) than on Incongruent trials (> 80% response accuracy), regardless of thermal condition.

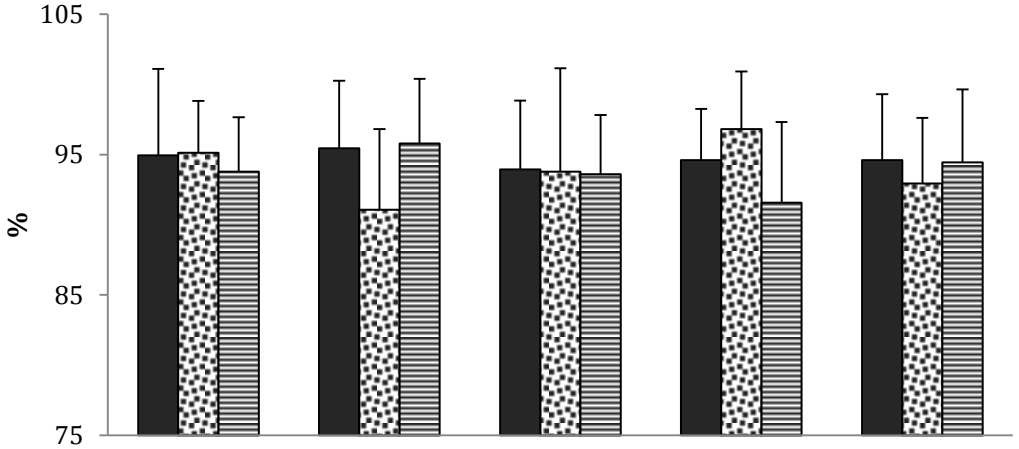
The one-way RM ANOVA for the change in response between baseline and the later LBNP+thermal provocation stage revealed no difference (P = 0.21) between thermal perturbations to overall trials for response accuracy (depicted in Figure 5). Effect size for the treatment conditions was η^2_p = 0.16, indicating that 16% of the variance observed was accounted for by thermal conditions. When analyzed separately, no significant difference was seen between thermal conditions were evident for either Congruent (P = 0.51) or Incongruent trials (P = 0.21) for the change in these responses. Calculated effect sizes were η^2_p = 0.07 and 0.12 for Congruent and Incongruent trials, respectively.

Although statistical significance was not achieved there was a noticeable trend for the change in response between baseline and later LBNP+thermal provocation stage. Overall, mild heating resulted in decreased response accuracy (overall = -2.1%; Congruent = -2.2%; Incongruent = -1.5%), whereas the cooling condition resulted in increased response accuracy (overall = +1.2%; Congruent = +1.7%; Incongruent = +1.0%).

A. Overall Trials



B. Congruent Trials



C. Incongruent Trials

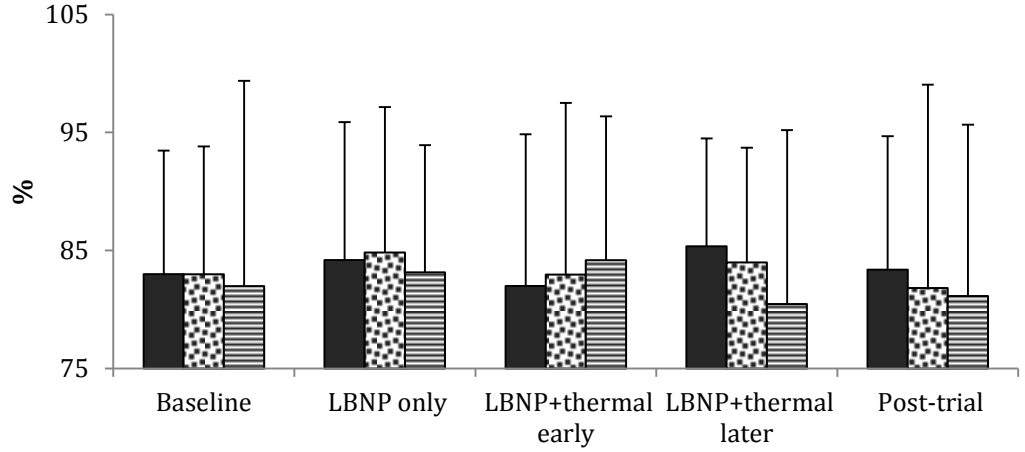


Figure 4: Flanker response accuracy. *Error bars represent + 1 standard deviation; No significant differences.*

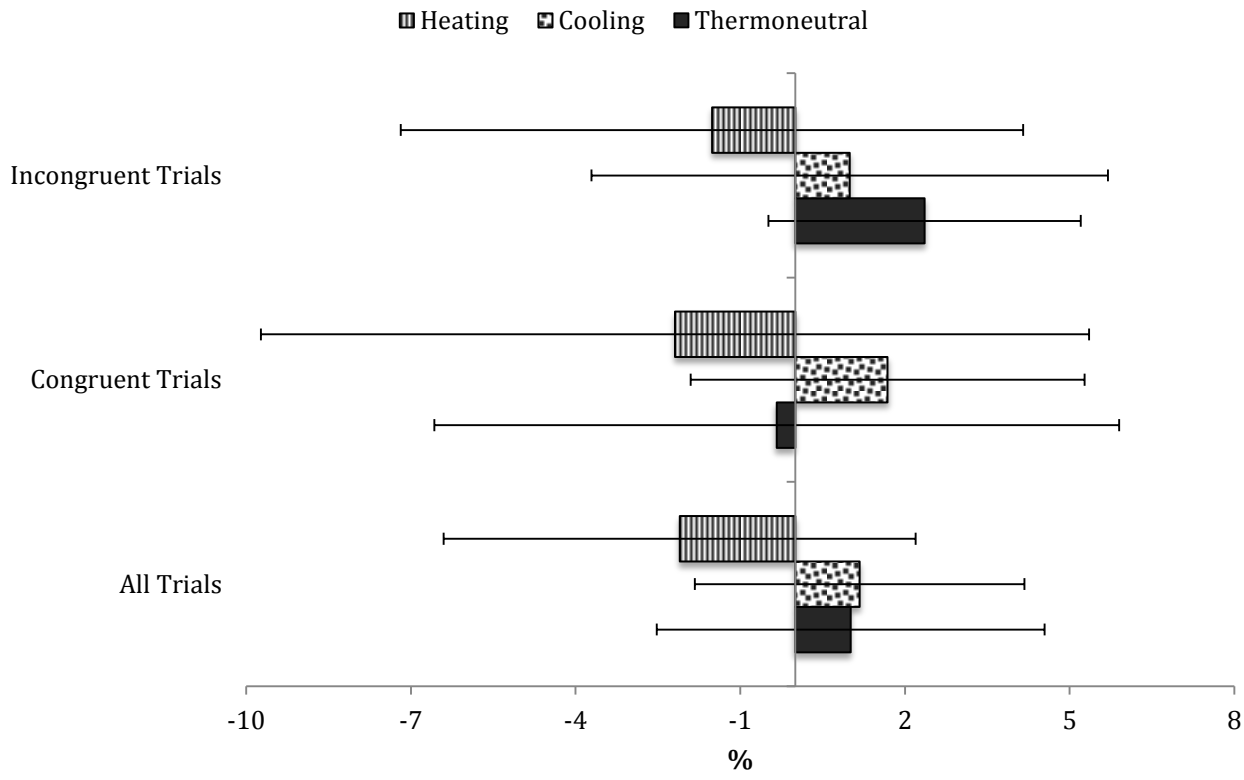


Figure 5: Flanker response accuracy change between baseline and later LBNP+thermal provocation.
Error bars represent + 1 standard deviation; No significant differences.

Flanker Reaction Time

Reaction time was the next Flanker assessment. This was calculated as the average time (in ms) it took for participants to respond to Flanker trials. If no response was given, an automatic response time between 1200-1300 ms (programmed time between stimuli) was applied.

The two-way RM ANOVA revealed an absence of an interaction between thermal perturbations and LBNP time [$F(4.4, 35.4) = 1.8$, $P = 0.15$] for reaction time latency to overall trials (see Figure 6A), suggesting that changes in reaction time were unaffected by the thermal provocation. Effect size for the interaction between condition and time was $\eta^2_p = 0.18$, indicating that 18% of the variance was accounted for by this interaction. (As shown

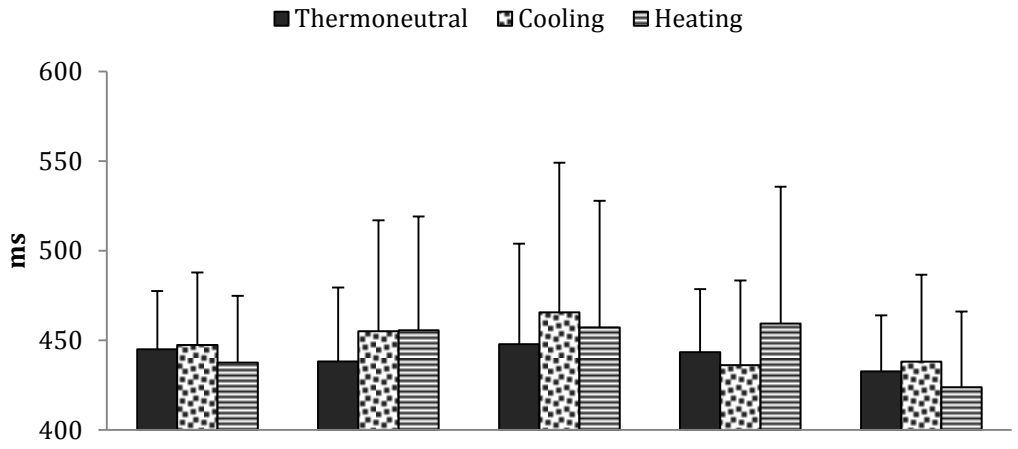
in Figure 7, the tendency, and thus the interaction approaching significance, appears to be due to a general slower response in the HEAT condition relative to the other two thermal manipulations). There was no main effect of time (P = 0.22) indicating that LBNP duration alone did not affect these response latencies.

When analyzed separately, no significant interaction was evident for either Congruent (P = 0.24; Figure 6B) or Incongruent trials (P = 0.10; Figure 6C). Calculated effect sizes were η^2_p = 0.15 for Congruent and η^2_p = 0.19 for Incongruent trials. There was also no main effect of time (Congruent, P = 0.25; Incongruent, P = 0.16). Despite a lack of significance, it appeared that participants responded quicker to Congruent trials (< 450 ms) than to Incongruent trials (< 500ms), irrespective of thermal condition. Regardless of condition, reaction time latency decreased (i.e., faster responses) from baseline to post-trial (Figure 6A-C), suggesting some potential enhancement of LBNP, a practice/learning effect, or perhaps a desire to quickly finish the cognitive test.

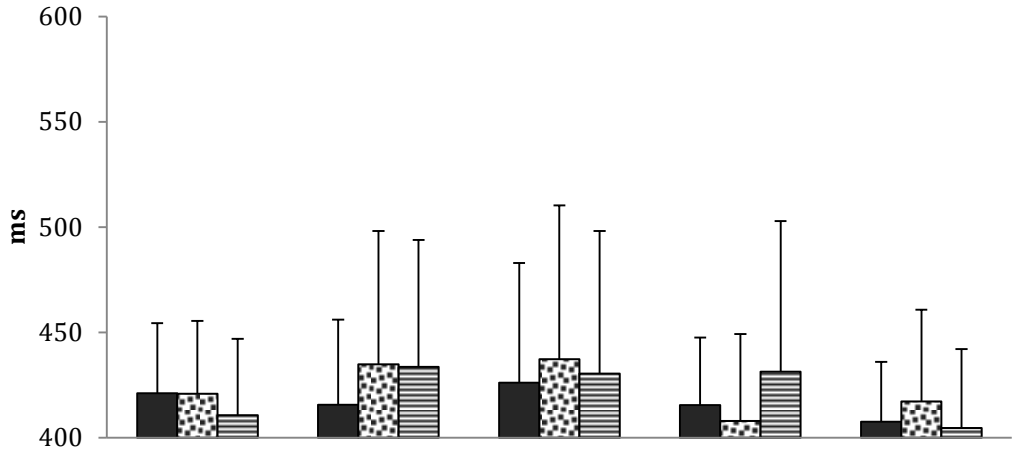
Analysis from the one-way RM ANOVA for the change in response between baseline and the later LBNP+thermal provocation stage revealed no difference (P = 0.13) between thermal perturbations to overall trial response for reaction time (Figure 7). Effect size for thermal conditions was η^2_p = 0.13, indicating that the different thermal perturbations (in combination with LBNP) accounted for 13% of the observed variance. When analyzed separately, no significant difference between thermal conditions was evident for either Congruent or Incongruent trials (P = 0.14 for both) for the change in these responses. Calculated effect sizes were η^2_p = 0.15 and 0.11 for Congruent and Incongruent trials, respectively.

Although statistical significance was not achieved, there was a noticeable trend for the change in response between baseline and the later LBNP+thermal provocation stage. Overall, mild heating increased (i.e., slowed) reaction time (overall = +21.9 ms; Congruent = +20.7 ms; Incongruent = +22.8 ms), whereas the cooling condition decreased (i.e., quickened) reaction time (overall = -11.3 ms; Congruent = -12.8 ms; Incongruent = -11.0 ms).

