Assessing Individual Sensitivity to the Thermal Grill Illusion: A Two-Dimensional Adaptive Psychophysical Approach

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Short-running title: Psychophysics of the Thermal Grill Illusion

Abstract

In the thermal grill illusion (TGI), the spatial alternation of non-noxious warm and cool temperatures elicits burning sensations that resemble the presence of noxious stimuli. Previous research has largely relied on the use of specific temperature values (i.e., 20°C and 40°C) to study this phenomenon in both healthy individuals and patient populations. However, this methodology fails to account for inter-individual differences in thermal sensitivity, limiting the precision with which TGI responses can be evaluated across diverse populations. To address this gap, we created a Two-Dimensional Thermal Grill Calibration (2D-TGC) protocol, enabling an efficient and precise estimation of the combinations of warm and cool temperatures needed to elicit burning sensations tailored to each individual. By applying the 2D-TGC protocol in 43 healthy participants, we demonstrated key findings: (1) The TGI can be thresholded using an adaptive psychophysical method. (2) Multiple combinations of warm and cool temperatures can elicit this phenomenon. (3) The protocol facilitated the identification of temperature combinations that elicit TGI with varying levels of probability, intensity, and perceived quality ranging from freezing cold to burning hot. (4) TGI responsivity can be quantified as a continuous variable, moving beyond the conventional classification of individuals as responders vs. non-responders based on arbitrary temperature values in the innocuous temperature range. The 2D-TGC offers a comprehensive approach to investigate the TGI across populations with altered thermal sensitivity, and can be integrated with other methods (e.g., neuroimaging) to elucidate the mechanisms responsible for perceptual illusions in the thermo-nociceptive system.

Perspective

This study reveals that the Thermal Grill Illusion can be accurately measured using psychophysical methods. The innovative Two-Dimensional Thermal Grill Calibration protocol allows for personalized temperature assessments, enhancing our understanding of thermal sensitivity variations and perceptual illusions in the thermo-nociceptive system across different populations.

Keywords: Pain, Thermosensation, Psychophysics, Thermal Grill Illusion, 2D-TGC

Introduction

Perceptual illusions represent a category of phenomena where the subjective experience of a stimulus diverges from its physical characteristics. Illusions challenge conventional understanding of perception, illustrating how sensory processing creates percepts that are seemingly counterintuitive with respect to the actual properties of a stimulus. Rather than mere deceptions, illusions reveal consistent, quantifiable responses, in terms of both eliciting conditions and perceptual attributes.[1]

Psychophysics has been pivotal in characterizing perceptual illusions, utilizing rigorous methodologies to map stimulus properties to subjective perception. While substantial progress has been made in various sensory domains, including visual and tactile,[2,3] the thermoceptive and nociceptive domains remain comparatively unexplored. Among thermo-nociceptive perceptual phenomena, the thermal grill illusion (TGI) is still not well understood. The TGI manifests as a burning sensation elicited by interlaced innocuous warm and cool stimuli on the skin.[4,5] Counterintuitively, this spatial alternation does not result in the perception of each individual stimulus independently, but instead gives rise to a new, qualitatively distinct sensation characterized by unique attributes of combined hot, cold and burning sensations.[7,8]

Progress in our understanding of the TGI has been constrained by a narrow focus on predetermined stimulation parameters, as for example temperatures of 20°C and 40°C,[4,5,9-16] or values that deviate by only one or two degrees Celsius from this standard set of warm and cool temperatures.[17-22] The reliance on fixed temperature combinations overlooks inter-individual variability in thermal perception and has led to an overly simplistic categorization of individuals as responders or non-responders,[14,23-27] without an adequate characterization of variability in temperature parameters at which the illusion manifests. Existing studies utilized fixed sets of temperatures found a responsiveness rate as low as 20-25%.[25]

Previous efforts to calibrate TGI temperatures on an individual basis involved setting these temperatures at a uniform distance from the thermal pain thresholds,[24,28-33] using a semi-automated procedure based on the method of constant stimuli,[7,34-36] or by asking participants to report when a gradual decrease in cold temperatures and increase in warm temperatures became painful.[37] These methods indicated large inter-individual variation in responsiveness, and estimated the response rate up to 70-80%,[24,29,36] significantly enhancing the proportion of the population in which TGI can be studied. The substantial differences in the response rate between studies using fixed vs. individually tailored temperatures indicates the importance of accounting for unique thermal sensitivity profiles when assessing TGI.

While previous TGI calibration methods offer some advantages over the fixed approaches, they still suffer from some limitations. The assumption of a uniform relationship between the thresholds for pain and for TGI may not be valid for all individuals. Further, the method of constant stimuli is in general inefficient and time-consuming. Finally, the use of dynamic temperature changes when assessing pain thresholds does not accurately mimic the temporal characteristics of TGI, where stimulation temperatures are maintained constant for an extended period, from several seconds up to minutes.

To address the lack of adaptive psychophysical investigations of TGI perception, we developed and validated an adaptive thresholding method. This method delineates a participant-specific Thermal Grill Psychometric Function (TGPF) within warm and cool temperature dimensions. This psychophysical calibration offers several advantages: it establishes a standardized and automated procedure, requiring 30 to 40 minutes for completion, and enables the assessment of individual differences in TGI thresholds without relying on dichotomous classifications such as responders vs. non-responders. Most significantly, this approach allows more precise, and efficient estimates of this perceptual illusion in terms of probability of occurrence, perceived intensity and quality of the sensation elicited from freezing cold to burning hot.

Materials and methods

Participants

The study involved 43 healthy individuals, across two experiments. The first experiment included 28 participants (age = 25.3 ± 5.6, 14 males), while the second experiment included 15 participants (age = 26.3 ± 6.6, 5 males). Across both experiments we maintained consistent inclusion and exclusion criteria. Participants were physically and psychologically healthy, as determined by the absence of any major neurological, psychiatric or pain-related disorder, and could not have made use of any analgesic medications or recreational drugs, either regularly or in the week leading up to the experiment. These criteria were based on self-reports. Prior to the inclusion in the study, all participants received comprehensive briefings regarding the research procedures and provided their informed consent. The study adhered to the ethical guidelines outlined in the Declaration of Helsinki and received approval from the local Institutional Review Board at the Danish Neuroscience Center at Aarhus University.

Sample size considerations

As this is the first investigation using the 2D-TGI protocol, there were no prior studies to inform power calculations or effect size estimates. Consequently, we based our sample size on common practices in psychophysical research. We ensured that the sample size was sufficient to investigate the phenomena under study while also allowing for replication of our initial findings in a second experiment.

