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Body temperatures, thermal comfort, and neuropsychological responses to air temperatures ranging between 12°C and 39°C in people with Multiple Sclerosis

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ABSTRACT

The negative effects of thermal stress on Multiple Sclerosis (MS)' symptoms have long been known. However, the underlying mechanisms of MS heat and cold intolerance remain unclear. The aim of this study was to evaluate body temperatures, thermal comfort, and neuropsychological responses to air temperatures between 12 and 39 °C in people with MS compared to healthy controls (CTR). Twelve MS (5 males/7 females; age: 48.3 ± 10.8 years; EDSS range: 1–7) and 11 CTR participants (4 males /7 females; age: 47.5 ± 11.3 years) underwent two 50-min trials in a climatic chamber. Air temperature was ramped from 24 °C to either 39 °C (HEAT) or 12 °C (COLD) and we continuously monitored participants' mean skin (T_{sk}) and rectal temperatures (T_{rec}), heart rate and mean arterial pressure. We recorded participants' self-reported thermal sensation and comfort, mental and physical fatigue, and we assessed their cognitive performance (information processing). Changes in mean T_{sk} and T_{rec} did not differ between MS and CTR neither during HEAT nor COLD. However, at the end of the HEAT trial, 83% of MS participants and 36% of CTR participants reported being "uncomfortable". Furthermore, self-reports of mental and physical fatigue increased significantly in MS but not CTR ($p < 0.05$), during both HEAT and COLD. Information processing was lower in MS vs. CTR ($p < 0.05$); yet this cognitive impairment was not exacerbated by HEAT nor COLD ($p > 0.05$). Our findings indicate that neuropsychological factors (i.e. discomfort and fatigue) could contribute to MS heat and cold intolerance in the absence of deficits in the control of body temperature.

1. Introduction

Climate change is one of the greatest threats to human survival and it is accompanied by extreme, long-term changes in weather patterns, including more frequent and prolonged heat waves and cold spells [1,2]. Considerable increases in global temperatures have occurred over the last few decades, and concerns have arisen about excess mortality rates due to heat and cold stress around the world [1,3]. Patients with chronic illnesses, such as those who suffer from neurodegenerative diseases, may be particularly vulnerable to excessive heat and cold stress. Our understanding of the physiological and pathological effects of heat and cold stress on healthy people has grown dramatically in the last decades [4]; nevertheless, our knowledge on how these environmental stressors impact neurological patients like those with Multiple Sclerosis (MS) remain fragmentary, due to an under representation of these clinical groups in heat and cold stress research.

MS is the most frequent autoimmune neurological disease in young people, with >2.5 million individuals affected worldwide. Currently, there is no cure for MS, and it is considered a major public health issue [5]. A unique aspect of MS is that patients may suffer from temperature sensitivity, a temporary worsening of their MS symptoms [6] as a result of increases (i.e. namely Uhthoff's phenomenon or heat sensitivity) and/or decreases (i.e. namely cold sensitivity) in body temperatures (i.e. skin and core/internal temperatures) [7]. Specifically, when body temperature changes, neural transmission in de-myelinated neurons in the central nervous system (CNS) may be slowed or blocked, resulting in pseudo-exacerbations, i.e. a temporary worsening of symptoms without actual myelin inflammation or damage [7–9], which subsides when body temperature reverts to its normothermic levels [7,10].

Up to 80% of MS patients report heat sensitivity [11], which is

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considered an "invisible MS symptom" [12,13]. Increases in body temperatures, such as those caused by sunlight exposure [14,15] or hot water immersion [16], can cause a rapid loss of motor function, rendering MS patients physically restrained and potentially exposed to fatal hyperthermia [16]. Warm ambient temperatures may diminish postural stability [17] and affect cognitive state [18], both of which increase the risk of falls in MS patients [19,20]. Previous research indicated that heat intolerance in MS does not seem attributable to thermoregulatory impairments [21], however, it may impact MS symptoms such as fatigue, pain, concentration and urination urgency [22]. The exacerbation of the MS symptoms may have profound implications for MS quality of life . The high prevalence of heat intolerance in this clinical group [23,24,] creates barriers to maintaining appropriate physical activity levels [25] and conducting normal working activities [,26], which in turn can cause employment loss, early retirement, and healthcare cost burdens .

Aside from heat sensitivity, it is also known that 15% of people with MS experience worsening symptoms during winter, exposure to cold ambient temperatures, and during cold baths [27]. The presence of demyelinating lesions in the hypothalamus, the main area of the CNS that controls body temperature, appears to be the primary driver of cold sensitivity in MS resulting in thermoregulatory dysfunction in the form of blunted autonomic responses (i.e. vasoconstriction, shivering) to cold stress [28]. While cold sensitivity is less common than heat sensitivity in MS [29,30], cold-induced pseudo-exacerbations can also impact patients' quality of life significantly.

The adverse effects of heat and cold on MS have been known for over 100 years [11]. However, we still know very little on how a) changes in body temperatures for a given heat load; and b) neuropsychological mechanisms (e.g. thermal discomfort and self-reported fatigue), contribute to heat and cold intolerance in people with MS [31]. Neuropsychological mechanisms underlying heightened thermal discomfort during heat and cold exposures have been understudied in MS, despite these could offer insights on why certain patients may report heat and cold intolerance in the absence of any thermoregulatory impairment [1]. We know that thermal discomfort is described as a state of mind associated with dissatisfaction with the surrounding thermal environments [32–34]. Research in the built environment has indicated that people with MS are likely to report being dissatisfied with warm and cold environments that have air temperatures below and above 23 °C (57). In addition, recent evidence has indicated that when given the opportunity to alleviate exercise-induced heat stress via voluntary cooling, people with MS engage in this behaviour to a greater extent than healthy controls, secondary to the experience of greater discomfort for the same change in body temperatures [35]. It is therefore reasonable to hypothesise that perceptual mechanisms involved in thermal discomfort could be at least partly responsible for MS heat and cold intolerance.

Whilst the preliminary evidence described above is encouraging, we still lack systematic investigations on the relationship between air temperature, body temperatures, and neuropsychological status in people with MS exposed to a broad range of heat and cold stress. Furthermore, we lack evidence on the impact that this may have on typical cognitive symptoms in MS, such as decreased information processing. Hence, the aim of this study was to evaluate body temperatures, thermal comfort, and neuropsychological responses (i.e. self-reported physical and mental fatigue) to air temperatures ranging between 12 and 39 °C in people with MS. We hypothesised that people with MS would present greater changes in body temperatures along with greater increases in thermal discomfort and self-reports of fatigue than healthy counterparts for a given change in air temperature (i.e., either increases and decreases), with potential detrimental effects to cognitive performance under thermal stress.

2. Methods

2.1. Ethical approval

The testing procedures were explained to each participant, and they all gave written informed consent for participation. The study was approved by the Loughborough University Ethics Sub-Committee for Human Participants (#R17-P094), and testing procedures were in accordance with the tenets of the Declaration of Helsinki (note: the study was not registered in a database).

2.2. Participants

Using G*Power 3 software (Heinrich-Heine-Universität Düsseldorf, Germany) we performed a sample size calculation based on a mean difference between groups of 1.0 ± 0.5 °C (mean ± SD) in whole-body mean skin temperature (T_{sk}) following heat exposure. This effect size was based on data from Dufour and Candas (65), who reported a similar heat-induced difference in mean T_{sk} between a younger and older group of participants exposed to passive heating conditions alike the ones used in the current study. We considered this as an appropriate and meaningful effect size, given the paucity of data on passive heat/cold exposures in MS participants, as well as based on some similarities between MS and older individuals in their greater vulnerability to heat. The resulting effect size $f = 1$, combined with an $\alpha = 0.05$ and a β (power) = 0.8, determined a minimum sample of eight participants per group. Accordingly, we first recruited twelve people with MS (MS group; $N = 12$; 5 males / 7 females; age: 48.3 ± 10.8 years; height: 1.72±0.13 m; body mass: 76.5 ± 17.5 kg; Expanded Disability Status Scale range: 1–7), who presented with various disease courses [i.e. relapsing-remitting ($N = 7$), primary ($N = 4$) and secondary progressive ($N = 1$) MS]. We appreciate that those disease courses present distinct pathophysiological pathways, and the inclusion of various MS types in this experiment was also driven by constraints associated with convenience sampling. Second, we recruited a sex- and age-matched healthy control (CTR) individual for each MS participant but MS participant ID8 (i.e. due to time-constrains with study completion). CTR individuals reported no sensory, cardiovascular, neurological, or metabolic diseases (CTR group; $N = 11$; 4 males / 7 females; age 47.5 ± 11.3 years; height: 1.69 ±0.08 m; body mass: 74.4 ± 16.7 kg). Participants individual characteristics are reported in Table 1. In the MS group, MS participant 10 reported taking the immunomodulator Copaxone, and the MS participant 5 reported taking the spasticity medication Baclofen. In addition, MS participant 5 self-reported commonly experiencing moderate anxiety and pain catastrophizing; MS participant 6 self-reported commonly experiencing moderate stress, depression and anxiety, and pain catastrophizing; MS participant 9 self-reported commonly experiencing moderate stress, depression, and anxiety; and MS participant 12 self-reported commonly experiencing moderate anxiety.

