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Painful cold-heat segmental pulse stimulation provokes the thermal pain illusion

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ABSTRACT

Purpose/Aim: The thermal grill illusion is a paradoxical pain sensation induced by simultaneous exposure to spatially separated, non-painful, cold, and warm stimuli. This study aimed to determine whether paradoxical sensations are also evoked by simultaneous exposure to painful cold-heat stimuli and whether the mechanism involves modulation by segmental and extra-segmental spatial integration.

Materials and Methods: Sensory perceptions were triggered by simultaneous application of painful cold-heat pulse stimuli using a developed bedside tool equipped with quantitative thermal stimulator devices. Four conditions were investigated: (1) one device placed on the forearm (condition 1, control); (2) two devices placed on the forearm (condition 2, ipsilateral segmental integration); (3) two devices placed on the forearm and ipsilateral thigh (condition 3, extra-segmental integration); and (4) two devices placed bilaterally on the forearms (condition 4, contralateral segmental integration). The evoked perceptions of paradoxical heat sensation and the loss of cold or heat sensation were evaluated.

Results: The aforementioned phenomena were experienced by 11(35.4%), 3(9.7%), 3(9.7%), and 0(0.0%) subjects for conditions 1–4, respectively. Fisher's exact test revealed significant differences (p=.001) among the four conditions. However, Bonferroni *post hoc* analysis revealed significant differences only between conditions 1 and 4 (p=.005).

Conclusions: Simultaneous painful cold–heat pulse stimulation can induce paradoxical sensations similar to those shown for non-painful thermal (cold and heat) stimuli. They were predominantly evoked by ipsilateral integration. Paradoxical sensations have diagnostic value, and quantifying them using a simple bedside tool may be useful in the clinical setting.

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Painful thermal pulse stimulation; paradoxical sensation; thermal pain illusion

Introduction

Quantitative sensory testing (QST) is used to assess the progression of certain diseases, such as neuropathic pain, and to evaluate conditions involving sensory loss (small and large nerve fibre dysfunction) and gain (hyperalgesia, allodynia, and hyperpathia) (Rolke et al. 2006). QST is considered to be useful for delineating the underlying mechanisms of neuropathic pain and other chronic pain entities (Rolke et al. 2006). The German Research Network on Neuropathic Pain recommends a QST battery consisting of seven sensory tests that measure 13 parameters (Rolke et al. 2006), one of which is paradoxical heat sensation (PHS) experienced during the thermal sensory limen procedure in which the applications of warm and cold stimuli are alternated (Rolke et al. 2006). This PHS can be evaluated separately for specific diagnostic purposes (Lang et al. 2006; Rolke et al. 2006).

The "thermal grill illusion" (TGI) is a paradoxical pain sensation induced by the simultaneous application of non-painful cold and warm stimuli using a grill-like apparatus that applies the stimuli in close proximity (Craig and Bushnell 1994; Bach et al. 2011; Lindstedt et al. 2011). Although central modulation is a component of the mechanism underlying the TGI (Craig and Bushnell 1994; Craig et al. 1996; Davis et al. 2004; Kern et al. 2008; Lindstedt et al. 2011), the peripheral contribution of this sensation has been examined in less detail. The central modulation aspect of the TGI has been shown in patients with borderline personality disorder, and N-methyl-D-aspartate (NMDA)-mediated neurotransmission has been suggested to be involved (Bekrater-Bodmann et al. 2015). Additionally, another study reported that the TGI is experienced in patients with schizophrenia (Boettger et al 2013).

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PHS and the TGI are influenced by individual variability (Rolke et al. 2006), although few studies have investigated the contributing factors. As the traditional TGI is evoked by non-painful thermal pulses, it is currently unknown if exposure to painful thermal pulses can likewise provoke paradoxical sensations. It is also unknown which central integration strategy is optimal for provoking a possible paradoxical sensation.

This study had the following three aims: (1) to develop a simple bedside tool for evoking responses to the simultaneous application of painful cold and heat stimuli; (2) to determine if the simultaneous application of spatially separated, painful cold and heat stimuli can evoke paradoxical sensations; and (3) to study the influence of spatial integration in the neural mechanism by altering the spatial separations between stimuli within the same ipsilateral segment (ipsilateral segmental integration), between two different spinal segments (extra-segmental integration), and between contralateral segments (contralateral segmental integration).

Materials and methods

Subjects

The study was conducted at the Division of Dental Anaesthesiology, Department of Diagnostic and Therapeutic Sciences, Meikai University School of Dentistry. Written informed consent was obtained from all subjects before inclusion in the study, which was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Meikai University (A1507). The study was registered as a University Hospital Medical Information Network Clinical Trials Registry (UMIN-CTR) Clinical Trial (Unique ID: UMIN000037547).

Subjects were eligible to be included in the study if the following criteria were satisfied: (1) more than 20 years old; (2) healthy and pain-free; and (3) able to provide informed consent. The exclusion criteria were as follows: (1) the presence of a serious medical condition, such as any acute or chronic pain, or neurological, psychiatric, or neuromuscular diseases; (2) current use of any pain medication within the 24 hours prior to the start of the investigation; and (3) the inability to provide informed consent.

Quantitative thermal stimulator device

A customized quantitative thermal stimulator device (VTH-3500; VICS, Tokyo, Japan) was developed to deliver tonic painful pulse stimulation (Figure 1). The quantitative thermal stimulator device consisted of a ceramic contact plate (30×30 mm) that was cooled or heated with a Peltier element. The temperature was continuously measured by a thermometer placed on the surface of the Peltier element. The baseline temperature was 32 °C (neutral temperature). Temperatures ranging from 10°–40 °C were obtained with a ramp time of 5 °C/s, whereas temperatures ranging from 0 to 10 °C and 40 to 45 °C were obtained with a ramp time of 0.5 °C/s.

