Loughborough University

This item was submitted to Loughborough's Research Repository by the author.
Items in Figshare are protected by copyright, with all rights reserved, unless otherwise indicated.

Thermosensory micromapping of warm and cold sensitivity across glabrous and hairy skin of male and female hands and feet

PLEASE CITE THE PUBLISHED VERSION

https://doi.org/10.1152/japplphysiol.00158.2018

PUBLISHER

© American Physiological Society

VERSION

AM (Accepted Manuscript)

PUBLISHER STATEMENT

This paper was accepted for publication in the journal Journal of Applied Physiology and the definitive published version is available at https://doi.org/10.1152/japplphysiol.00158.2018.

LICENCE

CC BY-NC-ND 4.0

REPOSITORY RECORD

Filingeri, Davide, Hui Zhang, and Edward A. Arens. 2019. “Thermosensory Micromapping of Warm and Cold Sensitivity Across Glabrous and Hairy Skin of Male and Female Hands and Feet”. figshare. https://hdl.handle.net/2134/35082.

Thermosensory micromapping of warm and cold sensitivity across glabrous and hairy skin of male and female hands and feet

Davide Filingeri[1,2], Hui Zhang[2], Edward A. Arens[2]

[1]THERMOSENSELAB, Environmental Ergonomics Research Centre, Loughborough University, Loughborough, United Kingdom

[2] Center for the Built Environment, University of California at Berkeley, Berkeley, CA, USA

Running head: Warm and cold thermosensory mapping of human hands and feet

Key words: Thermoreceptors, Sensation, Sex, Skin, Body Temperature Regulation

Corresponding author's address:

Davide Filingeri, PhD

THERMOSENSELAB

Environmental Ergonomics Research Centre

Loughborough University

Loughborough, LE11 3TU

United Kingdom

Email: d.filingeri3@lboro.ac.uk

Phone: +44 (0) 1509 222661

Downloaded from www.physiology.org/journal/jappl by ${individualUser.givenNames} ${individualUser.surname} (131.231.103.055) on June 13, 2018.
Copyright © 2018 American Physiological Society. All rights reserved.

Abstract

The ability of hands and feet to convey skin thermal sensations is an important contributor to our experience of the surrounding world. Surprisingly, the detailed topographical distribution of warm and cold thermosensitivity across hands and feet has not been mapped, although sensitivity maps exist for touch and pain. Using a recently developed quantitative sensory test, we mapped warm and cold thermosensitivity of 103 skin sites over glabrous and hairy skin of hands and feet in male (30.2±5.8y) and female (27.7±5.1y) adults matched for body-surface-area (M 1.77±0.2m^2; F 1.64±0.1m^2; p=0.155).

Findings indicated that warm and cold thermosensitivity varies by 5-fold across glabrous and hairy skin of hands and feet, and that hands (warm/cold sensitivity: 1.25/2.14 vote·°C^{-1}) are twice as sensitive as the feet (warm/cold sensitivity: 0.51/0.99 vote·°C^{-1}). Opposite to what known for touch and pain sensitivity, we observed a characteristic distal-to-proximal increase in thermosensitivity over both hairy and glabrous skin (i.e. from fingers/toes to body of hands and feet), and found that hairy skin is more sensitive than glabrous. Finally, we show that body-surface-area-matched males and females presented small differences in thermosensitivity, and that these differences are constrained to glabrous skin only.

Our high-density thermosensory micromapping provides the most detailed thermosensitivity maps of hands and feet in young adults available to date. These maps offer a window into peripheral and central mechanisms of thermosensory integration in humans, and will help guiding future developments in smart skin and sensory neuroprostheses, in wearable energy-efficient personal comfort systems, and in sport and protective clothing.

Downloaded from www.physiology.org/journal/jappl by ${individualUser.givenNames} ${individualUser.surname} (131.231.103.055) on June 13, 2018.
Copyright © 2018 American Physiological Society. All rights reserved.

New & Noteworthy

We provide the most detailed thermosensitivity maps across glabrous and hairy skin of hands and feet in males and females. Our maps show that: thermosensitivity varies by 5-fold across hands and feet; distal regions (e.g. fingers, toes) are less sensitive than proximal (e.g. palm, sole); hands are twice as sensitive as feet; males and females present small thermosensitivity differences. These findings will help guiding developments in sensory neuroprostheses, wearable comfort systems, and in sport/protective clothing.

Downloaded from www.physiology.org/journal/jappl by ${individualUser.givenNames} ${individualUser.surname} (131.231.103.055) on June 13, 2018.
Copyright © 2018 American Physiological Society. All rights reserved.

Introduction

Temperature sensing is a fundamental input in most animal species, including humans (20, 50). As homeothermic mammals, we rely on sensing the thermal state of our body and surroundings to regulate our body temperature (61). Yet temperature sensing in the form of skin thermal sensations is also a critical sensory attribute that enables our experience of the surrounding world (20). The warmth of a caress, or the coldness of dipping our toes in the sea, are common yet fundamental sensory experiences that accompany our life from its very first start, and that help shape our social and physical being (1, 11, 49). Such perceptual thermal experiences are often conveyed through humans' most important explorative and sensory structures, their hands and feet (52).

While there is vast knowledge about hands and feet as *thermoregulatory* structures for providing heat and cold defence responses (i.e. cutaneous vasodilation / vasoconstriction) (69), their function and characteristics as *thermosensory* structures have rarely been investigated (44). This is surprising, as detailed understanding of thermosensation in hands and feet has practical value in subjects such as helping restore naturalistic touch in amputees though sensory prosthesis and smart skin (9, 21, 41, 59, 63), and in designing effective personal comfort systems (73), thermal wearables (64), and sport and protective clothing (69).

In humans and primates, skin temperature sensing is mediated by free nerve endings of the Aδ- and C-type classes (i.e. thermoreceptors) (6, 7, 13, 42), selectively conveying warm and cold afferent inputs via the anterolateral spino-thalamic tract, to neural centres located in the insular and somatosensory cortices (12, 16, 60). Human temperature sensing is not homogenous across the body (55), but in fact it varies significantly depending on the skin region (e.g. face and trunk are generally more sensitive than the limbs) (23, 26, 57). While commonly observed in humans (18, 23, 27, 53, 66), this sensory feature has not been fully

Downloaded from www.physiology.org/journal/jappl by ${individualUser.givenNames} ${individualUser.surname} (131.231.103.055) on June 13, 2018.
Copyright © 2018 American Physiological Society. All rights reserved.

77 investigated in animal models of mammalian thermosensation (51, 71), leaving our
78 understating of its underlying neurobiology somewhat speculative.
79 The presence of regional differences in temperature sensing in humans is in line with what
80 has long been known about regional differences in touch sensitivity (2, 38), and more
81 recently, in pain acuity (46). Interestingly, large topographical differences in touch and pain
82 sensitivity are present across relatively small body areas, such as the palm of the hand. This
83 glabrous skin region exhibits a proximal-to-distal (i.e. palm to fingertips) increase in touch
84 sensitivity (37, 39), and in pain acuity (48).
85 Differences in touch and pain receptor densities across the hand (30, 38, 48), and in the size
86 of the receptive fields of cortical neurons (47), contribute to the heterogeneous touch and pain
87 sensitivity of our palms. This observation was first exemplified in the classic sensory
88 homunculus developed by Penfield (58). In contrast to the knowledge above, it has not been
89 fully elucidated yet whether thermosensitivity varies substantially across hands and feet, and
90 whether the variation has a similar topography as touch and pain.
91 To date, only Li et al. (44) has attempted to characterize the topography of warm and cold
92 sensitivity of the glabrous skin of the palm. By mapping thermosensitivity with threshold
93 detection methods across 23 locations of the palm in males and females, this study indicated
94 that warm and cold sensitivity varies largely across this relatively small area, with proximal
95 sites (e.g. base of the palm) showing higher sensitivity than the distal sites (e.g. fingers) (44).
96 It was also found that females are on average more thermosensitive than males (44), although
97 differences in body surface area between sexes could have contributed to this observation
98 (i.e. the smaller females might have shown higher sensitivity due to the relatively larger
99 proportion of their skin being stimulated).
100 While Li et al.' study (44) has provided initial evidence for the fact that the human palm
101 could present a heterogeneous distribution of thermosensitivity, the study did not evaluate the

Downloaded from www.physiology.org/journal/jappl by ${individualUser.givenNames} ${individualUser.surname} (131.231.103.055) on June 13, 2018.
Copyright © 2018 American Physiological Society. All rights reserved.

entire hand (i.e. no assessment of the hairy skin of the dorsum), nor the foot. It also used a methodology (i.e. threshold detection, where the smallest perceivable temperature change is identified) that is unlikely to be representative of a real-life, supra-threshold thermal stimulus (e.g. when dipping a finger in the bath to check its temperature). Finally, it assessed sexes differences without matching groups for body size, which might create a potential bias in the context of thermal spatial summation (17). As a result, our knowledge on the thermosensitivity of hands and feet in humans, and of its topographical distribution across the hairy (i.e. dorsum) and glabrous portions (i.e. palm and sole) of these sensory structures, remains limited.

To fill this gap, we mapped topographical differences in warm and cold thermosensitivity across 103 locations of both hairy and glabrous skin of the hand and foot in young males and females, using a magnitude estimation paradigm. We assessed sex differences by matching males and females for body surface area, in order to isolate the independent effect of sex on local thermosensitivity. We hypothesized that, in line what known for touch sensitivity and pain acuity, the distribution of skin thermosensitivity would vary across the hand and foot with a proximal-to-distal pattern (i.e. higher sensitivity from the body of hands and feet to fingertips and toes). Furthermore, we hypothesized that sex differences in thermosensitivity would be minimal between body surface area-matched male and female individuals.

Methods

Participants

Sixteen age-matched healthy adults, eight females and eight males, volunteered to participate in the present study. All participants were college students and junior researchers without any

Downloaded from www.physiology.org/journal/jappl by ${individualUser.givenNames} ${individualUser.surname} (131.231.103.055) on June 13, 2018.
Copyright © 2018 American Physiological Society. All rights reserved.

neural or perceptual contraindications, non-smokers, moderately active (performing at least 5h of exercise a week) and had lived in the Berkeley area (California, USA) for at least 3 months prior to the test. Participants' characteristics are presented in Table 1.

The male and female groups comprised an almost identical proportion of Caucasian (4F/3M) and Asian ethnicities (4F/5M). Female participants were well spread across a typical 28-day menstrual cycle (mean day= 15.4; SD= 8.9), with 4 of them taking oral contraceptives.

In addition to being age-matched, male and female participants were purposely matched for body surface area (see Tab. 1). Spatial summation is a well-known phenomenon in thermal sensitivity (68), where given the same thermal stimulus, increasing the area of skin being thermally stimulated increases the magnitude of the resulting thermal sensation (14). Accordingly, matching males and females for body surface area ensured that a similar proportion of their body would be stimulated with our fixed-area thermal stimulus (i.e. a 1.32cm^2 thermal probe; see Table 1 column *"proportion of BSA stimulated"*), and that any confounding effect driven by sex differences in body size would be limited (17). Body surface area correlates well with hand and foot surface areas, with the latter generally corresponding to ~1% of total body surface area (3, 56, 65)

The project conformed to the Helsinki Declaration and was approved by the Institutional Committee for the Protection of Human Subjects of the University of California at Berkeley. Participants were naïve as to the purpose of the experiments and they each gave written informed consent. All testing occurred during the months of March and April.

Experimental design

All participants took part in one experimental session, during which they underwent a standardized quantitative thermosensory test (duration ~1h) in a climatic chamber under thermo-neutral environmental conditions (air temperature= 23°C; relative humidity= 50%).

Downloaded from www.physiology.org/journal/jappl by ${individualUser.givenNames} ${individualUser.surname} (131.231.103.055) on June 13, 2018.
Copyright © 2018 American Physiological Society. All rights reserved.

This quantitative test was adapted from the one we recently developed and tested in both healthy individuals (23, 24) and in neurological patients undergoing thermal stress (22). The thermosensory test was designed to quantify local thermosensitivity of 103 skin sites across the hairy and glabrous skin of hands and feet in response to locally applied skin warming and cooling stimuli (i.e. ±5°C from a baseline temperature of 31°C; duration of stimulation: 5s), whose temperature is within the range for maximal activation of both cutaneous cold (i.e. 27 – 22°C) and warm (i.e. 36 – 42°C) thermoreceptors (19). A schematic representation of the experimental design is presented in Fig. 1.

Figure 2 presents the topographical distribution of the 103 skin sites mapped. We assessed both hairy and glabrous skin as there is evidence that thermosensitivity varies across these types of skin (67), owing to both physiological (e.g. density of sensory innervation; (55)) and biophysical factors (e.g. differences in thickness of the epidermal layer and related thermal conductance; (34). Participants were trained to report on a 11-point Numerical Rating Scale (Fig. 1D) the magnitude of local thermal sensations elicited by the skin warming and cooling stimuli (Fig. 1C), which were delivered with a hand-held 1.32cm^2 thermal probe (Fig. 1A; NTE-2A, Physitemp Instruments Inc., USA; probe response rate: 2.43^{o}C/s) to each skin site (Fig. 1B) in a randomised order.

The density and anatomical location of the 103 skin sites tested (Fig. 2) were chosen in order to map as much skin area as possible across hairy and glabrous skin of hands and feet, in relation to the size of the thermal probe. All tested skin sites were on the left side of the body, assuming bi-lateral symmetry (10).

Local skin temperature (T_{sk}) variations at the contact site between the skin and thermal probe were monitored and recorded before, during, and after the application of each stimulus, using a fast-response thermocouple microsensor (Fig. 1A; time constant: 0.005s; tip diameter: 0.3mm; IT-1E, Physitemp Instruments Inc., USA), located on the probe's surface, and

Downloaded from www.physiology.org/journal/jappl by ${individualUser.givenNames} ${individualUser.surname} (131.231.103.055) on June 13, 2018.
Copyright © 2018 American Physiological Society. All rights reserved.

interfaced with a Microprobe Thermometer (accuracy: ±0.1°C between 0-50°C; BAT-12, Physitemp Instruments Inc., USA). A single-blind psychophysical design was used for the present study, with the same investigator performing all testing.

Experimental protocol

Participants arrived to the laboratory on testing days, after having refrained from caffeine and alcohol in the 12h preceding the experiment. They changed into shorts and t-shirt (no shoes were worn), and moved into the climatic chamber.

Five wireless temperature sensors (iButtons, Maxim, USA) were taped to five skin sites on the right side of the body (i.e. cheek, bicep, abdomen, lateral lower back and back lower thigh) with medical tape (3M, USA) in order to record local T_{sk} (10-s intervals), to be used for the estimation of mean T_{sk} for the entire body according to the equation of Houdas and Ring (1982):

$$\text{Whole body mean } T_{sk} = (CheekT_{sk} \times 0.07) + (BicepT_{sk} \times 0.19) + (AbdomenT_{sk} \times 0.175) + (LateralLowerBackT_{sk} \times 0.175) + (ThighT_{sk} \times 0.39)$$

Five-minute averages were determined for mean T_{sk} data.