Matching MS and CTR groups by age, sex, and (to the extent possible) body dimensions, aimed to minimize confounding factors. Exclusion criteria for relapsing-remitting MS participants were having had a (self-reported) relapse in the three months prior to the experiment (i.e. defined as being at least 3 months out from receiving a steroid injection and/or being hospitalized), and (applicable to all MS participants) to be currently taking medications that directly affect cognition. Three MS participants (P5, P10, and P12) reported previous experience of abnormal sensitivity to wetness on their skin. The phase of the menstrual cycle was not controlled in the female participants. All participants had lived in the UK for at least 2 years prior to testing and they had not travelled outside of the UK for at least 3 months prior to testing.

Participants were instructed to refrain from: 1) performing strenuous exercise in the 48 h preceding testing; 2) consuming caffeine or alcohol in the 24 h preceding testing; 3) consuming food in the 3 h preceding testing. All testing took place at Loughborough (UK) between June 2017 and July 2019, spanning different seasons. There we no differences

Table 1
Individual characteristics of the 12 MS participants (i.e., MS ID), and 11 healthy CTR tested (i.e., CTR ID). Each individual with MS but ID8 was had a sex- and age-matched CTR. Shaded rows for the MS ID indicate participants reporting experience of wetness sensing abnormalities. Ethnicity: *A*= Asian; WE= White European. EDSS= Expanded Disability Status Scale. MS type: RR= Relapsing Remitting; PP= Primary Progressive; SP= Secondary Progressive. MS Medications.

MS ID	Sex	Age	Height (m)	Body mass (Kg)	Ethnicity	EDSS (self-reported)	MS type	MS Medications	CTR ID	Sex	Age (y)	Height (m)	Body mass (Kg)	Ethnicity
1	M	38	1.66	69.0	A	1	RR	–	1	M	37	1.77	70.6	WE
2	F	58	1.73	68.9	WE	6.5	RR	–	2	F	61	1.68	63.2	WE
3	F	59	1.6	47.8	WE	6.5	PP	–	3	F	60	1.63	76.6	WE
4	M	44	1.78	76.3	WE	1	RR	–	4	M	44	1.78	56.5	WE
5	F	51	1.57	99.4	WE	6.5	PP	Baclofen	5	F	50	1.54	83.8	A
6	M	63	1.97	96.0	WE	6.5	SP	–	6	M	62	1.70	83.4	WE
7	F	33	1.68	104.7	WE	3.5	RR	–	7	F	32	1.71	58.4	WE
8	M	61	1.78	89.5	WE	6	PP	–		M				WE
9	F	53	1.74	61.1	WE	6	PP	–	8	F	55	1.60	66.2	WE
10	M	47	1.92	77.6	WE	7	RR	Copaxone	9	M	48	1.82	73.9	WE
11	F	33	1.63	63.7	WE	3.5	RR	–	10	F	31	1.72	116.7	WE
12	F	40	1.61	63.6	A	3	RR	–	11	F	42	1.67	68.9	WE
Mean (SD)		48.3 (10.8)	1.72 (0.13)	76.5 (17.5)		4.7 (2.2)			Mean (SD)		47.5 (11.3)	1.69 (0.08)	74.4 (16.7)	

between the MS and CTR groups in the frequency of testing across seasons (i.e. MS group: 12 tests carried out during winter months / 8 tests carried out during spring months / 16 tests carried out during summer months; CTR group: 10 tests carried out during winter months / 6 tests during spring months / 17 tests during summer months) as well as in average outdoor temperatures (i.e. MS group: 15.8 ± 6.2 °C vs. CTR group: 12.8 ± 8.2 °C; T-test $p = 0.09$). It should be noted that the participants of the current study are the same as the ones who took part in a related investigation recently reported in [36].

2.3. Experimental design

We used a single-blind approach based on a repeated-measure design. All participants took part in 2 experimental trials on 2 separate days in counterbalanced order, and with a minimum 48-hour interval between them. During each trial, participants underwent either one of two 50-min air temperature ramps in a climatic chamber, i.e., HEAT, (target air temperature: 39 °C; relative humidity: 50%), or COLD (target ambient temperature: 12 °C; relative humidity: 50%). The HEAT and COLD trials were designed to induce large changes in whole-body mean Tsk, but not core (rectal) temperature (Trec). This was achieved by ramping the air temperature in the climatic chamber from a 24 °C baseline to the target 39 °C or 12 °C during the 50-min exposure.

We chose a mean Tsk manipulation to explore the effects of temperature sensitivity in MS (as opposed to a core temperature manipulation) [6], as this is a more realistic and relevant scenario encountered by people with MS who may be exposed to sunlight, warm, or cold environments in their daily life. We are aware that the long-standing view on temperature-induced symptoms worsening in MS is that this is driven by temperature-dependant slowing of neural conduction within the central nervous system, due to changes in internal core temperature of as little as ~0.5 °C [37]. However, such instances result from increases in core temperature induced by large heat loads, which are likely to be commonly experienced only by people with MS who undergo exercise at significant intensities and/or in warm environments. In this regard, experimental and epidemiological data indicates that warm ambient-induced increases in Tsk can decreases postural stability [17] and worsens cognitive status in pwMS [38], thereby supporting a role for changes in mean Tsk in worsening MS symptoms. The choice of 50% relative humidity is based on previous empirical evidence [39,40] to minimise its effects on heat balance and thermal comfort [33].

During all trials, we measured body mass prior to and following the experimental protocol to determine whole-body fluid loss, which was adjusted for fluid intake (allowed to be ad libitum). Also, we continually monitored participants' mean Tsk and Trec, heart rate (HR) and blood pressure (used for the estimation of mean arterial pressure, MAP), and we required participants to self-report their whole-body thermal sensation and comfort, mental and physical fatigue. Finally, we assessed participants' cognitive performance at beginning and at the end of each exposure (see Experimental protocol for details).

2.4. Experimental protocol

Participants arrived at the laboratory on testing days and underwent preliminary measurements and preparation. They changed into running shorts (and sport-bra) before we assessed their semi-nude body mass on a precision scale (SECA 874, Germany), and their height on a wall stadiometer. They then self-inserted a rectal thermometer 12-cm beyond the anal sphincter (Viamed Ltd, West Yorkshire, UK) to record T_{rec} as an indicator of core temperature. Skin thermistors (Grant, Cambridge, UK) were taped to six locations on the left side of the body (cheek, upper chest, outer mid lower arm, hand dorsum, anterior thigh and lower lateral back) to record local T_{sk} for the estimation of mean T_{sk} according to the following equation [41]:

$$mean\ T_{sk} = (cheek\ T_{sk} \times 0.14) + (upper\ chest\ T_{sk} \times 0.19) + (\text{outer mid lower arm } T_{sk} \times 0.11) + (hand\ dorsum\ T_{sk} \times 0.05) + (anterior\ tigh\ T_{sk} \times 0.32) + (lower\ lateral\ back\ T_{sk} \times 0.19)$$

Both T_{rec} and local T_{sk} were recorded at 2 Hz during all trials via a dedicated data acquisition system (USB-Temp, MCCdaq, USA) and custom-written software (DASYLab, MCCdaq, USA). Following this preparation, participants moved into the climatic chamber, which was regulated at ~24 °C (~50% relative humidity) and underwent 25 min of resting on a chair to adjust to the environmental conditions. During this 25-min baseline, participants were familiarised with the experimental procedures and performed a test of cognitive performance assessing information processing, via the Symbol Digit Modality Test (SDMT), as per Multiple Sclerosis Functional Composite measure [42]. This test was then repeated at the end of the 50-min exposure. Upon termination of the baseline SDMT, participants HR and blood pressure were measured via an automated blood pressure monitor and this was repeated at 15-min intervals during the experimental session. Participants also self-reported their baseline thermal sensations and comfort, as well as their physical and mental fatigue status on 7-point Likert scales (thermal sensation: +3 Hot; +2 Warm; +1 Slightly warm; 0 Neutral; −1 Slightly cool; −2 cool; −3 Cold; thermal comfort: +3 Very comfortable; +2 Comfortable; +1 Slightly comfortable; 0 Neutral; −1 Slightly uncomfortable; −2 Uncomfortable; Experience of physical/mental fatigue: Not at all: 1; Very little: 2; Little: 3; Moderately: 4; Enough: 5; A lot: 6; Extremely: 7) [2]. These self-reports were then collected again either at 15-min intervals (i.e. thermal sensation and comfort) or at the end of the

exposure (i.e. physical and mental fatigue) during all experimental sessions.

