Title: Cold stimulation without touch: a method for perceptual and neurophysiological studies of thermal processing and multimodal interactions.

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Highlights (4 points)
- Thermal and tactile sensory pathways interact at many processing stages, yet most studies on cold thermosensation fail to control for concomitant tactile input from the thermal stimulator itself.
- We developed a new method to deliver thermo-controlled non-tactile cold stimuli by combining dry ice, a thermal camera, motorised stages, and custom-written code.
- The method was validated for the study of thermal perception by estimating thresholds for contactless cold perception in humans.

Abstract (250 words)

Background: Thermal and tactile stimuli are transduced by different receptor classes. However, mechano- and thermo-sensitive afferents interact at spinal and supraspinal levels. Yet, most cold stimulation studies are confounded by mechanical contact, making these interactions difficult to isolate. Methods for precise control of purely thermal stimulations remain challenging, particularly in the cold range.

New Method: We developed a flexible, multi-purpose, non-tactile, focal, temperature-controlled cold stimulator. This method controls the exposure of a target skin region to a dry-ice source. Using a thermal camera to monitor skin temperature, and adjusting the source-skin distance accordingly, we could deliver non-tactile cold stimuli with customisable profiles, for studying different aspects of thermal sensation.

Results: To validate our method, we measured absolute and relative thresholds for cold sensation without mechanical contact in 13 human volunteer participants, using the method of limits. We found that the absolute cold detection threshold was 32.71^{o}C ± 0.88 ^{o}C. This corresponded to a threshold relative to each participant's baseline skin temperature of -1.08 ^{o}C ± 0.37 ^{o}C.

Comparisons with Existing Method: Our method allows controllable cold stimulation without the confound of mechanical contact, in a controllable and focal manner, for the first time.

Conclusions: We report a non-contact cold thermal stimulator and accompanying control system. We used this to measure a 'pure' cold threshold, in the absence of confounding touch. Our method enables more targeted studies of both cold sensory pathways, and of cold-touch interactions.

Keywords:

Perception / Sensation / Temperature / Mechanosensation / Cold

1 Introduction

Humans and other animals feel thermal events thanks to thermoreceptors in the skin. These are interspersed with other receptors which are sensitive to different physical modalities such as skin pressure. The classical, labelled-line view states that different sensations arise from distinct receptors and afferent fibre pathways. However, interactions between modalities are well-known (Cahusac & Noyce, 2007; Ho et al., 2011; Melzack & Wall, 1965), and occur at molecular, neuronal and cognitive levels in the sensory pathway. Most research on cold sensations has used mechanical contact stimulators. As a result, the cold sensations studied are confounded with tactile inputs, and quite possibly modulated by them. While cold-mechanical co-stimulation is natural, it precludes an analytic psychophysical approach to 'pure' cold sensations. The logical way to study these interactions would involve comparing the effects of a purely thermal stimulus with the effects of a combined thermal and mechanical stimulus.

Mechanistic studies of thermal sensation would therefore benefit from a purely thermal cold stimulation technique, which did not involve skin contact and mechanoreceptor activation. This technique would in turn allow interactions between cold and other sensations to be studied. To our knowledge, only four previous studies have successfully used non-contact stimuli for cold thermosensory testing. Bujas (1937) used a non-contact method based on blowing chilled air at the skin. The resulting air pressure presumably involved at least a minimal level of mechanoreceptor stimulation, that would exceed that caused by radiation or convection methods. In the other 3 studies, skin temperature was decreased without touch using radiation and/or passive convection transfer between dry ice (CO_2 solid form) and the skin (Cataldo et al. 2016; Ferrè et al., 2018; Hardy & Oppel, 1938). However, the cold stimulation in these studies lacked precise spatial and temporal control and thus could not produce point-estimates of cold perceptual sensitivity of the kind used in psychophysical and clinical testing.

We have therefore developed a flexible, multi-purpose, non-tactile, focal, temperature-controlled cold stimulator. Here, we describe three potential stimulation scenarios using this system. We validated our system by a study of human thresholds for cold perception in the absence of touch.

