PHYSIOLOGICAL CONSIDERATIONS OF HEAT INTOLERANCE IN PEOPLE WITH MULTIPLE SCLEROSIS

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CANDIDATE'S CERTIFICATE

I, Georgia Chaseling, hereby declare that the work presented in this thesis is, the best of my knowledge, original except as acknowledged in text. I hereby declare that I have not submitted this material, either in full or in part, for a degree at this or any other institution.

Georgia Chaseling

Dated: 3rd of September, 2018

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Abstract

Up to 80% of people diagnosed with multiple sclerosis (MS) experience Uhthoff's phenomenon, which is characterised by a temporary worsening of neurological symptoms and a concomitant onset of fatigue during exercise and/or with exposure to a hot environment. In order to understand the best strategies to mitigate the onset of heat-related MS symptoms and associated fatigue, we need to closer examine the underlying physiological mechanisms responsible for this phenomenon. The purpose of the present thesis was to explore the potential thermo-physiological mechanisms responsible for Uhthoff's phenomenon in heat-sensitive MS patients during rest and exercise in hot (up to 35°C) environments. Specifically, study 1 sought to determine whether resting core temperature and metabolic rate was elevated in people with relapsing-remitting MS and to assess whether an elevated resting core temperature was associated with subjective measures of physical, cognitive and psychosocial fatigue. Study 2 sought to determine whether a contributing factor to heat intolerance in MS patients, was in part, a greater rise in core temperature by virtue of a blunted thermoregulatory response during exercise in warm (30°C) and hot (35°C) environments. This study measured deep core temperature, alongside sweating and skin blood flow responses in people with relapsing-remitting MS, compared to healthy controls while cycling in climate-controlled chamber. Finally, study 3 assessed whether ingestion of cold-water during exercise in a warm environment could prolong exercise tolerance in heat-sensitive people with MS.

Summary of Findings

Study 1 was designed to reassess the previously reported notion that resting core temperature was elevated in people with relapsing-remitting MS, compared to healthy controls when using best practice, precision thermometry. Resting rectal (T_{re}) and esophageal (T_{eso}) temperature, and metabolic rate were measured in 28 MS patients and 27 age-matched controls in a 25°C, 30% RH and 30°C, 30% RH environment. Tympanic membrane (T_{tym}) temperature was measured in a subset of 16 MS and 15 aged-matched controls in a 30°C, 30% RH environment only. A modified fatigue impact scale (MFIS) questionnaire was also used to assess psychological, physical and cognitive fatigue in the 30°C condition. Participants were asked to avoid exercise ~24 h prior to and caffeine consumption ~12 h prior to data collection. All data was collected between the hours of 0800 – 1300. Irrespective of ambient temperature, no between-group differences were observed for T_{re} (MS: 37.07±0.30°C; CON: 37.18±0.30°C; P=0.29), T_{eso} (MS: 36.84±0.42°C; CON: 36.92±0.29°C; P=0.36) or resting VO_2 (MS: 3.9±0.2 $ml \cdot kg^{-1} \cdot min^{-1}$; CON: 3.9±0.2 $ml \cdot kg^{-1} \cdot min^{-1}$; P=0.67). Similarly, no between-group differences were observed for T_{tym} (MS: 36.52±0.38°C; CON: 36.61±0.33°C; P=0.55) in the 30°C condition. Resting T_{re} did not correlate with subjective measures of fatigue: physical: r= -0.11, P=0.67; cognitive: r= -0.14, P=0.60; and psychosocial: r=0.05, P=0.84. Findings from this study do not support those previously shown. Indeed, core temperature at rest when measured using precision thermometry widely recognised among the thermal physiology community as best-practice was not elevated in people with relapsing-remitting MS, compared to age-matched controls. Furthermore, there is no evidence that resting core temperature is associated with subjective measures of psychosocial, cognitive or physical fatigue.

Study 2 investigated the thermoregulatory response in 22 people with relapsing-remitting MS, while cycling at a fixed heat production (4 $W \cdot kg^{-1}$) for 40 minutes, in a warm (30°C, 30% RH) or hot (35°C, 30% RH) environment, compared to 22 age- and massed-matched healthy controls. Throughout the study, T_{re} and T_{sk}, as well as local sweat rate (LSR) and skin blood flow (SBF) were continuously measured. Irrespective of ambient temperature a delayed change in mean body temperature (ΔT_b: $0.9 \times T_{re} + 0.1 \times T_{sk}$ [P=0.002]) and time at onset of sweating (P=0.002) on the forearm, but not the upper back (P=0.46) were observed in people with MS compared to healthy controls, despite a similar onset time of SBF (MS: 11±5 min; CON: 11±6 min; P=0.89) and ΔT_b for SBF onset (MS: 0.09±0.09°C; CON: 0.12±0.11°C; P=0.57). However, despite a blunted peripheral sudomotor response, the rise T_{re} (MS: 0.38±0.18°C; CON: 0.37±0.18°C; P=0.67) after 40 minutes of exercise was similar between the MS and healthy control group in both the warm and hot environments. The change in T_{sk} during exercise was greater in the MS (1.50±0.72°C: P=0.02) compared to the CON group (1.00±0.67°C). In conclusion, while a mild sudomotor dysfunction is evident in people with MS, this thermoregulatory impairment is only enough to alter the superficial tissue temperature (i.e. skin) but not deep core temperature during exercise in warm and hot environments.

Study 3 investigated the effect of cold (CLD; 1.5°C) compared to thermoneutral (NEU; 37°C) water ingestion on exercise time to exhaustion in 10 people with relapsing-remitting MS compared to 10 aged-matched healthy controls (CON). All participants were required to cycle at 40% of their VO_{2max} for 60 minutes (or until volitional exhaustion) in a warm (30°C, 30% RH) environment while ingesting 3.2 $ml \cdot kg^{-1}$ of either cold or thermoneutral fluid after the 15^{th}, 30^{th} and 45^{th} minute of exercise. T_{re} and T_{sk} alongside heart rate (HR) were measured throughout. All

CON participants were able to cycle for 60 minutes in both the CLD and NEU trials, while only 3 out of 10 MS participants could complete 60 minutes of cycling in the NEU trial. The remaining 7 MS participants all cycled longer (P=0.006) in CLD (46.4±14.2 min) compared to NEU (32.7±11.5 min), despite similar elevations in absolute T_{re} (NEU: 37.32±0.34˚C; CLD: 37.28±0.26˚C; P=0.44), change in T_{re} (NEU: 0.38±0.21˚C; CLD: 0.34±0.24˚C), absolute T_{sk} (NEU: 34.48±0.47˚C; CLD: 34.44±0.54˚C; P=0.82) and HR (NEU: 114±20 bpm CLD: 113±18 bpm; P=0.38) for the same exercise volume. Taken together, these findings support the use of a practical cooling strategy to enhance exercise tolerance for people with MS. Results from this study also lend insight into the potential role of thermal perception in the modulation of exercise tolerance for heat-sensitive MS individuals.

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Dissemination of Results

Results culminating from the studies of this thesis which have been published, submitted for publication and/or presented at scientific conferences.

Publications

1. **Chaseling, G.K**., Filingeri, D., Barnett, M., Hoang, P., Davis, S. & Jay, O. (2017). Cold-water ingestion improves exercise tolerance of heat-sensitive people with MS. *Medicine and Science in Sports and Exercise. 50(4)*, 643-648 DOI: 10.1249/mss.0000000000001496
2. **Chaseling, G.K**., Allen, D., Vucic, S., Barnett, M., Frohman, E., Davis, S., Jay, O. (2018). Core temperature is not elevated at rest in people with relapsing-remitting multiple sclerosis. *Multiple Sclerosis and Related Disorders.* (Submitted for peer review: MSARD-D-18-00453)

Conference Presentations

1. **Chaseling, G**.K. (2018). Thermoregulation in multiple sclerosis. Invited presentation. *Physiology and Pharmacology of Temperature Regulation.* Split, Croatia.
2. **Chaseling, G.K**., Allen, D., Vucic, S., Barnett, M., Davis, S.L., Jay, O. (2018). Core temperature is not elevated in relapsing remitting people with multiple sclerosis. *Progressive MS Alliance Scientific Congress.* Toronto, ON, Canada.

3. **Chaseling, G.K**., Filingeri, D., Davis, S. & Jay, O. (2018). Thermoregulation in heat-sensitive MS patients performing physical activity in the heat. *American College of Sports Medicine.* Minneapolis, MN, USA.
4. **Chaseling, G.K**., Filingeri, D., Barnett, M., Davis, S. & Jay, O. (2017). Body temperature regulation in MS patients performing physical activity in the heat. *Progress in MS Research Conference.* Sydney, NSW, Australia.
5. **Chaseling, G.K**., Filingeri, D., Barnett, M., Davis, S. & Jay, O. (2017). Cold fluid ingestion prolongs time to exhaustion in people with multiple sclerosis exercising in the heat. *Progress in MS Research Conference.* Sydney, NSW, Australia.
6. **Chaseling, G.K**., Filingeri, D., Barnett, M., Davis, S. & Jay, O. (2016). Cold fluid ingestion extends exercise capacity of heat-sensitive individuals with MS in a warm environment. *Experimental Biology.* San Diego, CA, USA.
7. **Chaseling, G.K**., Filingeri, D., Jay, O. (2016). Heat-sensitivities in MS patients. *Science of Sport, Exercise and Physical Activity in the Tropics.* Townsville, QLD, Australia.

Other publications relating to the thesis, written during the doctoral candidature, but not formally included in the thesis

1. Filingeri, D., **Chaseling, G.K**., Hoang, P., Barnett, M., Davis, S. L., & Jay, O. (2017). Afferent thermosensory function in relapsing–remitting multiple sclerosis following exercise-induced increases in body temperature. *Experimental physiology*, *102*(8), 887-893 (Appendix A).

2. **Chaseling G.K.**, Jay, O. (August, 2018). Active Voice: In warm environments, a cold drink improves exercise tolerance of heat-sensitive multiple sclerosis patients. ACSM Sports Medicine Bulletin.

TABLE OF CONTENTS

List of Figures

Figure 5.2 Mean and error (standard deviation) for local sweat rate (LSR) of the upper back (A) and forearm (B) for the MS (grey circles) and CON (black circles). Values are pooled from the 30°C and 35°C trials for upper back (time-disease-trial interaction: P = 0.87) and forearm (time-disease-trial interaction: P = 0.12) LSR. Asterisk (*) denotes P < 0.05

Figure 5.3 Change in mean body temperature plotted against the rise in upper back (A) and forearm (B) local sweat rate (LSR). Values are pooled from the 30°C and 35°C trials for upper back (disease-trial interaction: P = 0.74) and forearm (disease-trial interaction: P = 0.72) LSR. Mean and error (standard deviation) for the time of LSR onset for the upper back (C) and forearm (D) between the MS and CON groups. Values are pooled from the 30°C and 35°C trials for upper back (disease-trial interaction: P = 0.69) and forearm (disease-trial interaction: P = 0.85) time at onset. Asterisk denotes P < 0.05

Figure 5.4 Mean and error (standard deviation) values of cutaneous vascular conductance (CVC) of the forearm (A) following 40 min of exercise expressed as a percent of baseline and time at onset for skin blood flow (B) for the forearm. Values are pooled from the 30°C and 35°C trials for CVC (disease-trial interaction: P = 0.54) and time at onset of skin blood flow (disease-trial interaction: P = 0.87)

Chapter Seven

Figure 7.1 Individual data and group means (with SD) at the end of exercise in the NEU (yellow) trial compared to the same time point in the CLD (black) trial for multiple sclerosis (MS: squares) and healthy controls (CON: circles). Values given for: Exercise time to exhaustion with a maximum of 60 min. Asterisk (*) indicates P<0.05 between the NEU and CLD trial for the MS group

Figure 7.2 Individual data and group means (with SD) at the end of exercise in the NEU (yellow) trial compared to the same time point in the CLD (black) trial for multiple sclerosis (MS: squares) and healthy controls (CON: circles). Values given for: Exercise time to exhaustion with a maximum of 60 min. Asterisk (*) indicates P<0.05

List of Tables

Chapter Two

Chapter Three

Chapter Seven

Abbreviations

Term	Abbreviation	Term	Abbreviation
Ambient Temperature	T_a	Mean arterial pressure	MAP
Analysis of variance	ANOVA	Mean body temperature	T_b
Body surface area	BSA	Mean skin temperature	T_{sk}
Central nervous system	CNS	Metabolic energy expenditure	M
Cold	CLD	Metabolic heat production	M-W
Conductive heat transfer	K	Modified fatigue impact scale	MFIS
Confidence interval	CI	Multiple sclerosis	MS
Control	CON	Neutral	NEU
Convective heat transfer	C	Oxygen consumption	VO_2
Core temperature	T_{core}	Percent oxygen consumption	$\%VO_2$
Cutaneous vascular conductance	CVC	Primary-progressive MS	PPMS
Degrees Celsius	°C	Radiative heat transfer	R
Disease modifying treatment	DMT	Rectal temperature	T_{re}
Esophageal temperature	T_{eso}	Relapsing-remitting MS	RRMS
Evaporative heat loss	E_{sk}	Relative humidity	RH
Expanded disease severity scale	EDSS	Respiratory heat loss	R_{esC+E}
External work	W	Seconds	s
Foot	Ft	Secondary-progressive MS	SPMS
Heart rate	HR	Skin blood flow	SBF
Heat production	H_{prod}	Skin wettedness	ω
Heat stored within the body	S	Standard deviation	SD
Hours	h	Students t-test	t-test
Kilograms	Kg	Tympanic temperature	T_{tym}
Local sweat rate	LSR	Whole-body sweat loss	WBSL
Maximum oxygen consumption	VO_{2max}	Years old	Y

CHAPTER I

INTRODUCTION

1.0 INTRODUCTION

Multiple sclerosis (MS) is a progressive auto-immune disease of the central nervous system (CNS) whereby demyelination of neurons results in lesions and atrophy of the brain and spinal cord. Approximately 25,000 Australians and 2.5 million people globally are living with MS [1]. Damage to myelin sheaths and neuronal connections compromises the functional integrity of the autonomic nervous system causing motor and sensory problems for all MS patients. Most commonly, people may experience fatigue [2], cognitive decline [3], loss of balance [4], blurred vision, sensory enhancement (tingling or burning) and/or loss (numbness) [5] and intolerance to the heat [6]. Indeed, up to 80% of people with MS experience heat intolerance, otherwise known as Uhthoff's phenomenon which is characterised by a temporary worsening of symptoms and concomitant fatigue during exercise or exposure to hot environments [6]. An intolerance to the heat can be quite disabling for people with MS. Alongside a temporary worsening of symptoms, MS patients also report an overall reduced capacity to perform household and/or work related tasks [2], an inability to self-care and the need for medical attention [2] when they 'feel hot'. Despite the prevalence and impact of heat intolerance, the underlying physiological mechanisms are not well understood.

Original research by Davis and Rasminsky [7,8] demonstrated the effect of changes in temperature on neuronal conduction in damaged peripheral nerves. It was hypothesised that as the temperature of a damaged nerve increased, the amplitude of an action potential decreased, at times resulting in complete conduction block. Subsequent cooling resulted in restoration of conduction and function of a nerve [8,9]. This research alluded to the idea that small rises in core temperature (0.2 to 0.5°C) for people with MS would reduce or block conduction in

demyelinated nerves, causing a temporary worsening of MS symptoms, which was reversible once core temperature returned to resting values. Notably, recent research has indicated that people with MS may be at an inherent disadvantage during exercise and/or heat exposure due to an elevated core temperature at rest which is associated with greater levels of subjective fatigue compared to healthy controls [10,11]. However, the robustness of this evidence seems questionable given that the authors deemed a resting core temperature of ~37.0°C to be elevated and more importantly, core temperature was measured using a standard off-the-shelf infrared ear thermometer in an uncontrolled environment. This topic will be addressed further in chapter 3. It is also possible that heat intolerance in people with MS is compounded by an impaired thermoregulatory capacity secondary to MS that results in greater rises in core temperature compared to healthy people. However, evidence supporting this notion is inconclusive, and no study has previously assessed the thermoregulatory capacity of people with MS during exercise in hot environments (i.e. >25°C), therefore the study detailed in chapter 4 will investigate thermoregulation during exercise in hot environments in people with MS.

In attempt to avoid critical rises in body temperature and the subsequent worsening of symptoms, MS patients often report avoiding physical activity and/or going outdoors. However, a large body of research has also demonstrated the marked benefits of regular physical activity for this population as a disease modifying therapy [12] and for improving strength and cardiorespiratory health [13,14], sleep quality, sense of worth, and reductions in central and peripheral fatigue [15]. MS health organisations and professionals often provide loose guidelines as to how MS individuals should stay cool and avoid an onset of symptoms during hot weather and/or physical activity [16]. However, these guidelines typically suggest impractical or

expensive strategies such as staying indoors from 10 am – 3 pm, avoiding the outdoors completely during hot weather [17], or wearing heavy cooling vests [18]. Furthermore, strategies such as drinking water [19] are offered without any existing evidence regarding their efficacy for mitigating heat intolerance in people with MS. Most commonly, people with MS will use air-conditioning to keep themselves cool [2,20]. Indeed, in Australia approximately 82% of people with MS use air-conditioning throughout the year and spend up to 14-times more (~$2 million annually) on air-conditioning compared to a healthy population. As such, it is evident that there is a need to identify both practical and economical evidence-based cooling strategies that can be used at home or in the work place. The study described in chapter 5 will explore the efficacy of cold fluid ingestion on exercise tolerance for heat-sensitive people with MS cycling in a hot environment.

1.2 OBJECTIVE AND HYPOTHESES

The specific objective and hypotheses governing each of the original research chapters are as follows:

Study 1: The aim of this study was to reassess the notion that resting core temperature is elevated in RRMS patients when measured using precision thermistors placed in the esophagus, rectum and tympanic membrane in a controlled, warm (30°C, 30% RH) and neutral (25°C, 30%RH) environment, compared to age-matched healthy controls. 2) To assess whether people with MS demonstrate a higher resting metabolic rate compared to healthy controls. 3) To identify whether resting rectal temperature is associated with subjective measures of fatigue in people with RRMS.

Hypotheses: 1) People with RRMS will not demonstrate an elevated resting rectal, tympanic or esophageal temperature, compared to age-matched controls. 2) Resting metabolic rate will be similar between MS and control participants. 3) No association will be observed between rectal temperature and subjective measures of fatigue.

Study 2: To assess whether people with MS demonstrate impaired thermoregulatory responses, resulting in a greater rise in core temperature while exercising in a warm (30°C, 30% RH) and hot (35°C, 30% RH), compensable environment compared to mass- and age-matched control participants

Hypothesis: Relative to control participants, people with MS will demonstrate larger rises in core temperature secondary to a blunted sweat response.

Study 3: To examine the effect of ingesting cold (1.5°C) compared to thermoneutral (37°C) water on exercise tolerance at a fixed low relative intensity (~40%VO_{2max}), and the elevation in core temperature of heat-sensitive relapsing-remitting MS participants in a warm (30°C, 30% RH) environment

Hypotheses: It is hypothesised that with thermoneutral water ingestion, exercise time will be shorter for MS compared to age- and fitness-matched control participants. It is also hypothesized that compared to thermoneutral water ingestion exercise time of MS participants will be extended with cold water ingestion due to a blunted rise in core temperature.

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CHAPTER II

REVIEW OF LITERATURE

2.0 MULTIPLE SCLEROSIS

Multiple sclerosis (MS) is an auto-immune, demyelinating disease of the central nervous system (CNS). Lesions and scars that reside on the brain and spinal cord result in progressive and chronic disability. Approximately 25,000 Australians and 2.5 million people worldwide are diagnosed with MS [1].

The degree of neurologic impairment for people with MS is guided by the expanded disability severity scale (EDSS) which assesses the functional and sensory capacity of an individual [2]. Specifically, the EDSS assesses a person's visual, pyramidal, cerebellar, sensory, ambulation, bowel and bladder dysfunction. The EDSS ranges from 1 to 10 (1: minimal disability, slight functional impairment, 5: disability can impair daily activity and the ability to walk, 7: disability impairs walking beyond 5 m and person shows dysfunction in four or more functional categories, 10: death). Parallel to disease severity are three classifications of MS (Figure 2.1) that refer to the time course and progression of the disease [3].

Relapsing-remitting MS (RRMS): Approximately 80% of people with MS are diagnosed with RRMS. This classification describes an individual who experiences a definitive relapse (a worsening of neurologic symptoms) followed by a full, or close to full recovery. The length, severity and worsening of neurologic symptoms will differ between people [3].

Secondary-progressive MS (SPMS): People with SPMS all begin with RRMS. This classification describes a person who experiences definitive relapses however their disease course can progress in the absence of a relapse, in addition to a progressively worse baseline state between relapses [3].

Primary-progressive MS (PPMS): People with PPMS will experience a gradual yet progressive decline with their disease from diagnosis without the presence of a relapse. It is possible that these people will experience temporary improvements in their progression. Only ~10% of people are diagnosed with PPMS [3].

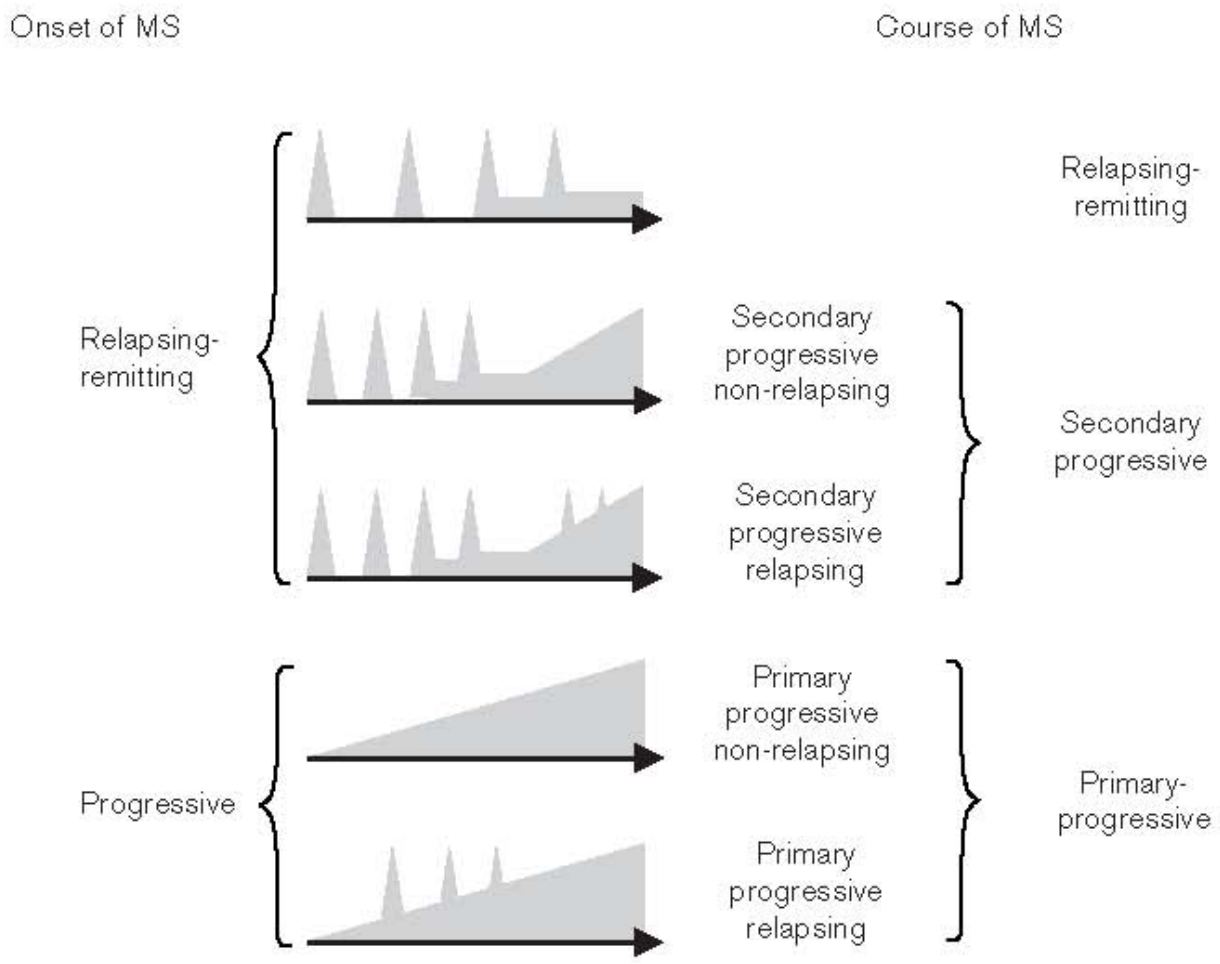

Figure 2.1. Classification and clinical course of MS. Figure taken (with permission) from Confavreux and Vukusic [4].

It is important to note that a person's EDSS score does not correlate with their disease classification. That is, a person diagnosed with RRMS can have the same EDSS as a person diagnosed with SPMS and PPMS. Albeit, due to the nature of PPMS and SPMS, a person within this disease classification is more likely to increase their EDSS score over time, compared to a person with RRMS. Within the scope of this PhD, only patients diagnosed with RRMS and an EDSS of 1-5 were recruited for our research. This was decided given the greater prevalence of people diagnosed with RRMS (>80%) and the likelihood of these individuals being more physically active.

2.0.1 Uhthoff's Phenomenon

In 1890, Wilhelm Uhthoff [5] was the first to demonstrate an intolerance to the heat for people with MS. After a bout of exercise, patients with MS developed amblyopia (lazy eye), changes in visual acuity, colour perception disturbances and leg weakness. On cessation of exercise, symptoms in all four patients slowly diminished. The term 'Uhthoff's phenomenon' is now used to describe a transient worsening of signs and symptoms in MS patients during exercise or when exposed to hot environments.

2.0.2 History of Heat Intolerance

Between 1926 and 1938, MS was thought to be a bacterial disease. As such, several attempts were made to treat MS with hyperpyrexia [6-12] while observations of patient responses were recorded. Notably, the use of diathermy (inducing high body temperatures with electrical currents) over the spinal cord demonstrated symptom improvements in 10 out of 13 patients in a study by Stephenson [6]. The same was observed by Neymann [10] who reported

symptom improvements in 11 out of 25 patients treated with electropyrexia (artificially induced fever) and endured elevated core temperatures of ~40.5°C for ~8 h. However, despite some observed benefits of inducing hyperthermia, there were also numerous reports of a severe worsening of health and death during these studies [9,10]. In 1937, Simons [13] studied the effect of hot and cold ambient temperatures (heating and cooling strategies are unknown) on symptom worsening in MS patients through the use of questionnaires. Findings from this study demonstrated the heat decreased strength for 62% of patients, and 24% experienced worsening of their spasticity. The cold had little effect on symptom worsening and in some cases, cold exposure improved strength and spasticity in ~35% of patients.