Once instrumented, participants sat on a stool where they rested for the entire test. Thirty minutes were allowed for adaptation to the environmental conditions, and for baseline recordings. During this time, participants were familiarized with the quantitative thermosensory test. The detailed procedures for familiarization and execution of the quantitative thermosensory test are presented below, along with the methods for quantifying and mapping local thermosensitivity.

Quantitative thermosensory test: familiarization and calibration

Downloaded from www.physiology.org/journal/jappl by ${individualUser.givenNames} ${individualUser.surname} (131.231.103.055) on June 13, 2018.
Copyright © 2018 American Physiological Society. All rights reserved.

During the 30-min adaptation, participants were briefed about the general producers underlying the quantitative thermosensory test. They were informed that non-painful warming and cooling stimuli would be delivered separately to each of 103 different sites across their hands and feet using a thermal probe. To avoid any expectation bias, no information was given about the temperature of the stimuli, or whether the same stimuli would be applied to different skin areas.

The 103 skin sites targeted for stimulation were marked with a washable marker to assure consistency in the location of stimulation. Participants were then instructed that, when requested by the investigator, they would be expected to report the magnitude of the very first local thermal sensation resulting from each stimulus application. They would use a 0-10 numerical rating scale whose anchor points 0 and 10 were respectively labelled as "Not hot/Not cold at all" and "Very Hot/Very Cold". This scale is similar to the one used by Gerrett et al., (2014) and Ouzzahra et al. (2012) in similar studies, and its choice was based on extensive evidence supporting the applicability and reliability of numerical rating scales for somatic sensations in humans (19, 32).

To ensure consistency in the use of the scale, participants were calibrated to its anchor points. This was achieved by delivering 3 separate stimuli with the thermal probe to a representative skin site, and by asking participants to associate the resulting thermal sensations to the specific anchor point. The first stimulus corresponded to a temperature of 31°C, which was similar to that of the skin, and which induced neither a warm nor a cold thermal sensation. After confirming the absence of any thermal sensation, participant were informed that they should associate the anchor point 0 "Not hot/Not cold at all", to this absence of thermal sensation. The second and third stimuli corresponded to ±10°C from a baseline temperature of 31°C. These cold and warm stimuli were twice as large as the warming and cooling stimuli that would be used for the quantitative thermosensory mapping (i.e. ±5°C from a baseline

Downloaded from www.physiology.org/journal/jappl by ${individualUser.givenNames} ${individualUser.surname} (131.231.103.055) on June 13, 2018.
Copyright © 2018 American Physiological Society. All rights reserved.

224 temperature of 31°C), and were delivered to induce thermal sensations that participants were
225 instructed to associate to the "Very Hot/Very Cold" anchor points of the scale.
226 Once the calibration was completed, participants underwent some practice trials where they
227 were allowed to experience the actual testing stimuli (i.e. ±5°C from a baseline temperature
228 of 31°C) on a variety of skin sites, and were informed that these stimuli would be similar to
229 the ones to be used during the thermosensory mapping. Participants were also encouraged to
230 practice the use of the rating scale during these practice trials, and were informed that local
231 sensations would have to correspond to their first sensation upon stimulation, and that this
232 would be reported at the request of the investigator, within 5s of delivering the stimulus.
233 Pilot studies indicated 5s as a sufficient time for the set stimuli to reach their target absolute
234 temperatures (i.e. 26 and 36°C).
235 The above described familiarization protocol ensured that all participants were calibrated to
236 the scale and fully familiar with the testing procedures upon commencing the actual
237 experiment.
238
239 *Quantitative thermosensory test: execution*
240 Upon termination of the familiarization, the quantitative thermosensory test initiated.
241 Participants rested on a stool, facing away from the skin area stimulated. They were
242 instructed to only focus on the numerical rating scale positioned in front of them, and to
243 report their local sensation upon request. The hand or foot were then selected as the first
244 extremity to be tested, according to a between-participants counterbalanced order.
245 Testing for both the hand and the foot was split between the hairy (i.e. dorsum of hands and
246 foot) and glabrous parts (i.e. palm of the hand and foot sole), and mapping of all skin sites on
247 one part (e.g. palm of the hand) was completed, before moving to the next part (e.g. dorsum
248 of the hand). A 5-min break was allowed in between testing of hands and feet.

Downloaded from www.physiology.org/journal/jappl by ${individualUser.givenNames} ${individualUser.surname} (131.231.103.055) on June 13, 2018.
Copyright © 2018 American Physiological Society. All rights reserved.

Whenever the hand was tested, participants placed it on a fabric cushion on a table, with the palm resting in a comfortable position, facing either upwards or downwards. Whenever the foot was tested, participants placed their lower leg on a fabric cushion on a lowered stool, with the foot freely suspended beyond the stool.

Once a comfortable position was achieved, the investigator began testing of the first skin site. First, the investigator set the thermal probe at 31°C (i.e. neutral temperature) and placed this gently on the skin site to be tested, with a pressure sufficient to ensure full contact with the skin. Five seconds were allowed for the local T_{sk} to stabilize. This was monitored via the surface thermocouple, and was recorded before delivery of the first stimulus. Following on to the initial stabilization, the +5°C skin warming or the -5°C cooling stimulus was delivered, and after 5s from delivery, the participant was requested to report their local thermal sensation (Fig. 1C). Along with the local sensation, the local T_{sk} at the 5-s stimulation was also recorded, to determine the ΔT_{sk} change from pre-stimulation. At this point, the probe was re-set to 31°C, and after a 5-s break, the second stimulus (i.e. a warming stimulus in case of a previous cooling one and vice versa) was delivered (Fig. 1C). Pilot studies indicated 5-s as a sufficient time to ensure that baseline T_{sk} and neutral sensations would be re-established. The order of delivery of warming and cooling stimuli was balanced within-participants.

Once both warm and cold sensitivity was assessed on a skin site, the investigator moved the probe on the next skin site, and the same procedure as above, was performed until all skin sites were tested.

Quantifying local thermosensitivity

We collected data on local changes in T_{sk}, and local thermal sensations, for each of the 103 skin site tested, as a result of both the skin warming and cooling stimuli.

Downloaded from www.physiology.org/journal/jappl by ${individualUser.givenNames} ${individualUser.surname} (131.231.103.055) on June 13, 2018.
Copyright © 2018 American Physiological Society. All rights reserved.

273 T_{sk} and local thermal sensations data were combined to calculate an index of local
274 thermosensitivity as follow:

$$Thermosensitivity\ (\frac{vote}{°C}) = \frac{thermal\ sensation\ (vote)}{\Delta\ local\ T_{sk}\ (°C)}$$

275 This thermosensitivity index provided, for each skin site, a normalised indication of the
276 sensation resulting from a unit change in local T_{sk}.
277
278 *Thermosensitivity maps*
279 To aid with visualization of regional thermosensory patterns, the data collected were used to
280 generate high-density thermosensitivity maps. Maps were created separately for males and
281 females, for hairy and glabrous skin, and for warming and cooling.
282 High-density thermosensory maps were generated using a custom written MatLab script (The
283 MathWorks, Inc., USA). Average data per group (n=8) were entered into a matrix composed
284 of the coordinates (X;Y) of the skin site of interest (which were based on representative
285 images of the palm/dorsum of the hands and sole/dorsum of the foot, see Fig.2), and the
286 associated thermosensitivity value (Z). MatLab interpolation and extrapolation functions
287 were used to create HeatMap objects, which were then superimposed over images of the
288 extremity of interest, and morphed accordingly with an imaging software (Photoshop; Adobe,
289 USA).
290
291 *Statistical analysis*
292 In order to evaluate changes in whole-body thermal state during the test in male and females,
293 mean T_{sk} data were analysed by means of a two-way mixed-model ANOVA, with sex as
294 independent factor, and time as repeated factor.
295 In order to determine whether sensitivity to skin warming and cooling varied across skin sites
296 and between male and females, thermosensitivity data were analysed separately for warming

Downloaded from www.physiology.org/journal/jappl by ${individualUser.givenNames} ${individualUser.surname} (131.231.103.055) on June 13, 2018.
Copyright © 2018 American Physiological Society. All rights reserved.

297 and cooling stimuli, and for hairy and glabrous parts of hands and feet, by means of a two-
298 way mixed-model ANOVA, with sex as independent factor and skin site as repeated factor.
299 In the event of statistically significant main effects or interactions, post-hoc analyses were
300 conducted with Fisher's LSD tests.
301 Analysis for the glabrous part of the hand included data for skin sites 1 to 23. Analysis for the
302 hairy part of the hand included data for skin sites 24 to 49. Analysis for the glabrous part of
303 the foot included data for skin sites 23 to 43. Analysis for the hairy part of the foot included
304 data for skin sites 1 to 22 and 44 to 54.
305 In order to explore inter-individual variability in local thermosensitivity, coefficient of
306 variations [i.e. (SD/mean)*100)] were calculated for each skin site tested for both warming
307 and cooling stimuli, in both males and females. Mean differences in inter-individual
308 variability between sexes were assessed by means of unpaired t-tests. Data were then
309 summarised into heat maps to display skin sites of high and low inter-individual variability in
310 local thermosensitivity.
311 In order to determine overall thermosensitivity differences between the hand and the foot,
312 thermosensitivity data from hairy and glabrous skin sites were grouped for warm and cold
313 sensitivity and for males and females, and compared between hands and feet by means of
314 paired t-tests. Similarly, to determine overall thermosensitivity differences between glabrous
315 (palms and soles) versus hairy skin (back of hands and feet), data from hands and feet were
316 grouped for warm and cold sensitivity and for males and females, and compared between
317 hairy and glabrous skin by means of paired t-tests.
318 Finally, correlation analyses between warm and cold thermosensitivity across all skin site
319 tested were performed separately for males and females.

Downloaded from www.physiology.org/journal/jappl by ${individualUser.givenNames} ${individualUser.surname} (131.231.103.055) on June 13, 2018.
Copyright © 2018 American Physiological Society. All rights reserved.

Data are reported as means, SD, and 95% Confidence Intervals. Observed power was computed using $\alpha = 0.05$. Statistical analysis was performed using GraphPad Prism (version 6.0; GraphPad Software, La Jolla, CA, USA).

Results

Whole body mean T_{sk}

Average mean T_{sk} did not change over the course of the experiment ($F_{(10, 40)} = 0.6063$; $p=0.799$) and was maintained within a neutral range (i.e. 31-34°C) (25), with no differences ($F_{(1, 4)} = 0.2124$; $p=0.668$) between males (mean T_{sk}=32.14°C; SD 0.08) and females (mean T_{sk}=31.64°C; SD 0.18).

Hand: glabrous skin warm thermosensitivity

In the male group, mean warm thermosensitivity across glabrous skin (i.e. sites 1 to 23) was 0.89 vote/°C [95%CI= 0.80, 0.98], and varied between a minimum of 0.55 to a maximum of 1.22 vote/°C (Fig. 3). In the female group, mean warm thermosensitivity across the same skin sites was 1.23 vote/°C [95%CI= 1.09, 1.38], and varied between a minimum of 0.57 to a maximum of 1.68 vote/°C (Fig. 3). Differences in warm thermosensitivity between males and females were not statistically significant ($F_{(1, 14)} = 1.97$; $p=0.181$).

While no clear sex differences were observed, warm thermosensitivity varied significantly across the palm of the hand ($F_{(22, 308)} = 1.94$; $p=0.007$), with regional patterns that were similar between male and females ($F_{(22, 308)} = 0.878$; $p=0.624$).

The centre of the palm (skin site 17), along with the area at the base of the thumb (skin site 19), presented some of the highest warm sensitivity in both males (site 17= 1.22 vote/°C; site

Downloaded from www.physiology.org/journal/jappl by ${individualUser.givenNames} ${individualUser.surname} (131.231.103.055) on June 13, 2018.
Copyright © 2018 American Physiological Society. All rights reserved.

19= 1.16 vote/°C) and females (site 17= 1.54 vote/°C; site 19= 1.68 vote/°C). On the contrary, the thumb (skin site 22) and the intermediate portion of the fifth digit (skin site 11), presented some of the lowest warm sensitivity in both males (site 22= 0.55 vote/°C; site 11= 0.92 vote/°C) and females (site 22= 0.87 vote/°C; site 11= 0.57vote/°C).

Statistical significance values for multiple sites comparison are listed in *Supplementary Material 1*.

Hand: glabrous skin cold thermosensitivity

In the male group, mean cold thermosensitivity across glabrous skin (i.e. sites 1 to 23) was 1.49 vote/°C [95%CI= 1.40, 1.59], and varied between a minimum of 0.83 to a maximum of 1.81 vote/°C (Fig.). In the female group, mean cold thermosensitivity across the same skin sites was 1.99 vote/°C [95%CI= 1.86, 2.12], and varied between a minimum of 1.17 to a maximum of 2.56 vote/°C (Fig. 3).

Cold thermosensitivity varied largely across the palm of the hand in both males and females ($F_{(22, 308)}$= 1.93; p=0.008). However, and contrary to what observed for warm thermosensitivity, we observed a tendency for the female group to present an overall higher cold thermosensitivity than their male counterparts ($F_{(1, 14)}$= 3.29; p=0.090).

Similar regional patterns of cold sensitivity were observed across the palm in both groups ($F_{(22, 308)}$= 1.00; p=0.459), with the base of the palm (skin site 20) presenting high sensitivity in both males (site 20= 1.82 vote/°C) and females (site 20= 2.39 vote/°C).

In addition, females presented significantly higher cold sensitivity than males on specific skin sites, such as the intermediate portion of the second digit (skin site 2; mean difference=+ 0.95 vote/°C, [95%CI= 0.14, 1.75]), the distal portion of the fifth digit (skin site 10; mean difference=+ 0.90 vote/°C, [95%CI= 0.09, 1.70]), the middle part of the top of the palm (skin

Downloaded from www.physiology.org/journal/jappl by ${individualUser.givenNames} ${individualUser.surname} (131.231.103.055) on June 13, 2018.
Copyright © 2018 American Physiological Society. All rights reserved.

site 14; mean difference 0.86 vote/°C, [95%CI= 0.05, 1.67]), and the medial area at the base of the palm (skin site 21; mean difference 0.81 vote/°C, [95%CI= 0.01, 1.61]).

Statistical significance values for multiple sites comparison are listed in *Supplementary Material 1*.

Hand: hairy skin warm thermosensitivity

In the male group, mean warm thermosensitivity across hairy skin (i.e. sites 24 to 49) was 1.27 vote/°C [95%CI= 1.12, 1.42], and varied between a minimum of 0.28 to a maximum of 1.79 vote/°C (Fig. 3). In the female group, mean warm thermosensitivity across the same skin sites was 1.42 vote/°C [95%CI= 1.27, 1.58], and varied between a minimum of 0.78 to a maximum of 2.12 vote/°C (Fig. 3). Differences in warm thermosensitivity between males and females were not statistically significant ($F_{(1, 14)}$= 0.3409; p=0.568).

While no clear sex differences were observed, warm thermosensitivity varied largely across the dorsum of the hand ($F_{(25, 350)}$= 2.72; p<0.0001), with regional patterns that were similar between male and females ($F_{(25, 350)}$= 1.153; p=0.280).