2 Materials and methods

To deliver non-tactile cold stimulation, we used dry ice (CO_2). The dry ice was held in a container, which varied according to the experimental application. The container was secured on a support which could be moved in three axes using motorised linear stages (Fig. 1A) (A-LSQ150B and X-LSQ150B series, Zaber Technologies Inc.). To control the exposure of the skin to the dry ice, we placed a polystyrene shutter below the syringe tip, and controlled the shutter with a servo motor (SG90 Micro Servo Motor KY66-5, Longruner), driven by an Arduino Mega 2560. The shutter was closed between trials. To measure the temperature of the skin immediately below the syringe tip, we used a thermal camera module temporal resolution: 8.7 Hz, Field of View: 57º & camera resolution: 60 x 120) (Lepton 3.5, Teledyne FLIR), interfaced with a computer through a I/O module (PureThermal 2 - FLIR Lepton I/O Smart module, Teledyn FLIR).

To control the position of the thermal camera, we used a second set of 3 linear stages (2 stepper motor controllers LSM100B-T4 and 1 stepper motor controller LSM200B-T4, Zaber Technologies Inc.), which interfaced with the computer through controllers (2 stepper motor controllers X-MCB2 and 1 stepper motor controller X-MCB1, Zaber Technologies Inc.). These moved the thermal camera under computer control.

The linear stages were positioned relative to the participant's left hand. Three red lasers (5V 650nm 5mW, HiLetgo®) fixed to the wall pointed at the hand dorsum. The participant's skin was marked with ink at the beam locations, so the experimenter could visually monitor the position of the participant's hand throughout (Fig. 1A). To control the hardware, build the experiment and analyse the data, custom Python and Arduino code were written (see GitHub repository: xxx).

Using these general principles, we realised three separate stimulation scenarios suitable for psychophysical and neurophysiological experiments. Firstly, we developed a focal cold stimulus to measure relative cold thresholds. Secondly, we developed a temperature feedback-controlled PID solution for delivering prolonged customised cold stimulus profiles. Thirdly, we produced a wide area rapid-cooling thermal pulse, designed to investigate a cold-evoked EEG potential. Here, we provide psychophysical data for scenario 1 and single-stimulation data from scenarios 2 and 3.

2.1 Scenario 1: Focal cold stimulation for pure cold threshold measurements

In this set-up, the dry ice container was a syringe with a blunt needle (BD Emerald Hypodermic Syringe - Luer Slip Concentric - 10ml, BD). The syringe was wrapped in aluminium foil to reduce thermal loss. To obtain a constant pressure on the dry ice powder throughout, a weight of 1600 g was placed on the syringe plunger and a continuous rotation servo (FS5106R, Feetech) pressed on the plunger and the weight via a 3D printed linear stage (Fig. 1A).

Thermal image recording started 2 s before the shutter opened. After shutter opening, the skin immediately below the syringe tip was exposed to convection of cold air cooled by the dry ice. Further, the skin lost heat to the cold syringe by radiation. As a result, the skin temperature gradually decreased, as recorded by the thermal camera.

A region of interest (ROI, Fig. 1A & E) under the syringe tip was selected for online image analysis. Because the thermal camera was located slightly to the side of the syringe, and therefore had an oblique view, the circular ROI in the image had an elliptical projection (3.37x3.32 mm) on the skin. The pixel values in degrees Kelvin (K) were transformed into degrees Celsius (^{o}C) and the temperature of the ROI was obtained by performing the mean across all the pixels within the ROI.

The capacity of the device to cool the skin decreases as the distance from the dry ice to the skin increases. We constructed a linear regression model (Appendix A) for selecting an appropriate distance according to the desired temperature range. For this scenario, we used a 5-cm distance.