In 1950-1951[14,15] a series of studies were carried out to assess the effect of whole and partial body immersion in cold (18.8 – 22.7°C), warm (29.4- 36.6°C) and hot (40.5 – 48.8°C) water. These studies were seminal in identifying the precipitating factors that cause a worsening of symptoms for people with MS. In almost all instances, cold (18.8 – 22.7°C) and warm (29.4-36.6°C) water whole body immersion resulted in no change of neurological symptoms, only a few patients experienced discomfort with cold water immersion [14,15]. Yet, when patients were completely submerged in hot water, a reaction of local (arm and leg) and/or generalised weakness was noted, alongside dysarthria and changes in visual acuity. A worsening of neurologic symptoms was recorded in one patient after only 8 minutes of whole body immersion in hot water. Indeed, this patient, along with two others, lost complete motor control and were unable to prevent themselves from sliding completely into the bath when unsupported [15]. Notably, even when patients only submerged their arm in hot water, the same symptoms of generalised weakness, changes in visual acuity and dysarthria were recorded (Table 2.2). A

worsening of symptoms that occurred with only one arm immersed in hot water was reversed almost instantaneously when the arm was removed from the bath. What was more remarkable from these findings was the effect of arterial occlusion on symptom worsening when a single arm was placed in hot water. Indeed, occluding the submerged arm prevented any symptoms worsening, suggesting that warmed blood travelling back towards the heart and around the body may be responsible for a temporary worsening of symptoms in MS patients. Following these investigations, for the next twenty years, [16-21] all research conducted confirmed a temporary worsening of symptoms during heat exposure. Specifically, Edmund and Fog [16] reported sensory disturbances, ataxia, dysarthria, changes in visual acuity and a reduction in tendon reflexes with hot water submersion. Furthermore, in 1959, Nelson [17] established a correlation between the rise in core (oral) temperature and the onset of symptoms in MS compared to other neurologically impaired patients.

In 1971, Davis [22] investigated the potential link between an increase in ambient temperature and a decrease in axonal conductivity of a demyelinated nerve. Davis reported a decrease in the effective transmission of a signal (safety factor) of a demyelinated nerve compared to a myelinated nerve, leading to a reduction in the rate of depolarization and evoked potentials. It was noted that increases in nerve temperature as small at 0.5°C would cause a decrease in the amplitude of an action potential, and at some points, complete conduction block would occur. While important, one must cautiously interpret these findings given that observations were of damaged frog and guinea pig nerves, exposed outside of the animal's body and were not in vivo experiments performed on MS patients.

Most research conducted after 1970 focused on the effects of heat on neuro-ophthalmology for MS patients with optic neuritis [23-28]. Many patients with MS demonstrated abnormalities with visual acuity [24] alongside a decrease in visual evoked potentials [26] following acute bouts of heating. A decrease in somatosensory evoked potentials has also been reported in MS patients who exhibit signs of a fever [26] (core temperature > 39°C) and following whole body heating in a 60°C sauna [27]. It was also during this time that researchers reported the efficacy of a hot bath to diagnose MS [29]. However, this test was quickly dismissed when neurological signs that occurred due to immersion in hot water would persist for lengthy periods [30] and it became evident that symptoms that developed during hot water immersion did not return to baseline even after a patient was cooled [31].

Endeavouring to understand the cause for heat sensitivities in MS individuals, Post, et al [32] speculated that low somatostatin levels in the cerebral spinal fluid of MS patients during a relapse may be a trigger for heat-related symptoms. However in 1986, Emre [33] postulated that somatostatins could not be the cause of heat-induced symptoms given that exposure to hot environments do not cause a relapse, yet a temporary worsening of symptoms, and reduced somatostatin levels were only evident during a clinical relapse.

In 1987, Honan [34] commented that when people with MS are exposed to cold environments, an increase in metabolic heat production induced via shivering caused a worsening of symptoms in 6 out of 6 patients. Further case studies have been reported on MS patients who have died following four hours of sun exposure [35,36], and other patients who have experienced permanent worsening of their symptoms after obtaining third degree burns [37].

From the early 2000's, most research investigating heat intolerance in people with MS examined the influence of core temperature on symptom worsening [38-41] or changes in cognition [41,42]. To the best of our knowledge, there is little research that has explored the influence of tissue temperature such as skin and muscle and afferent thermal sensation on heat-related symptoms and associated fatigue. Indeed, the exact cause of symptom worsening during exercise and/or heat exposure for people with MS seems inconclusive. Although it is apparent that an increase in core temperature may play a role in symptom worsening, from the history of literature, it is also evident that people with MS can experience a transient worsening of symptoms even in the absence of increases in core temperature [17,34,43,14]

					Observations				
Immersion Conditions					**Tested Performances**				
Patients	*Time (min)*	*Temperature (°C)*	*Time until reaction to heat (min)*	*Untested subjects report of weakness*	*Decrease in grip strength*	*Decrease in leg strength*	*Decrease in Visual Acuity*	*Decrease in Dysarthria*
MS Group									
MS 1	46	45.5	18: Left*	Marked	0%	0%	Moderate	None	Moderate
MS 2	34	45.5	8: Right*	Marked	50%	25%	n/a	None	Marked
MS 3									
a)	44	44.4	20: Right*	Marked	66%	75%	Moderate	Moderate	Marked
b)	29	45	8: Left*	Marked	50%	60%	n/a	Moderate	Marked
MS 4									
a)	27	45.5	12:Left*	Marked	0%	60%	Moderate	Moderate	Marked
b)	50	44.4	10: Right*	Marked	n/a	n/a	n/a	Moderate	Moderate
MS 5	42	44.4	5: Left*	Moderate	n/a	n/a	Marked	Moderate	Moderate
Control Group									
CON 1	22	46.1	Right	None	10%	0%	n/a	None	None
CON 2	27	46.1	Right	None	0%	0%	n/a	None	None
CON 3	24	46.1	Right	None	0%	0%	n/a	None	None
CON 4	21	46.1	Right	None	0%	0%	n/a	None	None
CON 5	24	46.1	Right	None	0%	0%	n/a	None	None
CON 6	21	46.1	Right	None	0%	0%	n/a	None	None

* Indicates the arm that was immersed in hot water n/a: Not applicable

Table 2.1. Data from this table represents information recorded following single arm immersion in hot water for MS and control participants. Data represents the a) temperature of the water, b) time until symptom onset, c) subjective signs of weakness and d) other symptoms that were experienced by MS patients. This table was redrawn from Guthrie [15].

2.1 HUMAN HEAT BALANCE

At rest, the human body regulates an internal temperature of ~37.0 ± 0.5°C. Humans are continuously exposed to a changing environment, to which the body must respond to regulate internal temperature. There are six interactive parameters that influence the thermal environment to which humans respond. There are four environmental parameters; air temperature, radiant temperature, humidity and air velocity, and two personal parameters; activity and clothing properties [44]. An increase in metabolic rate produces considerable amounts of heat within the body that must be subsequently transferred to the surrounding environment to prevent overheating. When heat production (H_{prod}) exceeds heat loss, thermoregulatory effector responses will act to minimize the amount of heat that is stored within the body. The maintenance of heat balance between the body and the surrounding environment can be explained using the following equation:

$$M - W = E + R + C + K + S$$

Where: M is metabolic energy expenditure; W is external work; E is evaporative heat loss from the skin surface; R is radiative heat loss; C is convective heat loss; K is conductive heat loss and S is the heat stored within the body.

Collectively, R, C and K are considered dry heat exchange or sensible heat loss and E is evaporative heat exchange or insensible heat loss. The interaction between ambient and radiative temperature, humidity and air velocity, alongside metabolic heat production and clothing properties will, in part, influence heat loss from the body to the surrounding environment [44].

Indeed, when considering heat balance at rest, in neutral environments, dry heat transfer will adequately maintain a relatively stable body temperature [44]. However, sensible heat loss will become progressively diminished as ambient temperature becomes closer to skin temperature, thus leading to a greater reliance on skin surface evaporation for the maintenance of heat balance [45].

Radiative heat transfer (R) is the exchange of heat via electromagnetic energy between the skin and physical objects emitting/absorbing radiation within the surrounding environment. The emissivity of an object, alongside the surface area and angle of exposure to a radiative source and the temperature difference between the skin and a radiative source, all determine R [44]. Indoors, mean radiant temperature is equivalent to air temperature, permitting there are no surrounding objects that emit radiative heat. The sun is the primary source of radiative heat outdoors. However the effect of solar radiation on heat exchange depends upon the time of day, season, and cloud coverage [44].

Convective heat transfer (C) from the skin surface is directly dependent upon the temperature gradient between ambient (T_a) and skin temperature (T_{sk}) and body surface area. When air velocity is greater than ~0.2 m/s [46] forced air flow predominates, in contrast to air velocities below 0.2 m/s where self-generated airflow will primarily contribute to C. It follows that when T_a is lower than T_{sk}, there will be heat loss to the surrounding environment, but when T_a exceeds $T_{sk,}$ there will be heat gained from the environment. Furthermore, convective heat transfer may be influenced by clothing worn on an individual, however this will also depend upon posture and the insulation properties of the clothes worn [47].

Conductive (K) heat transfer occurs when the skin is in contact with another object. The rate of K is determined by the conductivity of an object, the total surface area in contact, the time spent in contact and the temperature gradient between an object and the skin surface [46,44]. Typically, K is negligible unless there is direct contact with an object, such as laying in a cold or hot bath [48], being in contact with ice blocks [25] or water perfused suits [49]. However, conductive heat exchange between the skin and the environment, particularly during exercise (e.g. when running and only the feet are in contact with the ground) is minimal in humans.

The primary avenue of heat loss during exercise in the heat is evaporation of sweat secreted onto the skin surface (E_{sk}) [45,50]. The rate of E_{sk} is determined by the partial pressure gradient of water vapour between the skin surface and ambient air (humidity). Importantly, it is the absolute, not relative humidity (RH) that determines the amount of sweat that will vaporise [51,52]. Approximately 2426 J of latent heat energy are required to vaporise 1 g of sweat [53]. Evaporative heat loss is determined using the following equation from Gagge [54].

$$E_{sk} = h_e \cdot \omega \cdot (P^{sk} - P^{a})$$

Where E_{sk} is evaporative heat loss; h_e is the evaporative heat transfer coefficient; ω is the fraction of the skin surface covered in sweat (skin wettedness); P_{sk} - P_a is the difference in the partial pressure of water vapour between the skin and ambient air.

In fixed environmental conditions, the theoretical maximum potential for evaporative heat loss (E_{max}) is the evaporative heat loss limit from a completely wet skin surface (i.e. a ω = 1) [53]. Submaximal rates of E_{sk} relative to E_{max} can be described using the concept of skin

wettedness, where the ratio of E_{sk} and E_{max} is the fraction of the skin surface that is covered in sweat that would result in E_{sk} for a given environment [53]. The amount of skin wettedness required (ω_{req}) for heat balance represents the theoretical portion of skin surface that must be covered in sweat to achieve E_{req} and is calculated as the ratio between E_{req} and $E_{max.}$ The amount of evaporation required (E_{req}) to maintain heat balance is determined by metabolic H_{prod} (M-W) and environmental (T_a) parameters. At rest or during exercise, the rate of whole body sweating is largely dependent upon absolute E_{req}, T_a and T_{sk} and heat production [55,56].

Attaining a ω of 1.00 is only possible in heat acclimated individuals [50] otherwise, it is likely without heat acclimation, a person may attain a ω of 0.85. ω is also related to sweating efficiency (the percentage of sweat that evaporates and contributes to heat loss) as such; any sweat secreted onto the skin surface that drips off the body will not provide any additional evaporative cooling. At a ω of 1.00, sweating efficiency will be ~50% [57], however a decrease is efficiency can occur at a critical ω of 0.5 to 0.7 for nude individuals and 0.2 when clothed [57].

When dry heat loss is not sufficient to offset an increase in heat production either during exercise, or passive heat exposure, then evaporative heat loss is required. An increase in air flow across the skin surface will also increase E_{max}, which means that the skin wettedness required for heat balance goes down and sweating efficiency improves (only if there are decrements in sweating efficiency in the first place). This may be particularly beneficial in hot and humid environments where an increase of air velocity that crosses the skin surface will enhance evaporative heat loss [57].

To maintain zero heat storage (S), heat produced and transferred within the body must be equalled by heat loss (E + R + C + K) to the surrounding environment. During exercise, H_{prod} is determined by metabolic energy expenditure (M) and the portion of that heat which is used to create mechanical work (W; in watts). H_{prod} will also depend on the mechanical efficiency and economy of an individual [58,59] which is defined as the portion of metabolic energy expenditure that is converted to external work and is expressed as a percentage. The rate of M is governed by the absolute rate of oxygen consumption (VO_2) and the proportion of oxygen that is used to catabolize carbohydrates and fats. M can be calculated using the following equation.

$$M = \mathrm{VO_2} \cdot \frac{\left(\left(\frac{RER-0.7}{0.3}\right).Ec\right) + \left(\left(\frac{1-RER}{0.3}\right).Ef\right)}{60} \cdot 1000\ [\mathrm{W}]$$

Where: VO_2 is the rate of oxygen consumption ($L \cdot min^{-1}$); RER is the respiratory exchange ratio defined by the ratio of carbon dioxide produced and oxygen used during metabolism; Ec and Ef are the energetic equivalents of carbohydrate (21.13 $kJ \cdot L^{-1}$ of O_2) and fat (19.62 $kJ \cdot L^{-1}$ of O_2) respectively.

At rest, metabolic heat production is ~100 W. This H_{prod} may also depend upon body composition [60], ambient conditions [61], fever [62], and circadian rhythm [63]. Diurnal changes in H_{prod} and loss due to circadian rhythms elicit changes in core temperature by up to 1°C over a 24 h sleep-wake cycle. However under varying conditions [64] small volumes of sympathetic outflow to the skin vasculature allow for changes in blood flow to adequately control S [65]. This is particularly so in thermoneutral environments where thermoregulatory responses such as sweating or shivering are not necessary to regulate S [66].

During active or passive heating, changes in T_{core} are the result of a cumulative imbalance between H_{prod} and heat loss to the environment [67]. However, individual thermoregulatory responses and the subsequent rise in core temperature are highly variable [59]. To assess population differences in thermoregulation, many researchers employ a fixed percent of maximal oxygen capacity ($\%VO_{2max}$) exercise protocol [68]. These protocols are used as it is assumed that working at a fixed % of VO_{2max} yields a similar rise in core temperature between groups, irrespective of maximal aerobic capacity [69]. However, when considering the heat balance equation, a group working at a greater $\%VO_{2max}$ would undoubtedly produce greater amounts of metabolic heat and therefore would require a greater amount of evaporation to maintain heat balance. This was recently demonstrated by Jay et al [70] who suggested that aerobic fitness should not independently alter the rise in core temperature during exercise. Indeed, when cycling at a fixed $\%VO_{2max}$, fitter individuals (~60 $ml \cdot kg^{-1} \cdot min^{-1}$) demonstrated a greater rise in rectal temperature (ΔT_{re}: 1.43°C) compared to less fit (~40 $ml \cdot kg^{-1} \cdot min^{-1}$) mass- and BSA- matched individuals (ΔT_{re}; 0.89°C), however when cycling at a fixed heat production relative to total body mass, which represents the internal heat sink of an individual ($W \cdot kg^{-1}$), irrespective of the concomitant $\%VO_{2max}$, the rise in T_{re} was similar between groups. Smoljanic et al [58] also demonstrated thermoregulatory responses were not altered by aerobic fitness for individuals running on a treadmill. Indeed, Smoljanic's research highlighted that people with a low running economy will demonstrate greater changes in T_{core} at a fixed running speed compared to highly economical runners, however when running speed was fixed to elicit a heat production relative to body mass, the rise in core temperature was similar between groups, irrespective of aerobic capacity.

More recently, work by Cramer and Jay postulated that in order to eliminate any systematic differences in the exercise-induced rise in T_{core} due to biophysical characteristics, researchers should prescribe exercise at an intensity that will elicit a fixed metabolic heat production per unit of total body mass ($W \cdot kg^{-1}$) irrespective of relative intensity [67,70,55,59]. Indeed, large differences in body mass independently alter the rise in T_{core} when exercising at an absolute work load [67]. This is explained by an inverse relationship between the change in body heat content and the subsequent rise in T_{core} with body mass [71]. As such, larger individuals are likely to have a smaller rise in T_{core} at a fixed absolute heat production compared to a smaller individual due to the variability in body mass [71,67]. Body surface area will also influence heat exchange with the environment. Rates of evaporative, convective and radiative heat exchange will be greater for people who have a higher BSA [59]. It is important to consider differences in body mass and surface area, particularly when comparing between group thermoregulatory responses to passive and or active heating. Specifically, when assessing thermoregulation between people with MS and healthy controls at rest and during exercise, controlling for morphological characteristics means that dry heat exchange and the E_{req} for heat balance should be similar between groups. As such, any differences in T_{core} and T_{sk} or sweat rates would be due to the disease itself [72].

2.1.1 Core Temperature

Core temperature may be regarded as temperature of the brain, deep tissues and blood [73]. It is difficult to obtain a direct measure of core temperature from a single point within the body. As such, there are multiple sites that researchers may use to measure and record T_{core}. The rectum, esophagus and tympanic membrane are the preferred measurement sites for thermal

physiological studies [74-78] and are the three core temperature sites that will be reported within this thesis. Rectal temperature (T_{re}) at rest, is generally higher than esophageal (T_{eso}) [79] and tympanic membrane temperature (T_{tym}) [73], which is likely due to a lower rate of blood flow to the splanchnic area, which in turn decreases the amount of internal conductive and/or convective heat exchange of this tissue region [73]. Blood supply to the rectal tissues is received from the superior rectal artery, which stems from the aortic abdominal artery from the splanchnic area [80]. In some situations, such as assessing core temperature at rest, a low thermal inertia in the rectum may be advantageous as this measurement remains relatively stable under mildly varying environmental conditions [73]. Indeed, because of its validity and accuracy, T_{re} is commonly measured in clinical [81,77] and athletic [82,74] settings for diagnosing fever and heat stroke respectively and in laboratory setting as an indication of deep tissue temperature at rest or during exercise in hot and cold environments [83,61,84].

The distal esophagus is bound by the heart and pulmonary arteries, and because it has a relatively low heat capacity, T_{eso} is finely regulated by the convective heat transfer of the blood from surrounding tissues [79,73]. Esophageal temperature is highly sensitive to changes in central blood temperature and whole-body heat storage [75] which promote the reliability of this measurement, specifically when assessing thermoeffector responses to heat exposure [85-87] and for detecting hypo- and hyper-thermia in intraoperative and postoperative adult patients [77,88,89]. Esophageal temperature may prove difficult to measure within some populations due to the discomfort it can cause. Furthermore, the placement of a sensor within the esophagus means this measurement site may not be ideal for assessing cooling interventions, such as cold fluid ingestion.

Blood to the tympanic membrane is supplied from the maxillary and posterior auricular artery, as such, T_{tym} can provide a valid indication of blood temperature entering the hypothalamus [44,90]. There are many controversies surrounding the use of the tympanic membrane as a measure of core temperature given the accuracy of this measure heavily depends upon the placement of a temperature sensor relative to the tympanic membrane, which can be influenced by the curvature of the ear canal, build-up of cerumen within the ear [91], and the temperature of the environments and skin surrounding the neck and ear [92]. The method of measuring T_{tym} may also heavily influence the accuracy and validity of this measure. Indeed, many clinicians may use an infrared ear thermometer to measure T_{tym} as it provides a quick and practical alternative of measuring core temperature. This may be problematic due to the placement of an infrared thermometer in the ear, which means a measure may give a better indication of auditory canal temperature, which is heavily influenced by T_{sk} of the face and head [93,94]. Nonetheless, if measured correctly [90], T_{tym} will provide an accurate measure of core temperature and may be useful for assessing changes in core temperature [95,96] or core temperature at rest [96].

2.1.2 Skin Temperature

Skin temperature is considered the 'shell' of the body and is critical with respect to the heat balance parameters mentioned in section 2.1. Skin temperature is also important in determining transcutaneous heat flux [97] and mean body temperature [$0.9 \times T_{core} + 0.1 \times T_{sk}$ (T_b)] which is used as a feedback signal for effector responses alongside precipitating factors such as thermal sensation and comfort [98]. Skin temperature is not uniform across the body and is therefore expressed as a weighted average. For example, Ramanathan [99] developed an

equation for mean skin temperature using four sites across the body (chest 30%, shoulder 30%, thigh 20%, and calf 20%), while Nadel [100] developed a novel approach in determining mean T_{sk} by basing regional weightings on the thermal sensitivity of each location (face 21%, cheat 21%, back 21%, abdomen 17%, thigh 15%, calf 8%, upper arm 12%, forearm 6%). The number of skin sites needed to determine T_{sk} is influenced by ambient temperature and the potential variability of skin temperature across the body. As such, in warm environments four skin temperature sites will be sufficient, in thermoneutral conditions, 8-12 sites and in cold environments, 8-12 sites [101].

2.2 AUTONOMIC THERMOREGULATION

2.2.1 Peripheral and Central Control of Temperature Regulation

Cold and warm temperature sensitive neurons (thermoreceptors) located both centrally (brain, spinal cord and viscera) and peripherally (skin and muscles) within the body, are responsible for temperature control of the body [102]. Thermoreceptors provide afferent information regarding changes to the body's thermal status, which trigger effector responses that activate the autonomic processes of temperature control [102-104]. The preoptic area of the hypothalamus acts as the control centre control for heat production (posterior preoptic area) and heat loss (anterior preoptic area) mechanisms [66]. Furthermore, thermoreceptors embedded within the epidermis and dermis layers of the skin provide afferent signaling for autonomic, as well as behavioural thermoregulation [103].

At rest, or during exercise, a combination of afferent signals from both peripheral and central thermoreceptors serve to maintain T_{core} and are responsible for efferent outputs such as

the onset and thermosensitivity of sweating [66,105] and vasodilation [106,107]. Typically, the rise in T_{core} dictates the onset of an efferent response and peripheral input (T_{sk}) governs the slope (sensitivity) of that efferent response [108,109]. The relative contributions of central and peripheral input for heat loss are 9:1 [109,97,110] in hot/warm conditions, meaning that a 1°C change in T_{core} will elicit and efferent response 9 times greater than a 1°C change in T_{sk}. However the onset and slope of efferent output may be altered by physical training [111], heat acclimation [112], baroreceptor unloading [113] and dehydration [86].

In absence of a rise in core temperature, deviations in T_{sk} can contribute to the regulation of efferent responses [97]. For example when sitting in a hot room or at the beginning or exercise, there is a is an initiation of sweating due to a rise in T_{sk} in absence of a change in T_{core} [100,105]. However, even without a detectable change in T_{core} and T_{sk}, Van Beaumont [114] observed sweating within 1.5 to 2 seconds of the onset of exercise, which was also observed by Gisolfi [115] in 1970. It was hypothesised that a non-thermal neural activation of sweating predominates at the beginning of exercise, however as work or heat exposure continues, sweating will be controlled by thermal factors such as mean body temperature [116].

Traditionally, it follows that thermal homeostasis is maintained around a single set core temperature point, and minor deviations away from this set point will elicit an efferent response [117]. However it is more likely that peripheral and central thermoreceptors provide integrated feedback regarding body heat storage and activate an efferent response relative to the rate of heat storage [66,64]. Lastly, it is possible that afferent and/or efferent signalling is compromised for those individuals who demonstrate damage within the central nervous system. Indeed, for people with MS, it is possible that slowing or complete block of neuronal signals due to an increase in

body temperature will affect afferent input and/or efferent output, thereby compromising one's ability to regulate body temperature [22,118]. This topic will be discussed later within the thesis.

2.2.3 Skin Blood flow

Regulation of cutaneous circulation is essential to sustain heat balance at rest and during exposure to hot and cold environments. Skin blood flow is controlled by sympathetic adrenergic vasoconstrictor and sympathetic vasodilator nerves which innervate nonglabrous skin. This is in comparison to glabrous skin, defined as skin of the palms, soles and lips which is only innervated by sympathetic vasoconstrictor nerves [119-122]. In brief, sympathetic vasoconstrictor nerves release norepinephrine to interact with cutaneous arterioles and alter the dilation of blood vessels. At rest, in thermoneutral environments, the vasoconstrictor system is active [122,106] and small amounts of sympathetic outflow to the skin vasculature allow for changes in blood flow to adequately control body temperature [65]. Cutaneous blood flows at ~250 $ml \cdot min^{-1}$ contributing to approximately 100 W of heat loss, equal to metabolic heat production at rest [122].

During exercise, increases in T_{core} and T_{sk} elicit a central response to activate vasodilation. This active vasodilation is responsible for 80-90% of blood that is redirected to the skin surface [119]. Redistribution of blood allows for convective heat transfer from the core to skeletal muscles and then T_{sk} for heat exchange to surrounding environment [123]. The transfer of heat from the body's core to the skin is dependent upon the T_{core} to T_{sk} gradient and the rate of skin blood flow which is dependent upon vascular resistance [106]. Independently of changes in T_{core}, the degree of active vasodilation depends on the temperature of the skin [119,123,124].

Indeed, when T_{sk} is cool (~30°C) the active vasodilator response to rises in T_{core} will be supressed [124]. On the other hand, when T_{sk} is high (~37°C) the cutaneous vasculature should be completely dilated.

During exercise, with an increase in metabolic heat production, there becomes a competitive demand between blood that is directed towards the cutaneous vasculature and oxygen supply to the working muscles. Cutaneous sympathetic vasoconstrictor and vasodilator output contribute to baroreflex control of blood pressure, which is particularly important during prolonged exercise and/or heat stress [122]. Vasoconstriction of other areas such as the splanchnic region, is paralleled with increases in cardiac output, allowing for adequate redistribution of blood to the vasculature of the skin and working muscles [122]. However, with the need for adequate circulation of blood around the body, it is possible that cardiac demands will lead to orthostatic intolerance and syncope particularly in hot environments [125].