The proximal portion of the fourth digit (skin site 30), along with the area in between the metacarpophalangeal joint of the second digit and the base of the thumb (skin site 36), presented some of the highest warm sensitivity in both males (site 30= 1.74 vote/°C; site 36= 1.79 vote/°C) and females (site 30= 1.97 vote/°C; site 36= 1.76 vote/°C). On the contrary, the area over the metacarpophalangeal joint of the second digit (skin site 33) and the middle area at the base of the hand (skin site 40), presented some of the lowest warm sensitivity in both males (site 33= 0.59 vote/°C; site 40= 0.99 vote/°C) and females (site 33= 1.12 vote/°C; site 40= 0.79 vote/°C).

Statistical significance values for multiple sites comparison are listed in *Supplementary Material 1*.

Downloaded from www.physiology.org/journal/jappl by ${individualUser.givenNames} ${individualUser.surname} (131.231.103.055) on June 13, 2018.
Copyright © 2018 American Physiological Society. All rights reserved.

394

395 *Hand: hairy skin cold thermosensitivity*

396 In the male group, mean cold thermosensitivity across hairy skin (i.e. sites 24 to 49) was 2.19
397 vote/°C [95%CI= 2.06, 2.32], and varied between a minimum of 1.63 to a maximum of 2.70
398 vote/°C (Fig.). In the female group, mean cold thermosensitivity across the same skin sites
399 was 2.52 vote/°C [95%CI= 2.41, 2.63], and varied between a minimum of 1.82 to a
400 maximum of 3.04 vote/°C (Fig. 3).
401 While no sex differences were observed, ($F_{(1, 14)}$= 1.566; p=0.231), cold thermosensitivity
402 varied significantly across the dorsum of the hand ($F_{(25, 350)}$= 1.98; p=0.003), with regional
403 patterns that were similar between male and females ($F_{(25, 350)}$= 1.38; p=0.103)
404 The area across the centre of the dorsum (skin sites 36 and 37) and the base of the thumb
405 (skin site 39) presented some of the highest warm sensitivity in both males (site 36= 2.32
406 vote/°C; site 37= 2.63 vote/°C; site 39= 2.71 vote/°C) and females (site 36= 2.82 vote/°C; site
407 37= 2.46 vote/°C; site 39= 3.04 vote/°C). On the contrary, the area over the
408 metacarpophalangeal joints of the second and fifth digits (skin sites 33 and 35), presented
409 some of the lowest cold sensitivity in both males (site 33= 1.76 vote/°C; site 35= 1.66
410 vote/°C) and females (site 33= 2.36 vote/°C; site 35= 1.82 vote/°C).
411 Statistical significance values for multiple sites comparison are listed in *Supplementary*
412 *Material 1*.
413

414 *Hand: inter-individual variability in thermosensitivity*

415 Inter-individual variability in warm thermosensitivity was greater in males than in females
416 (mean difference= +10.5% [95% CI= 0.6, 20.4]; p=0.038), and ranged largely across the skin
417 site tested, from a minimum of 39.2% (skin site 48) to a maximum of 186% (skin site 11) in

Downloaded from www.physiology.org/journal/jappl by ${individualUser.givenNames} ${individualUser.surname} (131.231.103.055) on June 13, 2018.
Copyright © 2018 American Physiological Society. All rights reserved.

418 males (mean= 79.1%), and from a minimum of 34.4% (skin site 32) to a maximum of
419 117.6% (skin site 42) in females (mean= 68.6%) (Fig. 5).
420 Inter-individual variability in cold thermosensitivity was greater in males than in females
421 (mean difference= +6.3% [95% CI= 1.2, 11.4]; p=0.016), and ranged largely across the skin
422 site tested, from a minimum of 16.5% (skin site 26) to a maximum of 72.1% (skin site 11) in
423 males (mean= 43.7%), and from a minimum of 31.1% (skin site 3) to a maximum of 81.1%
424 (skin site 12) in females (mean= 37.37%) (Fig. 5).
425 All in all, it appeared that inter-individual variability in thermosensitivity was: 1) more
426 pronounced in males than in females for both warm and cold; 2) greater in some specific skin
427 sites across the glabrous and hairy skin of the hand; and 3) greater overall for warm than cold
428 sensitivity.
429
430 *Foot: glabrous skin warm thermosensitivity*
431 In the male group, mean warm thermosensitivity across glabrous skin (i.e. sites 23 to 43) was
432 0.25 vote/°C [95%CI= 0.19, 0.31], and varied between a minimum of 0 to a maximum of
433 1.53 vote/°C (Fig. 4). In the female group, mean warm thermosensitivity across the same skin
434 sites was 0.46 vote/°C [95%CI= 0.37, 0.55], and varied between a minimum of 0.21 to a
435 maximum of 0.79 vote/°C (Fig. 4).
436 Warm thermosensitivity varied largely across the sole of the foot in both males and females
437 ($F_{(20, 260)}$= 2.17; p=0.003).
438 The centre portion of the sole (skin sites 35 and 38) presented some of the highest warm
439 sensitivity in both males (site 35= 0.53 vote/°C; site 38= 0.38 vote/°C) and females (site 35=
440 0.75 vote/°C; site 38= 0.79 vote/°C), while the distal part of the hallux (skin site 23) and the
441 centre of the heel (skin site 43) presented some of the lowest warm sensitivity in males (site

Downloaded from www.physiology.org/journal/jappl by ${individualUser.givenNames} ${individualUser.surname} (131.231.103.055) on June 13, 2018.
Copyright © 2018 American Physiological Society. All rights reserved.

23= 0.13 vote/°C; site 43= 0.08 vote/°C) and females (site 23= 0.26 vote/°C; site 43= 0.23 vote/°C).

Despite neither sex presenting an overall higher sensitivity *per se* ($F_{(1, 13)}$= 3.03; p=0.105), there was a tendency for some specific skin sites to be more sensitive in females than in males ($F_{(20, 260)}$= 1.569; p=0.060).

Specifically, females presented significantly higher warm sensitivity than males on the superior portion of the arch (skin site 34; mean difference=+ 0.55 vote/°C, [95%CI= 0.14, 0.96]), the centre (skin site 38; mean difference=+ 0.41 vote/°C, [95%CI= 0.01, 0.82]), and the lateral portion of the sole (skin site 39; mean difference +0.58 vote/°C, [95%CI= 0.17, 0.99]).

Statistical significance values for multiple sites comparison are listed in *Supplementary Material 1*.

Foot: glabrous skin cold thermosensitivity

In the male group, mean cold thermosensitivity across glabrous skin (i.e. sites 23 to 43) was 0.75 vote/°C [95%CI= 0.55, 0.94], and varied between a minimum of 0.04 to a maximum of 1.78 vote/°C (Fig. 4). In the female group, mean cold thermosensitivity across the same skin sites was 0.55 vote/°C [95%CI= 0.34, 0.75], and varied between a minimum of 0.04 to a maximum of 1.65 vote/°C (Fig. 4).

Cold thermosensitivity varied largely across the sole of the foot in both males and females ($F_{(20, 260)}$= 8.48; p<0.0001).

The area over the arch (skin sites 34 and 37) presented some of the highest cold sensitivity in both males (site 34= 1.45 vote/°C; site 37= 1.78 vote/°C) and females (site 35= 1.35 vote/°C; site 38= 1.09 vote/°C), while the distal part of the hallux (skin site 23) and the centre of the

Downloaded from www.physiology.org/journal/jappl by ${individualUser.givenNames} ${individualUser.surname} (131.231.103.055) on June 13, 2018.
Copyright © 2018 American Physiological Society. All rights reserved.

heel (skin site 43) presented some of the lowest cold sensitivity in males (site 23= 0.47 vote/°C; site 43= 0.04 vote/°C) and females (site 23= 0.29 vote/°C; site 43= 0.25 vote/°C). Despite neither sex presenting an overall higher sensitivity *per se* ($F_{(1, 13)}$= 0.73; p=0.408), there was a clear trend for some specific skin sites to be more sensitive in males than in females ($F_{(20, 260)}$= 2.04; p=0.006).

Specifically, males presented significantly higher cold sensitivity than females on the proximal part of the second toe (skin site 26; mean difference=+ 0.74 vote/°C, [95%CI= 0.05, 1.43]), the distal part of the fourth toe (skin site 29; mean difference=+ 0.72 vote/°C, [95%CI= 0.03, 1.41]), and the centre portion of the arch (skin site 37; mean difference +0.69 vote/°C, [95%CI= 0.01, 1.38]).

Statistical significance values for multiple sites comparison are listed in *Supplementary Material 1*.

Foot: hairy skin warm thermosensitivity

In the male group, mean warm thermosensitivity across hairy skin (i.e. sites 1 to 22 and 44 to 55) was 0.52 vote/°C [95%CI= 0.45, 0.60], and varied between a minimum of 0.16 to a maximum of 0.89 vote/°C (Fig.). In the female group, mean warm thermosensitivity across the same skin sites was 0.65 vote/°C [95%CI= 0.55, 0.75], and varied between a minimum of 0.16 to a maximum of 1.24 vote/°C (Fig. 4).

No sex differences in thermosensitivity were observed ($F_{(1, 13)}$= 1; p=0.335), and warm thermosensitivity varied largely across the dorsum of the foot ($F_{(33, 429)}$= 2.117; p<0.001), with regional patterns that were similar between male and females ($F_{(33, 429)}$= 0.93; p=0.574). The central portion of the dorsum of the foot (skin sites 15, 16, 17), presented some of the highest warm sensitivity in both males (site 15= 0.89 vote/°C site; 16= 0.73 vote/°C; site 17= 0.77 vote/°C) and females (site 15= 0.83 vote/°C site; 16= 0.78 vote/°C; site 17= 1.24

Downloaded from www.physiology.org/journal/jappl by ${individualUser.givenNames} ${individualUser.surname} (131.231.103.055) on June 13, 2018.
Copyright © 2018 American Physiological Society. All rights reserved.

vote/°C). In contrast, the proximal portion of the hallux (skin site 1) and the distal portion of the fifth toe (skin site 8), presented some of the lowest warm sensitivity in both males (site 1= 0.19 vote/°C; site 8= 0.45 vote/°C) and females (site 1= 0.32 vote/°C; site 8= 0.17 vote/°C). Statistical significance values for multiple sites comparison are listed in *Supplementary Material 1*.

Foot: hairy skin cold thermosensitivity

In the male group, mean cold thermosensitivity across hairy skin (i.e. sites 1 to 22 and 44 to 55) was 1.23 vote/°C [95%CI= 1.09, 1.36], and varied between a minimum of 0.18 to a maximum of 2.01 vote/°C (Fig. 4). In the female group, mean cold thermosensitivity across the same skin sites was 1.18 vote/°C [95%CI= 1.07, 1.30], and varied between a minimum of 0.48 to a maximum of 1.87 vote/°C (Fig. 4).

No sex differences in thermosensitivity were observed ($F_{(1, 13)}$= 0.02; p=0.893). Cold thermosensitivity varied largely across the dorsum of the foot ($F_{(33, 429)}$= 2.99; p<0.0001) with regional patterns that were similar for males and females ($F_{(33, 429)}$= 1.19; p=0.213).

The central portion of the dorsum of the foot (skin sites 15), exhibited some of the highest cold sensitivity in both males (site 15= 1.62 vote/°C site) and females (site 15= 1.88 vote/°C site).

In contrast, the proximal portion of the hallux (skin site 1) and the distal portion of the fourth toe (skin site 6), exhibited some of the lowest cold sensitivity in both males (site 1= 1.17 vote/°C; site 6= 1.27 vote/°C) and females (site 1= 0.83 vote/°C; site 8= 0.67 vote/°C). Statistical significance values for multiple sites comparison are listed in *Supplementary Material 1*.

Foot: inter-individual variability in thermosensitivity

Downloaded from www.physiology.org/journal/jappl by ${individualUser.givenNames} ${individualUser.surname} (131.231.103.055) on June 13, 2018.
Copyright © 2018 American Physiological Society. All rights reserved.

Inter-individual variability in warm thermosensitivity was greater in males than in females (mean difference= +23.2% [95% CI= 7.4, 39.0]; p=0.004), and ranged largely across the skin site tested, from a minimum of 51.1% (skin site 7) to a maximum of 264.6% (skin site 43) in males (mean= 123.3%), and from a minimum of 44.7% (skin site 15) to a maximum of 213.3% (skin site 1) in females (mean= 100.1%) (Fig. 5).

Inter-individual variability in cold thermosensitivity was similar between males and females (mean difference= +0.85% [95% CI= -16, 17.7]; p=0.920), yet ranged largely across the skin site tested, from a minimum of 37.8% (skin site 13) to a maximum of 264.6% (skin sites 42 and 43) in males (mean= 94.9%), and from a minimum of 35.6% (skin site 18) to a maximum of 282.8% (skin site 30) in females (mean= 94%) (Fig. 5).

In sum, it appeared that inter-individual variability in thermosensitivity: 1) was more pronounced in males than in females with regards to warm sensitivity only; 2) was greater in some specific skin sites across the glabrous and hairy skin of the foot; 3) was overall greater for warm than cold sensitivity.

Hand vs. Foot overall thermosensitivity

Comparison between overall thermosensitivity of the hand versus the foot indicated that, for both males and females, the hand to be twice as warm sensitive (male hand vs. foot mean difference= 0.75 vote/°C [95%CI=0.46, 1.04], p=0.001; female hand vs. foot mean difference= 0.75 vote/°C [95%CI=0.45, 1.05], p=0.001), and twice as cold sensitive as the foot (male hand vs. foot mean difference= 0.93 vote/°C [95%CI=0.38, 1.47], p=0.006; female hand vs. foot mean difference= 1.32 vote/°C [95%CI=0.90, 1.75], p<0.001), (Fig. 6).

Hairy vs Glabrous. skin overall thermosensitivity

Downloaded from www.physiology.org/journal/jappl by ${individualUser.givenNames} ${individualUser.surname} (131.231.103.055) on June 13, 2018.
Copyright © 2018 American Physiological Society. All rights reserved.

Comparison between overall thermosensitivity of hairy skin (back of hands and feet) versus glabrous (palms and soles) indicated the hairy skin to be more warm sensitive (male hairy vs. glabrous mean difference= 0.34 vote/°C [95%CI=0.20, 0.45], $p<0.001$; female hairy vs. glabrous mean difference= 0.19 vote/°C [95%CI=0.02, 0.36], $p=0.029$), and more cold sensitive (male hairy vs. glabrous mean difference= 0.59 vote/°C [95%CI=0.41, 0.77], $p<0.001$; female hairy vs. glabrous mean difference= 0.58 vote/°C [95%CI=0.31, 0.85], $p<0.001$) than glabrous skin, in both males and females (Fig. 7).

Association between overall warm and cold thermosensitivity

Correlation analyses performed on data from all skin sites tested across hand and feet showed a significant association between warm and cold sensitivity in both males (Pearson r= 0.80 [95%CI= 0.71, 0.86]; $R^2= 0.64$; $p<0.0001$) and females (Pearson r= 0.83 [95%CI= 0.76, 0.88]; $R^2= 0.69$; $p<0.0001$) (Fig. 8), with a tendency for cold to be greater than warm sensitivity. The significant association between warm and cold sensitivity indicated that hands and feet contained areas that were highly sensitive to temperature changes *per se*, irrespective of their direction (i.e. warming or cooling).

