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Warm hands, cold heart: progressive whole-body cooling increases warm thermosensitivity of human hands and feet in a dose-dependent fashion

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What is the central question of this study?

Investigations on inhibitory/facilitatory modulation of vision, touch and pain show that conditioning stimuli outside the receptive field of testing stimuli modulates the central processing of visual, touch and painful stimuli. We asked whether contextual modulation also exists in human temperature integration.

What is the main finding and its importance?

Progressive decreases in whole-body mean skin temperature (the conditioning stimulus) significantly increased local thermosensitivity to skin warming, but not cooling, (the testing stimuli) in a dose-dependent fashion. In resembling the central mechanisms underlying endogenous analgesia, our findings point to the existence of an endogenous thermosensory system in humans that could modulate local skin thermal sensitivity to facilitate thermal behaviour.

Abstract

While inhibitory/facilitatory central modulation of vision and pain has been investigated, contextual modulation of skin temperature integration has been unexplored. Hence, we tested whether progressive decreases in whole-body mean skin temperature (T_{sk}) (a large conditioning stimulus) alter the magnitude estimation of local warming and cooling stimuli applied to hairy and glabrous skin. On 4 separate occasions, 8 males (27 ± 5 y) underwent a 30-min whole-body cooling protocol (water-perfused-suit; temperature: 5°C), during which a quantitative thermosensory test, consisting of reporting perceived magnitude of warming and cooling stimuli ($\pm 8^\circ\text{C}$ from 30°C baseline) applied to the hand (palm/dorsum) and foot (sole/dorsum), was performed before cooling and every 10 min thereafter. The cooling protocol resulted in large progressive reductions in whole-body T_{sk} (10 min: -3.36°C (95% CI: $-2.62, -4.10$); 20 min: -5.21°C ($-4.47, -5.95$); 30 min: -6.32°C ($-5.58, -7.05$); $p < 0.001$), with minimal changes ($\sim 0.08^\circ\text{C}$) in rectal temperature. While thermosensitivity to local skin cooling remained unchanged ($p = 0.831$), sensitivity to skin warming increased significantly at each level of whole-body T_{sk} for all skin regions (10 min: $+4.9\%$ ($-1.1, +11.0$); 20 min:

+6.1% (+0.1, 12.2); 30 min: +7.9% (+1.9, +13.9); $p=0.009$). Linear regression indicated a $1.2\% \cdot ^\circ\text{C}^{-1}$ increase in warm thermosensitivity with whole-body skin cooling. Overall, large decreases in whole-body T_{sk} significantly facilitated warm, but not cold, sensory processing of local thermal stimuli, in a dose-dependent fashion. In highlighting a novel feature of human temperature integration, these findings point to the existence of an endogenous thermosensory system that could modulate local skin thermal sensitivity in relation to whole-body thermal states.

Key words: Body temperature regulation, nervous system, perception, skin, thermoreceptors

Abbreviations: ANCOVA, analysis of covariance; T_{sk} , mean skin temperature; T_{re} , rectal temperature

Introduction

Sensing temperature changes in the external and internal environment, i.e. thermoreception, represents an important sensory feature, that allows humans to effectively regulate autonomic and behavioural thermoregulatory responses required to maintain thermal homeostasis and ensure survival (Hensel, 1973; Cabanac, 2010; Filingeri, 2016). The physiological importance of thermoreception is particularly evident in the context of pathological conditions associated with thermosensory deficit. Indeed, in neurological diseases such as multiple sclerosis, impairments in thermosensory integration contribute to autonomic dysfunction (Davis *et al.*, 2010; Okuda *et al.*, 2014).

Beside its role in autonomic body temperature regulation (Cotter & Taylor, 2005), the transduction of tissues' temperatures (e.g. skin and core) into neural inputs allows the central nervous system to produce thermal sensations (Darian-Smith, 1984). In humans, neuro-anatomically and –physiologically distinct cold- and warm-sensitive neurons, namely thermoreceptors, sub serve temperature coding (Zotterman, 1936). While thermoreceptors are found both peripherally (i.e. skin and muscles) (Campero *et al.*, 2001; Graven-Nielsen *et al.*, 2002) as well as centrally (i.e. brain, spinal cord and viscera) (Boulant & Bignall, 1973; Nakamura, 2011) in the body, as to date, the majority of the knowledge on temperature-

sensitive neurons sub-serving conscious thermal sensations is based on the analysis of skin afferents and of their central projections (Craig *et al.*, 2000; Campero *et al.*, 2001).

In humans and primates, fast conducting myelinated A δ fibers innervate the skin with varying density depending on skin site (Filingeri, 2016), selectively respond to skin cooling (range: 30 to 14°C; maximum impulse frequency within 27 – 22°C range; conduction velocity: 3.8 to 4.4 m s⁻¹; receptive field: <1 mm) and mediate innocuous cold sensations (Darian-Smith *et al.*, 1973). On the other hand, unmyelinated C-nerve fibers respond to skin warming, fire optimally within a temperature range of 30 to 45°C (maximum impulse frequency within 36 – 42°C range; conduction velocity: 0.4 to 2 m s⁻¹ receptive field: <1 mm) and mediate innocuous warm sensations (Konietzny & Hensel, 1975; Filingeri, 2016) (note: a sub-class of C fibers, i.e. C2, responds to noxious skin cooling <15°C and mediates noxious cold sensations) (Campero *et al.*, 2009). Anatomically, both cold- and warm-sensitive skin afferents transmit their sensory inputs to the insular cortex via the spino-thalamic tract (Filingeri, 2016). Functionally, sudden variations in skin temperature trigger changes in thermoreceptors' peak and frequency of discharge, and the magnitude of these changes is then centrally integrated to determine the intensity and timing of a thermal sensation (Darian-Smith, 1973; Darian-Smith *et al.*, 1979).

The evidence above has contributed significantly to the basic understanding of how changes in local skin temperature are coded and determine the magnitude of skin thermal sensations (Darian-Smith, 1984). However, such insights arise from experimental studies investigating neural activity of single cells in isolation from the potential impact that changes in the temperature of other body regions [superficial (e.g. skin and muscles) and deeper (e.g. core viscera, brain)] could have on the central integration of temperature. As a result, we face a lack of mechanistic knowledge on whether changes in the temperature of areas adjacent or peripheral to the receptive field of a specific cutaneous thermoreceptor alter the receptor's sensitivity to changes in skin temperature, the spinal and supra-spinal integration of a thermal stimulus, and ultimately the resulting thermal sensation. Specifically, no evidence is currently available on the potential influence of contextual changes in superficial (e.g. whole-body mean skin temperature) and deep (e.g. core) body temperatures on local thermal sensitivity of human skin.