Upon termination of the 25-min baseline, and depending on the experimental session, the ambient temperature was ramped to a target 39 °C (HEAT) or 12 °C (COLD), for the following 50 min. Immediately after completion of the 50-min exposure, participants were de-instrumented, exited the climatic chamber, and their semi-nude body mass was assessed again on a precision scale.

3. Statistical analysis

3.1. Environmental data

To confirm the validity and reproducibility of our air temperature ramps within and between groups, we analysed air temperature data (5-min intervals) separately for the HEAT and COLD trials, for the independent and interactive effects of time (11 levels) and group (MS vs. CTR) by means of a 2-way mixed model ANOVA. The same analysis was performed with relative humidity data (5-min intervals). In the event of a significant main effect or interaction, post-hoc analyses were carried out by means of Tukey's multiple comparison tests.

3.2. Body temperature, fluid loss, and cardiovascular data

To determine the effects of the air temperature ramps on changes in mean T_{sk} between groups, we analysed mean T_{sk} data (5-min intervals) separately for the HEAT and COLD trials, and for the independent and interactive effects of time (11 levels) and group (MS vs. CTR) by means of a 2-way mixed model ANOVA. The same analysis was performed with T_{rec} data (5-min intervals). In the event of a significant main effect or interaction, post-hoc analyses were carried out by means of Tukey's multiple comparison tests.

By design, we expected the air temperature ramps to largely affect mean T_{sk} but not T_{rec} in our resting participants. Accordingly, we combined data from both the HEAT and COLD trials and proceeded to analyse the relationship between the mean ambient temperature reached every 5 min over the 50 min of each trial, and the corresponding mean T_{sk} of each individual participant, separately for MS and CTR, by means of regression analysis. We fitted both linear and non-linear models and determined best fit by means of extra-sum-of-squares F test.

Furthermore, we identified the individual minimum and maximum mean T_{sk} observed amongst MS and CTR participants at baseline (i.e., minute "0″) of both HEAT and COLD trials and used these as boundary values to identify a thermo-neutral zone of mean T_{sk}. Subsequently, we used these boundary values, in conjunction with the individual relationships between air temperature and mean T_{sk}, to determine the corresponding, group-level, thermo-neutral zone of air temperatures. This was achieved by identifying the air temperatures at which mean T_{sk} was beyond the thermo-neutral zone of mean T_{sk} in ≥75% of participants in each group.

To determine the effects of the air temperature ramps on changes in HR and MAP between groups, we analysed mean HR and MAP data (15-min intervals) separately for the HEAT and COLD trials, and for the independent and interactive effects of time (4 levels) and group (MS vs. CTR) by means of a 2-way mixed model ANOVA. In the event of a significant main effect or interaction, post-hoc analyses were carried out by means of Tukey's multiple comparison tests.

To determine the effects of the air temperature ramps on changes in whole-body fluid loss between groups, we analysed body mass data (adjusted for fluid intake during the trial) separately for the HEAT and COLD trials, and for the independent and interactive effects of time (2 levels, pre- vs. post-trial) and group (MS vs. CTR) by means of a 2-way mixed model ANOVA. In the event of a significant main effect or interaction, post-hoc analyses were carried out by means of Tukey's multiple comparison tests.

3.3. Thermal comfort and neuropsychological data

To determine the effects of the air temperature ramps on changes in thermal comfort between groups, we implemented a "Time to Event" analysis of thermal comfort scores and used the score "−2 Uncomfortable" as the event of interest. Time To Event (or survival) analyses are used to determine the expected duration of time until one event of interest occurs (Macin et al., 2006). In the context of the present study, time during the HEAT and COLD trials is associated with changes in air temperature. Accordingly, we identified the mean air temperatures corresponding to each time point at which thermal comfort scores were collected for each participant (i.e., 15-min intervals), separately for HEAT and COLD trials, and used these value to perform an equivalent "Air temperature to Event" analysis, by means of a log-rank test [43]. With the log-rank test, we compared the "Air temperature to Event" distributions of the MS and CTR groups during HEAT and COLD. Furthermore, we calculated the Hazard Ratio differences in the rate of reaching the score "−2 Uncomfortable" between MS and CTR using the Mantel-Haenszel method [44]. Hazard ratios were only reported when the "Air temperature to Event" distributions were significantly different between the two groups. The same series of analyses above (i.e., "Air temperature to Event" analysis) was also performed with thermal sensation data, using the score "+3 Hot" and "−3 Cold" as the event of interest for the HEAT and COLD trials, respectively.

We also analysed the correlation between self-reported EDSS scores, and individual thermal discomfort scores recorded by each MS participant at the end of both HEAT and COLD trials, in order to establish the association between self-reported motor disability and the degree of discomfort experienced at the end of the thermal exposures.

Regarding self-reported physical and mental fatigue scores at baseline and following HEAT and COLD in MS and CTR, these were analysed by means of multiple non-parametric Wilcoxon tests (i.e. paired comparisons between pre vs. post exposure within groups) and multiple Mann-Whitney U tests (i.e. unpaired comparisons between pre and post exposure between groups).

3.4. Cognitive performance

To determine the effects of the air temperature ramps on changes in SDMT performance, we analysed SDMT scores separately for the HEAT and COLD trials, and for the independent and interactive effects of time (2 levels) and group (MS vs. CTR) by means of a 2-way mixed model ANOVA. In the event of a significant main effect or interaction, post-hoc analyses were carried out by means of Tukey's multiple comparison tests.

All quantitative data analysis was performed on GraphPad Prism 8 (USA). Data are reported as mean ± standard deviation, and 95% CI, unless otherwise stated. Where individual datasets were missing from the analysis due to technical problems, sample sizes for analyses are reported (i.e., N).

4. Results

4.1. Environmental data

When considering air temperature data during the HEAT trial, we found a statistically significant effect of time [$F(10), 180 = 229.6$; $P < 0.0001$; 77% explained variance], but not group [$F[1,18] = 0.01669$; $P = 0.898$; 0.01% explained variance], nor a time x group interaction [$F[10], 180 = 0.6511$; $P = 0.768$; 0.2% explained variance], on changes in air temperature. Specifically, air temperature increased similarly for MS and CTR participants by 14.7 °C [95%CI: 13.1, 16.4; $P<0.0001$] over the 50-min HEAT trial, reaching an absolute value of 38.9 ± 1.7 °C in MS ($N = 11$) and 39.1 ± 2.8 °C in CTR ($N = 9$) (Fig. 1A).

When considering relative humidity data during the HEAT trial, we found a statistically significant effect of time [$F(10), 190 = 5.666$; $P <$