A. Overall Trials



B. Congruent Trials



C. Incongruent Trials

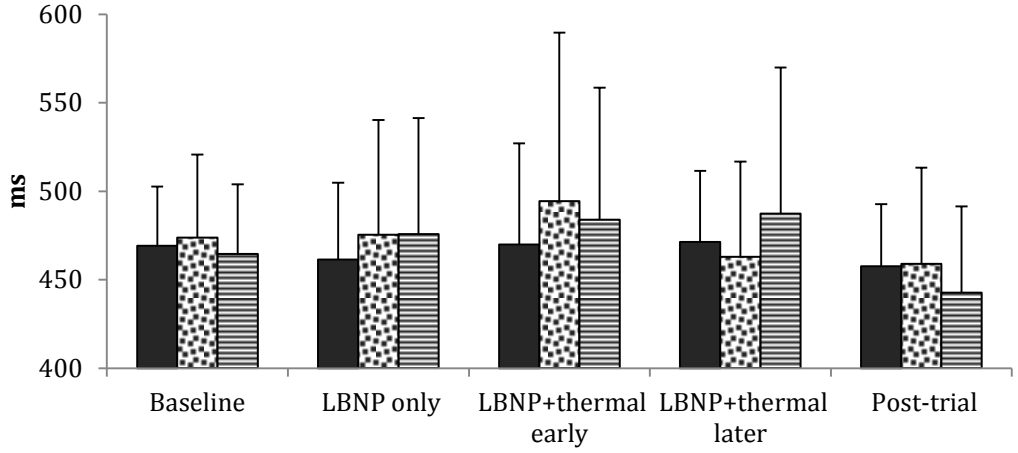


Figure 6: Flanker reaction time. *Error bars represent + 1 standard deviation; No significant differences.*

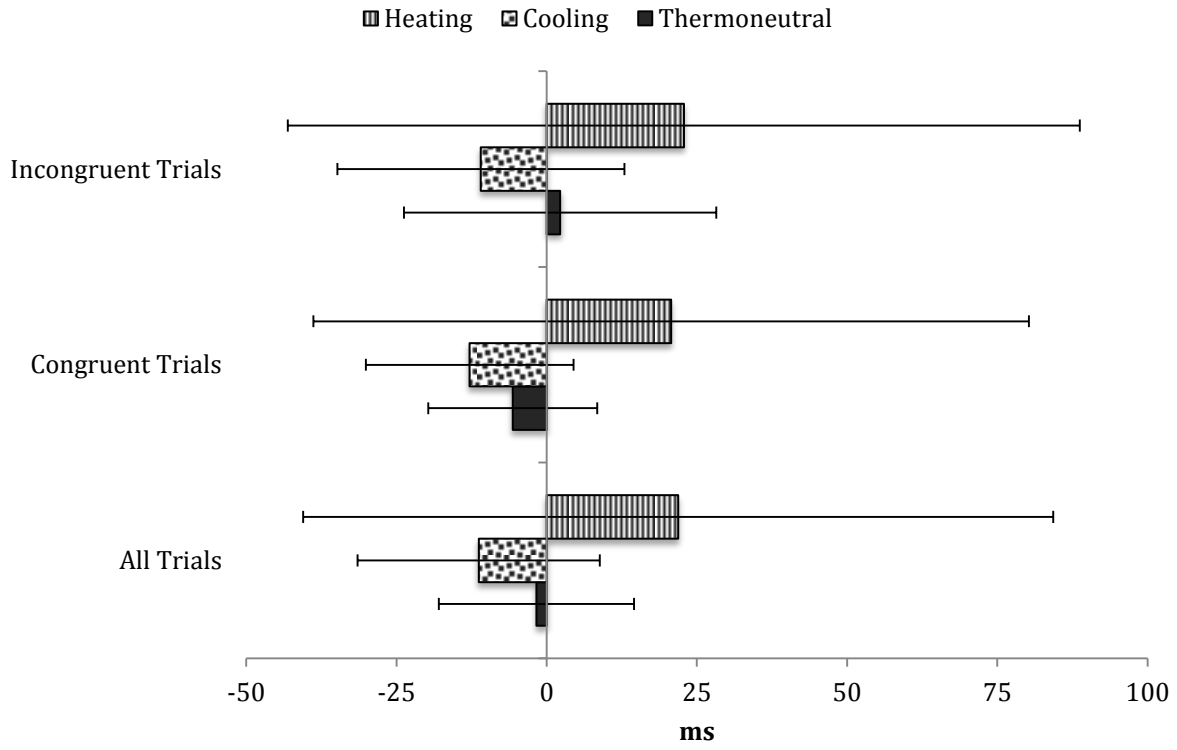


Figure 7: Flanker reaction time change between baseline and later LBNP+thermal provocation. *Error bars represent + 1 standard deviation; No significant differences.*

Flanker Reaction Time Variability

The final Flanker assessment was reaction time variability. This was calculated as the standard deviation of reaction time (in ms) it took for participants to respond to the Flanker trials.

Analysis from the two-way RM ANOVA revealed an absence of an interaction between the thermal perturbation conditions combined with LBNP and time [$F(8, 64) = 1.5$, $P = 0.16$] for reaction time (RT) variability to overall trials (see Figure 8A), suggesting that changes in RT variability were unaffected by the thermal provocation in combination with LBNP. The effect size for the interaction between thermal condition and time was $\eta^2_p = 0.03$, indicating that 3% of the variance was account for by this interaction. There was no

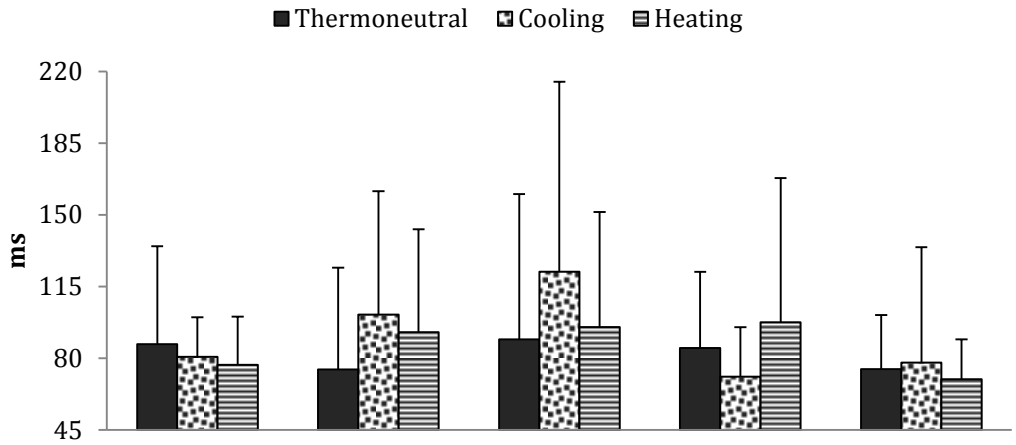
main effect of time [$F(4, 64) = 1.9$, $P = 0.13$] on overall RT variability, indicating that LBNP duration alone did not affect these responses.

When analyzed separately, no significant interaction was evident for either Congruent ($P = 0.35$; Figure 8B) or Incongruent trials ($P = 0.19$; Figure 8C). Calculated effect sizes were $\eta^2_p = 0.04$ and 0.03 for Congruent and Incongruent trials, respectively. The main effect of time was also not significant for either Congruent ($P = 0.20$) or Incongruent ($P = 0.14$) trials examined separately. Overall, it appeared that performance variability was similar for both Congruent (< 120 ms) and Incongruent trials (< 120ms), regardless of thermal condition.

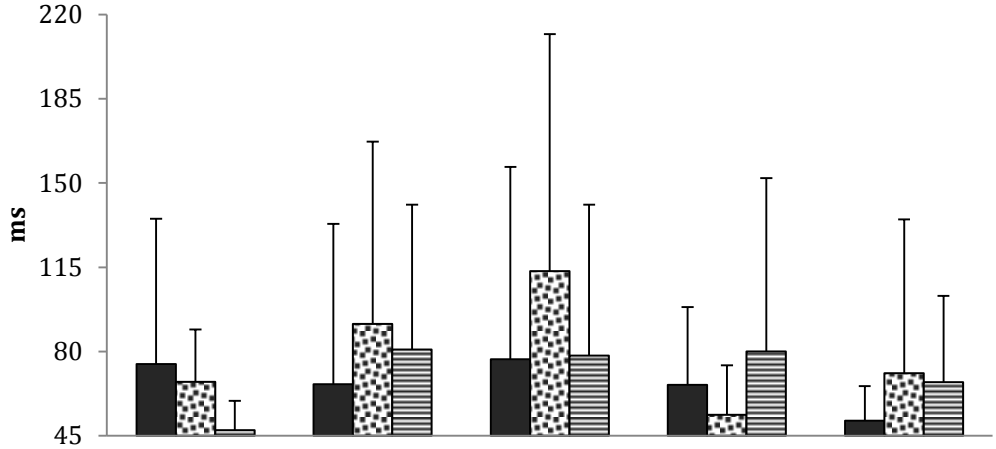
The one-way RM ANOVA for the change in response between baseline and the later LBNP+thermal provocation stage revealed no difference ($P = 0.30$) between thermal perturbations to overall trial response for RT variability (Figure 9). Effect size for thermal conditions was $\eta^2_p = 0.10$, indicating that 10% of the variance observed was accounted for by thermal condition. When analyzed separately, no significant difference between thermal conditions was evident for either Congruent ($P = 0.22$) or Incongruent trials ($P = 0.64$) for the change in this response. Calculated effect sizes were $\eta^2_p = 0.15$ and 0.04 for Congruent and Incongruent trials, respectively.

Although statistical significance was not achieved there was a noticeable trend for the change in response variability between baseline and the later LBNP+thermal provocation stage. Overall, mild heating increased RT variability (overall = +20.9 ms; Congruent = +32.7 ms; Incongruent = +13.4 ms), whereas the cooling condition decreased RT variability (overall = -9.7 ms; Congruent = -13.7 ms; Incongruent = -8.3 ms; see Figure 9).

A. Overall Trials



B. Congruent Trials



C. Incongruent Trials

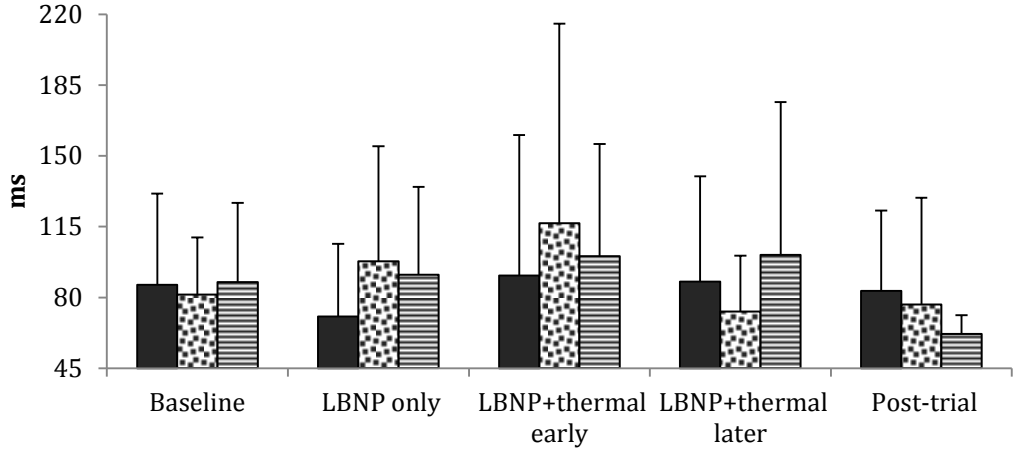


Figure 8: Flanker reaction time variability. *Error bars represent + 1 standard deviation; No significant differences.*

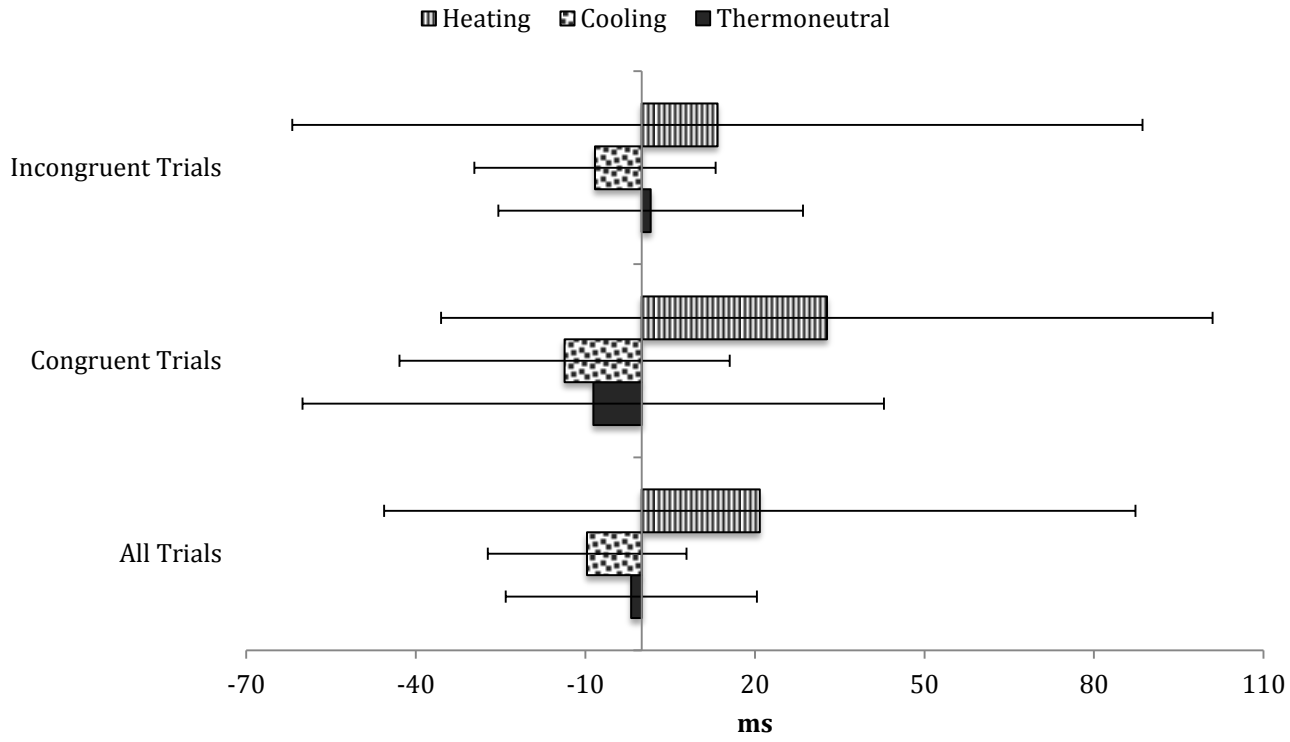


Figure 9: Flanker reaction time variability change between baseline and later LBNP+thermal provocation. *Error bars represent + 1 standard deviation; No significant differences.*

Affective Valence and Thermal Sensations

Figure 10 illustrates the average reported affective valence, from the Feeling Scale (Hardy & Rejeski, 1989), at 10 min increments for all conditions; the dashed line indicates the application of LBNP, and the dotted line indicates the start of the thermal perturbation. Interaction between thermal perturbations and LBNP time did not reveal significant changes [$F(14, 110) = 1.4$, $P = 0.16$], suggesting that affective valence was unaffected by thermal provocations. Effect size for the interaction between condition and time was $\eta^2_p = 0.01$, indicating 1% of the variance observed was accounted for by this interaction.

However, there was a significant effect of time [$F(7, 110) = 11.4$, $P < 0.001$] regardless of thermal condition. FS scores for minutes 30 ($P = 0.003$; 2.1 FS), 40 ($P < 0.001$; 1.9 FS), 50 ($P < 0.001$; 1.7 FS) and 60 ($P < 0.001$; 1.8 FS) were significantly less than

baseline (minutes 0 and 10) values of 3.0 FS. Similarly, FS scores at minutes 40 (P = 0.03; 1.9 FS), 50 (P = 0.003; 1.7 FS) and 60 (P = 0.01; 1.8 FS) were significantly less than the LBNP only stage (minute 20) score of 2.6 FS. At minutes 30 (P = 0.03; 2.1 FS), 40 (P = 0.004; 1.9 FS), 50 (P < 0.001; 1.7 FS), 60 (P = 0.002; 1.8 FS), FS scores were significantly less than post-trial FS scores of 2.8. Essentially, affective valence began to change slightly (becoming less positive) at the onset of LBNP only, and continued to decrease until the end of the trial; during post-trial, FS returned to baseline scores. Further, the change in response between baseline (minute 10) and the last LBNP+thermal stage (minute 60) revealed no difference [$F(2,16) = 0.3$, P = 0.8] between thermal perturbations to affective valence.