That contextual modulation in human cutaneous temperature integration have been so far unexplored is surprising, particularly as this has been extensively investigated

psychophysically (human observers) and neurophysiologically (primate models) in the areas of vision (Mizobe *et al.*, 2001; Lochmann *et al.*, 2012), touch (Laskin & Spencer, 1979; Short *et al.*, 1990), hearing (Wehr & Zador, 2003) and pain (Le Bars *et al.*, 1979b; Staud *et al.*, 2003). For example, it appears that cortical superficial layer complex visual cells' responses to retinotopic stimulation of their receptive field (i.e. the region of the visual space which selectively activates a specific cell) are either suppressed or facilitated by the presence of visual stimuli concurrently applied outside their receptive field (Kapadia *et al.*, 1995). These observations have led to the identification of neural mechanisms of surround-inhibitions and -facilitation and of their role in figure-ground segregation in scene processing (Angelucci *et al.*, 2002). In the context of pain processing, it has long been known that *conditioning* noxious stimuli delivered peripherally to a skin site where a noxious *testing* stimulus is applied, result in a top-down inhibition of pain at the testing site (Le Bars *et al.*, 1979a, 1979b).

Based on the above, it would be reasonable to expect that similar inhibitory or facilitatory modulation could occur in the central integration of cutaneous thermal stimuli, and that this could be quantifiable psychophysically in humans. The aim of this study was therefore to investigate contextual modulation on human cutaneous thermosensory integration.

Specifically, we aimed to assess whether local cold and warm skin sensitivity of human hands and feet (i.e. the *testing* sites) is altered by selective decreases in whole-body mean skin temperature (i.e. the *conditioning* stimulus) and whether this effect is dependent on the magnitude of the conditioning stimulus. In line with mechanisms of central modulation of both vision and pain, here we developed a human experimental model to test the hypothesis that decreases in whole-body mean skin temperature (i.e. a large conditioning stimulus) would significantly change the magnitude estimation of local skin warming and cooling testing stimuli in a dose-dependent fashion (i.e. the greater the change in whole-body mean skin temperature, the greater the changes in local skin thermosensitivity).

Methods

Ethical Approval

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 of the finger pad following local compression ischemia (Filingeri *et al.*, 2014a), to determine a required sample size of 8 individuals for the current study. As such, eight healthy males (age: 27 ± 5 y, height: 173 ± 7 cm, mass: 75.8 ± 7.3 kg) with no history of cardiovascular, neurological and sensory-related disorders volunteered to participate in this study. At the time of the study, participants were not taking any medications nor supplements. All participants gave their written informed consent for participation. The test procedure and the conditions were explained to each participant. The University of Sydney Human Research Ethics Committee approved the study design and testing procedures were in accordance with the tenets of the Declaration of Helsinki.

Experimental design

A repeated measure design was employed requiring all participants to take part in four separate experimental trials. During each trial, participants repeated the same standardized quantitative thermosensory test with different levels of conditioning (i.e. different levels of whole-body mean skin temperature).

The standardized quantitative thermosensory test consisted in participants having to report on a visual analogue scale the magnitude of local thermal sensations elicited by skin warming and cooling stimuli (i.e. Δ temperature variation: $\pm 8^\circ$ C from a baseline temperature of 30° C; rate of temperature change: 2.43° C/s) delivered to one of four skin sites on hands and feet with a 25 cm^2 thermal probe (NTA-2A; Physitemp Instruments Inc., USA). We chose 38 and 22° C testing stimuli as they are non-noxious temperatures and are in the temperature range for maximal activation of both cutaneous cold (i.e. $27 - 22^\circ$ C) and warm (i.e. $36 - 42^\circ$ C) thermoreceptors (Filingeri, 2016).

In order to obtain different levels of conditioning (i.e. different levels of whole-body mean skin temperature) in a repeatable fashion, participants underwent a 30-min whole-body cooling with a tube-lined water perfused suit (Med-Eng, Ottawa, Canada) worn over their underwear. The suit covered the entire body except the head, hands and feet (which were left bare during all trials) and was connected to a water tank containing stirred water maintained at 5° C. Water could be perfused continuously through the suit by two electrical pumps and

its temperature was monitored continuously using a thermistor (TM400, Covidien, Mansfield, MA, USA) at the inlet of the suit.

Participants were in a semi-reclined position throughout the duration of each trial, and underwent 15 min of rest in a thermo-neutral room (22°C, 50% RH) before ambient temperature was lowered to 15°C, 50% RH when whole-body cooling began. Accordingly, the quantitative thermosensory test was performed before cooling, to assess baseline thermal sensitivity under thermo-neutral conditions; and then every 10 min during the 30-min whole-body cooling to assess contextual modulation of local thermo-sensitivity at different levels of whole-body mean skin temperature.

We performed the standardized quantitative thermosensory test on four different skin regions (each one tested on a separate trial): 1) the thenar eminence of the palm of the right hand; 2) the dorsum of the right hand (mid-distance between the distal portion of the proximal phalanx of the middle finger and the wrist joint); 3) the sole of the right foot (mid-point of the medial longitudinal arch); 4) the dorsum of the right foot (mid-distance between the distal portion of the proximal phalanx of the third toe and the ankle joint). We chose to test four different skin regions belonging to both hairy (i.e. dorsum of hand and foot) and glabrous skin sites (i.e. palm and sole) in order to characterize contextual modulation across all types of skin, and to assess the potential reproducibility of any overall contextual effect. Thermal sensitivity appears indeed to vary between hairy and glabrous skin sites (Stevens & Choo, 1998), due to both physiological (e.g. density of sensory innervation) (Norrzell *et al.*, 1999) and biophysical factors (e.g. differences in epidermal layer's thickness and related thermal conductance) (Iannetti *et al.*, 2006).

We selected a 5° C water temperature for the suit in order to generate a moderate and progressive whole-body cooling without the risk of inducing painfully cold sensations. Indeed, pilot studies demonstrated that, due to the insulation provided by the suit and due to the tubing density (note: tube are contained within the fabric of the suite and not in direct contact with the skin), perfusing 5° C water through the suit for 30 min would result in a repeatable progressive reduction in whole-body mean skin temperature no greater than ~8° C. Mean skin temperatures for a resting standard-sized individual (i.e. body mass 70 Kg; body surface area 1.8 m²) (Du Bois & Du Bois, 1989) exposed to a neutral environment (e.g. ambient temperature ~22 °C) is usually between ~30 and ~34 °C (Hensel, 1973; Gagge & Gonzalez, 1996). Hence, our cooling protocol appeared appropriate to progressively lower

whole-body mean skin temperature to an extent (i.e. $\sim 22\text{-}24^{\circ}\text{C}$) which would be large enough to represent a considerable conditioning stimulus, while being well above the cold pain skin temperature threshold (i.e. $\sim 14^{\circ}\text{C}$). In support of the above, pain sensations were never reported by any participant during any piloting nor experimental sessions.