Stimuli

All thermal stimuli were delivered using a Thermal Cutaneous Stimulator (TCS II, QST.Lab), comprising five distinct stimulation zones. Stimuli designed to elicit the TGI consisted of three zones set to warm temperatures and two zones to cool temperatures, arranged in an alternated spatial pattern. Unimodal stimuli consisted of either three adjacent zones set to warm temperatures, or two adjacent zones set to cool temperatures only. The remaining zones were maintained at a baseline temperature of 30°C (Fig 1). The two experiments involved the use of two distinct TCS II probes. In experiment 1, we used a T06 probe, with each stimulation zone measuring 7 x 28mm, covering a surface area of 10 cm2, and a nominal rate of temperature change of 20°C/s. In experiment 2, we used a T11 probe, with each stimulation zone measuring 7.4 x 24.2 mm, resulting in a total surface area of 9 cm2, and a nominal rate of temperature change of 100°C/s. In both experiments, the ramp rate was set to the maximum allowed by each thermode, and each stimulus was maintained at target temperature for two seconds, before the temperature of all five zones returned to baseline (30°C). The inter-trial interval, before the next stimulus presentation, lasted between two and four seconds. The thermode was repositioned every three trials to one of three possible locations on the volar forearm, to minimize potential habituation or sensitization effects. Further, the order of stimulus presentation was randomized both within and across participants to control for potential variability in sensitivity across the distinct zones of the volar forearm. The computerized task was created with the Psychophysics Toolbox Version 3 (PTB-3).[38]

Procedure

We developed an adaptive thresholding procedure aimed at accurately identifying combinations of warm and cool temperatures that elicit the distinct burning sensation characteristic of the TGI. From these data, we derived the TGPF, detailing the relationship between specific warm and cool temperature combinations and the corresponding probabilities of reporting a burning sensation (Fig 2A). In addition to TGI thresholding, we assessed unimodal cold and heat burning pain psychometric functions using a Bayesian adaptive thresholding procedure known as "Psi".[29] Finally, to validate our TGI thresholding approach, participants rated the intensity of their perceived cold, warm and burning sensations using three sequential Visual Analog Scales (VAS) in response to a subset of stimuli defined based on TGI thresholds, as well as unimodal cold and heat pain thresholds.

Adaptive staircasing: Estimating TGI thresholds

For staircasing of the TGI, we developed a two-dimensional adaptive procedure to identify combinations of warm and cool temperatures that elicited burning sensations. This staircase was implemented using the Functional Adaptive Sequential Testing (FAST) toolbox[39] (https://github.com/edvul/FAST-matlab) in MATLAB (R2020a). The FAST toolbox enables the adaptive testing of multiple dimensions simultaneously by augmenting the mathematical characterization of the psychometric function (Ψ) (Fig 2B), relating a given performance level on a task not only to the intensity of a single independent variable and the steepness of the curve, but also by considering the influence of a mediating variable. The relationship between the independent variable and the mediating variable is mathematically described by the threshold function F (Fig 2C). This function can take many shapes and is characterized by an array of parameters, which are estimated experimentally.

This approach is constrained by three assumptions: i) the psychometric function (Ψ) translates independently across the threshold function F; ii) the slope is constant for points along the threshold function F; and iii) other parameters of the psychometric function (lapse and guess rates) are fixed. The algorithm is initiated with priors for each parameter and employs Bayes' theorem to update the posterior probability distribution iteratively, ensuring that the prior for each trial is the previous trial's posterior. The FAST toolbox can be flexibly applied in various sensory systems and experimental conditions, requiring three main definitions tailored to each specific setup: the configuration of the threshold function F's equation, a sampling strategy, and a criterion for optimization.

In this study, we modeled the probability of experiencing burning sensations (p) using a logistic psychometric function (Ψ) with inverse steepness (S), as a function of warm (t_w) and cool (t_c) temperatures. These warm and cool temperatures were linked by the threshold function F as detailed in Equation 1. The priors for t0 and t30 were specified as Gaussian distributions, N(30,10) and N(50,10), respectively. Meanwhile, the parameters λ and S were assigned uniform distributions within the ranges 0 - 4 and 0.001 - 20, respectively. The adaptive procedure determined which temperatures to present for each trial using the following sampling strategy. First, the algorithm randomly selected a cold temperature (t_c) within the range between 0°C to 27°C (Experiment 1) and 0°C to 30°C (Experiment 2), with discrete intervals of 3°C. Second, it dynamically adjusted the warm temperatures (t_w) to aim for a specific response probability (25%, 50%, or 75% levels), assigned randomly for each trial. To do so, it determined the most likely values for each free parameter (posterior modes) and used them to determine the warm temperature needed to achieve the target burning probability. This optimization process was repeated, starting from the random selection of a temperature in the cold range, if the selected t_w exceeded 50°C or was below the baseline temperature (t_b).

Adaptive staircasing: Estimating thermal pain thresholds

For adaptive staircasing of cold and heat burning (i.e., pain) thresholds, we used the Psi method, implemented via the Palamedes toolbox[40] in MATLAB (R2020a). Psi is a Bayesian adaptive algorithm designed for efficient estimation of psychometric function parameters, specifically the threshold (location parameter) and slope (rate-of-change parameter).[41] It operates by iteratively updating a posterior probability distribution on these parameters based on each response of the participant, to optimize stimulus placement for threshold and slope estimations. A similar approach was previously used to estimate the threshold and slope of psychometric functions for cold and warm detection.[42,43]

In Experiment 1, individual pain thresholds were estimated based on 30 stimuli, using a logistic psychometric function and uniform priors. The heat pain threshold prior was set within the range of 35°C to 50°C, while the cold pain one spanned from 0°C to 29°C. The slope prior ranged from 0.001 to 6. The guess rate was set to 0, and the lapse rate was set to 0.1. In Experiment 2, each pain threshold was estimated based on 50 stimuli, using a cumulative normal psychometric function. The heat pain threshold prior was uniform in the 35°C to 50°C range, while for cold pain it spanned from 0°C to 30°C. The value of the slope prior ranged from 0.001 to 6. The guess and lapse rates were both set to 0.05. The changes implemented in Experiment 2 were aimed to enhance the precision and reliability of pain threshold estimates.

Additionally, in Experiment 2 we introduced 10 demonstration trials before cold and warm pain threshold assessments, with the aim to familiarize the participants with the procedure and with different stimulation intensities. The intensities of these trials were determined using an up-down staircase, with step size decreasing as a function of the number of reversals. For cold pain, the initial temperature value was set at 20°C, and the initial downward step size was 5°C. The downward step size gradually decreased at each reversal at a rate of 1°C, and was coupled with a consistent upward step size of 2°C. Cold temperature cut-offs were 0°C and 30°C. For heat pain, the initial temperature value was set at 38°C, the initial upward step size was 3°C, diminishing at a rate of 1°C at each reversal, while the downward step size was fixed at 2°C. Warm temperature cut-offs were 35°C and 50°C.

For each stimulus trial in either experiment, participants were asked to report whether they felt a burning sensation using a binary yes/no answer. The choice of wording to prompt the participant response was identical for both TGI and unimodal procedures. This consistency in wording was deliberately maintained across all procedures to minimize potential biases in perception and facilitate participants' use of a consistent criterion for their responses.