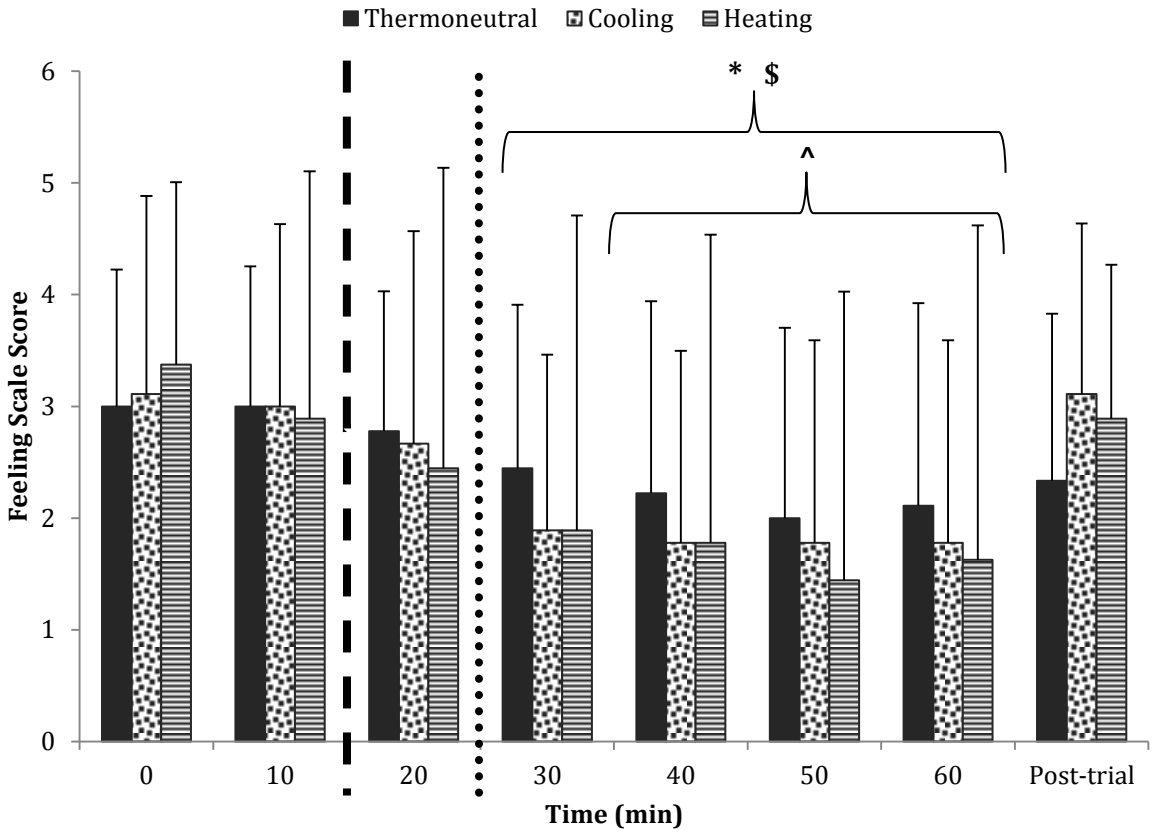


Figure 10: Feeling Scale. *Error bars represent + 1 standard deviation; dashed line, application of lower body negative pressure (LBNP); dotted line, start of mild heating, skin surface cooling or remained thermoneutral; significant difference with main effect of time (P < 0.001); *, significantly less than baseline (minutes 0 and 10); ^, significantly less than LBNP only stage (minute 20); $, significantly less than post-trial*

Average perceptions of thermal sensations reported every 10 min for all conditions is shown in Figure 11; the dashed line signifies the application of LBNP, and the dotted line signifies the start of the thermal perturbation. A significant interaction was evident with significant changes [$F(14, 110) = 43.5$, $P < 0.001$] occurring at minutes 30, 40, 50 and 60. Effect size for the interaction between condition and time was $\eta^2_p = 0.43$, indicating 43% of the variance was accounted for by this interaction.

Thermal Sensations (TS) scores remained stable at 4.0 TS, or "comfortable", during baseline (minutes 0 and 10) and the LBNP only stage (minute 20) for all conditions. Thermal sensations began to change when the thermal perturbation was introduced at

minute 30. As expected, participants reported feeling: (a) significantly ($P < 0.001$) warmer during mild heating at minutes 30 (5.0 TS), 40 (5.2 TS), 50 (5.3 TS) and 60 (5.5 TS) than thermoneutral and cooling trials; (b) significantly ($P < 0.001$) cooler during skin surface cooling at minutes 30 (2.4 TS), 40 (2.3 TS), 50 (2.4 TS) and 60 (2.5 TS) than thermoneutral and mild heating conditions; (c) and "comfortable" during thermoneutral trials, with TS values not really changing at all.

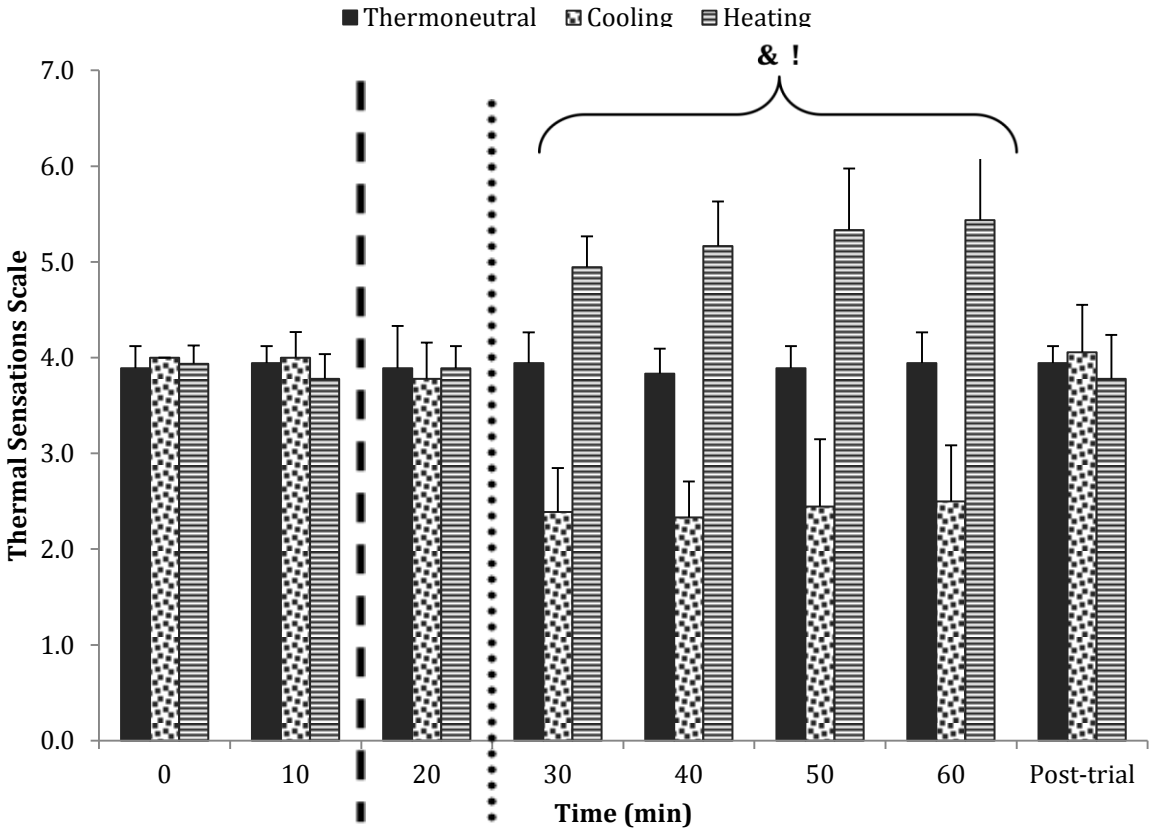


Figure 11: Thermal Sensations. *Error bars represent + 1 standard deviation; dashed line, application of lower body negative pressure (LBNP); dotted line, start of mild heating, skin surface cooling or remained thermoneutral; &, significantly greater than thermoneutral and cooling; !, significantly less than thermoneutral and mild heating*

Based on the correlation coefficient (r-value) from the Pearson correlation analysis, there was no significant relationship between the reported TS scores and mean skin temperature at minute 60 for any of the thermal perturbations (*NEUT*: r = -0.4, P = 0.23); *COOL*: r = 0.02, P = 0.95; *HEAT*: r = -0.6, P = 0.09). During the post-trial period, TS scores returned to baseline values of 4.0 or "comfortable" for all three thermal conditions. Further, the change in response between baseline (minute 10) and the last LBNP+thermal stage (minute 60) revealed a significant difference [$F(2,16) = 16.7$, $P < 0.001$] between thermal perturbations to affective valence.

Table 2 illustrates the correlations between TS scores and Flanker performance, and the change in TS from baseline and Flanker performance during LBNP+thermal (early) and LBNP+thermal (later). A significant negative relationship (r = -0.7, P = 0.05) was observed between TS scores and RT variability during the LBNP+thermal (early) stage of heating trials. As TS scores increased (i.e., participants felt warmer), Flanker RT variability decreased. The coefficient of determination (r^2) is 0.49, which means that 49% of the variation in mean RT variability can be predicted from the relationship between TS scores and heating at the LBNP+thermal (early) stage. Conversely, 61% of the variation in mean RT variability cannot be explained.

		LBNP+Thermal (early)			LBNP+Thermal (later)		
		Accuracy	*RT*	*Variability*	*Accuracy*	*RT*	*Variability*
Thermal Sensations Score	*NEUT*	*r* = -0.1	*r* = -0.1	*r* = 0.2	*r* = -0.4	*r* = -0.4	*r* = 0.4
	COOL	*r* = -0.5	*r* = 0.2	*r* = 0.5	*r* = -0.6	*r* = 0.1	*r* = 0.4
	HEAT	*r* = 0.5	*r* = -0.5	*r* = -0.7*	*r* = 0.4	*r* = -0.2	*r* = -0.3
Change in Thermal Sensations Score from Baseline	*NEUT*	*r* = 0.1	*r* = 0.1	*r* = 0.2	*r* = -0.1	*r* = -0.3	*r* = 0.2
	COOL	*r* =-0.3	*r* = 0.3	*r* = 0.4	*r* = -0.4	*r* = 0.1	*r* = 0.3
	HEAT	*r* = -0.4	*r* = -0.2	*r* =-0.2	*r* = 0.2	*r* = -0.0	*r* = -0.1

Table 2: Pearson correlation between Thermal Sensations, (TS) and changes in TS from baseline, and Flanker performance during LBNP+Thermal (early) and LBNP+Thermal (later) stages. *COOL, cooling condition; HEAT, mild heating condition; NEUT, thermoneutral condition; RT, reaction time; *, significant (p< 0.05) correlation.*

Aerobic Fitness

The one-way ANCOVA, controlling for aerobic capacity (i.e., $VO2_{max}$) confirmed that even after accounting for any differences in aerobic capacity, there was no difference in the behavioral data (i.e., Flanker task) related to cognitive performance (*response accuracy*: overall trials, $P = 0.83$, $\eta^2_p = 0.02$; Congruent trials, $P = 0.41$, $\eta^2_p = 0.07$; Incongruent trials, $P = 0.20$, $\eta^2_p = 0.11$; *reaction time*: overall trials, $P = 0.96$, $\eta^2_p = 0.003$; Congruent trials, $P = 0.96$, $\eta^2_p = 0.003$; Incongruent trials, $P = 0.81$, $\eta^2_p = 0.02$; *reaction time variability*: overall trials, $P = 0.95$, $\eta^2_p = 0.004$; Congruent trials; $P = 0.31$, $\eta^2_p = 0.09$; Incongruent trials, $P = 0.29$, $\eta^2_p = 0.11$).

Since aerobic fitness was relatively homogenous, the variability in the cognitive task may have been due to other independent variables, such as age. A one-way ANCOVA, controlling for age determined that there was a significant interaction between thermal condition and age for response accuracy on Congruent trials only ($P = 0.03$). The effect size for the interaction was $\eta^2_p = 0.25$, indicating 25% of the variance was accounted for by the relationship between thermal condition and age. Further analyses determined that the regression equation for NEUT trials (NEUT = 7.755-(0.271*age)) shows that the coefficient for age in years is -0.271 (-27.1%) in response accuracy during Congruent trials. During the COOL condition, the regression equation (COOL = -0.0210+(0.057*age) shows that the coefficient for age is 0.057 (5.7%) in response accuracy for Congruent trials. The regression equation during HEAT (HEAT = -21.046+(0.631*age) shows that the coefficient for age is 0.631 (63.1%) in response accuracy for Congruent trials. It thus appears that age has a larger effect in the HEAT condition than in the COOL or NEUT conditions.

CHAPTER 5

DISCUSSION

Hemorrhage from major trauma is the leading cause of death in both civilian and battlefield settings (Eastridge et al., 2011; Soreide et al., 2007). Currently, the standard of medical care is to warm hemorrhagic patients, given the detrimental effects of hypothermia associated with trauma (Martin et al., 2005; Peng & Bongard, 1999). However, heating a normothermic hemorrhaging victim can decrease arterial pressure (Crandall & Gonzalez-Alonso, 2010; Wilson et al., 2006), which may compromise perfusion pressure to the brain and perhaps cognitive function. Since cooling interventions have been shown to have beneficial (Alam et al., 2005; Bandelow et al., 2010) or sustained effects (Caldwell et al., 2012; Giesbrecht, Arnett, Vela & Bristow, 1993) on cognitive function, they may provide similar benefits to a normothermic hemorrhaging individual.

The purpose of this investigation was to evaluate and compare the effects of mild heating and skin surface cooling during a mild simulated hemorrhage challenge on an index of cognitive function. To our knowledge, previous studies have not adequately evaluated the occurrence of cognitive impairments during the combination of hemorrhage and mild heating. Overall, we observed that for the applied level of simulated hemorrhage (30 mmHg LBNP), HEAT did not significantly ($P < 0.05$) compromise cognitive function, at least in terms of the ability to ignore distracting stimuli and preventing those distractions from disrupting cognitive performance, while COOL was not beneficial. However, performance trends were observed that were in the direction of the hypotheses; perhaps a larger sample

size (discussed in detail later on) would have led to significant outcomes. Perceptions of affective valence (i.e., how good or bad the individual felt at that moment) and thermal sensations were in flounced to a greater extent by the thermal conditions than cognitive measurements (i.e., Flanker task). Additionally, given the homogeneity of the participants' aerobic capacity, the extent to which aerobic fitness may modify these effects remains inconclusive.

