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Authors
Filingeri, Davide
Zhang, Hui
Arens, Edward A

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Characteristics of the local cutaneous sensory thermo-neutral zone

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

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

[2] Environmental Ergonomics Research Centre, Loughborough Design School, Loughborough University Loughborough, United Kingdom

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Corresponding author's current address:
Davide Filingeri, PhD
Environmental Ergonomics Research Centre
Loughborough University
Loughborough, LE11 3TU
United Kingdom
Email: d.filingeri3@lboro.ac.uk
Phone: +44 (0) 1509 222661

ABSTRACT

Skin temperature detection thresholds have been used to measure human cold and warm sensitivity across the temperature continuum. They exhibit a sensory zone within which neither warm nor cold sensations prevail. This zone has been widely assumed to coincide with steady-state local skin temperatures between 32-34°C, but its underlying neurophysiology has been rarely investigated. Here we employ two approaches to characterize the properties of sensory thermo-neutrality, testing for each whether neutrality shifts along the temperature continuum depending on adaptation to a preceding thermal state. The focus is on local spots of skin on the palm. Ten participants (30.3±4.8 y) underwent two experiments. Experiment 1 established the cold-to-warm inter-detection-threshold range for the palm's glabrous skin, and its shift as a function of 3 starting skin temperatures (26, 31 or 36°C). For the same conditions, Experiment 2 determined a thermally neutral zone centered around a thermally neutral point in which thermoreceptors' activity is balanced. The zone was found to be narrow (~0.98 to ~1.33°C) moving with the starting skin temperature over the temperature span 27.5-34.9°C (Pearson $r = 0.94$; $p<0.001$). It falls within the cold-to-warm inter-threshold range (width: ~2.25 to ~2.47°C) but is only half as wide. These findings provide the first quantitative analysis of the local sensory thermo-neutral zone in humans, indicating that it does not occur only within a specific range of steady-state skin temperatures (i.e. it shifts across the temperature continuum) and that it differs from the inter-detection-threshold range both quantitatively and qualitatively. These findings provide insight into thermoreception neurophysiology.

NEW AND NOTEWORTHY:

Contrary to a widespread concept in human thermoreception, we show that local sensory thermo-neutrality is achievable outside the 32-34°C skin temperature range. We propose that sensory adaption underlies a new mechanism of temperature integration. Also, we have developed from vision research a new quantitative test addressing the balance in cutaneous cold and warm thermoreceptors' activity. This could have important clinical (assessment of somatosensory abnormalities in neurological disease) and applied (design of personal comfort systems) implications.

KEYWORDS

Thermo-neutral zone, thermoreceptors, skin, temperature, psychophysics

INTRODUCTION

Temperature detection in humans is a separate sensory modality (see Filingeri, 2016 for a comprehensive review), extending in a single dimension in opposite directions (neutral->cool->cold; neutral->warm->hot). This is in a way similar to the black-grey-white axis in vision, which since Hering (Hering 1874) has been regarded not as unipolar but bi-directional, i.e. reaching from grey to black on one side and from grey to white on the other, something for which there is a functional and indeed structural neural basis (see Westheimer, 2007 for a review).

Detection thresholds have traditionally been the first step in analyzing the perception of sensory signals; accordingly, extensive knowledge is available about the minimum detectable temperature increments and decrements of non-noxious thermal stimuli applied to the human skin (Lele 1954; Kenshalo et al. 1968; Yarnitsky and Ochoa 1991).

We know that detection thresholds are asymmetrical between cold and warm temperatures and that, depending on the starting skin temperature (Kenshalo et al. 1961) and on the body region and size of the area stimulated (Stevens et al. 1974; Defrin et al. 2009), temperature increments or decrements of 0.003 up to 10°C are required to trigger warm and cold thermal sensations (Hardy and Oppel 1937; Lele 1954). From this knowledge it is possible to quantify the inter-detection-threshold range, a range of temperatures within which it is not possible to create a temperature change sufficient to induce a perceived change in cold and warm sensations (Oppel and Hardy 1937; Lele 1954; Darian-Smith 1984; Hirosawa et al. 1984).

While threshold studies have been essential for our fundamental understanding of human thermosensation and for the development of clinical diagnostic tools (e.g. evaluation of somatosensory abnormalities) (Arendt-Nielsen and Yarnitsky 2009; Moloney et al. 2012), they have however been limited for assessing the characteristics of *sensory thermo-neutrality*, where under normal conditions and functioning, neither a clear warm nor a cold sensation prevail.

A human *sensory thermo-neutral zone* does indeed appear to exist. When a resting standard-sized individual (i.e. body mass 70 Kg; body surface area 1.8 m^2, clothing insulation: 0.6 clo) (Du Bois and Du Bois 1916) is exposed to an environment whose ambient temperature is ~24°C), natural skin temperatures across the body range between ~30 and ~34°C (Hensel 1973; Gagge and Gonzalez 1996). At these skin temperatures, individuals do not usually report any prevailing warm or cold thermal sensation and are therefore believed to be in a state of sensory thermo-neutrality.

Evidence from primate studies has indicated that on-going activity in cold- and warm-sensitive cutaneous thermoreceptors overlaps at steady state skin temperatures in the range of 32 to 35°C (Hensel 1973; Darian-Smith 1984). The coincidence of the skin temperature ranges for sensory thermo-neutrality and for thermoreceptors' firing balance has therefore contributed to the prevalent views that 30 to 34°C is the sole range of local skin temperatures within which thermal neutrality can be achieved (Gagge et al. 1967; Hensel 1973), and also that the sensory thermo-neutral zone depends on neural balance between cold and warm afferent inputs (see Fig. 1 for steady state response curves at different skin temperatures).

These beliefs are now incorporated into current clinical testing of temperature detection thresholds, where it is a prescribed and standardized requirement to start the local assessment of detection thresholds from a baseline skin temperature in the range of ~30 and ~34 °C (Rolke et al. 2006a; Backonja et al. 2013), as this is described as the "neutral range" (Rolke et al. 2006b). However, it is important to highlight here that the perceptual and neurophysiological nature of the zone of sensory thermo-neutrality between warm and cool sensations is still largely unknown.

While previous report have provided insights on some parameters of thermo-neutrality (e.g. this could vary from a range of starting temperatures, i.e. 15 - 38°C) (Lele 1954), the latter has never been-assessed directly with a specifically designed quantitative test.

Accordingly, there is a need to examine the properties of the sensory thermo-neutral zone, to quantify its width, and assess whether it is fixed or shifts with adaptation to preceding skin temperature. Characterizing the perceptual and neurophysiological nature of sensory thermo-neutral zone could also provide insights into the central integration of peripheral thermal afferents.

The aim of this study was to characterize the properties of the local cutaneous sensory thermo-neutral zone in humans. To this end, we adapted a psychophysical testing procedure used in visual neuroscience to assess dichromatic vision (Hurvich and Jameson 1960), to assess sensory thermo-neutrality on a local representative skin site. Our method is designed to allow a concurrent assessment of the quantitative (i.e. thermo-neutral temperature and range) and qualitative (i.e. whether sensations were experienced as warm or cold) aspects of the thermal stimuli used within the same individual test. It can therefore provide insights not only into the boundaries of thermal detection (i.e. upper and lower temperature limits of the thermo-neutral zone) but also into the quality of the sensation experienced within these boundaries (i.e. absence of prevalence in either cold or warm sensation).

As temperature detection thresholds have been known to change as a function of starting skin temperatures (e.g. cold and warm thresholds become smaller with colder and warmer skin temperatures respectively) (Lele 1954; Kenshalo et al. 1968; Hirosawa et al. 1984), it might be reasonable to hypothesize that the sensory thermo-neutral zone might also similarly shift across the temperature continuum. Accordingly, we evaluated two hypotheses: 1) the zone of sensory thermo-neutrality falls within the inter-threshold range for warm and cold temperature detection; 2) contrary to a current belief, the sensory thermo-neutral zone shifts across the temperature continuum as a function of starting skin temperature, rather than being maintained only within a specific range of steady-state skin temperatures.

METHODS

Participants

A power calculation was performed with an α of 0.05, a β of 0.05, and an effect size f of 2.63 (based on pilot testing) to determine a required sample size of 6 individuals for the current study (G*Power 3 software, Heinrich-Heine-Universität Düsseldorf, Germany). Ten participants, four females (all Caucasians) and six males (3 Caucasians and 3 Asians) (age: 30.3 ± 4.8 y; body mass: 67.8 ± 11.1 Kg; height: 171.0 ± 18.0 cm; body surface area: 1.8 ± 0.2 m^2), volunteered to participate in experiments 1 and 2. All participants were college students and junior researchers without any 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. They were naïve as to the purpose of the experiments and they each gave written informed consent. Two female participants were tested during the follicular phase of their menstrual cycle (i.e. within day 1 to 14) while the other two during the luteal phase of their menstrual cycle (i.e. within day 15 to 28). The latter two participants were also taking oral contraceptives during the study. All testing occurred during February and March 2016. 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. All participants attended a familiarization trial prior to the main experimental sessions.

Experimental design

To determine the properties of the sensory thermo-neutral zone we performed two experiments, the first one involving a traditional approach to temperature detection thresholds, and the second one involving our new method to assess thermo-neutrality.

In Experiment 1, temperature detection thresholds and their shift as a function of different starting skin temperatures (i.e. 26, 31 or 36°C) were determined with a classical staircase method (Rolke et al. 2006b). The resulting inter-threshold range represents a zone of thermal insensitivity[1] where changes in temperature do not give rise to perceptible changes in the on-going thermal sensation (Hensel 1981). In Experiment 2, we characterized the sensory thermo-neutral zone and determined the skin temperature range in which neither warm nor cold sensation prevail. This too was done for the same range of starting skin temperatures. The center of the palm on the glabrous skin of the hand was chosen as the target local skin site for assessment in all testing because of its accessibility and of common use within clinical assessment of temperature thresholds (Walk et al. 2009).