This whole-body cooling protocol was also selected for its effectiveness in minimizing potential changes in core temperature. Indeed, whole-body skin cooling first triggers cold-defence responses (i.e. cutaneous vasoconstriction and shivering thermogenesis) that decrease heat loss, increase heat production and ultimately minimize changes in core temperature under moderate cold stress (Zeisberger & Roth, 2011). Mechanistically, limiting changes in core temperature was deemed important to ensure that conditioning (i.e. change in whole-body mean skin temperature) and test stimuli (i.e. change in local skin temperature) would stimulate primarily the same category of afferent receptors, i.e. cutaneous thermoreceptors, and that potential contributions from thermoreceptors innervating deeper tissues (i.e. core viscera) would be reduced to a minimum.

Overall, the experimental design outlined above allowed us to assess the effects of progressively greater levels of surround conditioning (i.e. different levels of whole-body mean skin temperature) on local sensitivity of four skin regions of the human extremities to warming and cooling pulses symmetrical in the size and magnitude of the temperature change (i.e. $\pm 8^{\circ}\text{C}$). A schematic representation of the experimental design is presented in figure 1.

Experimental protocol

Participants were instructed to refrain from alcohol, caffeine, and exercise in the 12 h prior to testing. All four trials were performed in a balanced order, at the same time of day to avoid potential effects of circadian rhythm and were separated by at least 48 h.

Upon arrival, subjects voided their bladders before standing height and semi-nude body mass were measured with a wall-mounted stadiometer and digital scale (ID1 MultiRange, Mettler Toledo, Columbus, OH, USA; precision $\pm 1\text{ g}$). After, participants self-inserted a general-purpose pediatric thermistor probe (TM400, Covidien, Mansfield, MA, USA) 12 cm beyond the anal sphincter, to monitor and record rectal temperature (T_{re} ; an indicator of core temperature). Participants then entered a climatic chamber to complete instrumentation procedures.

Four thermistors integrated into 2.5-cm² heat flux sensors (Concept Engineering, Old Saybrook, CT) were taped over the chest, deltoid, thigh at the mid- point between the anterior superior iliac crest and the knee joint, and over the calf, all on the right side of the body using double-sided adhesive disks (3M Health Care, Neuss, Germany) and surgical tape (Transpore, 3M, London, ON, Canada) (note: all these skin sites were covered by the suit during the whole-body cooling protocol). A weighted average (i.e. chest (30%); deltoid (30%); thigh (20%); calf (20%)) (Ramanathan, 1964) was used to estimate whole-body mean skin temperature (T_{sk}) – the primary measure of the level of surround conditioning.

Following the completion of instrumentation procedures, participants donned the tube-lined water perfused suit and lay supine on a bench. No water was perfused through the suit until the whole-body cooling protocol commenced.

Next, the thermal probe used for the quantitative thermosensory test was secured to one of the four hand or foot skin sites targeted for stimulation with an adjustable Velcro© band, in order to ensure full contact with the skin for the duration of the trial. The thermal probe was set and maintained at 30°C. After fifteen minutes of baseline thermometric data collection, and before the whole-body cooling protocol begun, the first quantitative thermosensory test was performed to assess baseline thermal sensitivity in the absence of any contextual modulation.

The quantitative sensory test was similar to the one used by Filingeri et al. (Filingeri *et al.*, 2014a, 2014b) and was performed as follows. The cooling stimulus (i.e. Δ temperature variation: -8° C) was delivered from the baseline of 30° C. As soon as the cooling stimulus reached the target temperature (i.e. 22° C; thermal probe response time: <4 s), participants were instructed to immediately report their local thermal sensation on a hand-scored 200 mm visual analogue scale. The anchor points of this scale were “Very cold” (on the left of the scale; 0 mm point) and “Very hot” (on the right of the scale; 200 mm point) with “Neutral” marking the middle point (100 mm point). As soon as the local sensation was recorded, the probe was reset to the baseline of 30° C (response time: <4 s). After ten seconds at 30° C, the warming stimulus (i.e. Δ temperature variation: +8° C) was delivered. Participants again reported their local thermal sensation, after which the probe was reset to 30° C. By maintaining (i.e. pre-stimulation) and re-adapting (i.e. post-stimulation) local skin temperature at 30° C, we eliminated any confounding factors associated with variations in skin temperature of the testing site during the whole-body cooling protocol.

The order of delivery of cooling and warming stimuli was randomised and then counter-balanced within participants (i.e. within the same trial and between trials) as well as between participants. Participants were fully familiarized with the quantitative sensory test procedure, testing stimuli and scoring system during the first visit to the Laboratory.

After completing the baseline thermosensory test under thermo-neutral conditions (22°C, 50% RH) ambient temperature was lowered to 15°C, 50% RH, the 30-min whole-body cooling protocol commenced, and the same quantitative thermosensory test repeated after 10, 20 and 30 min of whole-body cooling.

Statistical analysis

All data are reported as mean \pm standard deviation (SD) unless otherwise stated. All thermosensitivity data were analysed separately for warming and cooling stimuli. Pre-whole-body cooling thermo-sensitivity was analysed using a one-way repeated measures ANOVA, with the independent factor of skin site (4 levels: palm, dorsum of hand, sole, and dorsum of foot). Local thermal sensations during the whole-body cooling protocol were expressed as a percent change (Δ %) from baseline and analysed using a two-way repeated measures ANOVA with the independent factors of condition skin site (4 levels) and time (4 levels: pre-stimulation, and after 10, 20, 30 min of whole-body cooling). The same ANOVA model was also used to assess the dependent variables of whole-body T_{sk} and T_{re} . A Greenhouse-Geisser correction was applied if the assumption of sphericity was violated. In the event of a significant main effect or skin site-by-time interaction, post-hoc analysis was performed on cumulative data using Tukey's range test for multiple comparisons. Cumulative data were calculated by grouping data on e.g. changes in thermal sensation for skin warming and skin cooling and on whole-body T_{sk} and averaging them over the skin site tested. Finally, in order to investigate whether the modulation of local thermal sensitivity would be proportional to degree of change in whole-body T_{sk} , we separately assessed the relationship between cumulative changes in local warm and cold sensitivity as a function of cumulative changes in whole-body T_{sk} using linear regression analyses (note: cumulative changes were averaged over skin sites). The slopes of these regression models were compared using an analysis of covariance (ANCOVA). In all analyses, $p < 0.05$ was used to establish significant differences. Estimated marginal means and 95% confidence intervals (CI) were used to investigate the

main effects and interactions of the variables. Observed power was computed using $\alpha=0.05$. Statistical analysis was performed using GraphPad Prism (version 6.0, GraphPad Software, La Jolla, CA).