Assessment of temperatures for cold and heat stimuli ("decision period")

The subjective assessment of temperatures for the cold and heat stimuli was determined on the non-dominant forearm using a quantitative thermal stimulator device in a randomised order. The probe temperature was set at a neutral temperature (32.0 °C), then manually increased or decreased via a personal computer (PC) (Figure 2). For the continuous evaluation of subjective assessments of pain intensity induced by hot and cold temperatures, a custom-made electronic visual analogue scale (VAS) (0–100 mm) was applied, employing sliding electric resistance and a PC. The left endpoint (0) of the electronic VAS indicated "no pain", and the right endpoint (100) indicated the "worst pain imaginable". Subjects who did not experience a pain intensity of 70/100 mm on the VAS before reaching the cut-off temperature of 0 or 45 °C were excluded from the study. The temperatures that induced cold and heat pain at an intensity of approximately 70/100 mm on the VAS were applied in the subsequent experiment ("pulse period").

Four conditions of simultaneously applied painful thermal pulse stimulation ("pulse period")

Condition involving painful thermal pulse stimulation at one site (condition 1, control)

Painful cold–heat pulse stimulation was applied to the non-dominant forearm, 5 cm from the fossa ("site 1"), for 5 min (Figure 3(a)). The painful cold–heat pulse stimulation consisted of a sequence of repeatedly alternating cold and hot temperatures, delivered over 20 s intervals (Figure 3(b)). The pulse duration was 40 s (0.025 Hz).

Conditions involving painful thermal pulse stimulation at two sites (conditions 2, 3, and 4)

Two quantitative thermal stimulator devices (device 1 and device 2) applied cold and heat stimuli to three different sites in the three conditions (Figure 3(a)). In condition 2, the two devices were placed at "site 2" (non-dominant forearm, 5 cm apart; ipsilateral segmental integration). In condition 3, they were placed at "site 3" (non-dominant forearm and ipsilateral thigh; extra-segmental integration). In condition 4, the devices were placed at "site 4" (bilateral forearms; contralateral segmental integration). In conditions 2, 3, and 4, quantitative thermal stimulator devices were placed 5 cm from the fossa of the forearm or knee. The painful cold–neutral pulse stimulation consisted of a sequence of repeated alternations between a temperature causing cold pain and the neutral temperature (32 °C), whereas the painful heat–neutral pulse stimulation consisted of a sequence of repeated alternations between a temperature causing heat pain and the neutral temperature (32 °C) (Figure 3(b)). For all three conditions (2, 3, and 4) the stimuli were delivered repeatedly at 20 s intervals for 5 min, with a pulse duration of 40 s (0.025 Hz). Cold–neutral and heat–neutral pulse stimulations were randomly assigned to two sites in each of the three conditions, as were devices 1 and 2.

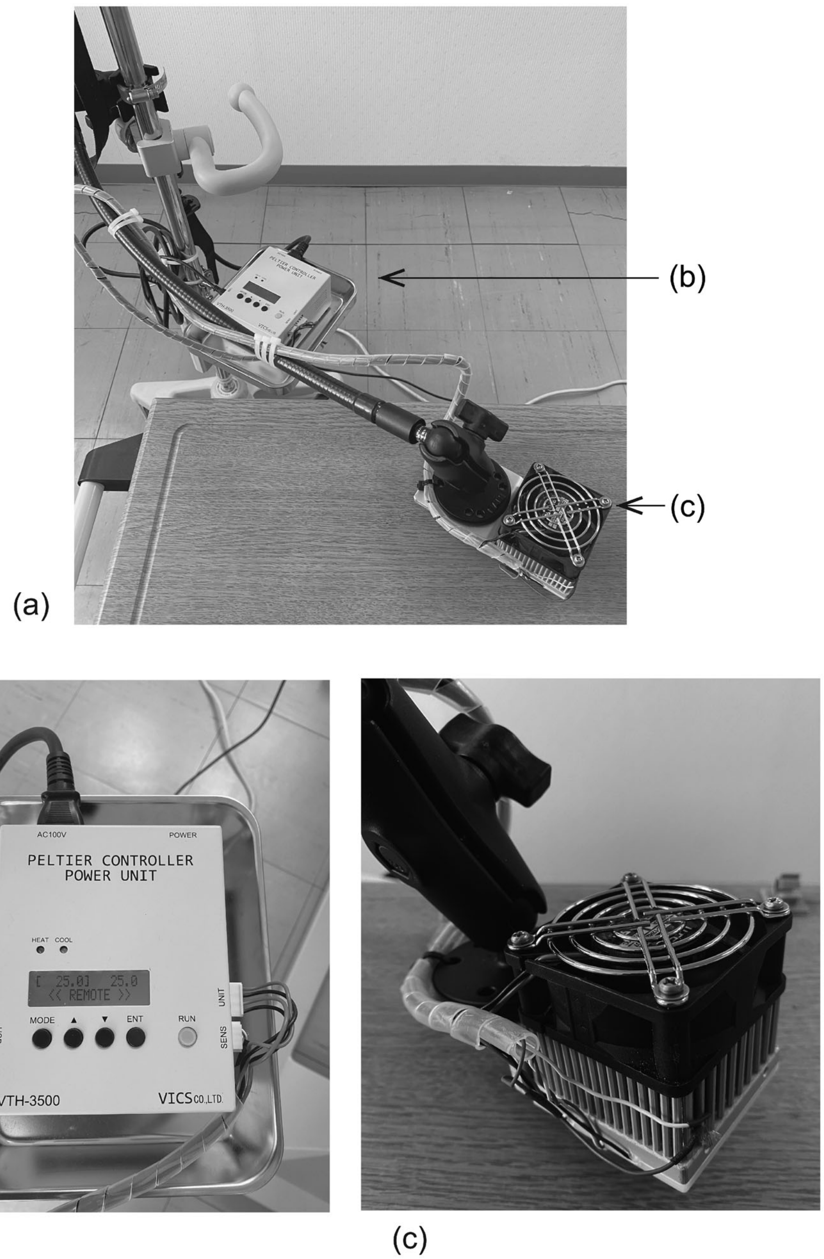

Figure 1. Quantitative thermal stimulating device (VICS, Tokyo) (a) consisting of a controller box (b) and a probe (c). (a) A broader overview of the device, with (b) representing the controller power unit and (c) representing the probe. Electric current to the Peltier element is controlled by a microcomputer in a controller box (b) connected to a PC via serial communication. Probe of the quantitative thermal stimulating device (c).