To measure cold thresholds, we used the method of limits (MoL) (Dyck et al., 1993). At the start of each trial, a tone sounded to alert the participant, and the shutter opened, exposing the participant's skin to the dry ice, and leading to a progressive decrease of the measured temperature in the ROI. The participant was instructed to press a foot pedal when they first felt a cold sensation on the stimulated skin region. When the pedal was pressed, the stimulator shutter closed, the tone terminated, and the final skin temperature was stored (Fig. 1E). We measured cold thresholds on the hand dorsum of 13 participants (mean age: 24.1, std: 3.54), obtaining 40 estimates per participant. To allow skin temperature to return to baseline, 4 locations of a square grid with side of 2 cm were randomly stimulated. The same location was restimulated only after 2 other locations had been visited, ensuring a minimum 30 s for thermal recovery between stimulations at each site.

As well as measuring the absolute threshold, we used the data from each trial to calculate the relative threshold, i.e., the smallest drop in temperature from baseline that the participant could detect (ΔT) (Hafner et al., 2015). Unlike contact thermal stimulators, our stimulator does not set the initial temperature of the skin before each stimulation. We observed a high variability in the baseline skin temperature across participants and locations. Because we avoided rapid restimulations, this presumably reflects natural variability unrelated to the experimental procedure. Thus, ΔT is arguably a more ecologically valid threshold measurement of cold sensation than an absolute measurement. Our method and procedure are suited to account for this variability.

To measure ΔT, an average of the baseline skin temperature within the ROI was taken across multiple frames in the 300 ms before shutter opening. Then, the temperature of the ROI upon pedal press was subtracted from the previous averaged baseline value to obtain ΔT (Fig. 1B).

Appropriate risk management procedures, notably around handling dry ice, were implemented. The research protocol was approved by the local ethical committee. Room temperature fluctuations and air currents were minimised by closing windows and doors.

2.2 Scenario 2: Feedback temperature-controlled custom cold stimulation

This scenario allowed delivery of temperature-controlled non-tactile cold stimulation for psychophysical paradigms which require second-lasting and constant temperature.

Raising the cold source resulted in less cooling, while lowering it towards the skin produced more cooling. Therefore, to achieve desired temperature readings from the thermal camera, we continuously adjusted the distance between dry ice and skin (Fig. 1C).

A PID algorithm closed the feedback loop between thermal image and the cold source height above the skin. First, a desired temperature is set. Then, the thermal camera detects the temperature of a skin ROI, and a simple PID feedback controller sends position commands to the linear stage, adjusting the height of the container until the desired temperature is reached. This allows precise temporal and spatial control of skin temperature for psychophysical experiments. For instance, in combination with a non-tactile warm stimulator, a temperature-controlled radiant Thermal Grill Illusion (TGI) could be elicited for the first time.

In this set-up, the dry ice was held in a carboard container. The cardboard container had dimensions 10.2x10.2x21.8 cm with a total volume of 1600 ml. It was filled with 300 g of dry ice. The base was perforated with a 6 mm diameter copper tube. For these studies, the ROI had a projected elliptical shape on the skin of 5x4 mm. The interior of the container was covered with foil and its exterior with polystyrene foam in order to limit thermal loss and convection to the copper tube.

2.3 Scenario 3: Rapid, wide-area, high-intensity cold stimulation

This scenario allowed delivery of fast and wide non-tactile cold stimulation for electrophysiological recordings. Event-related EEG potentials require strong stimuli with rapid onsets. Steep cooling ramps cause synchronous activation of many cold afferents, and therefore improve the signal-to-noise ratio of event-related EEG potentials.

In this set-up, the dry ice container for scenario 2 was used, but the base was perforated with three outlet tubes to increase the stimulation area. Therefore, the exposed skin area was larger, and the skin ROI was a 10x8 mm ellipse. Cold exposure led to a rapid temperature decrease at 20^{o}C/s (Fig. 1D). Previous studies have shown that a cooling ramp of 10-17^{o}C/s is sufficient to detect a reproducible evoked potential (De Keyser et al., 2018; Duclaux et al., 1974). Thus, our stimulation method is feasible for rapidly cooling a large patch of skin without touch, and potentially measuring purely thermal EEG responses.

3 Results

Our stimulator successfully delivered cold stimulation without touch. We determined absolute and relative temperature threshold of cold detection (Fig. 1B & F). We also achieved sustained, temperature-controlled cold stimulation suitable for psychophysical studies of cold perception with stimuli varying in intensity, location, and duration (Fig. 1C). Finally, we demonstrated a rapid decrease in skin temperature without touch, which is suitable for electrophysiological recordings (Fig. 1D).