All experiments were performed in an environmental chamber maintained at an ambient temperature of 25 °C and 50% relative humidity. Participants reported to the laboratory on 3 separate occasions at the same time of day. During each of the 3 visits to the laboratory, both temperature detection thresholds (i.e. experiment 1) and thermo-neutral zone (i.e. experiment 2) were assessed. The tests were always carried out in the same order, with a 15 minute seated break period between experiment 1 and 2. The difference between visits consisted in the starting skin temperature (i.e. 26, 31 or 36°C) from which the experiments were performed.

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[1] Hensel used the term 'thermal indifference' for describing this zone (Hensel 1981). Although detecting change is the same as detecting a 'difference', the term 'indifference ' most typically is used to indicate disinterest or unimportance. We therefore use the term 'insensitivity' to describe the zone between detection thresholds.

We chose 26, 31 or 36°C starting skin temperatures as they are in the range of maximal activation of cold (i.e. 26°C) and warm (i.e. 36°C) thermoreceptors, as well as within their overlapping area of activation (i.e. 31°C) (Hensel 1981).

Upon arrival to the laboratory, participants changed into t-shirt, running shorts and trainers and entered the environmental chamber. Five wireless thermistors (iButtons, Maxim) were taped to five skin sites on the right side of the body (i.e., cheek, abdomen, upper arm, lower back, and back lower thigh) to record local skin temperatures. The five temperature measurements were recorded at 1-min intervals throughout the tests, averaged every 5 min, and then weighted according to the work of Houdas and Ring (Houdas and Ring 1982) to give an estimate of mean skin temperature for the entire body. Following instrumentation, participants rested on a chair for 15 min to allow for baseline thermometric data to stabilize. Following the stabilization period, to ensure that pre-testing whole-body and local hand thermal sensation would be within comfortable ranges, thermal sensations and comfort for whole-body and local hand were assessed on an ASHRAE 7-point scale (Olesen and Brager 2004). At this point, the experiments were initiated.

Experiment 1 – Detection thresholds and inter-threshold zone

An electronically controlled thermode with custom written software (see *testing apparatus* section below) was used to deliver thermal stimuli to participants' skin. The probe, mechanically supported, was gently lowered to make light contact with the skin of the participant's left palm, the arm resting comfortably on a table (Fig. 2). Participants were instructed to follow the instructions on the screen visible to them when prompted. The thermode temperature was initially set to one of three starting temperatures, 26, 31 or 36°C, and maintained there throughout the run, except for the 10-sec during which increment or decrement temperature steps were delivered and participants reported their sensation. After several minutes' adaptation, a run was started.

Each run consisted of a 5-s waiting phase (message on screen: "Wait"), during which the probe temperature was set at the specific starting temperature. The participant was instructed to consider the local sensation experienced during this phase as a reference sensation. The 5-s phase was followed by a 4-s warning interval (message on screen: "Get ready") during which the probe temperature was raised or lowered by a fixed step (*see below for details*). At the end of the 4-s warning interval, a signal appeared (message on screen: "Did you feel a change?") and the participant reported on a window tab whether a change in sensation occurred from the one experienced during the waiting phase (message on screen: "Yes / No"). (Note: according to (Hensel 1981) a 4-s interval is sufficient for a temperature pulse to penetrate the skin and reach thermoreceptors' depth). A 6-s interval was available for response. Immediately after the response the probe was returned to the starting temperature and a new run started. In case of a late response, the previous temperature stimulus cycle would be repeated.

The temperature stimuli and the way the probe's temperature raised or lowered during each run was based on a staircase method. First, when a warm threshold had to be determined, an up-step stimulus of 2°C from the starting temperature was delivered; depending on whether the participant detected or not such change, the successive stimulus was either 0.4°C smaller or greater than the first stimulus respectively. Whenever a stimulus was detected, the following one would be 0.4°C smaller (i.e. down-step) until the participant no longer detected a change from the starting temperature. Whenever this occurred, a reversal in the direction of the following stimulus occurred (i.e. 0.4°C up-step), until the participant again detected a change from the starting temperature. A test ended whenever a participant moved between up- and down-steps 0.4°C apart six consecutive times. The mean of six pairs of temperatures at which the subject first sensed and then failed to sense was determined as the participant’s detection threshold for this condition. Figure 3 presents a schematic representation of how the threshold was determined. This process was also followed for cold thresholds differing only in that the first stimulus consisted of a 2°C down-step rather than of an up-step. The size of the inter-threshold zone was calculated individually based on the difference between the relative cold and warm thresholds.

Experiment 2 – Sensory thermo-neutral zone

During experiment 2, the same thermode as in Experiment 1 was gently applied to the palm of the hand and its temperature was initially set to one of three starting temperatures, 26, 31 or 36°C , depending on the testing day.

The Experiment 2 testing procedure randomly delivered one of seven temperature stimuli differing by -3, -2, -1, 0, +1, +2, +3 °C from the starting temperature. Accordingly, stimuli ranged between 23 and 29°C for the 26°C starting temperature, between 28 and 34°C for the 31 °C starting temperature, and between 33 and 39 °C for the 36 °C starting temperature.

After an initial 4-s waiting phase, the first temperature stimulus was delivered; 3 s following delivery the participant was then prompted with a 2-alternative forced choice and had to report on the screen, if necessary by guessing, whether the stimulus was perceived as “warm” or “cold”.

Once the participant reported the sensation, the probe temperature returned to the starting temperature, and a 4-s waiting phase initiated, after which a new temperature stimulus was delivered. Each of the seven temperature stimuli was randomly presented 15 times during each test, cumulating a total of 105 stimuli presentations for each starting temperature. Figure 4 presents a schematic representation of how a test was performed.

This 2-alternative forced choice paradigm used a binary scoring system, with a “cold” response designated as *0* and a “warm” response as *1.* 105 stimulus presentations constituted a test, after which the best-fitting Gaussian ogive relating the average score s $(0>s>1.0)$ to the stimulus temperature was determined for each participant under each starting condition. Determination of individual best-fitting Gaussian ogives allowed the calculation of the temperature range corresponding to sensory thermo-neutrality. Figure 5 presents a schematic representation of how this range was determined. The temperature value on the 50th percentile on the ogive corresponds to the point of subjective equality between *cold* and *warm* responses. It was therefore considered to be the neutral temperature, at which neither a cold nor a warm sensation prevails. The temperature value on the 25th percentile on the ogive corresponds to the point of subjective equality between *cold* responses and neutrality. It was considered the lower bound of the neutral zone, below which a cold sensation begins to prevail over a neutral one. The temperature value on the 75th percentile on the ogive corresponds to the point of subjective equality between *warm* responses and neutrality. It was considered the upper bound of the neutral zone, above which a warm sensation begins to prevail over a neutral one. Finally, the temperature range between 25th and 75th percentiles on the ogive corresponds to the width of the sensory thermo-neutral zone for each participant at that specific starting temperature, representing the temperature range within which neither cold nor warm sensations prevailed over the neutral.

Testing apparatus

A thermosensory analyzer was used (NTA-2, Physitemp, USA), consisting of a control unit connected to a 1.32 cm^2 circular thermal probe (thermode). The probe's contact surface could be set to a precision of 0.1°C within the operating range 15-42°C, and was under computer control. Temperature stimuli were delivered at a rate of temperature change of 2.43°C/s. Compliance was measured by independently monitoring the skin temperature beneath the probe with a calibrated thermocouple.

The delivery of the testing paradigms used in the experiments was fully automated via two custom-written python scripts, which also allowed the on-line visualization and recording of testing results. During both experiments, recorded temperatures corresponding to thresholds and neutral zone were that of the thermode, as acquired via the computer interface. It is understood that transmission, diffusion and transduction effects would make the intra-cutaneous receptor stimuli differ in unknown ways depending on their depth and areal density, but this study follows a Brindley Class A psychophysical experiment in addressing the outer arc between temperatures delivered to the skin surface and subject responses (Brindley 1970).

Statistical analysis

All data are reported as mean ± standard deviation (SD) and 95% confidence intervals (CI) unless otherwise stated. Temperature detection thresholds and values for the width of the inter-threshold range were analyzed using a two-way repeated measures ANOVA with the independent factor of starting skin temperature (3 levels: 26, 31, 36°C) and modality (2 levels: cold, warm); and a one-way repeated measures ANOVA with the independent factor of starting skin temperature (3 levels: 26, 31, 36°C). Neutral temperatures and values for the width of the thermo-neutral zone were both analyzed using a one-way repeated measures ANOVA with the independent factor of starting temperature (3 levels: 26, 31, 36°C). To assess whether the neutral temperature would be a function of the starting skin temperature, we assessed the relationship between these two variables by means of correlation and linear regression analysis. Finally, mean skin temperature values recorded during each test and values for whole-body thermal sensation and comfort were analyzed separately using a one-way repeated measures ANOVA with the independent factor of starting temperature (3 levels: 26, 31, 36°C). A Greenhouse-Geisser correction was applied if the assumption of sphericity was violated. In the event of a significant main effect, post-hoc analysis was performed using Tukey's range test for multiple comparisons. Statistical analysis was performed using GraphPad Prism (version 6.0, GraphPad Software, La Jolla, CA).

RESULTS

Data Exclusion

Though the majority of our participants produced concordant results, there were two exceptions. During Experiment 1, two participants did not detect temperature changes within the entire non-noxious range (between ~15 and ~42°C). Accordingly, detection threshold data are based on eight participants. Similarly, during Experiment 2, one participant reported the sensation of "warm" for all temperature stimuli at 26°C, and another "cold" for all stimuli at 26°C. These individuals' responses under all other conditions and in Experiment 1 were not exceptional. Accordingly, data from these two subjects were excluded from the ogive ensemble average, which is therefore also based on eight participants.