Experimental protocol

All experiments were performed at a constant room temperature (25 °C) (Figure 4). During the decision period, temperature assessments for the cold and heat stimuli were conducted in a randomizeds order at 10 min intervals using a quantitative thermal stimulator device. Initiations of the painful thermal pulse stimulation sequence (pulse period) occurred 30 min after the decision period.

In the test session, painful thermal pulse stimulation was applied, whereas the same protocol was performed in the control session but at a neutral temperature (32 °C).

Subjective sensations were evaluated by an open-ended interview question after assessing the temperatures for the cold and heat stimuli in the decision period, and for every 20 s interval in the pulse period. The phrasing of the open-ended interview question was as follows: "Please describe the sensation evoked by the thermal stimuli." The pain intensity resulting from painful thermal pulse stimulation was rated continuously using the custom-designed electronic VAS (0–100 mm). Subjects were instructed to move the VAS indicator to describe the pain evoked by painful thermal pulse stimulation. The temperature of each quantitative thermal stimulator device was continuously recorded.

The four conditions (conditions 1, 2, 3, and 4) were randomly assigned, with a 20 min break between conditions. All subjects participated in two sessions of experiments (test session and control session) one week apart, with the order decided randomly.

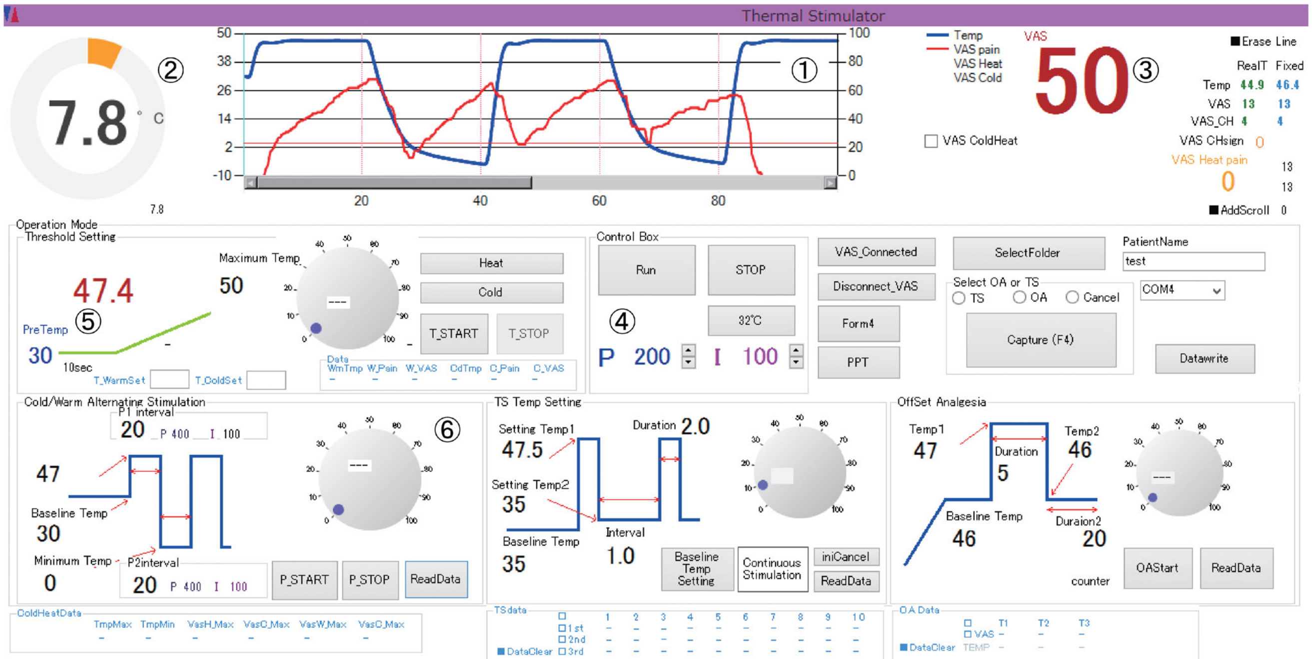

Figure 2. Layout of the PC display for adjusting the parameters of the cold and heat stimuli. (1) The area of the display showing the probe temperature (thick line) and the electronic visual analogue scale (VAS) values for cold stimulation, heat stimulation, and cold–heat pulse stimulation (thin line). (2) The areas of the display indicating the probe temperature. (3) The electronic VAS values for pain assessments. (4) Settings for the *p* value and I value. (5) Settings for cold and heat stimulation. (6) Settings for cold–heat pulse stimulation.

Data analysis

One-way analysis of variance (ANOVA) and Tukey's multiple comparison tests were used for the statistical analysis of temperature and VAS values for thermal pulse stimulation among the four conditions during the pulse period. To identify differences in the manifestation of the thermal pain illusion (TPI) among the four conditions, the data were analysed using Fisher's exact test, followed by a Bonferroni *post hoc* correction. Statistical analyses were performed using EZR (version 1.54) (Kanda 2013). Statistical significance was defined as $p<.05$. Temperatures and VAS values are presented as the mean ± standard deviation.

Sample size calculation

A priori power analysis was performed to establish the necessary sample size for this study using G*Power (Faul et al. 2007) (version 3.1.9.7), with a probability of type I error of 0.05, a power of 0.8, an effect size of 0.3, and three degrees of freedom. Based on these parameters, the power analysis demonstrated that a total sample size of 122 was required for this study.

Results

Subjects

One subject who did not report VAS values over 70 mm on the 0–100 VAS for the cold and heat stimuli was excluded from the study, resulting in a total of 31 subjects (19 men and 12 women, aged 25–45 years) included in the final analysis. Therefore, 124 samples across the four conditions were sufficient for ensuring statistical power based on the sample size calculation.

