Temporal Contrast Enhancement in Thermosensation: A Framework for Understanding Paradoxical Heat Sensation

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Highlights

- Paradoxical Heat Sensation (PHS) is an illusion of heat during skin cooling
- We propose thermal contrast enhancement as a unifying explanation for this paradox
- Thermal contrast predicted PHS prevalence in healthy individuals (N = 208)
- Our model explains previously unaccounted for psychophysical features of PHS

In Brief

Mitchell et al. demonstrate that contrast enhancement principles are applicable to thermosensory perception and provide a comprehensive framework for understanding paradoxical heat sensation, a previously enigmatic perceptual phenomenon.

Abstract

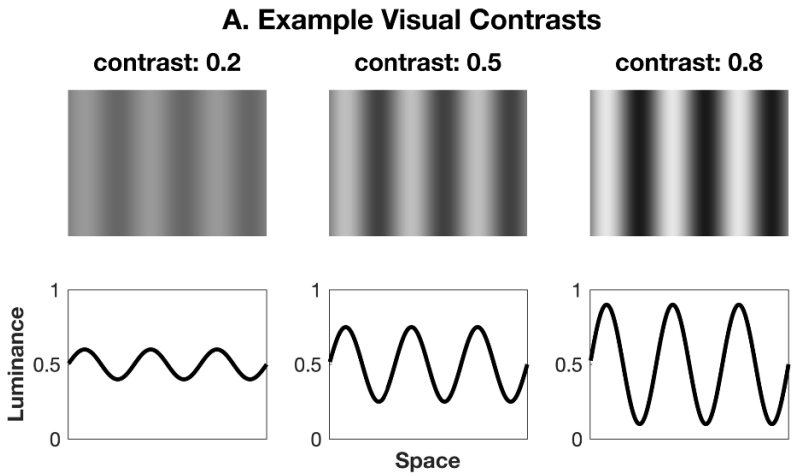
Paradoxical Heat Sensation (PHS) is the remarkable feeling of warmth or heat pain while the skin is cooling (Hämäläinen et al., 1982; Pavlicek & Jenkins, 1933). Despite its initial documentation over 100 years ago (Goldscheider, 1884), a unified explanation for this perplexing experience remains elusive, defying traditional models of thermosensation. Here, we apply contrast enhancement principles, known for their instrumental role in understanding visual illusions, to the domain of thermosensation. Contrast enhancement describes the amplification of two contrasting visual features (Hess et al., 1998), such as the enhanced perception of an edge between a light and dark bar. We extend this concept to thermosensation, which encompasses an enhancement of the difference between sequential warming and cooling of the skin and predict that this mechanism underlies the experience of PHS. Remarkably, thermal contrast, defined as the normalised difference between successive temporal warm and cold temperatures, predicts the occurrence of PHS. Our findings reveal compelling evidence supporting the role of thermal contrast in the generation of PHS, shedding light on its underlying mechanism and offering a framework for understanding broader encoding principles in thermosensation.