Experiment 1 – Detection thresholds and inter-threshold range

As can be observed in figure 6A, thermal detection thresholds were found to be asymmetrical, with warm thresholds being generally greater than cold ones ($F_{(1, 7)}$=23.79; p=0.002). For example, at the 31°C starting skin temperature, the warm threshold corresponds to +2.07 ± 1.33 °C while the cold threshold to -0.40 ± 0.30 °C. It was also found that thresholds changed significantly depending on the starting skin temperature ($F_{(2, 14)}$=8.513; p=0.004) (Fig. 6A). For example, at the 36°C starting skin temperature, the warm threshold is significantly smaller (mean difference: -1.62 °C; 95% CI -3.02 to -0.22°C; p=0.021), while the cold threshold is significantly larger (mean difference: +1.40 °C; 95% CI +2.80 to +0.004°C; p=0.050) than the values recorded at the 31°C starting skin temperature. Overall, these results indicate that at higher starting skin temperatures, participants exhibited a greater sensitivity to warmth and a lower sensitivity to cold. While detection thresholds changed depending on the starting skin temperature, the width of the inter-threshold range remained constant ($F_{(1.474, 10.32)}$ = 0.04; p=0.91), with average values of 2.36 (±2.63), 2.47 (±1.35) and 2.25 °C (±1.06) at 26, 31 and 36°C starting skin temperatures respectively (Fig. 6B).

Experiment 2 – Sensory thermo-neutral zone

Figure 7 shows Gaussian ogives fitting results from a typical participant performing the test at the 26, 31 and 36°C starting skin temperatures.

Overall, neutral temperatures were found to change significantly depending on the starting skin temperature ($F_{(1.366, 9.564)}$=85.43; p<0.001), with average values being 27.46 (±1.54), 31.07 (±0.77) and 34.92°C (±0.80) at 26, 31 and 36°C starting skin temperatures respectively. As seen in Figure 8A, neutral temperatures are significantly associated with the starting skin temperatures (Pearson r= 0.94; p<0.001), the latter factor explaining 89% of the variability in the neutral temperatures. While neutral temperatures change depending on the starting skin temperature, the width of the thermo-neutral zone remains constant ($F_{(1.55, 10.85)}=0.6226$; $p=0.515$), with average values of 1.27 (±1.13), 0.98 (±1.11) and 1.33 °C (±0.70) at 26, 31 and 26°C starting skin temperatures respectively (Fig. 8B).

Mean skin temperature and whole-body thermal sensation and comfort

Mean skin temperature values did not differ ($F_{(1.502, 9.013)}=0.3016$; $p=0.686$) across all experiments and conditions, being on average 34.15 ± 0.58, 33.97 ± 0.74 and 34.20 ± 0.65°C at 26, 31 and 36°C starting skin temperature respectively. Similarly, whole-body thermal sensation ($F_{(1.747, 15.72)}=1.982$; $p=0.173$) and comfort ($F_{(1.966, 17.69)}=3.047$; $p=0.0737$) did not differ across all experiments and conditions, being on average in the range of 'neutral' to 'slightly warm' and of 'just comfortable' to 'comfortable' respectively.

DISCUSSION

Figure 9 summarizes the primary findings of these experiments: the palm's average warm and cold detection thresholds and related inter-threshold range, as well as the neutral temperatures and widths of the thermo-neutral zone as functions of the three starting skin temperatures assessed. It is seen that the human sensory thermo-neutral zone is quite narrow (i.e. ~0.98 to ~1.33 °C), that over a considerable span of skin temperatures (between 27.5 and 34.9 °C) it moves along with the starting skin temperature while maintaining a relatively constant width, and that it is contained within the thermally insensitive zone between the cool and warm detection thresholds. Both the sensory thermo-neutral zone and the inter-threshold range depend on the starting skin temperature; but they do not coincide. The latter is almost twice as wide

(~2.25 to ~2.47°C versus ~0.98 to ~1.33°C) and has different offsets on the warm side versus the cold side.

Altogether, our results indicate that sensory thermo-neutrality is not constrained to a specific skin temperature range (i.e. 32-34°C) as previously thought and that, at least at a local level, can be shifted well outside this range. The observed shift in sensory thermo-neutrality across a skin temperature range of 27.5 and 34.9 °C is likely the result of some form of sensory and neurophysiological adaptation.

Adaptive sensory thermo-neutrality: psychophysical substrates

Comparing the results of the traditional staircase method used for determining detection thresholds against results from our new thermo-neutral zone method highlights the difference between qualitative and quantitative aspects of thermal sensation. The dissociation between the *quantitative* (i.e. temperature detection threshold) and *qualitative* (whether a sensation is cool or warm) aspects of thermal sensation was first described by Kenshalo et al. (Kenshalo et al. 1961). This distinction is important in the understanding of thermoneutrality. For example, the observation that a drop of almost 2°C in skin temperature is required to trigger a change in sensation in skin adapted to 36°C (see Fig. 6A) does not necessarily imply that temperatures within the 36 to 34.2°C range are not perceived as warm. It could be that the ongoing sensation at 36°C is that of warmth and that there is a ~2°C range of thermal insensitivity to either warm or cool temperature changes. The changes to skin temperature in detection threshold tests could be perceived by the subject as diminishing (e.g. "less warm") or increasing (i.e. "progressively colder") the existing sensation, or perceived as a switch to the opposite sensation.

Hence, the staircase method discovers a zone of thermal insensitivity (in which temperature might change without conscious detection) that is not synonymous with sensory neutrality as discovered by our new test procedure.

It is important to note that the difference observed between thermal insensitivity and neutrality is larger on the warm side of the temperature spectrum; the lower end of the thermo-neutral zone is closer to the cold detection threshold (see Fig. 9). The larger difference between the warm detection threshold and the upper margin of the thermo-neutral zone may be evidence of a greater temperature change needed to trigger a clear change in sensation (i.e. an unmistakable warm sensation) than the change needed to induce a loss of thermal neutrality. Cutaneous warm sensitivity appears to be lower than cold sensitivity due to lower density of warm-sensitive skin afferents (Filingeri 2016) and in their neurophysiological properties (e.g. warm thermoreceptors have significantly lower conduction velocities than cold thermoreceptors) (Darian-Smith 1973; Darian-Smith et al. 1979). Differences in depth of warm and cold receptors could also be a likely factor.

Adaptive sensory thermo-neutrality: neural substrates

In mammalian models, physiological recording of the afferent neurons has revealed rather invariant and overlapping impulse rates in cold- and warm-sensitive cutaneous thermoreceptors at steady state skin temperatures in the range of 32 to 35^{o}C (Hensel 1973; Darian-Smith 1984). This observation has contributed to the concept that simultaneous afferent firing represents the neural substrate of sensory thermal neutrality (Hensel 1973, 1981). Accordingly, it would be reasonable to hypothesize that, as long as there is balance in firing rates between cold and warm thermoreceptors, thermo-neutrality might be experienced outside the 32 to 35°C skin temperature range.

It is known that at temperatures below the range of 30 to 34 °C, cold thermoreceptors show an increase in steady-state discharge frequency, while warm thermoreceptors become progressively silent; similar responses (however in the opposite direction) occur at temperatures above the range of 30 to 34 °C (Hensel and Kenshalo 1969; Hensel and Iggo 1971; Johnson 1973). Such changes in the balance between warm and cold receptors would indicate that if neutrality were the result of a balanced neural activity, the same would not be achievable at temperatures above or below 30–34 °C, unless some mechanism changed the reciprocal activity in warm and cold thermoreceptors.

In this respect, an important feature of thermal integration in cutaneous first-order thermo-sensory neurons is adaptation, a phenomenon with both short- (Darian-Smith 1984) and long-term components (Kozyreva 2006). Cutaneous thermoreceptors are sensitive to dynamic changes in temperature, and undergo a decrease over time in their discharge frequency at a maintained steady state skin temperature (Darian-Smith 1984). This underlies the progressive decrease in the magnitude of an on-going thermal sensation following initial exposure to a thermal stimulus (Kenshalo and Scott 1966).

It could be speculated that the ongoing discharge of cold or warm thermoreceptors adapted to temperatures outside the overlapping range of steady state firing (30–34 °C skin temperature) would diminish within seconds from the initial change in skin temperature. The initial thermal sensation (e.g. coldness) experienced outside the 30–34 °C range would be reduced in its magnitude (i.e. less cold) to an extent proportional to the reduction in (e.g. cold) thermoreceptors' firing rate.

It could be argued that such a reduction in firing rate in the primarily active class of thermoreceptors (e.g. cold) would still be not enough to re-establish neural balance (hence sensory neutrality) between both classes of thermoreceptors. The results of this study tend to confirm this argument. When starting at temperatures of 26 or 36°C, thermo-neutrality did not occur exactly at 26 or 36°C, but at skin temperatures slightly above and below these values (see Fig. 9). The presence of these temperature differences supports the possibility that at those skin temperatures experienced as neutral, neural balance between warm and cold receptors could have been occurring.

Let us take the example of the 26°C starting temperature. Under these conditions, the initial increase in firing rate in cold receptors (along with the silencing of warm receptors) would have likely been reduced (along with the initial cold sensation) after adaption had occurred (e.g. seconds after the initial exposure). At this point, a slight increase in skin temperature (as the one required to reach the neutral temperature recorded here) would have further suppressed the already low on-going firing in the cold receptors, making the balance in activity between the nearly silent warm receptors, and the minimally active cold receptors, almost “neutral”. From a sensory point of view, the warming-induced reduction in the on-going cold sensation would have likely passed through a “neutral state” before being experienced as a clearly detectable warm sensation. This is in line with previous psychophysical findings which have shown that at adapting skin temperatures outside the thermoregulatory neutral range (i.e. <30-34°C<), sudden changes in skin temperature are initially perceived as reducing the initial persisting thermal sensation (e.g. stimulus perceived as less cold), before inducing new thermal sensations (e.g. warm sensation) aligned to the direction of the temperature change (e.g. increase in temperature) (Kenshalo et al. 1961). In this particular case, changes in skin temperature from adapting values outside the 30-34°C range would initially reduce activity in cold fibers before reaching the level of maximal activation of warm receptors. This, along with the fact that warm sensitive fibers have a lower peak frequency response and lower cumulative impulses to sudden temperature changes when adapted to temperatures below the thermo-neutral range (Darian-Smith et al. 1979), could explain why at skin temperatures outside the 30 – 34 °C range, sudden changes in skin temperature are not immediately experienced as the sensation expected for the resulting direction of temperature change, but are instead experienced as a reduction in the intensity of the opposite thermal sensation.

