Afferent thermosensory function in relapsing-remitting Multiple Sclerosis following exercise-induced increases in body temperature

Davide Filingeri[1,2]; Georgia Chaseling[1]; Phu Hoang[3]; Michael Barnett[4]; Scott L Davis[5]; Ollie Jay[1]

[1]*Thermal Ergonomics Laboratory, Faculty of Health Sciences, University of Sydney, NSW, AUSTRALIA*

[2]*Environmental Ergonomics Research Centre, Loughborough Design School, Loughborough University, UNITED KINGDOM*

[3]*Neuroscience Research Australia, NSW, AUSTRALIA*

[4]*Brain and Mind Centre, University of Sydney, NSW, AUSTRALIA*

[5]*Department of Applied Physiology & Wellness, Southern Methodist University, USA*

Type of submission: Short Communications

Running title: Heat-sensitivity and thermosensory function in MS

Key words: Multiple Sclerosis, Body Temperature Regulation, Thermoreceptors, Skin

Word count: 2352

Number of references: 23

Corresponding author:

Davide Filingeri PhD

Environmental Ergonomics Research Centre, Loughborough Design School

Loughborough University

Loughborough LE11 3TU UK

Phone: +44 01509 228314

E-mail: d.filingeri3@lboro.ac.uk

What is the central question of this study?

Between 60-80% of multiple sclerosis patients (MS) experience transient symptoms worsening with increases in body temperatures (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^{o}C were sufficient to decrease cold, but not warm, skin thermosensitivity (~10%) in MS, across a wider temperature range than what is observed in age-matched healthy individuals. These findings provide novel evidence on the impact of heat-sensitivity on afferent function in MS, which could be useful for clinically evaluating this neurological disease.

Abstract

In multiple sclerosis (MS), increases in body temperature result in transient worsening of clinical symptoms (heat-sensitivity /Uhthoff's phenomenon). While 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 novel quantitative sensory test. Eight relapsing-remitting MS patients (3M/5F; 51.4±9.1 y; EDSS score: 2.8±1.1) and 8 age-matched controls (CTR; 5M/3F; 47.4±9.1 y) rated perceived magnitude of two cold (26; 22°C) and warm (34; 38°C) stimuli applied to the dorsum of the hand, pre and post 30-min cycling in the heat (30°C air; 30% RH). Exercise produced similar increases in mean body temperature in MS (+0.39°C [95%CI: +0.21, +0.53] p=0.001) and CTR (+0.41°C [95%CI: +0.25, +0.58] p=0.001). These changes were sufficient to significantly decrease thermosensitivity 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 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 across a wider (including milder/colder) temperature range than what is observed in CTR, provides novel evidence on the impact of rising body temperature on afferent neural function in MS. Also, our findings support the use of our novel approach to investigate afferent sensory function in MS during heat stress.

Abbreviations: MS, multiple sclerosis; CTR, control;

Introduction

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

While 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 sunlight exposure (Davis *et al.*, 2010). This translates in MS patients experiencing severe challenges in maintaining appropriate physical activity levels (White & Dressendorfer, 2004), as well as in conducting normal working activities (e.g. early retirement due to heat intolerance and fatigue is highly prevalent amongst MS patients) (Palmer *et al.*, 2013). There is therefore a need to better understand the pathophysiology of heat sensitivity and its impact on normal physiological functions to develop appropriate interventions aimed at improving life quality in MS.

Mechanistically, the transient effects of heat-sensitivity on efferent autonomic functions (e.g. control of eye movements; regulation of thermoregulatory sweating) have been investigated in MS patients (e.g. rises in body temperature induce transient slowing of horizontal saccadic eye movements; Davis *et al.*, 2008; thermoregulatory sweating is blunted under 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 as somatosensory abnormalities, amongst which 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 our skin temperature represents the key trigger of behavioral 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, assessing how skin temperature sensing is impacted by heat-sensitivity could be critical to better understand what behavioral 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 to non-invasively evaluate somatosensory function within normally functioning non-myelinated pathways and within demyelinated afferent pathways in MS. Indeed, the neuro-anatomical and -physiological differences between the human peripheral and central pathways for cold (served by myelinated nerve fibers) and warm (served by non-myelinated nerve fibers) 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 concurrently and non-invasively evaluate both myelinated and non-myelinated afferent pathways is

particularly relevant in the context of a demyelinating disease such as MS (Noseworthy *et al.*, 2000).