A change in vasomotor tone can also occur via local heating and cooling [106, 122]. Indeed, an initial spike in skin blood flow from a warm local stimulus is driven by neural mechanisms, namely C-afferent fibers that stimulate neuro-transmitters to act upon the smooth muscle [106, 122]. Following this initial spike, there is a complex integration of both neural and non-neural factors that control skin blood flow with local heating [106]. An in-depth overview of the chemical messengers that contribute to vasodilation of local heating will not be discussed within this thesis, however this information can be found in a Comprehensive Physiology review by Johnson et al [106].

2.2.3 Sweating

Humans have two types of sweat glands, apocrine and eccrine. Apocrine sweat glands are primarily located on the palmar, plantar, axilla, forehead and pubic regions of the body [126]. Sweat produce from apocrine glands is primarily activated by a psychological stimulus. Eccrine sweat glands reside across the entire body and are primarily responsible for producing sweat for body temperature regulation during exercise and/or exposure to hot environments [127]. The distribution, density and secretory activity of eccrine sweat glands across the body varies considerably [128,129].

Sweating is controlled by the integration of central and peripheral input. An input stimulus sends efferent information down cholinergic sympathetic neurons to the secretory cells of eccrine sweat glands. Once this process occurs, acetylcholine is released to stimulate sweating [127]. Within the sweat gland, a hypotonic solution is formed via active reabsorption of sodium and chloride which eventually reaches the skin surface [130].

The initial onset of sweating is due to the activation of sweat glands, and the rate of sweat production is the result of increased sweat output per active gland [131]. Early reports by Benzinger [132] demonstrated an increased sweat rate during steady state exercise was almost proportional to increases in T_{tym} and T_{sk}. These findings were later confirmed by Nielson et al [133] and Nadel [108] who demonstrated a correlation between a rise in T_b and the onset of sweating. While it is evident that T_b regulates sweating via central mechanisms, research has also demonstrated the influence of peripheral and visceral thermoreceptors to independently modulate local and/or whole-body sweating rate independently of T_{core} [134-136]. Bothorel [134]

demonstrated a reduction in sweat rate across the entire body when T_{sk} on the right, but not the left thigh was decreased. Furthermore, Van Beaumont [136] reported differences in sweat gland output on the forearm with different local T_{sk}, but a constant T_{re}. Lastly, Morris et al [83] demonstrated the influence of thermoreceptors that reside in the gut to increase or decrease sweat output with 1.5°C and 50.0°C water ingestion, independently of any changes in T_{core} or T_{sk}. In all instances, deviations in sweating rate occurred almost immediately following the application of a cold or hot stimulus. It therefore appears that activation of local thermoreceptors considerably contributes to thermoregulatory control independently of core and skin temperature.

From a thermoregulatory perspective, sweat production, and the subsequent evaporation of sweat must be adequate to compensate for H_{prod} during exercise. With diseases such as MS, sweat production during exercise may be blunted due to autonomic dysfunction of the sudomotor system, potentially eliciting a greater rise in core temperature. This topic will be discussed in the next section.

2.3 THERMOREGULATION IN MS

2.3.1 Thermoregulation During Rest in Normothermic Environments

At rest, T_{core} remains around ~37.0°C however, throughout a 24 h sleep-wake cycle, T_{core} can change by up ±0.5°C [63] with the highest T_{core} occurring in the afternoon and the lowest T_{core} occurring in the morning. In people with MS, some studies have observed changes in visual acuity associated with the circadian phase changes in body temperature [19,137]. Namerow [19], identified a worsening of visual acuity in an MS patient with optic neuritis in the afternoon (Oral temperature: ~37.0°C) compared to the morning (oral temperature: ~36.0°C) which was also

observed by Romani [137]. Research has also demonstrated greater levels of subjective fatigue in the afternoon and evening compared to the morning in MS patients [138,139], however no direct relationship between fatigue and circadian rhythm has been established.

More recently, it has been suggested that individuals with relapsing-remitting (RRMS) but not secondary-progressive MS (SPMS), present with an elevated core temperature (~37.0°C) at rest (Figure 2.2), compared to healthy controls (36.8°C) and this elevated core temperature is associated with greater levels of subjective fatigue [140,141]. Irrespective of changes in T_{core} due to circadian rhythm, the mechanisms explaining an elevated T_{core} at rest in MS patients, particularly in normothermic environments, remain unclear. The authors of this research postulated that an elevated T_{core} in RRMS patients compared to patients with progressive forms of the disease (secondary- and primary-progressive), was attributed to inflammation within the CNS, akin to inflammatory induced fever [142] in healthy populations. Problematically if MS related inflammation was to elevate T_{core}, akin to the mechanisms of a fever, clinical manifestations such as an increased basal metabolic rate and cutaneous vasoconstriction [62,143] would also be evident. Nonetheless, there have been no reports of resting vasomotor dysfunction [144] or abnormal basal metabolic rates [145] in association with a core temperature of ~37.0°C in MS patients. Moreover, the robustness of these findings are questionable considering the authors deemed a resting T_{core} of ~37.0°C to be "elevated", and furthermore, core temperature was recorded using a standard, off-the-shelf infrared ear thermometer in an uncontrolled environment at apparently random times during the day [140,141]. As such, it is unclear whether T_{core} is truly elevated in RRMS patients and whether subjective fatigue is associated with resting T_{core}.

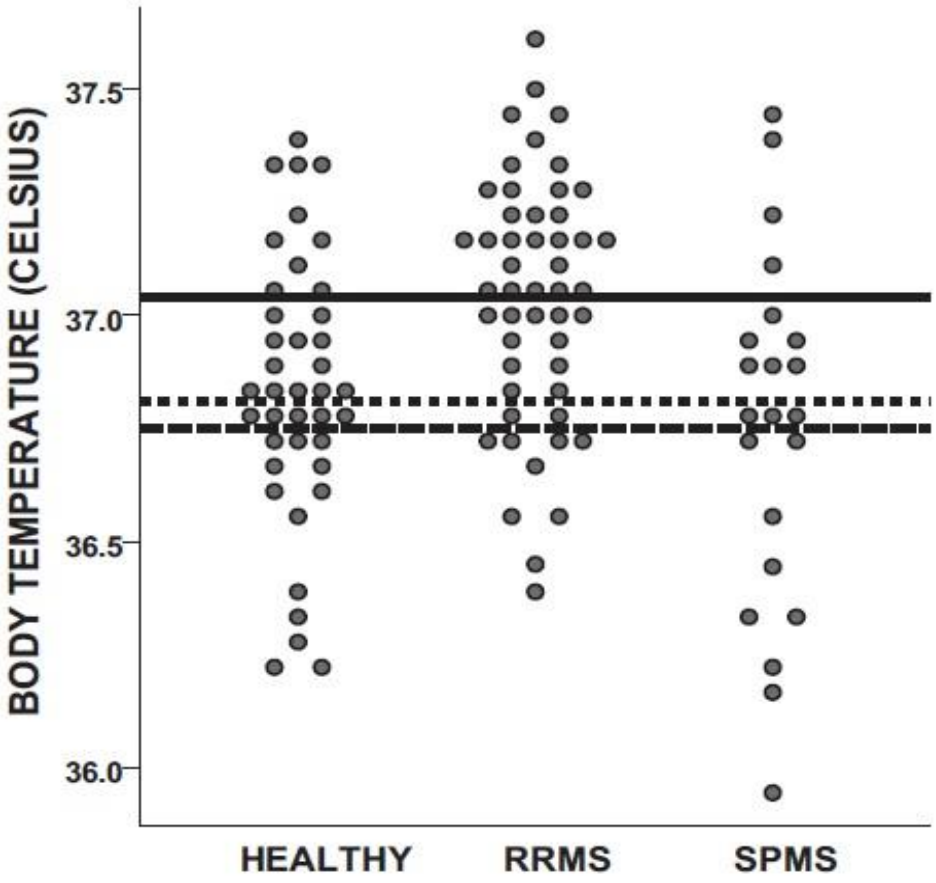

Figure 2.2 Body temperatures in healthy persons, patients with RRMS, and patients with SPMS. Lines indicate the mean body temperature for healthy controls (dotted), patients with RRMS (solid), and patients with SPMS (dashed). Figure taken (with permission) from Sumowski et al [140].

2.3.1 Thermoregulation During Active and Passive Heating

To date, few studies have assessed the integration of central and peripheral control of temperature regulation in people with MS during active and/or passive heating. In 1968, Noronha [146] reported qualitative evidence of sudomotor dysfunction in people with MS during a bout of passive heating. Whole body sweat output was assessed using quinizarin powder, a grey powder that covers the body and turns black when in contact with sweat. Regional differences in sweat production were observed in 25 out of 60 MS patients. Using the same

quinizarin powder test, Vas [147] in 1969 reported abnormal, or an absence of sweating in 13 out of 37 men and Cartlidge [148] in 1972, who reported abnormal sweating in 20 out of 50 males who were passively heated. All these studies [146-148] commented that the degree of sweating abnormalities/absence was correlated with a greater disease severity. However, during bouts of passive heating, no studies reported symptom worsening or abnormal rises in core temperature.

Further work by Noronha [146] investigated the use of a cholinergic agonist agent on sweat output for MS patients who previously demonstrated abnormal/absence sweating. There was an increase in sweat output for patients who showed abnormal sweating but not in those patients who had a complete absence of sweating. Similarly, Davis et al [149] concluded that a blunted sweating response observed in MS patients was the result of impaired sweat gland activation and not sweat output of activated glands. Furthermore, Allen et al [144] investigated the sudomotor response to passive heating in a 48°C water perfused suit and reported that the average sweat rate in people with MS was 0.17 $mg \cdot cm^{-2} \cdot min^{-1}$ lower compared to healthy controls for the same rise in core temperature (0.8°C).

Despite a blunted sudomotor response, people with MS demonstrate normal vasomotor responses to passive heating. Cartlidge [148] reported normal vasomotor responses in MS patients despite a blunted sudomotor response to passive heating. Allen et al [144] also observed that a blunted sudomotor response to whole body passive heating was not paralleled with blunted vasomotor activity. Anderson et al [150] reported both central and peripheral mediated sympathetic vasomotor reflex responses were normal in MS patients compared to non-MS patients, despite observations of sudomotor dysfunction. Anderson and Cartlidge both postulated

that sudomotor and vasomotor pathways must be controlled somewhat separately for these differences to occur.

Problematically, research investigating sudomotor function in people with MS has yet to identify whether a blunted sweat response is large enough to elicit greater rises in core temperature, specifically in a non-encapsulated environment [139,140]. Furthermore, it is currently unknown whether heat sensitivities occur by virtue of a blunted sweat response that cause people with MS to get hotter during exercise and/or exposure to hot environments. It is well established that exercise is an integral component of symptom management and well-being for people with MS [151], however, many people with MS do not partake in regular physical activity due to their intolerance to the heat. As such, it is evident that research is needed to identify whether autonomic dysfunction impairs central and peripheral control on temperature regulation to the point that it is contributing factor to the development of Uhthoff's phenomenon.

2.4 COOLING STRATEGIES IN MS

In 1959, Watson [152] demonstrated the effects of cold air or water immersion on symptom improvement in people with MS. Even without an increase in body temperature, 8 patients demonstrated improvements with vision, spasticity and weakness with decreases in body temperature of 0.34 to 1.2°C. Notably, cold water immersion had no effect on symptom improvement for those patients who demonstrated no decrease in body temperature [152]. Capello [153] studied the effects of a 'cooling program' on symptom improvement for MS patients. The program involved 2 × 45-minute bouts of cooling (temperature unknown), every day for one month. MS patients improved their disability status (EDSS) following a month of

persistent cooling, and psychological benefits following one day's worth of cooling was also noted. The authors hypothesised that the benefits of cooling arose from an improvement in the safety factor (effective transmission of a signal) of neural conductivity and increases in the amplitude of evoked potentials. This idea was further investigated by Robinson et al [154] who reported that cooling did not change or improve somatosensory evoked potential in MS compared to healthy control participants following a bout of cooling using an ice vest. In 2000, White el at [48] assessed the effects of 30 min lower limb cooling (16°C) on fatigue and gait following 40 minutes of exercise. Immediately following exercise, fatigue was lower and time to walk 25 ft was reduced compared to an exercise bout where patients were not pre-cooled. However, the transient effects of cooling were observed 30 minutes following cessation of exercise when both fatigue and gait had returned to baseline values in both the pre-cooling and no-cooling trials.

Research investigating the effects of cooling on symptom improvement in MS patients has been done so in the absence of prior increases in body temperature [18,152,153,155,156]. Beenakker [38] investigated the effects of a power charged head-neck cooling vest on self-reported fatigue, postural sway and muscle strength. Following three hours of cooling, improvements in subjective fatigue, postural sway and muscle strength without a reduction in tympanic membrane temperature were reported. However, the clinical significance of these results may be somewhat overshadowed given it took 3 h to achieve any noticeable difference in the measures reported. Grahn et al [157] in 2007 demonstrated the efficacy of cooling one hand in a 18-22°C glove on exercise time in heat-sensitive MS patients. Hand cooling elicit a ~30% increase in time spent walking on a treadmill compared to no hand cooling. No measure of T_{core}

or T_{sk} were reported, however the authors suggested that heat loss via conduction allowed the body to reduce T_{core} and subsequently improve performance. In this study, participants were walking on the treadmill at a speed of 0.8 to 4.8 $km \cdot h^{-1}$ at a slope ranging between 0 – 8 %. Because T_{core} or T_{sk} was not measured, it is unclear whether conductive heat loss in the cooled hand was sufficient to offset heat production during exercise for the MS participants, and it is likely that a local vasoconstriction would have minimized net conductive heat loss over a relatively small absolute surface area. Meyer-Heim [156] also reported an improvement in subjective fatigue and a decreased time to walk 25 ft. (by 4 s) in MS patients cooled with a 4°C garment wrapped around the left and right thigh, while resting in a 23°C room. While skin temperature measured underneath the cooling garment undoubtedly decreased during cooling, both tympanic membrane and skin temperature measured outside of the cooling garment did not decrease following 1 h of cooling. These findings further highlight that a) improvements in fatigue and nominated symptoms seem to occur in the absence of any notable physiological changes, and b) the clinical significance of these findings is questionable given that it took a minimum of 1 h of cooling to elicit a ~4 second decrease in a 25 ft. walk test. Conversely, Gossman [42] reported no change in cognitive fatigue and cognition in MS patients cooled via a 13°C water perfused vest resting in a 23°C room. The authors from this study hypothesised that no improvements in fatigue were observed due to the specificity of the fatigue (cognitive fatigue only as opposed to physical) that was being study.

Within this literature, it has become evident that in the absence of a rise in T_{core} and T_{sk}, MS symptoms and associated fatigue may transiently improve with the application of a cooling strategy, although the mechanisms that explain this improvement seem to be unclear.

Traditionally, the onset of heat-related symptoms and associated fatigue arise during exercise or when exposed to hot environments, however, few studies have investigated the efficacy of cooling strategies with heat exposure or during exercise to prevent the onset of symptoms for people with MS. As such, it is evident that further research is needed to establish evidence based practical and economical cooling strategies that can be used by people with MS.

Globally, MS organisations and researchers [158] suggest MS patients keep cool by 1) staying hydrated [159-161], 2) wearing cooling vests [159,162,161], 3) using air-conditioning [159,162,161,160], pre-cooling (before exercise) [163] or staying indoors [163,161]. However, evidence to support the efficacy of these cooling interventions is dubious and it is unknown whether cooling strategies such as wearing an ice vest or staying hydrated mitigate the onset of symptoms that heat-sensitive MS patients experience during exercise or when exposed to warm environments.

A popular strategy used to alleviate the compounding effects of heat-related fatigue in healthy populations, particularly during exercise, is the ingestion of cold fluid. Indeed, Lee et al [164] demonstrated a ~23% increase in time to exhaustion with cold fluid (4°C) ingestion prior to and during a bout of cycling in a hot (35°C) environment. Furthermore, Mündel et al [165] and Trong et al [166] also demonstrated an increase in exercise capacity with cold fluid ingestion compared to warm fluid ingestion during a bout of exercise in the heat. The efficacy of cold fluid ingestion on exercise tolerance has not been investigated for people with MS. As such, Chapter 5 of this thesis will investigate the influence of cold fluid ingestion of exercise capacity in heat-sensitive MS individuals exercising in a hot environment.

2.5 CONCLUSION

The history of literature investigating heat intolerance of people with MS extends beyond the scope of this thesis. While it is evident that being intolerant to the heat is problematic for people with MS, the underlying mechanisms responsible are still not well understood. From an autonomic thermoregulatory control perspective, there is a need to understand whether a) people with MS demonstrate elevated metabolic rates and core temperature at rest in thermoneutral environments and b) whether autonomic impairments are large enough to result in meaningfully greater rises in core temperature to the extent that thermoregulatory impairments may be at least partly responsible for heat intolerance in MS patients during exercise in hot environments. It is also evident that there is a need to identify practical and economical cooling strategies that can be used at home and/or work that can assist in symptom management, but more importantly investigate the efficacy of cooling strategies to improve exercise tolerance of people with MS in the heat.

The overall purpose of this thesis was to a) investigate thermoregulatory responses in heat sensitive people with MS at rest (study 1) and during exercise (study 2) in a thermoneutral and hot environment and b) identify a practical and simple cooling strategy to improve exercise tolerance for heat sensitive individuals during exercise in the heat (study 3). Specifically, this thesis sought to determine whether resting core temperature and metabolic is elevated in people with MS, compared to healthy controls in temperate and hot environments. Furthermore, to assess whether an elevated core temperature at rest is associated with greater levels of subjective fatigue thereby placing people with MS at an inherent disadvantage during exercise or exposure to hot environments. Secondly, mechanistically investigate whether autonomic

thermoregulatory responses such as sweating, and vasodilation are independently impaired in people with relapsing-remitting MS while cycling in a hot environment. Finally, this thesis will investigate the efficacy of cold fluid ingestion on exercise tolerance for people with MS while cycling in hot environments.

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CHAPTER III

STUDY 1: CORE TEMPERATURE IS NOT ELEVATED AT REST IN PEOPLE WITH RELAPSING-REMITTING MULTIPLE SCLEROSIS

Core temperature is not elevated at rest in people with relapsing-remitting multiple sclerosis

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Author contributions: GC and OJ conceived and designed experiments; GC and DA performed experiments; GC analyzed data; GC and OJ interpreted data; GC drafted manuscript; GC, SLD and OJ. edited/revised manuscript; GC, DA, SLD, SV, MB and OJ approved final draft of manuscript. MB and SV recruited participants for this study (Appendix A).

Abstract

Purpose: To reassess the notion that people with multiple sclerosis (MS) do not demonstrate an elevated resting core temperature when measured using best-practice precision thermometry.

Method: Across two international data collection sites (Sydney and Dallas), twenty-eight relapsing-remitting MS patients and 27 aged-matched controls (CON) were exposed to either 30°C, 30% relative humidity (RH) (Sydney) or 25°C, 30%RH (Dallas) environments. Resting rectal (T_{re}) and esophageal (T_{eso}) temperature and resting metabolic rate was measured in MS (n=28) and CON (n=27) groups who completed the 25°C and 30°C trials. Tympanic membrane (T_{tym}) temperature was measured in MS (n=16) and CON (n=15) groups in the 30°C condition. A modified fatigue impact scale (MFIS) questionnaire was used to assess psychosocial, physical and cognitive fatigue in the 30°C condition.

Results: Irrespective of ambient temperature, no group differences were observed for T_{re} (MS: 37.07±0.30°C; CON: 37.18±0.30°C; P=0.29), T_{eso} (MS: 36.84±0.42°C; CON: 36.92±0.29°C; P=0.36) or resting VO_2 (MS: 3.89±0.18 ml·kg^{-1}·min^{-1}; CON: 3.98±0.17 ml·kg^{-1}·min^{-1}; P=0.67). Similarly, no group differences were observed for T_{tym} (MS: 36.52±0.38°C; CON: 36.61±0.33°C; P=0.55) in the 30°C condition. Resting T_{re} did not correlate with subjective measures of fatigue: physical: r= -0.11, P=0.67; cognitive: r= -0.14, P=0.60; and psychosocial: r=0.05, P=0.84.

Conclusion: Contrary to recent reports, resting core temperature and metabolic rate is not elevated in relapsing-remitting MS patients compared to healthy controls when measured using precision thermometry. Furthermore, no association was observed between resting T_{re} and any subjective measures of fatigue in a subset of participants with MS.

Keywords: Body temperature, Uhthoff's phenomenon, Fatigue, Heat sensitivity

Introduction

It is well established that people with multiple sclerosis (MS) experience *Uhthoff's phenomenon*, which is characterised by a transient worsening of symptoms with physical activity and/or exposure to hot environments [1]. Symptom severity is often different for each individual but in most instances, is accompanied by a rapid onset of fatigue [2]. While heat-related fatigue affects up to 90% of people living with MS [2], the underlying physiological mechanism is not well understood [3].

Seminal work by Davis [4] established a potential link between a relatively small rise in core body temperature (~0.2 to 0.5°C) and the concomitant onset of heat-related fatigue in people with MS. Nonetheless, two recent studies [5,6] reported that people with relapsing-remitting but not secondary-progressive demonstrate a slightly higher resting core temperature (~37.0°C) compared to healthy control subjects (~36.8°C), and that this *higher* resting core temperature was associated with greater subjective measures of fatigue. In both of these studies [5,6], core temperature was measured in the auditory canal via infrared thermometry using a standard off-the-shelf measurement unit, and in an uncontrolled environment. Yet, it is well established in the thermal physiological literature that core temperature measurements using this device do not agree well with more reliable measurements of core temperature assessed with precision thermistors placed in the esophagus or rectum [7-11]. When measuring core temperature using infrared ear thermometry, the 95% limits of agreement exceed those limits deemed acceptable (±0.3°C) for clinical practice [12,13]. Indeed, compared to pulmonary artery temperature (+0.45°C [95% CIs: -0.29 to +1.13°C]) and rectal temperature (+0.07°C [95% CIs: -0.66 to +0.79°C)] infrared ear thermometry performs poorly [9]. Infrared ear thermometry even

fails to detect fever as defined by rectal temperature in four out of ten adults [11,14]. Notwithstanding these methodological concerns, from a physiological perspective it is challengeable that 1) a resting core temperature of ~37.0°C, which lays comfortably within the normal resting limits of internal body temperature [15], can be considered "elevated"; and 2) that a difference in resting core temperature of <0.2°C between population groups could be considered physiologically significant to the extent that it may be sufficient to induce fatigue in MS patients. The latter point is especially so given that core temperature can change by up to 1.0˚C over a 24-h sleep-wake cycle [16].

The physiological mechanisms explaining any potential elevated core temperature in MS patients are not clear. Elevated resting core temperature in only relapsing-remitting MS patients have also been attributed [5,6] to a greater prevalence of systemic inflammation during this stage of the disease compared to those patients with secondary and primary-progressive MS [17]. It has been argued [5,6] that the core temperature set point in MS patients is elevated due to systemic inflammation in the central nervous system, akin to inflammatory induced fever [18] in healthy populations. However, it is well documented that fever is an *acute* inflammatory response to cell injury in the brain [19] and is associated with clinical manifestations such as an increased basal metabolic rate and cutaneous vasoconstriction [20,21]. To the best of our knowledge, there have been no reports of resting vasomotor dysfunction [22] or abnormal basal metabolic rates [23] in association with a core temperature of ~37.0°C in MS patients.

Taken together, the aims of the current study were to test the following hypotheses: a) people with relapsing-remitting MS do not demonstrate an elevated resting core temperature when measured using precision thermistors placed in the esophagus, rectum and tympanic

membrane in a controlled, temperate (25°C, 30%RH) and warm (30°C, 30% RH) environment compared to age and mass-matched healthy controls; b) people with relapsing-remitting MS do not demonstrate a higher resting metabolic rate compared to age and mass-matched healthy controls; and c) there is no association between resting core temperature and subjective measures of fatigue in people with relapsing-remitting MS.

Methods

Approval for this study was attained from the Human Research Ethics Committees at the University of Sydney (AUS) and Southern Methodist University (USA). All participants provided informed consent prior to their involvement in the study. A total of 28 relapsing-remitting MS (MS) patients and 27 age- and mass-matched controls (CON) were recruited for this study. Sixteen MS and 15 CON participants completed trials in a climate-controlled chamber regulated at 30°C, 30% relative humidity (RH) at the Thermal Ergonomics Laboratory, University of Sydney, New South Wales; while 12 MS and 12 CON subjects completed their trial in a climate-controlled chamber regulated at 25°C, 30% RH at the Integrative Physiology Laboratory, Southern Methodist University, Dallas, TX. To ensure the no influence of the ambient environment on resting core temperature, two different environmental temperatures were tested. These ambient temperatures were chosen as they define the 'thermoneutral zone', where body temperature regulation at rest will occur in the absence of sweating [24].The study protocol was standardised between laboratories and all measurement tools used were identical. All testing was performed between 8:00 am and 1:00 pm to avoid potential effects of circadian rhythm. All participants avoided the consumption of alcohol and caffeine ~12 h prior and did not partake in any exercise ~24 h prior to participating in the study. All participants were non-

smokers and free of any cardiovascular and/or metabolic diseases. Prior to any measurements being recorded, participants were asked to sit quietly for 30 minutes in the climatic chamber to ensure a steady-state core temperature was reached. Following this, data was recorded for 15 minutes and the last minute of rest was used for data analysis. Core temperature values were deemed stable when they did not change by ±0.05°C within a five minute period. Participant characteristics are detailed in Table 3.1.

Instrumentation

Thermometry: Rectal (T_{re}), esophageal (T_{eso}), and tympanic membrane (T_{tym}) temperature was measured using general-purpose paediatric thermistors (TM400, Covidien, Mansfield, Massachusetts, USA). For measures of T_{re} the thermistor was self-inserted to a depth of ~15 cm past the anal sphincter [25]. For measures of T_{eso}, the thermistor was inserted to a depth of 40 cm through the left or right nostril, estimated to be at the level of the area bound by the left ventricle [26]. T_{re} and T_{eso} measurements were performed in both the 25°C, 30% RH (USA) and 30°C, 30% RH conditions (AUS). T_{tym} was only measured in the 30°C, 30% RH condition (AUS). For measures of T_{tym}, the thermistor was covered with a cotton tip, placed in the aural canal until resting near the tympanic membrane and then insulated with cotton wool and ear defenders [27]. T_{tym} was deemed acceptable if the temperature was greater than ~36.4°C and/or within 0.2°C of T_{eso} [27]. All temperature measurement methods employed follow standard procedures acknowledged internationally as best practice in the field of thermal physiology [28,25,27,29].

