Research Paper

Assessment of brain mechanisms involved in the processes of thermal sensation, pleasantness/unpleasantness, and evaluation

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\begin{abstract}
The conscious perception of thermal stimuli is divided into two categories: thermal sensation (i.e., discriminative component) and pleasantness/unpleasantness (i.e., hedonic component). There have been very few studies which clearly dissociated the two components. The aim of the present study was 1) to identify brain regions involved in perception of thermal stimuli per se, dissociating those related to the two components, and additionally 2) to examine brain regions of the explicit evaluation processes for the two components. Sixteen participants received local thermal stimuli of either 41.5 °C or 18.0 °C during whole-body thermal stimuli of 47.0 °C, 32.0 °C, or 17.0 °C. The local stimuli were delivered to the right forearm with the Peltier device. The whole-body stimuli delivered through a water-perfusion suit was aimed to modulate thermal pleasantness/unpleasantness to the local stimulus. The local stimulation at the same temperature was conducted five times with 30-s intervals. Brain activation was assessed by functional magnetic resonance imaging (fMRI), and the participants were asked to report their ratings of thermal sensation and pleasantness/unpleasantness following the cessation of each local stimulus. Local thermal stimulation activated specific brain regions such as the anterior cingulate cortex, insula, and inferior parietal lobe, irrespective of the temperature of local and whole-body stimuli; however, no specific activation for hot or cold sensation was observed. Different brain regions were associated with pleasantness and unpleasantness; the caudate nucleus and frontal regions for pleasantness, and the medial frontal and anterior cingulate cortex for unpleasantness. In addition, the explicit evaluation process for the discriminative and hedonic components immediately following the cessation of local stimulus involved different brain regions; the medial prefrontal cortex extending to the anterior cingulate cortex, insula, middle frontal cortex, and parietal lobes during the explicit evaluation of thermal sensation, and the medial prefrontal cortex, posterior cingulate cortex, and inferior parietal lobes during that of pleasantness/unpleasantness.
\end{abstract}

Introduction

Thermoregulation maintains the thermal condition of the body at an appropriate level for survival. For this purpose, homeothermic animals, including human beings, continuously and subconsciously monitor core body temperature (i.e., temperature of the central and visceral organs) which reflects the thermal condition of the internal body, and skin temperature, which reflects the thermal condition of the environment. When necessary, autonomic (e.g., non-shivering thermogenesis and skin vasodilation) and behavioral (e.g., heat-escape behavior) thermoregulatory responses are enacted (Tan et al., 2016; Tan and Knight, 2018). Core body temperature is monitored by thermo-sensitive neurons in the central nervous system, whereby the hypothalamic preoptic area (POA) plays an important role. Changes in skin temperature activates dorsal root ganglia cells. This information is sequentially conveyed to the spinal dorsal horn, external lateral part of the parabrachial nucleus, and POA, respectively (Nakamura and Morrison, 2008; Tan et al., 2016; Tan and Knight, 2018). Human beings may also consciously monitor thermal condition; this is thought to be mediated by the cerebral cortex.

Conscious thermal perception is divided into thermal sensation (i.e., discriminative component) and pleasantness/unpleasantness (i.e.,...
hedonic component) (Cabanac, 1971; Hensel, 1981). The discriminative component is defined as the objective evaluation of skin temperature (Mower, 1976). The hedonic component is defined as an affective feeling regarding the thermal condition of the body (Cabanac, 1979; Attia and Engel, 1981; Attia, 1984). Mower (1976) clarified that the two components are independent by psychophysiological experiment. More recently, Nakamura et al. (Nakamura et al., 2008, 2013) reported that, when cold or heat stimulus was applied to local skin, the thermal pleasantness/unpleasantness was altered, depending on environmental condition of subjects (i.e. hot or cold). However, the thermal sensation remained unchanged. For example, facial cooling induced similar cold sensation in both hot and cold environments: however, thermal pleasantness was evoked only in a hot environment. The results may also suggest independence of the two components of thermal perception.