In light of the above, the aim of this study was to assess afferent thermosensory function in MS under conditions of exercise-induced increases in body temperature (in the range of what is shown to induce heat-sensitivity, i.e. Δ~0.5°C) (Davis *et al.*, 2010) using a novel quantitiave sensory testing paradigm (Filingeri *et al.*, 2017*a*). We hypothesized that exercise-induced increases in body temperature would reduce cold (served by myelinated fibers), but not warm (served by non-myelinated fibers), local skin thermosensitivity in relapsing-remitting MS patients compared to 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 which employed 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 8 individuals per group for the current study. As such, 8 individuals diagnosed with relapsing-remitting MS (MS group; 3M/5F; 51.4±9.1 y;

75.3±10.3 kg; 171±8cm; Expanded Disability Status Scale (EDSS) score: 2.8±1.1) and 8 age-matched, otherwise healthy control individuals (CTR group; 5M/3F; 47.4±9.1 y; 81.6±18.9 kg; 172±10 cm), participated in this study.

All participants took part in one experimental session. During this session, we used a novel quantitative sensory testing paradigm to assess perceived magnitude of cold and warm temperature stimuli applied to the dorsum of the hand. Our novel 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: 35 to 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.

MS and CTR participants used a hand-scored 200 mm visual analogue 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°C and 38°C from a 30°C baseline) and two cold stimuli (26°C 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, USA), at rest and during the 30^{th} 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/between participants.

Throughout the experimental session, rectal temperature (Mallinckrodt Medical, USA) and a 4-point mean skin temperature estimation (Concept Engineering, USA) were recorded every 5 s. Mean body temperature was estimated as follow: [(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 two-tailed paired t-tests. We assessed the effects of group (MS vs. CTR) and of stimulus temperature (34 vs. 38°C; 22 vs. 28°C) on baseline (i.e. prior to exercise) magnitude estimation of warm and cold stimuli with a mixed model ANOVA (note: cold and warm stimuli data were analyzed separately). We then assessed changes in magnitude estimation of warm and cold stimuli from pre- to post-cycling with individual 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 [CI].

Results

Changes in mean body temperature

Mean body temperature was significantly and similarly elevated after 30 min of cycling in both MS (mean difference: +0.39°C [+0.21, +0.53] p=0.001) and CTR (mean difference: +0.41°C [+0.25, +0.58] p=0.001).

Magnitude estimation of warm and cold stimuli

Prior to exercise, there were no differences between MS and CTR in the magnitude estimation of warm (p=0.172) and cold stimuli (p=0.267).

Similarly, exercise-induced increases in mean body temperature did not induce any change in the magnitude estimation of warm stimuli from pre-exercise values, neither in the CTR (34°C stimulus mean difference: 1.0 mm [-26.3, 28.3] p=0.93, Fig. 1A; 38°C stimulus mean difference: -9.6 mm [-25.1, 5.8] p=0.185, Fig. 1C), nor in the MS group (34°C stimulus mean difference: 2.5 mm [-10.5, 15.5] p=0.633, Fig. 1B; 38°C stimulus mean difference: 1.2 mm [-26.7, 29.3] p=0.919, Fig. 1D).

Contrariwise, MS and CTR experienced a reduction in cold sensitivity with elevations in body temperature, which extended across a wider temperature range (including milder/colder temperatures) in the MS as compared to 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. 2C), MS patients showed a significantly reduced cold sensitivity to both 22°C (mean difference: -18.7 mm [-29.9, -7.5] p=0.006; Fig. 2D) and 26°C stimuli (mean difference: -13.2 mm [-24.5, -1.9] p=0.027; Fig. 2B).

When expressed as 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°C and 22°C stimuli respectively. In CTR, 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°C and 22°C stimuli respectively.

Discussion

For the first time, we assessed afferent somatosensory function in MS relative to age-matched CTR during exercise-induced increases in body temperature using our newly developed quantitative sensory test of afferent thermosensory function. We observed that, while under thermo-neutral conditions (prior to exercise) perceived magnitude of warm and cold stimuli appeared intact, 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 under 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 should be noted that MS participants experienced the 22°C stimulus post exercise to be as cold as the 26°C prior to exercise (compare Fig. 2D Post-EX with Fig. 2B Pre-EX), despite the same participants clearly distinguished between these two stimuli prior to exercise (compare Fig. 2B Pre-EX with Fig. 2D 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 novel 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* (sub-cortical/cortical) neural structures (Filingeri, 2016). Due 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 on heat-induced alterations in the processing of afferent somatosensory inputs within central neural centers.

While 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 be also 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^{o}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, it cannot be excluded that an interaction between pathological (i.e. demyelination) and physiological (i.e. exercise analgesia) mechanisms could underlie our observed heat-induced modulation of afferent thermosensory function in MS.

While 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 under exercise-induced heat stress, a novel 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/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 occurring under heat stress, the perceptual benefits for MS users of such devices (e.g. improving thermal comfort during exercise/sunshine exposure) could be indeed 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 elevations 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 quantitatively characterize thermal stress-induced changes in afferent sensory function in MS within both clinical and experimental contexts. From a clinical perspective, this knowledge could be indeed beneficial to support the design of quantitiave testing procedures supporting early clinical detection, 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, sweating) (Davis *et al.*, 2008, 2010). As afferent sensory

abnormalities are highly prevalent symptoms in MS (Leocani *et al.*, 2003), we propose that our novel methodology could be implemented in future experimental approaches to quantitatively characterize 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.