Resting metabolic rate: Breath-by-breath resting oxygen consumption was measured via a metabolic cart (Quark CPET, Cosmed, Asia Pacific PTY, Sydney, Australia) [28,30] . Resting metabolic rate (RMR) was calculated using the following equation [28]:

$$\text{RMR} = \text{VO}_2 \cdot \left(\left(\frac{RER - 0.7}{0.3} \right) \cdot Ec \right) + \left(\left(\frac{1 - RER}{0.3} \right) \cdot Ef \right) \text{[kJ·min}^{-1}\text{]}$$

Where: VO_2 is the rate of oxygen consumption ($L \cdot min^{-1}$); RER is the respiratory exchange ratio; Ec and Ef are the energetic equivalents of carbohydrate (21.13 $kJ \cdot L^{-1}$ of O_2) and fat (19.62 $kJ \cdot L^{-1}$ of O_2), respectively.

Fatigue Questionnaire

The modified fatigue impact scale (MFIS) is a multidimensional scale consisting of 21 questions that require an answer ranging from 0 (never) to 4 (almost always) [31]. The MFIS covers questions of trait fatigue that pertain to physical, cognitive and psychosocial domains. The total time required to complete this questionnaire was ~10 minutes. Fatigue scores were calculated separately for each domain; physical (out of 36), cognitive (out of 40) and psychosocial (out of 8) where a low score was indicative of marginal fatigue and a high score indicated extreme fatigue [31]. Participants who attended the 30°C trials only completed the MFIS. The MFIS questionnaire was completed on the day of a participants' trial.

Statistical analysis

All data are expressed as the mean and SD (±). A two-way ANOVA employing a non-repeated factor of condition (two levels: 25°C and 30°C) and a non-repeated factor of disease (two levels: MS and CON) was used to analyse measures of T_{re}, T_{eso}, resting metabolic rate, RER

and oxygen consumption. Measures of T_{tym} were compared between MS and CON groups in the 30°C condition only, using a two-tailed independent sample t-test employing an α of 0.05. The association between resting T_{re} and fatigue in the 30°C, 30% RH condition were assessed within each domain (physical, cognitive and physcosocial) using a Pearson Correlation Coefficient test. All statistical analyses were performed using GraphPad Prism (v7.0, LA Jolla, CA, USA).

Results

Participant characteristics

Participant characteristics are presented in Table 3.1. All people with MS were diagnosed with relapsing-remitting MS with an EDSS of 2.9 ± 0.9 (range: 2 – 5) and a disease duration of 11.2 ± 10.4 y (range: 2 – 37 y). Disease modifying treatments (DMT) used by MS participants in this study are as follows: Tysabri (natalizumab), *n* = 7; Copaxone (glatiramer acetate), *n* = 4; Avonex (interferon beta-1a), *n* = 4; Gilenya (fingolimod), *n* =1; Tecfidera (dimethyl fumarate), *n* = 3; Lemtrada (alemtuzumab), *n* = 1; Fampridine (fampyra), *n* = 1; no DMT reported, *n* = 7. All data was collected between the hours of 8:00am and 1:00pm and there was no difference in the time at which data was collected between the MS and CON participants (P = 0.52).

Table 3.1. Participant characteristics

Group	Sex	Age (y)	Weight (kg)	Height (m)	BSA (m^2)
30°C Trial					
RRMS (*n*=16)	7 M/9 F	47 ± 11	77.6 ± 14.0	1.7 ± 0.1	1.9 ± 0.2
CON (*n*=15)	7 M/8 F	43 ± 10	78.0 ± 17.0	1.7 ± 0.1	1.9 ± 0.2
P value		0.26	0.93	0.91	0.88
25°C Trial					
RRMS (*n*=12)	3 M/9 F	39 ± 9	78.3 ± 14.2	1.8 ± 0.1	1.9 ± 0.2
CON (*n*=12)	3 M/9 F	36 ± 12	76.1 ± 15.6	1.7 ± 0.1	1.9 ± 0.3
P value		0.47	0.73	0.74	0.71

Core temperature

No differences were observed in resting T_{re} (MS: 37.07 ± 0.30°C, *n* = 28; CON: 37.18 ± 0.30°C, *n* = 27; P = 0.29; Figure 3.1A) or resting T_{eso} (MS: 36.84 ± 0.42°C, *n* = 19; CON: 36.92 ± 0.29°C, *n* = 18; P = 0.36; Figure 3.1B) between groups irrespective of ambient temperature (Trial × Disease interaction: P = 0.28 (T_{re}); P = 0.52 (T_{eso})). Moreover, no differences were observed for resting T_{tym} (MS: 36.52 ± 0.38°C, *n* = 15; CON: 36.61 ± 0.33°C, *n* = 15; P = 0.55) between groups in the 30°C condition (Figure 3.1C).

Metabolic rate

Irrespective of ambient temperature, no differences were observed (P = 0.67) between the MS (3.89 ± 0.18 $mL \cdot kg^{-1} \cdot min^{-1}$; *n* = 27) and CON (3.97 ± 0.17 $mL \cdot kg^{-1} \cdot min^{-1}$; *n* = 23) for measures of resting oxygen consumption (Trial × Disease interaction: P = 0.77; Figure 3.2A) or metabolic rate in the CON (5.78 ± 0.18 $kJ \cdot min^{-1}$; *n* = 19) compared to the MS (5.33 ± 0.21 $kJ \cdot min^{-1}$; *n* = 27; P = 0.12; Figure 2B) group, irrespective of ambient temperature (Trial × Disease interaction: P = 0.88). Furthermore, RER (MS: 0.84 ± 0.02; *n* = 27; CON: 0.85 ± 0.2; P

= 0.70; n = 23; Trial × Disease interaction: P = 0.81 Figure 3.2C) was similar between groups.

Fatigue

Within the MS participants, no association was observed between resting T_{re} and scores of physical (r= -0.11, P = 0.67; Figure 3.3A), cognitive (r= -0.14, P = 0.60; Figure 3.3B), or psychosocial (r= 0.05, P = 0.84; Figure 3.3C) fatigue.

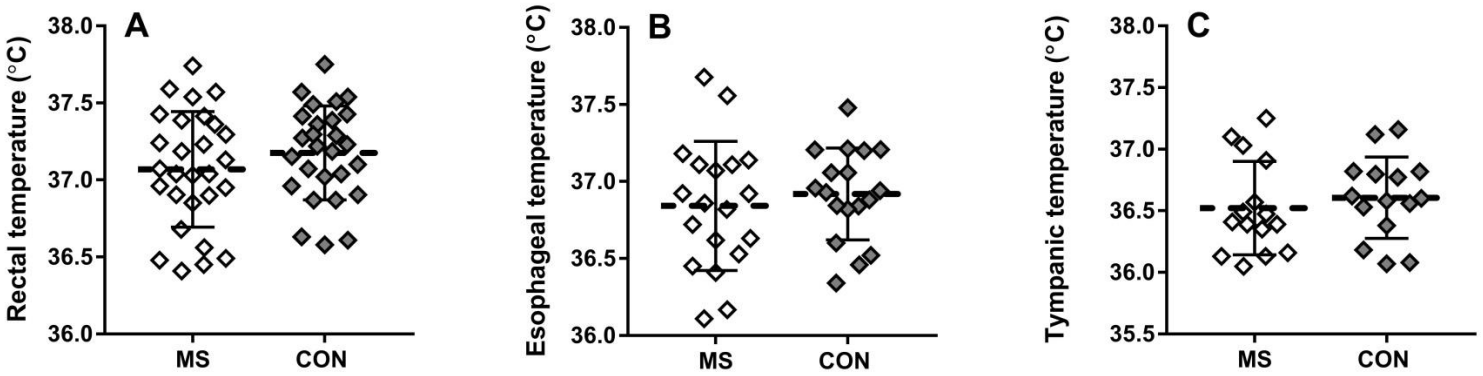

Figure 3.1. Individual data and group means for measures of resting rectal (A), esophageal (B) and tympanic membrane (C) temperature. Values are provided for the relapsing-remitting (MS) MS (white diamonds) and control (grey diamonds). Data pooled from the 25°C and 30°C trials (Panel A-B). Tympanic membrane temperature was measured in the 30°C trial only (C)

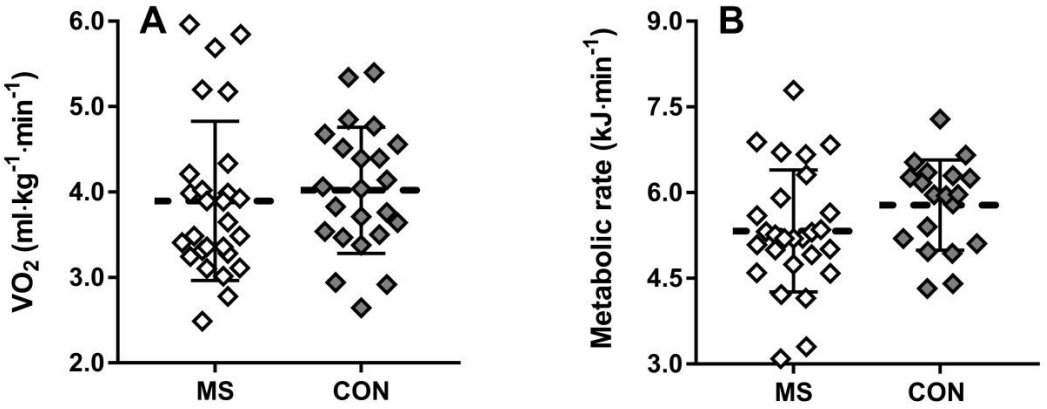

Figure 3.2. Individual data and group means for measures of resting oxygen consumption (A), and metabolic rate (B) in the 30°C and 25°C trials. Values are provided for the relapsing-remitting (MS) MS (white diamonds) and control (grey diamonds)

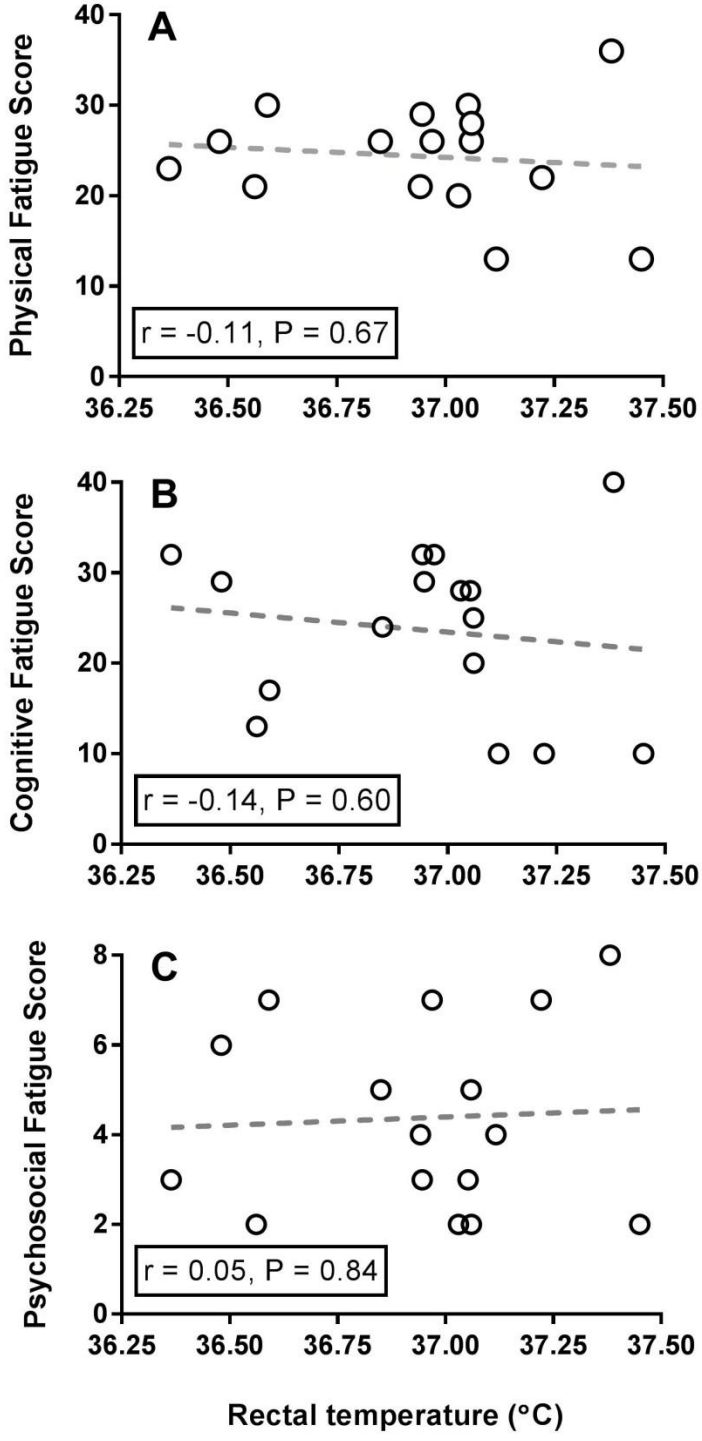

Figure 3.3. Correlation between individual values of resting rectal temperature with measures of physical (A), cognitive (B) and psychosocial (C) fatigue. The dashed line represents the line of best fit

Discussion

Using precision thermometry in the present study, no differences in esophageal, rectal or tympanic membrane temperature were observed between relapsing-remitting MS and healthy control participants during resting in a controlled environment of either 25°C or 30°C; an ambient temperature range that is within the standard boundaries of thermoneutrality at rest [1]. Furthermore, despite a higher resting metabolic rate in the CON group, no differences in resting oxygen consumption or RER were observed, nor was an association evident between resting rectal temperature and any subjective measures of fatigue (physical, cognitive, or psychosocial). These findings are contrary to recent research suggesting that resting core temperature, when measured in the auditory canal using infrared thermometry, is elevated (~0.2°C) in relapsing-remitting MS patients compared to healthy controls. Furthermore, it has been proposed that this elevated core temperature is associated with higher levels of fatigue in people with relapsing-remitting MS [2,3].

In almost all thermophysiological studies, the rectum or esophagus are preferred sites for measuring core temperature [4-8]. It is well documented that a temperature measured in the rectum is generally higher than temperature measured in the esophagus [9] - likely due to a lower rate of blood flow to the splanchnic area, which in turn decreases the amount of internal conductive/convective heat exchange of this tissue region [10]. Advantageously, a low thermal inertia in the rectum means that this measurement remains relatively stable under mildly varying environmental conditions at rest [10], and therefore arguably serves as the ideal measurement site to test the primary research question of the present study. Indeed, because of its validity and accuracy, rectal temperature is commonly measured in clinical [11,7] and athletic [12,4] settings

for diagnosing fever and heat stroke respectively. The lower esophagus is bound by the heart and pulmonary arteries, and because it has a relatively low heat capacity, esophageal temperature is finely regulated by the convective heat transfer from surrounding tissues [9,10]. The sensitivity of esophageal temperature to changes in central blood temperature and whole-body heat storage [5] are testament to the reliability of this measurement, specifically for detecting hypo- and hyper-thermia in intraoperative and postoperative adult patients [7,13,14]. The use of infrared ear thermometry may be useful in tracking acute *changes* in core temperature [4], however, few studies have successfully demonstrated the precision of this tool when measuring absolute core temperature [15,16,11,17-19]. A systematic review of 31 paediatric studies [15] demonstrated core temperature, when measured in the auditory canal with infrared thermometry, was severely under and/or overestimated (pooled mean: 0.29°C [95% CIs: -0.74 to 1.32°C]), as defined by rectal temperature when diagnosing fever (38.0°C as defined by rectal temperature). Similar findings were also reported by Stavem et al [16] when comparing infrared ear thermometry to pulmonary artery temperature for adults in intensive care (mean bias: 0.45°C [95% CIs: -0.29 to 1.19°C]).

The findings of the present study do not replicate those previously reported [2,3]. A direct measure of tympanic membrane temperature can be attained with a precision thermistor placed against the tympanic membrane, and when performed correctly, can potentially be a valid estimate of core temperature [20]. On the other hand, while infrared ear thermometry presents a relatively practical and quick method for measuring core temperature, and is commonly used in clinical settings, the accuracy of this method is heavily dependent upon the proximity of the sensor placement relative to the tympanic membrane which is affected by the curvature, length and circumference of the ear canal and the build-up of cerumen within the ear [19]. For this

reason, infrared ear thermometry often measures auditory canal surface temperature and not tympanic membrane temperature *per se*. Problematically, temperature measurements from the auditory canal can also be further influenced by ambient temperature and air flow [21-23]. Furthermore, if a thermometer placed in the ear does not rest within close proximity to the tympanic membrane, skin temperature of the face and neck will also alter auditory canal temperature [20,24]. Previously reported [2,3] differences in resting core temperature may have been the result of placement of the infrared sensor in the ear canal alongside differences in environmental conditions (i.e. ambient temperature and wind speed).

In the current study, external influences of the environment on resting core temperature were eliminated by tightly regulating ambient air temperature and humidity in a climate chamber (25°C, 30% RH or 30°C, 30% RH). Furthermore, all participants avoided physical activity ~24 h prior to testing, as per standard thermophysiological practice, to eliminate the possibility of elevated skin temperatures and body heat storage that could potentially contribute to elevated resting core temperatures upon arrival. Lastly, individual variability in resting core temperature can be dependent on the rate of heat transfer from the skin surface to the surrounding environment relative to body mass [25]. Although participant biophysical characteristics in previous studies [2,3] were not reported, it is possible that differences in body surface area-to-mass ratio between groups could explain a difference in resting core temperature. In the current study, all participant groups were matched for physical characteristics (Table 3.1), thus eliminating the potential for differences in core temperature due to variability in relative heat transfer.

It has been previously suggested that core temperature is higher in MS patients due to

systemic inflammation in the brain [2,3]. Despite a high prevalence of inflammatory attacks (a relapse) in MS patients, chronic and mild inflammation is also apparent in patients with secondary and primary-progressive MS [26,27]. Therefore, it seems unlikely that systemic inflammation would influence resting core temperature in MS patients only, and not all people diagnosed with MS. A recognised limitation of earlier studies [2,3] is that inflammation was not measured, thus making it difficult to confirm any link between inflammation and core temperature. Theoretically, an elevated core temperature by virtue of systemic inflammation would be accompanied by increases in metabolic rate. However, no difference in oxygen consumption and RER between MS and CON groups were observed in the present study. This observation is consistent with previous reports of similar resting metabolic rates and mitochondrial function of relapsing-remitting MS patients compared to healthy controls [28]. Notably, resting metabolic rate was higher in the CON group compared to the MS group. However, it is evident that this slightly greater resting metabolic rate in the CON group has no influence on resting core temperature compared to the MS group.

Finally, no association between subjective measures of physical, cognitive and psychosocial fatigue and resting core temperature was evident in the present study. These findings are also contrary with those in previous studies [2,3] where aural canal temperature was reported to be associated with elevated fatigue [3,2]. The MFIS is a subjective fatigue scale that relies heavily on individual experiences, interpretations and memory. Furthermore, the MFIS asks questions pertaining to fatigue over a four-week period and is not a direct indication of fatigue in the moment that core temperature is measured. As such, associating this subjective data with physiological measures may be problematic.

Limitations

The present study does not include secondary-progressive MS patients. Previous reports suggest that relapsing-remitting MS patients demonstrate an elevated core temperature compared to patients with secondary-progressive MS due to a difference in systemic inflammation. As such, it is unclear whether a difference in resting core temperature would be observed when using the current methodology between relapsing-remitting and secondary-progressive MS groups. The sample size of this study was smaller than in previous studies [2,3], and tympanic membrane temperature was measured in an even smaller number of participants (MS: n = 15; CON: n = 15), as this was only possible in the 30°C trial. Furthermore, due to participant discomfort, esophageal temperature was not measured in all participants (19 of 28, and 18 of 27 for the MS and CON group respectively). Nevertheless, according to Cohen's d [29] the magnitude of differences for T_{eso} (d = 0.22), T_{re} (d = 0.36), T_{tym} (d = 0.25) and resting metabolic rate (d = 0.29) further demonstrate a small difference between the MS and CON group means. Indeed, to observe a statistical difference in resting T_{eso}, T_{re} and T_{tym} between MS and CON groups, a respective sample size of 884, 324 and 680 participants would be required. However, based on the results of the current study, if such a mean difference was observed, it is likely that a) people with MS would have a lower resting core temperature compared to healthy controls, and b) this difference would be physiologically trivial. Therefore, we feel that additional participants would not change the conclusions of the present study. It is possible that resting core temperature may be influenced by DMT prescribed to people with MS. However, immediate prescription of DMT upon diagnosis is a part of the standard care procedures for people with MS [30] and does not seem to have any effect on resting core temperature for participants in the current study. Lastly, it is possible that severe dehydration (a 1-2% loss of total body mass) can

increase resting core temperature by approximately 0.2°C. While we did not measure hydration status upon arrival, participants were instructed to consume approximately 500 mL of fluid prior to their trial to avoid the possibility of dehydration.

Conclusion

In MS and CON groups matched for age and mass, resting rectal, esophageal and tympanic membrane temperature measured using precision thermometry were not different in either a 25°C, 30% RH or 30°C, 30% RH controlled environment. Similarly, resting metabolic rate was similar between the MS and CON group and there was no evidence of any association between resting rectal temperature and measures of physical, cognitive and psycho-social fatigue. The current study illustrates the importance of employing precision thermometric methods in controlled environmental conditions when assessing differences in resting core temperature between clinical population groups.

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CHAPTER IV

Uhthoff's phenomenon has previously been ascribed to people with relapsing-remitting MS who reached a critical absolute core temperature of ~37.0˚C. We reassessed this notion that an elevated resting core temperature would partially contribute to heat sensitivity for people with MS. Using precision thermometry, we demonstrated that indeed, absolute core temperature, at rest, does not attribute to Uhthoff's phenomenon. Therefore, the next question that arose from this chapter was to determine if people with MS reach a critical absolute core temperature faster during exercise, due to thermoregulatory dysfunction, irrespective of core temperature at rest.

From a thermal physiological perspective, the most apparent question would be whether people with MS demonstrate a blunted sweating response during exercise (in terms of how quick they start sweating and how they upregulate sweat output for a given rise in core temperature) due to autonomic dysfunction. If meaningful differences in sweating control were observed between and person with MS and a healthy control, then whole-body evaporative heat loss (the principal way humans dissipate heat from the body) would be lower, therefore resulting in a greater rise in core temperature, and thus potentially attributing to Uhthoff's phenomenon. Thus, the aim of chapter 5 was to assess the independent influence of relapsing remitting MS on thermoregulatory (sweating) control during exercise in the heat.

CHAPTER V

STUDY 2: THERMOREGULATORY RESPONSES OF MULTIPLE SCLEROSIS PATIENTS CYCLING IN WARM AND HOT ENVIRONMENTS

Thermoregulatory responses in multiple sclerosis patients cycling in warm and hot environments

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Author contributions: GC, DF and OJ conceived and designed experiments; GC and DF performed experiments; GC analysed data; GC, SLD and OJ interpreted data; GC drafted manuscript; GC, DF, AD, SLD and OJ edited/revised manuscript; MB and SV assisted in recruiting participants (Appendix B).

Abstract

Purpose: The impact of heat intolerance among people with multiple sclerosis (MS) is well documented. However, it is unclear whether this intolerance is due to an impaired thermoregulatory capacity, particularly during exercise. The aim of this study is to determine whether thermoregulation is independently altered in MS patients relative to healthy controls while cycling in a warm/hot environment.

Methods: Fourteen relapsing-remitting MS participants (EDSS 2.7±0.8; 47±9 y; 75.4±12.2 kg; 1.7±0.1 m) and 14 age- and mass-matched healthy controls (43±11 y; 78.6±17.0 kg; 1.7±0.1 m) cycled at a fixed metabolic heat production of 4 $W \cdot kg^{-1}$ on a semi-recumbent ergometer for 40 minutes in a 30˚C, 30%RH environment. A subset of 8 relapsing-remitting MS (EDSS: 2.6±0.5; 44±8 y; 82.3±18.2 kg; 1.7±0.1 m) and 8 healthy controls (44±12 y; 81.2±21.1 kg; 1.7±0.1 m) completed the same exercise intensity in a 35°C, 30%RH environment. Rectal (T_{re}) and mean skin (T_{sk}) temperature, upper back and forearm local sweat rate (LSR), and forearm cutaneous vascular conductance (CVC) were measured throughout.

Results: Irrespective of ambient temperature, the change in T_{re} (MS: 0.38±0.18°C; CON: 0.37±0.18°C; P=0.67) was similar between groups, but the change in T_{sk} was greater in the MS (1.50±0.72°C: P=0.02) compared to the CON group (1.00±0.67°C). After 40 min of exercise, forearm LSR (P=0.059) but not back LSR (P=0.78) was lower in the MS group. The change in mean body (ΔT_b) temperature (MS: 0.17±0.03°C; CON: 0.06±0.05°C; P=0.002) and onset time (MS: 15±2 min; CON: 7±1 min; P=0.002) was greater in the MS group for LSR at the forearm but not back (ΔT_b: MS: 0.18±0.21°C; CON: 0.08±0.09°C; P=0.10; time at onset: MS: 13±2 min;

CON: 8±2 min; P= 0.12). CVC (P=0.50), SBF onset time (MS: 11±5 min; CON: 11±6 min; P=0.89) and ΔT_b for SBF onset (MS: 0.09±0.09°C; CON: 0.12±0.11°C; P=0.57) was not different between the MS and CON group.

Conclusion: Even during exercise at temperatures as high as 35˚C, the mild region-specific sudomotor impairments in people with MS are not large enough to alter heat loss to the extent that greater rises in core temperature are observed. It therefore seems unlikely that intolerance to hot environments among people with MS can be attributed to thermoregulatory impairments.

Keywords: Uhthoff's Phenomenon, autonomic dysfunction, heat sensitivity, thermoregulation

Introduction

Multiple sclerosis (MS) is an autoimmune, inflammatory demyelinating disease of the central nervous system (CNS). Up to 80% of people with MS have an intolerance to the heat [1,2], also known as Uhthoff's phenomenon [3], which describes a transient worsening of symptoms with exposure to a hot environment and/or during physical activity. In some patients, this heat intolerance subsequently reduces the capacity to work and perform household tasks [4], and increases the risk of falling [5]. Indeed, ~30% of people with MS will leave their job, with an additional ~40% admitting their job is at risk due to heat intolerance and associated symptoms [4].