Discussion

Our high-density thermosensory micromapping resulted in the development of the most detailed thermosensitivity maps of hands and feet in healthy young adults available to date. Overall, our findings indicate that:

1. Thermosensitivity to warm and cold varies largely by up to 5-fold across the glabrous and hairy portions of both hands and feet (Fig. 3, 4), with a distal-to-proximal organisation, and with hairy skin being more thermosensitive than glabrous (Fig. 7);
2. The hand is twice as thermosensitive as the foot (compare Fig. 3 and 4; see Fig. 6);

Downloaded from www.physiology.org/journal/jappl by ${individualUser.givenNames} ${individualUser.surname} (131.231.103.055) on June 13, 2018.
Copyright © 2018 American Physiological Society. All rights reserved.

3. Body-surface-area-matched males and females present small differences in thermosensitivity of hands and feet, and that these differences are constrained to glabrous skin only;

Thermosensitivity varies largely across hands and feet, and between skin types

The heterogeneous topography of thermosensitivity we observed here presents a distal-to-proximal organisation on both the hand and the foot, with the palm and dorsum being more sensitive than the fingers (e.g. palm was twice as warm sensitive as the thumb; Fig. 3), and with the sole and dorsum being more sensitive than the toes (e.g. the area over the arch was three times as cold sensitives as the hallux; Fig. 4).

As this observation extends across both hairy and glabrous portions of both hands and feet, in both males and females, we suggest that the distal-to-proximal increase in thermosensitivity is likely to be a specific topographical feature of hands and feet thermosensitivity in humans. This finding is novel and surprising, particularly, as one would expect that due to their primary role in manipulation and gripping (8, 72), fingers and toes would be more sensitive than the rest of the hand and foot, as it is indeed the case for touch (37, 38) and pain sensitivity (48) of the palm.

A potential explanation to this finding is that, as opposed to tactile and pain sensations, thermosensation could play only a secondary role in exploratory touch; instead, thermosensory function could have developed to a greater sensitivity on skin regions other than fingers and toes (e.g. palms and soles), and particularly on hairy skin sites (e.g. dorsum of hands and feet), as its primary purpose is to support our thermoregulatory behaviour (20). The development of a higher thermosensitivity over hairy than glabrous skin would be biologically useful to help maintaining thermal homeostasis (Cabanac, 2011). As hairy skin covers the majority of our body, and as small changes over a large proportion of the body are

Downloaded from www.physiology.org/journal/jappl by ${individualUser.givenNames} ${individualUser.surname} (131.231.103.055) on June 13, 2018.
Copyright © 2018 American Physiological Society. All rights reserved.

likely to result in higher rates of heat transfer to the environment (15), the higher thermosensitivity of hairy skin could help adjusting our thermoregulatory behaviour promptly in response to thermal stress, and prior to the engagement of energy-demanding autonomic heat- (i.e. sweating) and cold-defence (i.e. shivering) responses (62).

The hypothesis above is supported by our current findings, as we observed that hairy skin (i.e. dorsum of hand and foot) was more sensitive than glabrous skin (i.e. palm and sole) (see Fig. 7). Furthermore, previous psychophysical evidence has found a higher density of cold and warm sensitive spots on the hand/foot dorsum as opposed to the palm/sole, suggesting higher peripheral innervation of this type of skin (31). It could be therefore proposed that the hairy skin covering hands and feet could play a more specific thermosensory role than the glabrous skin of fingers and toes, as the latter is likely to be more of a specialized area for tactile than thermal sensitivity.

It is also likely that a distal-to-proximal increase in intra-epidermal nerve fibers innervation could be present across hands and feet, and that this could underlie some of the distribution of thermosensitivity observed within glabrous and hairy skin sites. Evidence is available for a distal-to-proximal increase in intra-epidermal nerve fibers density from the distal leg to the trunk (43), and this observation would support the hypothesis for which the density of thermosensitive fibres could decrease as one moves away from the core of the body and towards the upper and lower extremities (i.e. fingers and toes).

Finally, differences in skin thickness between fingers/toes and palm/soles, as well as between hairy and glabrous skin, and related changes in heat diffusion/extraction to/from the epidermal layers where thermoreceptors are positioned, could also contribute to partly explaining the observed distal to proximal organization in thermosensitivity (34). There is evidence indicating that hairy skin presents higher sensitivity than glabrous skin to heat pain, but only when thermal stimuli are delivered via conductive heating (34). When radiant heat

Downloaded from www.physiology.org/journal/jappl by ${individualUser.givenNames} ${individualUser.surname} (131.231.103.055) on June 13, 2018.
Copyright © 2018 American Physiological Society. All rights reserved.

(e.g. laser pulses) stimulates the skin, regional differences between hairy and glabrous skin are eliminated (34), supporting the impact of thickness-depend mechanisms of heat transfer on stimulation of thermoreceptors. However, correlation between epidermal thickness and local thermosensitivity has been previously shown to be low across the palm (44). Furthermore, in the present study we observed the distal-to-proximal topographical trend to also extend across hairy skin, where differences in epidermal thickness between fingers/toes and the body of hands/feet are likely to be smaller than across glabrous skin. It is therefore likely that a combination of neurophysiological (e.g. peripheral innervation and central cortical representation) as well as biophysical factors (e.g. skin anatomy) could underlie the heterogeneous thermosensitivity we observed across hands and feet, as much as it is the case for touch and pain sensitivity of the palm (37, 48, 58).

Irrespective of whether our observed differences within and between the hairy and glabrous skin of hands and feet are neurally- or anatomically-driven, it is remarkable to note that humans seem to be well aware of them, as reflected in some our most common and instinctive thermal behaviours. For example, it is common practice in many cultures to check whether one's baby has a fever by placing the dorsum of our hands (and not the palm nor fingers) on their forehead. Furthermore, it is part of public health advice in the United Kingdom to check a bath's temperature with one's elbow (and not finger) when bathing a baby (54). These examples illustrates well the thermosensory nature of hairy skin, and could support the intriguing hypothesis for which some of our most important adaptive thermal behaviours could be rooted in the topographical differences in our hands and feet thermosensitivity, as shown in our thermosensitivity maps.

Hands are twice as thermosensitive as feet

Downloaded from www.physiology.org/journal/jappl by ${individualUser.givenNames} ${individualUser.surname} (131.231.103.055) on June 13, 2018.
Copyright © 2018 American Physiological Society. All rights reserved.

It is remarkable to note that the hand was on average twice as thermosensitive as the foot, in both males and females (Fig. 6). The higher thermosensitivity of hands than feet has been previously reported by our group (24) and by others (67), although such comparisons were based on a limited number of representative skin sites (e.g. the sole vs. the palm) (24). In expanding to thermosensory processing, these results are in line with evidence indicating that the presence of a greater cortical representation of hands as compared to feet in the human brain (58) is likely to underlie the greater sensitivity of the upper extremity to cutaneous stimulation. It could be therefore speculated that the higher thermosensitivity of the hands is likely to be more dependent on central (i.e. size of the central representation of target skin area), than on peripheral factors (i.e. skin receptors density), as it is the case for pain (48). Aside from its potential neural substrates, the pronounced difference in sensitivity between hands and feet is relevant in the context of its potential behavioural impact on thermoregulatory control and thermal comfort. Our observations indicate that a similar increase or decrease in local skin temperature would generate a perceptual signal twice as strong when arising from the hands as when arising from the feet. Along with the face, both hands and feet have been previously shown to have the strongest impact on thermal discomfort during exposure to warm and cold environments (4). In this context, it would therefore be worth establishing whether the greater sensitivity of the hand to a given skin temperature change would translate in a drive to behaviourally maintain/achieve/re-establish thermal comfort that is twice as strong as the one that would arise from a similar change in foot temperature.

It also interesting to note that, cold and warm sensitivities were highly associated across both hands and feet in both males and females (Fig. 8), although cold was overall higher than warm sensitivity. It has been repeatedly shown (44, 67) that there are particular “skin spots” with higher sensitivity to both warm and cold. Our findings for both hands and feet provide

Downloaded from www.physiology.org/journal/jappl by ${individualUser.givenNames} ${individualUser.surname} (131.231.103.055) on June 13, 2018.
Copyright © 2018 American Physiological Society. All rights reserved.

further evidence for the presence of such spots that are highly sensitive to temperature change *per se,* irrespective of its direction (i.e. warming or cooling). Finally, our inter-individual variability analysis clearly showed modality- and region-dependent differences in individual variability in thermosensitivity, with variability being lower for cold than warm sensitivity, and for the hand as opposed to the foot (Fig. 5). The lower variability for cold is likely to be dependent on the higher cold than warm sensitivity of the skin, which was confirmed in this (Fig. 5) as well as in previous studies (20, 25, 28, 31). Interestingly, our finding of higher inter-individual variability for the foot than hand is novel, and could be dependent on the lower thermosensitivity of this region (see Fig. 6), which is likely to result in less homogenous thermal responses between individuals.

Males and females present small thermosensitivity differences

A further major advance of this study is that we observed small sex differences in overall cold and warm thermosensitivity across hands and feet in our age- and body surface area-matched male and female groups. A slight trend was present, with females presenting a slightly higher sensitivity on glabrous (i.e. palms and soles), but not hairy (i.e. hand/foot dorsum), skin.

Numerous studies have analysed sex differences in thermosensitivity across the body, yet findings have been often contradictory, with females being alternatively reported as more sensitive (26, 27) or no different to males (67). Such contradictory evidence has often arisen from studies not matching sex groups for body surface area, and for the relative size of the stimulus (26, 44), with this resulting in the inability to ascribe potential thermosensitivity differences to sex differences *per se* (29), as opposed to size differences. To date, only the work by Inoue et al.(35) has provided evidence that differences in thermosensitivity across the body are still present (i.e. females are more sensitive than males) when both sexes present

Downloaded from www.physiology.org/journal/jappl by ${individualUser.givenNames} ${individualUser.surname} (131.231.103.055) on June 13, 2018.
Copyright © 2018 American Physiological Society. All rights reserved.

similar body surface areas. However, as Inoue's work tested only a single area of hands and feet, the question remained as to the potential distribution of sex-related difference in thermosensitivity across the entire hand and foot.

To overcome such gap in the literature, in this study we evaluated the distribution of thermosensitivity across the entire hand and foot in age- and body surface area-matched male and female and found that sex differences were overall small and only constrained to glabrous, and not hairy, skin.

In showing that thermosensitivity across hands and feet is similar between males and females when these are matched for body surface area, our study complements previous evidence showing that sex differences in thermophysiological responses of hands and feet are reduced when male and female groups are matched by body surface area (36, 45).

Limitations

The current study provides the most detailed topographical evaluation of the thermosensitivity of hands and feet in healthy young males and females. While the applied significance of our work lays in the detailed characterization of the thermal sensation that is likely to arise from thermal stimulation of a specific area of the skin under conditions that humans encounter on a daily base (e.g. touching a warm/cool surface), we also acknowledge that our findings provide limited evidence on the neurophysiological nature of the heterogeneous distribution of sensitivity across hands and feet as we observed it. Some methods are available to further explore whether such distribution of thermosensitivity could depend on the density of temperature-sensitive free nerve endings, or on their integration properties. These methods include: intraepidermal nerve fiber density via skin biopsy (40); and microneurography, to record *in vivo* neural activity from peripheral nerve fibers (70). While promising, the adoption of these techniques is also limited by some technical

Downloaded from www.physiology.org/journal/jappl by ${individualUser.givenNames} ${individualUser.surname} (131.231.103.055) on June 13, 2018.
Copyright © 2018 American Physiological Society. All rights reserved.

challenges that could be at the root for the lack of their current use in combination with high density mapping studies such as ours. The use of skin biopsies to evaluate intraepidermal nerve fiber density is indeed limited by the number of skin sites that a typical participant is likely to agree to have punctured. The use of microneurography in the evaluation of thermoreceptors has been very limited (21) due to the difficulties in identify and recording from thermoreceptive fibers (note: only a handful of recordings from human thermoreceptors have been made to date; see e.g. (6, 7)). In face of such methodological challenges, studies endorsing animal models could be proposed as an alternative approach; yet, while commonly observed in humans (18, 23, 27, 53, 66), the presence of regional differences in thermosensitivity has not been fully investigated in models of mammalian thermosensation (51, 71), leaving our understating of its underlying neurobiology somewhat speculative. It is hoped that our current work will stimulate future attempts to better elucidate the neural mechanisms that underlie our characteristically heterogeneous skin thermosensitivity, by combining some of the methodologies listed above.

Conclusions

Our high-density thermosensory micromapping resulted in the development of the most detailed thermosensitivity maps of hands and feet in healthy young adults available to date. We found that thermosensitivity to warm and cold varied largely by up to 5-fold across the glabrous and hairy portions of human hands and feet, with hands being twice as sensitive as the feet. We observed a characteristic distal to proximal increase in thermosensitivity over both hairy and glabrous skin (i.e. from fingers/toes to body of hands and feet), and found that hairy is more sensitive than glabrous skin. We therefore argue that distal-to-proximal organization is a specific topographical feature of hand and feet thermosensitivity in humans, and that thermosensitivity differences between skin sites highlight the role of hairy skin in

Downloaded from www.physiology.org/journal/jappl by ${individualUser.givenNames} ${individualUser.surname} (131.231.103.055) on June 13, 2018.
Copyright © 2018 American Physiological Society. All rights reserved.

739 behavioural thermoregulation, as opposed to the role of glabrous skin in exploratory touch.
740 Finally, we determined that body-surface-area matched males and females present small
741 differences in thermosensitivity and that these are constrained to glabrous skin only (i.e.
742 females present slightly higher cold and warm sensitivity over the palm and sole respectively,
743 while males present slightly higher cold sensitivity over the sole).
744 Our novel findings fill a knowledge gap on the sensory function of human hands and feet.
745 Also, by complementing the available evidence on the topography of touch and pain
746 sensitivity, these findings provides a more comprehensive picture on the sensory function of
747 two of our most important sensory and exploratory anatomical structures, i.e. our hands and
748 feet. As well as providing a window into the peripheral and central mechanisms of
749 thermosensory integration in humans, these maps will be valuable to guide future
750 developments and design in smart skin and prosthesis, in wearable energy-efficient personal
751 comfort systems, and in protective clothing.
752

753 **Competing interests**

754 The authors declare no competing interests.
755

756 **Author contributions**

757 DF, HZ, EA contributed to the conception and design of the work; DF performed the
758 experiments and data analysis; DF, HZ, EA contributed to the interpretation of the results; DF
759 drafted the work; DF, HZ, EA revised the work critically for important intellectual content.
760

761 **Funding**

Downloaded from www.physiology.org/journal/jappl by ${individualUser.givenNames} ${individualUser.surname} (131.231.103.055) on June 13, 2018.
Copyright © 2018 American Physiological Society. All rights reserved.

This work was supported by the ARPA-E (Advanced Research Projects Agency- Energy, DOE) DELTA (Delivering Efficient Local Thermal Amenities) program under contract DE-AR0000529.