Several neuroimaging studies using functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) have reported brain regions involved in the discriminative component: the cingulate, somatosensory, premotor, motor, prefrontal, and inferior parietal cortices were activated during both noxious and innoxious thermal stimuli (Casey et al., 1996; Davis et al., 1998; Craig et al., 2000; Tracey et al., 2000; Becerra et al., 2001; Olausson et al., 2005; Tseng et al., 2010; Peltz et al., 2011). In contrast, only a few studies have examined the neural correlates of the hedonic component (Kanosue et al., 2002; Rolls et al., 2008; Farrell et al., 2011). For example, an fMRI study by Rolls et al. (2008) demonstrated that activity in the mid-orbitofrontal and pregenual cingulate cortices as well as the ventral striatum were positively correlated with the strength of pleasant feelings about thermal stimuli to the left hand, while activity in the lateral orbitofrontal cortex was positively correlated with the strength of unpleasant feelings. These results may suggest that the hedonic and discriminative components are processed in different brain regions.

Previous studies have identified brain regions involved in thermal feeling, based on correlation of blood-oxygen-level dependent (BOLD) signals with subjective rating (Kanosue et al., 2002; Rolls et al., 2008; Farrell et al., 2011). However, thermal stimuli usually affect psychological assessment of hedonic and discriminative components of thermal perception simultaneously. Therefore, the studies may have drawn erroneous conclusions because the thermal stimuli were not designed to separate the two components.

In the present study, we first aimed to develop an experimental procedure to separate the two components of thermal perception. Then, we identified the responsible brain regions for each component using fMRI. Local hot or cold stimuli were applied to the forearm while the whole-body skin surface was heated or cooled simultaneously. A local hot stimulus during whole-body cooling generated a pleasant feeling, while a local hot stimulus during whole-body heating did not, despite the similar sensation of heat on the forearm. Moreover, we assessed the brain regions involved in the evaluation process of thermal stimulation, separate from thermal perception per se. For this purpose, fMRI signals were obtained while participants were explicitly rating the intensities of thermal sensation and affective feeling, which were conducted after local thermal stimulation.

Materials and methods

Participants

Sixteen healthy, right-handed, and non-smoking volunteers (13 males and three females; aged 24.4 ± 0.8 y [mean ± SE]) participated in the present study. Participants received reimbursement for participating in the study. None of the participants had any history of neurological or psychiatric illness. All participants gave their written informed consent for the experimental protocol, which was approved by the Human Research Ethics Committee of the Faculty of Human Sciences of Waseda University and the National Institute for Physiological Sciences. The experiment was conducted in accordance with the Declaration of Helsinki.
Two independent thermal stimulations were simultaneously administered to the participants; one was a local stimulus to the anterior plane of the left forearm, and the other was a stimulus to the skin surface of the whole body with the exception of the face, hands, and feet (Fig. 1A). The forearm stimulations (i.e., the local stimulations) were given by means of a Peltier apparatus (3-cm diameter covered with a thin copper border; Intercross 2000, Tokyo, Japan). The Peltier apparatus was attached to the skin surface with paper adhesion tape. The temperature of the apparatus was computer-controlled (LabVIEW 2013; National Instruments, Texas, USA), where it was initially held at 32.0 °C for 30 s followed by 20-s decrements from 23.0 °C to 18.0 °C (0.25 °C/sec for the 20 s; i.e., the local cold stimulation) or increments from 36.5 °C to 41.5 °C (0.25 °C/sec for the 20 s; i.e., the local hot stimulation), then held constant at 18.0 °C or 41.5 °C for 10 s, respectively (Fig. 1D). The same local thermal stimulation was repeated five times in each experimental run. A 30-s 32.0 °C stimulation was added to the end of the run. The local temperature of 32.0 °C induced neither hot nor cold sensation (i.e., thermoneutral temperature) (Kingma et al., 2012).