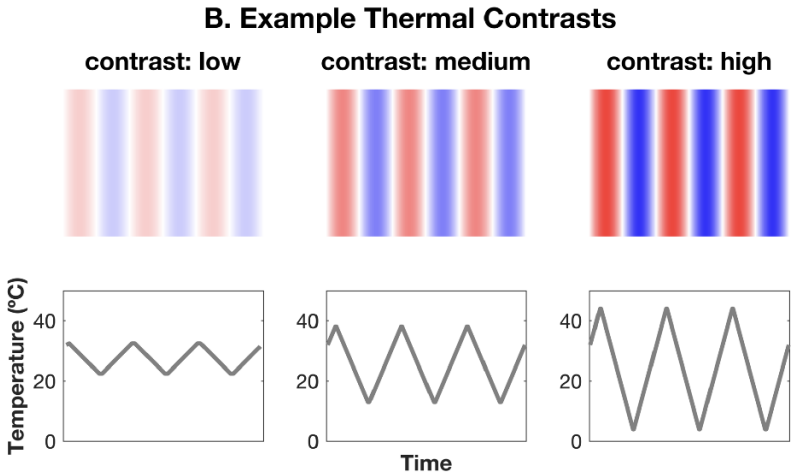
Introduction

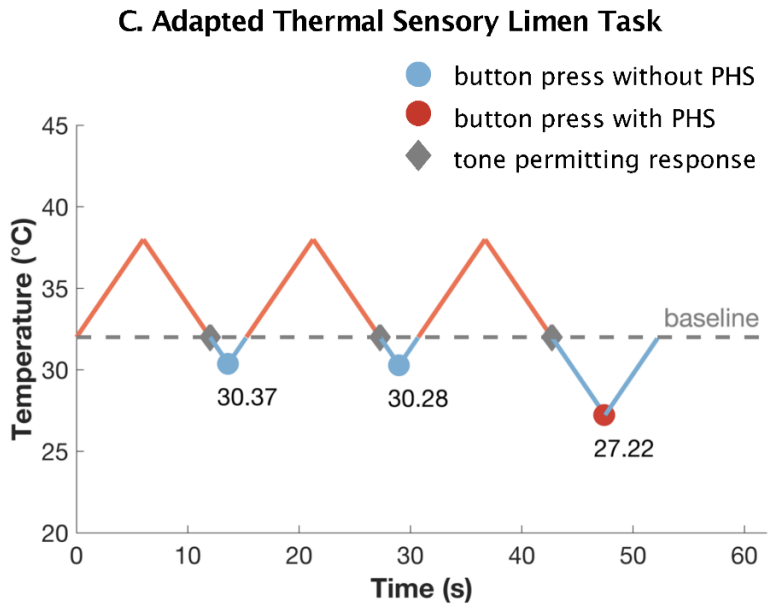
Among the various thermal sensations experienced by humans, Paradoxical Heat Sensation (PHS) stands out as a particularly intriguing phenomenon (Goldsheider, 1912; Hämäläinen et al., 1982; Hansen et al., 1996; Pavlicek & Jenkins, 1933). PHS refers to the illusory perception of warmth during the cooling of the skin and is typically perceived when warming and cooling is temporally alternated. It is during these dynamic thermal alternations that the human thermosensory system misinterprets a temperature change from warm to cool as warmth, heat or heat pain. Despite previous research efforts, the underlying mechanisms of this counterintuitive sensory experience have remained elusive. Clarifying these mechanisms is essential not only for advancing our understanding of PHS but also for uncovering the broader principles that govern human thermosensory perception.

Here, we demonstrate that PHS reflects a temporal contrast enhancement mechanism in the human thermosensory system. We propose that the dynamic interplay between subsequent warming and cooling on the skin elicits neural responses that amplify the perceived difference between these temperature sensations, culminating in the paradoxical experience of heat. Contrast enhancement refers to the phenomenon where boundaries between two contrasting features (for example, light and dark bars) are perceptually enhanced (Shapley & Tolhurst, 1973). This mechanism is fundamental for improving the sensitivity and discriminability of sensory information across various perceptual domains, including vision and audition (Hess et al., 1998; Mehta et al., 2021). In the visual domain, for instance, differences in luminance between spatially adjacent stimuli are accentuated by the nervous system to more effectively detect and process features of the sensory environment, such as boundaries or edges (Hess et al., 1998; Shapley & Tolhurst, 1973). Visual gratings, which consist of spatial patterns of alternating light and dark bars, provide a clear example of this principle (see Figure 1A).

Analogously, the Thermal Sensory Limen (TSL) task, which is typically employed to assess for the presence of PHS, can be considered as a temporal counterpart to visual gratings within the thermosensory system. In the TSL, warming and cooling are alternated at the same skin location, with these temperature changes representing the approximate peak and trough of a sinusoidal function over time (Figure 1B). A single trial of the TSL is defined as one thermal cycle where the temperature probe increases to the set maximum temperature, then decreases past baseline (32ºC) to the point at which the participant detects a change in sensation or pain, before returning to the baseline temperature. From this perspective, we defined the Thermal Contrast Function (see Equation 1), as the normalised difference between subsequent warm and cold temperatures for each trial. This function yields a standardised value that captures the maximum and minimum temperatures of a single TSL trial and can be compared across different conditions, experiments, or patient populations.







$$TCF = \frac{T_{warm} - T_{cold}}{T_{\max warm} - T_{\min cold}}$$

Figure 1: Contrast in the thermosensory domain. A) Visual gratings and corresponding sinusoidal waveforms representing three different contrasts; low (.20), medium (.50) and high (.80). The corresponding sinusoidal waveforms have a relatively low, intermediate and high amplitude, reflecting an increasing change in luminance and increasingly sharpened difference between light and dark bars. B) Example temporal profiles (warm = pink, cold = blue) and their corresponding Thermal Sensory Limen profiles for low, medium and high thermal contrast, that match the corresponding visual contrast level shown in A. C) An example of the adapted thermal sensory limen task sequence from one participant shows three experimental trials for the medium contrast condition, with peaks at a starting temperature of 38ºC and troughs at the point at which they detected a change in sensation. An auditory tone was presented when the temperature returned from peak to 32ºC, which corresponded to the beginning of the cooling phase. Participants pressed a button at perceived temperature changes (innocuous condition) or pain (noxious condition), followed by a description of the sensation (cold, warm, cold pain or heat pain). The TSL threshold corresponded to the temperature of the probe when the button was pressed. TCF = thermal contrast function used to calculate contrast for each TSL trial where 50ºC is the maximum possible temperature (*Tmax warm*) and 0ºC is the minimum possible temperature (*Tmin warm*).