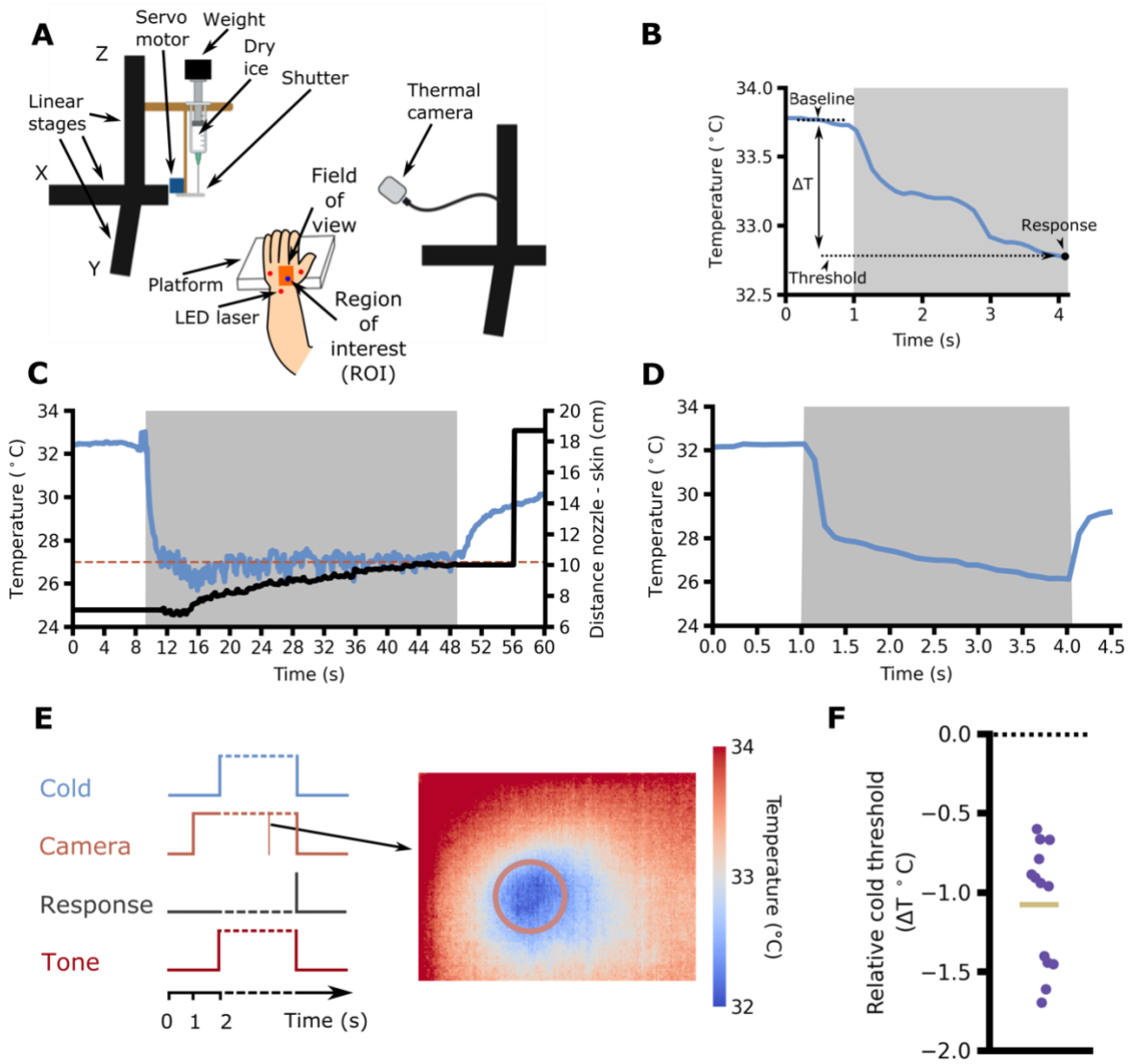

Fig. 1. A) An illustration of the set-up with the main components. B) Example of focal cold stimulation for determining cold thresholds by method of limits (scenario 1). The trace shows mean skin temperature in the skin ROI. The threshold level at which the participant first reported detecting cold is expressed relative to baseline (ΔT). The grey zone indicates the duration of cold stimulation (shutter is open). C) Example of feedback-controlled stimulation (scenario 2). The horizontal, dashed red line indicates the set-point for the PID controller. The height of the stimulator above the skin is adjusted by PID control to achieve the desired temperature D) Example of rapid, large-area cold stimulation (scenario 3). E) The panel to the left is a schematic displaying the temporal sequence of events in an MoL trial. The panel to the right shows a thermal image during dry ice stimulation. The orange circle represents the ROI. F) Cold detection thresholds relative to baseline skin temperature (ΔT) of 13 participants. Each datapoint represents the mean of 40 threshold estimates based on the method of Fig. 1B. The horizontal yellow line represents the mean.

Baseline temperature before cold stimulation was 33.78ºC ± 0.88 across 13 participants. The absolute threshold for reporting cold stimulation was 32.71ºC ± 0.88 SD across participants. Thus, the relative threshold for cold detection (ΔT) was -1.08 ± 0.37 SD across participants (Fig. 1F).

4 Discussion

We report methods suitable for studying thermal-tactile interactions. The classic method to study these would involve comparing the responses to thermal stimuli both with and without concomitant mechanoreceptor stimulation. However, most methods for delivering cold stimulation, notably thermodes (Duclaux et al., 1974; Green, 2009), inevitably involve mechanical stimulation. As a result, the neural and perceptual consequences of 'pure' cold stimulation have been little studied, and the mechanisms of thermo-tactile interactions are therefore poorly understood. Our novel method generates well-controlled cold stimulations without the confounds of mechanical touch, making such interactions experimentally accessible for the first time.