Refining the boundaries of the three dimensional TGI surface

While we defined a three-dimensional surface of warm-cool temperature pairs that were associated with specific probabilities of burning perception for each individual (i.e., the TGPF), these temperatures were not limited to the innocuous thermosensory range. We thus constrained the boundaries of the surface post hoc, based on the pain thresholds obtained using the Psi procedure, to define a TGI region where combinations of innocuous temperatures trigger an illusion of pain. Importantly, the temperatures presented to the participants were constrained within a range between minimum 0°C for cold and maximum 50°C for heat.

Subjective validation of the TGPF

To validate whether we adequately induced an illusion of pain, we asked participants to provide subjective ratings reflecting their perception of TGI and non-TGI control stimuli. TGI stimuli consisted of warm and cool temperature pairs along three curves, corresponding to probabilities of 25%, 50% and 75% of reporting a burning sensation. For each of these isoprobable curves, we selected three equidistant points within the TGI range (temperature pairs at the first, second and third quartile of each curve). Non-TGI control stimuli were the same warm and cool temperatures that comprised the TGI stimuli, but presented individually and paired with the baseline temperature of 30°C. Each unique TGI and non-TGI temperature combination was repeated five times, for a total of 135 stimulation trials, presented in a randomized order. After each stimulus, participants rated the intensity of their cold, warm, and burning sensations utilizing three separate Visual Analog Scales (VAS), presented in a randomized order. The lower limit (i.e., 0) corresponded to a complete absence of a sensation, while the upper extreme (i.e., 100) indicated the most intense sensation.

To investigate the perceived thermosensory quality of TGI and non-TGI stimuli, we calculated a thermosensory index reflecting whether each stimulus was perceived as predominantly cold or warm, based on cold and warm VAS ratings. This index was computed as the ratio of cold ratings to the sum of cold and warm ratings. In cases where the variable was undefined (i.e., both cold and warm ratings were zero), the ratio was set to 0.5.

Statistics

We analyzed perceptual variables of interest (VAS ratings, thermosensory index) using a mixed effects zero one inflated beta (ZOIB) regressions, with the logit link function, within the GAMLSS package in R.[44] Each VAS rating was analyzed using a separate ZOIB model (Table S1-S4). This modeling approach was appropriate to accurately account for the bounded nature of the VAS rating scale as well as the presence of zeros and ones in our data. Zero values were provided by a participant if they did not perceive any burning sensation or if the thermosensory rating contradicted the stimulation quality (e.g., cold ratings for warm stimuli and warm ratings for cool stimuli). The proportions of zeros were 24.4 ± 3.0% (mean ± standard error of the mean) for cold ratings, 15.9 ± 2.2% for warm ratings and 21.4 ± 3.3% for burning ratings. Instead, one values corresponded to the maximum rating the participants could provide. The proportions of ones were 0.5 ± 0.4% for cold ratings, 0.3 ± 0.2% for warm ratings and 0.6 ± 0.3% for burning ratings. The models concerning the distribution of ones only included an intercept for each participant, due to the low proportion of data points.

The mixed effect models concerning beta and zero distributions included the main effects and interactions of interest specified in the main text and in the supplementary tables (Table S1-S3). All models included trial number and stimulus duration as covariates. The trial number was considered to account for potential habituation or sensitization effects over time. The stimulus duration specifically reflected the time needed from baseline to two seconds at peak temperature, influenced by the target temperature itself and thermode performance. The random effects structure of the models included participants nested within the two experiments to effectively account for the use of two different thermodes across Experiment 1 and 2. Between experiment variance was negligible, indicating that the results from the two experiments were highly consistent.

Data visualization

Data were visualized using custom scripts in matlab and R, using the ggplot2 package and raincloud plots.[45]

Patient and public involvement in research

Patients and public were not involved in the study's conceptualization, design, conduct or dissemination of the study results.

Results

Adaptive psychophysical assessment of the Thermal Grill Psychometric Function (TGPF)

We aimed to identify specific combinations of warm and cool temperatures that evoke the burning sensation characteristic of the TGI. To achieve this, we estimated the TGPF using a two-dimensional adaptive method.[49] Formally, the TGPF is defined by two independent functions (Equation 1): a logistic psychometric function (Ψ) with a steepness parameter (S), which maps temperature pairs to the probability of experiencing a burning sensation (p); and a threshold function (F) that describes how different combinations of cool/cold (t_c), warm/heat (t_w) and baseline (t_b) temperatures influence the perception of burning. The threshold function includes three parameters: t0 (the warm temperature when t_c is 0°C), t30 (the warm temperature when t_c is 30°C), and λ (which captures the curvature of the function). The four free parameters (t0, t30, λ and S) are interactively estimated using a Bayesian approach.

$$\{ p = \Psi\left(t_w, \alpha, S\right) = \frac{1}{1+e^{-\frac{(t_w-\alpha)}{S}}}, \ where\ \alpha = F\left(t_c, t_0, t_{30}, \lambda\right) = t_0 + \left(t_{30} - t_0\right)\left(1 - \left(\frac{t_b-t_c}{t_b}\right)\right)^{\lambda}$$

The Thermal Grill Illusion is amenable to psychophysical thresholding

To demonstrate that the TGI can be quantitatively assessed using psychophysical thresholding, we analyzed individual variations in the estimated parameters after 100 trials (Fig 3A). For each parameter, we calculated the population mean ± standard error of the mean, by bootstrapping the individual level means and standard errors. The distribution of the parameters displayed a varied range of values, reflecting differences in sensitivity to TGI among individuals: t0 (32.1±11.3), t30 (49.4±7), λ (1.5±1.5) and S (4.1±2.7). Further, we investigated how trial-by-trial parameter estimates and their uncertainties evolved over trials (Fig S1-S2) and observed that the parameters' standard error consistently declined over the time course of the protocol, signifying increased precision in parameter estimates.

To characterize individual differences in TGI sensitivity, we plotted both group average and individual psychometric functions, focusing on a fixed cool temperature of 20°C (Fig 3B). The group average showed that a warm temperature of 41.7°C was required to achieve a 50% probability of reporting a burning sensation when paired with 20°C. The 95% confidence interval for this warm temperature was between 40.6°C and 43°C. Individual psychometric functions varied considerably, with some participants requiring lower warm temperatures and others needing higher temperatures to experience similar burning sensations. This variability highlights the limitations of using one-size-fits-all temperature stimuli in TGI studies and underscores the importance of individualized calibration.