Altogether, the evidence presented above would support the contention that the lack of a prevailing warm or cold sensation experienced outside the range of steady-state skin temperatures (i.e. ~30 to ~34°C) traditionally considered to provide thermosensory neutrality (Gagge et al. 1967) has a neural substrate of balanced activity between cold and warm sensitive thermoreceptors, once these have adapted to cooler or warmer skin temperatures. It would also appear that whether the current thermal experience itself is characterized as warm, cold, or thermally neutral will depend on how the difference in the maintained discharge rates from the periphery are preserved or modulated as they are handed on to higher neural centers in the spinal cord, brain stem and cortical regions (Filingeri et al. 2017).

Finally, mention should be made that we encountered, even among only 10 not obviously unsuitable participants, two who responded quite differently from the others, and not just by magnitudes that might be thought to be still within a range of normal scatter. In view of the ion-channel molecule receptor basis of thermosensation (Vriens et al. 2014), for which genetic variation is to be expected, and in accord with the now widely-understood molecular genetic basis of color vision and its deficiencies, we expect that the application of the methods described here will be useful for probing individual differences in thermal sensitivity in both health and neurological disease, as well as possible psychophysical and behavioral correlates of molecular heterogeneity.

Other body sites

A potential limitation of this study is that experiments were conducted on one local representative skin site. To address this, our group used these same methods to obtain preliminary results on another skin site (volar surface of the forearm) in 5 participants (Fig. 10). It can be observed that the forearm results closely match those for the palm (compare figures 9 and 10). The forearm thermo-neutral zone is also contained within the inter-threshold range, and both zones shift with the starting skin temperature. Despite the low sample size, such patterns are already statistically significant. Interestingly, the width of the inter-threshold and thermo-neutral zones is wider in the forearm than in the palm. This observation could indicate lower thermal sensitivity in the forearm as compared to the palm. Overall, it would therefore appear that similar mechanisms of sensory thermo-neutrality could be occurring across different skin regions and that the methods tested here could be also used to characterize regional differences in these sensory processes.

Further studies will also be necessary to assess whether the width of the sensory thermo-neutral zone changes with the size of the skin region affected. Recent evidence indicates that the whole-body skin temperature range for perceptual comfort (and possibly also for neutrality) might not coincide with the classic thermoregulatory thermo-neutral zone (Kingma et al. 2014). As spatial summation has been shown to play a significant role in afferent thermal integration (Stevens et al. 1974), it is anticipated that if the entire skin surface of the body is considered as the ‘target area’, the dynamic neutral range observed here will have altered width and positioning on the temperature spectrum.

PERSPECTIVES

From a fundamental perspective, determining the characteristics of the sensory thermos-neutral zone is essential to understanding whether and how the balance in activity between cold- and warm-sensitive afferents influences thermal sensations, whether shifts in this balance alter output sensations, and whether central modulation of peripheral afferents occurs (Filingeri et al. 2017). Clinically, this zone could be used as an objective index of neural balance in cold and warm afferents integration, much as the ON-OFF balance in the visual processing of blackness and whiteness represents for visual integration (Westheimer 2007). Such a quantitative approach could be useful in evaluating somatosensory abnormalities in neurological patients (e.g. Multiple Sclerosis, Parkinson's Disease).

From an applied perspective, characterizing the sensory thermo-neutral zone is important in the field of indoor thermal comfort (Kingma et al. 2014). First, traditional thermo-physiological modeling is based on neutral set-points whose typically fixed values strongly influence predicted outcomes. Second, in the effort to reduce building energy consumption and its impact on climate change (Kingma and van Marken Lichtenbelt 2015), there is major benefit in harnessing occupants' ability to adapt to the environment (de Dear and Brager 1998; Hoyt et al. 2015). One adaptive opportunity is in 'personal comfort systems' that directly heat/cool parts of occupants, such as heated/cooled chairs (Pasut et al. 2015) and local devices that condition hand, foot, and face (Zhang et al. 2015). Such systems aim at providing thermal neutrality and comfort within environments that are cooler or warmer than the traditional range of comfortable indoor temperatures. Understanding sensory thermo-neutrality in such complex thermal environments is key to designing energy-efficient approaches to indoor thermal comfort.

CONCLUSION

For the first time to our knowledge, we have provided a quantitative mapping of the human sensory thermo-neutral zone and shown that, at least at a local level, this does not lie only within a specific range of steady-state skin temperatures, but that it shifts across the temperature continuum as a function of the starting skin temperature, while maintaining a relatively constant width. These findings highlight a hitherto unexamined feature of human thermoreception, that thermo-sensory neutrality is an adaptive phenomenon.

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FIGURE CAPTIONS

Figure 1. A schematic representation of the coincidence of the temperature ranges for sensory thermo-neutrality and for thermoreceptors' firing balance within the 30 to 34°C temperature-dependent activity in peripheral cold- and warm-sensitive thermoreceptors and related cold, warm and neutral zones.

Figure 2. Experimental set up. The 1.32 cm^2 round thermal probe (red circle) is held in light contact with the participant's left palm, the arm resting comfortably on a table. The participant is prompted by a signal on a computer screen and reports the response by activating a mouse button.

Figure 3. Determination of individual warm (A) and cold (B) temperature detection thresholds with the staircase method. This schematic representation shows data from a representative participant. To determine a threshold, the probe's temperature raised or lowered during each run as following. First, an up-step (if determining a warm threshold) or a down-step (if determining a cold threshold) stimulus of 2°C from the starting temperature was delivered; depending on whether the participant detected or not such change, the successive stimulus was either 0.4 °C smaller or greater than the first stimulus respectively. Whenever a stimulus was detected, the following one would be 0.4 °C smaller (i.e. down-step) until the participant no longer detected a change from the starting temperature. Whenever this occurred, a reversal in the direction of the following stimulus occurred (i.e. 0.4 °C up-step), until the participant detected again a change from the starting temperature. A test ended whenever a participant moved between up- and down-steps 0.4 °C apart for six consecutive times. Accordingly, tests presented variable duration (as it can be observed in the figure when comparing panel A and B) depending on participants' performance. The mean of six pairs of temperatures at which the subject first sensed and then failed to sense was determined as the participant's detection threshold. Warm and cold thresholds

where assessed separately and the inter-threshold range was calculated based on the sum of the relative cold and warm thresholds.

Figure 4. The testing procedure used during Experiment 2. This consisted in randomly delivering one of seven temperature stimuli differing by -3, -2, -1, 0, +1, +2, +3 °C from either 26, 31 or 36°C starting temperature. Each of the seven temperature stimuli was randomly presented 15 times during each test, cumulating a total of 105 stimuli presentations for each starting temperature. Whenever a temperature stimulus was delivered, the participant was then prompted with a 2-alternative forced choice and had to report on the screen, if necessary by guessing, whether the stimulus was perceived as "warm" or "cold". Once the participant reported the sensation, the probe temperature returned to the starting temperature, and a 4-s waiting phase initiated, after which a new temperature stimulus was delivered.

Figure 5. Determination of individual temperature range corresponding to sensory thermo-neutrality. This schematic representation shows a hypothetical Gaussian ogive resulting from 105 scores (i.e. warm or cold) resulting from exposure to 7 temperature stimuli in the 28-34 °C range. The 50th percentile on the ogive corresponds to the point of subjective equality between cold and warm responses and it is therefore considered as the neutral temperature. The temperature values on the 25th and 75th percentiles on the ogive corresponded to the points of subjective equality between cold and neutral and between warm and neutral responses respectively, and are therefore considered as the lower and upper bounds of the thermo-neutral zone. Accordingly, the temperature range between 25th and 75th percentiles on the ogive corresponds to the width of the sensory thermo-neutral zone.

Figure 6. Detection thresholds and inter-threshold range. Panel A shows relative mean (n= 8) and 95% CI values for changes in skin temperature required to induce a detectable warm and

cold sensation at different starting skin temperatures (T_{sk}) (note: mean absolute detection thresholds for each starting T_{sk} are shown parenthetically). Panel B shows individual and mean (n= 8) and 95% CI values for inter-threshold ranges at different starting skin temperatures. * denotes $p<0.05$.