Acknowledgements

We would like to thank Mr Francisco Peralta (Mechanical Engineering graduate, University of California Berkeley) for developing the MatLab script used to produce the maps. We also thank the 16 volunteers for participating to the study.

References

1. **Ackerley R, Backlund Wasling H, Liljencrantz J, Olausson H, Johnson RD & Wessberg J**. Human C-Tactile Afferents Are Tuned to the Temperature of a Skin-Stroking Caress. *J Neurosci* 34: 2879–2883, 2014*a*.
2. **Ackerley R, Carlsson I, Wester H, Olausson H & Backlund Wasling H**. Touch perceptions across skin sites: differences between sensitivity, direction discrimination and pleasantness. *Front Behav Neurosci* 8: 54, 2014*b*.
3. **Amirsheybani HR**, **Crecelius GM**, **Timothy NH**, **Pfeiffer M**, **Saggers GC**, **Manders EK**. The natural history of the growth of the hand: I. Hand area as a percentage of body surface area. *Plast Reconstr Surg* 107: 726–733, 2001.
4. **Arens E**, **Zhang H**, **Huizenga C**. Partial- and whole-body thermal sensation and comfort—Part II: Non-uniform environmental conditions. *J Therm Biol* 31: 60–66, 2006.
5. **Cabanac M**. Heat Stress and Behavior. *Compr Physiol 2011, Supplement 14: Handbook of Physiology, Environmental Physiology: 261-278. First published in print 1996. doi: 10.1002/cphy.cp040113,* 1996.
6. **Campero M, Baumann TK, Bostock H & Ochoa JL**. Human cutaneous C fibres activated by cooling, heating and menthol. *J Physiol* 587: 5633–5652, 2009.
7. **Campero M, Serra J, Bostock H & Ochoa JL**. Slowly conducting afferents activated by innocuous low temperature in human skin. *J Physiol* 535: 855–865, 2001.

Downloaded from www.physiology.org/journal/jappl by ${individualUser.givenNames} ${individualUser.surname} (131.231.103.055) on June 13, 2018.
Copyright © 2018 American Physiological Society. All rights reserved.

8. **Changizi M, Weber R, Kotecha R & Palazzo J**. Are wet-induced wrinkled fingers primate rain treads? *Brain Behav Evol* 77: 286–290, 2011.
9. **Chortos A, Liu J & Bao Z**. Pursuing prosthetic electronic skin. *Nat Mater* 15: 937-950, 2016.
10. **Claus D & Hilz M**. Methods of measurement of thermal thresholds. *Acta Neurol Scand* 76: 288-296, 1987.
11. **Craig A**. How do you feel? Interoception: the sense of the physiological condition of the body. *Nat Rev Neurosci* 3: 655–666, 2002.
12. **Craig A, Chen K, Bandy D & Reiman E**. Thermosensory activation of insular cortex. *Nat Neurosci* 3: 184–190, 2000.
13. **Darian-Smith I**. " Cold" fiber population innervating palmar and digital skin of the monkey: responses to cooling pulses. *J Neurophysiol* 36: 325-346, 1973.
14. **Darian-Smith I**. Thermal sensibility. *Compr Physiol 2011, Supplement 3: Handbook of Physiology, The Nervous System, Sensory Processes: 879-913. First published in print 1984. doi: 10.1002/cphy.cp010319*, 1984.
15. **Darian-Smith I & Johnson K**. Thermal sensibility and thermoreceptors. *J Invest Dermatol* 69: 146-153, 1977.
16. **Davis KD, Kwan CL, Crawley AP & Mikulis DJ**. Functional MRI study of thalamic and cortical activations evoked by cutaneous heat, cold, and tactile stimuli. *J Neurophysiol* 80: 1533–1546, 1998.
17. **Defrin R, Petrini L & Arendt-Nielsen L**. Spatial summation of thermal sensations depends on skin type and skin sensitivity. *Exp brain Res* 198: 29–36, 2009.
18. **Donaldson H**. On the temperature-sense. *Mind* os-X, 398–416, 1885.
19. **Farrar JT, Young JP, LaMoreaux L, Werth JL & Poole RM**. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. *Pain* 94: 149–158, 2001.
20. **Filingeri D**. Neurophysiology of skin thermal sensations. *Compr Physiol* 6: 1429–149, 2016.
21. **Filingeri D & Ackerley R**. The biology of skin wetness perception and its implications in manual function and for reproducing complex somatosensory signals in neuroprosthetics. *J Neurophysiol* 117: 1761–1775, 2017.
22. **Filingeri D, Chaseling G, Hoang P, Barnett M, Davis SL & Jay O**. Afferent thermosensory function in relapsing-remitting Multiple Sclerosis following exercise-induced increases in body temperature. *Exp Physiol* 102: 887-893, 2017*a*.

Downloaded from www.physiology.org/journal/jappl by ${individualUser.givenNames} ${individualUser.surname} (131.231.103.055) on June 13, 2018.
Copyright © 2018 American Physiological Society. All rights reserved.

23. **Filingeri D, Fournet D, Hodder S & Havenith G**. Body mapping of cutaneous wetness perception across the human torso during thermo-neutral and warm environmental exposures. *J Appl Physiol* 117: 887–897, 2014.
24. **Filingeri D, Morris NB & Jay O**. 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, 2017*b*.
25. **Filingeri D, Zhang H & Arens EA**. Characteristics of the local cutaneous sensory thermo-neutral zone. *J Neurophysiol* 117: 1797–1806, 2017*c*.
26. **Gerrett N, Ouzzahra Y, Coleby S, Hobbs S, Redortier B, Voelcker T & Havenith G**. Thermal sensitivity to warmth during rest and exercise: a sex comparison. *Eur J Appl Physiol* 114: 1451-1462, 2014.
27. **Gerrett N, Ouzzahra Y, Redortier B, Voelcker T & Havenith G**. Female thermal sensitivity to hot and cold during rest and exercise. *Physiol Behav* 152: 11–19, 2015.
28. **Green BG**. Temperature perception and nociception. *J Neurobiol* 61: 13–29, 2004.
29. **Greenspan JD & Kenshalo D**. The primate as a model for the human temperature-sensing system: 2 area of skin receiving thermal stimulation (spatial summation). *Somatosens Mot Res* 2: 315–324, 1985.
30. **Hauer P, Stocks A, McArthur JC, Cornblath DR & Griffin JW**. Epidermal Nerve Fiber Density. *Arch Neurol* 55: 1513–1520, 2008.
31. **Hensel H**. *Thermoreception and temperature regulation*, Issue 38 o. Academic Press, 1981.
32. **Hjermstad MJ, Fayers PM, Haugen DF, Caraceni A, Hanks GW, Loge JH, Fainsinger R, Aass N & Kaasa S**. Studies comparing numerical rating scales, verbal rating scales, and visual analogue scales for assessment of pain intensity in adults: A systematic literature review. *J Pain Symptom Manage* 41: 1073–1093, 2011.
33. **Houdas Y & Ring E**. *Human body temperature-Its measurement and regulation*. Plenum Press,New York, NY, 1982.
34. **Iannetti GD, Zambreanu L & Tracey I**. Similar nociceptive afferents mediate psychophysical and electrophysiological responses to heat stimulation of glabrous and hairy skin in humans. *J Physiol* 577: 235–248, 2006.
35. **Inoue Y, Gerrett N, Ichinose-Kuwahara T, Umino Y, Kiuchi S, Amano T, Ueda H, Havenith G, Kondo N.** Sex differences in age-related changes on peripheral warm and cold innocuous thermal sensitivity. Physiol Behav 164: 86–92, 2016.
36. **Jay O & Havenith G**. Finger skin cooling on contact with cold materials: an

Downloaded from www.physiology.org/journal/jappl by ${individualUser.givenNames} ${individualUser.surname} (131.231.103.055) on June 13, 2018.
Copyright © 2018 American Physiological Society. All rights reserved.

investigation of male and female responses during short-term exposures with a view on hand and finger size. *Eur J Appl Physiol* 93: 1–8, 2004.

37. **Johansson RS & Vallbo AB**. Detection of tactile stimuli. Thresholds of afferent units related to psychophysical thresholds in the human hand. *J Physiol* 297: 405–422, 1979*a*.
38. **Johansson RS & Vallbo AB**. Tactile sensibility in the human hand: relative and absolute densities of four types of mechanoreceptive units in glabrous skin. *J Physiol* 286: 283–300, 1979*b*.
39. **Johansson RS, Vallbo AB & Westling G**. Thresholds of mechanosensitive afferents in the human hand as measured with von Frey hairs. *Brain Res* 184: 343–351, 1980.
40. **Kawakami T**, **Ishihara M**, **Mihara M**. Distribution Density of Intraepidermal Nerve Fibers in Normal Human Skin. *J Dermatol* 28: 63–70, 2001.
41. **Kim J, Lee M, Shim HJ, Ghaffari R, Cho HR, Son D, Jung YH, Soh M, Choi C, Jung S, Chu K, Jeon D, Lee S-T, Kim JH, Choi SH, Hyeon T & Kim DH**. Stretchable silicon nanoribbon electronics for skin prosthesis. *Nat Commun* 5, 5747, 2014.
42. **Konietzny F & Hensel H**. Warm fiber activity in human skin nerves. *Pflügers Arch Eur J Physiol* 267: 265–267, 1975.
43. **Lauria G, Holland N, Hauer P, Cornblath DR, Griffin JW, McArthur JC.** Epidermal innervation: changes with aging, topographic location, and in sensory neuropathy. J Neurol Sci 164: 172–178, 1999.
44. **Li X, Petrini L, Defrin R, Madeleine P & Arendt-Nielsen L**. High resolution topographical mapping of warm and cold sensitivities. *Clin Neurophysiol* 119: 2641–2646, 2008.
45. **Lunt H & Tipton M**. Differences in conductive foot cooling: a comparison between males and females. *Eur J Appl Physiol* 114: 2635–2644, 2014.
46. **Mancini F, Bauleo A, Cole J, Lui F, Porro CA, Haggard P & Iannetti GD**. Whole-body mapping of spatial acuity for pain and touch. *Ann Neurol* 75: 917–924, 2014.
47. **Mancini F, Haggard P, Iannetti GD, Longo MR & Sereno MI**. Fine-grained nociceptive maps in primary somatosensory cortex. *J Neurosci* 32: 17155–17162, 2012.
48. **Mancini F, Sambo CF, Ramirez JD, Bennett DLH, Haggard P & Iannetti GD**. A fovea for pain at the fingertips. *Curr Biol* 23: 496–500, 2013.

Downloaded from www.physiology.org/journal/jappl by ${individualUser.givenNames} ${individualUser.surname} (131.231.103.055) on June 13, 2018.
Copyright © 2018 American Physiological Society. All rights reserved.

49. **McGlone F, Wessberg J & Olausson H**. Discriminative and Affective Touch: Sensing and Feeling. *Neuron* 82: 737–755, 2014.
50. **McKemy DD**. Temperature sensing across species. *Pflugers Arch* 454: 777–791, 2007.
51. **Milenkovic N, Zhao W-J, Walcher J, Albert T, Siemens J, Lewin GR & Poulet JFA**. A somatosensory circuit for cooling perception in mice. *Nat Neurosci* 17: 1560–1566, 2014.
52. **Mountcastle VB**. *The Sensory Hand: Neural Mechanisms of Somatic Sensation*. Harvard University Press, 2005.
53. **Nakamura M, Yoda T, Crawshaw L, Yasuhara S, Saito Y, Kasuga M, Nagashima K & Kanosue K**. Regional differences in temperature sensation and thermal comfort in humans. *J Appl Physiol* 105: 1897–1906, 2008.
54. **National Health Service**. Washing and bathing your baby [Online]. 2015. https://www.nhs.uk/conditions/pregnancy-and-baby/washing-your-baby/.
55. **Norrsell U, Finger S & Lajonchere C**. Cutaneous sensory spots and the "law of specific nerve energies": history and development of ideas. *Brain Res Bull* 48: 457–465, 1999.
56. **Oommen A**, **Mainker A**, **Oommen T**. A Study of the Correlation Between Hand Length And Foot Length In Humans. *JAnatSoc India* 54: 1–9, 2005.
57. **Ouzzahra Y, Havenith G & Redortier B**. Regional distribution of thermal sensitivity to cold at rest and during mild exercise in males. *J Therm Biol* 37: 517–523, 2012.
58. **Penfield W & Boldrey E**. Somatic Motor and Sensory Representation in Man. *Brain 4*, 389–443, 1937.
59. **Raspopovic S, Capogrosso M, Petrini FM, Bonizzato M, Rigosa J, Di Pino G, Carpaneto J, Controzzi M, Boretius T, Fernandez E, Granata G, Oddo CM, Citi L, Ciancio AL, Cipriani C, Carrozza MC, Jensen W, Guglielmelli E, Stieglitz T, Rossini PM, Micera S.** Restoring Natural Sensory Feedback in Real-Time Bidirectional Hand Prostheses. *Sci Transl Med* 6, 222ra19-222ra19, 2014.
60. **Rolls ET, Grabenhorst F & Parris BA**. Warm pleasant feelings in the brain. *Neuroimage* 41: 1504–1513, 2008.
61. **Romanovsky A**. Thermoregulation: some concepts have changed. Functional architecture of the thermoregulatory system. *Am J Physiol Regul Integr Comp Physiol* 292: R37-R46, 2007.

Downloaded from www.physiology.org/journal/jappl by ${individualUser.givenNames} ${individualUser.surname} (131.231.103.055) on June 13, 2018.
Copyright © 2018 American Physiological Society. All rights reserved.

62. **Schlader ZJ**, **Coleman GL**, **Sackett JR**, **Sarker S**, **Chapman CL**, **Johnson BD**. Activation of autonomic thermoeffectors preceding the decision to behaviourally thermoregulate in resting humans. *Exp Physiol* 9: 1218–1229, 2016.
63. **Shao Y, Hayward V & Visell Y**. Spatial patterns of cutaneous vibration during whole-hand haptic interactions. *Proc Natl Acad Sci U S A* 113: 201520866, 2016.
64. **Smith M, Warren K, Cohen-Taguchi D, Shames S, Sprehn K, Schwartz J, Zhang H, Arens E.** Augmenting smart buildings and autonomous vehicles with wearable thermal technology. *Proceedings of HCI Internationa*l, July, Boston: 550-561. https://escholarship.org/uc/item/9q24x8p3, 2017
65. **Stettler DD**, **Das A**, **Bennett J**, **Gilbert CD**. Lateral connectivity and contextual interactions in macaque primary visual cortex. *Neuron* 36: 739–750, 2002.
66. **Stevens J**. Variation of cold sensitivity over the body surface. *Sens Processes* 3: 317, 1979.
67. **Stevens J & Choo K**. Temperature sensitivity of the body surface over the life span. *Somatosens Mot Res* 15:13-28, 1998.
68. **Stevens J, Marks L & Simonson D**. Regional sensitivity and spatial summation in the warmth sense. *Physiol Behav* 13: 825–836, 1974.
69. **Taylor NAS, Machado-Moreira CA, van den Heuvel AMJ & Caldwell JN**. Hands and feet: physiological insulators, radiators and evaporators. *Eur J Appl Physiol* 114: 2037–2060, 2014.
70. **Vallbo AB**, **Hagbarth K-E**, **Wallin BG**. Microneurography: how the technique developed and its role in the investigation of the sympathetic nervous system. *J Appl Physiol* 96: 1262–1269, 2004.
71. **Vriens J, Nilius B & Voets T**. Peripheral thermosensation in mammals. *Nat Rev Neurosci* 15: 573–589, 2014.
72. **Witney AG, Wing A, Thonnard J-L & Smith AM**. The cutaneous contribution to adaptive precision grip. *Trends Neurosci* 27: 637–643, 2004.
73. **Zhang H, Arens E & Zhai Y**. A review of the corrective power of personal comfort systems in non-neutral ambient environments. *Build Environ* 91: 15–41, 2015.