We showed that our stimulator could deliver a decreasing temperature ramp to a selected skin region. We could thus reliably estimate focal cold detection thresholds without tactile stimulation. These estimates can be compared with cold thresholds obtained in Quantitative Sensory Testing (QST) studies. Several such studies have reported normative values for cold and warm thresholds (Table 1). All these studies used thermode stimulators, thus introducing a tactile element. Therefore, by comparing our threshold values with the ones obtained by these studies, we could indirectly understand the effect of touch on cold processing.

Study	Nº of subjects	Age	% female	Stimulation parameters: psychophysical method/ thermal stimulator/ skin region	Mean (SD) absolute threshold (ºC)	Mean (SD) threshold relative to baseline skin temparature (ΔT)
Rolke et al., 2006	180	17-75	61%	Method of limits. TSAII thermodes. Thenar eminence.	30.9 (-)	-
Hafner et al., 2015	101	21-70	48%	Method of limits. TSAII thermodes. Thenar eminence.	-	approx. -1.0 (2.5)
Wang et al., 2014	20	21-35	50%	Method of limits. Medoc thermodes. Dorsum hand.	30.3 (1.5)	-
Van Den Bosch et al., 2017	69	8-17	60%	Method of limits, signal detection. TSAII thermodes. Thenar eminence.	30.7 (0.7)	-

Table 1. Summary of selected QST studies reporting cold thresholds. Abbreviations in table: MOL, Method of Limits & SDT, Signal Detection Theory.

As seen in Table 1, the mean absolute threshold of cold perception obtained through our study (32.71ºC) is less extreme than those obtained through previous QST studies. This is consistent with the hypothesis that concomitant touch may affect the threshold for cold perception.

However, three factors complicate direct comparison of our results with previous QST studies. First, those studies set the baseline temperature with the same value for all

trials and participants. Crucially, they did not report the detection threshold relative to baseline skin temperature. Secondly, thermal sensitivity varies across skin regions and body parts, potentially contributing to differences in threshold estimates between studies. Thirdly, spatial summation is minimal in our study given the small size of the stimulated area (3.37x3.32 mm). In contrast, spatial summation in most QST studies will be greater, given that thermode sizes are between 15x15mm and 50x50mm. Hafner et al. (2015) estimated relative cold thresholds at -1°C. Their estimate is thus comparable to ours, despite a much larger stimulus allowing stronger spatial summation. However, stimulator contact may also have inhibited cold perception in their setup. Comparing the two methods, the lack of any tactile-thermal inhibition in our setup may have offset the effects reduced spatial summation. Our method suggests that cold sensitivity may be higher than previous recognized.