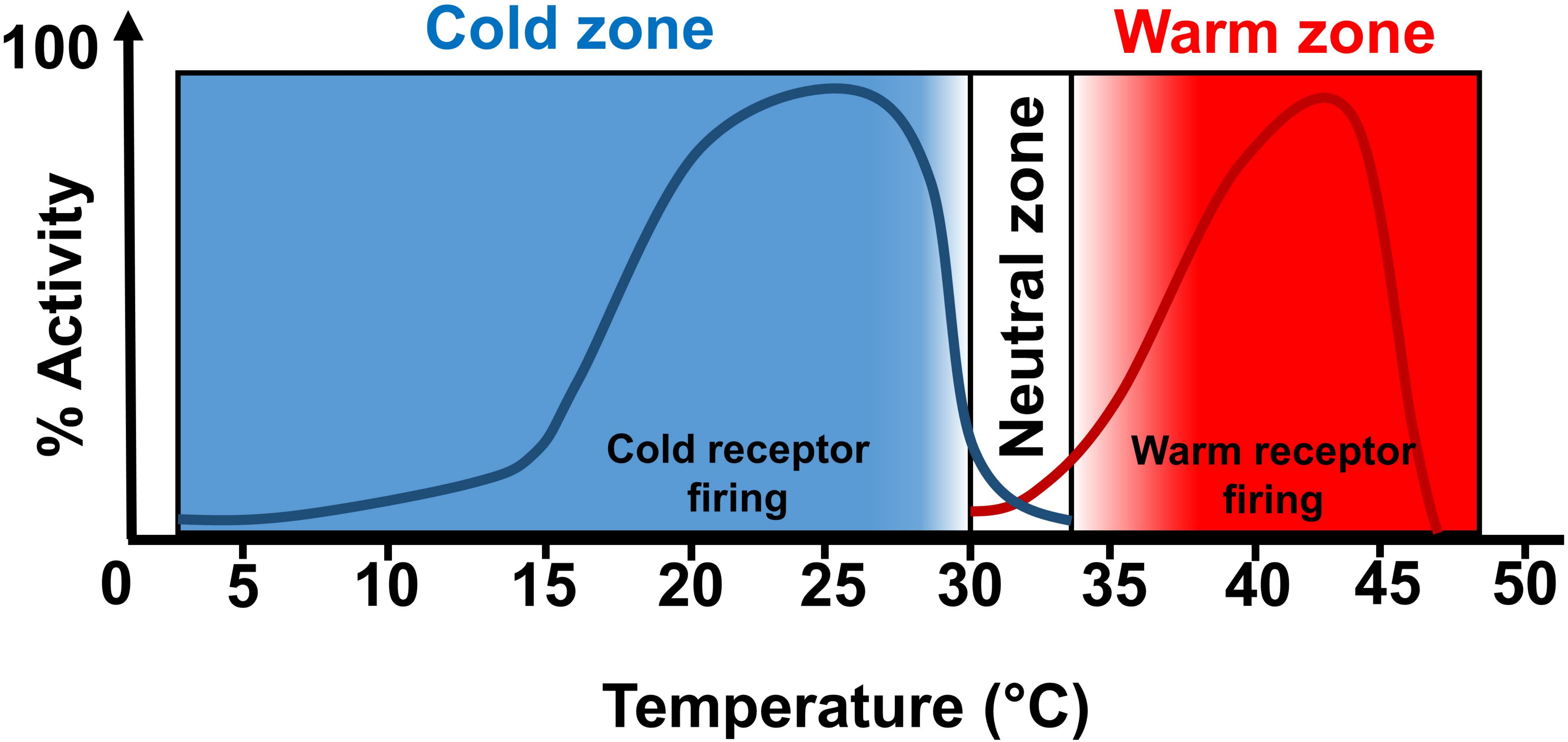
Figure 7. Frequency of thermal responses as a function of starting skin temperature (26, 31 and 36°C) for a typical participant. Seven stimuli were applied with probe temperature steps randomly selected to differ -3, -2, -1, 0, +1, +2 or +3°C from the starting skin temperatures (indicated by the vertical dashed lines). A cold response is scored 0, a warm response 1, and a Gaussian ogive fitted to the seven points. It yields a mean value, the temperature of which score is 0.5 and hence midway between the temperatures at which 25% of stimuli would be sensed as cooler and the temperature at which 25% as warmer. The mean represents measure of the thermo-neutral temperature (indicated by the horizontal dashed line originating at y=0.5) while the 25th and 75th percentile represent upper and lower limits of the thermo-neutral zone (indicated by the horizontal dashed lines originating at y= 0.25; 0.75). Separate experimental runs were carried out at base skin temperature of 26, 31 and 36°C. Each curve is based on 105 stimuli presentations in random order.

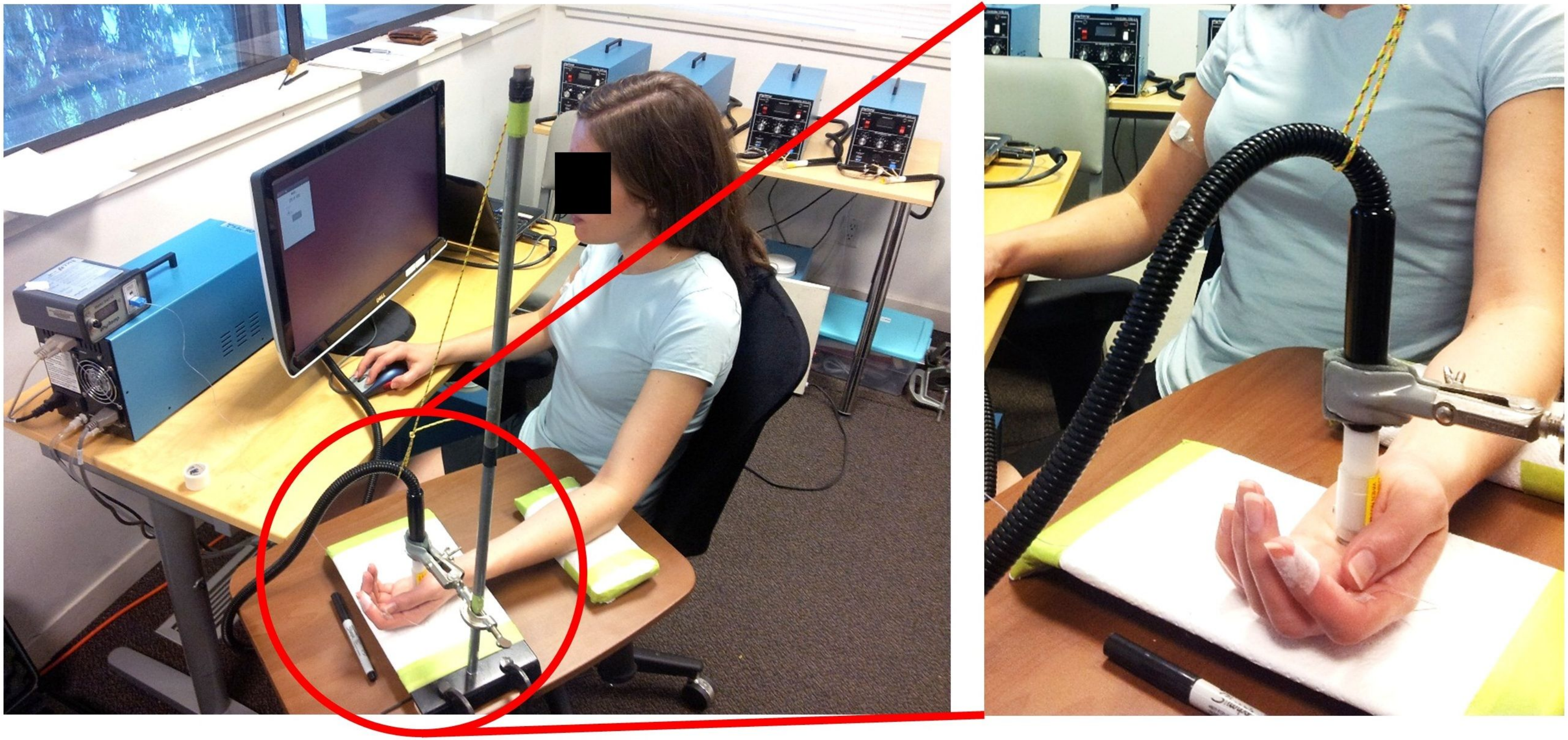
Figure 8. Neutral temperature and thermo-neutral zone. Panel A shows individual data (n=8) for calculated neutral temperatures as a function of different starting skin temperatures (T_{sk}). Regression line with 95% CI band is pictured. Panel B shows individual, mean (n= 8) and 95% CI values for the width of the thermo-neutral zone at different starting skin temperatures.

Figure 9. Palm's inter-threshold and thermo-neutral zones. Mean values (n=8) for warm and cold detection thresholds and related inter-threshold range, as well as neutral temperatures and width of the thermo-neutral zone, as a function the three starting skin temperatures (T_{sk}) assessed,

are pictured. CI intervals are given in Figure 4 for temperature thresholds and in Figure 6 for the thermo-neutral zone.

Figure 10. Forearm's inter-threshold and thermo-neutral zones. Mean values (n=5) for warm and cold detection thresholds and related inter-threshold range, as well as neutral temperatures and width of the thermo-neutral zone, as a function the three starting skin temperatures (T_{sk}) assessed, are pictured.


Cold zone
Warm zone
100
% Activity
Neutral zone
Cold receptor firing
Warm receptor firing
0
5
10
15
20
25
30
35
40
45
50
Temperature (°C)