To investigate the role of contrast enhancement in PHS, we conducted a study of 208 healthy participants using an adapted Thermal Sensory Limen (TSL) task featuring low, medium and high contrast conditions. These conditions were established by variations between a fixed maximum temperature, corresponding to the peak in the warm temperature range (at 32, 38, and 44ºC) and a variable minimum temperature, corresponding to the trough in the cold temperature range. This variable minimum temperature was determined by participants' responses based on two task instructions. Participants pressed a button upon experiencing either a change in sensation (innocuous task condition) or a painful sensation (noxious task condition). Each button press led to a reversal in the temperature fluctuation. Responses were permitted only when the probe's temperature entered the cold temperature range, below 32ºC to a minimum of 0ºC, set for safety purposes. An auditory tone signalled the start of the response window (Figure 1C).

The primary outcome measures were the prevalence and rate of innocuous and noxious PHS, and their associated thermal thresholds. Thresholds were the temperature at which participants noticed a sensation change (innocuous TSL threshold) or pain (noxious TSL threshold). Innocuous PHS was the reported experience of warmth, while noxious PHS was the reported experience of heat pain during the cooling phase of the TSL. To specifically address the role of contrast enhancement, we calculated the thermal contrast (Figure 1C, Equation 1) for each trial in low, medium and high contrast conditions.

Results

Increased contrast is associated with increased prevalence and rate of PHS

We first investigated whether the likelihood of a participant experiencing paradoxical heat sensation depended upon contrast level, defined by the low, medium and high contrast conditions. To this end, we compared the distribution of PHS occurrences across the three contrast levels (i.e., starting temperatures) and two TSL tasks (innocuous vs. noxious) using McNemar's Chi Squared tests (Figure 2A). As contrast increased, the number of individuals reporting innocuous PHS (i.e., PHS prevalence) increased from low to medium contrasts (32º to 38ºC, $\chi^2 = 3.78$, $p = .05$, g = 0.19), low to high contrasts (32º to 44ºC, $\chi^2 = 23.56$, $p < .001$, g = 0.35) and medium to high contrasts (38º to 44ºC, $\chi^2 = 11.02$, $p = .001$, g = 0.25). The number of individuals reporting noxious PHS did not exhibit a clear relationship with the increase in contrast (32º vs. 38º $\chi^2 = 0.25$, $p = .62$, g = 0.06; 32º vs. 44º $\chi^2 = 2.70$, $p = .10$, g = 0.15; 38º vs. 44 º $\chi^2 = 1.33$, $p = .25$, g = 0.13). Mixed effect regression models showed that the prevalence of innocuous PHS increased with increasing contrast (z = 4.88, $p <. 001$, $\beta = 1.28$, Model 1A), while the prevalence of noxious PHS did not significantly change as a function of contrast (z = -1.91, $p = .06$, $\beta = -.50$, Model 1B).

These results indicate that the prevalence and rate of innocuous, but not noxious, PHS are influenced by contrast created by the temporal alternation of warming and cooling of the skin. The observation that this effect was specific to PHS in the innocuous task suggests that this qualitative perceptual change relates to misperception of temperatures in the innocuous cold temperature range.

Contrast modulates innocuous and noxious thresholds during TSL

We next analysed whether the threshold temperatures at which individuals experienced a change in sensation or a painful sensation varied as a function of contrast (Figure 2B). Innocuous TSL thresholds decreased ($t = -6.23$, $\beta = -0.67$, $p < .001$, Model 2A), while noxious TSL thresholds increased with increasing contrast level ($t = 2.26$, $\beta = 1.50$, $p = .02$, Model 2B). A logistic regression model further found that the prevalence of innocuous PHS increased with increasing innocuous TSL thresholds ($p < .001$, OR = 0.35, 95% CI = 0.26 - 0.45), and increased with decreasing noxious TSL thresholds ($p = .001$, OR = 2.12, 95% CI = 1.44 - 3.14, Figure S1, Model 2C). This indicates both innocuous and noxious thermal thresholds are related to the presence of PHS and are jointly driven by thermal contrast.