Results

Baseline thermal sensitivity to skin warming and cooling

Baseline local thermal sensitivity to both cooling ($F= 3.93_{(2.52, 17.67)}$, $p= 0.030$) and warming pulses ($F= 5.20_{(1.94, 13.62)}$, $p= 0.021$) differed significantly between skin sites (Figure 2A-B). Specifically, when warming and cooling pulses were applied to the palm of the hand, these induced significantly warmer (mean difference: 25.8 a.u.; 95% CI: 11.6 to 43.9 a.u.; $p= 0.003$) and cooler (mean difference: 25.3 a.u.; 95% CI: 2.1 to 48.7 a.u.; $p= 0.034$) thermal sensations than when applied to the dorsum of the foot.

Whole-body mean skin temperature and rectal temperature during whole-body cooling protocol

Baseline whole-body T_{sk} did not differ between trials ($F= 0.38_{(2.37, 16.65)}$, $p= 0.721$) with a mean observed value of $32.11 \pm 0.78^\circ \text{C}$ (95% CI= 31.83 to 32.39° C). Similarly, baseline T_{re} did not differ between trials ($F= 0.55_{(2.14, 15.01)}$, $p= 0.598$) with a mean observed value of $36.90 \pm 0.33^\circ \text{C}$ (95% CI= 36.78 to 37.03° C). These results confirmed that the participants were in a thermo-neutral state at the beginning of each trial.

Following the onset of whole-body cooling, a significant reduction in whole-body T_{sk} was observed with time ($F= 213.8_{(3, 21)}$, $p<0.0001$), which was similar between all four experimental trials ($F= 1.98_{(3, 21)}$, $p=0.147$). Specifically, distinctly different whole-body T_{sk} values were attained at each time point, with whole-body T_{sk} reduced by 3.36°C (95%CI= 2.62 to 4.10° C; $p<0.001$) after 10 min, 5.21°C (95%CI= 4.47 to 5.95° C; $p<0.001$) after 20 min, and 6.32°C (95%CI= 5.58 to 7.05° C; $p<0.001$) after 30 min (Figure 3).

A small ($\sim 0.1^\circ \text{C}$) reduction in T_{re} ($F= 5.75_{(3, 21)}$, $p=0.004$), which was similar between all four experimental trials ($F= 0.58_{(3, 21)}$, $p=0.633$), was observed during whole-body cooling. Relative to baseline, T_{re} was lower by -0.08°C (95%CI= -0.01 to -0.14° C; $p= 0.007$) after 10 min, but did not change thereafter (Figure 3).

Overall, the observed large decreases in whole-body T_{sk} , along with the minimal changes in T_{re} , confirmed the effectiveness of whole-body cooling protocol in forcing whole-body T_{sk} to represent the main conditioning stimulus to local skin thermosensitivity.

Modulation of local thermosensitivity as a function of whole-body mean skin temperature

The influence of changes in whole-body T_{sk} on local skin thermosensitivity was dependent upon thermal modality. While local thermosensitivity to skin cooling remained unchanged ($F= 0.29_{(3, 21)}$, $p=0.831$) at all skin sites ($F= 1.16_{(3, 21)}$, $p=0.346$) despite the different whole-body T_{sk} at each time point, local thermosensitivity to skin warming was significantly altered by different levels of whole-body T_{sk} ($F= 4.89_{(3, 21)}$, $p= 0.009$) with no differences between skin sites ($F= 1.51_{(3, 21)}$, $p= 0.240$). Specifically, a significant and progressive increase in local thermosensitivity to the same warming pulse was observed with decreasing whole-body T_{sk} . Relative to baseline values, cumulative thermosensitivity to local skin warming increased by 4.9% (95%CI: -1.1 to 11.0%; $p=0.131$) after 10 min, 6.1% (95%CI= 0.1 to 12.2%; $p=0.045$) after 20 min, and 7.9% (95%CI= 1.9 to 13.9%; $p=0.007$) after 30 min (Table 1).

A significant association between the cumulative decrease in whole-body T_{sk} and the cumulative increase in thermal sensation induced by the same local skin warming pulse was observed ($r= -0.99$; $p= 0.009$) (figure 4). On the contrary, no such association was observed for cumulative changes in local thermosensitivity to skin cooling ($r= 0.34$; $p= 0.657$). These regression slopes differed significantly (warming: mean slope= -1.2; 95%CI= -2.0 to -0.4; cooling: mean slope= +0.1; 95%CI= -0.8 to +1.1; $F= 4.87_{(1, 60)}$, $p= 0.031$). A linear regression model was calculated ($y= -1.217x+0.2139$) indicating that a 1.2% increase in thermosensitivity to skin warming occurred per 1°C decrease in whole-body mean skin temperature.

Discussion

The primary finding of the present study is that conditioning stimuli in the form of progressive decreases in whole-body T_{sk} , significantly facilitated warm, but not cold, sensory processing of local thermal stimuli, in a dose-dependent fashion (i.e. +1.2%·°C⁻¹).

To our knowledge, this is the first time that a dose-dependent contextual modulation of local thermosensitivity is reported in humans. This phenomenon appears to be widespread and robust. Indeed, despite differences in local thermosensitivity to skin warming and cooling were present amongst the hairy and glabrous skin site tested (i.e. the palm was more sensitive than the dorsum of the foot), contextual modulation of local warm thermosensitivity occurred on both skin types and with no significant differences between the skin site tested.

Our findings are in line with evidence available on central mechanisms of contextual modulation of vision (Mizobe *et al.*, 2001; Lochmann *et al.*, 2012), touch (Short *et al.*, 1990) and pain (Le Bars *et al.*, 1979a, 1979b; Staud *et al.*, 2003), where the integration of afferent sensory inputs and resulting sensory experiences are significantly modulated by contextual stimuli exerting their influence via ascending and descending central pathways. We therefore believe that the results of this study highlight a novel feature of human thermosensory processing, which could be dependent on modulation of afferent thermosensory inputs within central neural pathways. Accordingly, we have hypothesized that both cortical and sub-cortical mechanisms could be involved in this central phenomenon.