PRIMARY AIM: Mild Heating vs. Skin Surface Cooling and Cognitive Function

Flanker Task. Since the ability to accurately make rapid decisions or allocate attention to pertinent tasks (e.g., battalion commander, incident commander, firefighter in a dangerous situation) while severely injured may be compromised, the Flanker task was chosen to evaluate the ability to handle conflict created by distracters (e.g., incongruent trials). As hypothesized, decreased response accuracy, increased reaction time (i.e., slower response) and more inconsistent performance was observed during mild heating trials. On the other hand, cooling trials presented with increased response accuracy, decreased reaction time (i.e., quicker response) and more consistent performance, although not at a level that reached statistical significance ($P > 0.05$, Figures 5, 7, 9).

Previous work (Takezawa & Miyatani, 2005) has shown an incongruent stimulus negatively influences response inhibition by making the response more difficult for the individual. With the Flanker task, this difficulty is achieved by flanking the relevant stimulus (i.e., a center arrow) with arrows pointing in the opposite direction. Although not statistically significant, this effect could be visually seen in the data set (Figures 4, 6, and 8) via decreased response accuracy coupled with increased reaction time and greater

variability in responses to incongruent trials than with congruent trials, regardless of thermal condition. Presumably, the incongruent flankers distract from the task at hand (identifying orientation of central arrow), resulting in decreased performance (Hommel, 2003). Further, the additional superimposed levels of conflict or stress (e.g., traumatic injury/simulated hemorrhage, thermal perturbations) may have supplemented these responses. Others (Giesbrecht et al., 1993; Pilcher et al., 2002) have mentioned that cognitive performance can be influenced by a multitude of factors, including, thermal environment, person, task and situation.

Simmons et al. (2008) reported that cognitive performance was unaffected unless thermal stress was sufficient enough to change core body temperature away from normal or steady state conditions. Although core temperature remained stable throughout each thermal experimentation day (37.0 ± 0.1°C), some performance trends were detected. According to the maximal adaptability model (Hancock & Vasmatzidis, 2003), thermal stress exerts its detrimental effects on cognitive performance by competing for and eventually draining attentional resources. Further, heating greatly compromises the control of blood pressure and cerebral perfusion via presyncopal symptoms (e.g., nausea, dizziness) during simulated hemorrhagic challenges (Durand et al., 2004; Wilson et al., 2002; Wilson et al., 2004), which may affect performance. Despite no significant change in cerebral perfusion and blood pressure during mild heating trials (compared with the other conditions; Figures 2 and 3), there was a slight decrease observed for both variables during the LBNP+thermal stages from baseline values. Although participants did not exhibit any presyncopal symptoms, some individuals did express feeling "sleepy" during the mild heating trial, which may have influenced their performance.

Although the heating stimulus was to simulate a blanket (i.e., current medical practice for treating hemorrhaging victims), ambient temperatures did persist in duration (40 min). Over time, attentional resources may have been progressively drained and perhaps caused the slight decline in performance that was observed. Further, experiencing multiple stressors (i.e., combination of LBNP and mild heating) can negatively influence the cognitive domains of vigilance, reaction time and memory (Lieberman et al., 2005b; Mahoney et al., 2007; Smith et al., 2001; van Wingen et al., 2012; Vasterling et al., 2006). Due to the level of attentional resources required to complete tasks, the level of performance deterioration is dependent upon the complexity of the task; whereas simple tasks are less vulnerable during heat exposure, more complex tasks have shown to be more sensitive (Pilcher et al., 2002). Although slight decrements in performance on the Flanker task were observed, it is a relatively simple information-processing task and changes in performance may not be as apparent as more complex tasks (e.g., Stroop test).

Similar to heat stress, whole body cooling associated with a reduction in core temperature (2-4°C) can impair cognitive functions, such as memory and concentration (Giesbrecht et al., 1993; Lockhart et al., 2005; Makinen, 2007). If cooling decreases core temperature below 35°C (hypothermia), symptoms of confusion, amnesia and decreased alertness can occur. Internal temperatures were maintained at 37 ± 0.1°C for all conditions in this investigation, which may explain why cognitive performance during cooling trials was not negatively impacted. Aside from changes in internal temperature, Bandelow et al. (2010) explained that increased perceived comfort during cooling might have allowed participants to perform better on a visuomotor task. Similarly, the perceived affective valence in this study was more pleasant during COOL conditions, compared with HEAT

(although not significant), which may explain why cognitive performance was not negatively influenced.

Makinen (2007) offered a theory explaining that general arousal levels are increased by mild or moderate cold exposure, which initially leads to improved performance that can degrade if exposure is prolonged or more severe. Performance on the Flanker task did not vary significantly across cooling exposure time (40 min), perhaps because the level of cooling was not severe enough to increase arousal to a level where performance could have been degraded.

In contrast to heating, Durand et al. (2004) and Wilson et al. (2002) reported preservation of blood pressure and cerebral blood flow to the brain during skin-surface cooling combined with a simulated hemorrhagic challenge. Additionally, the likelihood of presyncopal symptoms to occur is attenuated when blood pressure and cerebral perfusion are protected. Although in this study cerebral perfusion was not shown to be significantly different between thermal conditions (Figure 3), there was a significant increase in blood pressure once the cooling manipulation began, compared to the heating and thermoneutral conditions Figure 2). In an animal model, hypothermia during cerebral hypoxia (i.e., lethal hemorrhage) can preserve the viability of neurons and astrocytes (Alam et al., 2005). Observed performance trends seen in this investigation (refer to Figures 5, 7 and 9), specifically during cooling trials, could have been attributed to better control of mean arterial pressure coupled with less feelings nausea or dizziness (i.e., presyncopal symptoms), or possibly neuronal and astrocyte preservation. Further, Giesbrecht et al. (1993) indicated that unlike complicated tasks that call upon greater mental manipulation,

less complicated tasks (e.g., Flanker task) make fewer cognitive demands that were unaffected by immersion hypothermia.

Although it was predicted that aspects of cognitive performance would be influenced by the thermal manipulations and during LBNP, cerebral blood flow velocity was maintained (Figure 3), despite significant changes in arterial pressure (Figure 2). This suggests that cerebral autoregulation, a compensatory mechanism of hemorrhage, was activated to maintain constant blood flow to the brain (Cooke et al., 2004; Novak, Novak, Spies & Low, 1998; Tzeng et al., 2012). Additionally, Lewis et al. (2014) found that during reductions in oxygen delivery induced by cerebral hypoperfusion, the brain extracted more oxygen to compensate for the reduction in delivery. Since oxygen extraction was not measured in this study, it can only be speculated that this was occurring. Furthermore, once the capacity of the brain to extract oxygen is maximized beyond cerebral autoregulation further decreases in oxygen delivery would ultimately result in cognitive impairment and a loss of consciousness (Lewis et al., 2014). As a consequence, the indices of cognitive function, as assessed by the Flanker task, were unchanged.

Cerebral blood flow velocity would have significantly risen or fallen, with respect to blood pressure, if mean arterial pressure were outside of the autoregulated range of 60-160 mmHg (Duschek et al., 2007; Novak et al., 1998). To achieve mean arterial pressure below 60 mmHg, and thus a decline in cerebral perfusion that would influence cognitive function, the individual would be close to or at the point of hemorrhagic shock or syncope (i.e., fainting). Therefore the applied level of simulated hemorrhage (30 mmHg LBNP) may have been insufficient to significantly alter aspects of cognitive function, regardless of the thermal perturbations applied (i.e., NEUT, COOL, HEAT). Increasing the level of LBNP (i.e.,

> 30 mmHg), under the same experimental protocol, would further decrease blood pressure (during HEAT) and in turn cause cerebral hypoperfusion, and ultimately significantly impact cognitive performance. To achieve this, participants would have to be taken to their level of presyncope, or the point just prior to fainting. Due to individual variability, tolerance to LBNP levels varies; Rickards, Ryan, Cooke and Convertino (2011) classified individuals as high tolerance if they completed the 60 mmHg (equivalent to ~1000 mL of blood loss), and low tolerance if they did not complete this level. To determine each individual's presyncope level (for each thermal manipulation) and to test cognitive performance prior to this level, a total 6 laboratory visits would be required, which may be a challenge with recruitment and possible attrition rates:

Since changes in cognitive performance were explained by a variance of 10-20%, the study may not have had enough statistical power to detect the effect of cognitive responses to the different thermal perturbations. Follow-up power analyses for estimating the sample size necessary for a within-participants design that would include treatment and control conditions was conducted using response accuracy, RT, and RT variability values from this investigation, and resulted in an estimated sample size of 301, 237, and 8716 participants, respectively. In order for a significant effect to be observed with the Flanker task, a rather large sample size is needed, which may not be realistic (from either a time or financial perspective), suggesting that future studies should focus on other aspects of cognitive function (i.e., cognitive flexibility, working memory) either alone or in combination. While typical computerized cognitive test batteries tend to isolate aspects of cognitive performance, they may not represent the dynamism and complexity found in combat environments (Wong, 2005). Additionally, a multi-cognitive testing battery can

elevate stress levels (i.e., tachycardia, hyperventilation) that may be applicable to that experienced during warfare and fire suppression.

While knowledge regarding temperature environment, cognitive task and the experimental setting (laboratory) is available, information about the participants' intellect, skills, training, personality and mood were limited. Perhaps the latter factors relating to the individual may have affected the results more than the other variables examined. Future investigations should consider assessing personality traits or mood states to better comprehend their influence on cognitive performance during mild heating and cooling thermal conditions and hemorrhage. Although a lack of significance ($P > 0.05$) was observed in the behavioral data (i.e., Flanker task), analyses of the perceptual data revealed some differences due to the perturbations.

Affective Valence and Thermal Sensations. Affective valence characterizes the subjective affective experience (pleasant or unpleasant) an individual has at any moment in time and in response to any type of stimulus or challenge (Rose & Parfitt, 2008). The Feeling Scale (FS), an often-used measure of affective valence within an exercise paradigm, may be a valuable tool for examining affective valence under different modes of stress, such as hemorrhaging or heating. Overall, participants in this investigation reported feeling at least "fairly good" (FS score ≥ +1; see Figure 10) within and across all trials and conditions. Although not statistically different, greater decreases in FS scores were seen during mild heating trials, which may be a function of physiological variables.

For example, mild heating resulted in the greatest increase in heart rate (~20 beats·min^{-1}) in comparison to cooling and thermoneutral trials (~5 and 10 beats·min^{-1}, respectively). Tachycardia is a compensatory response that occurs to maintain adequate

systemic tissue perfusion during a hemorrhagic insult; with heart rate continuing to accelerate as hemorrhage becomes more challenging (Cooke et al., 2004). However, unwanted excessive elevations in HR may be an unpleasant experience. Although a significant difference was not found for cerebral perfusion and blood pressure during mild heating (compared with the other conditions; Figures 2 and 3), there was a slight decrease observed during the LBNP+thermal stages from baseline values. Reductions in blood pressure and accompanying cerebral hypoperfusion are accompanied by presyncopal symptoms, such as headache and dizziness (Duschek & Schandry, 2007), which may have influenced how participants felt during heating trials (i.e., somewhat greater reductions in FS score during the mild heating condition over time compared with the thermoneutral or cooling conditions).

In contrast to affective valence, perceptions of thermal stress (e.g., comfort, sensation) were more sensitive to the thermal perturbations (see Figure 9). Simmons et al. (2008) noted that thermal sensations (TS) are more sensitive to changes in skin temperature than core temperature. Since internal temperature was maintained throughout all trials (37.0 ± 0.1°C), changes in TS scores (Figure 11) were most likely attributed to mean skin temperature (T_{sk}) changes. Early reports noted that changes in thermal sensations were best associated with either lowering T_{sk} toward cold environments or increasing T_{sk} toward hot environments (Gagge, Stolwijk, & Hardy, 1967).

Increased heart rate variability has been reported to occur during exposure to different ambient temperatures, suggesting that sympathetic nerve activity may play a role in perceptions of thermal stress (Liu, Lian, &Liu, 2008). Additionally, during a hemorrhagic challenge, inhibition of the baroreceptor reflex, in response to decreased arterial pressure,

can cause an increase in sympathetic nerve activity (Levy & Pappano, 2007). When sympathetic nerve activity is elevated, effects of thermoregulation (e.g., vasoconstriction during cooling, sweating during mild heating), can correspond with TS scores. Despite a lack of significance, TS scores did relate to T_{sk} during the thermal conditions in that warmer TS scores were reported as T_{sk} increased, compared with baseline (i.e., normothermia), and cooler TS scores were reported when T_{sk} decreased, compared with baseline.

SECONDARY AIM: Aerobic Fitness and Cognitive Function

Aerobic fitness has been associated with better cognitive vitality (e.g., enhanced executive function, visuospatial processing, speeded processing; Colcombe & Kramer, 2003; Hillman et al., 2008; Themanson & Hillman, 2006). Increased fitness results in angiogenesis, or formation of new blood vessels and increased blood volume that may benefit cognitive function (Ratey & Loehr, 2011). The hypothesis that aerobic fitness might have a relationship with cognitive performance during a hemorrhagic injury was unable to be supported, in part due to the absence of a change in the indices of cognitive function as a result of the perturbations. It could also be that aerobic fitness was too homogenous in this sample for any effect to be detected. Based on the analysis performed (i.e., ANCOVA), aerobic fitness does not appear to affect cognitive performance, with respect to selective response inhibition, a subset of executive control function. Any differences observed between participants must be interpreted with caution, as the differences may simply be individual variability rather than a true fitness effect. Perhaps a larger range with this

variable (i.e., individuals with high and low VO_{2max} values) may have resulted in distinct differences in cognitive performance on the Flanker task based on aerobic fitness.

Variability on the Flanker task assessments (e.g., response accuracy, response time, performance variability) may have been due to other independent variables, such as age. Analyses confirmed that even after accounting for the differences in age, there was a significant difference on response accuracy for Congruent trials only. Age appeared to positively influence performance during HEAT trials in comparison to NEUT and COOL conditions. The coefficient from the regression equations indicated that for every additional year in age, response accuracy (on Congruent trials) was expected to decrease an average of 27.1% during NEUT, increase 5.7% during COOL, and increase 63.1% during HEAT. Middle-aged men (45-64 y) are more work-heat-intolerant and suffer more physiological strain during thermal stress than their younger counterparts (Pandolf, 1997). However, habitually active or aerobically trained middle-aged men tolerate and respond better to heat stress than younger individuals (Pandolf). As such age alone may not be the only factor influencing performance on the Flanker task, but one among a myriad of factors (e.g., body fat).