It is a widely held notion that an increase in core temperature from rest of 0.2 to 0.5°C will cause a transient worsening of MS symptoms due to a slowed or complete conduction block of temperature sensitive neurons [6,7]. A contributing factor to the rapid onset of heat intolerance may be a disproportionate rise in core temperature for a given metabolic heat load, by virtue of an impaired thermoregulatory response. A sufficient sweating and skin blood flow response is critical for regulating core body temperature during exercise and/or heat exposure. The onset of these effector responses and the rate at which sweat output and skin blood flow increases for a given rise in body temperature dictates the rate at which heat is stored within the body [8].

It has recently been reported that people with relapsing-remitting MS demonstrate a blunted sudomotor, but not vasomotor response when cycling at a fixed heat production in a neutral (25°C) environment [9]. Although this blunted sudomotor response was not large enough to alter the rise in core temperature compared to healthy controls [9], exercise in hotter

conditions that approach skin temperature (i.e. 30 to 35˚C) may elicit a net thermal load that exceeds the thermoregulatory capacity of people with MS sufficiently to cause much greater rises in body temperature for a given activity level. During uncompensable passive heating of MS patients with a 48°C water perfused suit, Allen at al [10] reported an average whole-body sweat rate that is 0.17 $mg \cdot cm^{-2} \cdot min^{-1}$ lower in people with MS relative to healthy control participants. If this difference in sweating is extended across the entire body surface, the parallel difference in evaporative potential should be sufficient to elicit up to a ~1.0°C greater rise in core temperature in MS participants after 40-min of exercise. Whether these observations translate directly to a hot non-encapsulated environment though, remains unknown.

To assess any differences in time-dependent changes in core temperature and sweating between MS and healthy populations, any differences in body size must be accounted for in the experimental design. It has been recently demonstrated that prescribing exercise intensity to elicit a fixed metabolic heat production per unit total body mass (i.e. $W \cdot kg^{-1}$), irrespective of relative exercise intensity (i.e. percentage of maximum oxygen consumption; $\%VO_2max$) eliminates any systematic differences in the exercise-induced rise of core temperature due to biophysical factors [11,12]. Similarly, if participant groups are matched for body size, such an approach will also elicit a similar evaporative requirement for heat balance (E_{req}) per unit surface area, which has been shown to determine steady-state local sweat rates, again irrespective of $\%VO_2max$ [11].

The overall aim of this study was to assess whether people with MS demonstrate impaired local sweat rate and skin blood flow responses to exercise in a warm (30°C, 30% RH) and hot (35°C, 30% RH) environment and whether these responses are sufficiently impaired to

elicit a greater rise in core temperature relative to age-matched control participants with a similar body size. We hypothesised that, compared to healthy control participants, people with MS would demonstrate larger rises in core and skin temperature secondary to a blunted sweat response, yet skin blood flow control would remain unaffected by MS.

Methods

Participants

Fourteen relapsing-remitting MS patients with a disease duration of 11 ± 10 y, an expanded disability severity scale of 2.7±0.8 (1 = no disability, minimal symptoms; 5 = moderate disability, impairing daily activities) and 14 control participants (MS: 47±9 y; 75.4±12.2 kg; 1.7±0.1 m; CON: 43±11 y; 78.6±17.0 kg; 1.7±0.1 m), matched for age and with a similar body size, were recruited to cycle in a warm (30°C, 30% RH) environment. A subset of 8 relapsing-remitting MS participants (Disease duration: 8±8 y; EDSS: 2.6±0.5; 44±8 y; 82.3±18.2 kg; 1.7±0.1 m) and 8 age and mass-matched control participants (44±12 y; 81.2±21.1 kg; 1.7±0.1 m) completed the same exercise bout in a 35°C, 30% RH room. These environmental conditions were chosen to represent the hottest temperature a heat-sensitive person with MS is likely to exercise in. Eligible participants were free of any cardiovascular or metabolic disorders, and MS participants were excluded if they had experienced a relapse six months prior to commencing the study or were taking disease modifying treatment that included a muscarinic antagonist. All participants were informed of any risks involved with the study and provided their written informed consent. This study was approved by the University of Sydney Human Research Ethics Committee (HREC: 2015/125).

Study design

All trials were performed in the Thermal Ergonomics Laboratory at the University of Sydney, Australia. All participants attended one preliminary trial and one experimental trial. During the experimental trials, participants cycled on a semi-recumbent ergometer at a fixed metabolic heat production (H_{prod}) of 4 $W \cdot Kg^{-1}$ for 40 minutes. Participants completed their trials in either a 30°C, 30% RH (14 MS, 14 CON) or 35°C, 30% RH (8 MS, 8 CON) environment. All participants abstained from alcohol and avoided strenuous exercise up to 24 h before their trial.

Instrumentation

Metabolic energy expenditure: Breath-by-breath metabolic rate (*M*) was calculated using indirect calorimetry via a metabolic cart (Quark CPET, Cosmed, Asia Pacific PTY, NSW, Australia). Minute-averaged values were calculated using the following equation [13]:

$$M = VO_2 \cdot \frac{\left(\left(\frac{RER-0.7}{0.3}\right).Ec\right) + \left(\left(\frac{1-RER}{0.3}\right).Ef\right)}{60} \cdot 1000 \text{ [W]}$$

Where: VO_2 is the rate of oxygen consumption ($L \cdot min^{-1}$); RER is the respiratory exchange ratio; Ec and Ef are the energetic equivalents of carbohydrate (21.13 $kJ \cdot L^{-1}$ of O_2) and fat (19.62 $kJ \cdot L^{-1}$ of O_2) respectively. External workload was regulated using a semi-recumbent cycle ergometer (Corival Recumbent, Lode B.V., Groningen, Netherlands). The rate of heat production (H_{prod}) was calculated as the difference between *M* and external workload (W) and then converted into $W \cdot kg^{-1}$ by dividing by total body mass.

Core Temperature: Rectal (T_{re}) temperature was measured using general-purpose paediatric thermistor (TM400, Covidien, Massachusetts, USA). The thermistor was self-inserted to a depth of ~15 cm past the anal sphincter [14].

Skin Temperature: was measured at four sites across the left side of the body using T-type thermocouples (Concept Engineering, Connecticut, USA), secured to the skin using surgical tape. Mean skin temperature (T_{sk}) was expressed as a weighted average in accordance with Ramanathan [15]: chest 30%, shoulder 30%, thigh 20%, and calf 20%. All thermometric measurements were sampled every 5 seconds (NI cDAQ-91722 module, National Instruments, Texas, USA) and displayed in real-time using LabView (v7.0, National Instruments). Mean body temperature (T_b) was estimated using a weighting of $0.9 \times T_{re}$ and $0.1 \times T_{sk}$ [16,17].

Cutaneous Vascular Conductance: Skin blood flow (SBF) was measured using single fibre laser-Doppler flowmetry (Moor MS-LDF, Axminster, United Kingdom) with the sensor placed on the mid-forearm ~5 cm distal to the antecubital fossa. Cutaneous vascular conductance (CVC) was formulated every ten minutes during exercise using the minute-averaged laser Doppler flux units divided by mean arterial pressure (see *Electrocardiograph and blood pressure*) and expressed as a percentage of baseline values.

Local sweat rates (LSR): were measured using 4.1-cm^2 ventilated sweat capsules, secured to the skin using surgical tape (Transpore®, 3M, Ontario, Canada). Capsules were placed on the left upper back ~5 cm above the scapular spine over the trapezium and mid-forearm ~5 cm distal to the antecubital fossa. Anhydrous air was passed through each capsule at a constant flow rate of 750 $mL \cdot min^{-1}$ (Omega FMA-A2307, Omega Engineering, Connecticut, USA) and the

temperature and humidity of outflowing air were measured every 5 s using factory-calibrated capacitance hygrometers (HMT333, Vaisala, Vantaa, Finland). LSR measures were calculated as the product of change in absolute humidity across the capsule and flow rate and expressed relative to the area under the capsule in $mg \cdot cm^{-2} \cdot min^{-1}$. Steady state sweating is the local rate of sweating which is determined by the evaporative requirement for heat balance for a given body surface area.

Absolute humidity was calculated using the following equation

$$Absolute\ humidity = 2.17 \cdot \frac{P_a}{T}\ kg \cdot m^{-3}$$

Where; P_a is the partial vapor pressure and T is the temperature in degrees Kelvin.

Electrocardiograph and blood pressure: A wireless 6-lead ECG system recorded measures of heart rate (Quark ECG stress system, Cosmed, NSW, Australia). The same ECG system was used concurrently with an automated blood pressure monitor that was strapped to the participant's arm throughout exercise (Tango M2, Suntech Medical, Inc. North Carolina, USA).

Preliminary trial

During the preliminary session, height and weight were recorded followed by a submaximal aerobic test on a semi-recumbent cycle ergometer. The submaximal test was used to determine the relationship between external work rate and oxygen consumption (VO_2) and thus H_{prod}. The submaximal test protocol started with a 5-min warm-up period followed by 5-min of rest, after which the participant was fitted with a face mask attached to a metabolic cart. Participants began cycling at a resistance of 20 W below the predicted workload to elicit an

individualized H_{prod} of 4 W·kg^{-1}, at a cadence of 60 rpm. The external workload of the bike was then increased by 20 W every three minutes for 4 separate stages or until volitional exhaustion [18].

Experimental trials

During the experimental trial, participants cycled on a semi-recumbent ergometer for 40 minutes in a climate chamber regulated at 30°C, 30% RH (30°C) or 35°C, 30% RH (35°C). Participants were instrumented, weighed and baseline data was collected for 15 minutes, after which they began to cycle at a H_{prod} of 4 W·kg^{-1}. At the cessation of exercise, ambient temperature was decreased to 20°C, 30% RH and participants were required to sit quietly for 30 minutes while they cooled down and measures of BP and HR were recorded.

Statistical Analysis

All data are expressed as a mean with standard deviation (±). A three-way mixed ANOVA with a repeated factor of time (5 levels: 0, 10, 20, 30 and 40 min), and non-repeated factors of ambient temperature (2 levels: 30°C and 35°C) and disease (2 levels: MS and CON) was used to analyse time-dependent changes in T_{re}, T_{sk}, HR, LSR at the forearm and upper back, and $\%CVC_{baseline}$ of the forearm. A two-way ANOVA employing the non-repeated factors of ambient temperature and disease was used to assess differences in baseline T_{re}, ΔT_b onset thresholds, time at response of onset, and thermosensitivity of LSR on the forearm and upper back and SBF on the forearm. Thermosensitivities for each participant were determined separately for LSR of the forearm and back, as well as SBF, using a simple linear regression for the period of linear increase until the start of a plateau in LSR and CVC plotted against the ΔT_b.

The level of significance for all analyses employed an α of 0.05. If a significant interaction or main effect was observed, individual differences were assessed using an independent Student's t-test. All post hoc comparisons employed a Bonferoni correction. Statistical analyses were performed with SPSS (version 24, IBM SPSS, Chicago, IL, USA) and all data were graphed using GraphPad Prism (Version 7 La Jolla, CA, USA).

Results

No time-disease-trial interaction for observed for any of the independent variables, as such, all data from the 30°C and 35°C trial was pooled and are displayed independently of environmental conditions.

Core and skin temperatures

Absolute T_{re} was similar between MS and CON groups (P = 0.30) at rest, irrespective of ambient temperature (P = 0.59). The change in T_{re} was not different (P = 0.67) between the MS and CON groups (MS: 0.38 ± 0.18°C; CON: 0.37 ± 0.18°C) after 40 min of exercise (Figure 5.1A) irrespective of ambient temperature (p = 0.56).

After 40 minutes of exercise, the change in T_{sk} was greater (P = 0.02) in the MS (1.50 ± 0.72°C) compared to the CON (1.00 ± 0.67°C) group (Figure 5.1B). However, this rise in T_{sk} for both the MS and CON groups was not influenced (P = 0.45) by ambient temperature (i.e. 30°C vs. 35°C).

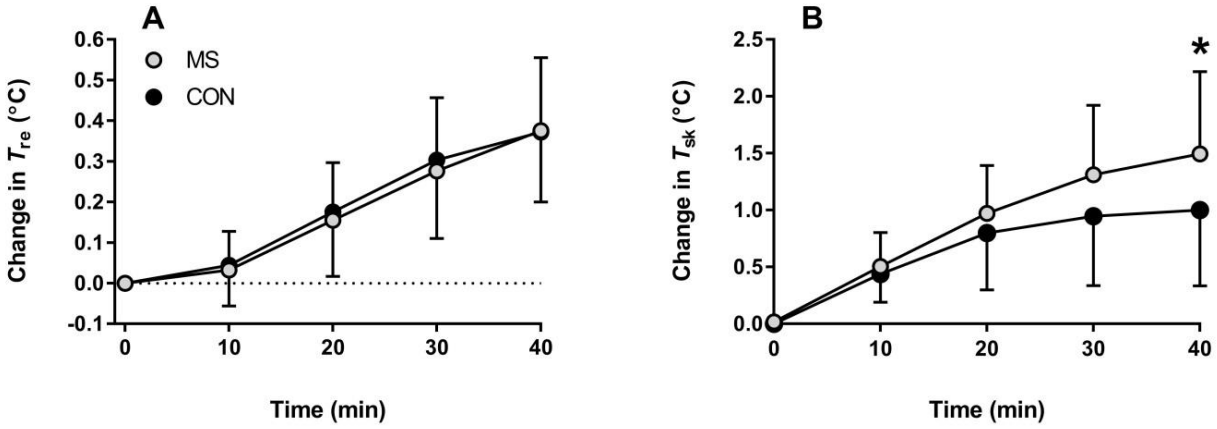

Figure 5.1A and 5.1B. Mean change and error (standard deviation) in rectal (A) and skin temperature (B) for the MS (grey circles) and CON (black circles) groups. Values are pooled from the 30°C and 35°C trial for T_{re} (time-disease-trial interaction: P = 0.59) and T_{sk} (time-disease-trial interaction: P = 0.45). Asterisk (*) denotes P < 0.05.

Sweating

Irrespective of ambient temperature (P = 0.87), local sweat rate of the upper back was not different (P = 0.46) between the MS and CON groups (Figure 5.2A). However, regardless of ambient temperature (P = 0.12) a time-disease interaction was observed for forearm LSR (P = 0.01). Specifically, forearm LSR was lower in the MS group at the 20th (P = 0.02), 30th (P = 0.04) but not the 40th (P = 0.06) min of exercise (Figure. 5.2B).

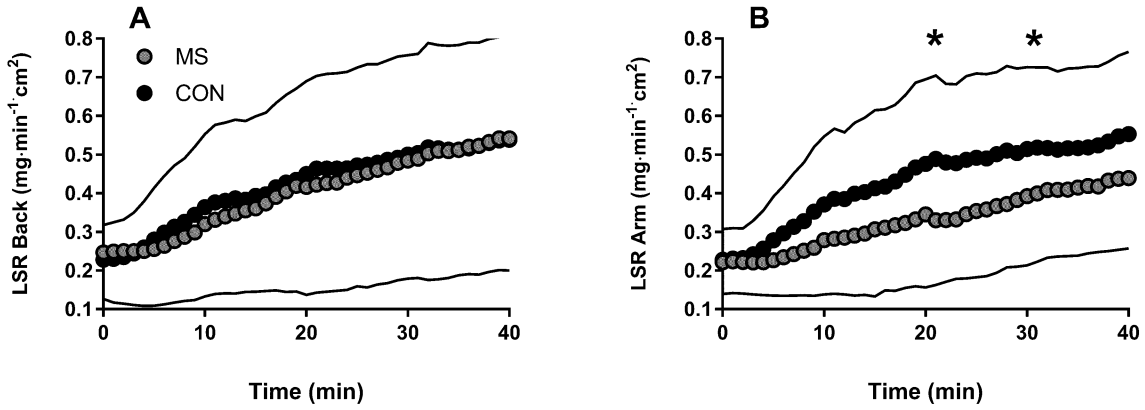

Figure 5.2A and 5.2B. Mean and error (standard deviation) for local sweat rate (LSR) of the upper back (A) and forearm (B) for the MS (grey circles) and CON (black circles). Values are pooled from the 30°C and 35°C trials for upper back (time-disease-trial interaction: P = 0.87) and forearm (time-disease-trial interaction: P = 0.12) LSR. Asterisk (*) denotes P < 0.05.

The change in mean body temperature onset threshold for the forearm and upper back LSR and the subsequent thermosensitivity are displayed in Fig. 5. No disease-ambient temperature interaction was observed for the onset of LSR at the forearm (P = 0.72) or upper back (P = 0.74). However, the change in mean body temperature for the onset of forearm sweating was greater (P = 0.002) in the MS (0.17 ± 0.03°C) compared to the CON (0.06 ± 0.05°C) group. No such difference was observed for upper back sweating (MS: P = 0.10). No disease-ambient temperature interaction was observed for forearm (P = 0.85) and upper back (P = 0.69) LSR onset time. On the other hand, the time at LSR onset (Figure 5.3C & D) was longer in the MS group for the forearm (P = 0.002) but similar between groups on the upper back (P = 0.12). The LSR thermosensitivity was not different between groups for either the forearm (P = 0.21) or the upper back (P = 0.69). The observed effects were the same irrespective of ambient temperature (forearm: P = 0.77; upper back P = 0.69).

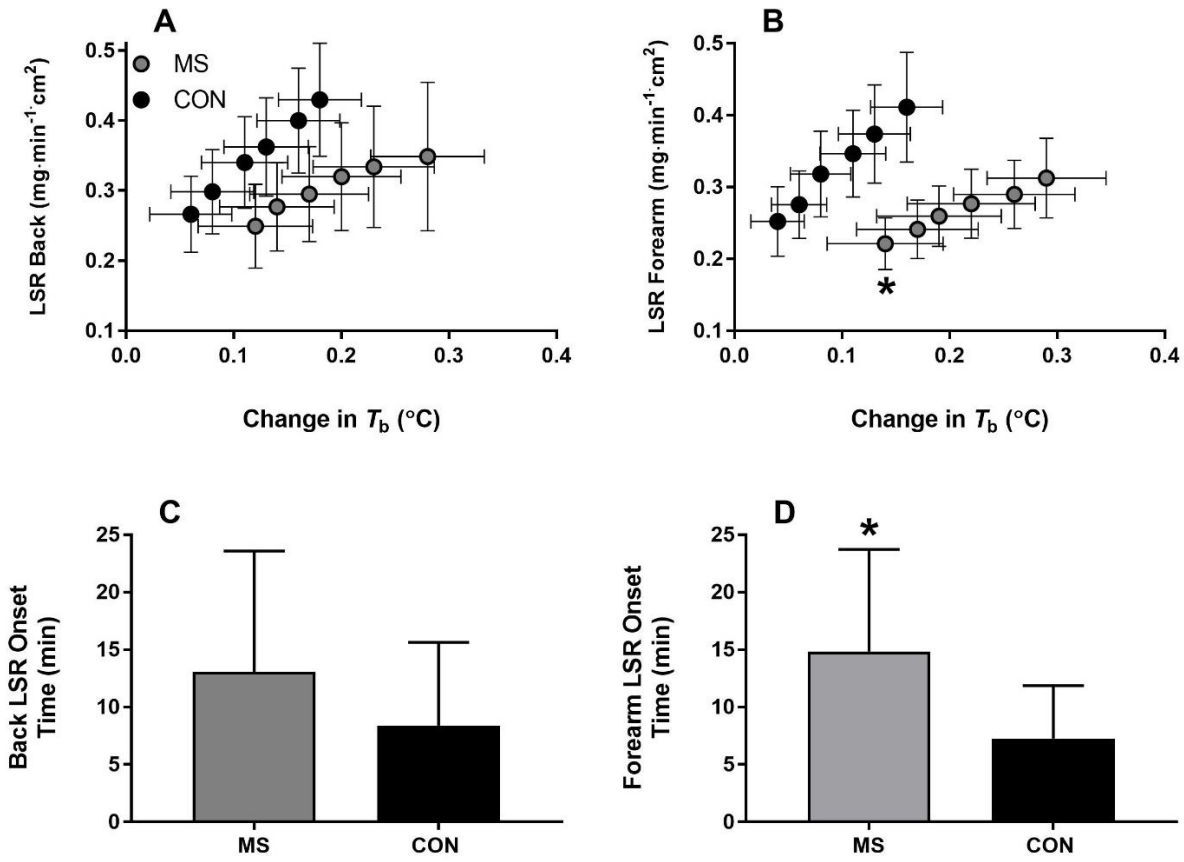

Figure 5.3A-D. Change in mean body temperature plotted against the rise in upper back (A) and forearm (B) local sweat rate (LSR). Values are pooled from the 30°C and 35°C trials for upper back (disease-trial interaction: P = 0.74) and forearm (disease-trial interaction: P = 0.72) LSR. Mean and error (standard deviation) for the time of LSR onset for the upper back (C) and forearm (D) between the MS and CON groups. Values are pooled from the 30°C and 35°C trials for upper back (disease-trial interaction: P = 0.69) and forearm (disease-trial interaction: P = 0.85) time at onset. Asterisk denotes P < 0.05.

Skin blood flow measurements

Irrespective of ambient temperature (P = 0.54), $\%CVC_{baseline}$ of the forearm was not different between the MS and CON (P = 0.50) groups (Figure 5.4A). The change in mean body temperature onset threshold for forearm skin blood flow (SBF) was similar (P = 0.57) in the MS (0.09 ± 0.09°C) compared to the CON (0.12 ± 0.11°C) group. Similarly, no differences were observed between the MS and CON group for the time at onset (Figure 5.4B) of forearm SBF

(MS: 11 ± 5 min; CON: 11 ± 6 min; P = 0.89) or the thermosensitivity (P = 0.49). These observed effects were the same irrespective of ambient temperature (ΔT_b: P = 0.38; onset time: P = 0.87; thermosensitivity: P = 0.32).

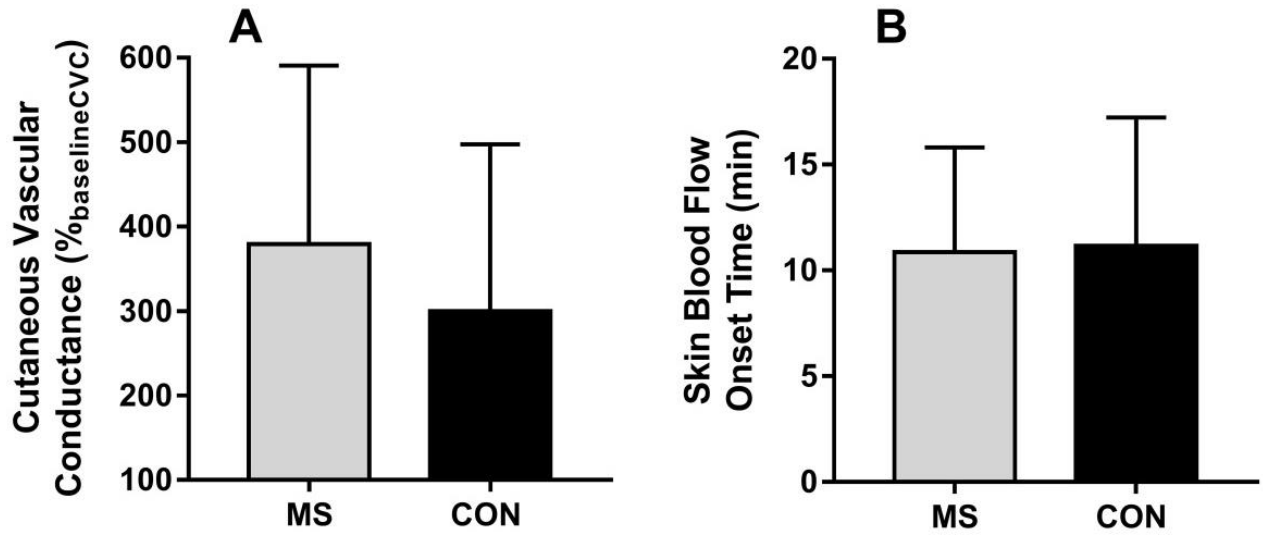

Figure 5.4A and 5.4B. Mean and error (standard deviation) values of cutaneous vascular conductance (CVC) of the forearm (A) following 40 min of exercise expressed as a percent of baseline and time at onset for skin blood flow (B) for the forearm. Values are pooled from the 30°C and 35°C trials for CVC (disease-trial interaction: P = 0.54) and time at onset of skin blood flow (disease-trial interaction: P = 0.87).

Heart rate

Irrespective of ambient temperature (P = 0.69), there was no disease-heart rate interaction (P = 0.75). Furthermore, heart rate was not different at rest (MS: 75 ± 3 bpm; CON: 70 ± 2 bpm; P = 0.26) or after 40 minutes of cycling (MS: 105 ± 5; CON: 104 ± 4; P = 0.91) between the MS and CON groups.

Discussion

Our collaborative group has recently shown that compared to healthy controls, people with MS demonstrate a blunted sudomotor, but not vasomotor response during exercise at a fixed

metabolic H_{prod} (4.5 $W \cdot kg^{-1}$) in a temperate climate (25°C, 30% RH) [9]. However, it was thought that due to the relatively cool conditions this blunted sweat response was not large enough to alter the rise in rectal and esophageal temperature following 60 minutes of exercise [9]. The findings of the present study extend our previous investigations to much hotter conditions (up to T_a=35°C). We found that when cycling at a fixed H_{prod} of 4 $W \cdot kg^{-1}$ at these temperatures, the blunted sudomotor response in people with MS has regional specificity with decrements only observed on the forearm, but not the upper back. In parallel a greater rise in mean skin temperature was observed. However, similar rises in rectal temperature occurred between the MS and CON group throughout 40 minutes of exercise. Collectively, these data demonstrate that while a mild sudomotor impairment is present in people with MS, this is not sufficient to compromise heat loss during exercise to the extent that greater levels of deep body temperature occur with MS even at hot (up to 35°C) ambient temperatures.