Downloaded from www.physiology.org/journal/jappl by ${individualUser.givenNames} ${individualUser.surname} (131.231.103.055) on June 13, 2018.
Copyright © 2018 American Physiological Society. All rights reserved.

Tables

Table 1. Participants' characteristics, including age, mass, height, body surface area (BSA), and proportion of BSA stimulated by the fixed-size (i.e. 1.32cm^2) thermal probe used, are reported for the male and female groups. Statistical differences between groups for each characteristic were assessed by means of independent group t-tests, with cut-off probability value for significance set at p=0.05.

	Age (years)	**Mass (Kg)**	**Height (m)**	**BSA (m^2)**	**Proportion of BSA stimulated (%)**
Males (n=8)	30.2 ± 5.8	67.8 ± 13.4	1.69 ± 0.1	1.77 ± 0.2	0.0076 ± 0.0009
Females (n=8)	27.7 ± 5.1	58.0 ± 5.4	1.66 ± 0.1	1.64 ± 0.1	0.0081 ± 0.0005
Probability	0.381	0.076	0.546	0.155	0.184

Downloaded from www.physiology.org/journal/jappl by ${individualUser.givenNames} ${individualUser.surname} (131.231.103.055) on June 13, 2018.
Copyright © 2018 American Physiological Society. All rights reserved.

Figure legends

Figure 1. Schematic representation of the experimental design and protocol. Panel A shows the combination of thermal probe and thermocouple microsensor used to deliver thermal stimuli and record changes in probe-skin interface temperature, respectively. Panel B shows application of the probe on a representative skin site of the palm. Panel C presents an overview of the stimulation protocol, where 5s-cooling and –warming pulses were delivered at the skin, in a counterbalanced order, and with 5s in between them. At the end of each 5s-stimulation, participants reported their local thermal sensation, using the numerical rating scale showed in panel D.

Figure 2. Topographical distribution of the 103 skin sites tested over the glabrous and hairy skin of hands and feet.

Figure 3. Warm and cold thermosensitivity maps for glabrous and hairy skin of the hand in males and females. Maps shows mean data for each sex group (n=8) and are based on the 49 sites tested over the hand.

Figure 4. Warm and cold thermosensitivity maps for glabrous and hairy skin of the foot in males and females. Maps shows mean data for each sex group (n=8) and are based on the 54 sites tested over the foot.

Figure 5. Inter-individual variability in thermosensitivity for the hand (upper half panel) and the foot (lower half panel). Heat maps are presented and show coefficients of variation for warm and cold thermosensitivity, in males (n=8) and females (n=8), and for all 103 skin sites

Downloaded from www.physiology.org/journal/jappl by ${individualUser.givenNames} ${individualUser.surname} (131.231.103.055) on June 13, 2018.
Copyright © 2018 American Physiological Society. All rights reserved.

tested.

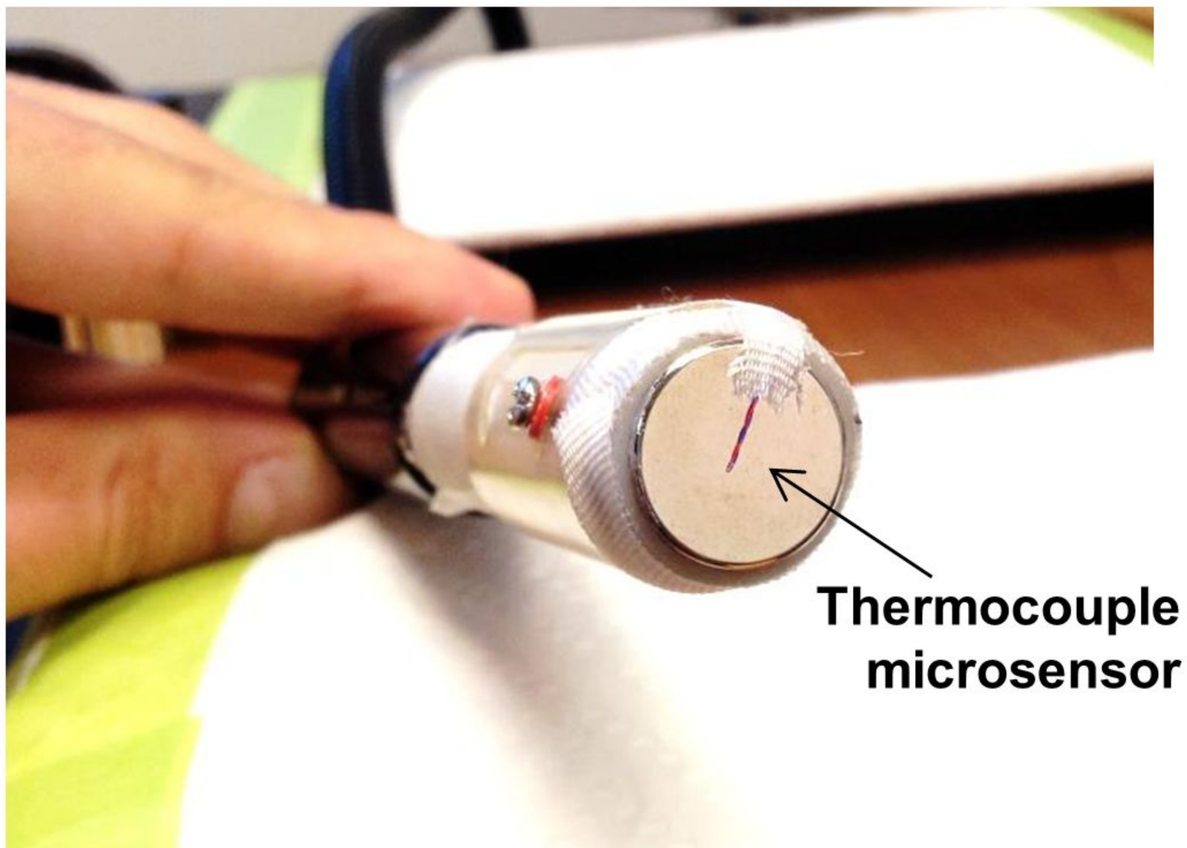
Figure 6. Hand and foot overall thermosensitivity in males and females. Each graph presents a comparison of the overall warm and cold thermosensitivity of the hand (49 sites) versus the foot (54 sites) for males (n=8) and females (n=8). It can be observed that the hand is significantly more sensitive than the foot for both warming and cooling, and in both males and females. Probability values for statistical comparisons between hands and feet thermosensitivity are shown.

Figure 7. Glabrous and hairy skin overall thermosensitivity in males and females. Each graph presents a comparison of the overall warm and cold thermosensitivity of the glabrous skin of both (includes all skin sites over palms and soles) versus the hairy skin (includes all skin sites over back of hands and feet) for males (n=8) and females (n=8). It can be observed that the hairy skin is significantly more sensitive than the glabrous skin for both warming and cooling, and in both males and females. Probability values for statistical comparisons between hairy and glabrous skin thermosensitivity are shown.

Figure 8. Association between overall warm and cold thermosensitivity in males and females. Each graph presents the association between the warm and cold thermosensitivity of all 103 skin sites tested across hands and feet in males (n=8) and females (n=8). Pearson correlation coefficients and probability values for statistical significance are shown.

Downloaded from www.physiology.org/journal/jappl by ${individualUser.givenNames} ${individualUser.surname} (131.231.103.055) on June 13, 2018.
Copyright © 2018 American Physiological Society. All rights reserved.

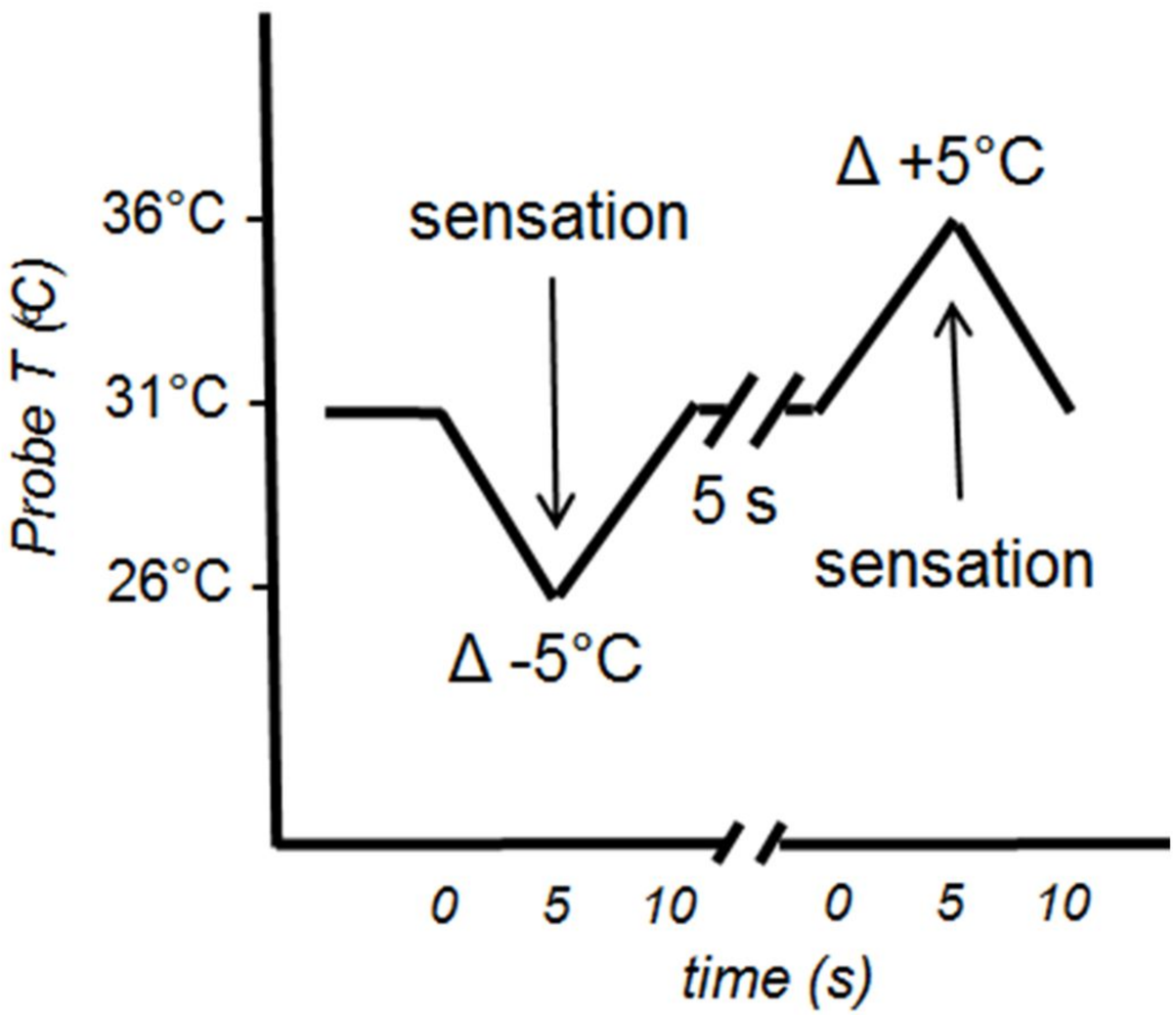
A



B



C

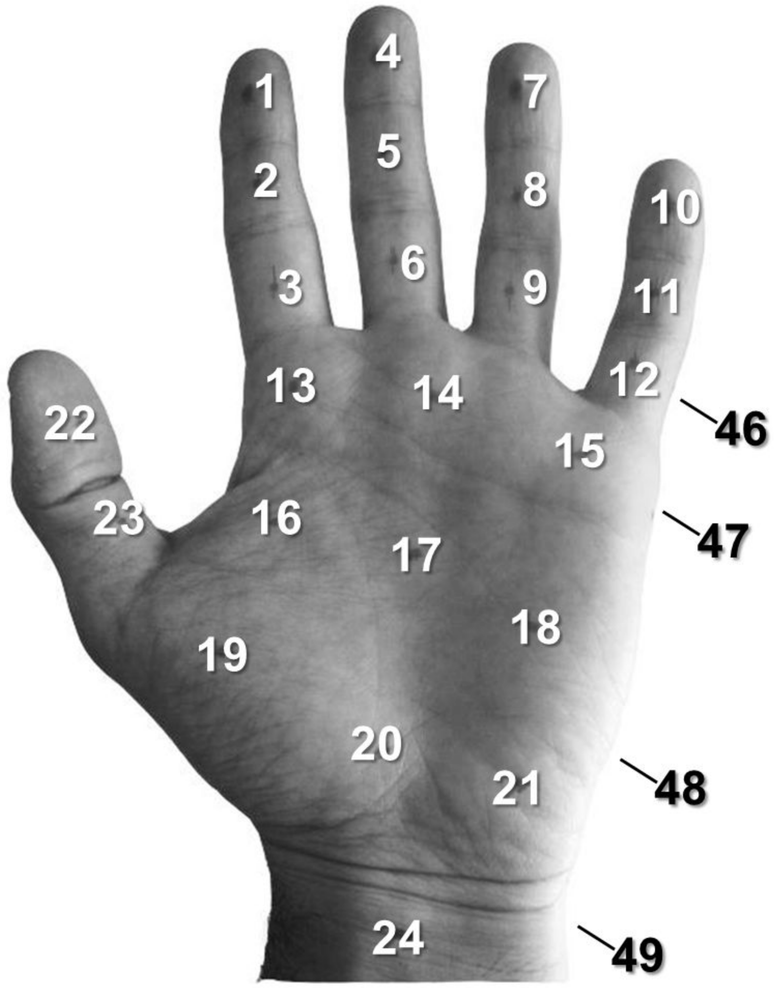


D

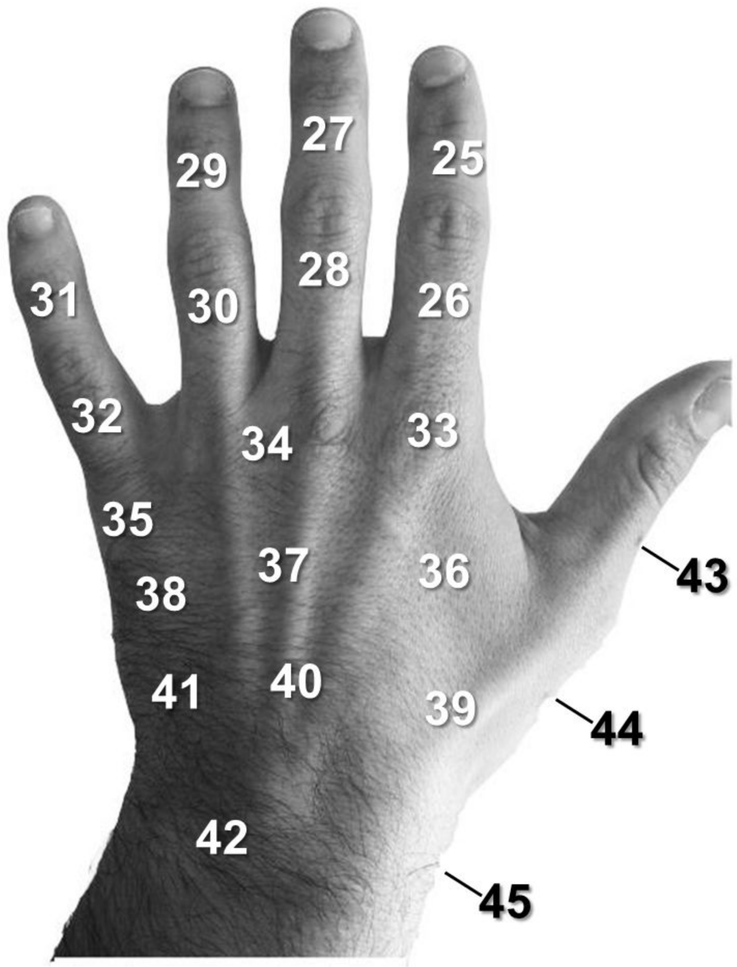
Very Hot	10	Very Cold
	9	
	8	
	7	
	6	
	5	
	4	
	3	
	2	
	1	
Not hot at all	0	Not cold at all