The whole-body thermal stimulation was delivered through a water-perfusion suit (Med-Eng, Ottawa, Canada), which was densely lined with inner surface tubes (Egan et al., 2005). Water at a temperature of 17.0 °C (i.e., the whole-body cold stimulation), 32.0 °C (i.e., the whole-body neutral stimulation), or 47.0 °C (i.e., the whole-body hot stimulation) was perfused continuously at a rate of 2 l/min within the tubes. The perfusion of 32.0 °C water induced thermoneutral sensation (Kingma et al., 2012).

There were six thermal conditions in the experiment, combining the local thermal stimuli (i.e., cold and hot stimuli) and the whole-body thermal stimulations (i.e., cold, neutral, and hot stimulations): \( C_{bodyClocal}, N_{bodyClocal}, H_{bodyClocal}, C_{bodyHlocal}, N_{bodyHlocal}, \) and \( H_{bodyHlocal} \) (Fig. 1B). C, N, and H represent cold, neutral and hot stimulations, respectively; and body and local denote the whole body and local stimulations, respectively.

**Experimental procedure**

Participants arrived at the laboratory at least 1 h before starting the experiment. They were allowed to drink 500 ml of water and take lavatory breaks throughout the experiment. Before MRI scanning, participants were instructed to wear the water-perfusion suit and a pair of socks, and relax into a chair. Their skin temperatures under the suit were monitored with thermocouples at the anterior chest, abdomen, forearm, and thigh for approximately 10 min until their skin temperature became stable after the water perfusion started. They were then taken into the MRI scanning room. Ear canal temperature (CE thermal, Nipro, Osaka, Japan) was measured before and after the MRI scanning.

There were two fMRI runs for each of the six thermal conditions, resulting in a total of 12 fMRI runs per subject. The order of the six different thermal conditions was counterbalanced across participants, but four runs of the same whole-body stimulation conditions were conducted in succession (e.g., two \( C_{bodyClocal} \) runs, two \( C_{bodyHlocal} \) runs, two \( H_{bodyClocal} \) runs, two \( H_{bodyHlocal} \) runs, two \( N_{bodyClocal} \) runs, and two \( N_{bodyHlocal} \) runs). Participants rested in an anteroom before each of the three different whole-body stimulus conditions, and relaxed in a chair until the skin temperature became stable under the whole-body stimulation condition. Each fMRI run consisted of five local stimulation blocks of the same temperature of 30-s duration each, interleaved with a 10-s evaluation and a 20-s rest period (Fig. 1C). Green and white fixations were presented at the center of the screen during the local thermal stimulation and rest periods, respectively. To avoid any potential perceptual illusion of local thermal stimulation during rest periods, we gave the cues to the participants to recognize the onset and offset of the local thermal stimulation. The color change of the cues was not likely to affect the neural activation related to thermal perception. This is because the statistical analyses for the fMRI data would dissociate sustained brain activities during the 30-s thermal stimulation from the transient brain activities due to the color change.

During the 10-s evaluation period, the participants made two ratings as to the given local thermal stimuli with a visual analogue scale (VAS), which was shown on the center of the screen. Within the initial 5 s of each evaluation period, the participants made a judgment as to how hot or cold they had perceived the local thermal stimulation to be (i.e., thermal sensation rating) indicating the left or right side of the VAS as very cold or very hot, respectively. During the subsequent 5 s, they judged the pleasantness or unpleasantness they had felt for the local thermal stimulation (i.e., thermal pleasantness/unpleasantness rating), indicating the left or right side of the VAS as very unpleasant or very pleasant, respectively. The participants held a button box with their right hand and responded by pressing two buttons with their index and middle fingers to move and stop a bar at an appropriate position on the VAS.

All visual stimuli were presented using Presentation software (Neurobehavioral Systems, Albany, CA) and projected onto a half-transparent viewing screen located behind the head coil. The participants viewed the projected stimuli through a mirror attached to the head coil. The participants’ responses were also recorded using Presentation software.