In Fig 4, we presented TGPFs for 16 representative participants to showcase the variability in TGI sensitivity. In these graphs, the three colored curves represent temperature combinations eliciting a burning sensation with 25%, 50% and 75% probability. Additionally, a dashed black curve indicated the estimated boundary where participants reported sensations as predominantly cold or warm. Individual participants' stimulation parameters were represented by dots. The lower and upper bounds of each burning probability curve was determined by cold and heat psychometric functions. Thus, temperature pairs for which $t_c < \Psi cold(p)$ or $t_w > \Psi heat(p)$ are not displayed. These results corroborated the notion of considerable inter-individual variability in TGI sensitivity, not only in terms of probability of occurrence, but also concerning the thermosensory qualia associated with the illusion.

Defining the boundaries of the Thermal Grill Illusion

While the TGPF maps a range of temperature combinations that induce burning sensations, these combinations may include temperatures in both innocuous and noxious ranges. To focus on the true TGI, where innocuous temperatures elicit pain-like sensations, we established boundaries based on individually determined cold and heat burning (i.e., pain) thresholds. We assessed cold and heat pain psychometric functions separately, identifying specific temperatures that participants perceived as burning when presented alone. These thresholds served as the lower and upper limits of the TGI region within the three-dimensional TGPF surface. The mean threshold parameters were $\alpha = 5.3 \pm 6.1$°C for cold pain (Fig S3) and $\alpha = 45.2 \pm 2.7$°C for heat pain (Fig S4), with slope parameters $\beta = 0.9 \pm 1.9$ for cold pain (Fig S3) and $\beta = 0.7 \pm 0.9$ for heat pain (Fig S4).

Evaluating the probability of occurrence, magnitude, and quality of TGI perception

To validate our TGPF-based temperature combinations, participants rated burning (Fig 5A-C), cold (Fig 5D-F), and warm (Fig 5G-H) sensations, using Visual Analog Scales (VAS) after receiving specific TGI and control stimuli. The TGI stimuli consisted of warm and cool temperature pairs along three curves corresponding to 25%, 50%, and 75% probabilities of experiencing a burning sensation. For each probability level, three equidistant temperature pairs were selected. These temperatures corresponded to the first, second and third quartiles within the range demarcated by cold and heat pain psychometric functions at the two extremes. Control stimuli involved presenting the same warm and cool temperatures individually, paired with a baseline temperature.

Participants rated the intensity of their burning, cold, and warm sensations after each stimulus. These VAS ratings were analyzed using mixed effects zero one inflated beta regressions. Analyses on the beta distribution (i.e., continuous values greater than 0 and less than 1) revealed that TGI stimuli elicited significantly more intense burning sensations compared to the corresponding unimodal stimuli. Specifically, the intensity of burning sensations increased during TGI (Fig 5B), compared to unimodal cool stimuli ($\beta = -0.26$, 95% CI = [-0.44; -0.07], $p < .05$, Fig 5A), or unimodal warm stimuli ($\beta = -0.38$, 95% CI = [-0.57; -0.18], $p < .0001$, Fig 5C). Further, for all types of stimuli, the intensity of burning sensations increased with increasing burning probability levels ($\beta = 1.66$, 95% CI = [1.44; 1.88], $p < .0001$, Fig 5B) and this increase was more pronounced (steeper slope) for TGI compared to unimodal cool stimuli ($\beta = -0.78$, 95% CI = [-1.12; -0.44], $p < .0001$, Fig 5A) or warm stimuli ($\beta = -0.47$, 95% CI = [-0.83; -0.11], $p < .05$, Fig 5C).

For cold sensations, TGI stimuli and unimodal cool stimuli elicited similar cold intensity ratings ($\beta = 0.10$, 95% CI = [-0.06; 0.27], p = 0.21, Fig 5D and 5E), but the increase in cold sensation with higher burning probability levels was significant only for unimodal cool stimuli ($\beta = 0.78$, 95% CI = [0.46; 1.09], $p < .0001$, Fig 5D), and not for TGI stimuli ($\beta = -0.03$, 95% CI = [-0.28; 0.22], p = 0.81, Fig 5E). Further, for warm sensations, TGI stimuli and unimodal warm stimuli elicited similar warm intensity ratings ($\beta = -0.08$, 95% CI = [-0.23; 0.08], p = 0.33, Fig 5H and 5I). The increase in warm sensations with higher burning probability levels was significant for both TGI ($\beta = 1.70$, 95% CI = [1.49; 1.91], $p < .0001$, Fig 5H) and unimodal warm stimuli ($\beta = -0.60$, 95% CI = [-0.89; -0.30], $p < .0001$, Fig 5I).

These findings are in line with the conceptualization of the TGI as reflecting heat enhancement, accompanied by burning or painful sensations. This clear pattern of responses validated the effective elicitation of the TGI using TGPF, and demonstrated how the selection of distinct temperatures effectively shapes the illusion in accordance with varying probability levels.

Assessment of the thermosensory qualia of TGI perception

While we revealed a modulation of the intensity of burning sensations across three distinct burning probability levels, the TGI burning sensation was remarkably consistent within each probability level. For temperature combinations within the same isoprobable curve, corresponding to the first, second, and third quartiles within the range demarcated by cold and heat pain psychometric functions, participants reported similar burning sensations ($\beta = -0.03$, 95% CI = [-0.17; 0.11], $p = 0.69$, Fig 5). This finding aligns with the principles of the TGPF, indicating that a diverse range of temperature combinations can induce similar burning sensations. However, despite consistent burning sensations within each probability level, the perceived thermal quality of the TGI varied depending on the specific temperature pairs. To quantify this, we calculated a thermosensory index for each stimulus, defined as the ratio of the cold rating to the sum of cold and warm ratings. An index closer to one indicates a predominantly cold perception, while an index closer to zero suggests a predominantly warm perception. This ratio provides information on how individuals perceive the thermal aspect of the TGI, beyond the intensity of burning sensations alone (Fig 6).

Our analysis showed that the thermosensory index for TGI stimuli varied significantly with different temperature pairs within the same probability level. This variation was more pronounced for TGI stimuli compared to unimodal warm stimuli ($\beta = 0.48$, 95% CI = [0.08; 0.88], $p < .05$, Fig 6), and unimodal cool stimuli ($\beta = 0.47$, 95% CI = [0.10; 0.84], $p < .05$, Fig 6). This result indicated that as we moved along the same equiprobable curve, we observed larger variations in the perceived thermosensory quality of the TGI stimuli, compared to when the unimodal stimulus was either warm or cool. In addition, a main effect of burning probability indicated that with increasing burning probability, the perceived thermosensory quality became predominantly warmer, irrespective of stimulus type ($\beta = -0.46$, 95% CI = [-0.62; -0.30], $p < .0001$, Fig 6). Overall, these results indicate that it is in principle possible to identify temperature combinations that elicit TGI with distinct thermosensory attributes, from cold to warm, within the same individual.