Competing interests

The authors report no competing interests.

Author contributions

All experimental testing was performed at the Thermal Ergonomics Laboratory, Faculty of Health Sciences, University of Sydney, Australia. All authors contributed to the conception and design of the study. DF and GC performed data acquisition. DF 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 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.

Funding

This work was supported by Multiple Sclerosis Research Australia [Incubator Grant 14-009; Grant holders: Jay, Barnett, Hoang and Davis] and by the Australian Government, Department of Education [Endeavor Post-Doctoral Research Fellowship; Holder: Filingeri].

Acknowledgements

The authors are thankful to Prof George Havenith (Loughborough University) for loaning the thermo-sensory analyser used in this study.

References

Allen DR, Huang M, Parupia IM, Dubelko AR, Frohman EM & Davis SL (2017). Impaired sweating responses to a passive whole-body heat stress in individuals with multiple sclerosis. *J Neurophysiol* doi: 10.1152/jn.00897.2016

Davis SL, Frohman TC, Crandall CG, Brown MJ, Mills DA, Kramer PD, Stüve O & Frohman EM (2008). Modeling Uhthoff's phenomenon in MS patients with internuclear ophthalmoparesis. *Neurol* **70,** 1098–1106.

Davis SL, Wilson TE, White AT & Frohman EM (2010). Thermoregulation in multiple sclerosis. *J Appl Physiol* **109,** 1531–1537.

Dostrovsky J & Craig A (1996). Cooling-specific spinothalamic neurons in the monkey. *J Neurophysiol* **76**, 3656-3665.

Faul F, Erdfelder E, Lang AG & Buchner A (2007). G*Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behav*

Res Methods 39, 175–191.

Filingeri D (2016). Neurophysiology of Skin Thermal Sensations. *Compr Physiol* **6**,1429-1491.

Filingeri D, Fournet D, Hodder S & Havenith G (2014). Why wet feels wet? A neurophysiological model of human cutaneous wetness sensitivity. *J Neurophysiol* **112,** 1457–1469.

Filingeri D, Morris NB & Jay O (2017*a*). Warm hands, cold heart: progressive whole-body cooling increases warm thermosensitivity of human hands and feet in a dose-dependent fashion. *Exp Physiol* **102,** 100–112.

Filingeri D, Zhang H & Arens EA (2017*b*). Characteristics of the local cutaneous sensory thermo-neutral zone. *J Neurophysiol* **117**, 1797-1806.

Gagge A & Gonzalez R (1996). Mechanisms of heat exchange: biophysics and physiology. *Compr Physiol 2011, Supplement 14: Handbook of Physiology, Environmental Physiology: 45-84. First published in print 1996.*

Gerrett N, Ouzzahra Y, Coleby S, Hobbs S, Redortier B, Voelcker T & Havenith G (2014). Thermal sensitivity to warmth during rest and exercise: a sex comparison. *Eur J Appl Physiol* **114,** 1451-1462.

Iannetti GD, Truini A, Romaniello A, Galeotti F, Rizzo C, Manfredi M & Cruccu G (2003). Evidence of a specific spinal pathway for the sense of warmth in humans. *J Neurophysiol* **89,** 562–570.

Iredale KF & Nimmo MA (1997). The effect of aging on the lactate threshold in untrained men. *J Aging Phys Act* **5,** 39–49.

Kanagaratnam M, Pendleton C, Almeida D, Pettit J & Baker MD (2017). Diuretic

sensitive electroneutral Na + movement and temperature effects on central axons. *J Physiol* doi: 10.1113/JP273963.

Kiernan MC (2017). Some do not like it hot. *J Physiol* doi: 10.1113/JP274183.

Koltyn K (2000). Analgesia following exercise: a review. *Sport Med* **29,** 85–98.

Leocani L, Martinelli V, Natali-Sora MG, Rovaris M & Comi G (2003). Somatosensory evoked potentials and sensory involvement in multiple sclerosis: comparison with clinical findings and quantitative sensory tests. *Mult Scler* **9,** 275–279.

Noseworthy J, Lucchinetti C, Rodriguez M & Weinshenker B (2000). Multiple Sclerosis. *N Engl J Med* **343**, 938-952.

Ossipov MH, Dussor GO & Porreca F (2010). Central modulation of pain. *J Clin Invest* **120,** 3779–3787.

Ouzzahra Y, Havenith G & Redortier B (2014). Regional distribution of thermal sensitivity to cold at rest and during mild exercise in males. *J Therm Biol* **37,** 517-523.