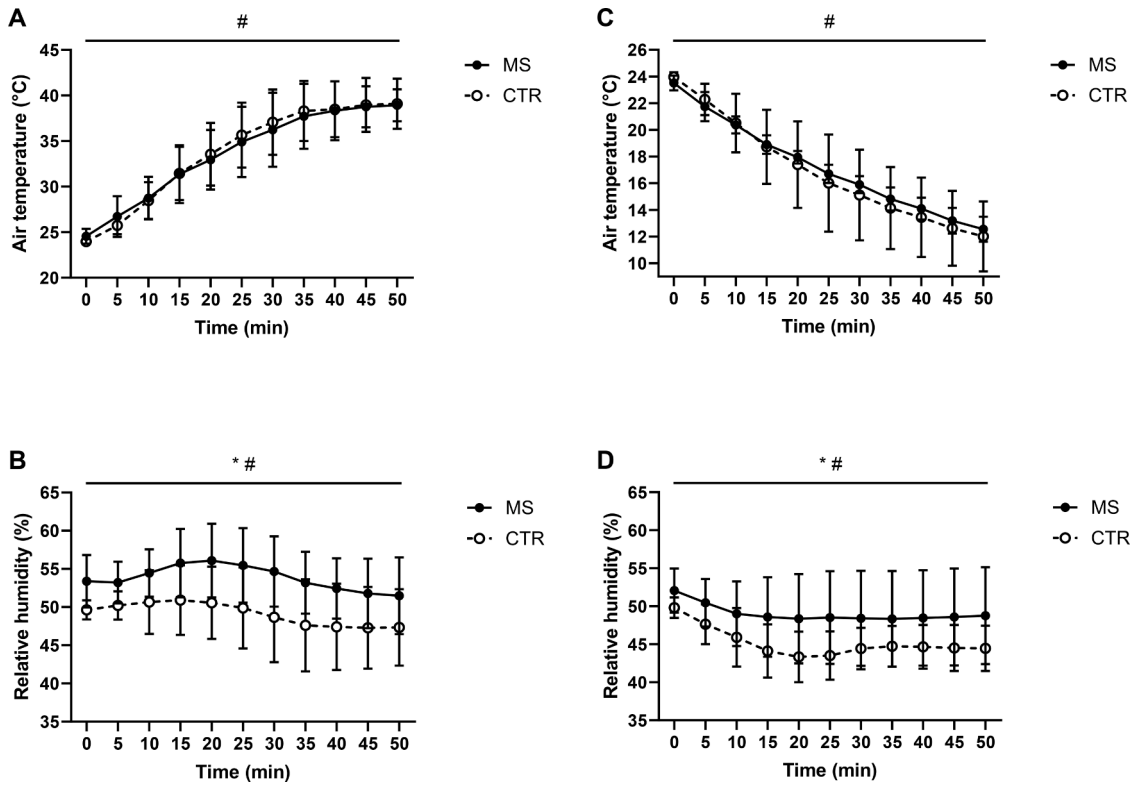

Fig. 1. Group data (mean ± SD) for air temperature (A & C) and relative humidity (B &D) during 50-min HEAT (A & B) and COLD (C & D) trials in MS ($N = 12$; 7F/5 M) and CTR ($N = 11$; 7F/4 M). # denotes a main effect of time (2-way mixed ANOVA; $p<0.05$). * denotes a main effect of group (2-way mixed ANOVA; $p < 0.05$).

0.0001; 7% explained variance], and group [F(1, 19) = 8.882; P = 0.007; 21% explained variance], but no time x group interaction [F[10], 190 = 0.6040; P = 0.809; 0.8% explained variance], on changes in relative humidity. Regarding the main effect of group, we found that MS experienced a slightly higher relative humidity (i.e., 53.8%) than CTR (i.e., 49.1%) across the HEAT trial (difference MS vs. CTR: +4.7%, 95%CI: +1.4, +8) (Fig. 1B). Regarding the main effect of time, we observed a slight decrease in relative humidity from minute 10 until the end of the HEAT trials (difference 10 vs. 50 min: −3.1%, 95%CI: −6.0; 0.2; P = 0.018) (Fig. 1B).

When considering air temperature data during the COLD trial, we found a statistically significant effect of time [F(10), 190 = 346.4; $P <$ 0.0001; 79% explained variance], but not group [F[1, 19] = 0.1941; P = 0.664; 0.1% explained variance], nor a time x group interaction [F(10), 190 = 1.369; P = 0.197; 0.3% explained variance], on changes in air temperature. Specifically, air temperature decreased similarly for MS and CTR participants by 11.5 °C [95%CI: 10.5, 12.4; $P < 0.0001$] over the 50-min COLD trial, reaching an absolute value of 12.5 ± 0.9 °C in MS ($N = 12$) and 12.0 ± 2.6 °C in CTR ($N = 9$) (Fig. 1C).

When considering relative humidity data during the COLD trial, we found a statistically significant effect of time [F(10), 190 = 15.10; $P <$ 0.0001; 8% explained variance], but not group [F(1, 19) = 4.13; P = 0.056; 14% explained variance], and no time x group interaction [F(10), 190 = 1.216; P = 0.283; 0.7% explained variance], on changes in relative humidity. Regarding the main effect of time, we observed a slight decrease in relative humidity during the COLD trials (difference 0 vs. 50 min: −4.3%, 95%CI: −6.1; −2.5; $P < 0.0001$ (Fig. 1D). Whilst this difference did not reach statistical significance, we found that MS experienced a slightly higher relative humidity (i.e., 49.0%) than CTR (i.e., 45.2%) across the COLD trial.

4.2. Body temperature, cardiovascular and fluid loss data

When considering mean T_{sk} data during the HEAT trial, we found a statistically significant effect of time [F (1.457, 30.60) = 392.7; $P <$ 0.0001; 66% explained variance], but not group [F(1,21) = 0.01167; P = 0.915; 0.01% explained variance], on changes in mean T_{sk}. Specifically, mean T_{sk} increased similarly for MS and CTR participants by 3.7 °C [95%CI: 3.1, 4.4; $P < 0.0001$] over the 50-min HEAT trial, reaching an absolute value of 35.2 ± 0.7 °C in MS ($N = 12$) and 34.9 ± 1.1 °C in CTR ($N = 11$) (Fig. 2A).

When considering T_{rec} data during the HEAT trial, we found a statistically significant effect of time [F (3.049, 60.07) = 11.81; $P <$ 0.0001], but not group [F(1, 21) = 0.3017; P = 0.588], on changes in T_{rec}. Specifically, T_{rec} decreased similarly for MS and CTR participants by 0.25 °C [95%CI: 0.08, 0.41; $P = 0.0010$] over the 50-min HEAT trial, reaching an absolute value of 36.75 ± 0.37 °C in MS ($N = 12$) and 36.68 ± 0.34 °C in CTR ($N = 10$) (Fig. 2B).

When considering mean T_{sk} data during the COLD trial, we found a statistically significant effect of time [F (1.902, 39.57) = 288.4; $P <$ 0.0001], but not group [FF(1, 21) = 0.01892; P = 0.891], on changes in mean T_{sk}. Specifically, mean T_{sk} decreased similarly for MS and CTR participants by 5.3 °C [95%CI: 4.4, 6.2; $P < 0.0001$] over the 50-min COLD trial, reaching an absolute value of 26.2 ± 1.5 °C in MS (N = 12) and 26.0 ± 1.6 °C in CTR ($N = 11$) (Fig. 2C).

When considering T_{rec} data during the COLD trial, we found a statistically significant effect of time [F (2.354, 46.85) = 7.519; P = 0.0008], but not group [F(1, 21) = 3.994; $p = 0.058$], on changes in T_{rec}. Specifically, T_{rec} decreased similarly for MS and CTR participants by 0.16 °C [95%CI: 0.02, 0.30; $P = 0.0149$] over the 50-min COLD trial, reaching an absolute value of 36.88 ± 0.29 °C in MS ($N = 12$) and 36.60 ± 0.32 °C in CTR ($N = 10$) (Fig. 2D).

Regarding the thermo-neutral zone of mean T_{sk}, we identified the individual minimum and maximum mean T_{sk} observed amongst MS and CTR participants at baseline (i.e., minute "0″) of both HEAT and COLD trials to be 29.8 and 32.7 °C, respectively. As described in the statistical analysis section, we used these boundary values, in conjunction with the individual relationships between air temperature and mean T_{sk}, to

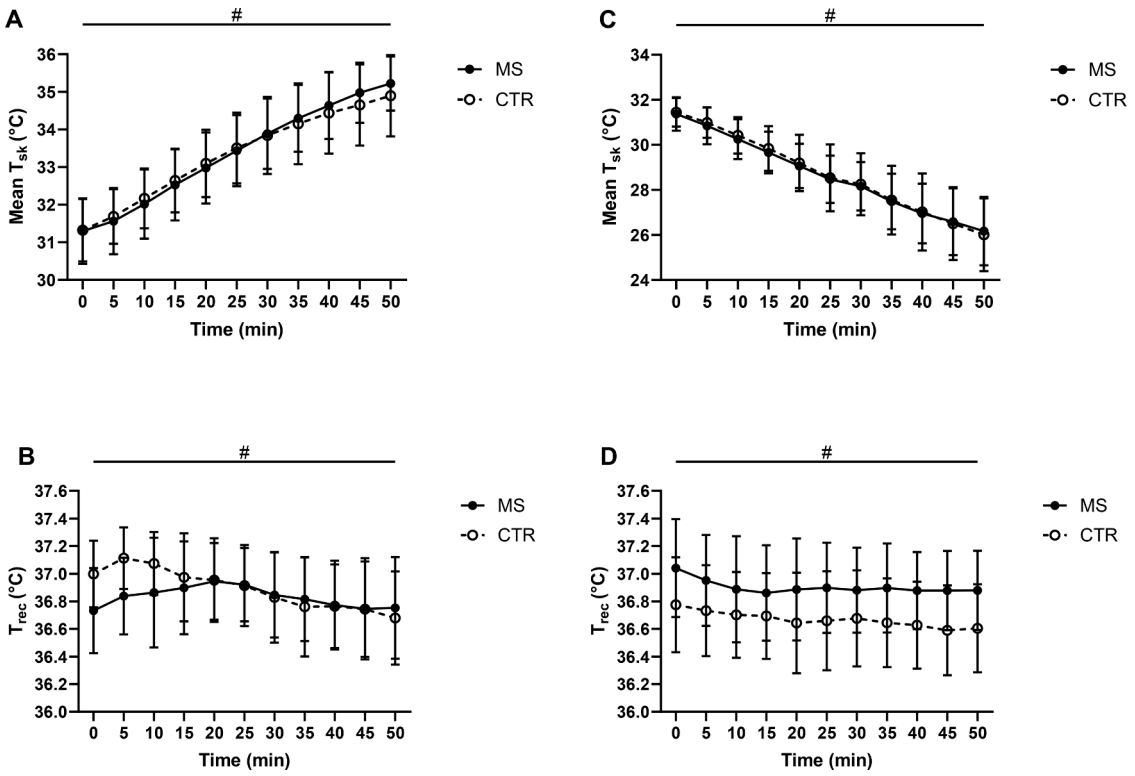

Fig. 2. Group data (mean ± SD) for mean T_{sk} (A & C) and T_{rec} (B &D) during 50-min HEAT (A & B) and COLD (C & D) trials in MS ($N = 12$; 7F/5 M) and CTR ($N = 11$; 7F/4 M). # denotes a main effect of time (2-way mixed ANOVA; $p < 0.05$).