Decision period

Temperature for the cold and heat stimuli

In the test session, the temperature for the cold and heat stimuli were 3.6 ± 1.1 °C and 43.7 ± 0.8 °C, respectively. In the control session, the neutral temperatures of the two measurements were 31.9 ± 0.2 °C and 31.9 ± 0.1 °C, respectively.

VAS values for the cold and heat stimuli

In the test session, the VAS values for the cold and heat stimuli were 74.4 ± 3.0 mm and 77.3 ± 5.4 mm, respectively. In the control session, the VAS values for the neutral temperatures of the two measurements were 0.1 ± 0.4 mm and 0.1 ± 0.5 mm, respectively.

Assessment of subjective perceptions

All subjects reported cold, heat, and neutral sensations in response to cold, heat, and neutral stimuli, respectively.

Pulse period

The peak temperatures for the cold and heat stimuli in conditions 1–4 in the test and control sessions are shown in Table 1. The VAS values for the cold and heat stimuli in conditions 1–4 in the test and control sessions are shown in Table 2.

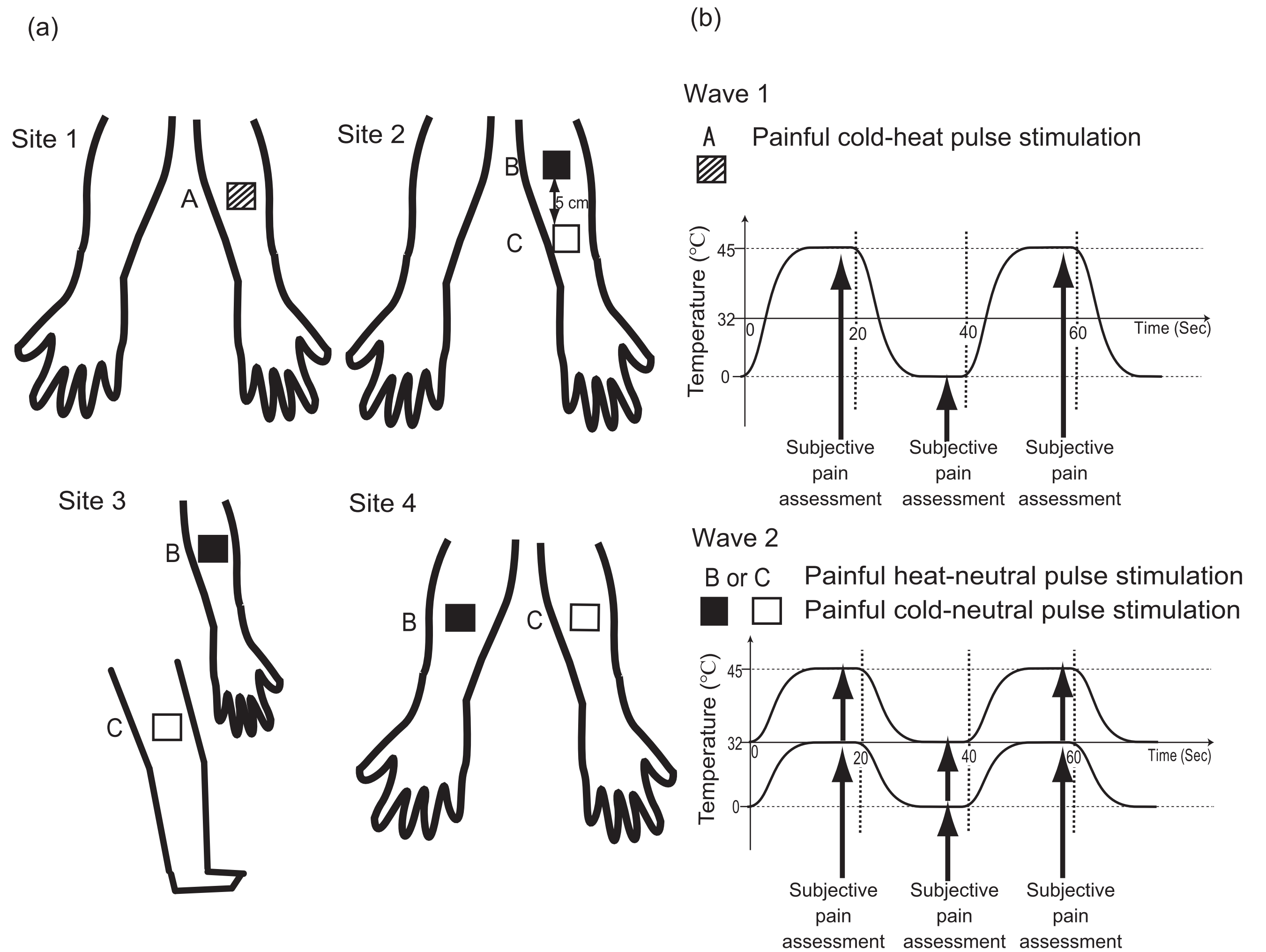

Figure 3. Conditions for the simultaneous application of painful thermal pulse stimulation. (a) Painful cold–heat pulse stimulation (pulse duration: 40 s), with one quantitative thermal stimulator device (device 1; A: hatched square) applied 5 cm from the fossa of the non-dominant forearm (site 1) (condition 1, control). Conditions with two quantitative thermal stimulator devices (devices 1 and 2; B or C: black square or white square) placed in the following locations: (1) on the non-dominant forearm, 5 cm apart (site 2) (condition 2, ipsilateral segmental integration); (2) on the non-dominant forearm and ipsilateral thigh (site 3) (condition 3, extra-segmental integration); and (3) on the bilateral forearms (site 4) (condition 4, contralateral segmental integration). Quantitative thermal stimulator devices were positioned 5 cm from the fossa of the forearm or knee. (b) Wave 1 shows an example of cold–heat pulse stimulation at temperatures of 0 °C and 45 °C, respectively (condition 1). Wave 2 shows an example of painful heat–neutral pulse stimulation (pulse duration: 40 s) at a heat temperature of 45 °C and painful cold–neutral pulse stimulation (pulse duration: 40 s) with a cold temperature of 0 °C. The neutral temperature was set at 32 °C (conditions 2, 3 and 4). Subjective sensations were assessed via open questioning for every 20 s interval. Devices 1 and 2 were randomly assigned as B or C.