Palmer AJ, Colman S, O'Leary B, Taylor BV & Simmons RD. (2013). The economic impact of multiple sclerosis in Australia in 2010. *Mult Scler* **19**: 1640-1646.

Schlader ZJ, Simmons SE, Stannard SR & Mündel T (2011). The independent roles of temperature and thermal perception in the control of human thermoregulatory behavior. *Physiol Behav* **103,** 217–224.

White L & Dressendorfer R (2004). Exercise and multiple sclerosis. *Sport Med* **34,** 1077–1100.

Figure Legends

Figure 1. Impact of exercise-induced increases in body temperature on skin thermosensitivity to warm stimuli in CTR (A, C) and MS (B, D). Individual (n=8) and mean (±95% CI) values for magnitude estimation of local thermal sensations resulting from 34°C (A, B) and 38°C (C, D) stimuli pre- and post- 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, neither in the CTR nor in the MS group.

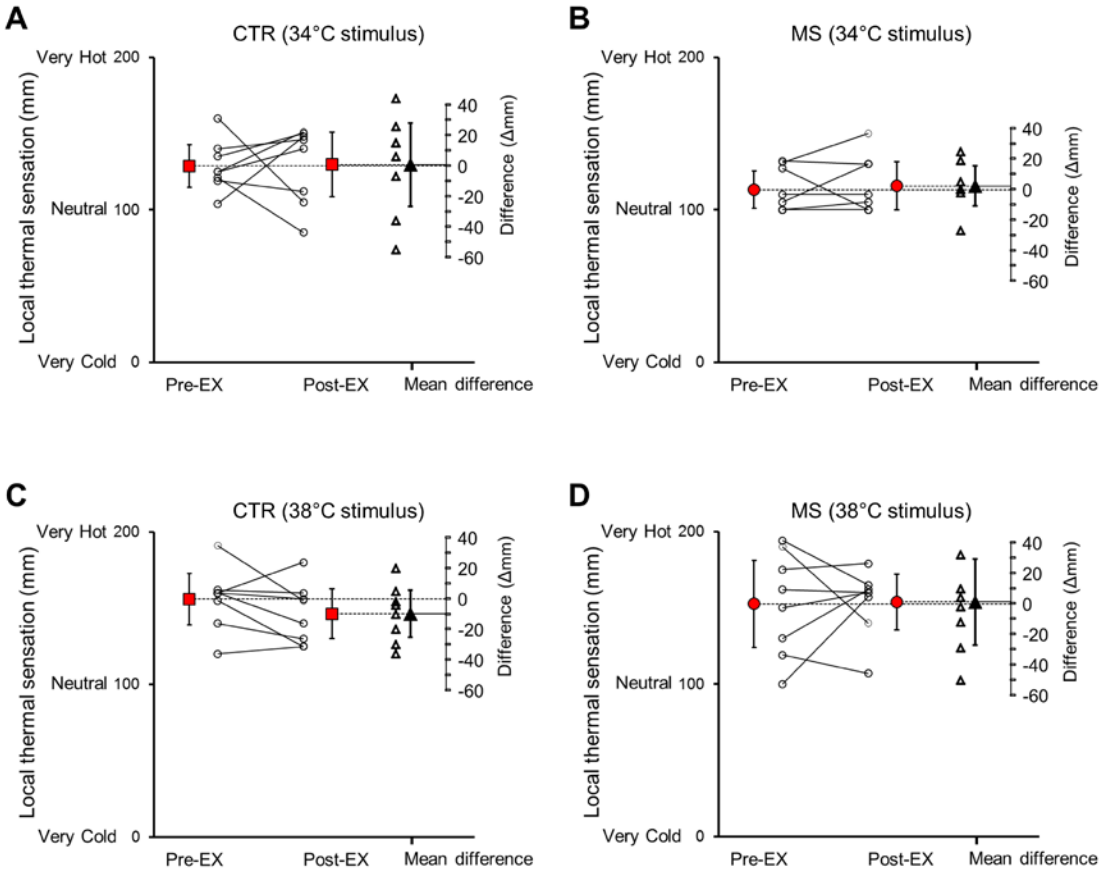

Figure 2. Impact of exercise-induced increases in body temperature on skin thermosensitivity to cold stimuli in CTR (A, C) and MS (B, D). Individual (n=8) and mean (±95% CI) values for magnitude estimation of local thermal sensations resulting from 26°C (A, B) and 22°C (C, D) stimuli pre- and post- 30-min cycling are shown. It can be observed exercise-induced increases in mean body temperature induced reduction in cold sensitivity in MS and CTR, although these were more pronounced in the MS group (i.e. both sensitivity to 26 and 22°C was reduced). * denotes statistically significant difference at $p<0.05$.