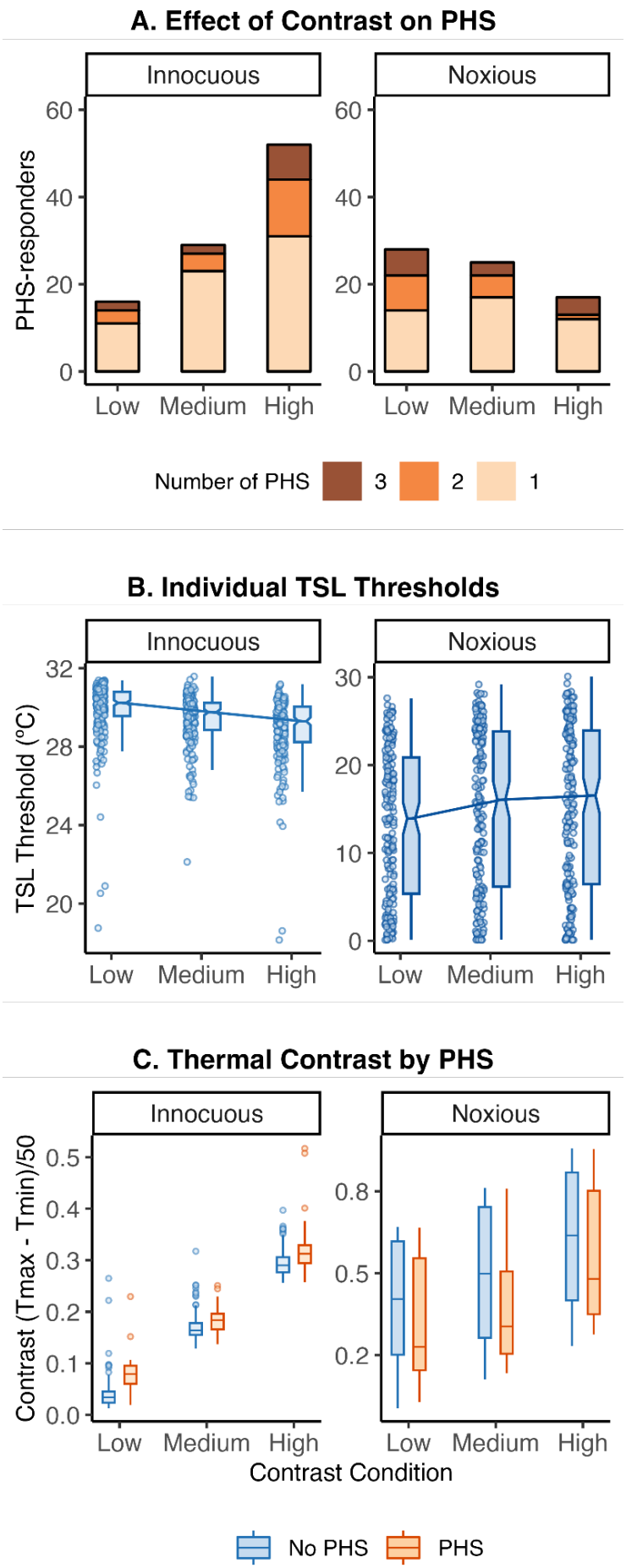

A. Effect of Contrast on PHS
Innocuous
Noxious
PHS-responders
60
40
20
0
Low
Medium
High
Number of PHS
3
2
1
B. Individual TSL Thresholds
TSL Threshold (°C)
32
28
24
20
30
10
C. Thermal Contrast by PHS
Contrast (Tmax - Tmin)/50
0.5
0.4
0.3
0.2
0.1
0.0
0.8
Contrast Condition
No PHS
PHS

Figure 2: The effect of thermal contrast on TSL thresholds and PHS. A) The overall rate of innocuous PHS increases with increasing contrast, whilst contrast does not affect noxious PHS. PHS prevalence (number of participants with PHS) and rate (the total number of PHS over three trials) are shown for each contrast condition and task. B) Thermal contrast also affects TSL temperatures in both task conditions. TSL temperatures at which participants detected a change in sensation (innocuous) decrease with increasing contrast, whilst TSL temperatures at which participants detect a painful sensation (noxious) increase with increasing contrast. Box plots show median with confidence intervals (notches), the dots show the individual participant mean. Noxious TSL thresholds below .10ºC were removed for visualisation purposes only. C) Thermal contrast defined by Equation 1 (the Thermal Contrast Function) increases with contrast condition (starting temperature) but is higher in individuals who experience PHS for the innocuous condition, and lower in the noxious condition, compared to those participants who experience veridical cold. Note scale differences between innocuous and noxious panels.

PHS relates to temporal contrast enhancement in the thermosensory system

To demonstrate further evidence for our thermal contrast model, we quantified the relationship between temporal thermal contrast and individual TSL thresholds in each trial using an equation adapted from vision science. This equation defines the thermal contrast as the normalised difference between the maximum and minimum temperatures for each trial of the TSL (Thermal Contrast Function, Equation 1). Alongside this, we ran logistic regression models to determine the predictive value of thermal contrast on PHS (*see* STAR Methods for full model equations).