Continuous characterization of TGI responsivity

TGI responsivity is defined by the positive difference between burning ratings for temperature pairs vs. individual temperature stimuli. However, previous research has largely defined TGI responsivity dichotomously as responders vs. non-responders based on how participants responded to fixed temperature pairs, most commonly 20 and 40°C. Our approach based on TGPF estimation allows for the continuous characterization of TGI responsivity by calculating a responsivity index. To analyze TGI responsivity, we rescaled burning ratings from 0 to 1, and computed the mean burning rating for each of the three types of stimuli at each of the three burning probabilities. We then subtracted the mean burning sensation elicited by the TGI stimulus from the mean burning sensation elicited by the unimodal stimulus associated with the strongest burning sensation. This yielded a value for each participant and burning probability, ranging from -1 to 1; where negative values indicated enhanced burning sensation for the unimodal stimulus, while positive values indicated enhanced burning sensation for temperature combinations, using identical objective temperatures. A value of 0 suggested no difference between the burning ratings when stimuli were unimodal or temperature pairs. Using uncertainty propagation, we derived a 68% and 95% confidence intervals for each participant and burning probability for the responsivity index. The resulting distribution in our sample is depicted in Fig 7 and Fig S5, sorted from lowest to highest responsivity index within each burning probability. It is important to note that, at least in this study, it was not possible to distinguish whether some individuals were truly non-responders (e.g., sensitivity index overlapping zero) or whether the protocol reached suboptimal estimates for those individuals.

Discussion

This study has established the Thermal Grill Illusion (TGI) as a quantifiable phenomenon through the application of psychophysical methods. By introducing the Two-Dimensional Thermal Grill Calibration (2D-TGC) protocol, we provided a psychophysical framework capable of delineating a range of temperature combinations that effectively induce TGI. This method can estimate varying probabilities of experiencing the illusion, and pinpoint distinct temperature combinations eliciting varying degrees of perceived intensity and thermosensory quality, thus accounting for the considerable variability in how this phenomenon is perceived by different individuals.

Validation of the 2D-TGC protocol was achieved using Visual Analog Scale (VAS) ratings from participants, confirming the successful elicitation of the illusion through the spatial alternation of warm and cool temperatures, as opposed to presenting each temperature individually. Participants reported burning sensations of similar magnitude across all temperature combinations along the same isoprobable curve, corresponding to the probabilities of 25%, 50%, and 75% for reporting burning sensations. This demonstrated that a variety of temperature combinations can equally provoke the illusion. Further, we showed large inter-individual variability with respect to the required warm temperature when the cool temperature was set at 20°C, indicating the limitations of choosing fixed temperatures, such as 20°C and 40°C, to assess the TGI.[4,5,9-11,13-16] In particular, using our specific thermode, 20°C needed to be paired with a temperature between 40.6 and 43°C to elicit the illusion with 50% probability in most individuals.

One unique advantage of this approach is its capability of quantitatively characterizing two perceptual dimensions inherent to the TGI, related to illusory pain and temperature enhancement. Characteristically, the TGI manifests as pronounced burning sensations, accompanied by enhanced perception of warmth or cold.[6,8,36] We showed that burning sensations increased in magnitude depending on the specific isoprobability curve (increasing from 25% to 50% and 75%) and that thermosensory qualities varied depending on both the quartile (increased heat progressing from the first to the second and the third quartiles) and the isoprobability curve (increased heat progressing from 25% to 50% and 75%) from which the temperature pairs were sampled. These results indicate that the TGI can manifest with a broad spectrum of intensity and thermosensory qualities within the same individual. Our approach thus quantifies not only between-subject variability in this phenomenon, but also captures within-subject variations in how the illusion is experienced across a comprehensive range of temperature values.

Previous research aiming to calibrate TGI temperatures based on individual pain thresholds found an association between the magnitude of the TGI and the difference between warm and cool stimuli, suggesting that larger temperature differentials correlate with a higher likelihood of experiencing the illusion.[24,28] The 2D-TGC method enhances this understanding by precisely defining the threshold function F, which quantifies the impact of temperature differentials on the probability of perceiving the illusion. Furthermore, our approach incorporated a parameter-optimization procedure that customizes these temperature differentials for each individual, thereby accommodating and fine-tuning the protocol to reflect each participant's unique sensitivity to the burning sensation.

Overall, the 2D-TGC provides an efficient and precise tool for TGI assessment, with key implications for future experimental and clinical research. This approach supersedes the traditional dichotomous classification of participants into responders or non-responders based on static, arbitrary temperature values in the innocuous temperature range, a practice previously commonplace in the field, (e.g.,[14,20,26].) As a result, our approach addresses common challenges associated with participant recruitment by eliminating the need to exclude non-responders at the screening stage or to limit analysis to a subset of responders. Further, it allows for the assessment of TGI responsivity on a continuum, rather than a dichotomous attribute, offering a granular quantification of the TGI phenomenon across multiple perceptual features.

The ability to adaptively titrate the TGI through psychophysical staircasing is particularly relevant for clinical studies involving between-group comparisons. Previous studies investigating whether TGI is enhanced or reduced in specific clinical populations failed to account for the inter-individual differences in thermal sensitivity (e.g.,[21,22].) Given the proposed role of TGI as a model for chronic pain in conditions such as central neuropathic[46,47] and nociplastic pain,[11,29] adopting an approach that captures the entire spectrum of individual responses to TGI is crucial for elucidating its significance in clinical settings.

A key limitation of our modeling approach is the assumption of a fixed slope across the surface defined by the TGPF. An improved version would account for changes in slopes, especially at the edges of the TGI region. We expect that steeper slopes towards the heat pain boundary and flatter curves towards the cold pain boundary may provide a more accurate representation of the space of temperatures eliciting this illusion. However, an increased number of trials would be necessary for estimating varying slopes.

A second limitation is the choice of stimulation patterns. In this specific experiment, we only tested one spatial pattern consisting of three warm and two cool zones in alternation. Results may differ with other spatial patterns, such as two warm and two cool, or two warm and three cool stimuli in alternation. The approach described in this study can be adapted to test potential differences associated with the equal or unequal spatial distribution of contrasting temperatures.

A third limitation concerns the uncertainty related to the true nature of the thermosensory input for some of the stimulation temperatures. The classic definition of the TGI posits that the illusion occurs when innocuous thermosensory inputs elicit a perception typically associated with nociceptive activity. However, we could not neurophysiologically confirm the absence of any nociceptive activity in response to intense heat or cold temperatures. Our view of the TGI departs from its mainstream interpretation, as we interpret this phenomenon as related to spatial contrast enhancement, along a continuum from innocuous to noxious temperatures. Future research is warranted to further investigate this phenomenon across both innocuous and noxious temperatures to fully comprehend the mechanisms underlying spatial contrast enhancement in thermosensation and nociception.