determine the corresponding, group-level, thermo-neutral zone of air temperatures (Fig. 3). Accordingly, we found that for both MS (Fig. 3A) and CTR (3B), the boundaries of the thermo-neutral zone of air temperatures corresponded to 17.7 and 35.2 °C.

When considering HR data during the HEAT trial, we found no statistically significant effect of time [F (1.507, 31.65) = 1.179; $P = 0.308$], nor group [F(1, 21) = 0.9727; $P = 0.335$], on changes in HR (Fig. 4A). Baseline HR was 78±14 bpm in MS and 70±13 bpm in CTR. At 45 min into the trial this parameter corresponded to 79±17 bpm in MS and 72 ±14 bpm in CTR.

When considering HR data during the COLD trial, we found a statistically significant effect of time [F (1.735, 36.44) = 3.758; $P = 0.0384$], but not group [F(1, 21) = 0.6725; $P = 0.421$], on changes in HR (Fig. 4B). Baseline HR was 73±13 bpm in MS and 69±16 bpm in CTR. At 30 min into the trial this parameter had decreased to 67±10 bpm in MS and 64±10 bpm in CTR.

When considering MAP data during the HEAT trial, we found no statistically significant effect of time [F (1.944, 40.83) = 2.017; $P = 0.147$], nor group [F(1, 21) = 0.1394; $P = 0.712$], on changes in MAP (Fig. 4C). Baseline MAP was 88±11 mmHg in MS and 86±13 mmHg in CTR. At 45 min into the trial this parameter corresponded to 86±11 mmHg in MS and 82±11 mmHg in CTR.

When considering MAP data during the COLD trial, we found a statistically significant effect of time [F (2.476, 52.00) = 10.74; $P < 0.0001$], but not group [F(1, 21) = 0.1768; $P = 0.678$], on changes in MAP (Fig. 4D). Baseline MAP was 89±11 mmHg in MS and 88±9 mmHg in CTR. At 45 min into the trial this parameter had increased to 99±13 mmHg in MS and 95±16 mmHg in CTR.

When considering fluid loss data during the HEAT trial, we found a statistically significant effect of time [F(1, 21) = 28.3; $P < 0.0001$], but

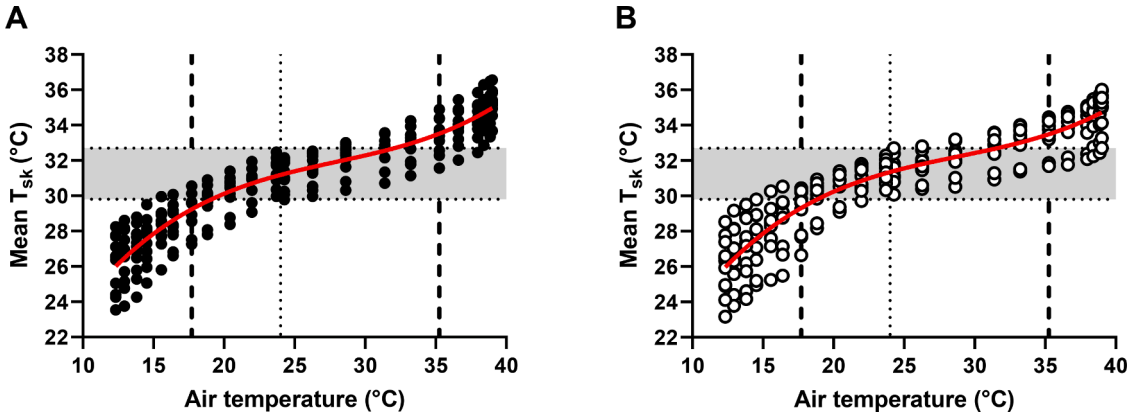

Fig. 3. Individual data (dots) and group mean (line in red) for mean T_{sk} for MS (A; $N = 12$; 7F/5 M) and CTR (B; $N = 11$; 7F/4 M) as a function of exposures to 12–39 °C air temperatures during HEAT and COLD. grey band indicates a zone of thermo-neutral T_{sk}. Dotted line indicates baseline air temperature of 24 °C. Dashed lines indicate the boundaries of the thermo-neutral zone of air temperature.

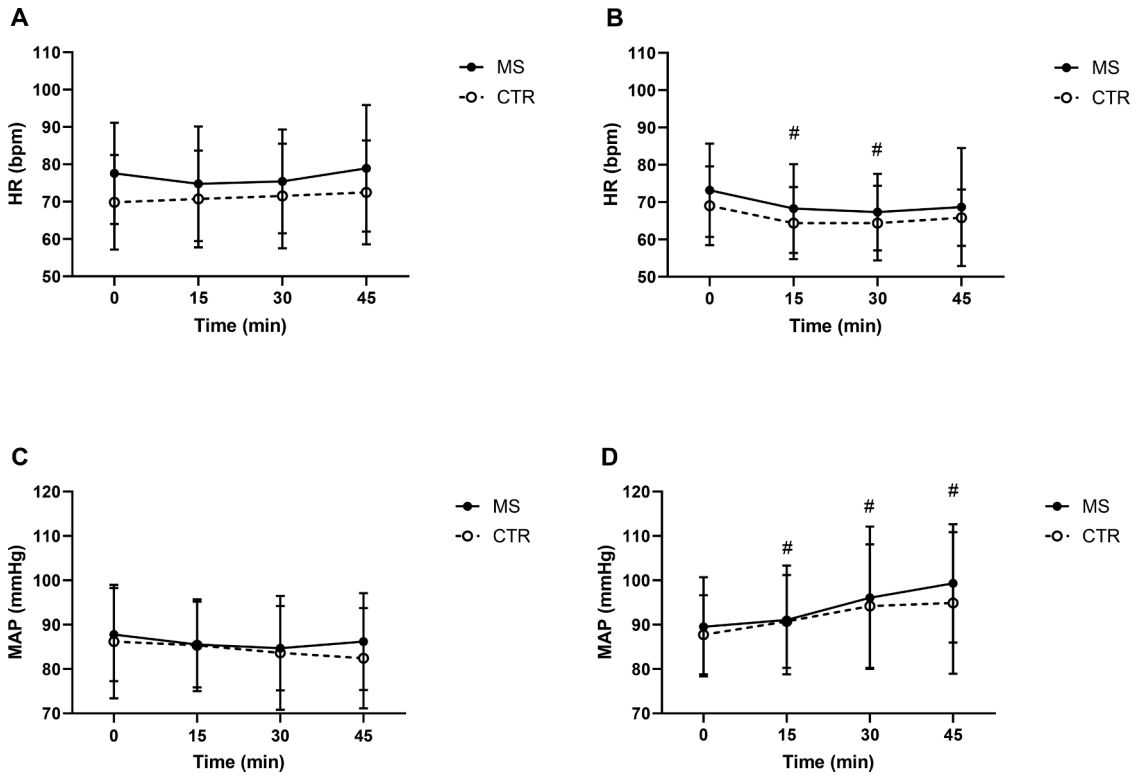

Fig. 4. Group data (mean ± SD) for mean HR (A & B) and MAP (C &D) during 50-min HEAT (A & C) and COLD (B & D) trials in MS ($N = 12$; 7F/5 M) and CTR ($N = 11$; 7F/4 M). # denotes a statistically significant difference from time point 0 ($p < 0.05$).

not group [F(1, 21) = 0.09507; $P = 0.760$], on changes in body mass. Specifically, adjusted-body mass decreased similarly for MS and CTR participants by 112 g [95%CI: 68, 155; $P < 0.0001$] following the 50-min HEAT trial. When considering fluid loss data during the COLD trial, we found a statistically significant effect of time [F(1, 21) = 14.33; $P = 0.001$], but not group [F(1, 21) = 0.1213; $P = 0.731$], on changes in body mass. Specifically, adjusted-body mass decreased similarly for MS and CTR participants by 80 g [95%CI: 36, 214; $P = 0.0011$] following the 50-min COLD trial.