**fMRI data acquisition**

We used a 3-Tesla MRI scanner (MAGNETOM Verio, Siemens, Erlangen, Germany) equipped with a 32 channel phased array head coil. Functional brain images were obtained during the 12 runs in an axial-oblique position covering the whole brain with a multiband Echo-Planar Imaging sequence (Moeller et al., 2010) (repetition time [TR] = 1000 ms, echo time [TE] = 30 ms, flip angle = 80 degrees, field of view [FOV] = 192 mm2, 60 slices, in-plane resolution = 2 mm × 2 mm, slice thickness = 2.5 mm including 0.5 mm gap, multiband factor = 6) that was sensitive to BOLD contrast. The number of T2*-weighted images was 330 for each fMRI run. A high-resolution anatomical T1-weighted image (MPRAGE; TR = 1.8 s, TE = 1.98 ms, flip angle = 9 degrees, FOV = 256 mm2, 176 slices, voxel size = 1 mm × 1 mm × 1 mm) was also acquired for each participant. Foam padding was placed around each participant’s head to minimize head movement.

**Statistical analysis of behavioral data**

The VAS scores of thermal sensation and pleasantness/unpleasantness ratings were separately subjected to analyses of variance (ANOVAs) with repeated-measures using local (cold and hot) and whole-body (cold, neutral, and hot) as within-subject factors. Bonferroni post hoc multiple comparison tests were conducted to evaluate differences among conditions. We also analyzed the bivariate correlational relationship between VAS scores of thermal sensation and pleasantness/unpleasantness ratings under each condition, after confirming data normality by the Kolmogorov-Smirnov test. Statistical evaluations were performed using the IBM SPSS Statistics 22 software (IBM, Chicago, USA). All values are presented as means ± SE. Statistical significance was set at a level of \( p < 0.05 \).

**fMRI data analysis**

The MRI data were analyzed with SPM8 software (Wellcome Department of Imaging Neuroscience, London, UK) implemented in MATLAB R2012a (MathWorks, Sherborn, MA, USA). First, all the images were spatially realigned to the mean image. After a high-resolution image was coregistered onto the mean image, all volumes were normalized to the MNI space (Montreal Neurological Institute [MNI] template) using a transformation matrix obtained from the normalization process of the high-resolution image of each individual
participant to the MNI template. The normalized and resliced images were then spatially smoothed with Gaussian kernel of 8 mm (full width at half-maximum; FWHM) in the X, Y, and Z axes.

After preprocessing, statistical analysis for each participant was conducted using a general linear model (Friston et al., 1995). At the first level, local thermal stimulation, thermal sensation rating, and pleasantness/unpleasantness rating were modeled separately with a 30-s, 5-s, and 5-s duration, respectively; convolving a hemodynamic response function. In the results, the following three neural processes were separately modeled as regressors: 1) perception of local thermal stimulation, 2) evaluation of thermal sensation induced by thermal stimuli, and 3) evaluation of pleasantness/unpleasantness for thermal stimulation. In addition, six regressors for movement parameters obtained in the realignment process were entered in the design matrix. An additional regressor of the mean signal from the cerebrospinal fluid (CSF) was also included in the design matrix. High-pass filters (128 s) were applied to the time-series data. An autoregressive model was used to estimate the temporal autocorrelation. The signals of images were scaled to a grand mean of 100 overall voxels and volumes within each run. The parameter estimate for perception of local thermal stimuli was

Fig. 2. (I) VAS scores (means ± SE) for the thermal sensation (A and C in the local cold and hot stimuli, respectively) and pleasantness/unpleasantness (B and D in the local cold and hot stimuli, respectively) during three different whole body thermal conditions. ** p < 0.01; *** p < 0.001 (II) Correlative relationship between VAS scores of thermal sensation and pleasantness/unpleasantness ratings under each protocol. Significant correlations were observed in the CbodyClocal and CbodyHlocal conditions.
formed for each of the six thermal stimulation conditions (i.e., $C_{body/Clocal}$, $N_{body/Clocal}$, $H_{body/Clocal}$, $C_{body/Hlocal}$, $N_{body/Hlocal}$, and $H_{body/Hlocal}$) from the least-square fit of the model to the time-series data at each voxel. For each of the thermal sensations and pleasantness/unpleasantness ratings, the parameter estimate was computed combining all six thermal stimulation conditions. Images of the parameter estimates representing related neural activities (i.e., contrast images) were created for each participant.