Sweat rates are predominantly determined by the amount of evaporation required to maintain heat balance [19], which by design was fixed between the MS and CON groups in the present study. Nevertheless, MS participants still demonstrated a lower sweat rate on the forearm (but not on the upper back) relative to healthy controls. Mechanistically, this lower localised sudomotor output seemed to be a result of a delayed onset relative to the change in mean body temperature in the MS group. A rise in deep and peripheral tissues temperatures during exercise in the heat activates local temperature-sensitive neurons that relay afferent information to the preoptic area of the anterior hypothalamus [20]. Neuronal firing rates are subsequently altered to elicit an efferent response such as an increase in sudomotor output. The present observation of a blunted forearm sweating response in the MS group indicates that pathophysiological events

within the CNS with MS may in some way impair this process. Indeed, it is known that injured neurons cause a reduction in conduction velocity and depress the efficiency of a postsynaptic response relative to a presynaptic stimulus [21-23]. Noronha [24] and Andersen [25] reported qualitative evidence of sudomotor impairments in MS patients during a bout of passive heating using the quinizarin powder test method. According to both studies [24,25] intravenous pilocarpine (a sympathetic cholinergic agonist) adequately increased whole body sweating rate in patients who previously demonstrated a blunted sweating response to passive heating. They postulated that a likely cause of sudomotor dysfunction for people with MS is the damage to neurons within the descending sudomotor pathway. Despite a blunted onset of the sudomotor response on the forearm in the present study, MS participants were still able to achieve the required steady-state sweat rate after ~40 minutes of exercise. As such, demyelination of neurons potentially only transiently weakens the temporal sudomotor response to exercise.

Secondary to CNS impairments, it is also possible that insufficient stimulation of sweat glands due to physical inactivity [26] or avoiding exposure to hot environments may alter the central and peripheral adaptions to exercise in the heat [27-29]. Armstrong [23] suggested the neural adaptations to heat exposure, such as synaptic plasticity (in this instance, an increase in synapse strength), allow for adequate physiological control in hot environments. Accordingly, a decrease of synaptic plasticity may reflect irregular use of the thermoregulatory control system such as a delayed onset of sweating or a reduction in sweating rate [29,23]. Furthermore, Sato and Sato [27] demonstrated for physically active people, sweat glands had a higher cholinergic sensitivity, produced more sweat per unit volume of the gland, and were typically larger compared to self-reported sedentary people. Taken together, it is possible that heat-sensitive MS

patients demonstrate a blunted sudomotor response because of a) a reduction in the neuronal adaptations that occur with repeated heat exposure, b) a reduction in cholinergic sensitivity, c) a decrease in muscarinic cholinergic synapses and/or d) sweat gland atrophy, particularly if these patients avoid exercise and/or hot environments to prevent fatigue or a worsening of symptoms [30].

It is widely acknowledged that local sweat rate can vary considerably across different regions of the body in healthy individuals [31-33], however it is unclear why sweating was blunted on the forearm only and not the upper back in people with MS. Region-specific differences in sweating rate have been observed in elderly (>64 y) compared to young men [32,34] during whole body passive heating. These previous studies reported a lower sweat gland output on the thigh and back in an elderly compared to a young population, while forehead, chest or forearm sweat gland output was similar between groups. It was hypothesised that these region-specific differences in sweating were the result of sweat gland atrophy and/or decreased cholinergic sensitivity [34]. Demyelination and scarring within the CNS is highly variable in terms of location and severity [24]. While we can only speculate, it is possible that a blunted sudomotor response on the forearm is due to a) demyelination specific regions within the CNS and/or b) local sweat gland atrophy. Nevertheless, irrespective of the underlying cause, the rise in core temperature was ultimately similar between MS and CON participants. Therefore, any differences in evaporative heat loss secondary to the lower sweat rates in the MS group on the forearm must have been minimal and/or compensated for greater sweating/evaporation at other body regions that were not measured, even at ambient temperatures up to 35°C.

There was a greater rise in T_{sk} in the MS group which may have been related to the greater evaporation in the CON group alongside lower local sweat rates, allowing for further cooling of the skin. However, it is evident that the benefit of any additional cooling was superficial and ultimately not great enough to alter the rise in core temperature. A greater rise in T_{sk} in the MS group may contribute to a warmer thermal perception (feeling hot) and perceived exertion during exercise. It is well known that sensations of warmth and an elevated perception of effort are predominantly driven by skin temperature particularly when a person starts exercise from a state of thermoneutrality/comfort [35-38]. Given one of the primary concerns for people with MS is heat-related fatigue, it is possible that higher mean skin temperatures contribute to elevated sensations of exertion, particularly during exercise.

Lastly, skin blood flow control in people with MS was similar compared to healthy controls, as previously observed [10,39]. Cartlidge [39] reported an impaired sudomotor response in people with MS during passive heating in a water bath, despite no apparent impairment in vasomotor function. Similarly, Allen et al [10] reported differences in sweat output, but not cutaneous vascular conductance in MS compared to CON groups following a bout of whole body heating in a 48°C water perfused suit. It is therefore clear that pathways within the sympathetic nervous system exist that are impacted by MS are restricted to the sudomotor apparatus [40].

Limitations

It is unclear whether the blunted forearm sweat response in the MS group led lower whole body sweat losses as this was not measured in the present study. Nevertheless, the primary concern for people with MS during heat exposure is heat-related fatigue, which is presently

believed to be tied to the rise in core temperature [41]. It follows that irrespective of whether whole-body sweating was reduced in parallel with forearm LSR in the MS group or not, any MS-related reductions in sudomotor output were apparently insufficient to alter core temperature. Due to technical limitations, we were unable to collect maximum skin blood flow values in the present study. While skin blood flow values are preferably reported as a percentage of a maximum response attained with local heat post-exercise, many studies present CVC values as a percent of baseline. However, the variability of baseline values was minimized by allowing for 15 minutes of baseline data collection in a controlled environment [42]. Another possible limitation is the use of rectal instead of esophageal temperature to assess thermoeffector control. Obtaining esophageal temperature within this specific population proved difficult. Esophageal temperature measures were only obtained in 8 MS and 6 CON participants in the 30°C trials and in no MS or CON participants in the 35°C trials. As such, an insufficient number of esophageal temperature values were attained to conduct an appropriately powered thermoeffector analysis.

Conclusion

Despite a mild impairment of sweating on the forearm alongside slightly greater rises in mean skin temperature, deep core temperature in people with MS is not greater during exercise at a fixed heat production in a warm (30°C, 30% RH) or hot (35°C, 30% RH) environment. Future research does not need to focus on thermoeffector impairment during exercise for this population as any associated differences in skin surface evaporation seem to be minimal.

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Conflicts of Interest

The authors have no conflicts of interest to disclose.

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CHAPTER VI

Collectively, chapters 3 and 5 demonstrated that while core temperature is not apparently influenced by MS, sudomotor control, to a mild extent, is. Nonetheless, this apparent impairment in sudomotor control is not sufficient enough to reduce whole-body evaporation to the extent that people with MS get hotter during exercise, even in air temperatures as high as 35˚C. The fact remains though that people with MS do experience a temporary worsening of their symptoms during exercise, albeit, MS organizations regularly recommend that people with MS use various cooling strategies to mitigate a temporary worsening of their symptoms. One strategy that is commonly recommended is the ingestion of cold water. Drinking cold water increases internal conductive heat loss and may reduce body core temperature during exercise in the heat. Cold fluid ingestion may also counteract mild reductions in skin surface evaporation due to the sweating impairments in people with MS as identified in chapter 5. Therefore, the aim of chapter 7 is to assess the influence of drinking cold water, which is readily available to most people, during exercise in the heat on exercise tolerance. Exercise tolerance in this case can be an indicator of MS-related heat sensitivity if compared to age and fitness-matched people without MS in the same environment.

CHAPTER VII

STUDY 3: COLD WATER INGESTION IMPROVES EXERCISE TOLERANCE OF HEAT-SENSITIVE PEOPLE WITH MULTIPLE SCLEROSIS

Cold-Water Ingestion Improves Exercise Tolerance of Heat -Sensitive People with Multiple Sclerosis

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Author contributions: GC, DF and OJ conceived and designed experiments; GC and DF performed experiments; GC analysed data; GC, DF and OJ interpreted data; GC drafted manuscript; GC, DF, MB, PH, SLD and OJ edited/revised manuscript; MB and PH assisted in recruiting participants (Appendix C).

Abstract

Purpose: Heat intolerance commonly affects the exercise capacity of people with multiple sclerosis (MS) during bouts of hot weather. Cold-water ingestion is a simple cooling strategy but its efficacy for prolonging exercise capacity with MS remains undetermined. We sought to identify whether cold-water ingestion blunts exercise-induced rises in body temperature and improves exercise tolerance in heat-sensitive individuals with MS.

Methods: On two separate occasions, 20 participants (10 relapsing-remitting MS (EDSS: 1- 5); 10 age-matched healthy controls (CON)) cycled at ~40% VO_{2max} at 30°C, 30%RH until volitional exhaustion (or a maximum of 60 min). Every 15 minutes, participants ingested 3.2 mL·kg^{-1} of either 1.5°C (CLD) or 37°C (NEU) water. Rectal (T_{re}) temperature, mean skin (T_{sk}) temperature, and heart rate (HR) were measured throughout.

Results: All 10 CON, but only 3 of 10 MS participants completed 60 minutes of exercise in NEU trial. The remaining 7 MS participants all cycled longer (P=0.006) in CLD (46.4±14.2 min) compared to NEU (32.7±11.5 min), despite a similar absolute T_{re} (NEU: 37.32±0.34°C; CLD: 37.28±0.26°C; P=0.44), change in T_{re} (NEU: 0.38±0.21°C; CLD: 0.34±0.24°C), absolute T_{sk} (NEU: 34.48±0.47°C; CLD: 34.44±0.54°C; P=0.82) and HR (NEU: 114±20 beats·min^{-1}; CLD: 113±18 beats·min^{-1}; P=0.38) for the same exercise volume.

Conclusions: Cold-water ingestion enhanced exercise tolerance of MS participants in the heat by ~30% despite no differences in core and mean skin temperatures or heart rate. These findings support the use of a simple cooling strategy for mitigating heat intolerance with

MS and lend insight into the potential role of cold-afferent thermoreceptors that reside in the abdomen and oral cavity in the modulation of exercise tolerance with MS in the heat.

Keywords: Uhthoff's phenomenon, fatigue, physical activity, heat sensitivities.

Introduction

It is well documented that during physical activity and/or exposure to hot environments individuals with multiple sclerosis (MS) can experience heat intolerance (1), which is typically characterized by a rapid onset of fatigue (2). Despite its prevalence, the underlying mechanisms responsible for this phenomenon (Uhthoff's) remain somewhat inconclusive. Nevertheless, since the work by Davis (3) and Rasminsky (4) it has been generally considered that a rise in core temperature of ~0.5°C induces heat-related fatigue secondary to slowed or blocked conduction of demyelinated nerves. As such, people with MS are regularly advised to remain indoors during hot weather, and limit physical activity, which can substantially impact employability and/or quality of life (5).

Some cooling strategies administered before and/or during heat exposure successfully mitigate the development of heat-related fatigue in people with MS (6). However, these methods, such as 30 minutes of lower body cold water immersion (7) or donning an ice vest (8) can prove impractical in the context of everyday life and incompatible with many jobs. Cold fluid ingestion during physical activity is a simple strategy that is presently recommended by, among others, the National MS Society (9) the MS Society (UK) (10) and MS Queensland (Australia). Indeed, drinking cold water could effectively mitigate elevations in core temperature and associated fatigue as it introduces an internal heat loss avenue (via conduction) in addition to evaporative and convective heat loss from the skin surface. Nevertheless, to the best of our knowledge, no study has yet assessed whether cold fluid ingestion during exercise in the heat can mitigate rises in core temperature and accompanying fatigue in people with MS.

The aim of this study was to examine the effect of ingesting cold (1.5°C) compared to thermoneutral (37°C) water on exercise tolerance at a fixed low relative intensity (~40%VO_2max), and the elevation in core temperature of heat-sensitive relapsing-remitting MS participants in a warm (30°C) environment. It was hypothesized that with thermoneutral water ingestion, exercise time would be shorter for MS compared to age- and fitness-matched control participants. It was also hypothesized that compared to thermoneutral water ingestion exercise time of MS participants would be extended with cold water ingestion due to a blunted rise in core temperature.

Methods

Participants

Twenty participants, 10 individuals with relapsing-remitting MS, an expanded disability status scale (EDSS) range of 2-4.5 (1 = No disability, slight dysfunction in one area, 4.5 = significant disability with some limitation of daily activities (11)) and 10 age, height and weight-matched healthy controls with a similar estimated aerobic fitness (Table 5.1) were recruited for this study based on a power calculation (Heinrich-Heine-Universität Düsseldorf, Germany) employing an α of 0.05, a 1-β of 0.95 and an effect size of 1.55 for the main outcome variable of exercise performance with cold fluid ingestion in the heat (12). All MS participants had a self-reported intolerance to the heat. All participants were informed of any risks associated with the study before providing written informed consent. The study was approved by the University of Sydney Human Research Ethics Committee (HREC No: 2016/214).

Table 7.1. Participant demographics

	MS (*n*=10)	**CON (*n*=10)**	***P***
Sex	4M/6F	5M/5F	
Age (y)	47±9.2	43.8±5.5	0.35
Weight (kg)	82.5±15.7	76.1±15.7	0.41
Height (cm)	1.7±0.1	1.7±0.1	0.64
BSA (m^2)	1.9±0.2	1.9±0.3	0.57
VO_{2max} ($L \cdot min^{-1}$)	2.4±1.4	2.9±0.9	0.27

Measurements

Rectal (T_{re}) temperature was measured using a general-purpose paediatric thermistor (TM400, Covidien, Mansfield, MA, USA) self-inserted to a depth of 12 cm past the anal sphincter. Skin temperature was measured at four sites on the right side using thermistors (Concept Engineering, Old Saybrook, CT, USA) attached with hypoallergenic tape (Blenderm, 3M, Sydney, NSW, Australia). Mean skin temperature (T_{sk}) was estimated using a weighted average in accordance to Ramanathan (13). All thermometric measurements were sampled at 5 seconds intervals (NI cDAQ-91722 module, National Instruments, Austin, TX, USA) and displayed in real-time using LabView (v7.0).

Heart rate (HR) was measured using a wireless 6-lead ECG (Quark T12x Asia Pacific PTY, Sydney, NSW, Australia) monitoring system. Electromagnetic gel was applied to 4 foam electrodes, which were then placed under the right and left clavicle, the right and left 6^{th} intercostal and then covered with tape. Prior to the placement of the electrodes, the skin surface was shaved and cleaned with alcohol to ensure minimal signal interference.

Protocol

Each participant completed one preliminary trial and two experimental trials. During the preliminary trial, participants performed an incremental submaximal exercise protocol (beginning at 45 W increasing 20 W every three minutes for a total of four stages) on a semi-recumbent cycle ergometer (Corival Recumbent, Lode BV, Groningen, Netherlands) in a 20˚C room. Heart rate and oxygen consumption (Quark CPET, Cosmed, Asia Pacific PTY, Sydney, NSW, Australia) were measured during each 3-min stage. A least square regression equation was employed using sub-maximal heart rate and oxygen consumption at the end of each stage and extrapolated to the maximum age-predicted heart rate (220-age) (14) to determine VO_{2max} using the YMCA protocol (15). Individualized workloads (40% of predicted VO_{2max}) were calculated for the subsequent experimental trials.

Participants completed two experimental trials separated by a minimum of 48 h in a climate-controlled chamber at 30˚C and 30% relative humidity until i) volitional exhaustion, or ii) a maximum of 60 minutes. Participants were required to complete both trials at the same time of day to avoid any disparity in resting core temperature due to circadian rhythm. If any participant presented with a resting T_{re} more than 0.2˚C away from their previous trial, the trial would not commence. Participants cycled on a semi- recumbent cycle ergometer at a fixed relative intensity (~40%VO_{2max}) and consumed a 3.2 ml·kg^{-1} aliquot of water (in <1 minute) after the 15th, 30th and 45th minute of exercise.

Participants consumed either thermoneutral (37˚C) water (NEU) or cold (1.5˚C) water (CLD) during each experimental trial. The presentation of trials was balanced

between participants. The temperature of the water ingested in the NEU trial was maintained using a hydrostatic controlled water bath (DA05A, Polyscience, Niles, IL, USA). The temperature of the water ingested in the CLD trial was maintained in a thermos filled with ice. Immediately prior to fluid ingestion, the temperature of the fluid was verified using a factory-calibrated glass precision thermometer (Durac Plus, Blue Spirit, Cole-Parmer, Vernon Hills, IL, USA) with a certified range between –1°C and +100°C and with an accuracy of ±0.1°C, and the required mass of water was measured using a balance with a precision of 0.1 g (MS12001L, Mettler Toledo, Columbus, OH, USA). Breath-by-breath oxygen consumption was continuously monitored to ensure participants were exercising at the target rate of oxygen consumption associated with a fixed estimated relative intensity throughout both trials.

Statistical Analysis

A two-way mixed ANOVA employing the repeated factor of water temperature (CLD, NEU) and the non-repeated factor of group (MS, CON) was used to examine exercise time to exhaustion (with a maximum of 60 min). The T_{re}, T_{sk} and HR at the time of exhaustion in the shortest trial for each individual were also compared to the same time point in the other trial within the MS and CON groups using paired sample t-tests. A within-group analysis of the effect of water temperature was employed for these measures due to different exercise times between the CON and MS groups. Furthermore, within the CLD trial for the MS group, the T_{re} and T_{sk} values at the same time as the time of exhaustion in the NEU trial were compared to the values at end-exercise using a paired sample t-test. Finally, an independent samples t-test was used to examine HR between CON and MS participants at 30 minutes of exercise for both the NEU and

CLD trials. All statistical analyses employed an α of 0.05 and were performed using GraphPad Prism (v6.0, LA Jolla, CA, USA).

Results

Exercise time was shorter in the MS group compared to the CON group (P=0.002), however an interaction was observed between water temperature and group (P<0.001). Specifically, all 10 CON participants completed 60 minutes of exercise in both the NEU and CLD trials (Figure 7.1). On the other hand, while only 3 of 10 participants in the MS group completed 60 minutes of exercise in the NEU trial, 5 of 10 MS participants completed 60 minutes of exercise in the CLD trial, and all 7 MS participants who could not complete the NEU trial cycled longer (Figure 7.1) in the CLD trial (NEU: 32.7±11.5 min; CLD: 46.4±14.2 min; P=0.006). During rest in the NEU trial (MS: 70.1± 11.3; CON: 77.2±24.5 beats·min^{-1}; P = 0.51) and CLD trial (MS: 74.3±9.5; CON: 72.9±11.1 beats·min^{-1}; P = 0.78) and following 30 minutes of exercise, HR responses in the NEU trial (MS: 104±15 beats·min^{-1}; CON: 96±10 beats·min^{-1}; P=0.22) and the CLD trial (MS: 103±17 beats·min^{-1}; CON: 92±12 beats·min^{-1}; P=0.17) were not different, despite being moderately higher for the MS group throughout exercise.

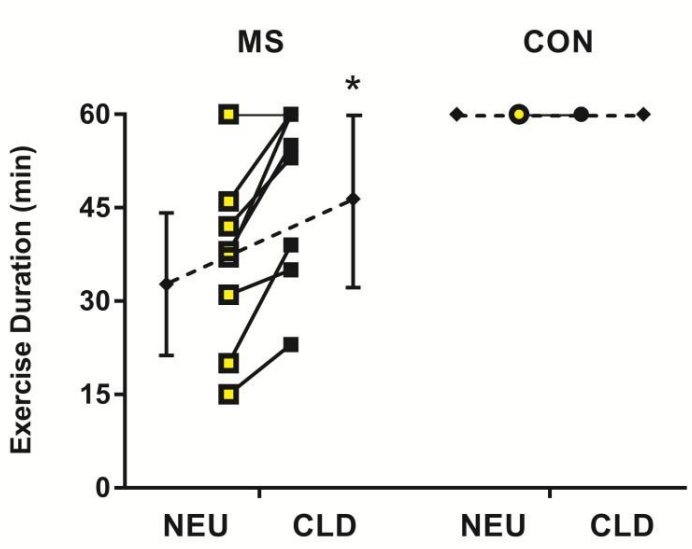

Figure 7.1. Individual data and group means (with SD) for exercise duration in the NEU (yellow) trial and CLD (black) trial for multiple sclerosis (MS: squares) and healthy controls (CON: circles). Values given for: Exercise time to exhaustion with a maximum of 60 min. Asterisk (*) indicates P<0.05 between the NEU and CLD trial for the MS group

Absolute T_{re} at rest in the NEU (MS: 36.93±0.40˚C; CON: 36.89±0.31˚C; P = 0.82) and CLD (MS: 36.87±0.33˚C; CON: 36.92±0.32˚C; P = 0.94) were not different. In the MS group, at the time of exhaustion in the NEU trial, change in T_{re} (P=0.66; Figure 5.2A), absolute T_{re} (P=0.44; Figure 7.2C), T_{sk} (P=0.82; Figure 5.2E), and HR (NEU: 114±19 beats·min^{-1}; CLD: 113±17 beats·min^{-1}; P=0.45) were not different after the same amount of exercise time elapsed in the CLD trial. All 7 MS participants who cycled for longer in the CLD trial did so despite T_{re} (P=0.001) and T_{sk} (P=0.03) rising to higher values above the end NEU values when they did stop exercise (ΔT_{re}: 0.26±0.12°C vs. 0.40±0.23°C; ΔT_{sk}: 1.27±0.72°C vs. 1.47±0.79°C). In the CON group, end-exercise (i.e. after 60 min in all CON participants) change in T_{re} (P=0.05; Figure 7.2B), absolute T_{re} (P=0.25; Figure 7.2D), T_{sk} (P=0.33; Figure 7.2F), and HR (NEU: 99±11 beats·min^{-1}; CLD: 99±13; P=0.33) were not different between the NEU and CLD trial.

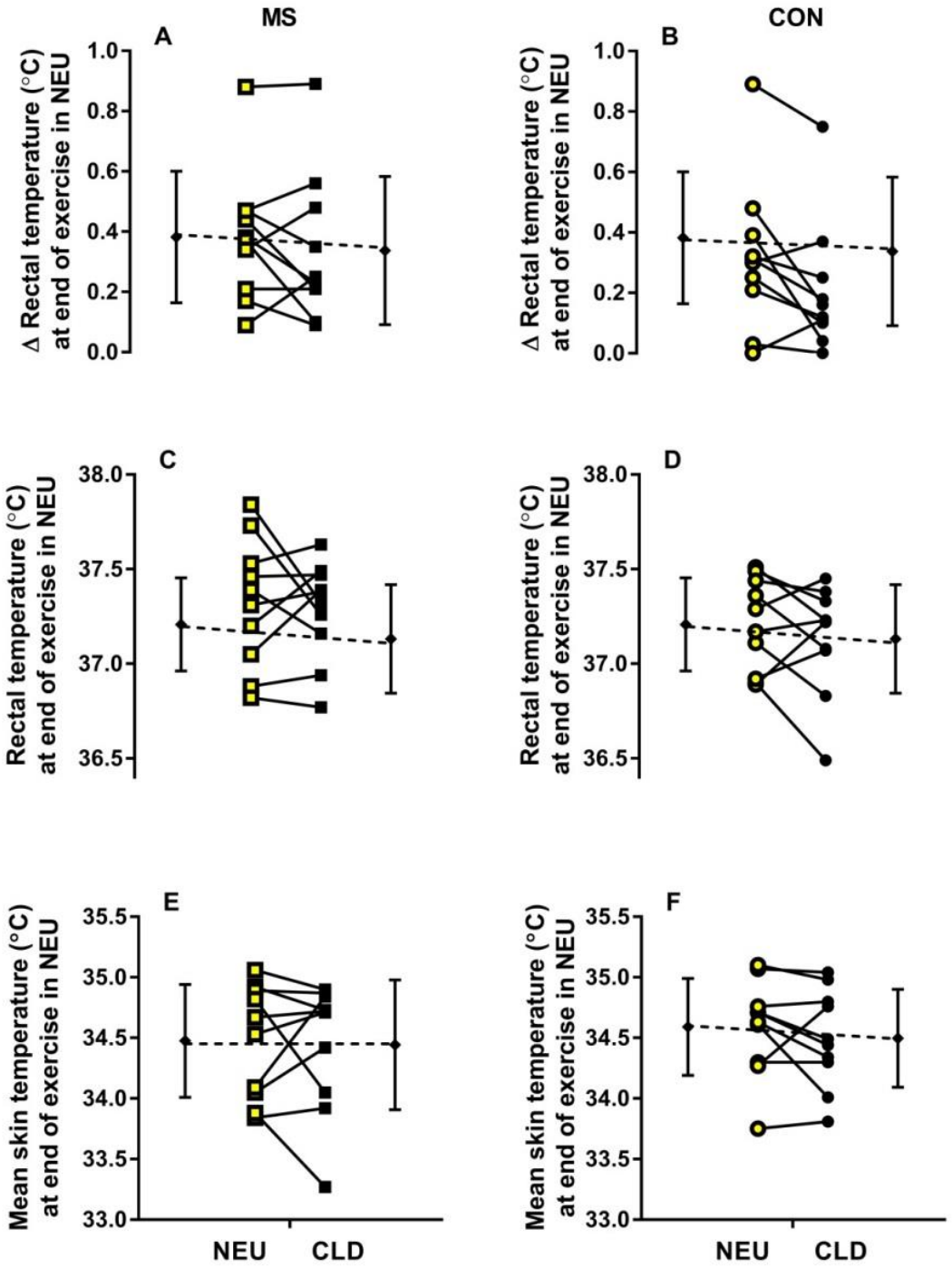

Figure 7.2A-F. Individual data and group mean (with SD) at the end of exercise in NEU (yellow) trial compared to the same time point in the CLD (black) trial for multiple sclerosis (MS: squares) and healthy controls (CON: circles). Values given for: change in rectal temperature from baseline (Panels A-B), absolute rectal temperature (Panel C-D), and absolute mean skin temperature (Panel E-F). Asterisk (*) indicates $P<0.05$.

Discussion

This study is the first to report the efficacy of cold-water ingestion for improving exercise tolerance in the heat in people with MS. Importantly, all MS participants that could not complete 60-min of exercise with the ingestion of thermoneutral water (NEU trial) due to volitional exhaustion, cycled for longer with ingestion of cold water (CLD trial). However, this longer exercise time in the CLD trial in the MS group was observed despite no influence of a lower ingested water temperature on core and skin temperatures as well as heart rate.