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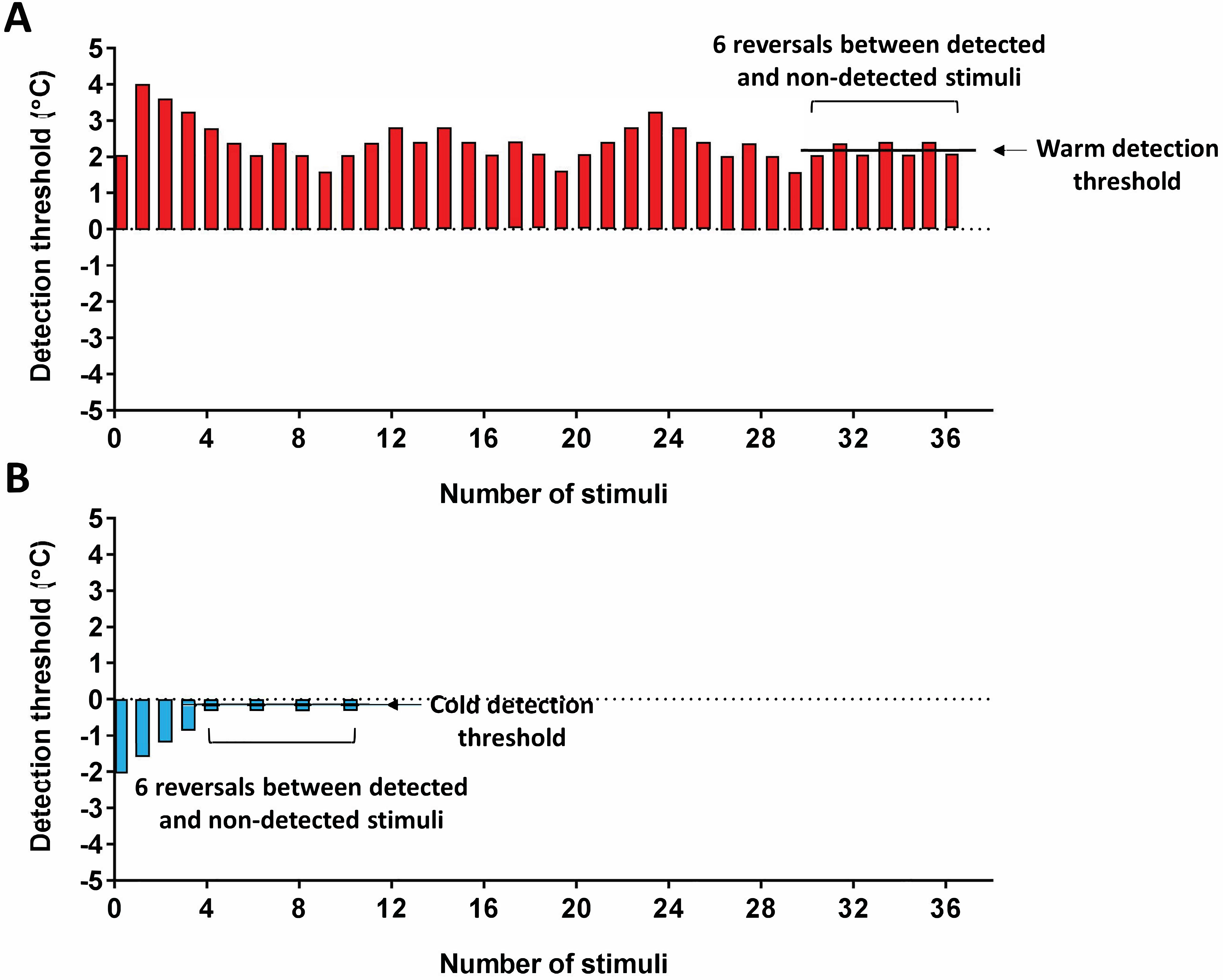
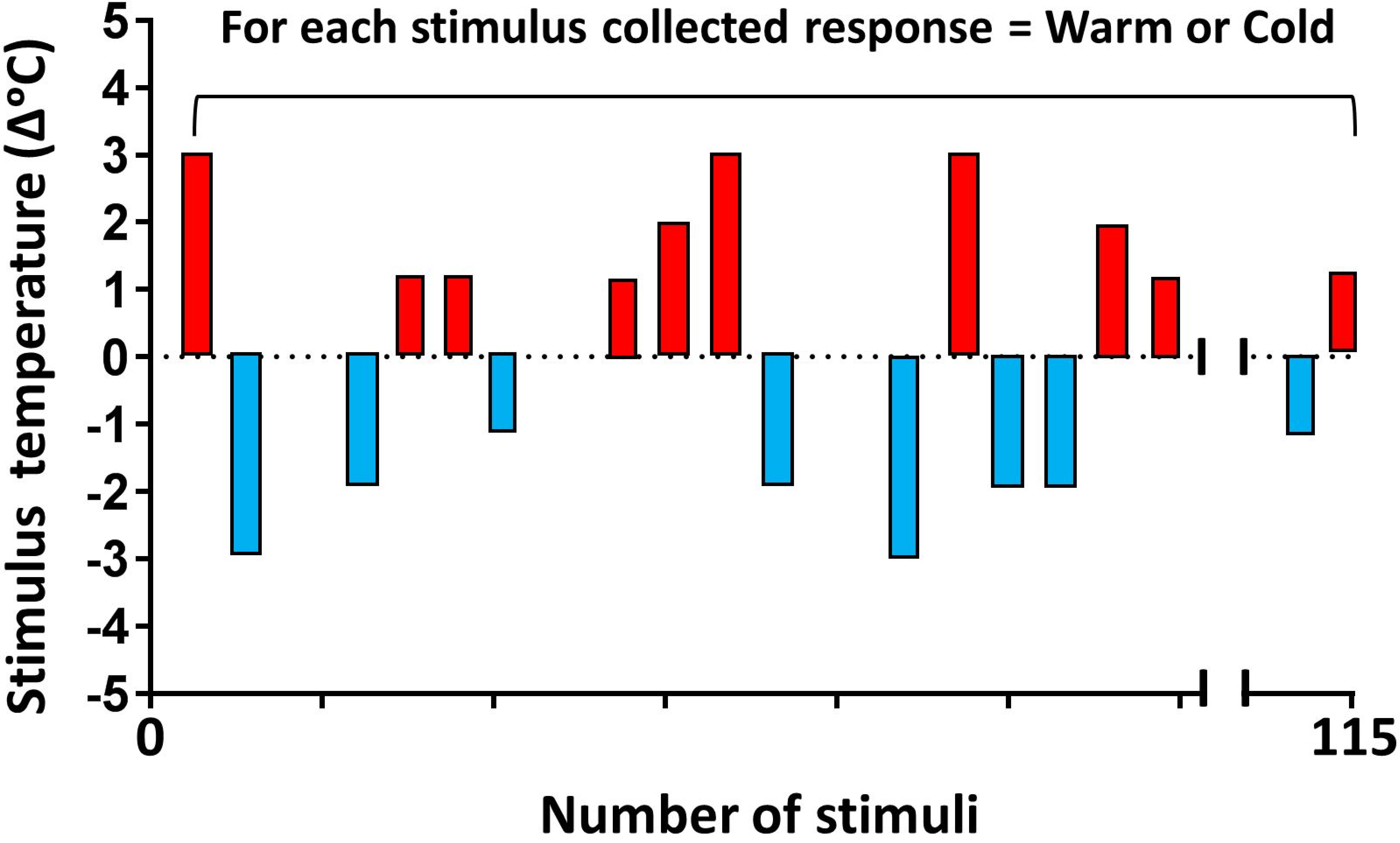