Our results have some limitations. First, the method of limits does not distinguish between two key components of sensory detection: sensitivity and bias. Further, we did not include 'catch' trials, in which the auditory tone would occur without any cold stimulation. The absence of catch trials could potentially induce a response bias, with participants responding based on the expectation that a cold sensation would occur. Thus, our measures of cold thresholds should not be taken as perfect estimates of sensitivity. However, this does not detract from the scientific value of the stimulator apparatus. Future studies could use psychophysical methods such as signal detection to estimate thermal sensitivity independent of bias.

Our purely thermal cold stimulator opens the possibility of investigating cold-touch interactions, seemingly for the first time. For example, cold thresholds could be measured in the presence or absence of concomitant touch. If an interaction between touch and thermal sensitivity is established, EEG studies could investigate the neurophysiological mechanisms underlying this interaction. Our rapid, large-scale cold stimulator could potentially allow future electrophysiological recordings of cold-evoked potentials, and of how they might be modulated by tactile input.

In our method, two modes of heat transfer contribute to skin cooling: convection and radiation. Convection cooling takes place as sublimated CO_2 and cooled air flow down from the container to the skin because they are more dense than ambient air. Radiative cooling also transfers thermal energy from warmer objects (the skin) to cooler ones (the stimulator). Our design cannot distinguish the respective contributions of convection and radiation to skin cooling. The very focal cooling achieved in scenario 1 suggests that convection dominates. One might object that cold air currents flowing downwards to the skin constitute a mechanical stimulus, and that our method is not therefore 'purely' thermal. We addressed this limitation by measuring the convection airflow in our exposure Scenario 1 with a Pitot tube, and calculating the resulting mechanical forces at the skin. The velocity of the airflow immediately below the syringe tip was measured as 4.0 m/s $\pm$ 0.30 SD (density of sublimated CO_2: 1.836 kg/m^3; MPXV7002DP pressure sensor, NXP). Calculations confirmed that the resulting forces on the skin were below published mechanoreceptor threshold values. Finally, in informal pilot testing, we gently blew air through the syringe at this velocity, and found that this level of airflow was not perceptually detectable (Appendix B). Therefore, our cold stimulator could be considered purely thermal, in the sense of having both high sensitivity (effectively stimulating cold afferents) and high specificity (not stimulating non-thermal afferents).

5 Conclusions

We describe a novel, flexible, multi-purpose, non-tactile, focal, temperature-controlled stimulator. We show how this device can be used for pure thermal stimulation in humans. Future studies can use our stimulation method in different psychophysical and neurophysiological experiments to establish a thermo-tactile interaction. Understanding the mechanisms of thermo-tactile and thermo-thermal interactions would help improving clinical treatments, thermal displays and other haptic devices.

Authors' contributions

I.E.R., C.M.L., G.I. and P.H. conceptualised the method and designed the experiment. I.E.R. developed the method and analysed the data. I.E.R. and M.C. performed the experiment. I.E.R, P.H. and M.C. wrote the manuscript.