Thermosensory facilitation: cortical mechanisms

Contextual modulation has long been described in the field of vision science (Jones, 1970; Kapadia *et al.*, 1995; Levitt & Lund, 1997). Suppressive and facilitatory contrast-dependent mechanisms between neurons responding to a visual stimulus and neurons in the surrounding receptive fields have been indeed identified as a specific cortical feature, dependent on long-range horizontal connections within the visual cortex (Stettler *et al.*, 2002). Interestingly, contextual facilitation has been reported in instances where the surround visual stimuli are oriented in the opposite direction to the ones presented within the center of the cell's receptive field (Levitt & Lund, 1997).

Conceptually, this contrast-enhanced facilitation in vision, resembles the psychophysical observations reported here. When warm stimuli applied on a local testing site were surrounded by thermal stimuli "oriented" in the opposite direction (i.e. skin regions surrounding the testing site were being actively cooled during the cooling protocol), thermosensory processing was significantly facilitated and the magnitude of the resulting thermal sensation was significantly greater (i.e. "warmer").

A contrast-dependent mechanism potentially related to the enhancement of stimulus saliency (Wehr & Zador, 2003) could be therefore hypothesised to underlie our findings. Whole-body-cooling-driven activity in cortical neurons whose receptive fields surrounded those of cortical neurons responding to skin warming within the testing site stimulated, could have indeed increased the intra-cortical contrast between these different thermally-sensitive neuronal populations. This increased intra-cortical contrast could have in turn determined an increase in the magnitude of the output thermal sensation resulting from the warming stimulus, despite the latter always resulted in the same physical change in skin temperature.

As it appears to be the case for visual (Angelucci *et al.*, 2002) and auditory (Wehr & Zador, 2003) phenomena, it could therefore be argued that our findings highlight a form of modulation of skin temperature integration that could be based on intra-cortical mechanisms. However, it cannot be excluded that sub-cortical and peripheral factors (e.g. pre- and post-synaptic effects on spinal second order neurons; activity of first order thermoreceptive neurons innervating the skin), as well as descending mechanisms of facilitatory control, could also contribute to the contextual modulation of thermosensory integration reported here.

Thermosensory facilitation: sub-cortical mechanisms

Sub cortical inhibition and facilitation of afferent somatosensory stimuli (i.e. touch/mechanical, pain) has been previously reported. Short *et al.* (Short *et al.*, 1990) observed that when conditioning air jet stimuli out-of the receptive field were applied concurrently to an air jet stimulus on the receptive field of mechanoreceptors innervating the glabrous skin of the cat, responses in spinal neurons were initially inhibited (i.e. out-of-field afferent inhibition) and successively facilitated (i.e. out-of-field afferent facilitation), with the extent of facilitation being proportional to the initial degree of inhibition. Similarly, spinal thermosensitive neurons identified in the cat' spinal cord have been also shown to present excitatory convergence from several cutaneous afferent fibers, as well as inhibitory inputs from regions near to their excitatory field (Christensen & Perl, 1970; Andrew & Craig, 2001). Based on this evidence, it could be therefore suggested that changes in sub-cortical mechanisms of temperature integration could have also contributed to the thermosensory facilitation observed in our human participants.

In line with what reported to occur for warm sensitive neurons in the cat' spinal cord (Andrew & Craig, 2001), it could be suggested that under our testing conditions, the whole-body cooling-dependent activity in cutaneous cold-sensitive neurons innervating the skin surrounding the testing sites, could have induced an on-going inhibition in spinal warm-sensitive neurons whose receptive fields corresponded to the testing sites. This contextual modulation could have presented a bi-phasic profile (i.e. initial inhibition is accompanied by proportional facilitation) similar to the one observed by Short et al. (Short *et al.*, 1990). It follows that if such a modulation was present, once the warming stimulus was delivered to the testing site, this would have generated a facilitated response in warm sensitive spinal neurons, whose magnitude might have been proportional to the degree of ongoing whole-body-cooling-driven inhibition. In neurophysiological terms, given the same warming pulse, a facilitated response could have translated in an increase in peak discharge frequency in the spinal warm-sensitive neuron. A "facilitated" increase in peak frequency in the spinal warm-sensitive neuron would have in turn translated in a greater input to cortical neurons within the therosensory insular cortex, hence in a "warmer" output thermal sensation. This hypothesis could be supported by the observation that warm therosensory facilitation was indeed proportional to the degree of surround conditioning (in the form of whole-body body cooling) (see figure 4).

The fact that therosensory facilitation was selective to warmth-sensing could even more strongly support the sub cortical nature of this phenomenon. Indeed, had therosensory facilitation relied on intra-cortical contrast, we would have expected to see therosensory inhibition for cold-sensing (i.e. a decrease in cold therosensitivity with progressive whole-body skin cooling). However, the latter was not observed and cold therosensitivity was maintained unchanged throughout the cooling protocol (see figure 4). It follows that the therosensory facilitation we observed could likely rely on sub cortical integration, as modulated by cutaneous thermoreceptive afferents. Being the modulation between cutaneous thermoreceptors cross modal in nature, the result of a whole-body cooling protocol would likely influence activity in warm-sensitive neurons only, with no effects of in-field cold-sensitive afferents; an observation confirmed by the results of the present study. The presence of such mechanisms would indicate that inputs relayed from cutaneous afferent neurons to the integration centres in the cerebral cortex, could be already processed at a sub cortical

level, an hypothesis in line with what recently shown for the processing of touch (Saal & Bensmaia, 2014).

A final argument for the presence of sub-cortical modulation of thermosensory inputs is provided by the evidence available on the central mechanisms of pain modulation (D’Mello & Dickenson, 2008; Ossipov *et al.*, 2010). It has long been known that descending pathways modulate nociceptive afferent inputs at a spinal level via either inhibition or facilitation of transmission to higher areas of the neuroaxis (Schmidt, 2013). Spinal wide dynamic range neurons responsive to cutaneous noxious stimuli (e.g. mechanical and thermal) present descending inhibition (i.e. diffuse noxious inhibitory controls) by higher order regions in the mid brain as part of an afferent-efferent loop belonging to the endogenous analgesic system (Le Bars *et al.*, 1979a; Heinricher *et al.*, 2009) . This system has been described as fundamental in modulating the conscious experience of pain according to environmentally-driven factors, attention, expectations and past experiences (Ossipov *et al.*, 2010).

Interestingly, pathological dysfunctions in diffuse noxious inhibitory control result in descending facilitation of afferent pain inputs (i.e. hyperalgesia) and in enhanced pain as observed in many acute and chronic pain conditions (Ossipov *et al.*, 2010).

