

Relationships between the paradoxical painful and nonpainful sensations induced by a thermal grill



Frédéric Adam^{a,1}, Pascal Alfonsi^{a,1}, Delphine Kern^a, Didier Bouhassira^{a,b,*}

^aInserm U-987, Centre d'Evaluation et de Traitement de la Douleur, CHU Ambroise Paré, Assistance Publique Hôpitaux de Paris, Boulogne-Billancourt, France

^bUniversité Versailles-Saint-Quentin, Versailles, France

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ABSTRACT

The simultaneous application of innocuous cutaneous warm and cold stimuli with a thermal grill can induce both paradoxical pain and paradoxical warmth (heat). The goal of this study was to investigate further the relationships between these paradoxical sensations. Stimuli were applied to the palms of the right hands of 21 volunteers with a thermode consisting of 6 bars, the temperature of which was controlled by Peltier elements. We assessed the quality and intensity of the sensations evoked by series of stimuli consisting of progressively colder temperatures combined with a series of given warm temperatures. We applied a total of 116 series of stimuli, corresponding to 785 combinations of warm and cold temperatures. The 2 paradoxical phenomena were reported for most of the series of stimuli ($n = 66$). In each of these series, the 2 phenomena occurred in the same order: paradoxical warmth followed by paradoxical pain. The difference between the cold–warm temperatures eliciting paradoxical warmth was significantly smaller than that producing paradoxical pain. The intensities of the warmth and unpleasantness evoked by the stimuli were directly related to the magnitude of the warm–cold differential. Our results suggest that there is a continuum between the painful and nonpainful paradoxical sensations evoked by the thermal grill that may share pathophysiological mechanisms. These data also confirm the existence of strong relationships between the thermoreceptive and nociceptive systems and the utility of the thermal grill for investigating these relationships.

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1. Introduction

The simultaneous application of innocuous cutaneous warm and cold stimuli with a thermal grill induces paradoxical painful (burning) and nonpainful (warmth or heat) sensations. These phenomena, first described over a century ago [1,44], have been reinvestigated in a number of recent studies [4–7,9,16,21,23–26,28,32,33,36,37,42].

The sensation of heat was first described at the end of the 19th century, but its nature and its relationships to pain were not clearly defined. In particular, it was not clear whether heat represented a new qualitatively different sensation or whether it was merely a composite of cold and warm sensations [8]. Nonpainful synthetic

heat has been reported in recent studies [23–25], but it also has been repeatedly demonstrated that with appropriate stimulus parameters, stimulation with a thermal grill consisting of alternate warm and cold bars induces a paradoxical painful burning sensation [9,16,21,36]. In particular, we showed in a large group of volunteers that the occurrence and intensity of paradoxical pain were directly related to the magnitude of the difference in temperature between the warm and cold bars of the grill [9].

In our previous study [9], we also observed a nonpainful paradoxical increase of warmth sensation with some of the thermal grill combinations. Our findings suggested that this paradoxical increase of warmth, which might correspond to the heat sensation described by early authors, was evoked by a smaller difference in temperature between the warm and cold bars than those producing paradoxical painful burning. However, we were unable to confirm these results, suggesting a possible continuum between the nonpainful and painful paradoxical sensations evoked by the thermal grill, because there were too few instances of small temperature differences in our experimental conditions.

* Corresponding author at: Inserm U987, Centre d'Evaluation et de Traitement de la Douleur, Hôpital Ambroise Paré, 9 Avenue Charles de Gaulle, 92100 Boulogne-Billancourt Cedex, France. Tel.: +33 (0) 1 49 09 59 46; fax: +33 (0) 1 49 09 44 35.

E-mail address: didier.bouhassira@apr.aphp.fr (D. Bouhassira).

¹ Frédéric Adam and Pascal Alfonsi contributed equally to this work.

The existence of a continuum between nonpainful and painful sensations might account for some of the conflicting results previously obtained concerning the nature of these phenomena and shed new light on their potential mechanisms. Therefore, our aim in this study was to investigate further the relationships between the painful and nonpainful paradoxical sensations evoked by the thermal grill. We systematically assessed in healthy volunteers the quality and intensity of the sensations evoked by a large range of combinations of warm and cold stimuli corresponding to temperatures systematically within the range between the normal heat and cold pain thresholds.

2. Methods

This study was performed on a group of paid healthy volunteers, with the approval of the appropriate ethics committee (CPP IdF VIII, Ambroise Paré Hospital, Boulogne-Billancourt, France). Participants were fully informed about the experimental procedures, and all gave written consent. All of the participants were right-handed and none had ever participated in a psychophysical study.

3. Study design

3.1. Equipment

As in previous studies [9,32,33], all of the thermal stimuli were produced with a thermode designed and built by Seicer (Mouy, France). The thermode consisted of 6 bars (1.2×16 cm) separated by 2 mm to ensure thermal isolation and covered with a copper plate. The temperature of the bars was controlled by thermoelectric Peltier elements (3 per bar). The temperatures of alternate (even- and odd-numbered) bars were monitored and controlled independently in the 5°C to 50°C range, generating various combinations of temperatures (ie, the patterns of the thermal grill). Thermistors within each bar provided continuous temperature feedback for the thermode–skin interface (resolution $\pm 0.3^\circ\text{C}$).