Comparison of temperatures for the four conditions during the pulse period

There was no significant difference in the temperatures for the cold stimuli among the four conditions (p=.09). However, one-way ANOVA revealed a significant difference in the temperatures for the heat stimuli among the four conditions (p=.001). Tukey's multiple comparison tests revealed that the temperature for the heat stimulus in condition 1 (43.2 ± 1.1 °C) was significantly lower that of condition 2 (43.9 ± 0.8 °C, p<.01), condition 3 (44.0 ± 0.7 °C, p<.01), and condition 4 (44.0 ± 0.7 °C, p<.01) (Table 1).

VAS values for the four conditions during the pulse period

Among the four conditions, one-way ANOVA and Tukey's multiple comparison tests revealed no significant difference in VAS values for the cold or heat stimuli (p>.05 and p=.25, respectively).

Assessment of subjective perceptions

Condition 1

The following symptoms were reported by some participants: (1) heat sensation during the cold stimulus phase (PHS) (2/31 subjects), and (2) loss of cold and/or heat sensation during painful cold–heat pulse stimulation (9/31 subjects) (Table 3).

Condition 2

PHS was experienced by 3/31 subjects during the cold stimulus phase.

Condition 3

The following symptoms were reported by some of the participants: (1) heat sensation experienced during the cold stimulus phase (PHS) (one of 31 subjects); (2) heat sensation experienced at a neutral temperature during painful cold–-neutral pulse stimulation (PHS) (one of 31 subjects); and (3)

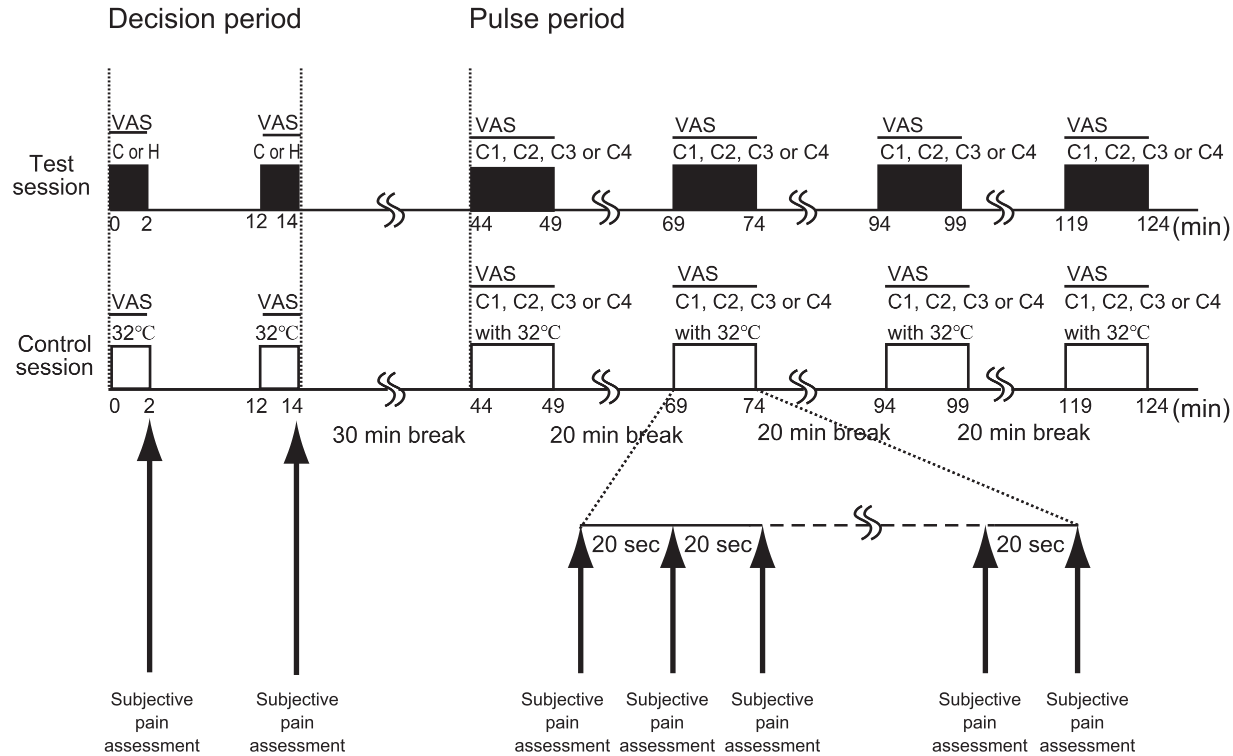

Figure 4. Timeline of the study. In the test session, assessment of temperatures for the cold and heat stimuli were conducted in a random order using a quantitative thermal stimulator device (device 1) 10 min apart (decision period). The painful thermal pulse stimulation sequence (pulse period) was initiated 30 min after the decision period. Subjective sensations were assessed via open questioning after evaluating the temperatures for the cold and heat stimuli during the decision period and for every 20-s interval in the pulse period (total duration of 5 min). The order of the four conditions (condition 1, condition 2, condition 3 and condition 4) was randomly assigned, with a 20 min break between conditions. The pain intensity resulting from painful thermal pulse stimulation was rated continuously using the electronic visual analogue scale (VAS). In the control session, a neutral temperature (32 °C) was applied and the same protocol was performed. C or H: Assessment of temperature for cold and heat stimuli, VAS: visual analogue scale. C1 (condition 1, control): One quantitative thermal stimulator device was placed on the non-dominant forearm. C2 (condition 2, ipsilateral segmental integration): Two quantitative thermal stimulator devices were placed on the non-dominant forearm, 5 cm apart. C3 (condition 3, extra-segmental integration): Two quantitative thermal stimulator devices were placed on the non-dominant forearm and ipsilateral thigh. C4 (condition 4, contralateral segmental integration): Two quantitative thermal stimulator devices were placed on the bilateral forearms.