In light of the neuro-anatomical and –physiological analogies in the central afferent projections for temperature and pain integration (i.e. both afferent pathways ascend through the antero-lateral spinothalamic tract and terminate their projections in the posterior insular cortex (Craig *et al.*, 1994; Han *et al.*, 1998; Craig, 2014; Segerdahl *et al.*, 2015), as well as in the perceptual nature of these homeostatic experiences (Craig, 2002), it could be therefore suggested that similar sub-cortical mechanisms of descending control of thermo-afferent inputs could be also involved in the central integration of skin temperature. Interestingly, descending control on pain afferents appears to distinguish between nociceptive A- and C-fibers (Heinricher *et al.*, 2009), a fact that is in line with our observation that thermosensory facilitation occurred selectively for warm (i.e. sub served by C-type fibers) but not cold (i.e. sub served by A- type fibers) local stimuli.

Unfortunately, classic studies on central descending modulation have focused on inhibition or facilitation of cutaneous noxious thermal and mechanical stimuli and of non-noxious mechanical stimuli only, with no investigation of non-noxious thermal stimuli as the ones used in this study (Le Bars *et al.*, 1979a, 1979b). While we believe our results point to this, further studies are therefore required to determine whether spinal integration of cutaneous

non-noxious thermal stimuli is also under descending control of a specific endogenous thermal system.

Thermosensory facilitation: physiological significance

The hypothesis of an endogenous thermal system in humans is intriguing for its behavioural implications. Indeed, the existence of specific mechanisms of thermosensory facilitation could carry physiological and behavioural significance as much as contextual effects in vision (Kapadia *et al.*, 1995) and pain (Heinricher *et al.*, 2009) do. The physiological purpose of such enhanced context-dependent thermosensitivity could indeed be to sharpen sensory discrimination (Wehr & Zador, 2003) and stimulus saliency (Le Bars *et al.*, 1979b).

However, what would be the behavioural advantage of developing (thermo-) sensory mechanisms that are modulated by surrounding (thermal) activity? According to an old concept of physiological usefulness previously described in the context of thermal pleasure (Cabanac, 1971), it could be speculated that the thermosensory facilitation observed here could increase individuals' sensitivity to stimuli which could help restoring thermal homeostasis, when the latter is shifted from neutrality. The fact that under the conditions of progressive-cold stress experienced during our protocol, warm-sensitivity increased selectively, could have been underlined by the physiological usefulness of an "enhanced" warm seeking behaviour in the cold. Interestingly, despite the contextual modulation recorded here might appear modest at first (a fact likely due to the relatively mild cold-stress we implemented), such effects showed a dose-dependency relationship. Accordingly, it appears that the more pronounced (and potentially threatening) the thermal challenge, the more substantial the increase in local thermosensitivity, a physiological feature that is in line with other well-known thermophysiological adaptation (e.g. heat loss responses to heat stress) showing a stimulus-dependent proportionality in their magnitude (Cramer & Jay, 2016).

A similar concept to the one proposed here is also postulated to underlie the behavioural advantage of having developed diffuse noxious inhibitory controls that, by decreasing the noise generated by on-going sensory stimuli when a salient pain stimulus arrives to higher centres, allow the behaviourally relevant new pain stimulus to clearly "stands out" (Le Bars *et al.*, 1979a; Heinricher *et al.*, 2009). Hence, we propose that, as much as is the case for the

endogenous analgesia system, the thermosensory facilitation observed here could be dependent on the presence of an endogenous thermosensory system whose function would be behaviourally advantageous in ensuring appropriate responses under life-threatening thermal challenges. This central mechanism could dynamically modulate the conscious experience of local skin temperature deepening on the thermal state of the body to optimize the behavioural usefulness of local thermal stimuli.

Limitations

While the potential behavioural significance of our findings is intriguing, their physiological and neural substrates need further experimental evidence to be confirmed. Physiologically, it would need to be demonstrated that a thermosensory facilitation would similarly occur for cold sensitivity under conditions of whole-body warming. While it is anticipated that investigating the effects of whole-body warming on local cold thermosensitivity could be challenging in light of inducing increases in whole-body T_{sk} of similar magnitude to what achieved in our cooling protocol, without concurrent changes in core temperature, it is hoped that such experimental approaches will be undertaken. From a neurophysiological perspective, it also appears necessary to confirm the psychophysical findings of this study with direct recordings of neuronal activity in primate models. Until such experimental approaches are undertaken, the involvement and role of generalized cortical or sub-cortical mechanisms of central modulation of peripheral inputs cannot be conclusively determined. Importantly, in light of the evidence for gender-related differences in thermal sensitivity (Gerrett *et al.*, 2014) and in central pain modulation (Staud *et al.*, 2003), it appears necessary to expand our findings with data from female individuals.

Finally, from a mechanistic point of view, it is important to highlight that the type of conditioning stimulus used here (i.e. whole-body cooling) induced greater physiological changes than simply modifying whole-body T_{sk} and that it cannot be excluded that such changes could have played a role in the thermosensory facilitation reported. For example, it could be argued that cold-induced systemic vasoconstriction and related decrease in skin blood flow to hands and feet could have altered the function of skin thermoreceptors. However, we have recently shown in humans that compression ischemia-induced reduction in skin blood flow do not alter local skin sensitivity to warm stimuli when these are applied to

both hairy and glabrous skin (Filingeri *et al.*, 2014a). Nevertheless, we suggest that in order further isolate the effects of thermosensory facilitation from any parallel physiological response associated with changes in body temperature, future studies should take advantage of chemicals such as menthol to condition skin sites and selectively activate peripheral thermoreceptors with no concurrent physical changes in local and whole-body temperatures.

Conclusion

For the first time to our knowledge, we report that contextual modulation of local thermosensitivity is present in humans and that this occurs in a modality-selective and dose-dependent fashion. We found that a large conditioning stimulus in the form of progressive decreases in whole-body mean skin temperature resulted in a selective increase in local thermosensitivity to skin warming (i.e. $1.2\% \cdot ^\circ\text{C}^{-1}$) but not cooling (which on the contrary remained unchanged). We propose that sub-cortical mechanisms of central inhibition and facilitation could likely represent the neural substrate of this human thermosensory feature, and that the latter could carry physiological significance in the context of maintaining thermal homeostasis. Overall, our findings are of fundamental, clinical and applied significance. Fundamentally, the outcomes of this study broaden our understanding of human thermosensory integration. Clinically, the new human experimental model developed here could be adopted to investigate alterations in thermosensory function in clinical populations. From an applied point of view, our observations could also be relevant in the context of occupational (e.g. military) performance and hand function under cold-stress and in extreme environments.