The prevalence of innocuous PHS increased with increasing innocuous thermal contrast (Figure 2C, $p < .001$, OR = 13.48, 95% CI 5.20 - 34.99). To understand the sensitivity vs specificity of this effect, we calculated the accuracy under (AUC) receiver operating characteristic (ROC) curves for four logistic regression models including thermal contrast (Figure 3). ROC curves indicated that a model that included innocuous and noxious TCF (Figure 3D, AUC = 0.76, AIC = 791) predicted the prevalence of innocuous PHS more accurately than three other comparison models that included contrast condition (Figure 3A), noxious TCF only (Figure 3B), and innocuous TSF only (Figure 3C). The marginal effects of the simplest model (Figure 3A) indicated a predictive probability of 6% in high contrast conditions, while in the winning model (Figure 3D) this probability increased up to 75% for trials with a higher innocuous contrast and lower noxious contrast (measured using the TCF).

As a control analysis, we aimed to confirm that the prevalence of PHS is driven by thermal contrast sensitivity specifically, rather than general detection and pain thresholds. We defined a logistic regression model predicting the prevalence of innocuous PHS from cold detection and cold pain thresholds obtained during the Quantitative Sensory Testing (QST) protocol. Our findings revealed that QST thermal thresholds were insufficient to predict the prevalence of PHS (Table S1). Therefore, computational modelling of PHS showed that thermal contrast created by the alternation of warming and cooling during the TSL specifically influences the prevalence of PHS, above and beyond thermal sensitivity measures, such as cold detection and cold pain thresholds.

While the prevalence of PHS is greatest for high contrast conditions, across all contrast levels TCF values more accurately predict the prevalence of PHS. Thermal contrast during TSL therefore underlies the prevalence of PHS, highlighting the role of temporal contrast

enhancement in the generation of paradoxical heat. Alongside this, the benefit of calculating contrast compared to using TSL temperatures alone, is that it allows for extraction of a single, standardised number that combines these measures, while accurately predicting PHS prevalence. Our model thus provides a powerful tool to quantify patterns of thermal sensitivity among different populations and across datasets and methods that adopt different TSL procedures.