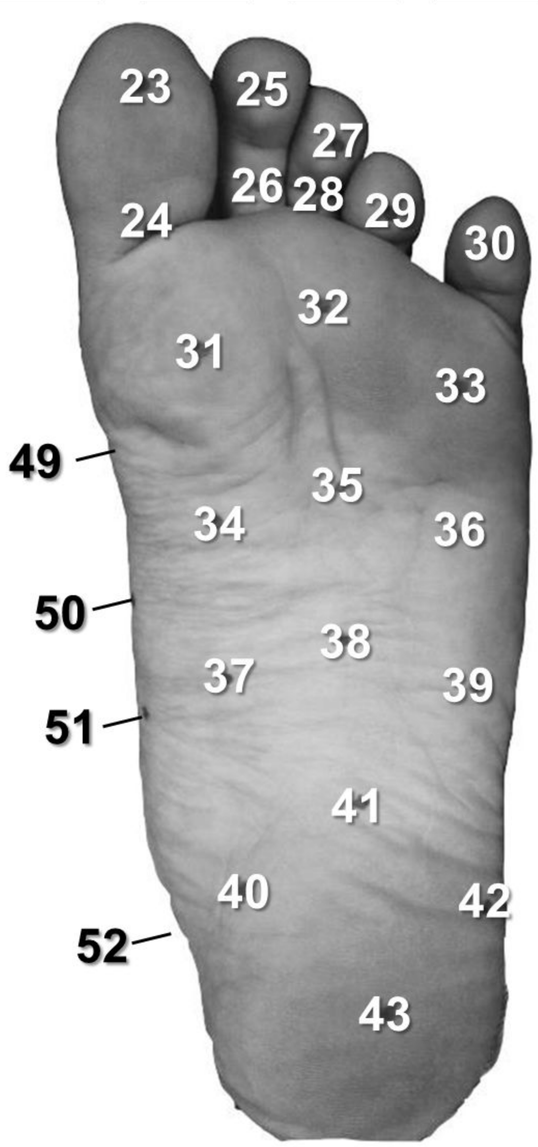
Downloaded from www.physiology.org/journal/jappl by ${individualUser.givenNames} ${individualUser.surname} (131.231.103.055) on June 13, 2018.
Copyright © 2018 American Physiological Society. All rights reserved.

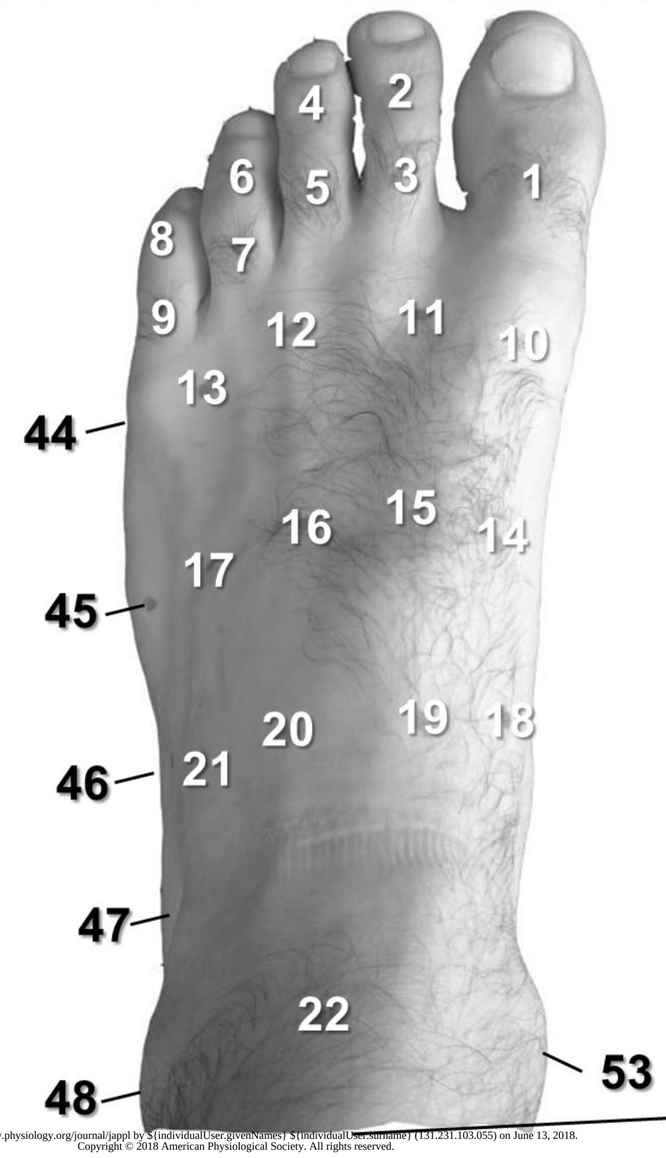
Glabrous



Hairy

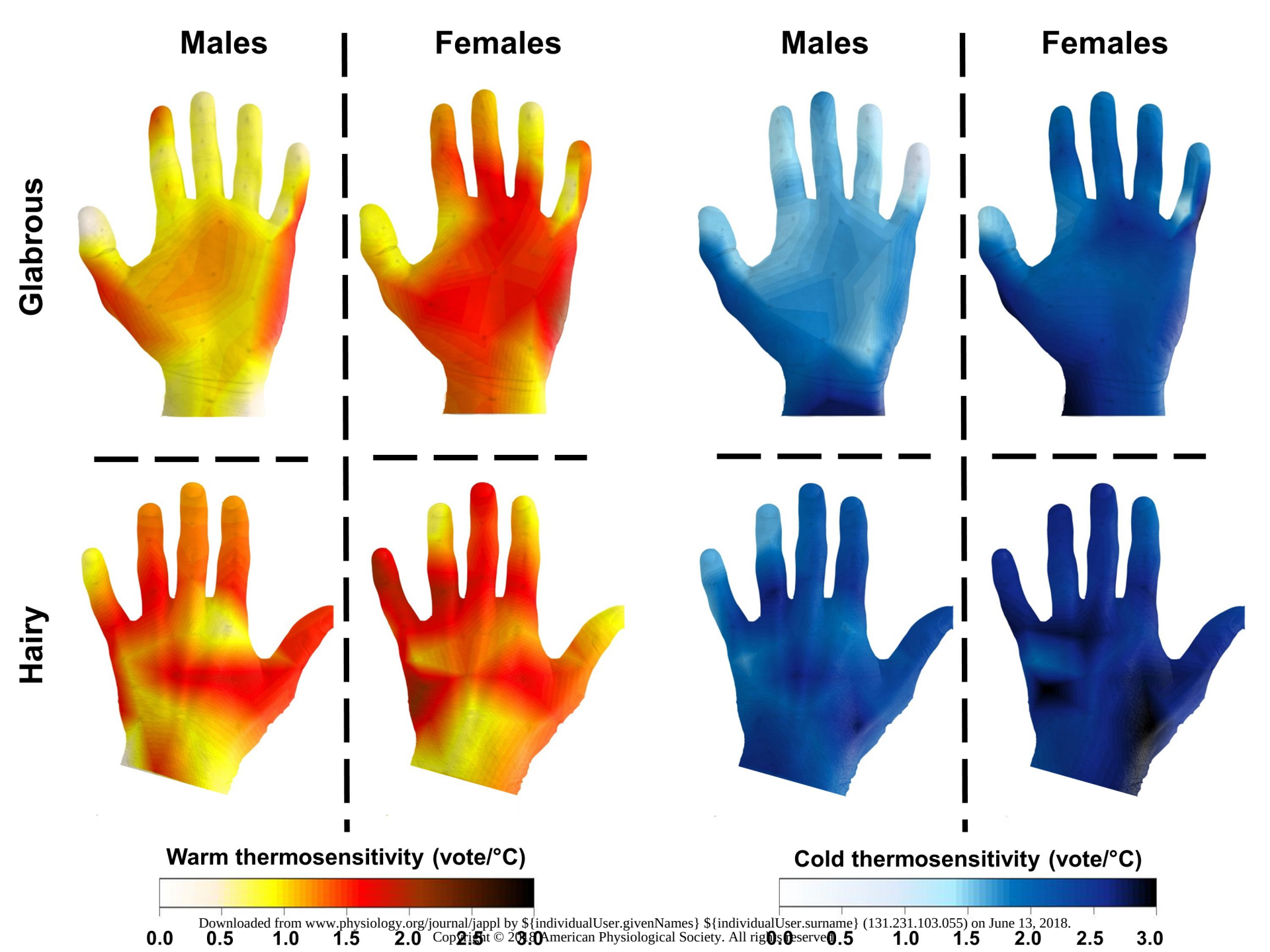




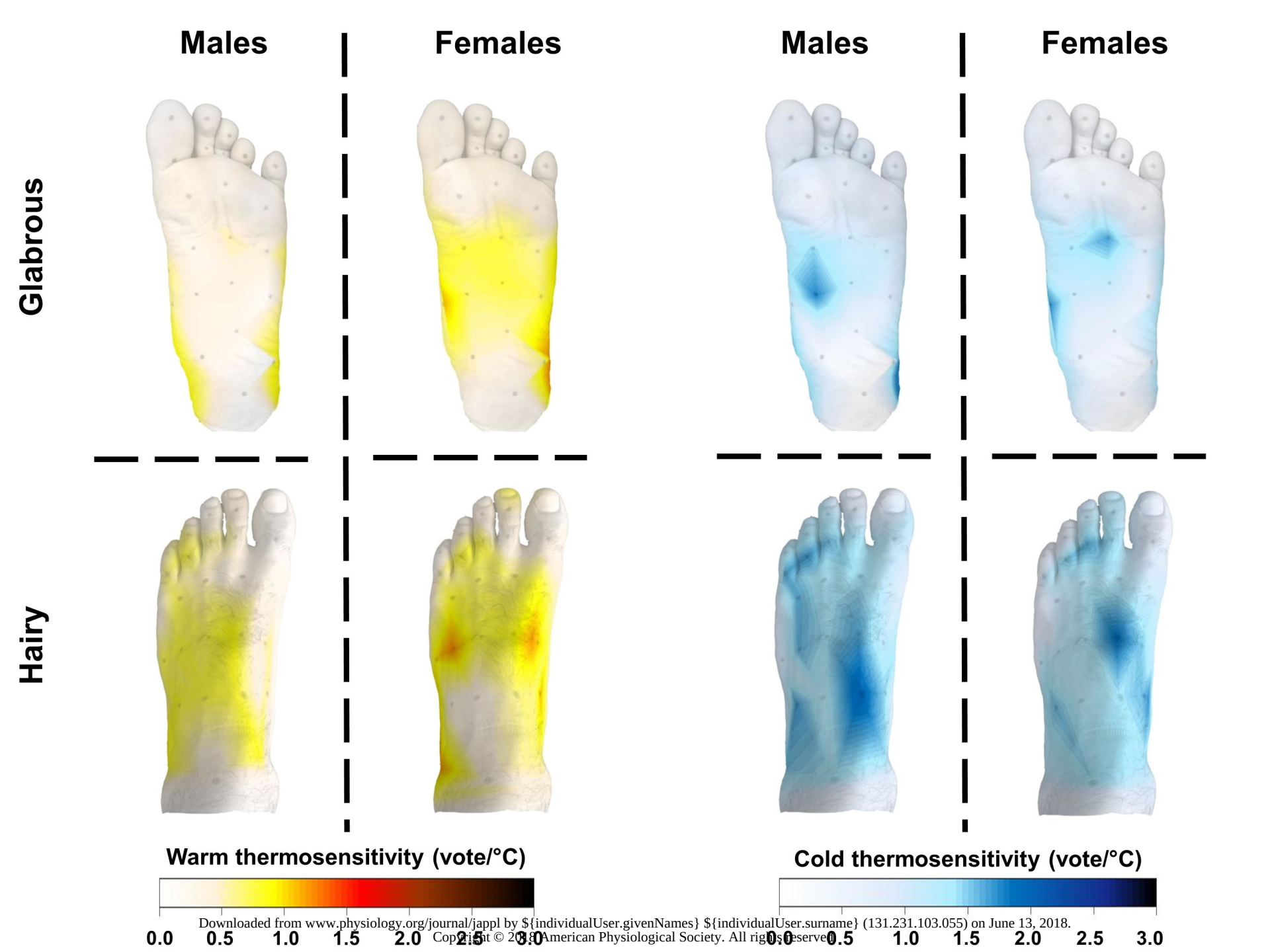


*54 (posterior part of the ankle)