CONCLUSIONS

The present findings may be applied to soldiers and firefighters, as well as any individual who is at risk of being hyperthermic coupled with a hemorrhagic injury (e.g., police officer, mine workers). This investigation provides information regarding whether heating a hemorrhaging soldier or firefighter on the battleground or fire ground should continue to be universally applied, or whether that decision should be predicated upon the

victim's core temperature (i.e., normothermia vs. hypothermia). Although statistically significant differences ($P < 0.05$) were not seen in measures of cognitive performance (i.e., response accuracy, reaction time and performance consistency), some performance trends were observed. Mild heating tended to compromise cognitive performance via decreased response accuracy coupled with increased reaction time and variability in performance; whereas cooling had increased response accuracy with decreased reaction time and performance variability. Other indices of cognitive function may have been affected in this protocol (e.g., working memory), but those assessed by the Flanker task (ability to ignore distracting information) were not.

However, it remains inconclusive whether considerations should be made regarding implementation of skin surface cooling, or a comparable cooling intervention, to treat a hemorrhaging soldier or firefighter who is not hypothermic. It appears that the applied level of simulated hemorrhage (30 mmHg LBNP) was insufficient to significantly alter cognitive function regardless of the thermal perturbation. Perhaps a more profound simulated hemorrhagic challenge (> 30mmHg) with the same thermal conditions would produce more significant changes. Additionally, given the homogeneity of the fitness levels of the participants, firm conclusions were unable to be developed regarding the extent to which aerobic fitness may modify cognitive performance during mild heating and simulated mild hemorrhage.

Since the current investigation involved young (29.9 ± 8.4 y), relatively fit men (40.4 ± 6.3 $ml \cdot kg^{-1} \cdot min^{-1}$), the conclusions drawn upon here only apply to this particular population. It would be of interest to determine if women with similar characteristics would produce comparable results. Additionally, recruiting based on aerobic capacity (i.e.,

individuals with high and low VO_{2max} values) may add to the preliminary results collected in this investigation. Both of these future investigations would further aid treatment of trauma injuries in military and firefighting personnel, both men and women, as well as active and sedentary individuals.

REFERENCES

Adam, G. E., Carter, R., Cheuvront, S. N., Merullo, D. J., Castellani, J. W., Lieberman, H. R., & Sawka, M. N. (2008). Hydration effects on cognitive performance during military tasks in temperate and cold environments. *Physiology & Behavior, 93,* 748–756.

Alam, H. B., Chen, Z., Ahuja, N., Chen, H., Conran, R., Ayuste, E. C., Toruno, K., Ariaban, N., Rhee, P., Nadel, A., & Koustova. (2005). Profound hypothermia protects neurons and astrocytes, and preserves cognitive functions in a swine model of lethal hemorrhage. *Journal of Surgical Research, 126,* 172–181.

Allcock, L. M., Kenny, R. A., Mosimann, U. P., Tordoff, S., Wesnes, K.A., Hildreth, A. J., & Burn, D. J. (2006). Orthostatic hypotension in Parkinson's disease: Association with cognitive decline? *International Journal of Geriatric Psychiatry, 21,* 778–783.

Ando, S., Hatamoto, Y., Sudo, M., Kiyonaga, A., Tanaka, H., & Higaki, Y. (2013). The effects of exercise under hypoxia on cognitive function. *Plos ONE, 8,* e63630.

BAA 11-1. (October 2010). United States Army Medical Research and Material Command. Retrieved from http://www.usamraa.army.mil/pages/baa_paa/BAA_11_1/BAA%2011-1.pdf

Bandelow, S., Maughan, R., Shirreffs, S., Ozgunen, K., Kurdak, S., Eroz, G., Binnet, M., & Dvorak, J. (2010). The effects of exercise, heat, cooling and rehydration strategies on cognitive function in football players. *Scandinavian Journal of Medicine & Science in Sports, 20,* 148–160.

Braude, D., Goldsmith, T., & Weiss, S. J. (2011). Assessing air medical crew real-time readiness to perform critical tasks. *Prehospital Emergency Care, 15,* 254–260.

Caldwell, J. N., Engelen, L., van der Henst, C., Patterson, M. J., & Taylor, N. A. S. (2011). The interaction of body armor, low-intensity exercise, and hot-humid conditions on physiological strain and cognitive function. *Military Medicine, 176,* 488–493.

Caldwell, J. N., Patterson, M. J., & Taylor, N. A. S. (2012). Exertional thermal strain, protective clothing and auxiliary cooling in dry heat: Evidence for physiological but not cognitive impairment. *European Journal of Applied Physiology, 112,* 3597–3606.

Castellani, J. W. (2003). Physiology of heat stress. In L. E. Armstrong (Ed.), *Exertional heat illness*. Champaign, IL: Human Kinetics.

Chapman, S. B., Aslan, S., Spence, J. S., DeFina, L. F., Keebler, M. W., Didehbani, N., & Lu, H. (2013). Shorter term aerobic exercise improves brain, cognition, and cardiovascular fitness in aging. *Frontiers in Aging Neuroscience, 5,* 1–9.

Colcombe, S., & Kramer, A. F. (2003). Fitness effects on the cognitive function of older adults: A meta-analytic study. *Psychological Science, 14,* 125–130.

Colcombe, S. J., Kramer, A. F., Erikson, K. I., Scalf, P., McAuley, E., Cohen, N. J., Webb, A., Jerome, G. J., Marquez, D. X., & Elavsky, S. (2004). Cardiovascular fitness, cortical plasticity, and aging. *Proceedings of the National Academy of Sciences, 101,* 3316–3321.

Cooke, W. H., Ryan, K. L., & Convertino, V. A. (2004). Lower body negative pressure as a model to study progression to acute hemorrhagic shock in humans. *Journal of Applied Physiology, 96,* 1249–1261.

Crandall, C. G., & Gonzalez-Alonso, J. (2010). Cardiovascular function in the heat-stressed human. *Acta Physiologica (Oxford), 199,* 407–423.

Durand, S., Cui, J., Williams, K. D., & Crandall, C. G. (2004). Skin surface cooling improves orthostatic tolerance in normothermic individuals. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology, 286,* R199–R205.

Duschek, S., & Schandry, R. (2007). Reduced brain perfusion and cognitive performance due to constitutional hypotension. *Clinical Autonomic Research, 17,* 69–76.

Eastridge, B. J., Cantrell, J., Oetjen-Gerdes, L., Zubko, T., Mallak, C., Wade, C. E., Simmons, J., Mace, J., Mabry, R., Bolenbaucher, R., & Blackbourne, L. H. (2011). Died of wounds on the battlefield: Causation and implications for improving combat casualty care. *The Journal of Trauma: Injury, Infection, and Critical Care, 71,* S4–S8.

Elsmore, T. F. (1994). SYNWORK1: A PC-based tool for assessment of performance in a simulated work environment. *Behavior Research Methods, Instruments, & Computers, 26,* 421–426.

Ely, B. R., Sollanek, K. J., Cheuvront, S. N., Lieberman, H. R., & Kenefick, R. W. (2013). Hypohydration and thermal stress affect mood state but not cognition or dynamic postural balance. *European Journal of Applied Physiology, 113,* 1027–1034.

Eriksen, B. A., & Eriksen, C. W. (1974). Effects of noise letters upon the identification of a target letter in a nonsearch task. *Perception & Psychophysics, 16,* 143–149.

Faerevik, H., & Reinersten, R. E. (2003). Effects of wearing aircrew protective clothing on physiological and cognitive responses under various ambient conditions. *Ergonomics, 46,* 780–799.

Faul, F., Erdfelder, E., Lang, A. G., & Buchner, A. (2007). G*Power 3: A flexible statistical power analysis program for the social, behavioral and biomedical sciences. *Behavior Research Methods, 39*, 175–191.

Ferris, L. T., Williams, J. S., & Shen, C. (2007). The effect of acute exercise on serum brain-derived neurotrophic factor levels and cognitive function. *Medicine and Science in Sports and Exercise, 39*, 728–734.

Frewen, J., Savva, G. M., Boyle, G., Finucane, C., & Kenny, R. A. (2014). Cognitive performance in orthostatic hypotension: Findings from a nationally representative sample. *Journal of the American Geriatrics Society, 62,* 117–122.

Gagge, A. P., Stolwijk, A. J., & Hardy, J. D. (1967). Comfort and thermal sensations and associated physiological responses at various ambient temperatures. *Environmental Research, 1,* 1–20.

Ganio, M. S., Armstrong, L. E., Casa, D. J., McDermott, B. P., Lee, E. C., Yamamoto, L. M., Marzano, S., Lopez, R. M., Jimenez, L., Bellego, L. L., Chevillotte, E., & Lieberman, H. R. (2011). Mild dehydration impairs cognitive performance and mood of men. *British Journal of Nutrition, 106,* 1545–1543.

Giesbrecht, G. G., Arnett, J. L., Vela, E., & Bristow, G. K. (1993). Effect of task complexity on mental performance during immersion hypothermia. *Aviation Space and Environmental Medicine, 64,* 206–211.

Giesbrecht, G. G., Jamieson, C., & Cahill, F. (2007). Cooling hyperthermic firefighters by immersing forearms and hands in 10°C and 20°C water. *Aviation, Space and Environmental Medicine, 78,* 561–567.

Hancock, P. A. (1986). Sustained attention under thermal stress. *Psychology Bulletin, 99,* 263–281.

Hancock, P. A., & Vasmatzidis, I. (2003). Effects of heat stress on cognitive performance: The current state of knowledge. *International Journal of Hyperthermia, 19,* 355–372.

Hardy, C. J., & Rejeski, W. J. (1989). Not what, but how one feels: The measurement of affect during exercise. *Journal of Sport & Exercise Psychology, 11,* 301–317.

Heckbert, S. R., Vedder, N. B., Hoffman, W., Winn, R. K., Hudson, L. D., Jurkovich, G. J., Copass, M. K., Harlan, J. M., Rice, C. L., & Maier, R. V. (1998). Outcome after hemorrhagic shock in trauma patients. *The Journal of Trauma: Injury, Infection, and Critical Care, 45,* 545–549.

Heims, H. C., Critchley, H. D., Martin, N. H., Jager, H. R., Mathias, C. J., & Cipolotti, L. (2006). Cognitive functioning in orthostatic hypotension due to pure autonomic failure. *Clinical Autonomic Research, 16,* 113–120.

Hillman, C. H., Erickson, K. I., & Kramer, A. F. (2008). Be smart, exercise your heart: Exercise effects on brain and cognition. *Nature Publishing Group, 9,* 58–65.

Hommel, B. (2003). Spatial asymmetries in the flanker-congruency effect: Attentional scanning is biased by flanker orientation. *Psychology Science, 45,* 63–77.

Horn, G. P., Blevins, S., Fernhall, B., & Smith, D. L. (2013). Core temperature and heart rate response to repeated bouts of firefighting activities. *Ergonomics, 56,* 1465–1473.

Hoyt, D. B., Dutton, R. P., Hauser, C. J., Hess, J. R., Holcomb, J. B., Kluger, Y., Mackway-Jones, K., Parr, M. J., Rizoli, S. B., Yukioka, T., & Bouillon, B. (2008). Management of coagulopathy in patients with multiple injuries: Results from an international survey of clinical practice. *The Journal of Trauma: Injury, Infection, and Critical Care, 65,* 755–765.

Kheirbek, T., Kochanek, A. R., & Alam, H. B. (2009). Hypothermia in bleeding trauma: A friend or a foe? *Scandinavian Journal of Trauma, Resuscitation and Emergency Medicine, 17,* 65–80.

Kivimaki, M., & Lusa, S. (1994). Stress and cognitive performance of firefighters during smoke-diving. *Stress Medicine, 10,* 63–68.

Levy, M. N., & Pappano, A. J. (2007). *Cardiovascular Physiology.* Philadelphia, PA: Mosby Elsevier.

Lewis, N. C. S., Bain, A. R., MacLeod, D. B., WIldfong, K. W., Smith, K. J., Willie, C. K., Sanders, M. L., … & Ainslie, P. N. (2014). Impact of hypocapnia and cerebral perfusion on orthostatic tolerance. *The Journal of Physiology, 592*, 5203–5219.

Lieberman, H. R., Bathalon, G. P., Falco, C. M., Kramer, M., Morgan, C. A., & Niro, P. (2005a). Severe decrements in cognition function and mood induced by sleep loss, heat, dehydration, and undernutrition during simulated combat. *Biological Psychiatry, 57,* 422–429.

Lieberman, H. R., Bathalon, G. P., Falco, C. M., Morgan, C. A., Niro, P. J., & Tharion, W. J. (2005b). The fog of war: Decrements in cognitive performance and mood associated with combat-like stress. *Aviation Space and Environmental Medicine, 76,* C7–C14.

Lieberman, H. R., Castellani, J. W., & Young, A. J. (2009). Cognitive function and mood during acute cold stress after extended military training and recovery. *Aviation, Space and Environmental Medicine, 80,* 629–636.

Liu, W., Lian, Z., & Liu, Y. (2008). Heart rate variability at different thermal comfort levels. *European Journal of Applied Physiology, 103,* 361–366.

Lockhart, T. L., Jamieson, C. P., Steinman, A. M., & Giesbrecht, G. G. (2005). Life jacket design affects dorsal head and chest exposure, core cooling and cognition in 10°C. *Aviation, Space and Environmental Medicine, 76,* 954–962.

Low, P. A., Opfer-Gehrking, T. L., McPhee, B. R., Fealey, R. D., Benarroch, E. E., Willner, C. L., Suarez, G. A., Proper, C. J., Felten, J. A., Huck, C. A., & Corfits, J. L. (1995). Prospective evaluation of clinical characteristics of orthostatic hypotension. *Mayo Clinic Proceedings, 70,* 617–622.

MacLeod, J. B. A., Lynn, M., McKenney, M. G., Cohn, S. M., & Murtha, M. (2003). Early coagulopathy predicts mortality in trauma. *The Journal of Trauma: Injury, Infection, and Critical Care, 55,* 39–44.

Mahoney, C. R., Hirsch, E., Hasselquist, L., Lesher, L. L., & Lieberman, H. R. (2007). The effects of movement and physical exertion on soldier vigilance. *Aviation, Space and Environmental Medicine, 78,* B51–B57.

Makinen, T. M. (2007). Human cold exposure, adaptation, and performance in high latitude environments. *American Journal of Human Biology, 19,* 155–164.

Martin, R. S., Kilgo, P. D., Miller, P. R., Hoth, J. J., Meredith, J. W., & Chang, M. C. (2005). Injury associated hypothermia: An analysis of the 2004 National Trauma Data Bank. *Shock, 24,* 114–118.