It is well documented that even small increases in body temperature are associated with a transient worsening of symptoms for individuals with MS (3, 4), otherwise known as Uhthoff's phenomenon (16). The development of fatigue, manifested by sensations of tiredness, is a common characteristic associated with Uhthoff's phenomenon and explains the shorter exercise time for 7 of the 10 MS participants who could not complete 60 minutes of exercise compared to CON group in the NEU trial. Although we attempted to match groups for aerobic fitness, it is evident that the MS group had an end-exercise HR that was ~15 beats·min^{-1} higher compared to the CON group in both trials. As such it is likely that VO_{2max} of the MS group was slightly overestimated and therefore this group worked at a slightly higher relative intensity than the 40%VO_{2max} target intensity. Nevertheless, 60 minutes of exercise at intensities as high as 60%VO_{2max} are sustainable even for older individuals (>60 y) with heart failure in the same environmental conditions as the present study (17). Therefore, the large difference in exercise duration in the MS group compared to the CON group cannot be attributed to differences in aerobic fitness; rather, they can be

primarily ascribed to the well-documented effects of MS on exercise capacity in the heat (1). Furthermore, given that relative exercise intensity and HR were consistent within the MS group between the NEU and CLD trials (NEU: 114±19 beats·min^{-1}; CLD: 113±17 beats·min^{-1}), the main finding that a longer exercise time occurs with cold-water ingestion remains independent of any potential differences in fitness.

Within the MS group, the longer exercise time to exhaustion in the CLD trial occurred despite a similar $T_{re,}$ T_{sk}, and HR at a comparable time point (i.e. same volume of exercise) than the time to exhaustion in the NEU trial for each individual. In other words, exercise tolerance in the heat was improved in the MS group with cold-water ingestion despite no independent influence of ingested water temperature on the development of thermal and cardiovascular strain with exercise time. Indeed, from the time point at which exercise exhaustion was reached in the NEU trial, T_{re} and T_{sk} in the CLD trial continued to rise to higher values by the time exercise stopped. It has been previously suggested that the underlying mechanism responsible for heat-related reduction in exercise performance in healthy athletes is potentially similar to heat sensitivity with MS, but with fatigue onset occurring alongside much smaller rises in body temperature with MS (18). It follows that heat-related decrements in the aerobic performance of healthy athletes can potentially be attenuated via the stimulation of cold-afferent receptors located in the oral cavity (12) and on the skin surface (19), without necessarily lowering core temperature. The present findings potentially support the notion that research examining the mitigation of heat- related decrements in exercise performance in healthy athletes may, at least to an extent, be translatable to the management of Uhthoff's phenomenon in the MS population.

Irrespective of participant group, for the same volume of exercise core and skin temperature were altered negligibly by ingested fluid temperature (Figure 5.2A, C and E), despite the greater internal heat loss via conduction with cold fluid ingestion. A recent series of studies (20-22) described fluid temperature-dependent alterations in sweating during exercise that are modulated, independently of core and skin temperatures, by visceral thermoreceptors located in the abdomen. Ultimately, the reduction in evaporative heat loss from the skin surface with cold fluid ingestion was found to counterbalance the greater internal heat loss, thereby yielding similar changes in whole body heat storage and thus similar changes in core temperature, irrespective of ingested fluid temperature (20). Although sweating rates are not reported in the present study, a similar fluid temperature- dependent modulation of skin surface evaporation could explain the similar levels of thermal strain between the NEU and CLD trials within both the MS and CON group. Another consideration is that the absolute amount of heat transfer generated by each 3.2 $ml \cdot kg^{-1}$ aliquot of 1.5°C water, even without any parallel alterations of skin surface evaporation, would only be ~35 kJ, which for an 82.5 kg individual with a mean body specific heat of 3.49 $kJ \cdot kg^{-1} \cdot °C^{-1}$ would yield a reduction in mean body temperature of only ~0.1°C.

Despite the profound impact of regular exercise on the physical and psychological health of individuals with MS (23), it has been reported that people with MS are less physically active (24), partly to avoid a temporary worsening of symptoms associated with an elevation in body temperature. Moreover, heat intolerance has been shown to greatly impact the capacity for many people with MS to remain among the workforce (5). Cold water ingestion is a simple strategy for improving exercise tolerance in the heat, which could be

used as an alternative to other less practical but currently recommended cooling strategies such as partial immersion in cold water prior to heat exposure (7) or donning an ice vest (25). It should be noted though that for individuals with MS susceptible to urinary incontinence, additional fluid ingestion might not prove an optimal solution. Therefore, future research must establish whether independently stimulating cold-afferent thermoreceptors in the oral cavity, via a cold mouth rinse, would be sufficient to mitigate heat-related decrements in exercise tolerance with MS, as reported with complete cold-water ingestion in the present study.

Limitations

The present study does not include subjective measures such as whole-body thermal sensation (WBTS) or rate of perceived exertion (RPE). As such, it is unclear whether alterations in WBTS and/or RPE contributed to the longer exercise duration in the heat with cold-water ingestion. Similarly, the onset and severity of MS-related symptoms were not specifically assessed during or after exercise, and we therefore cannot rule out that the longer exercise duration, which was apparently promoted by cold-water ingestion, resulted in any prolonged symptom-worsening post exercise. Future research should therefore investigate whether prolonged exercise duration affects heat related MS symptoms, and if ingesting cold water mitigates the development of MS symptom severity during exercise in the heat. As some participants reported some mild discomfort during cold fluid ingestion future research should also assess the efficacy of ingesting slightly warmer fluid temperatures.

The exercise time to exhaustion protocol with a fixed end-point of 60 minutes was selected to assess the capacity of an easily fatigued, non-athletic population. However, due to the large variability that is typically demonstrated in time to exhaustion studies, future research should examine the reliability of a different study design to assess performance in MS individuals such as a fixed RPE (26) or a time trial protocol (27). Finally, VO_{2max} values were estimated using HR and VO_2 responses at submaximal workloads that were then extrapolated to an age-predicted maximum HR level. However, to the best of our knowledge this formula has not been validated in an MS population and therefore merits further investigation particularly given that VO_{2max} seems to be slightly overestimated in the MS group in the present study.

Conclusion

In conclusion, the present study examined the influence of ingesting cold compared to thermoneutral water on exercise performance at a fixed low relative intensity (~40%VO_{2max}), and the concurrent elevation in core and skin temperature of heat-sensitive relapsing-remitting MS participants in a warm (30°C) environment. With thermoneutral water ingestion, exercise time was shorter in the MS group compared to age-matched controls, presumably due to the development of fatigue associated with Uhthoff's phenomenon. Cold-water ingestion resulted in a ~30% longer exercise time in the MS participants that could not complete 60 minutes of exercise in the thermoneutral water ingestion trial. However, while cold-water ingestion appeared to improve the exercise tolerance of the MS group in the heat, it did not blunt the rise in core and mean skin temperature with time. These findings provide a practical and simple strategy for individuals with MS

performing physical activity in hot environments and lend insight into the potential role of cold-afferent thermoreceptors that reside in the abdomen and oral cavity in the modulation of exercise tolerance with MS in the heat.

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Conflicts of Interest

There are no conflicts of interest to declare.

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CHAPTER VIII

GENERAL DISCUSSIONS AND CONCLUSION

SUMMARY

Multiple sclerosis is a demyelinating autoimmune disease of the central nervous system that results in scars and lesions in the brain and spinal cord. Symptoms most commonly experienced by people with MS include fatigue [1], cognitive decline [2], loss of balance [3], blurred vision, sensory enhancement (tingling or burning) and/or loss (numbness) [4], urinary incontinence [5] and sensitivities to the heat [6]. Up to 80% of people diagnosed with MS are sensitive to the heat, otherwise known as Uhthoff's phenomenon, which is characterised by a temporary worsening of symptoms when exposed to hot environments and/or during exercise. Despite its prevalence the underlying physiological mechanisms that cause heat sensitivities remain unclear. Many researchers have alluded to the idea that a rise in core temperature as small as 0.2 to 0.5°C will cause a temporary worsening of symptoms. However, very little evidence exists to support or refute the notion that a small rise in body temperature will trigger an onset of symptoms. Many people diagnosed with MS also experience autonomic dysfunction. Specifically, sudomotor dysfunction has been reported in MS patients during bouts of passive [7,8] heating, however, to the best of our knowledge, no research has investigated whether a blunted sweating response during exercise in warm and hot environments reduces heat loss from the body to the extent that people with MS demonstrated a greater rise in core temperature compared to a non-MS population. Indeed, if this was the case then thermoregulatory dysfunction may, at least in part, contribute to the development of Uhthoff's Phenomenon.

It is widely held that physical activity provides psychological and physiological health benefits for people with MS. Problematically, many people avoid physical activity, especially during the summer months, to avoid a temporary worsening of symptoms and associated fatigue

[9,10]. To understand how core temperature influences Uhthoff's phenomenon and how to mitigate the onset of symptoms at rest and during exercise, the capacity of autonomic thermoregulatory control in people with MS must first be determined at rest in both neutral and warm environments, and secondly during exercise in both warm and hot environments. Therefore, this thesis sought to 1) investigate whether resting core temperature is elevated in people with relapsing-remitting MS, compared to healthy controls and whether resting core temperature is associated with subjective fatigue levels, 2) determine whether people with relapsing-remitting MS demonstrate a greater rise in core temperature while cycling in a hot environment due to a blunted sweating response, and 3) after obtaining a clearer understanding of the thermoregulatory capacity in people with MS, we were able to determine a practical cooling strategy (cold fluid ingestion). As such, we assessed the effect of cold fluid ingestion on exercise capacity for people with MS compared to healthy controls while cycling in a hot environment. The primary findings of this thesis are as follows:

1. Chapter 3 disproved the notion that resting core temperature is elevated in patients with relapsing-remitting MS. Indeed, this study demonstrated that using precision thermometry is imperative when assessing small differences in core temperature between groups and thus, resting rectal, esophageal and tympanic temperature are similar between MS and health control groups.
2. Chapter 5 provided evidence that people with relapsing-remitting MS do not demonstrate greater rises in core temperature compared to healthy controls during exercise in the heat, despite a mild regional sudomotor dysfunction.

3. Chapter 7 demonstrated that, likely due to thermoreceptors within the mouth and upper gastrointestinal tract, ingestion of a cold (1.5°C) fluid during exercise in the heat can improve exercise capacity by ~30% by stimulating afferent receptors that provide information of cold sensations across the body. Importantly, this increase in exercise capacity occurred independently of changes in core and skin temperature.

As these main findings were discussed within their respective chapters, the following sections pertain to the implications and future directions because of the findings from this thesis.

IMPLICATIONS

Autonomic thermoregulation in MS

In chapter 3, the primary purpose of the investigation was to reassess the notion that rectal, esophageal and tympanic membrane temperature was elevated at rest in people with relapsing-remitting MS (RRMS) compared to healthy controls. Furthermore, the investigation sought to determine whether subjective measures of fatigue were associated with core temperature at rest. This study was designed based off previous research that demonstrated an elevated tympanic membrane temperature and associated fatigue in RRMS patients [11,12]. However, the physiological mechanisms that explained this elevated core temperature were unclear. When considering the human heat balance equation, a potential explanation for an elevated core temperature with MS may be a higher resting metabolic rate paralleled with vasomotor dysfunction, which can impair dry heat exchange at rest in normothermic conditions. However, why this would be limited to people with only RRMS and not secondary- or primary-progressive MS as suggested in previous studies [11,12] is difficult to understand. Ultimately,

our findings highlight that metabolic rate alongside rectal, esophageal and tympanic membrane temperature at rest is not elevated in people with RRMS compared to healthy controls. Furthermore, core temperature is not associated with subjective measures of physical, psychosocial or cognitive fatigue in neutral (25°C, 30% RH) and warm (30°C, 30% RH) environments. Lastly, while measures of skin blood flow were not reported for this study, there is a body of research to support the notion that vasomotor control is not impaired in people with MS during heat stress [7,13,8,14-16] therefore it seems unlikely to be impaired at rest in thermoneutral conditions.

In chapter 5, the purpose of the investigation was to elucidate whether a greater rise in core temperature during exercise in the heat, due to sudomotor impairments, was in part, responsible for heat intolerance in people with MS. Most research investigating sudomotor dysfunction in MS patients overlooked whether changes in core temperature were altered due to a blunted sweating response to passive heating. As such, it was unclear whether people with MS are sensitive to the heat during exercise due to a greater rise in core temperature, by virtue of a blunted sudomotor response. Findings from chapter 5 showed that although MS patients demonstrate a mild blunted sudomotor response on the forearm but not the upper back during 40 minutes of cycling in a warm (30°C, 30% RH) and hot (35°C, 30% RH) environment; this blunted sweating response is not sufficient to compromise heat loss during exercise to the extent that greater levels deep body temperature occur with MS even at hot (35°C) ambient temperatures. Notably, the rise in skin temperature was greater in MS participants following 40 minutes of exercise; however, this is likely due to a reduction in evaporation secondary to sudomotor dysfunction which was sufficient enough to impair superficial cooling (skin

temperature) however was not large enough to influence deep body temperature (rectal temperature). While it was hypothesised that MS patients would demonstrate a greater rise in core temperature compared to healthy controls, the findings from chapter 5 led to two major conclusions. Firstly, people with MS demonstrate sudomotor, but not vasomotor dysfunction, albeit, deep body temperature is not altered during exercise in warm and hot environments compared to healthy controls. This point is particularly important given in chapter 5, participants were cycling in ambient temperatures that are likely to represent the hottest conditions (30°C, 30%RH and 35°C, 30% RH) a heat sensitive person with MS is likely to expose themselves to. Secondly, knowing that autonomic thermoregulation in not compromised in people with MS, future research should focus more intently on developing strategies to mitigate the onset of heat-related symptoms and associated fatigue, and most notably, these strategies do not need to be developed to compensate for any major thermoregulatory dysfunction.

Uhthoff's Phenomenon and the role of core temperature

While it is evident that exercise and/or exposure to hot environments will undoubtedly cause a temporary worsening of symptoms in MS patients, there is little evidence that supports a direct relationship between a rise in core temperature and the onset of heat-related symptoms and associated fatigue. Indeed, research by Nelson [17] in 1969 demonstrated that even in the absence of a rise in core temperature, sitting in a hot bath induced a transient worsening of symptoms in MS patients. Similar findings were observed by Guthrie [18] who noted after only 8 minutes of whole body immersion in hot water MS patients presented with a worsening of symptoms. Furthermore, Poh et al [3] demonstrated a worsening of postural sway in MS individual exposed to hot environments, independently of changes in T_{core}. Lastly, and what may

be most surprising, almost all research investigating Uhthoff's phenomenon in MS patients, to the best of our knowledge, has only employed passive heating methods, and there was little to no replication of exercise induced symptom worsening for MS patients. This is of particular interest given Uhthoff's first reports of symptom worsening was in patients following a bout of exercise (active heating)[6].

Fatigue, characterised as a 'lack of energy and need for rest' [19,1] is the most commonly reported heat-related symptom for people with MS [1]. Because of the subjective nature of fatigue, there is currently no evidence that support the idea of a temperature threshold for the onset of heat-related fatigue. Indeed, Verikios [20] demonstrated that within Australia, 30% of people diagnosed with MS living in Tasmania are likely to turn on their air-conditioning to keep cool when outside temperatures are 20°C compared to only 3% of those people living in South Australia. Conversely, 85% of people diagnosed with MS living in South Australia are likely to turn their air-conditioning on when outside temperatures reach 30°C compared to ~96% of those people living in NSW. Furthermore, Bol et al [21] demonstrated there was no correlation between subjective measures of physical and mental fatigue and ambient temperature for people diagnosed with MS living in the Netherlands. However, most studies investigating heat-related fatigue within the MS population [1,19,22] employ subjective questionnaires that rely heavily on individual experiences, interpretations and memory. Nonetheless, most data reported on heat-related fatigue seem to suggest that the onset and severity heat-related fatigue is subjective and dependent on an individual's interpretation of how 'hot' they may feel. This raises questions as to whether a) core temperature actually influences heat-related fatigue for people with MS, b) whether heat induced fatigue occurs at lower rises in core temperature compared to

a healthy population [23] and c) whether there is a strong perceptual component to the onset of heat-related fatigue. Indeed, recent work by Filingeri et al [24] (Appendix D) demonstrated that a rise in rectal temperature as small as 0.4°C impairs cold peripheral thermal sensitivity compared to healthy controls. We hypothesised that small increases in core temperature impair afferent sensory signalling, potentially contributing to heat-related symptoms and fatigue in people with MS.

In chapter 7, we demonstrate for the first time, that heat sensitive people with MS can mitigate heat-related decrements in exercise tolerance when ingesting cold water, independently of changes in core and skin temperature. This study highlights several important points: firstly, heat-sensitive MS patients can exercise for ~30% longer by ingesting a cold drink, without altering the rise in core temperature. This is likely due to cold-afferent thermoreceptors that reside in the abdomen and oral cavity [24]. Secondly, cold fluid ingestion provides a practical and economical strategy that MS patients can use during exercise to mitigate the onset of heat-related fatigue. In doing so, improving exercise tolerance could allow MS patients to meet the weekly recommended physical activity requirements. Lastly, findings from this study suggest that there may be other physiological and perceptual mechanisms that influence heat-related fatigue for people with MS however future research is needed to investigate this notion. A final consideration for this study is that only 6 out of 10 participants were able to maintain exercise for 40 minutes compared to all 14 participants being able to exercise for 40 in study 2 of this thesis. This is primarily due the difference in exercise intensity between the two studies. Indeed, in study 2, participants were working at a fixed relative heat production, therefore exercise intensity

would differ greatly between participants and between study 2 and study 3 where participants were working at a fixed % of their maximal oxygen capacity.

FUTURE WORK

The results from the present data give rise to further research questions, some of which are described below.

In chapter 3, we established that resting core temperature was not elevated in people with MS, nor was it associated with elevated levels of fatigue. In chapter 5, we further highlight that during exercise in warm and hot environments, the rise in core temperature is similar between MS and control groups. Nonetheless, fatigue, specifically when exposed to hot environments is a big problem for most people diagnosed with MS. As such, future research should focus on identifying cooling strategies that could a) be used at home, work or during exercise to mitigate the onset of heat-related fatigue and symptom worsening and b) lessen the economic burden associated with symptom management. Future research should also consider the effect of heat intolerance for people with secondary- and primary-progressive MS.

In chapter 7, ingesting cold-fluid during exercise in a warm environment was beneficial in improving exercise tolerance by up to ~30% independently of changes in core and skin temperature for heat intolerant people with MS. No perceptual measures, such as thermal sensation or rate of perceived exertion were measured during this study, and it is unknown whether exercise tolerance was improved due to perceptual differences due to the cold fluid ingestion. As such, there is a need to understand the relative physiological and psychological contributions to heat intolerance in people with MS. Future research should also investigate

whether prolonged exercise duration affects heat related MS symptoms, and if ingesting cold water mitigates the development of MS symptom severity during exercise in the heat. Lastly, given up to 83% of people diagnosed with MS [5] can experience urinary incontinence, future research could explore alternative cooling strategies that will stimulate cold afferent thermoreceptors to elicit a cooling effect, without having to ingest large amounts of fluid, such as a cold mouth swill.

Limitations and delimitations

Multiple sclerosis participants included in the experimental chapters of this thesis present with RRMS only, have an EDSS of four or below, and are considered otherwise healthy. Due to the novelty of the research within this thesis, the inclusion of a physically able (EDSS of 5 or below) and otherwise healthy MS population was important to ensure that any differences that were reported within the respective thesis chapters were the results of the disease itself. However, it is unclear whether the results of any studies included in this thesis would be different if people with secondary-and/or primary progressive MS, with a higher EDSS score, and perhaps presenting with co-morbidities would change the results of the studies included in this thesis. Furthermore, many people with MS are on disease modifying treatments (DMT) and it is unclear how some of these treatments may affect the results within the experimental chapters. Specifically, in chapter 5, participants were excluded if they were taking any muscarinic receptor antagonists to ensure that any blunted sudomotor response to exercise was because of MS and not due to their DMT. However, whether MS patients taking a muscarinic receptor antagonist medication are at a greater risk of thermoregulatory impairment remains unclear.

Thesis Conclusions

The main findings from the experimental chapters in this thesis are as follows:

1. Thermoregulation at rest is not impaired in people with relapsing-remitting multiple sclerosis in neutral (25°C. 30% RH) and warm (30°C, 30% RH) environments. Specifically, resting metabolic rate, alongside rectal, esophageal and tympanic membrane temperature is not elevated at rest in people with MS compared to healthy controls. Furthermore, subjective measures of physical, cognitive and psychosocial fatigue are not associated with resting rectal temperature in people with relapsing-remitting MS. The results from chapter 3 highlight two important points
    a. When assessing differences in resting core temperature between clinical population groups, employing precision thermometric methods in controlled environmental conditions is imperative.
    b. People with MS are not at an inherent disadvantage in hot environments due to an elevated core temperature compared to healthy controls.
2. Despite mild autonomic impairment of sweating alongside slightly greater rises in mean skin temperature, people with MS do not get hotter during exercise at a fixed relative heat production in a warm (30°C, 30% RH) and hot (35°C, 30% RH) environments. Future research could investigate whether the same autonomic impairment is observed in patients with a higher disease status and whether this has a meaningful physiological impact.
3. Cold-water ingestion resulted in a ~30% longer exercise time to exhaustion in the MS participants that could not complete 60 minutes of exercise when ingesting room temperature water independently of rises in core and skin temperature. Furthermore, ingesting cold water

during exercise is a practical and economical strategy that can be employed to delay the onset of heat-related fatigue. These findings highlight that:

a. A rise in core temperature may not independently contribute to heat intolerance for people with MS
b. There may be other physiological and perceptual mechanisms that influence heat intolerance for people with MS.

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Appendix A

Attestation Statement for chapter 3

Faculty of Health Sciences
Author Contribution Statement

Candidate Name: Georgia Chaseling

Degree Title: Doctor of Philosophy (PhD)

Paper Title: Core temperature is not elevated at rest in people with relapsing-remitting multiple sclerosis

As the corresponding author of the above paper, I confirm that the above candidate has made the following contributions:

- Conception and design of the research
- Collection of data
- Analysis and interpretation of the findings
- Writing the paper and critical appraisal of content

Signed: OLLIE JAY Name: OLLIE JAY Date: 18-Jan-2019

Appendix B

Attestation Statement for chapter 5

Faculty of Health Sciences
Author Contribution Statement

Candidate Name: Georgia Chaseling

Degree Title: Doctor of Philosophy (PhD)

Paper Title: Thermoregulatory responses in multiple sclerosis patients cycling in warm and hot environments

As the corresponding author of the above paper, I confirm that the above candidate has made the following contributions:

- Conception and design of the research
- Collection of data
- Analysis and interpretation of the findings
- Writing the paper and critical appraisal of content

Signed: OLLIE JAY Name: OLLIE JAY Date: 18-Jan-2019

Appendix C

Attestation Statement for chapter 7

Faculty of Health Sciences
Author Contribution Statement

Candidate Name: Georgia Chaseling

Degree Title: Doctor of Philosophy (PhD)

Paper Title: Cold-Water Ingestion Improves Exercise Tolerance of Heat -Sensitive People with Multiple Sclerosis

As the corresponding author of the above paper, I confirm that the above candidate has made the following contributions:

- Conception and design of the research
- Collection of data
- Analysis and interpretation of the findings
- Writing the paper and critical appraisal of content

Signed: OLLIE JAY Name: OLLIE JAY Date: 18-Jan-2019

Appendix D

Other publications relating to the thesis, written during the doctoral candidature, but not formally included in the thesis

Exp Physiol 102.8 (2017) pp 887–893

Experimental Physiology

Short Communication

Afferent thermosensory function in relapsing–remitting multiple sclerosis following exercise-induced increases in body temperature

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Edited by: Michael White

New Findings

- **What is the central question of this study?**
  Between 60 and 80% of multiple sclerosis (MS) patients experience transient worsening of symptoms with increased body temperature (heat sensitivity). As sensory abnormalities are common in MS, we asked whether afferent thermosensory function is altered in MS following exercise-induced increases in body temperature.
- **What is the main finding and its importance?**
  Increases in body temperature of as little as ∼0.4°C were sufficient to decrease cold, but not warm, skin thermosensitivity (∼10%) in MS, across a wider temperature range than in age-matched healthy individuals. These findings provide new evidence on the impact of heat sensitivity on afferent function in MS, which could be useful for clinical evaluation of this neurological disease.

In multiple sclerosis (MS), increases in body temperature result in transient worsening of clinical symptoms (heat sensitivity or Uhthoff's phenomenon). Although the impact of heat sensitivity on efferent physiological function has been investigated, the effects of heat stress on afferent sensory function in MS are unknown. Hence, we quantified afferent thermosensory function in MS following exercise-induced increases in body temperature with a new quantitative sensory test. Eight relapsing–remitting MS patients (three men and five women; 51.4 ± 9.1 years of age; Expanded Disability Status Scale score 2.8 ± 1.1) and eight age-matched control (CTR) subjects (five men and three women; 47.4 ± 9.1 years of age) rated the perceived magnitude of two cold (26 and 22°C) and two warm stimuli (34 and 38°C) applied to the dorsum of the hand before and after 30 min cycling in the heat (30°C air; 30% relative humidity). Exercise produced similar increases in mean body temperature in MS [+0.39°C (95% CI: +0.21, +0.53) $P = 0.001$] and CTR subjects [+0.41°C (95% CI: +0.25, +0.58) $P = 0.001$]. These changes were sufficient to decrease thermosensitivity significantly to all cold [26°C stimulus, −9.1% (95% CI: −17.0, −1.5), $P = 0.006$; 22°C stimulus, −10.6% (95% CI: −17.3, −3.7), $P = 0.027$], but not warm, stimuli in MS. Contrariwise, CTR subjects showed sensitivity reductions to colder stimuli only [22°C stimulus, −9.7% (95% CI: −16.4, −3.1), $P = 0.011$]. The observation that reductions in thermal sensitivity in MS were confined to the myelinated cold-sensitive pathway and extended

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across a wider (including milder and colder) temperature range than what is observed in CTR subjects provides new evidence on the impact of rising body temperature on afferent neural function in MS. Also, our findings support the use of our new approach to investigate afferent sensory function in MS during heat stress.

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Introduction

Between 60 and 80% of individuals affected by the demyelinating disease multiple sclerosis (MS) experience heat sensitivity or Uhthoff's phenomenon, a characteristic transient worsening of clinical symptoms resulting from an increase in body (core) temperature of as little as 0.5°C (Davis *et al.* 2010).