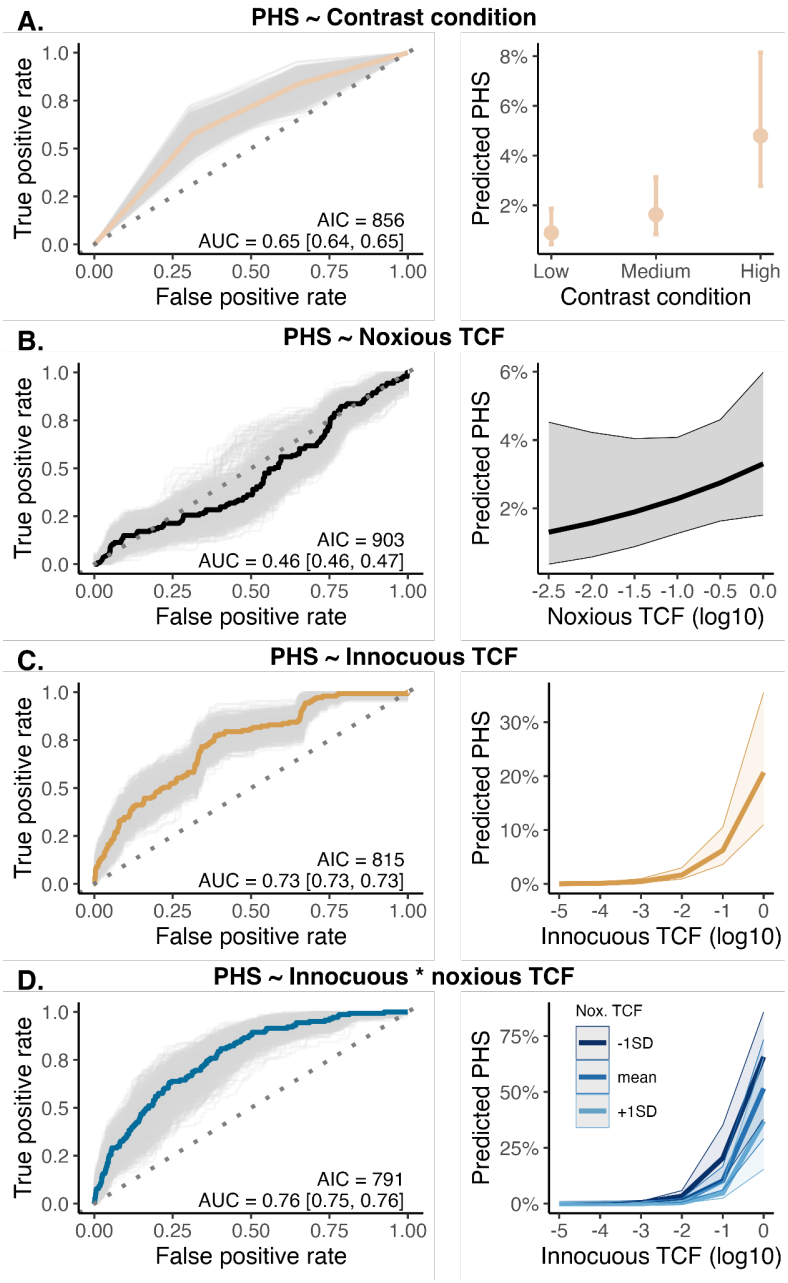


Figure 3: ROC curves (left panel) and predicted probability of PHS for each model (right panel) showing that thermal contrast predicts PHS prevalence. In the left panels ROC curves show the accuracy of each logistic regression model to predict innocuous PHS. The winning model is shown in panel D. Coloured lines show the ROC for the data-driven model, whilst the grey lines show bootstrapped simulated ROCs (n = 2000). The area under the curve (AUC) is displayed as an indicator

of model accuracy, with 95% confidence intervals of bootstrapped AUCs indicated in square brackets. Model fit is indicated by AIC. The right panels show the predicted probability of the marginal effects of each model to lead to a PHS trial. In the x-axis, higher innocuous and noxious TCF (log10) represents higher contrast. The predicted probability of a PHS trial increases from around 5% in the simplest model (panel A) to up to 75% if innocuous and noxious TCF values are included in the model (panel D). Error bars (panel A) and shaded areas (panels B-D) show low and high confidence intervals for marginal effects of each model predictor.

Discussion

The study of illusions within the visual system has been essential in unravelling fundamental mechanisms of perception. Here we capitalised on this to further our understanding of thermosensation through thermal nociceptive illusions. We assessed whether contrast enhancement, an established mechanism within the visual and auditory domains, is the driving mechanism behind PHS, using an adapted TSL task to create conditions of low, medium and high contrast. As a result, we were able to successfully define the relationship between PHS and temporal thermal contrast independently from other measures of thermal sensitivity. As understanding illusions in other perceptual domains has fostered increased understanding of complex sensory mechanisms, the computational approach motivated here should also inform our more general understanding of pain and thermosensory processes and their dysfunction in neurological diseases.

Prior research has overlooked the potential role of thermal contrast enhancement in PHS. This explanation could account for previously observed differences in PHS rate between healthy, young individuals (Hämäläinen et al., 1982; Magerl et al., 2010; Susser et al., 1999), older individuals (Magerl et al., 2010; Maier et al., 2010; Schaldemose et al., 2022), as well as patients with reduced thermosensory function due to peripheral and central nervous system disorders (Baron et al., 2017; Hansen et al., 1996; Magerl et al., 2010; Yosipovitch et al., 1995). For example, PHS is relatively infrequent in healthy individuals but more prevalent in patients with neuropathy (Vollert et al., 2022). This discrepancy was identified in studies that used the traditional TSL task, where individual thermal sensitivity shapes the extent of skin warming and cooling (e.g., Baron et al., 2017; Magerl et al., 2010). As reduced thermal sensitivity is likely to lead to increased thermal contrast during TSL, it is therefore challenging to disentangle whether PHS is a pathological sign related to thermosensory loss, or a result of known differences in TSL thresholds that naturally occurs as a consequence of reduced thermal sensitivity in these groups. Our approach allows us to explicitly test the role of PHS, irrespective of thermosensory sensitivity, and provides a standardised quantification of TSL outcome that can be compared across groups.

Thermal contrast enhancement as a driving mechanism for PHS unifies previously incongruous findings. For example, after skin sensitization using capsaicin, PHS responders exhibited higher warm and cold TSL thresholds, and therefore increased thermal contrast during the TSL task, compared to non-responders (Schaldemose et al., 2015). Similarly, variations in warming and cooling patterns during TSL that affect both the number and intensity of PHS (Hämäläinen et al., 1982; Schaldemose et al., 2022; Susser et al., 1999), can be reinterpreted using our current model. For example, previous findings showing increases in PHS after both pre-warming (Susser et al., 1999) and pre-cooling (Schaldemose et al., 2022) can be explained as a consequence of an increase in temporal thermal contrast. In light of this, we argue that contrast enhancement provides a powerful explanation for the presence of PHS and future research should carefully take into account the relation between thermal contrast and sensitivity in the manifestation of PHS.