4.3. Thermal comfort and neuropsychological data

When considering thermal comfort data during the HEAT trial, our "Air temperature to Event" analysis indicated that the MS and CTR probability curves differed by an extent that reached statistical significance [Log-rank (Mantel-Cox) test; Chi square: 4.518; $P = 0.033$]. Specifically, we found that, for equivalent air temperatures, a greater proportion of MS than CTR participants reported scores at or beyond "uncomfortable" (Fig. 5A). The Hazard Ratio analysis indicated that an MS participant had 3.9 times (95%CI: 1.1, 14.1) the probability to report "uncomfortable" by the next air temperature increase compared to a CTR participant, during the HEAT trial. At the end of the HEAT trial, 83% of MS participants and 36% of CTR participants had reported scores at or beyond "uncomfortable" (Fig. 5A).

When considering thermal sensation data during the HEAT trial, our "Air temperature to Event" analysis indicated that the MS and CTR probability curves did not differ significantly [Log-rank (Mantel-Cox) test; Chi square: 2.971; $P = 0.084$]. However, at the end of the HEAT trial, 87% of MS participants and 28% of CTR participants had reported scores at or beyond "Hot" (Fig. 5B).

When considering thermal comfort data during the COLD trial, our "Air temperature to Event" analysis indicated that the MS and CTR probability curves did not differ significantly [Log-rank (Mantel-Cox) test; Chi square: 0.03863; $P = 0.844$]. Furthermore, at the end of the COLD trial, 55% of MS participants and 45% of CTR participants had reported scores at or beyond "Cold", and this difference was not statistically significant (Fisher's exact test $P = 0.590$) (Fig. 5C).

When considering thermal sensation data during the COLD trial, our "Air temperature to Event" analysis indicated that the MS and CTR probability curves did not differ significantly [Log-rank (Mantel-Cox) test; Chi square: 0.2245; $P = 0.635$]. Furthermore, at the end of the COLD trial, 53% of MS participants and 47% of CTR participants had reported scores at or beyond "Cold", and this difference was not statistically significant (Fisher's exact test $P > 0.999$) (Fig. 5D).

We found no statistically significant association between self-reported EDSS scores, and maximum discomfort reported by the MS participants neither during the HEAT (Pearson $r = -0.19$; $p = 0.543$) nor the COLD trials (Pearson $r = 0.30$; $p = 0.333$).

When considering self-reported mental fatigue scores during HEAT, we found no differences at baseline between MS and CTR ($P = 0.116$); yet mental fatigue increased in MS following exposure (pre vs. post comparison $P = 0.015$) and to a level greater than that reported by CTR post exposure (MS vs. CTR post comparison $P = 0.006$) (Fig. 6A). We observed a similar trend for self-reported physical fatigue scores during HEAT, whereby we found no differences at baseline between MS and CTR ($P = 0.242$); yet physical fatigue increased in MS following exposure (pre vs. post comparison $P = 0.007$) and to a level greater than that reported by CTR post exposure (MS vs. CTR post comparison $P = 0.002$) (Fig. 6C). Note that due to technical problems, MS data for these analyses were based on an N of 9.

When considering self-reported mental fatigue scores during COLD, we found no differences at baseline between MS and CTR ($P = 0.330$); mental fatigue increased slightly in MS following exposure (pre vs. post comparison $P = 0.187$) and to a level greater than that reported by CTR post exposure (MS vs. CTR post comparison $P = 0.001$) (Fig. 6B). We observed a similar trend for self-reported physical fatigue scores during COLD, whereby we found no differences at baseline between MS and CTR ($P = 0.334$); yet physical fatigue increased in MS following

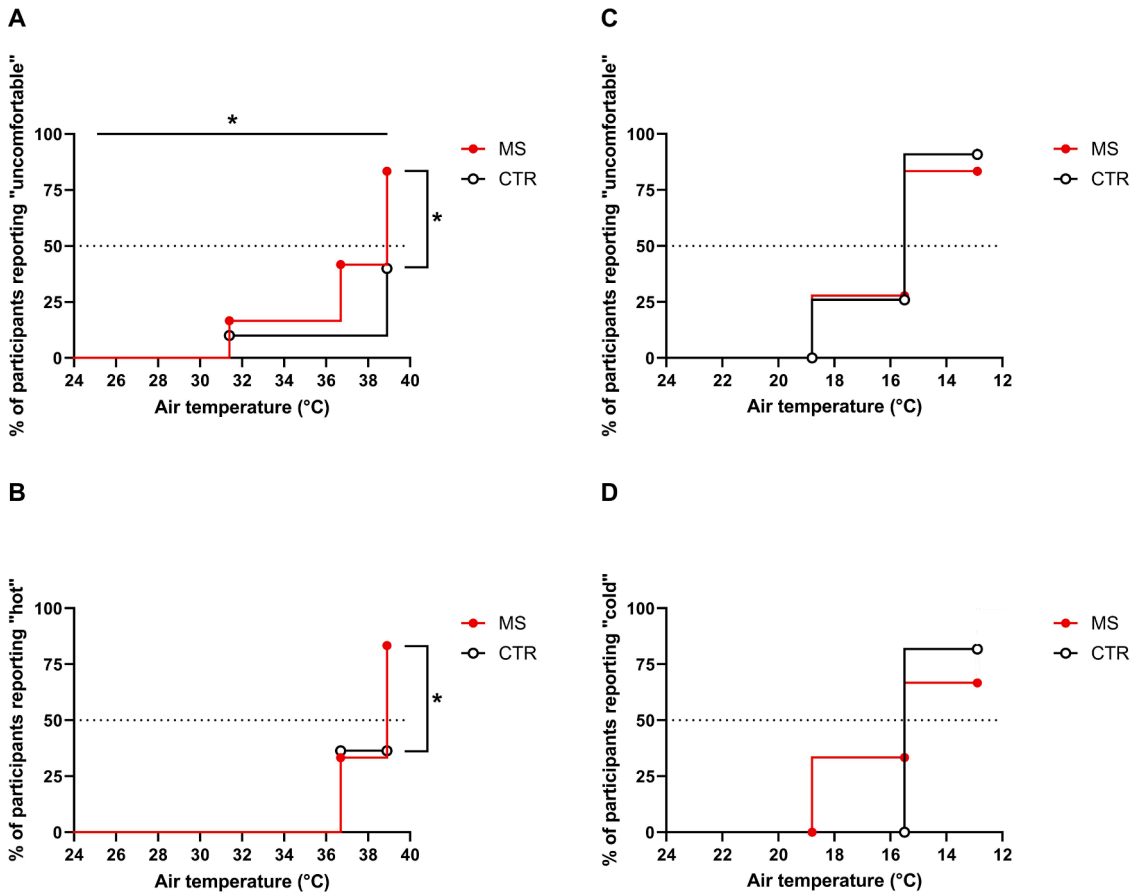

Fig. 5. Survival curves for the% of MS and CTR participants reporting "uncomfortable" as a function of air temperature during HEAT (A) and COLD (C). B & D present survival curves for the% of MS and CTR participants reporting "hot" and "cold" as a function of air temperature during HEAT and COLD, respectively. Horizontal * denotes a difference in the survival curve (log-rank test; $p < 0.05$). Vertical * denotes a difference in the response frequency at the end of the trials (Fisher's exact test; $p < 0.05$).

exposure (pre vs. post comparison $P = 0.046$) and to a level greater than that reported by CTR post exposure (MS vs. CTR post comparison $P = 0.001$) (Fig. 6D). Note that due to technical problems, MS data for these analyses were based on an N of 9.

4.4. Cognitive performance

When considering SDMT scores during HEAT, we found a significant effect of group [$F(1, 21) = 16.48$; $P = 0.0006$] but not time [$F(1, 21) = 0.2521$; $P = 0.620$] nor time x group interaction [$F(1, 21) = 0.1939$; $P = 0.664$]. Specifically, MS presented overall significantly lower SDMT scores (mean score: 44.5) than CTR (64.9; i.e. indicating lower information processing performance), which were unaffected by HEAT (mean difference: 20.4; 95%CI: 9.9, 30.8) (Fig. 7A).