Irrespective of these limitations, we provide evidence for the feasibility of thresholding procedures to capture different features of a perceptual phenomenon related to thermo-nociceptive interactions. This approach can be combined with neurophysiological or neuroimaging techniques to better understand the underlying mechanisms of TGI and can be applied in clinical studies to assess the relationship between TGI and chronic pain in diverse populations. Further, this multi-dimensional approach can be potentially adapted to investigate other thermal and pain phenomena, such as paradoxical heat sensations, a phenomenon similar to the TGI, but involving the temporal alternation of warming and cooling on the same skin area.[48-50]

In summary, we provided a principled psychophysical approach to calibrate the probability of TGI occurrence, and to quantify TGI responses across a comprehensive spectrum of perceptual states. This spectrum includes the entire range of sensations, from the intensity of burning sensations to the perception of the illusion on a continuum between freezing cold and burning heat. Our findings highlight the importance of adopting a multi-dimensional psychophysical framework for TGI assessment, facilitating an accurate representation of inter-individual differences in temperature and pain perception. Our method can be used in future studies to investigate illusions of pain in various clinical conditions, particularly those associated with chronic pain.

Code and data availability statement

All code and data will be available on GitHub and OSF following acceptance of the manuscript.

Disclosures

This work was supported by the European Research Council under the grants ERC-2020-StG-948838 (FF, CSD, JEF, AGM, CEK) and ERC-2020-StG-948788 (MGA, ASC). We also acknowledge funding from the Lundbeck Foundation under the grants R272-2017-4345 (MGA, NN) and R436-2023-991 (FF, JEF). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Acknowledgements

We thank Ed Vul for insightful comments on a preliminary version of the TGPF. We also thank Patrik Molnar and Sára Anna Szabó for help with data collection.

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Figure Legends

Fig 1. Experimental protocols and response parameters in the assessment of TGI perception. In the 2D-Thermal Grill Calibration participants received stimuli composed of interlaced warm (depicted in red) and cool (depicted in blue) zones for 2 seconds at the target temperature. They provided binary responses indicating the presence or absence of a burning sensation, and their perception as predominantly warm or cold. In the Cold Pain Calibration, stimuli consisting solely of cold zones were presented, and participants responded with a binary choice regarding the presence of a burning sensation. In the Heat Pain Calibration, stimuli consisting solely of warm zones were presented, and participants similarly responded with a binary choice about the sensation of burning. For validation purposes, participants provided VAS ratings for specific combinations of warm and cool temperatures eliciting TGI and non-TGI control stimuli, which consisted of unimodal warm or cool temperatures. Following each stimulus presentation, participants rated the intensity of their cold, warm, and burning sensations using three independent VAs scales, presented sequentially.

Fig 2. Illustration of the two-dimensional thermal grill calibration (2D-TGC) method. (A) The Thermal Grill Psychometric Function (TGPF) is characterized by two independent functions. **(B)** The first function (Ψ), depicted in black, represents an invariant psychometric function, mapping the probability of reporting a burning sensation from 0 to 1 at different cool and warm temperatures. **(C)** The second function (F), illustrated in purple, delineated how the perception of burning changes depending on different warm and cool temperatures. Through this approach, we successfully identified several pairs of warm and cool temperatures that were isoprobable, meaning that they induced a burning sensation with an equivalent likelihood at 25%, 50% and 75% probability levels. The boundaries of these isoprobable curves were defined by cold pain threhsolds, depicted by the blue area labeled as "Noxious Cold", and heat pain thresholds, depicted by the red area labeled as "Noxious Heat". We thus effectively mapped a 3D surface, indicated as "TGI region". Temperature combinations selected for VAS ratings are represented using three separate symbols, indicating the 1st (squares), 2nd (circles) and 3rd (triangles) quartiles of the TGI range at three specified probability levels of reporting a burning sensation. This protocol provides a comprehensive framework for assessing the TGI, which can be instrumental in both research and clinical settings.

Fig 3. Detailed analysis of the Thermal Grill Psychometric Function (TGPF). (A) Population distribution of the four parameters defining the TGPF. Dots represent individual data points. **(B)** Group average and individual psychometric functions defining the relationship between a set cool temperature of 20°C and the estimated warm temperatures required to elicit TGI, in the probability range from 0 to 1. Individual participants are represented by light gray lines, while the group mean estimates are depicted by a thick purple line. The shaded purple area around the population mean represents the 95% confidence interval, obtained using bootstrapping. The dashed line represents the group mean warm temperature (41.7°C) required to elicit TGI with a 50% probability, when the cool temperature is 20°C. The 95% confidence interval around this mean corresponds to [40.6°C; 43°C]. Overall, these results indicate considerable variations in the warm-cool temperature combinations needed to elicit TGI sensations across individuals and challenge the use of one-size-fits-all temperature stimuli in TGI assessment.

Fig 4: Thermal Grill Psychometric Functions (TGPF) for a subset of representative participants (N = 16). Each panel corresponds to an individual participant, with dots representing temperature pairs administered during the 2D-TGC procedure. The color of each dot reflects the binary response (cold/warm) provided by the participant. Blue dots indicate that participants selected cold, while red indicates that participants selected warm as a descriptor for their perceived thermosensory quality. The three colored curves indicate the estimated curves that elicited burning sensations with 25%, 50% and 75% probability (from bottom to top). The curves were color-coded to reflect the probability with which participants categorized the elicited sensations at a given temperature pair as either cold (blue) or warm (red). This was performed by weighting each point based on its euclidean distance from the curve. Dashed black lines represent the demarcation between cold vs. warm TGI sensations, after refitting the model using as input the quality of the TGI percept, instead of the presence/absence of burning. The two methods (euclidean distance and model refitting) provided highly similar outputs. Overall, these results indicate that it is feasible to identify several warm and cool temperature combinations that elicit TGI, with different levels of probability, and perceived thermosensory quality.

Fig 5: Overview of subjective ratings for TGI and non-TGI control stimuli. Mean VAS ratings (burn, cold, and warm) across different stimulus types: cool (A, D, G), TGI (B, E, H) and warm (C, F, I), and across three burning probabilities: $p = 0.25$, $p = 0.50$ and $p = 0.75$. Individual participant means are indicated by small dots and black lines connect the median value of the three burning probability levels. We show that the TGI was perceived as more burning than individual cool (A vs. B) and warm (B vs. C) stimuli. Further, the TGI was perceived as less cold than individual cool stimuli (D vs. E), but warmer than individual warm stimuli (H vs. I). Data points from isoprobable curves, corresponding to the three probability levels of reporting a burning sensation, were indicated by three variations of the same color.

Results showed that burning and warm ratings increased with increasing burning probability. However, distinct temperature pairs, belonging to the same isoprobable curve, elicited burning and warm sensations of similar intensity.

Fig 6. Perceived thermosensory qualities of TGI at equivalent intensity of burning sensation. TGI perception is typically characterized by burning sensations coupled with enhanced cold or warm thermosensory qualities. To quantify these thermosensory qualities in TGI perception, we derived a thermosensory index where values closer to one indicate a stronger sensation of cold, and values closer to zero indicate a more pronounced sensation of warmth. Each participant's average perception is represented by a small dot. The results revealed significant variability in thermosensory quality among individuals for stimuli that elicited comparable levels of burning sensations. While some individuals reported TGI as primarily cold, others experienced it as predominantly warm. However, on average, the data shows a group tendency towards the perception of warmth during TGI. This warmth perception varied with the intensity of the temperature pairs, with those in the first quartile being reported as colder compared to the more intensely warm sensations reported in the second and third quartiles. This pattern of results is compatible with the view that TGI reflects heat enhancement.