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. D.F., N.M. and O.J. contributed to the conception and design of the work; to interpretation and data analysis; and to drafting and

revising the work critically for important intellectual content. D.F. and N.M. also performed the data acquisition. 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.

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Tables legend

Table 1. Individual and cumulative modulation of local warm and cold thermosensitivity. Data represent mean percent change from baseline (\pm SD) in local thermosensitivity to warm and cold as assessed every 10 min during the whole-body cooling protocol. Effect size is reported in the form of mean absolute change (mm) from baseline in local thermosensitivity.

Skin site	Thermal modality	Percent change from baseline [absolute effect size]		
		10 min	20 min	30 min
<i>Back Hand</i>	<i>Warm</i>	+7.6% (\pm 11.3) [9.8 mm]	+8.9% (\pm 9.2) [12.1 mm]	+10.0% (\pm 8.6) [13.9 mm]
	<i>Cold</i>	-1.8% (\pm 10.8) [3.1 mm]	+0.1% (\pm 15.0) [0.5 mm]	-1.0% (\pm 12.4) [1.8 mm]
<i>Palm Hand</i>	<i>Warm</i>	+3.7% (\pm 6.3) [5.6 mm]	+8.3% (\pm 16.5) [10.6 mm]	+11.2% (\pm 15.3) [15.1 mm]
	<i>Cold</i>	-7.1% (\pm 7.7) [11.8 mm]	-3.4% (\pm 16.4) [7.6 mm]	-9.8% (\pm 16.8) [17.3 mm]
<i>Back Foot</i>	<i>Warm</i>	+8.6% (\pm 18.6) [9.4 mm]	+10.9% (\pm 19.2) [13.4 mm]	+10.7% (\pm 11.8) [12.4 mm]

<i>Sole Foot</i>	<i>Cold</i>	-1.9% (± 6.1) [2.8 mm]	-0.4% (± 6.4) [0.5 mm]	+1.6% (± 9.9) [2.3 mm]
	<i>Warm</i>	-0.3% (± 12.4) [0.8 mm]	-3.6% (± 8.5) [5.5 mm]	-0.1% (± 14.4) [0.4 mm]
	<i>Cold</i>	+2.7% (± 15.2) [2.6 mm]	+2.6% (± 17.2) [2.5 mm]	+4.9% (± 18.2) [5.3 mm]
<i>Cumulative</i>	<i>Warm</i>	+4.9 (± 12.6) [6.0 mm]	+6.1 (± 14.4) [7.7 mm]	+7.9 (± 12.8) [10.3 mm]
	<i>Cold</i>	-2.0 (± 10.5) [3.8 mm]	-0.3 (± 13.6) [1.5 mm]	-1.1 (± 14.8) [2.9 mm]

Figures legend

Figure 1. A schematic representation of the experimental design. Panel A shows a typical participant wearing the tube-lined water perfused suit used to induce progressive decreases in whole-body mean skin temperature (i.e. the conditioning stimulus). The thermal probe used to deliver the thermal stimuli at the testing sites is also shown. Testing sites included the dorsum and sole of the foot and the dorsum and palm of the hand (note: each site was tested on separate trials). Panel B shows the progression of a typical experimental trial while panel C shows the structure of the quantitative thermosensory test. It can be observed that the quantitative thermosensory test was performed before whole-body cooling to assess baseline thermosensitivity and then every 10 min during the cooling protocol to assess contextual modulation at different levels of whole-body mean skin temperature.

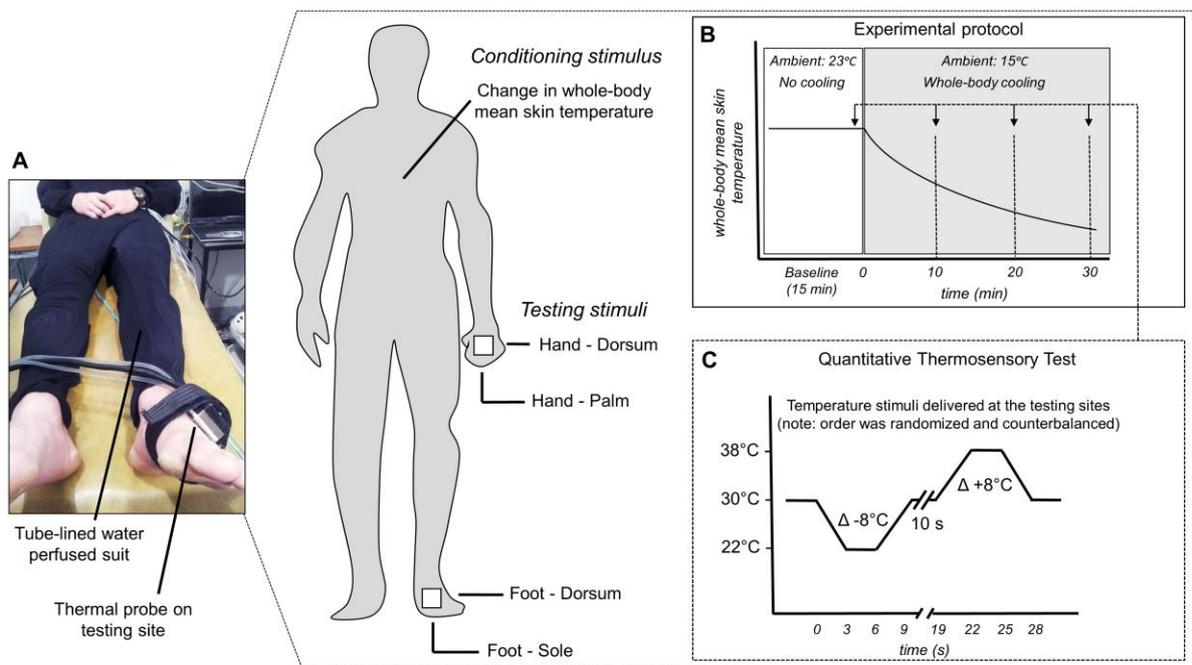


Figure 2. Individual (n= 8) and mean (95% CI) values for baseline thermal sensitivity (pre-whole-body cooling) to both skin warming (panel A) and cooling (panel B) for each of the four skin sites tested.