Conflict of interest

None

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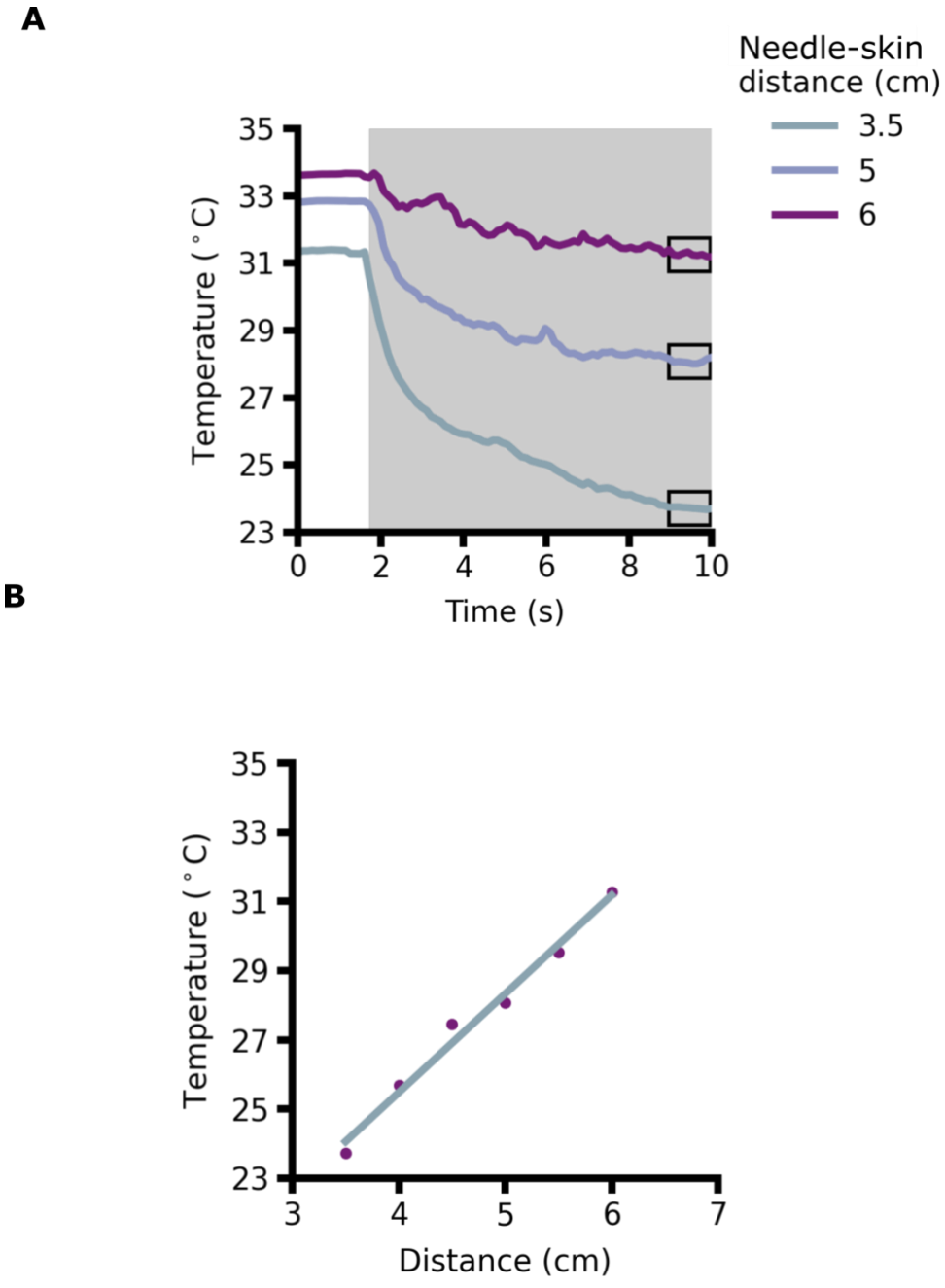
Appendix A – Linear regression model



Linear regression model. Thermal effects of distance between cold source and skin are used to create a linear regression model for obtaining feedforward stimulus parameters. A) Traces showing mean temperature of the skin ROI for 3 different distances between the needle and the skin. Each trace is the mean of 5 recordings at the given distance. The grey zone indicates the duration of cold stimulation (shutter is open). The black open boxes over indicate the data used to calculate the model represented in Fig. B. B) Dots showing the final temperature at each distance and trace showing the linear fit. At 6 different distances, 5 recordings of the skin temperature during cold stimulation were made. After performing the mean of the traces at each distance, the mean temperature during the final 1 s of stimulation was extracted (black box in Fig. A). A linear regression was used to model the relation between distance and temperature. The model could then be used to position the syringe either to allow a desired temperature to be reached, either using feedforward control, or as an initial estimate of distance for a feedback-controlled stimulation.