Although temperature-dependent conduction slowing and/or block in demyelinated axonal segments seems to trigger this phenomenon (Davis *et al.* 2010), its underlying pathophysiology is still mostly unclear (Kiernan, 2017). As a result, there is no available pharmacological intervention that can mitigate the burden posed by heat sensitivity on MS sufferers and on their quality of life (Kanagaratnam *et al.* 2017).

Heat sensitivity in MS can be triggered by routine daily life activities, such as light physical work, exercise or exposure to sunlight (Davis *et al.* 2010). This results in MS patients experiencing severe challenges in maintaining appropriate physical activity levels (White & Dressendorfer, 2004) and in conducting normal working activities (e.g. early retirement because of heat intolerance and fatigue is highly prevalent amongst MS patients; Palmer *et al.* 2013). There is therefore a need for better understanding of the pathophysiology of heat sensitivity and its impact on normal physiological functions in order to develop appropriate interventions aimed at improving quality of life in MS.

Mechanistically, the transient effects of heat sensitivity on efferent autonomic functions (e.g. control of eye movements and regulation of thermoregulatory sweating) have been investigated in MS patients [e.g. increase in body temperature induces transient slowing of horizontal saccadic eye movements (Davis *et al.* 2008); thermoregulatory sweating is blunted during heat stress (Allen *et al.* 2017)]. However, the impact of heat sensitivity on afferent sensory function, e.g. skin sensations, has escaped quantitative assessment in MS. This is surprising, particularly given that somatosensory abnormalities, including reductions in skin sensitivity to temperature, are highly prevalent MS symptoms (incidence of 50–55%; Leocani *et al.* 2003).

The ability to sense changes in skin temperature represents the key trigger of behavioural responses to environmental- and exercise-induced heat stress (e.g. reducing physical work, removing clothing, seeking shade; Schlader *et al.* 2011; Filingeri, 2016). Changes in skin temperature often occur largely in advance of those elevations in core temperature that appear to induce heat sensitivity in MS (e.g. when being exposed to sunshine); hence, the assessment of how skin temperature sensing is impacted by heat sensitivity could be crucial to a better understanding of what behavioural and physiological factors could modulate vulnerability to heat stress in MS patients.

In humans, conscious skin temperature sensing (i.e. afferent thermosensory function) represents a unique index of afferent function (Filingeri, 2016), and its assessment could prove advantageous for non-invasive evaluation of somatosensory function within normally functioning non-myelinated pathways and within demyelinated afferent pathways in MS. Indeed, the neuro-anatomical and neurophysiological differences between the human peripheral and central pathways for cold (served by myelinated nerve fibres) and warm (served by non-myelinated nerve fibres) skin thermosensitivity (Dostrovsky & Craig, 1996; Iannetti *et al.* 2003) allow for the independent assessment of myelinated and non-myelinated afferent neural pathways (Filingeri, 2016). The opportunity to evaluate both myelinated and non-myelinated afferent pathways concurrently and non-invasively is particularly relevant in the context of a demyelinating disease, such as MS (Noseworthy *et al.* 2000).

The aim of this study, therefore, was to assess afferent thermosensory function in MS in conditions of exercise-induced increase in body temperature (in the range of what is shown to induce heat sensitivity, i.e. $\Delta \sim 0.5$°C; Davis *et al.* 2010) using a new quantititave sensory testing protocol (Filingeri *et al.* 2017*a*). We hypothesized that exercise-induced increase in body temperature would reduce cold (served by myelinated fibres), but not warm (served by non-myelinated fibres), local skin thermosensitivity in relapsing–remitting MS patients compared with age-matched healthy individuals.

Methods

Ethical approval. All human testing procedures conformed to the standards set by the latest revision of the *Declaration of Helsinki* and received University of Sydney ethical approval (HREC# 2015/125). Written informed consent was obtained from all participants.

Procedures. Using G*Power 3 software (Heinrich Heine Universität Düsseldorf, Germany; Faul *et al.* 2007), a power calculation was performed that used an α of 0.05, a β of 0.20 and an effect size of 16.8, calculated from the mean difference in thermal sensation between a control and a sensory-impaired condition (Filingeri *et al.* 2014), to determine a required sample size of eight individuals per group for the present study. As such, eight individuals diagnosed with relapsing–remitting MS (MS group; three men and five women; 51.4 ± 9.1 years of age; 75.3 ± 10.3 kg; 171 ± 8 cm tall; Expanded Disability Status Scale score 2.8 ± 1.1) and eight age-matched, otherwise healthy, control individuals (CTR group; five men and three women; 47.4 ± 9.1 years of age; 81.6 ± 18.9 kg; 172 ± 10 cm tall) participated in this study.

All participants took part in one experimental session. During this session, we used a new quantitative sensory testing protocol to assess the perceived magnitude of cold and warm temperature stimuli applied to the dorsum of the hand. Our new quantitative sensory test of afferent thermosensory function is based on the one we recently developed and tested in healthy individuals to assess the effects of whole-body thermal stress on local skin thermosensitivity (Filingeri *et al.* 2017*a*).

Sensory testing was performed at rest and after 30 min of semi-recumbent cycling (intensity of 35–45% of individual maximal aerobic capacity; this intensity is well below the lactate threshold for untrained individuals of similar age; Iredale & Nimmo, 1997) performed in an environmental chamber regulated to 30°C ambient air and 30% relative humidity.

The MS and CTR participants used a hand-scored 200 mm visual analog scale [anchor points, very hot (0 mm) and very cold (200 mm); middle point, neutral (100 mm)] to rate the perceived magnitude of thermal sensations elicited by two warm (34 and 38°C from a 30°C baseline) and two cold stimuli (26 and 22°C from a 30°C baseline) applied to the non-glabrous skin of the dorsum of the left hand with a thermal probe (25 cm^2; Physitemp Instruments, Clifton, NJ, USA), at rest and during the 30th minute of cycling. The probe was kept in contact with the skin throughout the session and maintained at 30°C baseline before stimuli were delivered. Within 5 s of the warm or cold stimuli being delivered, participants reported their local thermal sensations. After each stimulus, the probe was reset to 30°C, and each stimulus was separated by 5 s. The order of delivery of the stimuli was randomized, counterbalanced within and between participants.

Throughout the experimental session, rectal temperature (Mallinckrodt Medical, St. Louis, MO, USA) and a four-point mean skin temperature estimation (Concept Engineering, Old Saybrook, CT, USA) were recorded every 5 s. Mean body temperature was estimated as follows: [(rectal temperature × 0.8) + (mean skin temperature × 0.2)] (Gagge & Gonzalez, 1996).

Statistical analysis. We assessed changes in mean body temperature from pre- to post-cycling with individual Student's two-tailed paired *t* tests. We assessed the effects of group (MS *versus* CTR) and of stimulus temperature (34 *versus* 38 and 22 *versus* 28°C) on baseline (i.e. before exercise) magnitude estimation of warm and cold stimuli with a mixed-model ANOVA (note that data from cold and warm stimuli were analysed separately). We then assessed changes in magnitude estimation of warm and cold stimuli from pre- to post-cycling with individual Student's two-tailed paired *t* tests. In all analyses, $P < 0.05$ was used to establish statistically significant differences. Data are reported as means and 95% confidence intervals (CIs).

Results

Changes in mean body temperature. Mean body temperature was elevated to a similar extent after 30 min of cycling in both MS [mean difference, +0.39°C (+0.21, +0.53), $P = 0.001$] and CTR subjects [mean difference: +0.41°C (+0.25, +0.58), $P = 0.001$].

Magnitude estimation of warm and cold stimuli. Before exercise, there were no differences between MS and CTR subjects in the magnitude estimation of warm ($P = 0.172$) and cold stimuli ($P = 0.267$).

Likewise, exercise-induced increases in mean body temperature did not induce any change in the magnitude estimation of warm stimuli from pre-exercise values, in either the CTR [34°C stimulus mean difference, 1.0 mm (−26.3, 28.3), $P = 0.93$, Fig. 1*A*; 38°C stimulus mean difference, −9.6 mm (−25.1, 5.8), $P = 0.185$, Fig. 1*C*] or the MS group [34°C stimulus mean difference, 2.5 mm (−10.5, 15.5), $P = 0.633$, Fig. 1*B*; 38°C stimulus mean difference, 1.2 mm (−26.7, 29.3), $P = 0.919$, Fig. 1*D*].

Contrariwise, MS and CTR subjects experienced a reduction in cold sensitivity with elevations in body temperature, which extended across a wider temperature range (including milder and colder temperatures) in the MS compared with the CTR group. While the CTR group presented reduced cold sensitivity to the 22°C stimulus only [mean difference, −16.6 mm (−30.1, −3.2), $P = 0.022$; Fig. 2*C*], MS patients showed a significantly reduced cold sensitivity to both 22 [mean difference,

−18.7 mm (−29.9, −7.5), $P = 0.006$; Fig. 2*D*] and 26°C stimuli [mean difference, −13.2 mm (−24.5, −1.9), $P = 0.027$; Fig. 2*B*].

When expressed as the percentage of change from pre-exercise values, the reductions in cold sensitivity in MS corresponded to −9.1 (−17.0, −1.5) and −10.6% (−17.3, −3.7) for the 26 and 22°C stimuli, respectively. In CTR subjects, percentages of change from pre-exercise values sensitivity corresponded to 1.7 (−16.3, +19.8) and −9.7% (−16.4, −3.1) for the 26 and 22°C stimuli, respectively.

Discussion

We assessed, for the first time, afferent somatosensory function in MS patients relative to age-matched CTR individuals during exercise-induced increases in body temperature using our newly developed quantitative sensory test of afferent thermosensory function. We observed that in thermoneutral conditions (before exercise), the perceived magnitude of warm and cold stimuli appeared intact, whereas exercise-induced increases in mean body temperature of as little as ∼0.4°C were sufficient to decrease cold, but not warm, local skin thermosensitivity (∼10%) in patients with MS. This reduction occurred across a wider temperature range (i.e. including milder and colder temperatures) than what is observed in age-matched healthy individuals, indicating a clear role for MS in independently modulating afferent thermosensory function during an exercise-induced increase in body temperature.

To give the reader an idea of what such a reduction in local cold thermosensitivity means in practice, it

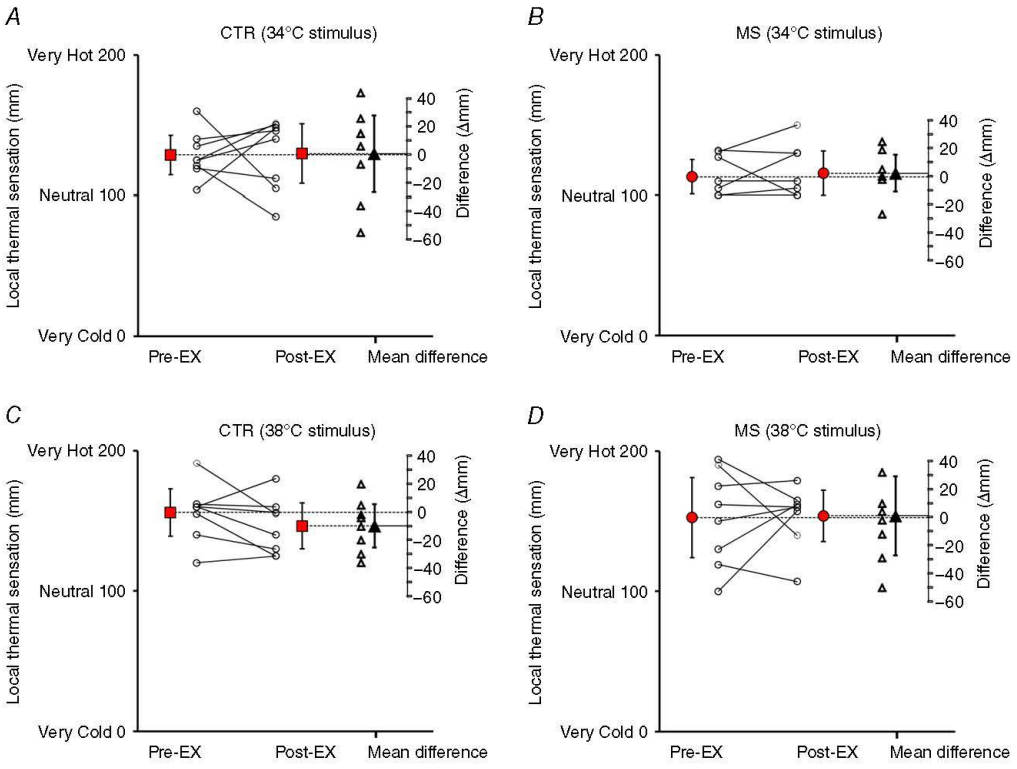

Figure 1. Impact of exercise-induced increase in body temperature on skin thermosensitivity to warm stimuli in control (CTR) subjects (*A* and *C*) and multiple sclerosis (MS) patients (*B* and *D*)
Individual ($n = 8$) and mean (±95% confidence interval) values for magnitude estimation of local thermal sensations resulting from 34 (*A* and *B*) and 38°C stimuli (*C* and *D*) before and after 30 min cycling are shown. It can be observed that exercise-induced increases in mean body temperature did not induce any change in the magnitude estimation of warm stimuli from pre-exercise values, in either the CTR or the MS group.

should be noted that MS participants experienced the 22°C stimulus postexercise to be as cold as the 26°C stimulus before exercise (compare Fig. 2*D* Post-EX with Fig. 2*B* Pre-EX), despite the same participants clearly distinguished between these two stimuli prior to exercise (compare Fig. 2*B* Pre-EX with Fig. 2*D* Pre-EX). As human cold sensitivity is known to be remarkably high (i.e. we are able to perceive stimuli of as little as 0.4°C below our skin temperature; Filingeri *et al.* 2017*b*), we believe that the magnitude of the observed reduction in MS cold thermosensitivity is therefore physiologically meaningful and could carry both fundamental and applied implications for the understanding and management of heat sensitivity in this neurological population.

Fundamentally, the observation that reductions in skin thermosensitivity in our MS group were confined to the myelinated cold-sensitive pathway could provide new evidence on the impact that increases in body temperature have on afferent transmission in demyelinated nerves in MS. In humans, magnitude estimation of skin thermal sensations is determined by afferent impulses produced by peripheral skin thermoreceptors (Filingeri *et al.* 2017*b*) and by their integration operated by central (subcortical/cortical) neural structures (Filingeri, 2016). Owing to the central, and not peripheral, nature of MS lesions within the nervous system (Noseworthy *et al.* 2000), it could be therefore suggested that the pronounced reduction in cold sensitivity observed in our relapsing–remitting MS group could be dependent

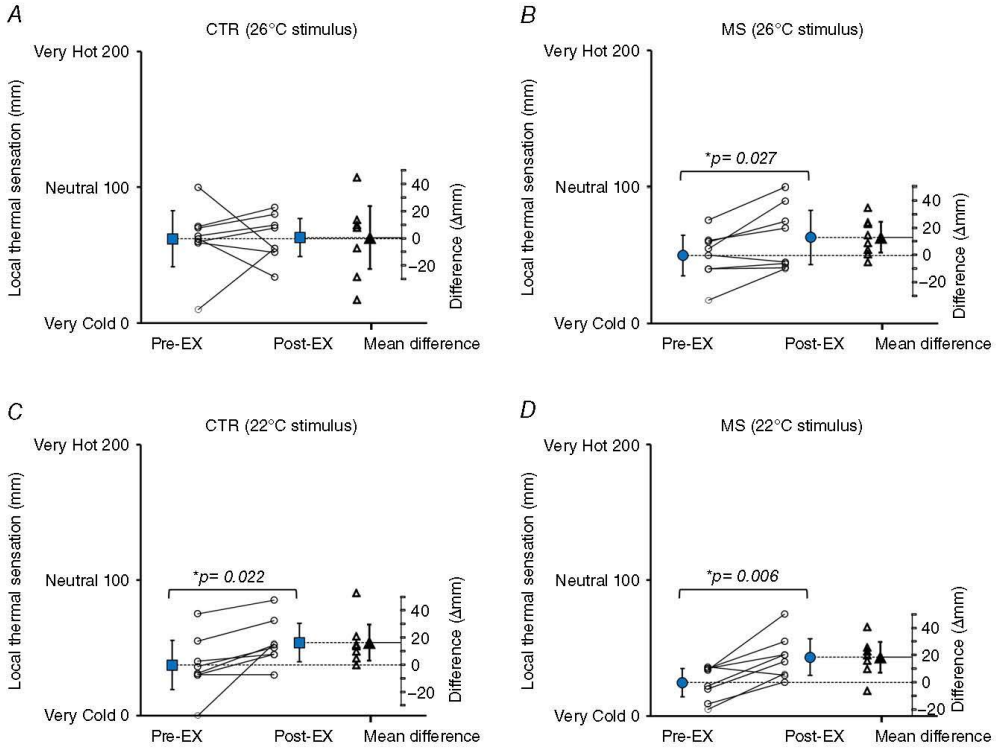

Figure 2. Impact of exercise-induced increase in body temperature on skin thermosensitivity to cold stimuli in CTR subjects (*A* and *C*) and MS patients (*B* and *D*)
Individual ($n = 8$) and mean (±95% confidence interval) values for magnitude estimation of local thermal sensations resulting from 26 (*A* and *B*) and 22°C stimuli (*C* and *D*) before and after 30 min cycling are shown. It can be observed that exercise-induced increase in mean body temperature induced a reduction in cold sensitivity in MS and CTR subjects, although this was more pronounced in the MS group (i.e. sensitivity to both to 26 and 22°C stimuli was reduced, $^*P < 0.05$, Student's two tailed paired *t*-test).

on heat-induced alterations in the processing of afferent somatosensory inputs within central neural centres.

Although our results point to a heat-induced alteration in central neural transmission, it should be noted that the observed modulation of local cold sensitivity in our MS group could also be dependent on additional mechanisms, amongst which is endogenous analgesia. Exercise-induced analgesia (Koltyn, 2000) has been previously shown to reduce cold (Ouzzahra *et al.* 2014) and warm sensitivity (Gerrett *et al.* 2014) in healthy individuals; an observation that is in line with the reduction in sensitivity to colder temperatures (i.e. 22°C) recorded in our CTR group. Furthermore, we recently discovered that whole-body thermal stress modulates local skin thermosensitivity in healthy adults (Filingeri *et al.* 2017*a*) via central mechanisms similar to those underlying endogenous analgesia (Ossipov *et al.* 2010). Hence, the possibility cannot be excluded that an interaction between pathological (i.e. demyelination) and physiological mechanisms (i.e. exercise analgesia) could underlie our observed heat-induced modulation of afferent thermosensory function in MS.

Although further studies are required to determine the exact physiological mechanisms underlying the thermosensory modulation observed here, our data indicate a clear role for MS in independently modulating afferent thermosensory function during exercise-induced heat stress, which is a new finding that could have important applied implications. For example, the fact that skin thermosensitivity to cold could be significantly reduced during heat stress in MS should be taken into account when designing or developing cooling aids (e.g. ice vests) aimed at mitigating the adverse effects of heat sensitivity (Davis *et al.* 2010). If not adequately tailored to the potential perceptual changes in temperature sensing that occur during heat stress, the perceptual benefits for MS users of such devices (e.g. improving thermal comfort during exercise and sunshine exposure) could be hindered by heat sensitivity-induced reductions in the ability to sense the 'true coldness' of these cooling interventions, when this is most needed (e.g. during elevation in body temperature).

Along with their fundamental and applied implications, our preliminary findings also support the use of our newly developed quantitative sensory test of afferent thermosensory function as a methodology to characterize thermal stress-induced changes in afferent sensory function quantitatively in MS within both clinical and experimental contexts. From a clinical perspective, this knowledge could be beneficial to support the design of quantitative testing procedures supporting early clinical detection and assessment of disease progression and treatment effectiveness in MS.

To date, research on the impact of heat sensitivity in MS symptoms has focused on the investigation of the efferent control of physiological functions (e.g. control of movements, blood pressure and sweating; Davis *et al.* 2008, 2010). Given that afferent sensory abnormalities are highly prevalent symptoms in MS (Leocani *et al.* 2003), we propose that our new methodology could be implemented in future experimental approaches to characterize quantitatively heat-stress-induced changes on both afferent and efferent physiological pathways in MS and provide a more comprehensive picture of the impact of heat sensitivity in MS. Afferent and efferent dysfunctions occur frequently and early in the disease (Leocani *et al.* 2003), and their concurrent assessment via specifically designed quantitative methods could be essential to improve our understanding of the pathophysiology of MS.

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Additional information

Competing interests

None declared.

Author contributions

All experimental testing was performed at the Thermal Ergonomics Laboratory, Faculty of Health Sciences, University of Sydney, Sydney, NSW, Australia. All authors contributed to the conception and design of the study. D.F. and G.C. performed data acquisition. D.F. performed data analysis and drafted the manuscript. All authors contributed to editing significant portions of the manuscript and figures. All authors approved the final version of the manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

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Acknowledgements

The authors are thankful to Professor George Havenith (Loughborough University) for loaning the thermosensory analyser used in this study.

Appendix E

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Wolters Kluwer

Title: Natural history of multiple sclerosis: implications for counselling and therapy
Author: Christian Confavreux and Sandra Vukusic
Publication: Current Opinion in Neurology
Publisher: Wolters Kluwer Health, Inc.
Date: Jun 1, 2002
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Title: Body Temperature Is Elevated and Linked to Fatigue in Relapsing-Remitting Multiple Sclerosis, Even Without Heat Exposure

Author: James F. Sumowski,Victoria M. Leavitt

Publication: Archives of Physical Medicine and Rehabilitation

Publisher: Elsevier

Date: July 2014

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Title: Afferent thermosensory function in relapsing–remitting multiple sclerosis following exercise-induced increases in body temperature

Author: Davide Filingeri, Georgia Chaseling, Phu Hoang, et al

Publication: Experimental Physiology

Publisher: John Wiley and Sons

Date: May 23, 2017

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Appendix F

Ethical approval for research

Ethical approval for chapter 3 and 5

THE UNIVERSITY OF SYDNEY

Research Integrity
Human Research Ethics Committee

Monday, 30 March 2015

Dr Ollie Jay
Exercise Health and Performance; Faculty of Health Sciences
Email: Ollie.jay@sydney.edu.au

Dear Ollie

I am pleased to inform you that the University of Sydney Human Research Ethics Committee (HREC) has approved your project entitled "**How much hotter do MS patients get during physical activity in the heat?**".

Details of the approval are as follows:

Project No.: **2015/125**

Approval Date: **17 March 2015**

First Annual Report Due: **17 March 2016**

Authorised Personnel: **Jay Ollie; Chaseling Georgia; Filingeri Davide; Hoang Phu;**

Documents Approved:

Date Uploaded	Type	Document Name
06/02/2015	Advertisements/Flyer	MSstudy Flyer
06/02/2015	Human Ethics Application Form	Doctors Letter
11/03/2015	Other Type	GP Letter Final
11/03/2015	Participant Consent Form	Consent Form Final
11/03/2015	Participant Info Statement	Participant Information Statement Final

HREC approval is valid for four (4) years from the approval date stated in this letter and is granted pending the following conditions being met:

Condition/s of Approval

- Continuing compliance with the National Statement on Ethical Conduct in Research Involving Humans.
- Provision of an annual report on this research to the Human Research Ethics Committee from the approval date and at the completion of the study. Failure to submit reports will result in withdrawal of ethics approval for the project.
- All serious and unexpected adverse events should be reported to the HREC within 72 hours.
- All unforeseen events that might affect continued ethical acceptability of the project should be reported to the HREC as soon as possible.

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The University of Sydney
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F +61 2 8627 8177
E ro.humanethics@sydney.edu.au
sydney.edu.au

ABN 15 211 513 464
CRICOS 00026A

THE UNIVERSITY OF SYDNEY

- Any changes to the project including changes to research personnel must be approved by the HREC before the research project can proceed.
- Note that for student research projects, a copy of this letter must be included in the candidate's thesis.

Chief Investigator / Supervisor's responsibilities:

1. You must retain copies of all signed Consent Forms (if applicable) and provide these to the HREC on request.
2. It is your responsibility to provide a copy of this letter to any internal/external granting agencies if requested.

Please do not hesitate to contact Research Integrity (Human Ethics) should you require further information or clarification.

Yours sincerely

Dr Stephen Assinder
Chair
Human Research Ethics Committee

This HREC is constituted and operates in accordance with the National Health and Medical Research Council's (NHMRC) National Statement on Ethical Conduct in Human Research (2007), NHMRC and Universities Australia Australian Code for the Responsible Conduct of Research (2007) and the CPMP/ICH Note for Guidance on Good Clinical Practice.

Ethical approval for chapter 7

THE UNIVERSITY OF SYDNEY

Research Integrity
Human Research Ethics Committee

Thursday, 21 April 2016

Dr Ollie Jay
Exercise Health and Performance; Faculty of Health Sciences
Email: Ollie.jay@sydney.edu.au

Dear Ollie

I am pleased to inform you that the University of Sydney Human Research Ethics Committee (HREC) has approved your project entitled "**Does a cool drink during exercise in the heat mitigate thermal strain for MS participants"**.

Details of the approval are as follows:

Project No.: **2016/214**

Approval Date: **20 April 2016**

First Annual Report Due: **20 April 2017**

Authorised Personnel: **Jay Ollie; Barnett Michael; Filingeri Davide; Chaseling Georgia; Hoang Phu;**

Documents Approved:

Date Uploaded	Type	Document Name
14/04/2016	Participant Info Statement	Participant Information sheet - clean
14/04/2016	Safety Protocol	Protocol - clean
29/03/2016	Questionnaires/Surveys	Demographics Questionnaire - Clean
15/02/2016	Participant Consent Form	Consent form
15/02/2016	Other Type	Neurologist/GP consent
15/02/2016	Other Type	Self-reporting medical clearance
15/02/2016	Advertisements/Flyer	Recruitment Flyer

HREC approval is valid for four (4) years from the approval date stated in this letter and is granted pending the following conditions being met:

Condition/s of Approval

- Continuing compliance with the National Statement on Ethical Conduct in Research Involving Humans.

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- Provision of an annual report on this research to the Human Research Ethics Committee from the approval date and at the completion of the study. Failure to submit reports will result in withdrawal of ethics approval for the project.
- All serious and unexpected adverse events should be reported to the HREC within 72 hours.
- All unforeseen events that might affect continued ethical acceptability of the project should be reported to the HREC as soon as possible.
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Please do not hesitate to contact Research Integrity (Human Ethics) should you require further information or clarification.

Yours sincerely

Glen Davis
E

Professor Glen Davis
Chair
Human Research Ethics Committee

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