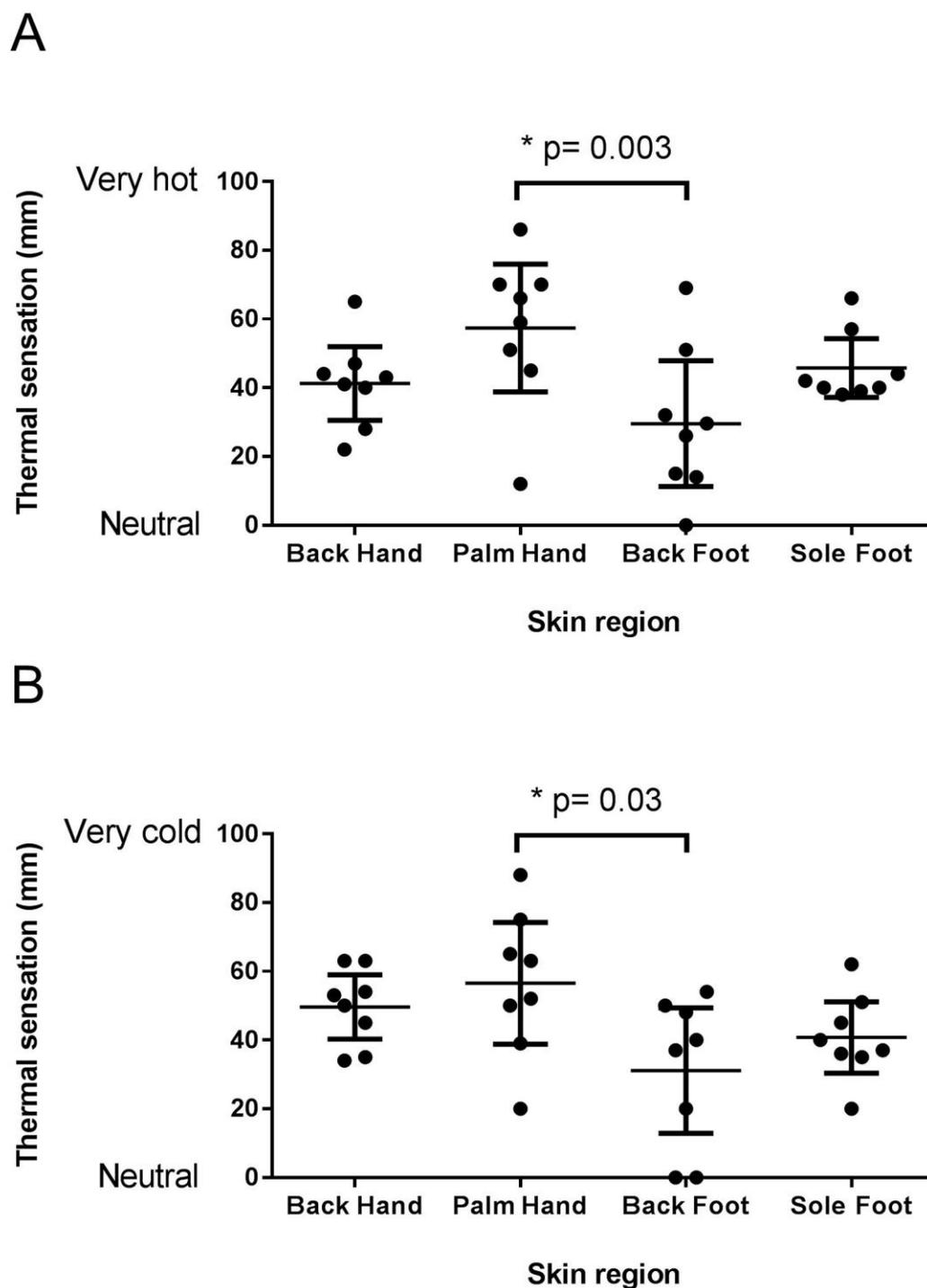


Figure 3. Mean (\pm 95%CI) changes in whole-body mean skin temperature (T_{sk}) and in rectal temperature (T_{re}) as a result of the 30-min whole-body cooling protocol.

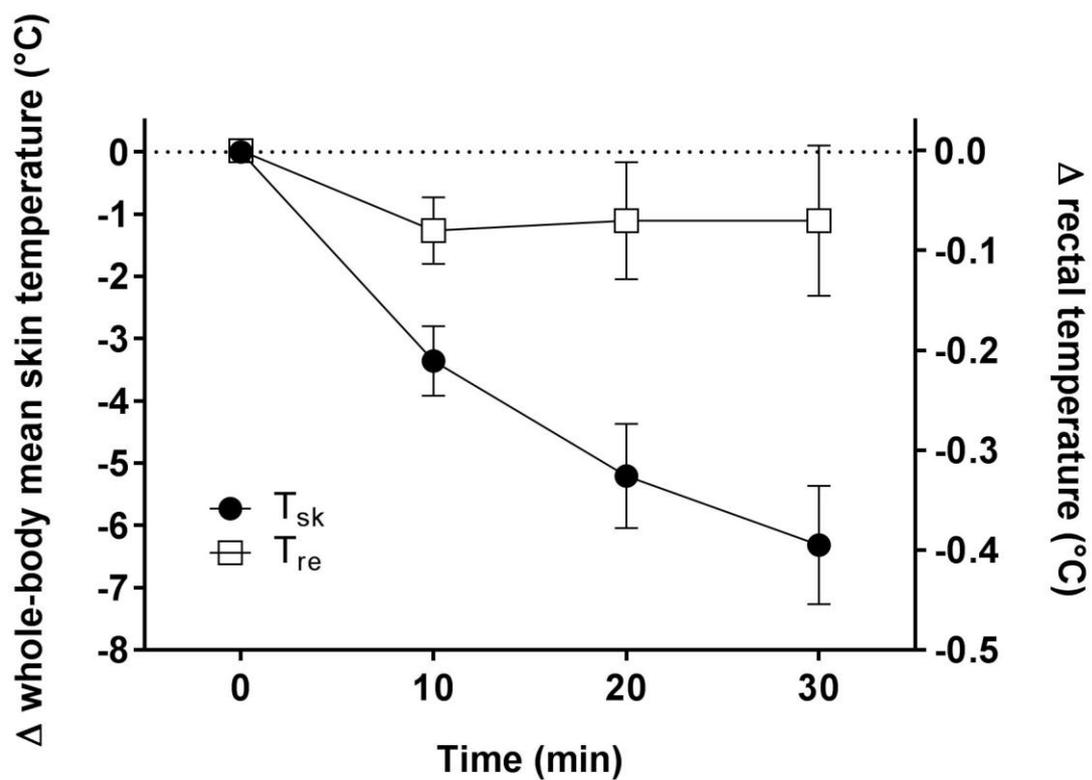


Figure 4. Mean (\pm 95%CI) changes in local thermal sensation for skin warming and skin cooling as a function of changes in whole-body T_{sk} . Asterisk (*) indicates a difference between slopes.