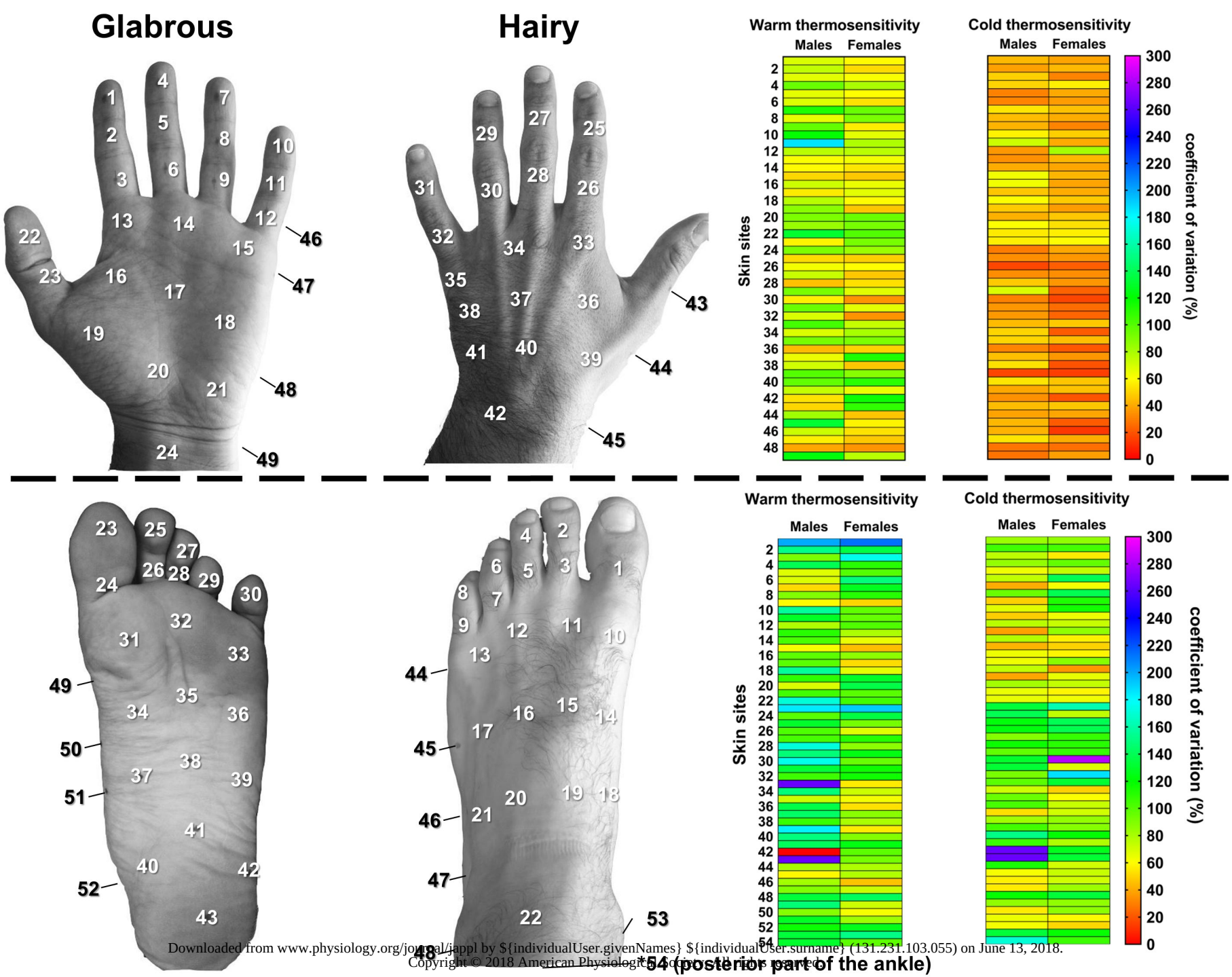
Downloaded from www.physiology.org/journal/jappl by ${individualUser.givenNames} ${individualUser.surname} (131.231.103.055) on June 13, 2018.
Copyright © 2018 American Physiological Society. All rights reserved.



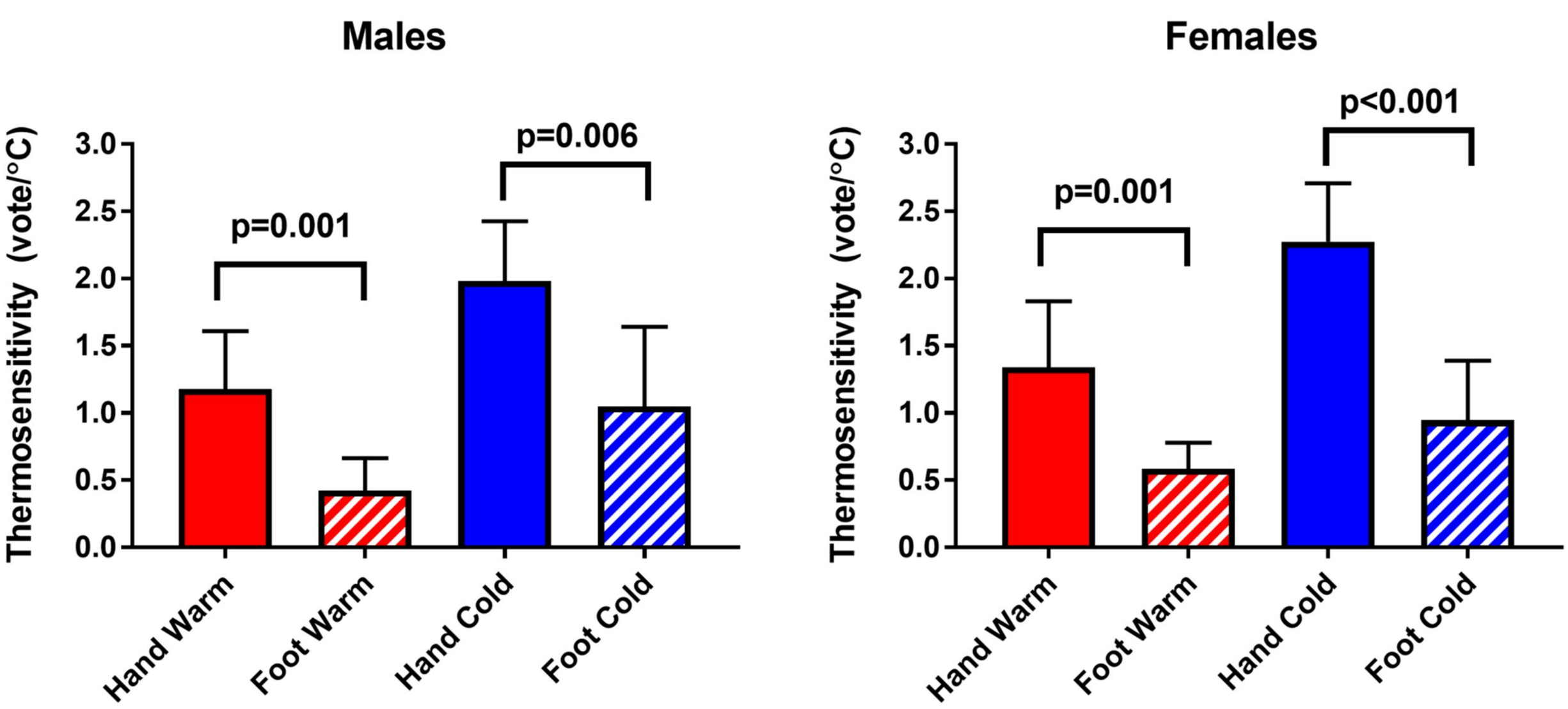
Downloaded from www.physiology.org/journal/jappl by ${individualUser.givenNames} ${individualUser.surname} (131.231.103.055) on June 13, 2018.
Copyright © 2018 American Physiological Society. All rights reserved.



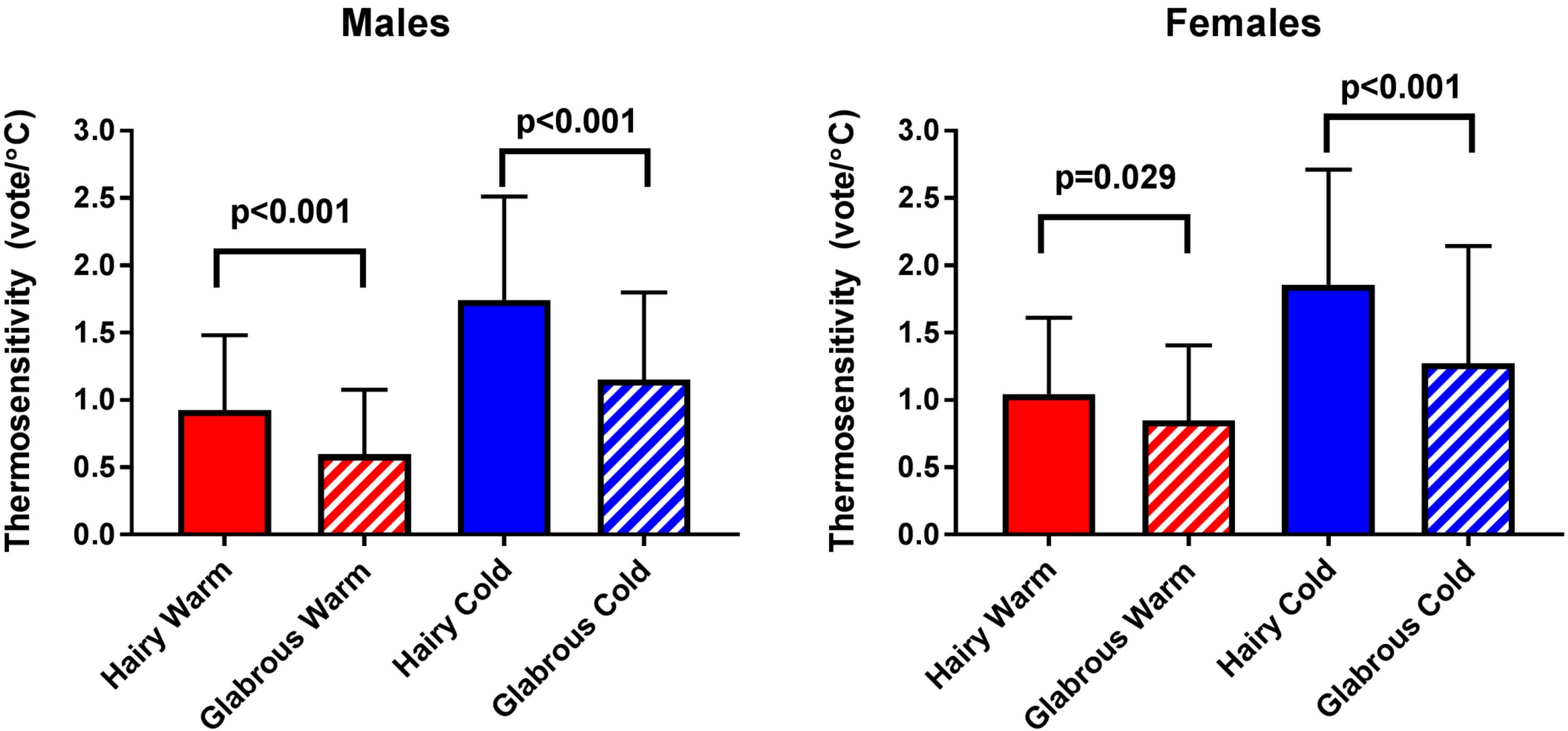
Downloaded from www.physiology.org/journal/jappl by ${individualUser.givenNames} ${individualUser.surname} (131.231.103.055) on June 13, 2018.
Copyright © 2018 American Physiological Society. All rights reserved.



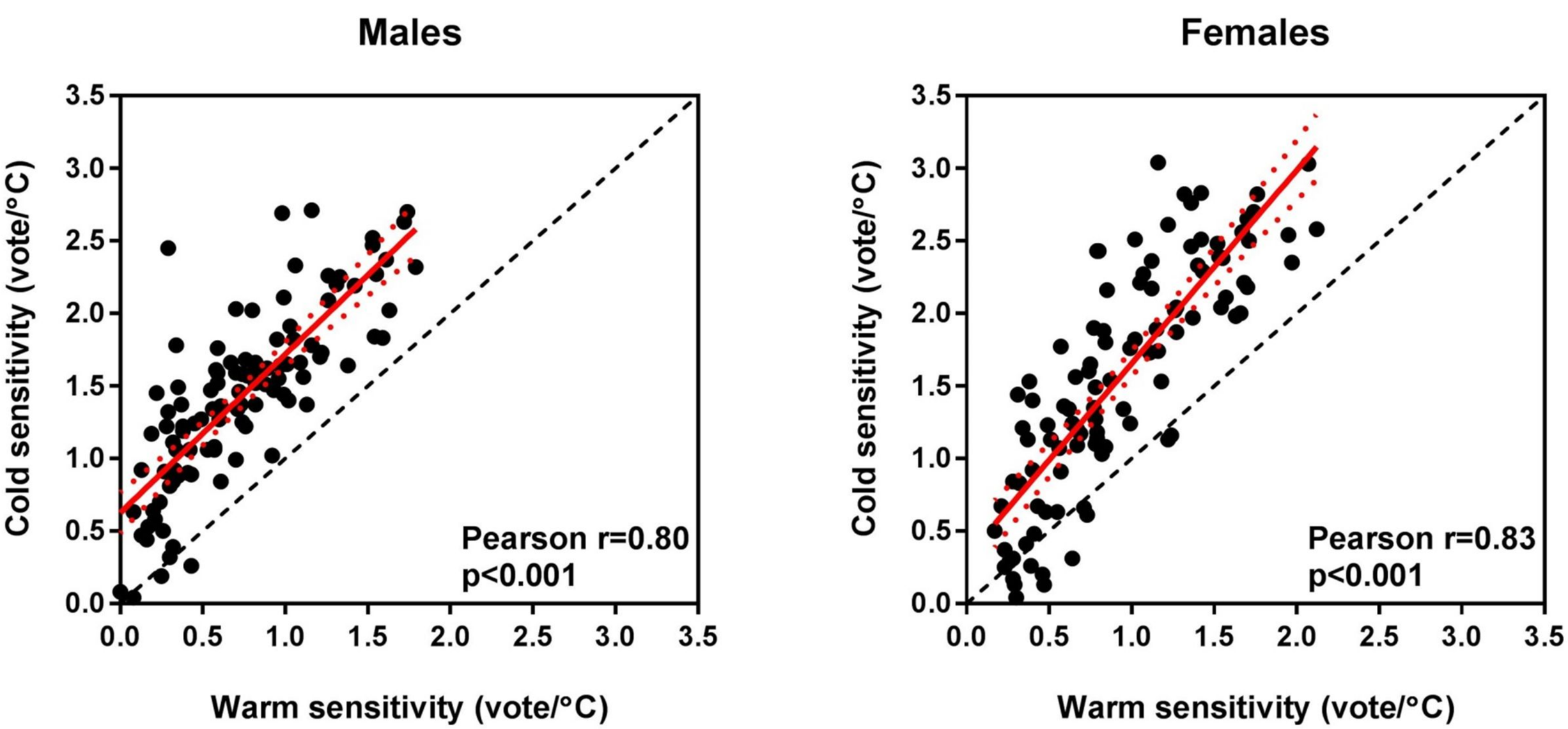
Downloaded from www.physiology.org/journal/jappl by ${individualUser.givenNames} ${individualUser.surname} (131.231.103.055) on June 13, 2018.
Copyright © 2018 American Physiological Society. All rights reserved.



Downloaded from www.physiology.org/journal/jappl by ${individualUser.givenNames} ${individualUser.surname} (131.231.103.055) on June 13, 2018.
Copyright © 2018 American Physiological Society. All rights reserved.



Downloaded from www.physiology.org/journal/jappl by ${individualUser.givenNames} ${individualUser.surname} (131.231.103.055) on June 13, 2018.
Copyright © 2018 American Physiological Society. All rights reserved.



Downloaded from www.physiology.org/journal/jappl by ${individualUser.givenNames} ${individualUser.surname} (131.231.103.055) on June 13, 2018.
Copyright © 2018 American Physiological Society. All rights reserved.