All experiments were performed at a constant ambient temperature (21°C). As in our previous studies [9,32,33], for each combination of cold and warm temperatures, volunteers were asked to place the palm of their right hand on the grill, orthogonally to the long axis of the bars, for 30 seconds. An interval of 3 minutes was left between stimuli.

3.2. Screening session

Volunteers were screened before full enrollment in the study to ensure selection of exclusively those displaying a pain response to the thermal grill–induced (paradoxical) pain. Based on the findings of our previous studies [9,32,33], responders were defined as those in whom the thermal grill–induced pain could be elicited with combinations of warm and cool stimuli at temperatures at least 4°C above the cold pain threshold (CPT) and at least 4°C below the heat pain threshold (HPT). At the beginning of the session, the neutral temperature (ie, neither cold nor warm) was determined (see later). Then the CPT and HPT were measured with a staircase algorithm. In this procedure, even-numbered bars were kept at the neutral temperature and the temperature of the odd-numbered bars was changed randomly (increased or decreased) by steps of 3°C to 0.5°C. After each stimulus, the subjects had to report whether they perceived the stimulus as painful or not. For a negative response, the next temperature step was 3°C. After the first painful stimulus, successive stimuli were changed (increased or decreased) by 0.5°C until the first nonpainful sensation was reported. Then, 2 stimuli consisting of a combination of CPT+4°C

and HPT–4°C were applied to verify the presence and stability of paradoxical pain.

3.3. Experimental session

The responders were invited to participate in 1 experimental session. At the start of the session, we determined for each subject the neutral temperature (ie, neither cold nor warm) with all the bars of the grill at the same temperature. The temperature of the palm was measured with an infrared thermometer (Thermopoint, Agema, Sweden) at the neutral temperature and then systematically before each stimulation. If the skin temperature varied by more than $\pm 0.2^\circ\text{C}$ in comparison with the baseline temperature, between 2 stimuli, the palm skin was gently cooled or heated to the control neutral temperature by direct contact with a perfusion bag set to ambient temperature or an electric warming pad (Hot-Dog Warming, Augustine Medical, Eden Prairie, MN) set to 42°C. The stimulation paradigm consisted of a series of systematic combinations of warm and cold temperatures adapted to each subject and allowing the testing of a large range of differences in temperature between the warm and cold bars of the grill.

The series of combinations of temperatures used for each subject consisted of several fixed warm temperatures combined with a series of decreasing cold temperatures. The fixed warm temperatures were: NT+2°C, NT+4°C, NT+6°C etc., up to HPT–4°C. Each of these fixed warm temperatures was combined with a series of cold temperatures: NT–2°C, NT–4°C, NT–6°C, etc., down to CPT+4°C. For example, if a volunteer had a CPT of 16°C, a HPT of 44°C, and a TN of 32°C, the following 4 series of combinations of warm and cold temperatures (that is a total of 24 stimuli) were applied:

1st series: [34°C to 30°C], [34°C to 28°C], [34°C to 26°C], [34°C to 24°C], [34°C to 22°C], [34°C–20°C].

2nd series: [36°C to 30°C], [36°C to 28°C], [36°C to 26°C], [36°C to 24°C], [36°C to 22°C], [36°C–20°C].

3rd series: [38°C to 30°C], [38°C to 28°C], [38°C to 26°C], [38°C to 24°C], [38°C to 22°C], [38°C to 20°C].

4th series: [40°C to 30°C], [40°C to 28°C], [40°C to 26°C], [40°C to 24°C], [40°C to 22°C], [40°C to 20°C].

3.4. Measurements

After each stimulus, the subjects were asked to rate the intensity of pain, unpleasantness, and warm and cold sensations felt at the end of the 30-second stimulation, on 4 different visual analog scales. These 0–100 mm visual analog scales were graduated as follows: no pain–worst possible pain, not unpleasant–very unpleasant, not hot–very hot, not cold–very cold. After the experiments, the first measurement of each series was taken as the reference for the series for the analyses of the results. The sensations elicited by the other combinations of the series were then classified into 3 categories:

Normal sensation (NS): NS corresponded to a nonpainful sensation that was described as less warm (ie, nonparadoxical) than the first stimulus of each series, consistent with the decrease in temperature of the cold bars of the grill.

Paradoxical pain (PP): PP was any painful sensation reported by the subjects that was considered as paradoxical because none of the warm and cold temperatures used in the various series exceeded the heat and cold pain thresholds. For each subject, the minimal difference between cold bar temperatures (CBT) and warm bar temperatures (WBT) evoking PP for the various series of combinations was defined as the paradoxical pain threshold.

Paradoxical increase of warmth sensation (PW): PW was defined as the sensation of greater warmth than the first

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