Fig 7. Responsivity index conditional on burning probabilities. The figure displays the responsivity index for three burning probabilities ($p = 0.25$, $p = 0.50$ and $p = 0.75$). The responsivity index is calculated as the difference between the mean burning rating elicited by the temperature combinations (i.e., TGI stimuli) and the mean burning rating elicited by either unimodal cool or warm (the highest mean rating is selected). Positive values indicate higher burning perception during TGI compared to the unimodal stimulus, 0 means no difference in the burning sensation across stimulus typed, and negative values indicate higher burning sensations for the unimodal stimulus compared to the temperature pairs. Using uncertainty propagation, we calculated the 68% confidence interval for the responsivity index of each participant, corresponding to one standard error above and below the mean in a normal distribution. A similar figure depicting the 95% confidence interval, corresponding to 1.96 standard errors above and below the mean in a normal distribution is reported as a supplementary figure (Fig S5). The y-axis represents individual participants ordered based on the magnitude of the thermosensory index (from low to high). This analysis demonstrates how TGI responsivity can be characterized continuously.

References

1. Nour MM, Nour JM. Perception, illusions and Bayesian inference. *Psychopathology*. 2015;48(4):217-221. doi:10.1159/000437271

2. Eagleman DM. Visual illusions and neurobiology. *Nat Rev Neurosci*. 2001;2(12):920-926. doi:10.1038/35104092

3. Longo MR, Haggard P. Weber’s illusion and body shape: Anisotropy of tactile size perception on the hand. *J Exp Psychol Hum Percept Perform*. 2011;37(3):720-726. doi:10.1037/a0021921

4. Craig AD, Bushnell MC. The thermal grill illusion: Unmasking the burn of cold pain. *Science*. 1994;265(5169):252-255. doi:10.1126/science.8023144

5. Craig AD, Reiman EM, Evans A, Bushnell MC. Functional imaging of an illusion of pain. *Nature*. 1996;384(6606):258-260. doi:10.1038/384258a0

6. Bach P, Becker S, Kleinböhl D, Hölzl R. The thermal grill illusion and what is painful about it. *Neurosci Lett*. 2011;505(1):31-35. doi:10.1016/j.neulet.2011.09.061

7. Fardo F, Finnerup NB, Haggard P. Organization of the Thermal Grill Illusion by Spinal Segments. *Ann Neurol*. 2018;84(3):463-472. doi:10.1002/ana.25307

8. Fardo F, Beck B, Allen M, Finnerup NB. Beyond labeled lines: A population coding account of the thermal grill illusion. *Neurosci Biobehav Rev*. 2020;108:472-479. doi:10.1016/j.neubiorev.2019.11.017

9. Averbeck B, Rucker F, Laubender RP, Carr RW. Thermal grill-evoked sensations of heat correlate with cold pain threshold and are enhanced by menthol and cinnamaldehyde. *Eur J Pain*. 2013;17(5):724-734. doi:10.1002/j.1532-2149.2012.00239.x

10. Averbeck B, Seitz L, Kolb FP, Kutz DF. Sex differences in thermal detection and thermal pain threshold and the thermal grill illusion: A psychophysical study in young volunteers. *Biol Sex Differ*. 2017;8(1):29. doi:10.1186/s13293-017-0147-5

11. Bäumler P, Brenske A, Winkelmann A, Irnich D, Averbeck B. Strong and aversive cold processing and pain facilitation in fibromyalgia patients relates to augmented thermal grill illusion. *Sci Rep*. 2023;13(1):15982. doi:10.1038/s41598-023-42288-7

12. Horing B, Kerkemeyer M, Büchel C. Temporal Summation of the Thermal Grill Illusion is Comparable to That Observed Following Noxious Heat. *J Pain*. 2024;25(5). doi:10.1016/j.jpain.2023.11.015

13. Hunter J, Dranga R, Wyk M van, Dostrovsky JO. Unique influence of stimulus duration and stimulation site (glabrous vs. Hairy skin) on the thermal grill-induced percept. *Eur J Pain*. 2015;19(2):202-215. doi:10.1002/ejp.538

14. Jutzeler CR, Warner FM, Wanek J, Curt A, Kramer JLK. Thermal grill conditioning: Effect on contact heat evoked potentials. *Sci Rep*. 2017;7(1):40007. doi:10.1038/srep40007

15. Leung A, Shukla S, Li E, Duann JR, Yaksh T. Supraspinal characterization of the thermal grill illusion with fMRI. *Mol Pain*. 2014;10:18. doi:10.1186/1744-8069-10-18

16. Matsuda S, Igawa Y, Uchisawa H, Iki S, Osumi M. Thermal Grill Illusion in Post-Stroke Patients: Analysis of Clinical Features and Lesion Areas. *J Pain Res*. 2023;16:3895-3904. doi:10.2147/JPR.S433309

17. Harper DE, Hollins M. Coolness both underlies and protects against the painfulness of the thermal grill illusion. *Pain*. 2014;155(4):801-807. doi:10.1016/j.pain.2014.01.017

18. Harper De, Hollins M. Conditioned pain modulation dampens the thermal grill illusion. *Eur J Pain*. 2017;21(9):1591-1601. doi:10.1002/ejp.1060

19. Li X, Petrini L, Wang L, Defrin R, Arendt-Nielsen L. The importance of stimulus parameters for the experience of the thermal grill illusion. *Neurophysiol Clin*. 2009;39(6):275-282. doi:10.1016/j.neucli.2009.06.006

20. Lindstedt F, Lonsdorf TB, Schalling M, Kosek E, Ingvar M. Perception of Thermal Pain and the Thermal Grill Illusion Is Associated with Polymorphisms in the Serotonin Transporter Gene. *PLoS One*. 2011;6(3):e17752. doi:10.1371/journal.pone.0017752

21. Sumracki NM, Buisman-Pijlman FTA, Hutchinson MR, Gentgall M, Rolan P. Reduced response to the thermal grill illusion in chronic pain patients. *Pain Med*. 2014;15(4):647-660. doi:10.1111/pme.12379

22. Kim HC, Chang MC, Oh SH, Lee SB, Yang SY, Shin DA. Thermal Grill Illusion in Chronic Lower Back Pain: A Case-Control Study. *J Pain Res*. 2023;16:1573-1579. doi:10.2147/JPR.S403387

23. Bekrater-Bodmann R, Chung BY, Richter I, et al. Deficits in pain perception in borderline personality disorder: Results from the thermal grill illusion. *Pain*. 2015;156(10):2084-2092. doi:10.1097/j.pain.0000000000000275