Appendix B. Airflow force and d' calculations.

Airflow force calculation

Dry ice is solidified CO_2. It sublimates directly from its solid state below -80ºC to a gaseous state at standard temperature and pressure. These characteristics make this material suitable for non-tactile cooling. The sublimation of dry ice produces airflow from the needle of the syringe. To obtain the force that this airflow exerts on the skin, we use the following formula for fluid dynamics:

$$F = P * A \qquad \text{(Formula 1)},$$

To calculate the force, we need to obtain the pressure (P) and the area (A) of the airflow when it collides with the skin.

In a fluid, the dynamic pressure is the kinetic energy per unit volume. To calculate the dynamic pressure, we can use the following formula:

$$p_D = \frac{1}{2} * \rho * v^2 \qquad \text{(Formula 2)},$$

where ρ is the density of the fluid and v is the speed of the fluid. We used the density of CO_2 at standard room temperature (25 ºC) and pressure (1 atm) - ρ = 1.84 kg/m^3. The velocity of the jet of air was measured with a pitot tube. The pitot tube was placed at 5 cm below the tip of the needle, which is the distance at which the skin was during the experiment described in Fig. 1F. The mean velocity of the jet of air sampled at 10 Hz and averaged over a 4 s period was 4.06 m/s (SD 0.30 m/s). Therefore, following from Formula 1, the dynamic pressure that the jet of air exerts on the skin is:

$$p_D = \frac{1}{2} * 1.84 * 4.06^2 = 15.16 \frac{N}{m^2} \quad .$$

To obtain the area of the airflow when it collides with the skin, we can use the ellipse drawn on the skin by the circular ROI taken from thermal camera measurements in scenario 1. The cooled area of the skin was measured as an ellipse with axis lengths 3.37 mm and 3.32 mm. The area of an ellipse is:

$$A = \pi * a * b \qquad \text{(Formula 3)}.$$

Therefore, the area cooled in scenario 1 was,

$$A = \pi * 3.32\, mm * 3.37\, mm = 3.52\, x\, 10^{-5}\, m^2 \quad .$$

Following from Formula 1, the force that the jet of air exerts on the skin is:

$$F = P * A = 0.53\, mN \quad ,$$

The estimated threshold for exciting a single mechanoreceptor afferent by punctate stimulation of glabrous skin was estimated using microneurography (Johansson et al., 1980). They found that RA units had a median threshold of 0.58 mN. PC units had a

median threshold of 0.54 mN. Slowly adapting SAI and SAII units had median values of 1.3 mN and 7.5 mN, respectively. In our setup, convection currents from the cold source may be assumed constant. Therefore, the mechanoreceptor afferents most likely to be stimulated are the SAI units. Therefore, the mechanical element of our cold stimulation is less than half the force level suggested to trigger a single mechanoreceptor afferent action potential. We therefore conclude that convection currents from our cold stimulator were unlikely to produce any effective mechanical stimulation.

D' for the detection of airflow

To further assess whether the mechanical stimulation generated by the minimal airflow during our main experiment was perceptually detectable, we performed a pilot Signal Detection Theory experiment.

The experimenter blew through the syringe on a participant's forearm. In 10 trials, the syringe was perpendicular to the skin and at distance of 5 cm (stimulus present). In another 10 trials, the syringe was moved away so that the participant's arm was not stimulated (stimulus absent). The participant was asked to detect the jet of air. For this experiment, 4 naïve, blindfolded participants were tested.

Before performing the experiment, the experimenter was trained to blow through the syringe to generate a jet of air with a velocity of 5.09 m/s as recorded by the Pitot tube. Therefore, the airflow of atmospheric air (density: 1.204 kg/m^3) produced a force of 0.55 mN.

On average, the hit rate was 26% and the false alarm rate was 15%. Across 4 participants, D' was 0.53 and the criterion response (c) was -0.94. This pilot psychophysical test suggests that the level of airflow (speed and area) generated by the syringe with dry ice was below perceptual detection threshold for mechanoreceptor sensations.

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