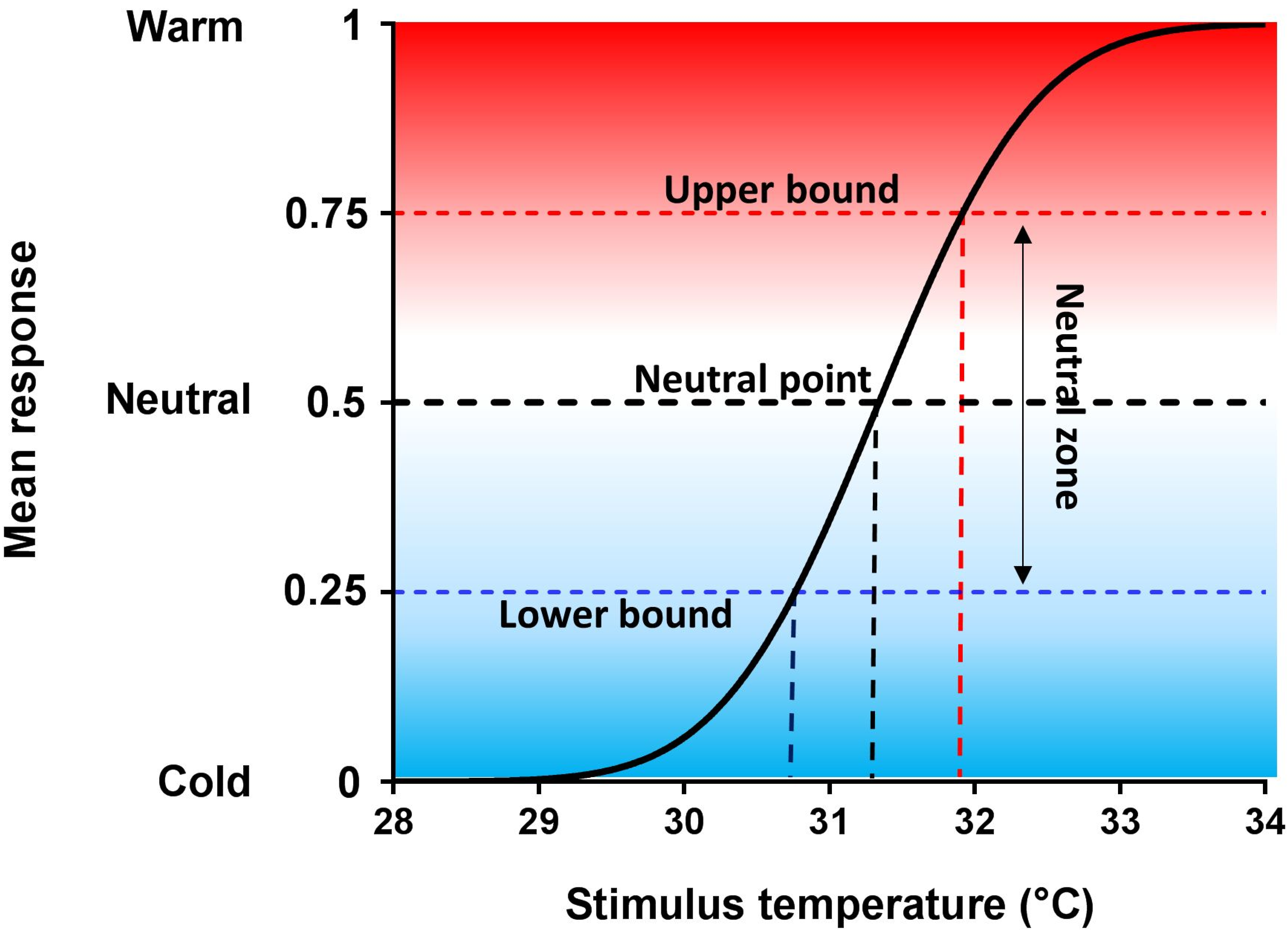
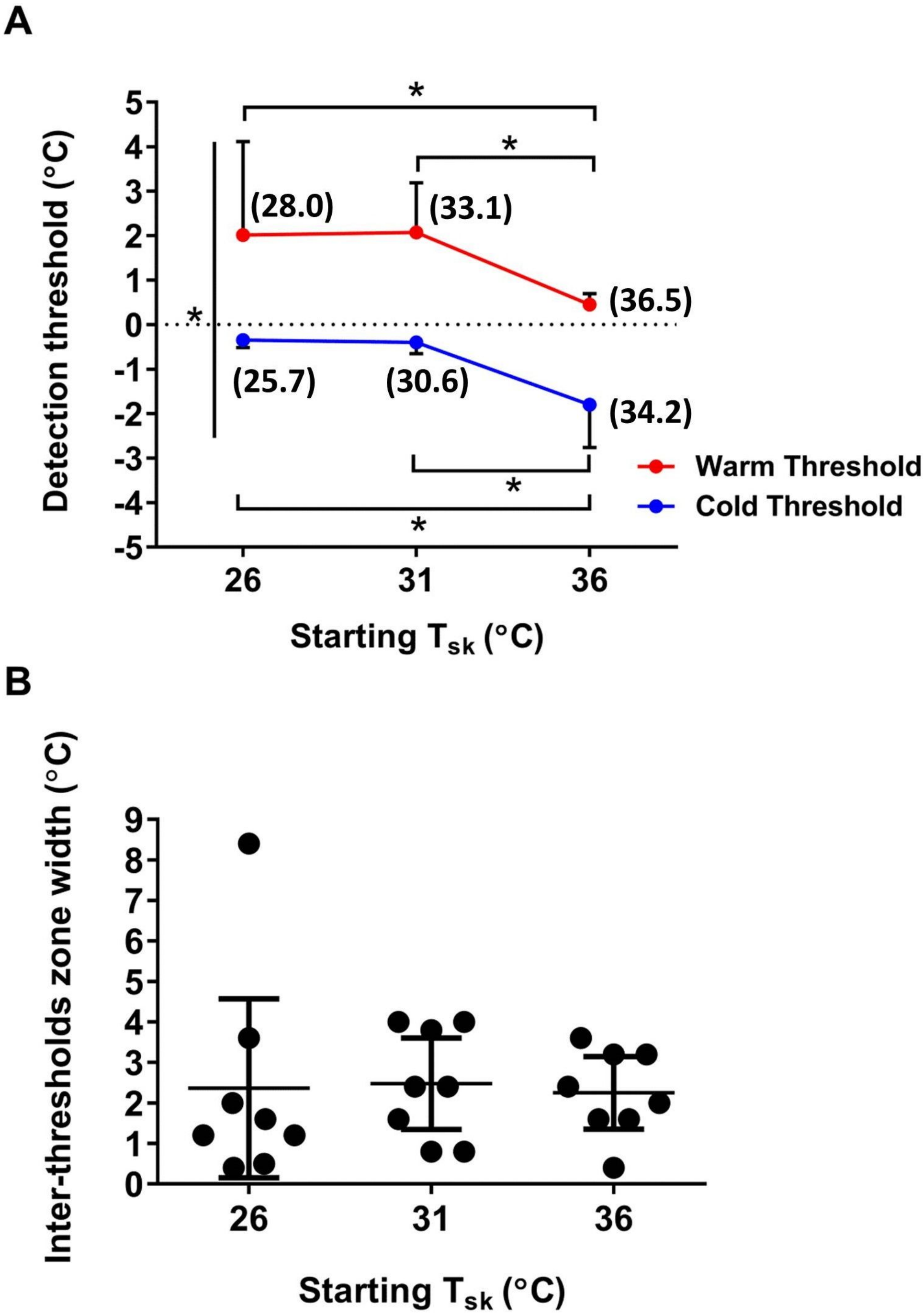
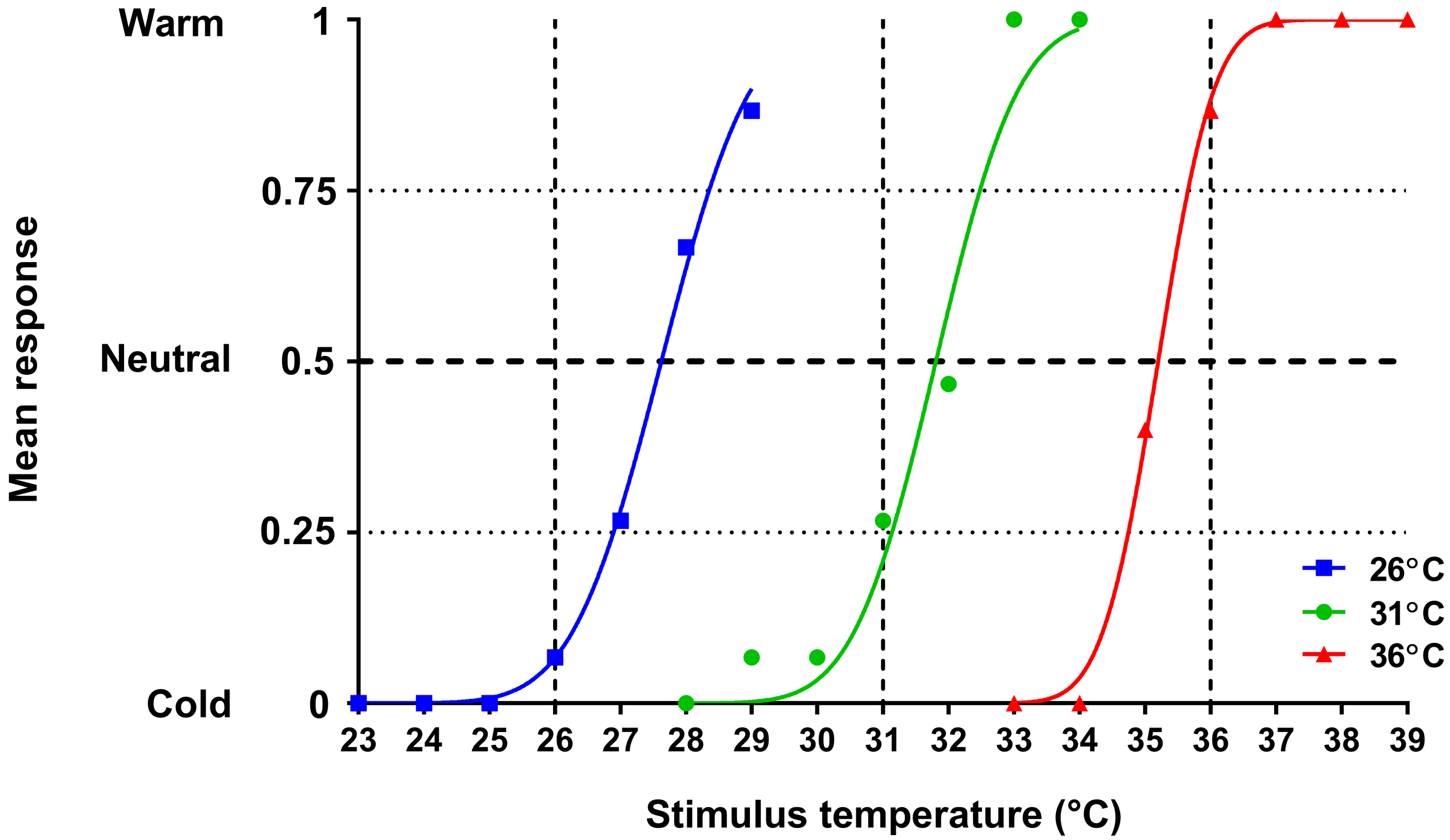
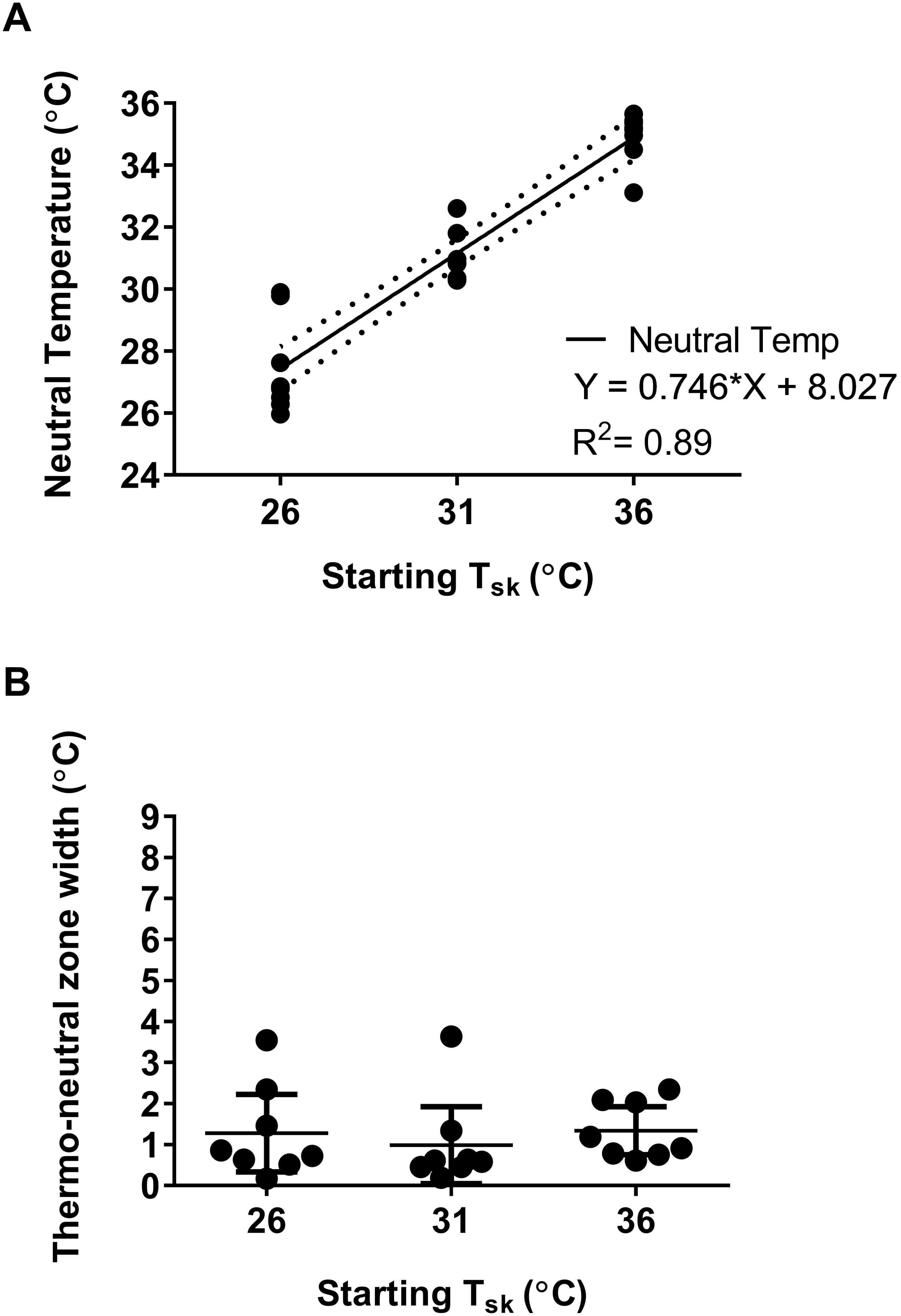