Morley, J., Beauchamp, G., Suyama, J., Guyette, F. X., Reis, S. E., Callaway, C. W., & Hostler, D. (2012). Cognitive function following treadmill exercise in thermal protective clothing. *European Journal of Applied Physiology, 112,* 1733–1740.

Muller, M. D., Gunstad, J., Alosco, M. L., Miller, L. A., Updergraff, J., Spitznagel, M. B., & Glickman, E. L. (2012). Acute cold exposure and cognitive function: Evidence for sustained impairment. *Ergonomics, 55,* 792–798.

Murray, N. P., & Russoniello C. (2012). Acute physical activity on cognitive function: A heart rate variability examination. *Applied Psychophysiology and Biofeedback, 37,* 219–227.

Nehlig, A. (2010). Is caffeine a cognitive enhancer? *Journal of Alzheimer's Disease, 20,* S85–S94.

Novak, V., & Hajjar, I. (2010). The relationship between blood pressure and cognitive function. *Nature Reviews Cardiology, 7,* 686–698.

Novak, V., Novak, P., Spies, J. M. & Low, P. A. (1998). Autoregulation of cerebral blood flow in orthostatic hypotension. *Stroke, 29*, 104–111.

Pandolf, K. B. (1997). Aging and human heat tolerance. *Experimental Aging Research, 23*, 69–105.

Peng, R. Y., & Bongard, F. S. (1999). Hypothermia in trauma patients. *Journal of the American College of Surgeons, 188,* 685–696.

Pereira, A. C., Huddleston, D. E., Brickman, A. M., Sosunov, A. A., Hen, R., McKhann, G. M., Sloan, R., Gage, F. H., Brown, T. R., & Small, S. A. (2007). An *in vivo* correlate of exercise-induced neurogenesis in the adult dentate gyrus. *Proceedings of the National Academy of Sciences, 104,* 5638–5643.

Perlmuter, L. C., Sarda, G., Casavant, V., & Mosnaim, A. D. (2013). A review of the etiology, associated comorbidities, and treatment of orthostatic hypotension. *American Journal of Therapeutics, 20,* 279–291.

Pilcher, J. J., Nadler, E, & Busch, C. (2002). Effects of hot and cold temperature exposure on performance: A meta-analytic review. *Ergonomics, 45,* 682–698.

Ratey, J. J., & Loehr, J. E. (2011). The positive impact of physical activity on cognition during adulthood: A review of underlying mechanisms, evidence and recommendations. *Reviews in the Neurosciences, 22,* 171–185.

Rickards, C. A., Ryan, K. L., Cooke, W. H. & Convertino, V. A. (2011). Tolerance to central hypovolemia: The influence of oscillations in arterial pressure and cerebral blood velocity. *Journal of Applied Physiology, 111*, 1048–1058.

Rose, E. A. & Parfitt, G. (2008). Can the Feeling Scale be used to regulate exercise intensity? *Medicine & Science in Sports & Exercise, 40,* 1852–1860.

Sambati, L., Calandra-Buonaura, G., Poda, R., Guaraldi, P., & Cortelli, P. (2014). Orthostatic hypotension and cognitive impairment: A dangerous association? *Neurological Science, 35,* 951–957.

Sawka, M. N., & Wenger, C. B. (1988). Physiological responses to acute exercise-heat stress. In K. B. Pandolf, M. N. Sawka, & R. R. Gonzalez (Eds.), *Human performance physiology and environmental medicine at terrestrial extremes*. Indianapolis, IN: Benchmark Press.

Shukitt-Hale, B., Banderet, L. E., & Lieberman, H. R> (1998). Elevation-dependent symptom, mood, and performance changes produced by exposure to hypobaric hypoxia. *The International Journal of Aviation Psychology, 8,* 319–334.

Simmons, S. E., Saxby, B. K., McGlone, F. P., & Jones, D. A. (2008). The effect of passive heating and head cooling on perception, cardiovascular function and cognitive performance in the heat. *European Journal of Applied Physiology, 104,* 271–280.

Smith, D. L., Manning, T. S., & Petruzzello, S. J. (2001). Effect of strenuous live-fire drills on cardiovascular and psychological responses of recruit firefighters. *Ergonomics, 44,* 244–254.

Smith, D. L., & Petruzzello, S. J. (1998). Selected physiological and psychological responses to live-fire drills in different gear configurations of firefighting gear. *Ergonomics, 41,* 1141–1154.

Soreide, K., Kruger, A. J., Vardal, A. L., Ellingsen, C. L., Soreide, E., & Lossius, H. M. (2007). Epidemiology and contemporary patterns of trauma deaths: Changing place, similar pace, older face. *World Journal of Surgery, 31,* 2092–2103.

Takezawa, T. & Miyatani, M. (2005). Quantitative relation between conflict and response inhibition in the Flanker task. *Psychological Reports, 97,* 515–526.

Tanaka, K. A., Key, N. S., & Levy, J. H. (2009). Blood coagulation: Hemostasis and thrombin regulation. *Anesthesia & Analgesia, 108,* 1433–1446.

Themanson, J. R., & Hillman, C. H. (2006). Cardiorespiratory fitness and acute aerobic exercise effects on neuroelectric and behavioral measures of action monitoring. *Neuroscience, 141,* 757–767.

Tomporowski, P. D. (2003). Effects of acute bouts of exercise on cognition. *Acta Psychologica, 112,* 297–324.

Toner, M. M., Drolet, L. L., & Pandolf, K. B. (1986). Perceptual and psychological responses during exercise in cool and cold water. *Perceptual and Motor Skills, 62,* 211–220.

Tuboly, G., Rudas, L., Csillik, A., Nagy, A., Benedek, K., Benedek, G., & Braunitzer. (2012). Haemodynamic parameters and cognitive function during modeled acute volume loss. *Acta Physiologica Hungarica, 99,* 118–125.

Tzeng, Y. C., Ainslie, P. N., Cooke, W. H., Peeble, K. C., Willie, C. K., MacRae, B. A., Smirl, J. D., … & Rickards, C. A. (2012). Assessment of cerebral autoregulation: The quandary of quantification. *American Journal of Physiology-Heart and Circulatory Physiology, 303*, H658–H671.

van Wingen, G. A., Geuze, E., Caan, M. W. A., Kozicz, T., Olabarriaga, S. D., Denys, D., Vermetten, E., & Fernandez, G. (2012). Persistent and reversible consequences of combat stress on the mesofrontal circuit and cognition. *Proceedings of the National Academy of Sciences, 109,* 15508–15513.

Vasterling, J. J., Proctor, S. P., Amoroso, P., Kane, R., Heeren, T., & White, R. F. (2006). Neuropsychological outcomes of Army personnel following deployment to the Iraq war. *The Journal of the American Medical Association, 296,* 519–529.

Vaynman, S., Ying, Z., & Gomez-Pinilla, F. (2004). Hippocampal BDNF mediates the efficacy of exercise on synaptic plasticity and cognition. *European Journal of Neuroscience, 20,* 2580–2590.

Vincent, A. S., Roebuck-Spencer, T., Lopez, M. S., Twillie, D. A., Logan, B. W., Grate, S. J., Friedl, K. E., Schlegel, R. E., & Gilliland, K. (2012). Effects of military deployment on cognitive functioning. *Military Medicine, 177,* 248–255.

Welles, A. P., Buller, M. J., Margolis, L., Economos, D., Hoyt, R. W., & Richter, M. W. (2013). Thermal-work strain during Marine rifle squad operations in Afghanistan. *Military Medicine, 178,* 1141–1148.

Wilson, T. E., Cui, J., Zhang, R., & Crandall, C. G. (2006). Heat stress reduces cerebral blood velocity and markedly impairs orthostatic tolerance in humans. *American Journal of Physiology- Regulatory, Integrative and Comparative Physiology, 291,* R1443–R1448.

Wilson, T. E., Cui, J., Zhang, R., Witkowski, S., & Crandall, C. G. (2002). Skin cooling maintains cerebral blood flow velocity and orthostatic tolerance during tilting in heated humans. *Journal of Applied Physiology, 93,* 85–91.

Wong, J. (2005). Software: SynWin version 1.2. *Ergonomics in Design: The Quarterly of Human Factors Applications, 13,* 30–32.

Yap, P. L. K., Niti, M., Yap, K. B., & Ng, T. P. (2008). Orthostatic hypotension, hypotension and cognitive status: Early comorbid markers of primary dementia? *Dementia and Geriatric Cognitive Disorders, 26,* 239–246.

Young, A. J., Sawka, M. N., Epstein, Y., Descristofano, B., & Pandolf, K. B. (1987). Cooling different body surfaces during upper and lower body exercise. *Journal of Applied Physiology, 63,* 1218–1223.

APPENDIX A

INFORMED CONSENT FORM

The University of Texas Southwestern Medical Center at Dallas
Texas Health Presbyterian Hospital Dallas – Institute for Exercise and Environmental Medicine

CONSENT TO PARTICIPATE IN RESEARCH

Title of Research:	Effects of Thermal Status on Markers of Blood Coagulation During Simulated Hemorrhage
Funding Agency/Sponsor:	U.S. Army Medical Research and Material Command
Study Doctors:	Craig G. Crandall, Ph.D. Zachary Schlader, Ph.D. Daniel Gagnon, Ph.D.
Research Personnel:	Jena Langlois, R.N. Naomi Kennedy, R.N. Eric Rivas, M.S. Paula Poh, M.S.
Research Monitor:	Benjamin D. Levine, M.D.

You may call the study doctors or research personnel during regular office hours at 214-345-4619 (IEEM). At other times, you may call Dr. Crandall at 972-522-8859.

Instructions:
Please read this consent form carefully and take your time making a decision about whether to participate. As the researchers discuss this consent form with you, please ask him/her to explain any words or information that you do not clearly understand. The purpose of the study, risks, inconveniences, discomforts, and other important information about the study are listed below. If you decide to participate, you will be given a copy of this form to keep.

Why is this study being done?
This study, which is funded by the U.S. Army Medical Research and Material Command, is being done to better understand the formation of blood clots in someone who has a bleeding injury and whose body temperature is normal or elevated. When a person is hot, their blood may not clot as well. Therefore, their body may not be able to help stop bleeding as well when they suffer an injury.

Why is this considered research?
This is a research study because it involves an organized, step-by-step investigation, including research development, testing and evaluation, designed to contribute information that can be used by many people. In this case, information will be collected

Study ID: STU 122011-011 Date Approved: 9/17/2014 Expiration Date: 9/2/2015

to better understand blood clotting in people who suffer trauma.

The following definitions may help you understand this study:

- Researchers means the study doctor and research personnel at the Institute for Exercise and Environmental Medicine (IEEM) at Texas Health Presbyterian Hospital Dallas.

Why am I being asked to take part in this research study?
You are being asked to take part in this study because you are a healthy male between the ages of 18 and 55.

Do I have to take part in this research study?"
No. You have the right to choose whether you want to take part in this research study. If you decide to participate and later change your mind, you are free to stop participation at any time.

If you decide not to take part in this research study it will not change your legal rights or the quality of health care that you receive at UT Southwestern Medical Center, Texas Health Presbyterian Hospital Dallas, or any of their affiliates.

How many people will take part in this study?
Thirty-three people are needed to complete this study. However, about 42 people will be considered to take part because we anticipate some may not qualify for the study while others may choose not to finish the study.

What is involved in the study?
If you volunteer to take part in this research study, you will be asked to sign this consent form and will have the following tests and procedures conducted. All of the tests and procedures are done solely for the purpose of the study and are not intended to diagnose or treat medical problems.

Screening Procedures

To help decide if you qualify for this study, the researchers will ask you questions about your health, including medications you take and any surgical procedures you have had. You will also be asked to provide your age, sex and ethnic origin.

You may also have the following exams, tests or procedures:

- Physical exam and medical history;
- Vital signs such as blood pressure and heart rate;
- Electrocardiogram (ECG), a tracing of the electrical activity of the heart; and
- Urine drug screen

Procedures and Evaluations during the Research

You have been invited to participate in one of three separate protocols. Because each protocol is unique, you are not required to participate in all three. If you agree to the procedures involved, please place your initials next to the protocol indicated by the researcher. All procedures are described in detail below after the protocols are explained.

_____ (Initials) **Protocol 1:** *Normal Temperature versus Passive Heat Stress*

Two visits are required for this protocol. The procedures performed during these visits will be identical, with the exception that during one visit you will maintain normal body temperature and the other visit you will be heated with a water perfused suit that you will wear. After 30 minutes of lying down and resting, you will be heated or kept at normal body temperature using the water-perfused suit. This will last for about 60 minutes. You will then experience lower-body negative pressure (LBNP). Following LBNP, we will return your temperature to normal (or it will remain normal) for another 60 minutes. Blood will be drawn 5 times during the testing (after 30 minutes of rest, before and immediately after LBNP, then 30 and 60 minutes after LBNP).

For this protocol, you will have the following procedures (see description below):

- Peripheral intravenous catheter
- Blood draw
- Heart rate and rhythm
- Blood pressure
- Internal temperature
- Skin temperature
- Control of whole-body temperature
- Lower body negative pressure (LBNP)
- Body weight
- Brain Blood Flow
- Urine sample
- Skin conductance, heat movement and body motion
- Tissue oxygen saturation and pH

_____ (Initials) **Protocol 2:** *Exercise and Dehydration*

Four visits will be required. On the first visit, you will undergo a peak exercise test which will be used to determine your fitness level. For the other three visits, the procedures performed will be identical, except that on one visit you will be allowed to drink water during exercise and during the other two you will not. After lying down and resting for 30 minutes, you will then exercise in a warm room, during the hydration and one of the dehydration trials the duration of exercise will be 90 minutes, but during the

other dehydration trial the duration of exercise will be less than 90 min. After exercise, you will experience lower-body negative pressure (LBNP). Following LBNP, you will continue lying down in a normal temperature room for 60 minutes. Blood will be drawn 6 times during the testing (after 30 minutes of rest, twice at the end of exercise, at the end of LBNP, then 30 and 60 minutes after LBNP).