When considering SDMT scores during COLD, we found a significant effect of group [$F(1, 21) = 18.83$; $P = 0.0003$] but not time [$F(1, 21) = 0.003600$; $P = 0.952$] nor time x group interaction [$F(1, 21) = 0.1282$; $P = 0.723$]. Specifically, MS presented overall significantly lower SDMT scores (mean score: 44.8) than CTR (65.1; i.e. indicating lower information processing performance), which were unaffected by COLD (mean difference: 20.3; 95%CI: 10.5, 29.9) (Fig. 7B).

4.5. Discussion

The aim of this study was to evaluate body temperatures, thermal comfort, and neuropsychological responses (i.e. self-reported physical and mental fatigue) to air temperatures ranging between 12 and 39 °C in people with MS. We hypothesised that people with MS would present greater changes in body temperatures along with greater increases in thermal discomfort and self-reports of fatigue than healthy counterparts for a given change in air temperature (i.e., either increases or decreases), with potential detrimental effects to cognitive performance under thermal stress.

The first relevant finding of this study is that we found no differences between MS and CTR in their thermometric (i.e. mean T_{sk}, T_{rec}) and fluid loss responses to changes in air temperature (see Fig.2), . Both HEAT and COLD resulted in slight decreases in T_{rec} (~0.2 °C) as well as in a cumulative 10- °C variation in mean T_{sk} across trials (minimum mean T_{sk} reached during COLD: ~26 °C; maximum mean T_{sk} reached during HEAT: ~36 °C) and in both groups. Both MS and CTR presented similar boundaries for the thermo-neutral zone of air temperature (i.e. corresponding to 17.7 and 35.2 °C), and they presented similar change in body mass following trials, which we interpreted as indicative of similar fluid loss mechanisms (i.e., whole-body sweat loss during HEAT and respiratory heat loss during COLD). Altogether, and contrary to our initial hypothesis on body temperature responses, our thermometric data indicated that our MS participants were as effective as the CTR group in regulating both their dry and evaporative heat exchange with their surrounding thermal environments and did not exhibit disproportionate changes in body temperatures for a given thermal load.

The second relevant finding of this study is that a greater proportion of MS than CTR participants reported scores at or beyond "uncomfortable" for equivalent air temperature increases during the HEAT trial. Specifically, at the end of the HEAT trial, 83% of MS participants and 36% of CTR participants had reported scores at or beyond "uncomfortable" (Fig. 4A). Similarly, at the end of the HEAT trial, 87% of MS

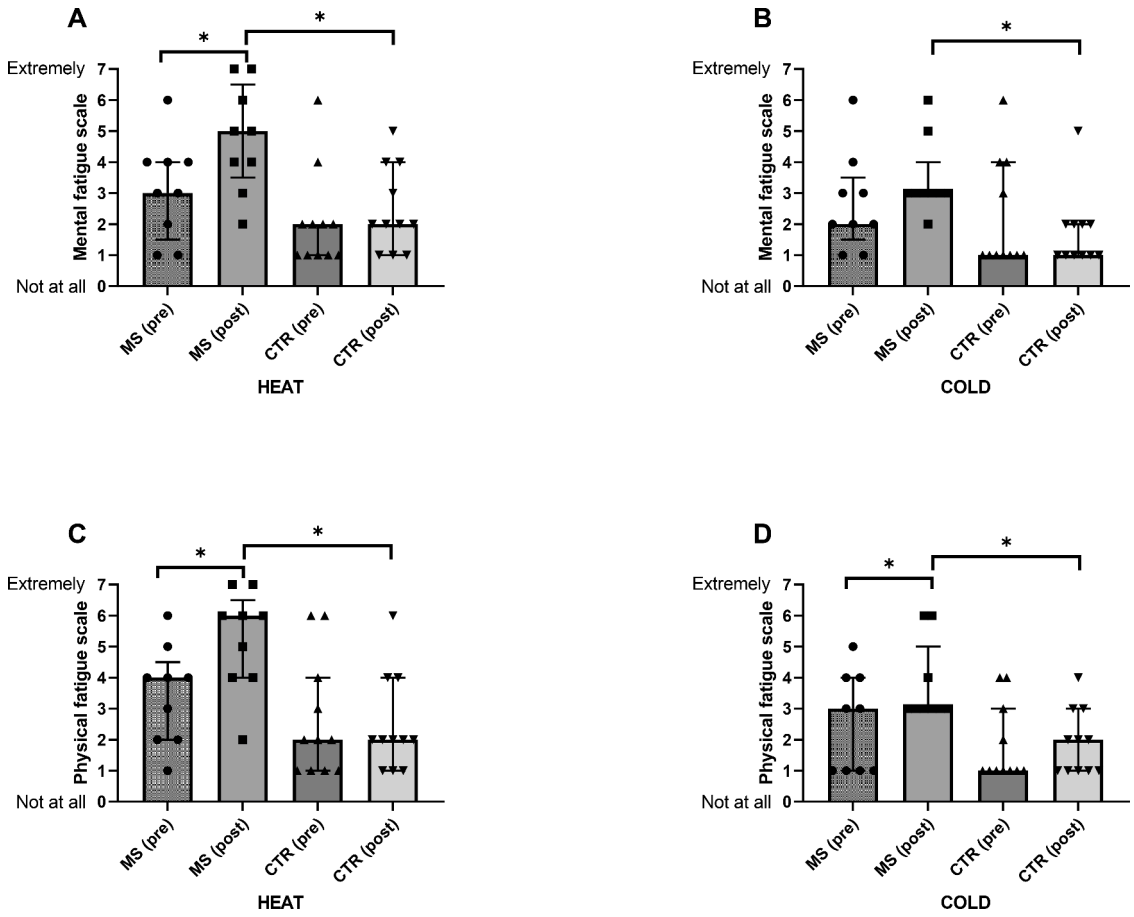

Fig. 6. Group data (median ± inter-quartile range) for self-reported mental (A & B) and physical fatigue (C &D) prior to and at the end of 50-min HEAT (A & C) and COLD (B & D) trials in MS ($N = 9$) and CTR ($N = 11$; 7F/4 M). * denotes a statistically significant difference ($p < 0.05$).

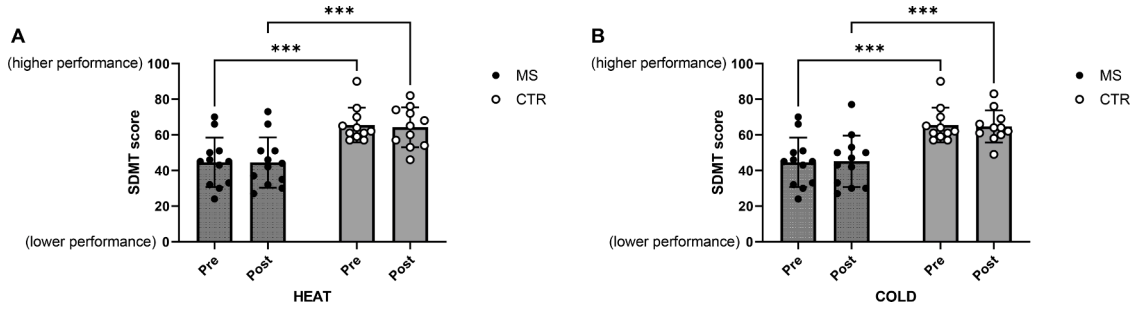

Fig. 7. Group data (mean ± SD) for SDMT scores prior to and at the end of 50-min HEAT (A) and COLD (B) trials in MS ($N = 12$; 7F/5 M) and CTR ($N = 11$; 7F/4 M). *** denotes a statistically significant difference ($p < 0.001$).

participants and 28% of CTR participants had reported scores at or beyond "Hot" (Fig. 4B). Interestingly, we did not observe the same effect during COLD, i.e. MS and CTR experienced coldness and discomfort with the same frequency and pattern as a result of decreases in body and air temperatures (Fig. 4C &D). Altogether, and in support of our initial hypothesis on perceptual responses, our thermal sensation and comfort data indicated that our MS participants were more likely to experience thermal discomfort than their healthy counterparts for a given change in body temperatures, although this applied to body heating only.

The third relevant finding of this study is that MS participants experienced significant increases in both their mental and physical fatigue during both HEAT and COLD, whilst CTR participants did not (Fig. 6). Of note, these increases in fatigue levels were of greater magnitude during HEAT (Fig. 6A and C) than COLD (Fig. 6B and D) and reached extreme levels for some MS participants. Altogether, these findings further supports our hypothesis that thermal stress, and the heat in particular, exacerbates fatigue levels (both mental and physical) in MS. Interestingly, this exacerbation in self-reported fatigue did not translate in any meaningful change in MS participants' cognitive performance following HEAT and COLD (Fig. 7). In this respect, it is important to note that our MS participants presented an underlying cognitive deficit, as confirmed by the significantly lower baseline SDMT scores than CTR (Fig. 7) [45].