A
Detection threshold (°C)
5
4
3
2
1
0
-1
-2
-3
-4
-5
0
4
8
12
16
20
24
28
32
36
Number of stimuli
6 reversals between detected and non-detected stimuli
Warm detection threshold
B
Detection threshold (°C)
5
4
3
2
1
0
-1
-2
-3
-4
-5
0
4
8
12
16
20
24
28
32
36
Number of stimuli
Cold detection threshold
6 reversals between detected and non-detected stimuli

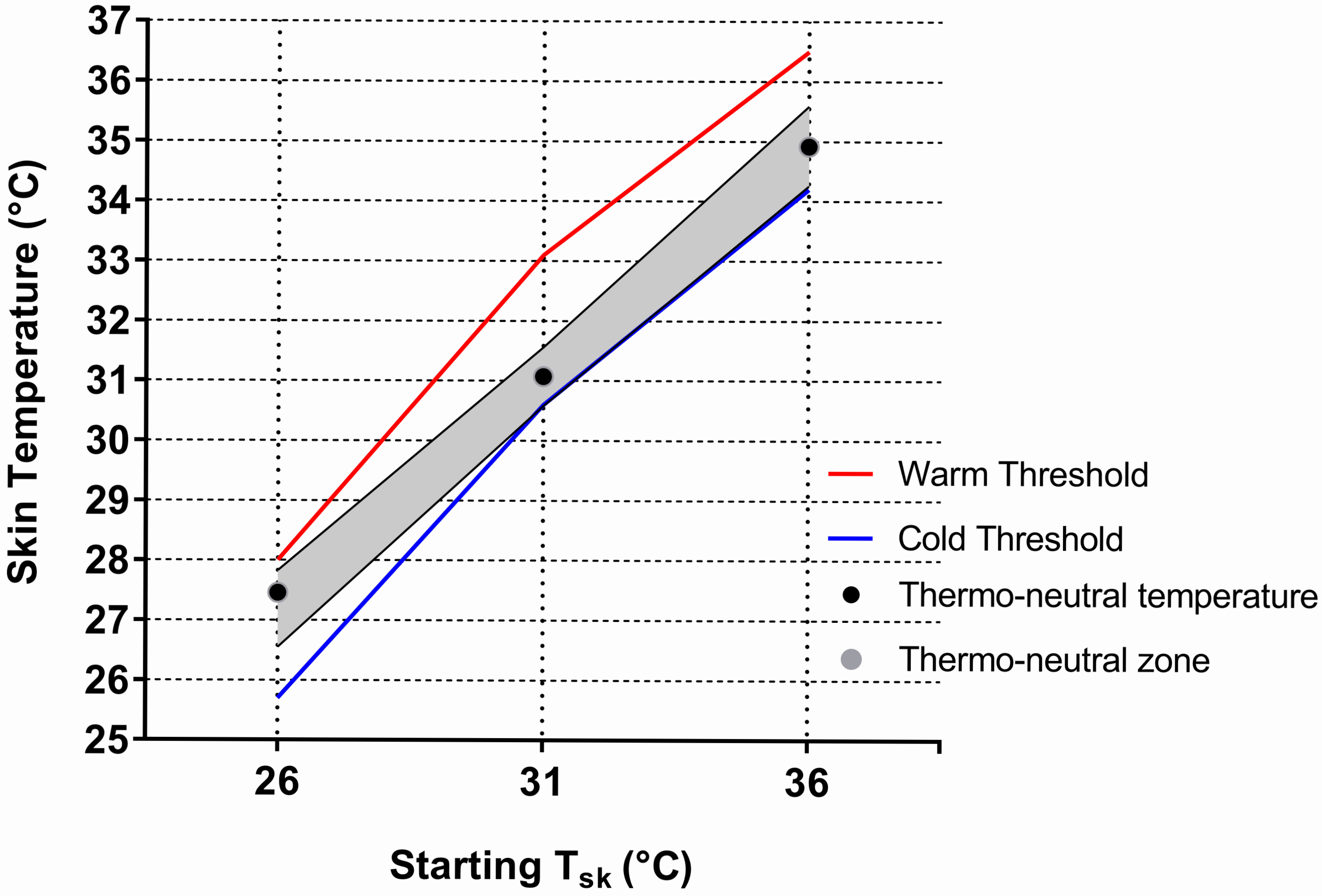

For each stimulus collected response = Warm or Cold
Stimulus temperature (Δ°C)
5
4
3
2
1
0
-1
-2
-3
-4
-5
0
115
Number of stimuli

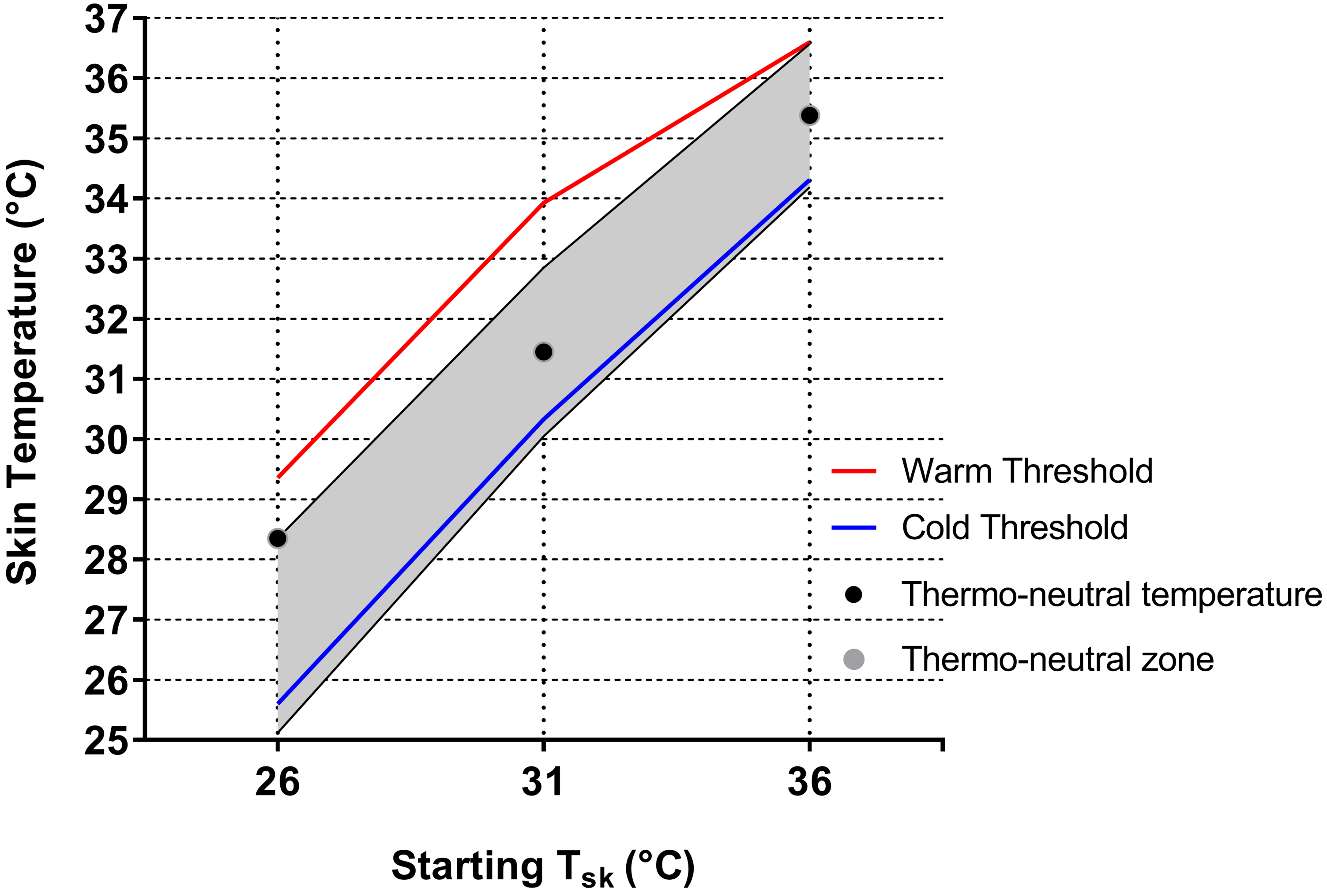

Warm
1
0.75
Upper bound
Neutral zone
Mean response
Neutral
0.5
Neutral point
0.25
Lower bound
Cold
0
28
29
30
31
32
33
34
Stimulus temperature (°C)


A
Detection threshold (°C)
5
4
3
2
1
0
-1
-2
-3
-4
-5
*
*
*
*
*
(28.0)
(33.1)
(36.5)
(25.7)
(30.6)
(34.2)
Warm Threshold
Cold Threshold
26
31
36
Starting T_{sk} (°C)
B
Inter-thresholds zone width (°C)
9
8
7
6
5
4
3
2
1
0
26
31
36
Starting T_{sk} (°C)


Warm
Neutral
Cold
Mean response
1
0.75
0.5
0.25
0
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
Stimulus temperature (°C)
26°C
31°C
36°C


A
Neutral Temperature (°C)
36
34
32
30
28
26
24
26
31
36
Starting T_{sk} (°C)
Neutral Temp
Y = 0.746*X + 8.027
R^2= 0.89
B
Thermo-neutral zone width (°C)
9
8
7
6
5
4
3
2
1
0
26
31
36
Starting T_{sk} (°C)


Skin Temperature (°C)
37
36
35
34
33
32
31
30
29
28
27
26
25
26
31
36
Starting T_{sk} (°C)
Warm Threshold
Cold Threshold
Thermo-neutral temperature
Thermo-neutral zone


Skin Temperature (°C)
37
36
35
34
33
32
31
30
29
28
27
26
25
26
31
36
Starting T_{sk} (°C)
Warm Threshold
Cold Threshold
Thermo-neutral temperature
Thermo-neutral zone