For this protocol, you will have the following procedures (see description below):

Visit 1	Visits 2 - 4
• Peak exercise test • Urine sample • Heart rate and rhythm • Blood pressure • Rating of Perceived Exertion	• Peripheral intravenous catheter • Blood draw • Heart rate and rhythm • Blood pressure • Internal temperature • Skin temperature • Lower body negative pressure (LBNP) • Body weight • Urine sample • Exercise in the heat • Skin conductance, heat movement and body motion • Tissue oxygen saturation and pH

_____ (Initials) **Protocol 3:** *Heating versus Cooling Trauma Patients*

Four visits will be required. On the first visit, you will undergo a peak exercise test to determine your fitness level, as well as complete a physical activity questionnaire and become familiar with the cognitive function tests. For the next three visits, the procedures will be identical, except that you will either be cooled, heated or remain at a normal temperature during each procedure. For each of these three visits, you will rest lying down for 30 minutes. During this 30 minute period your cognitive function will be assessed with approximately 5-10 minutes of tests. You will then be exposed to a low level of lower body negative pressure (LBNP) for 10 minutes. During the 10 minutes of LBNP, you will repeat the cognitive function tests. Once that is complete, you will either remain at normal body temperature, be warmed, or undergo skin surface cooling while the LBNP continues for an additional 40 minutes. During the 40 minutes of LBNP, you will have your cognitive function assess two more times. Blood will be drawn three times (after 30 minutes of rest, after 10 minutes of LBNP and at the end of LBNP).

For this protocol, you will have the following procedures (see description below):

- Peak exercise test
- Cognitive function testing

- Peripheral intravenous catheter
- Blood draw
- Heart rate and rhythm
- Blood pressure
- Internal temperature
- Skin temperature
- Lower body negative pressure (LBNP)
- Control of whole-body temperature
- Body weight
- Brain blood flow
- Urine sample
- Skin conductance, heat movement and body motion
- Tissue oxygen saturation and pH

Description of Procedures

Control of whole-body temperature:
Description of Procedure: For this procedure, you will wear a suit lined with plastic tubes. Control of your body temperature is accomplished by running water through the suit at different temperatures. To heat you, water ranging from approximately 116 - 122 °F (Protocol 1) or 104 - 111 °F (Protocol 3) will flow through the tubes. To cool you, the water will be approximately 50 - 63 °F, and to keep you normal temperature, it will be 93 °F. The duration of the heating or cooling will depend on how quickly your skin and body temperature change, although for most people it will be no longer than 60 minutes. For Protocol 1, your body temperature will be increased by approximately 2 - 3 °F. For Protocol 3, your body temperature will be increased about 1 °F and your skin will be cooled from approximately 93 °F (normal) to 86 °F. Following testing your temperature will be returned to normal.
Potential Risks: There are no risks associated with these temperature changes.
Duration of Procedure: The total duration of the heating or cooling varies from person to person but will be approximately 1 to 1.5 hours.

Internal temperature:
Description of Procedure: In order to measure your internal body temperature, at the beginning of each study you will swallow a pill about the size of a large vitamin. The pill will pass though the gastrointestinal tract in typically 1 – 7 days.
Potential Risks: Although they are rare, there are some risks associated with taking this pill. It is possible that you could inhale it into your lungs. The pill could also cause a perforation, blockage or infection of the intestinal tract. The pill could become stuck in your intestinal tract and require endoscopy or surgery to remove it. You should not take this pill if you weigh less than 80 pounds, nor should you take this pill if you have or have had any gastrointestinal disease or surgery or if you have any implanted medical devices. You may not have a magnetic resonance imaging (MRI) procedure performed with this pill in your body.

Duration of Procedure: Internal temperature will be measured during the entire experiment (approximately 3-5 hours).

Skin temperature:
Description of Procedure: Skin temperature will be measured by taping temperature probes to your skin.
Potential Risks: There is no risk associated with this procedure.
Duration of Procedure: Skin temperature will be measured during the entire experiment (approximately 3-5 hours).

Lower body negative pressure:
Description of Procedure: This procedure causes fluid in your body to shift from your chest and upper body to your lower body. While lying on your back, you will be sealed in a box-like chamber from the waist down. Suction will be applied inside the box to your lower body. The level of suction will increase until the researchers determine that the test is over or you request to stop.
Potential Risks: Dizziness, light-headedness, and nausea are common side effects. If this should happen, we will stop the procedure and you should begin to feel better almost immediately. On rare occasion, a person may faint.
Duration of Procedure: This procedure can last anywhere from 5-25 minutes except in Protocol 3 where a low level of suction will be applied for approximately 50 minutes.

Electrocardiogram:
Description of Procedure: Sticky patches will be applied to your skin to measure the heart's electrical signals.
Potential Risks: There is no risk or discomfort associated with this procedure.
Duration of Procedure: The electrocardiogram will be measured during the entire experiment (approximately 3-5 hours).

Finger blood pressure:
Description of Procedure: In order to continuously monitor your blood pressure during the experiment, a small blood pressure cuff will be placed on one of your fingers.
Potential Risks: Occasionally, some people experience some mild discomfort in the finger after a prolonged period of inflation. If this occurs, notify the researchers and the cuff will be deflated to give the finger a rest. Other than this potential discomfort, there are no known risks to this procedure.
Duration of Procedure: We will measure your blood pressure during the entire experiment (approximately 3-5 hours).

Blood pressure:
Description of Procedure: Your blood pressure will also be monitored using a cuff placed on your upper arm that is inflated and deflated periodically.
Potential Risks: Other than some potential discomfort associated with cuff inflation there is no risk to this procedure.

Duration of Procedure: The cuff will be on your upper arm during the entire experiment. We will take blood pressure measurements at different time points during the experiment. Each measurement will last approximately 30 seconds.

Brain blood flow:
Description of Procedure: A gel covered probe will be placed on the side of your forehead as well as the front of your neck. Sound waves will be used to record blood flow inside your head. This procedure is similar to standard ultrasound tests done to examine the health of babies prior to birth.
Potential Risks: There is no risk associated with this procedure.
Duration of Procedure: We will measure your brain blood flow during the entire experiment (approximately 3-5 hours).

Urine Sample:
Description of Procedure: You will be asked to urinate into a cup from which we will assess the density of your urine and conduct a drug screening test. Drugs that your urine will be screened for include marijuana, cocaine, opiates (such as heroin, morphine, hydrocodone, oxycodone and methadone), barbiturates, benzodiazepines, and methamphetamines. If this drug test is positive for one of these agents, you will not be permitted to participate in the study. A positive drug test will not be indicated in your records and this information will remain confidential.
Potential Risks: There is no risk associated with this procedure.
Duration of Procedure: You will be asked to urinate into a cup each visit.

Rating of Perceived Exertion:
Description of Procedure: You will be asked to rate on a standardized scale how hard you feel you are exercising.
Potential Risks: There is no risk or discomfort associated with this procedure.

Peripheral intravenous catheter:
Description of Procedure: A sterile catheter, which is a thin flexible plastic tube, will be inserted into an arm vein so that blood can be taken several times without having multiple sticks with a needle.
Potential Risks: There is a small risk of infection and a still smaller risk of a blood clot or breakage of the catheter. The likelihood of these complications is remote (about 1 in 10,000) when the procedure is carried out by trained personnel and proper equipment is used, as it will be in your case. There is also a small risk of the catheter perforating (going through) the vein or not being inserted into a blood vessel. Also, you may have discomfort, bleeding, and/or bruising. On a rare occasion, a person may feel dizzy or faint.
Duration of Procedure: The catheter will be in place for the entire experiment (approximately 3-5 hours).

Skin conductance, heat movement and body motion:
Description of Procedure: For this procedure, you will wear an armband (SenseWear Pro 3 heart rate-enabled armband) on your upper arm. This device measures the changes in the electrical activity of the skin brought on by an increased emotional or physical state, the heat that is flowing from your body to the environment, the motion of your body and your heart rate.
Potential Risks: Rarely this device may cause some skin irritation and redness (occurs in less than 1% of people).
Duration of Procedure: The armband will be on for the entire experiment (approximately 3-5 hours).

Tissue oxygen saturation and pH:
Description of Procedure: A small sensor, the CareGuide Near Infrared Reflectance Spectroscopy (NIRS), will be placed on your skin in order to measure the pH level (acid/base) and amount of oxygen in your muscle or brain.
Potential Risks: There is no known risk involved with this procedure.
Duration of Procedure: The sensor will remain in place for the entire experiment (approximately 3-5 hours).

Blood Draw:
Description of Procedure: Information about the blood clotting process will be examined by obtaining approximately 2 tablespoons of blood each draw from your peripheral intravenous catheter. The following tests will be performed:

- Standard Complete Blood Count (CBC) and chemistry profile including platelet count
- Prothrombin Time (PT)
- Activated Partial Thromboplastin Time (aPTT)
- Thromboelastograph Hemostasis Analysis
- D-dimer
- Fibrinogen
- Tissue Plasminogen Activator (tPA)
- Antithrombin III
- Protein C
- Plasminogen activator inhibitor-1 (PAI-1)
- Von Willebrand factor (vWF) antigen
- Factors V and VIII
- Venous Blood Gas

Potential Risks: There are no risks beyond those listed for a peripheral intravenous catheter.
Duration of Procedure: Blood will be taken 5 times in Protocol 1 (10 tablespoons), 6 times in Protocol 2 (12 tablespoons) and 3 times in Protocol 3 (6 tablespoons).

Peak Exercise Test:
Description of Procedure: This test measures your body's peak ability to use oxygen. The test involves exercising on a stationary bicycle beginning at a light/easy intensity and gradually increasing to a point at which you can no longer continue. The intensity of the exercise will get harder every couple of minutes. You will breathe regular room

air through a snorkel-like mouthpiece or facemask during this test, and air that you breathe out will be analyzed by a computer.
Potential Risks: Exercise rarely causes any problems in healthy people, but in individuals with known or hidden heart disease, the test may cause chest pain, dizziness, or bouts of irregular heart rhythm. Exercise will be stopped immediately if there are any signs of excessive strain. There is no additional risk involved with completing the peak exercise test beyond that normally associated with exercise and hard physical effort. During intense training and/or testing, the risk of having a heart attack or even dying goes up slightly; however, the risk during an exercise test in a person with no history of heart disease is low.
Duration of Procedure: The total duration of the test will be about 30 min (this includes 10-15 min of warm-up).

Exercise in the heat:
Description of Procedure: You will exercise by walking on a treadmill at a moderate and constant level for approximately 90 minutes. This exercise will be performed in a hot, moderately humid room (104 °F and 30% humidity). Body weight will be measured every 15 minutes during exercise. On one visit, you will drink pre-warmed water or a solution like Gatorade to replace any fluid lost because of sweating. On the other visit, you will not be given any fluid to drink. At various times during exercise, you will breathe through a snorkel-like mouthpiece or facemask while the air you breathe out is analyzed.
Potential Risks: Exercise in the heat can result in high body temperature and stress to your heart and blood vessels. Therefore, there is a risk of developing a heat-associated injury (heat exhaustion or heat stroke). However, we will monitor your internal temperature and vital signs (heart rate and blood pressure) closely in order to minimize this risk. Exercise will stop if your internal temperature reaches 103.1 °F, if you begin to feel light-headed or dizzy, or if you want to stop the test for any reason. Internal temperatures at or below 103.1 °F are well tolerated by most people and do not cause harmful effects.
Duration of Procedure: The total duration of the exercise period will be about 90 min.

Cognitive function testing:
Description of Procedure: This is a series of tests and questionnaires that will assess your attention and ability to identify important information. Additionally, your reaction time, mood and comfort will be determined.
Potential Risks: There are no risks associated with taking these tests. However, you may feel anxiety or stress while taking the tests.
Duration of Procedure: It will take approximately 5-10 minutes to complete these tests. These tests will be given multiple times during each visit.

Body Weight:
Description of Procedure: You will be asked to stand on a scale in a private room and provide a nude body weight. However, during the exercise in Protocol 2, you will be allowed to keep your clothes on when you weigh.
Potential Risks: There are no risks associated with this procedure.
Duration of Procedure: Each weight measurement will take about 30 seconds.

Oxygen Saturation:
Description of Procedure: The amount of oxygen in your blood will be measured by pulse oximetry by placing a sensor on either your finger, arm, leg or earlobe.
Potential Risks: There are no known risks associated with this procedure.
Duration of Procedure: Oxygen saturation will be measured during the entire experiment (approximately 3-5 hours).

How long can I expect to be in this study?
The table below outlines the number of visits per protocol and the expected duration of each visit.

	Protocol 1	Protocol 2	Protocol 3
Visit 1	4 hours	1 – 1.5 hours	2 – 2.5 hours
Visit 2	4 hours	4.5 – 5 hours	3 – 3.5 hours
Visit 3		4.5 – 5 hours	3 – 3.5 hours
Visit 4		4.5 – 5 hours	3 – 3.5 hours

You can choose to stop participating for any reason at any time. However, if you decide to stop participating in the study, we encourage you to tell the researchers. You may be asked if you are willing to complete some study termination tests.

What are the risks of the study?
Because of your participation in this study, you are at risk for the above mentioned side effects. You should discuss these with the researchers and your regular health care provider should you have any concerns.

Loss of Confidentiality
Any time information is collected; there is a potential risk for loss of confidentiality. Every effort will be made to keep your information confidential; however, this cannot be guaranteed.

Risks to Sperm, Embryo or Fetus

Males: Being in this research may damage your sperm, which could cause harm to a child that you may father while on this study. If you take part in this study and are sexually active, you must agree to use a medically-acceptable form of birth control. Medically-acceptable forms of birth control include:

(1) surgical sterilization (vasectomy), or
(2) a condom used with a spermicide (a substance that kills sperm).

Other Risks

There may possibly be other side effects that are unknown at this time. If you are concerned about other, unknown side effects, please discuss this with the researchers.

How will risks be minimized or prevented?

At all times during participation in the study, you and your results will be closely monitored to determine whether there are complications that need medical care. It is your responsibility to report any unusual signs, symptoms, or pain to the research team, keep appointments, and follow the recommendations of the study doctors or the research nurse. Also, report any change in your legal name, address, or telephone number.

All tests that are to be performed have safely been used in both healthy and diseased individuals. Throughout the tests you will be closely monitored by a highly skilled research nurse under the direction of Dr. Benjamin Levine.

What will my responsibilities be during the study?

While you are part of this study, the researchers will follow you closely to determine whether there are problems that need medical care. It is your responsibility to do the following:

- Ask questions about anything you do not understand.
- Keep your appointments.
- Follow the researchers' instructions.
- Let the researchers know if your telephone number or address changes.
- Tell the researchers before you take any new medication, whether it is prescribed by a doctor or is something purchased over the counter.
- Tell your regular doctor about your participation in this study.
- Report to the researchers any injury or illnesses you have while you are taking part in this study even if you do not think it is related.

If I agree to take part in this research study, will I be told of any new risks that may be found during the course of the study?

Yes. You will be told if any new information becomes available during the study that could cause you to change your mind about continuing to participate or that is important to your health or safety.

All the tests in this study are designed for research only, not for medical purposes. Even though the researchers are not looking at your tests to find or treat a medical problem, you will be told if they notice something unusual. You and your regular doctor can decide together whether to follow up with more tests or treatment. Because all research tests done in this study are not for medical purposes, the research results will not be sent to you or to your regular doctor.