Here we capitalised on theories established through our understanding of illusions in the visual system to provide a unifying explanation for PHS, an illusion that has previously defied coherent explanation. Specifically, we proposed thermal contrast enhancement mechanisms underlie the experience of PHS. We used an adapted version of the TSL task to

create conditions of low, medium and high contrast and developed a Thermal Contrast Function, which computes a single standardised number encoding the contrast on each TSL trial, for each individual. We established that increasing the thermal contrast, defined by a higher peak, of stimuli during the TSL increased both the rate and prevalence of PHS. Alongside this, computational models of PHS revealed that the individual thermal contrast predicted the prevalence of PHS in healthy individuals. These results highlight the link between PHS and contrast enhancement in the thermosensory system. Alongside this, we are able to provide a clear, concise explanation that is well-established in other perceptual domains, for the paradoxical presence of heat during cooling. A unifying interpretation of this paradox has powerful implications for how we understand and interpret the experience of pain or heat in response to innocuous stimuli.

Methods

Participants

Participants were recruited through the Center of Functionally Integrative Neuroscience, Aarhus University and tested as part of the EU COST Action CA18106 between August 2019 and March 2021. The data presented in this manuscript constitutes part of a larger data set of behavioural and MRI data from healthy participants. Recruitment criteria were healthy participants between the ages of 18 and 50 with no reported history of neurological illness or damage or pain disorders.

A total of 215 participants took part in the study, with seven participants excluded from further analysis due to missing trial data. The final sample consisted of 208 participants, consisting of 121 females, mean age = 24.97 years old (SD = 5.19, range = 18 - 49). This study was conducted in accordance with the Declaration of Helsinki and was approved by the Local Ethical Committee of Region Midtjylland, Denmark. Informed consent was obtained from all participants prior to the start of the study.

Tasks

The experimental paradigm involved placing a single (32 x 32 mm) peltier-based contact thermode (TSA stimulator, Medoc Advanced Medical Systems) on the dorsal surface of the participant's forearm and assessing thermal thresholds across both innocuous and noxious temperature ranges. We measured cold and warm thermal thresholds (i.e., detection, TSL and pain thresholds) following the procedure and instructions provided in the German Research Network on Neuropathic Pain (DFNS) Quantitative Sensory Testing (QST) battery (Maier et al., 2010; Rolke, Baron, et al., 2006; Rolke, Magerl, et al., 2006).

Subsequently, participants completed an adapted version of the TSL task (Schaldemose et al., 2022), where we defined three levels of thermal contrast, by controlling the warm starting temperature prior to each trial. In this task, participants were instructed to press a button as soon as they experienced a specific change in sensation during the cooling phase of a single thermal probe. The temperature of the probe ramped down, at a rate of 1ºC/sec, from one of three possible starting temperatures that defined our contrast conditions (32, 38 or 44ºC) eliciting a neutral, warm, or hot sensation, respectively. Once the probe reached the baseline temperature of 32ºC, an auditory tone was played to mark the start of the trial, prompting the participant to provide a response based on the given instructions. Participants were informed to press a button when they experienced any change in sensation (innocuous condition) or a painful sensation (noxious condition) and verbally report the quality of the sensation they experienced (e.g., cold, warm, cold pain or heat pain). The two task conditions were defined as innocuous and noxious to represent the quality of stimuli the participant should be experiencing in absence of any PHS, and to clearly distinguish TSL thresholds with cold and warm thermal detection and cold and heat pain thresholds defined through QST. If the starting temperature was set to baseline, 32ºC, the tone was played after two seconds of baseline temperature stimulation. After participants had pressed the button, the temperature of the probe increased at a rate of 1ºC/sec until it reached the fixed starting temperature (32, 38 or 44ºC), at which point the temperature decreased again, creating a temporal pattern of alternated warming and cooling of the skin (Figure 1C).

Variables

Dependent variables of interest were the prevalence and rate of paradoxical heat sensation (PHS) and thermal sensory limen (TSL) thresholds. A PHS was defined as the perception of warmth or heat (innocuous condition) or heat pain (noxious condition) during cooling of the skin. TSL thresholds corresponded to the temperature on the skin at the time of the participant's response and reflected the temperature at which participants experienced a change in thermal sensation (innocuous condition) or a painful percept (noxious condition) during cooling of the skin. Thermal contrast was quantified for each trial in each condition, in each participant using the Thermal Contrast Function (TCF, Equation 1, Figure 1C), which divides the difference between the warm and cold temperatures in each trial by the difference between the max and min temperature cut-offs (i.e., 50ºC - 0ºC).