Table 1. The peak temperatures for the cold and heat stimuli in conditions 1–4 in the test and control sessions (pulse period).

	Condition 1	Condition 2	Condition 3	Condition 4
Test session				
The peak temperature for cold stimulus (°C)	6.3 ± 2.9	6.1 ± 2.4	4.9 ± 2.0	5.5 ± 2.2
The peak temperature for heat stimulus (°C)	43.2 ± 1.1	43.9 ± 0.8*	44.0 ± 0.7*	44.0 ± 0.7*
Control session				
The neutral temperature for device 1 (°C)	31.9 ± 0.2	31.9 ± 0.2	31.9 ± 0.1	31.9 ± 0.2
The neutral temperature for device 2 (°C)	–	32.0 ± 0.1	32.0 ± 0.0	32.0 ± 0.0

$n = 31$; data are displayed as the mean ± SD. *$p < .01$ vs. condition 1. SD: standard deviation.
Condition 1: One quantitative thermal stimulator device was placed on the forearm. Condition 2: Two quantitative thermal stimulator devices were placed on the forearm, 5 cm apart. Condition 3: Two quantitative thermal stimulator devices were placed on the forearm and ipsilateral thigh. Condition 4: Two quantitative thermal stimulator devices were placed bilaterally on the forearms.

Table 2. The VAS values for the cold and heat stimuli in conditions 1–4 in the test and control sessions (pulse period).

	Condition 1	Condition 2	Condition 3	Condition 4
Test session				
VAS values for cold stimulus (mm)	55.3 ± 12.3	63.6 ± 15.7	59.8 ± 12.7	64.2 ± 13.0
VAS values for heat stimulus (mm)	69.6 ± 13.7	61.1 ± 20.0	65.1 ± 15.8	66.0 ± 15.7
Control session				
VAS values for neutral stimulus for device 1 (mm)	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
VAS values for neutral stimulus for device 2 (mm)	–	0.3 ± 1.6	0.0 ± 0.0	0.0 ± 0.0

$n = 31$; data are expressed as the mean ± SD. SD: standard deviation; VAS: visual analogue scale.
Condition 1: One quantitative thermal stimulator device was placed on the forearm. Condition 2: Two quantitative thermal stimulator devices were placed on the forearm, 5 cm apart. Condition 3: Two quantitative thermal stimulator devices were placed on the forearm and ipsilateral thigh. Condition 4: Two quantitative thermal stimulator devices were placed bilaterally on the forearms.

Table 3. Numbers and percentages of subjects who experienced the thermal pain illusion.

	Condition 1	Condition 2	Condition 3	Condition 4
TPI (+)	11 (35.4 %)	3 (9.7 %)	3 (9.7 %)	0 (0.0 %)
TPI (−)	20 (64.5 %)	28 (90.3 %)	28 (90.3 %)	31 (100.0 %)

$n = 31$, TPI: thermal pain illusion.
Condition 1: One quantitative thermal stimulator device was placed on the forearm. Condition 2: Two quantitative thermal stimulator devices were placed on the forearm, 5 cm apart. Condition 3: Two quantitative thermal stimulator devices were placed on the forearm and ipsilateral thigh. Condition 4: Two quantitative thermal stimulator devices were placed bilaterally on the forearms.

loss of cold sensation experienced during painful cold–neutral pulse stimulation (one of 31 subjects).

Condition 4

No subjects reported paradoxical or loss of cold and/or heat sensations. Fisher's exact test revealed a statistically significant difference (p=.001) among the four conditions. Bonferroni *post hoc* analysis showed a significant difference only between conditions 1 and 4 (p=.005); there were no significant differences between the other conditions (p>.05).

Discussion

In the present study, a simple bedside tool was employed for evoking responses to the simultaneous spatial application of painful cold and heat stimuli, which led some subjects to experience a paradoxical thermal sensation or a loss of thermal sensation. Specifically, the following phenomena were observed; (1) PHS during the cold stimulus phase in conditions 1, 2, and 3; (2) PHS at a neutral temperature during painful cold–neutral pulse stimulation in condition 3; (3) loss of cold or heat sensation during cold–heat pulse stimulation in condition 1; and (4) loss of cold sensation during painful cold–neutral pulse stimulation in condition 3. These paradoxical phenomena were defined as the TPI. No subject reported cold sensation during a heat stimulus phase or at a neutral temperature during painful heat–neutral pulse stimulation. To our knowledge, the present study is the first to report that the TPI can be triggered by painful cold–heat pulse stimulation in healthy human subjects.

Comparison of TPI, TGI, and PHS

Peripheral spatial integration might be critical when stimuli are delivered within a small skin area (Herget et al. 1941; Price et al. 1989). To limit such peripheral summation, the TPI was induced by applying only two stimuli, which were separated by at least 5 cm (conditions 2–4). Conversely, cortical mechanisms might contribute to the TPI in the case of multisensory integration (condition 1). For example, a previous study reported that the illusion was modulated by interactions between thermal and proprioceptive inputs (Marotta et al. 2015). Thalamic activity is increased in response to the TGI, but not to the constituent innocuous warm and cold temperatures (Lindstedt et al. 2011). Similarly, a right insular region was shown to be active in response to paradoxical heat stimulation, but was unaffected by dynamic cooling of the skin (Davis et al. 2004). These results imply that integration in the TGI can occur before the temperature-related neural signals reach the thalamic and insular regions. However, thermosensory perception is enabled by an extensive network of frontoparietal regions, indicating that supraspinal interactions are also fundamental for the generation of thermosensory perceptual experiences in both the non-painful (Fardo et al. 2017) and painful range (Davis et al. 2002). Interestingly, the centrally-mediated aspect of the TGI has been observed in patients with borderline personality disorder, and N-methyl-D-aspartate neurotransmission is believed to be involved (Bekrater-Bodmann et al. 2015). In addition, another study reported that the TGI is influenced in patients with schizophrenia (Boettger et al. 2013).