Autonomic dysfunction associated with MS can result in thermoregulatory impairments [11,21], and it has been previously suggested that this could in turn accelerate heat gain and increases in core temperature for a given heat load in people with MS [11]. Yet, recent evidence indicates that even in the presence of sudomotor dysfunction,

people with MS exercising in the heat exhibit increases in body temperatures (both core and skin) that are no different to those experienced by healthy individuals [40]. This observation has led to the conclusion that heat intolerance with MS may not be entirely attributable to thermoregulatory impairments [21]. Our findings on the body temperature responses of people with MS are in line with and further extend those of Chaseling et al. [21]. as we observed no differences in skin and core temperatures in response to passive exposures to ambient heating and cooling in the range of 12 to 39 °C. It is important to note that this study's combination of resting activity and environmental exposures would have resulted in thermoregulatory responses that consisted primarily of changes in the vasomotor tone of the skin (i.e. both vasodilation and vasoconstriction), as reflected by the large changes in skin temperature that we observed in both groups. Accordingly, our study provides novel evidence that the regulation of dry heat exchange by changes in skin temperature was preserved in the MS participants that we tested. This finding is also in line with the evidence provided by Vargas et al. [46]., who observed similar thermoregulatory responses between 7 MS and 7 healthy participants undergoing cycling exercise in a mildly warm environment.

It should be noted that the considerations above do not dispute the well-established pathophysiological role of relative increases in core temperature of >0.5 °C in triggering a worsening of MS symptoms [21]; yet they indicate that individuals with MS do not appear to "heat up" any faster than individuals without MS. Hence, our study's findings provide empirical evidence in support Chaseling et al. [21].' suggestion and those of others (e.g. see ref [46].) that mechanisms other than thermoregulatory impairments are likely involved in MS heat intolerance. In this regard, we believe that our findings provide evidence for a candidate, alternative mechanism for heat intolerance in MS, that is an MS-specific heightened sensitivity to thermal discomfort. This observation is in line with the recent findings of Vargas et al. [46]., who reported that, when given the opportunity to alleviate exercise-induced heat stress via voluntary cooling, people with MS engaged in this behaviour to a greater extent than healthy controls, secondary to the experience of greater discomfort for the same change in body temperature. As also suggested by Vargas et al. [46], we believe that a heightened sensitivity to thermal discomfort in MS could result from a combination of changes in both peripheral and central thermoreceptors' sensitivities to changes in body temperature, as supported by our previous results on quantitative thermo-sensory testing of this clinical group [47]. This maladaptive response could also contribute to the observed significant increase in self-reported mental and physical fatigue experienced by our MS participants following both HEAT and COLD. The psychobiology of physical and mental fatigue is complex, particularly when applied to conditions such as MS [47]. Recent evidence indicates that individuals with MS experience an impaired ability to correct deviations from a homoeostatic state (e.g. loss of thermo-neutrality) as a result of deficits to those central interoceptive networks that underpin emotional feelings associated with the motivation to restore homoeostasis [48]. Interestingly, central interoceptive networks involved in heightened fatigue in MS are located within the insular cortex, a well-known area for the integration of thermosensory afferents contributing to thermal sensation and comfort [49,50]. When applied to the context of the present experiment, this framework may therefore indicate that potential deficits to the MS groups' central interoceptive networks may have led to an inability to "correct" for a deviation in thermal homoeostasis (resulting from the passive heating and cooling), which could have in turn led to greater discomfort and greater feelings of mental and physical fatigue.

It should also be noted that negative thoughts associated with the thermal exposures, that is a "nocebo effect" (i.e. the experience of physiological and psychological symptoms because of the belief and anticipation of adverse outcomes) [51,52], may have also occurred within our MS group. Indeed, the MS fatigue framework referenced above also suggest that the derivation of perceptions from the interoceptive signals can be modulated by the psychological state of the individual. Accordingly, it cannot be excluded that some of the MS participants in this study may have anticipated the occurrence of pseudo-exacerbations during the heat exposure, which could have in turn led to more frequent reports of discomfort and increased fatigue. To confirm this hypothesis conclusively, one would need to determine whether people with MS who tend to anticipate a worsening of their MS symptoms because of heat do indeed present worse thermal discomfort profiles. Determining the association between individual psychological profile and resulting thermal behaviours could be clinically relevant, as it could inform better healthcare planning and occupational therapy in MS (e.g. patients experiencing this "nocebo effect" may present a greater tendency to stay indoors, avoid social interactions, and daily tasks outside of their house in warm climates).

Finally, it should be noted that the hypothesis of a heightened discomfort sensitivity in MS applies to heating, but not cooling, conditions. This may not be entirely surprising when considering that fewer people with MS are affected by cold (~15%) than heat [27]; yet, this observation questions whether greater discomfort is driven by changes in peripheral and central thermoreceptors' sensitivities to changes in body temperature (i.e. if receptors' sensitivity change in MS then one would expect this maladaptation to translate across the whole temperature continuum). Nevertheless, the hypothesis of a distinction between physiological and perceptual triggers of heat intolerance is plausible and also supported by evidence indicating that people with MS may experience high discomfort during exposures to hot ambient temperatures, yet they can still maintain a level of functional capacity [53–55]. This observation is in line with our findings that HEAT and COLD did not worsen information processing performance in MS. It is worth nothing that the heightened sensitivity to thermal discomfort to the heat was experienced by almost all MS participants (i.e. ten out of twelve participants reached threshold levels of discomfort at the end of the HEAT trial) despite the highly heterogenous nature of our MS group (i.e. MS participants differed in age, sex, ethnicity, presented varying courses of MS, large differences in EDSS, etc.; see Table1). This observation indicates that, irrespective of the stage and course of the disease, the presence of MS and the resulting neural damage may itself predispose individuals to developing deficits in central thermosensory integration, and consequently heat intolerance.

4.6. Limitations

There are some limitations to the present study. First, our thermal model is based around large manipulations of mean T_{sk} only. Hence, it remains to be stablished whether a similar relationship between changes in air temperature and comfort occurs at different core temperatures (i.e., both during hyper- and hypo-thermia). Whilst some evidence of these mechanisms is available during body heating (see 21 & 36), additional empirical data on the effects of core cooling are warranted. Second, our passive heating and cooling approach leveraged dynamic changes in air temperature, and therefore relatively short exposures to each absolute air temperature level. Whilst this approach offers an effective avenue to force changes in mean T_{sk} across a broad temperature range and to establish their relationship with discomfort, whether similar responses would be obtained at steady state air temperatures remains to be established. Third, we note that the sampling rate of our perceptual scores (i.e. 15-min intervals) may have resulted in an overestimation of the actual time (and associated air temperature) at which discomfort did onset (e.g. participants could have experienced a given level of discomfort before they had reached the time at which this would be collected as a perceptual score). Nevertheless, we believe that such an overestimation would not impact the observation of group-related differences in discomfort neither during nor at the end of the exposure. In other words, at the time of sampling (i.e. during the protocol as well at its end), more MS participants reported discomfort than CTR individuals. Finally, we acknowledge that MS participants experienced slightly higher relative humidity than CTR during HEAT and COLD trials

(i.e., ~4–5% difference). However, as relative humidity levels were maintained between 50 and 55% for both groups, this relatively small difference is unlikely to have caused meaningful differences in skin wetness and evaporative requirements for heat loss. This was confirmed by the lack of differences in fluid loss between groups, as well as by the fact that humidity slightly decreased over time during the trials for both groups.

5. Conclusion

Our findings indicate that neuropsychological factors (e.g. discomfort and fatigue) could contribute to MS heat and cold intolerance in the absence of deficits in the control of body temperatures. This perceptual maladaptation could be rooted in central deficits to interoceptive networks; yet, further functional evidence is required to establish causal relationships between neural damage and heightened thermal vulnerability in this clinical group.

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Ethical approval

The testing procedures were explained to each participant, and they all gave written informed consent for participation. The study was approved by the Loughborough University Ethics Sub-Committee for Human Participants (#R17-P094), and testing procedures were in accordance with the tenets of the Declaration of Helsinki (note: the study was not registered in a database).

Author contributions

AC, RB, and DF Conceptualizarion. AC Investigation, Data curation and Formal analysis. AC, RB, and DF Writing - orginal draft, Review and editing. DF Funding acquisition, DF and RB Supervision. All authors approved the final version of the manuscript and agreed 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.

Declaration of Competing Interest

The authors report no conflict of interest.

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