24. Bouhassira D, Kern D, Rouaud J, Pelle-Lancien E, Morain F. Investigation of the paradoxical painful sensation ('illusion of pain') produced by a thermal grill. *Pain*. 2005;114(1-2):160-167. doi:10.1016/j.pain.2004.12.014

25. Schaldemose EL, Horjales-Araujo E, Svensson P, Finnerup NB. Altered thermal grill response and paradoxical heat sensations after topical capsaicin application. *Pain*. 2015;156(6):1101. doi:10.1097/j.pain.0000000000000155

26. Scheuren R, Sütterlin S, Anton F. Rumination and interoceptive accuracy predict the occurrence of the thermal grill illusion of pain. *BMC Psychol*. 2014;2(1):22. doi:10.1186/2050-7283-2-22

27. Scheuren R, Duschek S, Schulz A, Sütterlin S, Anton F. Blood pressure and the perception of illusive pain. *Psychophysiology*. 2016;53(8):1282-1291. doi:10.1111/psyp.12658

28. Adam F, Alfonsi P, Kern D, Bouhassira D. Relationships between the paradoxical painful and nonpainful sensations induced by a thermal grill. *Pain*. 2014;155(12):2612-2617. doi:10.1016/j.pain.2014.09.026

29. Adam F, Jouët P, Sabaté JM, et al. Thermal grill illusion of pain in patients with chronic pain: A clinical marker of central sensitization? *Pain*. 2023;164(3):638-644. doi:10.1097/j.pain.0000000000002749

30. Caston RM, Davis TS, Smith EH, Rahimpour S, Rolston JD. A novel thermoelectric device integrated with a psychophysical paradigm to study pain processing in human subjects. *J Neurosci Methods*. 2023;386:109780. doi:10.1016/j.jneumeth.2022.109780

31. Kern D, Pelle-Lancien E, Luce V, Bouhassira D. Pharmacological dissection of the paradoxical pain induced by a thermal grill. *Pain*. 2008;135(3):291-299. doi:10.1016/j.pain.2007.12.001

32. Kern D, Plantevin F, Bouhassira D. Effects of morphine on the experimental illusion of pain produced by a thermal grill. *Pain*. 2008;139(3):653-659. doi:10.1016/j.pain.2008.07.001

33. Schaldemose EL, Raaschou-Nielsen L, Böhme RA, Finnerup NB, Fardo F. It is one or the other: No overlap between healthy individuals perceiving thermal grill illusion or paradoxical heat sensation. *Neurosci Lett*. 2023;802:137169. doi:10.1016/j.neulet.2023.137169

34. Böhme RA, Banellis L, Vejlø M, Allen M, Fardo F. No evidence for a link between mental health symptoms and thermal pain thresholds. PsyArXiv. Preprint. Published online January 2024. doi:https://doi.org/10.31234/osf.io/bc627

35. Ehmsen JF, Nikolova N, Christensen DE, et al. Uncertainty in Thermosensory Expectations Enhances an Illusion of Pain. BioRxiv. Preprint. Published online March 2024. doi:10.1101/2024.03.27.587070

36. Mitchell AG, Ehmsen JF, Christensen DE, Stuckert A, Haggard P, Fardo F. Disentangling the spinal mechanisms of illusory heat and burning sensations in the Thermal Grill Illusion. *Pain*. 2024; 165:2370–8. doi:10.1097/j.pain.0000000000003352

37. Defrin R, Benstein-Sheraizin A, Bezalel A, Mantzur O, Arendt-Nielsen L. The spatial characteristics of the painful thermal grill illusion. *Pain*. 2008;138(3):577-586. doi:10.1016/j.pain.2008.02.012

38. Kleiner M, Brainard D, Pelli D, Ingling A, Murray R, Broussard C. What's new in psychtoolbox-3. *Perception*. 2007;36(14):1-16.

39. Vul E, Bergsma J, MacLeod DIA. Functional adaptive sequential testing. *Seeing Perceiving*. 2010;23(5-6):483-515. doi:10.1163/187847510x532694

40. Prins N, Kingdom FAA. Applying the Model-Comparison Approach to Test Specific Research Hypotheses in Psychophysical Research Using the Palamedes Toolbox. *Front Psychol*. 2018;9:1250. doi:10.3389/fpsyg.2018.01250

41. Kingdom FAA, Prins N. Psychometric Functions. In: Kingdom FAA, Prins N, eds. *Psychophysics (Second Edition)*. Academic Press; 2016:55-117. doi:10.1016/B978-0-12-407156-8.00004-9

42. Courtin AS, Slootjes SM, Caty G, Hermans MP, Plaghki L, Mouraux A. Assessing thermal sensitivity using transient heat and cold stimuli combined with a Bayesian adaptive method in a clinical setting: A proof of concept study. *Eur J Pain*. 2020;24(9):1812-1821. doi:10.1002/ejp.1628

43. Courtin AS, Delvaux A, Dufour A, Mouraux A. Spatial summation of cold and warm detection: Evidence for increased precision when brisk stimuli are delivered over larger area. *Neurosci Lett*. 2023;797:137050. doi:10.1016/j.neulet.2023.137050

44. Rigby RA, Stasinopoulos DM. Generalized additive models for location, scale and shape. *J R Stat Soc, C: Appl Stat*. 2005;54(3):507-554. doi:10.1111/j.1467-9876.2005.00510.x

45. Allen M, Poggiali D, Whitaker K, Marshall TR, Langen J van, Kievit RA. Raincloud plots: A multi-platform tool for robust data visualization. *Wellcome Open Res*. 2019;4:63. doi:10.12688/wellcomeopenres.15191.2

46. Craig BAD. Can the basis for central neuropathic pain be identified by using a thermal grill? *Pain*. 2008;135(3):215-216. doi:10.1016/j.pain.2008.01.022

47. Rosner J, Andrade DC de, Davis KD, et al. Central neuropathic pain. *Nat Rev Dis Primers*. 2023;9(1):1-19. doi:10.1038/s41572-023-00484-9

48. Schaldemose EL, Andersen NT, Finnerup NB, Fardo F. When cooling of the skin is perceived as warmth: Enhanced paradoxical heat sensation by pre-cooling of the skin in healthy individuals. *Temperature*. 2023;10(2):248-263. doi:10.1080/23328940.2022.2088028

49. Mitchell AG, Fischer Ehmsen J, Basińska M, et al. Thermal contrast enhancement predicts paradoxical heat sensation. *Commun Psychol*. 2024;2(1):1-8. doi:10.1038/s44271-024-00083-8

50. Vollert J, Fardo F, Attal N, et al. Paradoxical heat sensation as a manifestation of thermal hypesthesia: A study of 1090 patients with lesions of the somatosensory system. *Pain*. 2024;165(1):216-224. doi:10.1097/j.pain.0000000000003014