Nociceptors respond to painful thermal stimuli, generating action potentials that are propagated via the dorsal horn of the spinal cord to higher brain centres, resulting in a sensation of pain (Vay et al. 2012). PHS was reported during skin cooling as early as 1912 (Susser et al. 1999) and has been found in 10–12% of healthy individuals (Hämäläinen et al. 1982; Hansen et al. 1996). In addition, the identification of PHS may be useful for specific diagnostic purposes; for instance, for peripheral arterial disease (Lang et al. 2006; Rolke et al. 2006). The TPI is similar to PHS in that the paradoxical sensation is triggered via cold and heat stimulation. One study in healthy subjects demonstrated that PHS is conducted peripherally via slow, unmyelinated C-fibres and not via the faster Aδ-fibres, with some groups proposing that PHS is encoded via the heat sensing pathway (Susser et al. 1999). Demyelination sites located in the central nervous system have been reported in patients with multiple sclerosis who experienced PHS (Hansen et al. 1996), suggesting that supraspinal sites are important for the integration of temperature sensation and may trigger the perception of PHS (Hansen et al. 1996). Overall, both peripheral and central mechanisms contribute to PHS.

The TGI refers to paradoxical sensations of heat and pain resulting from the simultaneous application of interlaced non-painful warm and cold stimuli on the skin (Craig and Bushnell 1994). The TPI is a paradoxical phenomenon in which a sensation of heat or a loss of sensation is elicited by painful cold–heat pulse stimulation of the skin, with a contact area of 30 × 30 mm. There are several important differences between the TGI and TPI that should be noted: (1) the TGI is induced by innocuous stimuli, whereas the TPI is induced by painful cold and hot stimuli; and (2) the TGI is caused by a grill, whereas the TPI is caused by pulse stimulation. Although there are differences in the stimulus modality between the TGI and TPI, the TPI is similar to the TGI in that both paradoxical phenomena are caused by cold and heat stimulation.

Possible mechanism to provoke the TPI

In the present study, the protocols of condition 1, condition 2, and condition 3 triggered the TPI. Condition 2 was designed to evaluate the role of ipsilateral segmental integration, whereas condition 3 was designed to assess the role of extra-segmental integration. The finding that conditions 2 and 3 resulted in some subjects experiencing the TPI means that it might be caused by ipsilateral central integration.

However, it is possible that both peripheral and central mechanisms could be involved in PHS (Hansen et al. 1996; Susser et al. 1999) and the TGI (Craig and Bushnell 1994; Craig et al. 1996; Green 2002; Davis et al. 2004; Defrin et al. 2008; Kern et al. 2008; Lindstedt et al. 2011; Fardo et al. 2018; Ferrè et al. 2018), a phenomenon similar to the TPI. It is also important to note that complex crosstalk among several cold and warm thermosensitive pathways shapes thermal perception, as the appearance of the TGI and PHS were shown to be altered by capsaicin application (Schaldemose et al. 2015). In addition to the central mechanisms, these results suggest that a role of peripheral mechanisms in the TPI cannot be ruled out.

Polymodal-nociceptive neurons responds to painful cold and heat stimulation (Campero et al. 1996; Simone and Kajander 1997; Cain et al. 2001; Story et al. 2003; Moran et al. 2011; Vay et al. 2012). However, the receptors involved in cold stimulation differ from nociceptors (Vay et al. 2012). In addition, the temperature threshold for cold pain is more ambiguous than the temperature threshold for heat pain (Pertovaara and Kojo 1985). While some subjects experienced the sensation of heat during exposure to a cold stimulus, no subject reported experiencing a cold sensation during exposure to a hot stimulus, consistent with the findings of previous reports (Pertovaara and Kojo 1985). Thus, when both cold and heat receptors are co-expressed in the same sensory nerve, temperature is thought to be distinguished by differences in the mechanisms underpinning the activation of thermoreceptors, subsequent information processing, and integration (Rossi and Neubert 2009). However, the details of the mechanisms underlying this process remain unclear, and there are several possible explanations for the finding that the TPI was evoked during cold–heat pulse stimulation.

The current results demonstrated that the TPI was not induced in all subjects. This individual variability may have resulted from differences in the responses of peripheral polymodal receptors or differences in the responses of the central pathway mediating the perception of cold and heat pain. In the present study, the protocol for condition 1 resulted in 35.4% (11/31) of subjects experiencing the TPI during painful cold–heat pulse stimulation, whereas the protocols for conditions 2 and 3 resulted in fewer subjects experiencing the TPI, and the protocol for condition 4 resulted in no TPI. The protocol for condition 1 appeared to provide sensitive discrimination that facilitated the perception of the TPI. The temperature for the heat stimulus in condition 1 was significantly lower than that of conditions 2, 3, and 4, despite the absence of statistically significant differences among the four conditions in terms of the VAS values for the cold and heat stimuli.

Overall, the protocol of condition 1 is the most suitable for clinical use because it results in the most sensitive discrimination for the TPI. The TPI is easier to evaluate with one device, and the temperature for the heat stimulus is lower than that of the other conditions.

Clinical implications

Elucidating the mechanism through which painful cold–heat pulse stimulation might lead to paradoxical sensations could improve the understanding of the processes driving neuropathic pain, postoperative pain, and other chronic pain entities. It could also help identify these diseases early and improve clinical outcome predictions.

Conclusion

The present study provided evidence that the simultaneous application of painful thermal (cold and heat) stimuli can induce paradoxical sensations, as was previously shown for non-painful thermal (cold and heat) stimuli. The paradoxical sensation was predominantly evoked by ipsilateral integration. Identifying paradoxical sensations is of diagnostic value; therefore, the simple bedside tool presented in this study may be useful in the clinical setting for the evaluation of sensations in patients with neuropathic pain, postoperative pain, and other chronic pain conditions.

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Disclosure statement

No potential conflict of interest was reported by the author(s).

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Data availability statement

The data that support the findings of this study are available from the corresponding author (Yuka Oono) upon reasonable request.

References

Bach P, Becker S, Kleinböhl D, Hölzl R. 2011. The thermal grill illusion and what is painful about it. Neurosci Lett. 505(1):31–35.