What should I do if I think I am having problems?
If you have unusual symptoms, pain, or any other problems while you are in the study, you should report them to the researchers right away. Telephone numbers where they can be reached are listed on the first page of this consent form.

If you have a sudden, serious problem, like difficulty breathing or severe pain, go to the nearest hospital emergency room, or call 911 (or the correct emergency telephone number in your area).

What are the possible benefits of this study?
If you agree to take part in this study, there will not be any direct benefit to you.

We hope the information learned from this study will benefit the U.S. military by aiding in the treatment of soldiers injured on the battlefield. Additionally, individuals at risk for traumatic injury who are consistently exposed to hot environments such as police officers, firefighters and construction workers may also be served.

What options are available if I decide not to take part in this research study?
This is not a treatment study. You do not have to participate.

Will I be paid if I take part in this research study?
Yes, you will be paid $25 per hour. We will not pay you less than $25 for your time (you will be paid for one hour even if you are only in the lab for 30 minutes) nor will we require you to participate for longer than 7 hours in one day.

There are no funds available to pay for parking expenses, transportation to and from the research center, lost time away from work and other activities, lost wages, or child care expenses.

Your Social Security Number (SSN) will be given to Texas Health Presbyterian Hospital Dallas in order to process your payment as required by law. This information will remain confidential unless you give your permission to share it with others, or if we are required by law to release it.

Will my insurance provider or I be charged for the costs of any part of this research study?
No. Neither you, nor your insurance provider, will be charged for anything done only for

this research study (i.e., the Screening Procedures, Experimental Procedures, or Monitoring/Follow-up Procedures described above).

What will happen if I am harmed as a result of taking part in this study?
It is important that you report any illness or injury to the research team listed at the top of this form immediately.

If you become injured during the protocol, and if that injury warrants further examination, we will arrange for you to be seen by competent medical personnel employed at the Institute for Exercise and Environmental Medicine. If further medical attention is needed, we will arrange transportation to the Hospital's Emergency Department via ambulance.

If you after you depart from the laboratory you feel like you are injured as a result of participating in this research, you are encouraged to contact a member of the research team and (if warranted) seek medical attention.
You, or your insurance company, will be responsible for payment of medical services that are provided by facilities other than the Institute for Exercise and Environmental Medicine.

Compensation for an injury resulting from your participation in this research is not available from Texas Health Presbyterian Hospital Dallas – Institute for Exercise and Environmental Medicine, Parkland Hospital & Hospital Systems or the University of Texas Southwestern Medical Center.

You retain your legal rights during your participation in this research.

Can I stop taking part in this research study?
Yes. If you decide to participate and later change your mind, you are free to stop taking part in the research study at any time.

If you decide to stop taking part in this research study, it will not affect your relationship with the UT Southwestern or Texas Health Presbyterian Hospital Dallas staff or doctors. Whether you participate or not will have no effect on your legal rights or the quality of your health care.

If you are a medical student, fellow, faculty, or staff at the Medical Center, your status will not be affected in any way.

If I agree to take part in this research study, can I be removed from the study without my consent?
Yes. The researchers may decide to take you off this study if:

- The researchers believe that participation in the research is no longer safe for you.

- The sponsor or the FDA stops the research for the safety of the participants.
- The sponsor cancels the research.
- You are unable to keep appointments or to follow the researcher's instructions.

Will my information be kept confidential?
Information about you that is collected for this research study will remain confidential unless you give your permission to share it with others, or if we are required by law to release it. You should know that certain organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- Representatives of government agencies, like the U.S. Food and Drug Administration (FDA), involved in keeping research safe for people;
- The U.S Army Medical Research and Material Command and/or the Department of Defense
- The UT Southwestern Institutional Review Board; and
- Texas Health Presbyterian Hospital Dallas.

In addition to this consent form, you will be asked to sign an "Authorization for Use and Disclosure of Protected Health Information." This authorization will give more details about how your information will be used for this research study, and who may see and/or get copies of your information.

Are there procedures I should follow after stopping participation in this research?
Yes. If you, the researchers, or the sponsor stops your participation in the research, you may be asked to do the following:

- Let the researchers know immediately that you wish to withdraw from the research.
- Return any unused study materials, including empty containers.
- Discuss your future medical care, if any, with the researchers and/or your personal doctor.

Whom do I call if I have questions or problems?
For questions about the study, contact Craig Crandall, Ph.D. at 214-345-4623 or Jena Langlois, R.N. at 214-345-4610 during regular business hours. You may also contact Dr. Crandall at 972-522-8859 after hours and on weekends and holidays.

For questions about your rights as a research participant, contact the UT Southwestern Institutional Review Board (IRB) Office at 214-648-3060.

SIGNATURES:

YOU WILL BE GIVEN A COPY OF THIS CONSENT FORM TO KEEP.
Your signature below certifies the following:

- You have read (or been read) the information provided above.
- You have received answers to all of your questions and have been told who to call if you have any more questions.
- You have freely decided to participate in this research.
- You understand that you are not giving up any of your legal rights.

_____
Participant's Name (printed)

_____ _____ _____ _____
Participant's Signature Date Time AM/PM

_____
Name of person obtaining consent (printed)

_____ _____ _____ _____
Signature of person obtaining consent Date Time AM/PM

APPENDIX B

HEALTH HISTORY FORM

Date_____

Name_____

LAST

FIRST MI

Address_____

_

STREET

APT #

_____

CITY

STATE ZIP CODE

Contact_____

HOME PHONE CELL PHONE

EMAIL

Date of Birth_____ Age_____ Gender_____ Hgt_____

Wgt_____

(MM/DD/YYYY)

Occupation_____Education

Completed_____

Emergency

Contact_____

NAME

RELATIONSHIP PHONE

Racial Origin: (SELECT **ONE** OF THE FOLLOWING)

- ☐ *American Indian or Alaska Native*
- ☐ *Asian* (includes persons from the Indian subcontinent)
- ☐ *Black or African American*
- ☐ *Native Hawaiian or Pacific Islander*
- ☐ *White*

☐ *More than one race*_____

☐ *I do not wish to disclose this information*

Ethnic Origin: (SELECT **ONE** OF THE FOLLOWING)

☐ *Hispanic or Latino*

☐ *Not Hispanic or Latino*

☐ *I do not wish to disclose this information*

Social History

My current exercise/activity level is: ☐ *satisfactory* ☐ *unsatisfactory* ☐ *I don't know*

Type of exercise/activity_____Frequency_____

My current weight is: ☐ *satisfactory* ☐ *unsatisfactory* ☐ *I don't know*

I ☐ *currently* ☐ *previously* ☐ *never* use diet and/or exercise to lose/gain weight

I ☐ *currently* ☐ *previously* ☐ *never* use medication/supplements to lose/gain weight

Is caffeine part of your diet? ☐ *currently* ☐ *previously*: date stopped_____ ☐ *never*

Source of caffeine_____Frequency_____

Tobacco Use: ☐ *none* ☐ *current use* ☐ *prior use* year started_____year quit_____

Type_____Amount_____Number of years_____

Alcohol Use: ☐ *never* ☐ *occasionally/rarely* ☐ *weekly*

☐ *daily*

Type_____Amount_____

Illicit Drug Use:

I ☐ *currently* ☐ *previously* ☐ *never* use illicit drugs (such as marijuana, crack, PCP, methamphetamines)

Type_____Last used_____

Contraception/Pregnancy Risk: (FEMALES ONLY)

I am currently using a reliable method of contraception.

☐ *YES* ☐ *NO* ☐ *I am not in a sexually active relationship*

It is possible that I am pregnant. ☐ *YES* ☐ *NO*

First day of your last menstrual period_____

Medical History

Allergies: (THIS INCLUDES MEDICATION, FOOD, AND/OR LATEX) ☐ *None Known*

Allergy/Intolerance	Describe Reaction

Please mark the box if you have ever seen a doctor for any of the following conditions:

☐ *asthma*
☐ *chronic bronchitis/emphysema*
☐ *other chronic lung disease*
☐ *tuberculosis*
☐ *high blood pressure*
☐ *high cholesterol*
☐ *diabetes*
☐ *heart disease/chest pain*
☐ *other heart trouble*
☐ *bleeding/clotting disorder*
☐ *headaches*
☐ *seizures/epilepsy*
☐ *stroke*
☐ *thyroid disorder*
☐ *ulcers*
☐ *diverticulosis/diverticulitis*
☐ *liver disease*
☐ *kidney disease*
☐ *urinary problems*
☐ *arthritis/joint problems*
☐ *chronic infection*
☐ *fainting spells*
☐ *recurrent fatigue*
☐ *cancer*

☐ *heart attack*
☐ *inflammatory bowel disease*
☐ *anxiety/depression (diagnosed)*
☐ *racing heart/palpitations*
☐ *bowel obstruction/ileus*
☐ *alcohol/substance abuse*
☐ *abnormal electrocardiogram (ECG)*
☐ *gallbladder disease*
☐ *mental illness*

Please list ALL surgeries and explain any checked boxes below:

_____

_____

Medications: (CURRENT MEDICATIONS INCLUDING OVER-THE-COUNTER, VITAMINS, AND HERBAL SUPPLEMENTS)

Medication	Dose/Amt	Frequency	Purpose

☐ The above medical history is correct to the best of my knowledge.

☐ I authorize the Institute for Exercise and Environmental Medicine to keep this information and any information gained from my participation in their studies in a database so that they may contact me regarding future studies.

Signature_____Date_____

_

Witness

Signature_____Date_____

APPENDIX C

INTERNATIONAL PHYSICAL ACTIVITY QUESTIONNAIRE (August 2002)

SHORT LAST 7 DAYS SELF-ADMINISTERED FORMAT

FOR USE WITH YOUNG AND MIDDLE-AGED ADULTS (15-69 years)

The International Physical Activity Questionnaires (IPAQ) comprises a set of 4 questionnaires. Long (5 activity domains asked independently) and short (4 generic items) versions for use by either telephone or self-administered methods are available. The purpose of the questionnaires is to provide common instruments that can be used to obtain internationally comparable data on health–related physical activity.

Background on IPAQ

The development of an international measure for physical activity commenced in Geneva in 1998 and was followed by extensive reliability and validity testing undertaken across 12 countries (14 sites) during 2000. The final results suggest that these measures have acceptable measurement properties for use in many settings and in different languages, and are suitable for national population-based prevalence studies of participation in physical activity.

Using IPAQ

Use of the IPAQ instruments for monitoring and research purposes is encouraged. It is recommended that no changes be made to the order or wording of the questions as this will affect the psychometric properties of the instruments.

Translation from English and Cultural Adaptation

Translation from English is supported to facilitate worldwide use of IPAQ. Information on the availability of IPAQ in different languages can be obtained at www.ipaq.ki.se. If a new translation is undertaken we highly recommend using the prescribed back translation methods available on the IPAQ website. If possible please consider making your translated version of IPAQ available to others by contributing it to the IPAQ website. Further details on translation and cultural adaptation can be downloaded from the website.

Further Developments of IPAQ

International collaboration on IPAQ is on-going and an ***International Physical Activity Prevalence Study*** is in progress. For further information see the IPAQ website.

More Information

More detailed information on the IPAQ process and the research methods used in the development of IPAQ instruments is available at www.ipaq.ki.se and Booth, M.L. (2000). *Assessment of Physical Activity: An International Perspective*. Research Quarterly for Exercise and Sport, 71 (2): s114-20. Other scientific publications and presentations on the use of IPAQ are summarized on the website.

INTERNATIONAL PHYSICAL ACTIVITY QUESTIONNAIRE

We are interested in finding out about the kinds of physical activities that people do as part of their everyday lives. The questions will ask you about the time you spent being physically active in the **last 7 days**. Please answer each question even if you do not consider yourself to be an active person. Please think about the activities you do at work, as part of your house and yard work, to get from place to place, and in your spare time for recreation, exercise or sport.

Think about all the **vigorous** activities that you did in the **last 7 days**. **Vigorous** physical activities refer to activities that take hard physical effort and make you breathe much harder than normal. Think *only* about those physical activities that you did for at least 10 minutes at a time.

1. During the **last 7 days**, on how many days did you do **vigorous** physical activities like heavy lifting, digging, aerobics, or fast bicycling?

   _____ **days per week**

   ☐ No vigorous physical activities → ***Skip to question 3***

2. How much time did you usually spend doing **vigorous** physical activities on one of those days?

   _____ **hours per day**

   _____ **minutes per day**

   ☐ Don't know/Not sure

Think about all the **moderate** activities that you did in the **last 7 days**. **Moderate** activities refer to activities that take moderate physical effort and make you breathe somewhat harder than normal. Think only about those physical activities that you did for at least 10 minutes at a time.

3. During the **last 7 days**, on how many days did you do **moderate** physical activities like carrying light loads, bicycling at a regular pace, or doubles tennis? Do not include walking.

   _____ **days per week**

   ☐ No moderate physical activities → ***Skip to question 5***

4. How much time did you usually spend doing **moderate** physical activities on one of those days?

_____ **hours per day**

_____ **minutes per day**

☐ Don't know/Not sure

Think about the time you spent **walking** in the **last 7 days**. This includes at work and at home, walking to travel from place to place, and any other walking that you might do solely for recreation, sport, exercise, or leisure.

5. During the **last 7 days**, on how many days did you **walk** for at least 10 minutes at a time?

_____ **days per week**

☐ No walking → ***Skip to question 7***

6. How much time did you usually spend **walking** on one of those days?

_____ **hours per day**

_____ **minutes per day**

☐ Don't know/Not sure

The last question is about the time you spent **sitting** on weekdays during the **last 7 days**. Include time spent at work, at home, while doing course work and during leisure time. This may include time spent sitting at a desk, visiting friends, reading, or sitting or lying down to watch television.

7. During the **last 7 days**, how much time did you spend **sitting** on a **week day**?

_____ **hours per day**

_____ **minutes per day**

☐ Don't know/Not sure

This is the end of the questionnaire, thank you for participating.

APPENDIX D

FEELING SCALE

+5	**VERY GOOD**
+4	
+3	**GOOD**
+2	
+1	**FAIRLY GOOD**
0	**NEUTRAL**
-1	**FAIRLY BAD**
-2	
-3	**BAD**
-4	
-5	**VERY BAD**

Adapted from Hardy & Rejeski, 1989

APPENDIX E

THERMAL SENSATIONS SCALE

0.0	**UNBEARABLY COLD**
0.5	
1.0	**VERY COLD**
1.5	
2.0	**COLD**
2.5	
3.0	**COOL**
3.5	
4.0	**COMFORTABLE (NEUTRAL)**
4.5	
5.0	**WARM**
5.5	
6.0	**HOT**
6.5	
7.0	**VERY HOT**
7.5	
8.0	**UNBEARABLY HOT**

Adapted from Toner et al., 1986 and Young et al., 1987