$$TCF = \frac{T_{warm} - T_{cold}}{T_{max\,warm} - T_{min\,cold}} \quad (1)$$

Procedure

Participants completed six trials (three practice, three experimental) for each contrast (32, 38 or 44ºC) and task condition (innocuous and noxious), resulting in a total of 36 TSL trials per participant. A single trial consists of the temperature probe increasing to the set maximum temperature, before decreasing past baseline (32ºC). At which point a tone was played to indicate the probe was in the cooling phase of the TSL. The temperature of the probe decreased until the point at which the participant detected a change in sensation or pain and then returned to the baseline temperature. The order of task conditions and starting temperatures was the same for all participants. Participants completed the innocuous TSL condition first before the noxious TSL condition. In both innocuous and noxious conditions, the first starting temperature was 32ºC, followed by 38ºC and then 44ºC. Task and trial orders were specifically chosen to reduce the likelihood of carryover effects from noxious stimulation of the skin into subsequent trials and dependent variables were extracted from the three experimental trials only.

Statistical analyses

All data analyses were performed using RStudio in R and results, figures and analysis code are available on GitHub (https://github.com/Body-Pain-Perception-Lab/PHS-SKN). All linear and logistic regression models were run using the *lme4* package in R (Bates et al., 2015).

The association between thermal contrast and the rate and prevalence of PHS was assessed using three McNemar's tests, to determine whether the difference between PHS number increased with increasing contrast level separately for innocuous and noxious conditions. Next, we conducted two mixed effect logistic regression models each with a fixed effect of thermal contrast (low 32ºC, medium 38ºC and high 44ºC) and random effect of participant ID, to test whether thermal contrast predicted the prevalence of innocuous (Model 1A) and noxious PHS separately (Model 1B). Due to the absence of a clear relationship between contrast conditions and noxious PHS, we conducted any following analyses on PHS that occurred during the innocuous TSL only.

$$innocuousPHS \sim contrastCondition + (1|ID) \quad \text{(Model 1A)}$$

$noxiousPHS \sim contrastCondition + (1|ID)$ (Model 1B)

To test the effect of contrast (starting temperature) on TSL threshold temperatures during innocuous and noxious conditions, we used two mixed-effect linear regression models (Models 2A and 2B) each with a fixed effect of contrast condition and random intercept of participant ID. Next, we ran a mixed effect logistic regression model with fixed effects of normalised (z-scored) innocuous and noxious TSL threshold to assess the relationship between TSL thresholds and PHS prevalence (Model 2C).

$innocuousTSL \sim contrastCondition + (1|ID)$ (Model 2A)
$noxiousTSL \sim contrastCondition + (1|ID)$ (Model 2B)
$innocuousPHS \sim innocuousTSL * noxiousTSL + (1|ID)$ (Model 2C)

To test whether thermal contrast predicts PHS prevalence, we modelled trial-by-trial thermal contrast (TCF) values in three mixed-effect logistic regression models (Models 3A-C). Fixed effects included the innocuous thermal contrast for each trial and the mean noxious thermal contrast across trials and a random intercept of participant ID. Both innocuous and noxious TCF values were transformed using log10 normalisation. To compare performance between the four contrast models (1A, 3A-C) to predict PHS, the areas under (AUC) receiver operator characteristic (ROC) curves were used to calculate model accuracy. To assess this uncertainty around AUC estimates, data were resampled, using the *resample* package in R (Hesterberg, 2022) into training and test data-sets, both of the same size as the original data. Each model was repeatedly (n=2000) fitted on a training data set, and performance of the model evaluated on a test data set. Bootstrapped samples were then used to model 95% confidence intervals fitted AUCs for each logistic regression model. This approach was chosen to test model accuracy over cross-validated n-fold to reduce the likelihood of over-inflation of accuracy due to the rare prevalence of PHS in certain conditions (e.g. number of innocuous PHS in the low contrast condition was 17/208).

To determine whether PHS is related specifically to thermal contrast during TSL over detection thresholds defined in the QST protocol, a final mixed-effect logistic regression model was conducted with warm and cold detection and pain thresholds measured through QST as fixed effects and participant ID as a random intercept.

$innocuousPHS \sim innocuousTCF * noxiousTCF + (1|ID)$ (Model 3A)
$innocuousPHS \sim innocuousTCF + (1|ID)$ (Model 3B)
$innocuousPHS \sim noxiousTCF + (1|ID)$ (Model 3C)

Author contributions

F.F. and K.S. conceived the study. A.G.M., M.B., A.S.C., J.F.E., C.S.D., R.A.B. and F.F. contributed ideas that led to the final analyses. A.G.M., J.F.E., M.B. and F.F. analysed the data. A.G.M., M.G.A., and F.F. wrote the manuscript. All authors discussed the results and contributed to the final version of the manuscript.

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