Bekrater-Bodmann R, Chung YB, Richter I, Wicking M, Foell J, Mancke F, Schmahl C, Flor H. 2015. Deficits in pain perception in borderline personality disorder: results from the thermal grill illusion. Pain. 156(10): 2084–2092.

Boettger MK, Grossmann D, Bär K-J. 2013. Increased cold and heat pain thresholds influence the thermal grill illusion in schizophrenia. Eur J Pain. 17(2):200–209.

Cain DM, Khasabov SG, Simone DA. 2001. Response properties of mechanoreceptors and nociceptors in mouse glabrous skin: an in vivo study. J Neurophysiol. 85(4):1561–1574.

Campero M, Serra J, Ochoa JL. 1996. C-polymodal nociceptors activated by noxious low temperature in human skin. J Physiol. 497(2):565–572.

Craig AD, Bushnell MC. 1994. The thermal grill illusion: unmasking the burn of cold pain. Science. 265(5169):252–255.

Craig AD, Reiman EM, Evans A, Bushnell MC. 1996. Functional imaging of an illusion of pain. Nature. 384(6606):258–260.

Davis KD, Pope GE, Crawley AP, Mikulis DJ. 2002. Neural correlates of prickle sensation: a percept-related fMRI study. Nat Neurosci. 5(11): 1121–1122.

Davis KD, Pope GE, Crawley AP, Mikulis DJ. 2004. Perceptual illusion of "paradoxical heat" engages the insular cortex. J Neurophysiol. 92(2): 1248–1251.

Defrin R, Benstein-Sheraizin A, Bezalel A, Mantzur O, Arendt-Nielsen L. 2008. The spatial characteristics of the painful thermal grill illusion. Pain. 138(3):577–586.

Fardo F, Finnerup NB, Haggard P. 2018. Organization of the thermal grill illusion by spinal segments. Ann Neurol. 84(3):463–472.

Fardo F, Vinding MC, Allen M, Jensen TS, Finnerup NB. 2017. Delta and gamma oscillations in operculo-insular cortex underlie innocuous cold thermosensation. J Neurophysiol. 117(5):1959–1968.

Faul F, Erdfelder E, Lang A-G, Buchner A. 2007. G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behav Res Methods. 39(2):175–191.

Ferrè ER, Iannetti GD, Dijk JA, Haggard P. 2018. Ineffectiveness of tactile gating shows cortical basis of nociceptive signaling in the thermal grill illusion. Sci Rep. 8(1):6584.

Green BG. 2002. Synthetic heat at mild temperatures. Somatosens Mot Res. 19(2):130–138.

Hämäläinen H, Vartiainen M, Karvanen L, Järvilehto T. 1982. Paradoxical heat sensations during moderate cooling of the skin. Brain Res. 251(1):77–81.

Hansen C, Hopf HC, Treede RD. 1996. Paradoxical heat sensation in patients with multiple sclerosis. Evidence for a supraspinal integration of temperature sensation. Brain. 119(5):1729–1736.

Herget CM, Granath LP, Hardy JD. 1941. Warmth sense in relation to the area of skin stimulated. Am J Physiol. 135(1):20–26.

Kanda Y. 2013. Investigation of the freely available easy-to-use software 'EZR' for medical statistics. Bone Marrow Transplant. 48(3):452–458.

Kern D, Pelle-Lancien E, Luce V, Bouhassira D. 2008. Pharmacological dissection of the paradoxical pain induced by a thermal grill. Pain. 135(3):291–299.

Lang PM, Schober GM, Rolke R, Wagner S, Hilge R, Offenbächer M, Treede RD, Hoffmann U, Irnich D. 2006. Sensory neuropathy and signs of central sensitization in patients with peripheral arterial disease. Pain. 124(1):190–200.

Lindstedt F, Johansson B, Martinsen S, Kosek E, Fransson P, Ingvar M. 2011. Evidence for thalamic involvement in the thermal grill illusion: an fMRI study. PLOS One. 6(11):e27075.

Marotta A, Ferrè ER, Haggard P. 2015. Transforming the thermal grill effect by crossing the fingers. Curr Biol. 25(8):1069–1073.

Moran MM, McAlexander MA, Bíró T, Szallasi A. 2011. Transient receptor potential channels as therapeutic targets. Nat Rev Drug Discov. 10(8): 601–620.

Pertovaara A, Kojo I. 1985. Influence of the rate of temperature change on thermal thresholds in man. Exp Neurol. 87(3):439–445.

Price DD, McHaffie JG, Larson MA. 1989. Spatial summation of heat-induced pain: influence of stimulus area and spatial separation of stimuli on perceived pain sensation intensity and unpleasantness. J Neurophysiol. 62(6):1270–1279.

Rolke R, Magerl W, Campbell KA, Schalber C, Caspari S, Birklein F, Treede RD. 2006. Quantitative sensory testing: a comprehensive protocol for clinical trials. Eur J Pain. 10(1):77–88.

Rossi HL, Neubert JK. 2009. Effects of hot and cold stimulus combinations on the thermal preference of rats. Behav Brain Res. 203(2): 240–246.

Schaldemose EL, Horjales-Araujo E, Svensson P, Finnerup NB. 2015. Altered thermal grill response and paradoxical heat sensations after topical capsaicin application. Pain. 156(6):1101–1111.

Simone DA, Kajander KC. 1997. Responses of cutaneous a-fiber nociceptors to noxious cold. J Neurophysiol. 77(4):2049–2060.

Story GM, Peier AM, Reeve AJ, Eid SR, Mosbacher J, Hricik TR, Earley TJ, Hergarden AC, Andersson DA, Hwang SW, et al. 2003. ANKTM1, a TRP-like channel expressed in nociceptive neurons, is activated by cold temperatures. Cell. 112(6):819–829.

Susser E, Sprecher E, Yarnitsky D. 1999. Paradoxical heat sensation in healthy subjects: peripherally conducted by A delta or C fibres? Brain. 122(2):239–246. e]

Vay L, Gu C, McNaughton PA. 2012. The thermo-TRP ion channel family: properties and therapeutic implications. Br J Pharmacol. 165(4): 787–801.