At the second-level analysis, the contrast images obtained from each participant were entered into group analyses with a random-effect model. First, to examine whether local thermal stimulation with a given temperature was processed in dissociable brain regions depending on temperatures of whole-body thermal stimulations, a one-way within-subjects ANOVA was conducted with the contrast images pertaining to the six thermal stimulation conditions. To examine brain regions commonly involved across all the six conditions, a conjunction analysis was also tested. Second, we examined the main effect of temperature of local thermal stimulation and whole-body thermal stimulation as well as the interaction between them. Furthermore, to examine possible differential effects of the temperature of whole-body thermal stimulation on perception of local thermal stimulation in detail, we conducted pairwise comparisons: $C_{body/Clocal}$ vs. $N_{body/Clocal}$, $C_{body/Clocal}$ vs. $H_{body/Clocal}$, $C_{body/Hlocal}$ vs. $N_{body/Hlocal}$, $C_{body/Hlocal}$ vs. $H_{body/Hlocal}$, $C_{body/Hlocal}$ vs. $H_{body/Hlocal}$, and $N_{body/Hlocal}$ vs. $H_{body/Hlocal}$. We also examined whether there were any positive and/or negative correlations between brain activities and participants’ subjective ratings for each of the six thermal conditions: i) brain activities during perception of the local thermal stimulation and the ratings of thermal sensation and pleasantness/unpleasantness, ii) those during the explicit evaluation process of the discriminative component and the rating of thermal sensation, and iii) those during the explicit evaluation process of the hedonic component and the rating of pleasantness/unpleasantness. Additionally, a conjunction analysis and paired $t$-test were conducted with the contrast images representing neural activities during the two ratings (i.e., thermal sensation and pleasantness/unpleasantness ratings) to examine both common and distinct brain regions involved in the two different evaluation processes for thermal stimulation. The statistical thresholds were set at $p = 0.001$ uncorrected for multiple comparisons at the voxel level, and $p = 0.05$ Family-wise error (FWE)-corrected for multiple comparisons at the cluster level (Slotnick, 2017). All the coordinates were reported in the MNI space. Brodmann areas and brain regions were identified based on the Talairach Atlas (Talairach and Tournoux, 1988) after converting MNI coordinates to Talairach space with a nonlinear transformation (http://imaging.mrc-cbu.cam.ac.uk/imaging/MniTalairach).

**Results**

**Change of mean skin temperature and ear canal temperature**

The mean skin temperatures ($T_{sk}$) were calculated according to the following expression: $T_{sk} = 0.25T_{fa} + 0.43T_{ch} + 0.32T_{th}$ (Roberts et al., 1977). The terms $T_{fa}$, $T_{ch}$, and $T_{th}$ were skin surface temperatures measured from the forearm, chest, and thigh respectively. When applying a 47.0 °C whole-body stimulus, $T_{sk}$ increased from 32.1 ± 0.3 °C to 33.8 ± 1.7 °C. $T_{sk}$ increased from 31.7 ± 0.3 °C to 33.1 ± 0.3 °C during the 32.0 °C whole-body stimulus sessions. $T_{sk}$ decreased from 32.6 ± 0.4 °C to 31.6 ± 0.2 °C when 17.0 °C water was perfused. Ear canal temperature remained unchanged during the whole-body stimulus protocols in the anteroom as well as before and after the fMRI imaging.

**Rating of thermal sensation and pleasantness/unpleasantness**

The rating of thermal sensation and pleasantness/unpleasantness of the forearm skin was conducted each time after the stimulation. Fig. 2-IA and -IC shows the rating values of thermal sensation when 18.0 °C (local: cold) and 41.5 °C stimuli (local: hot) were applied, respectively. ANOVAs revealed a significant main effect of local temperature ($F(1, 15) = 149.663, p < 0.001$), but no main effect of whole-body temperature or interaction. The average rating value of thermal sensation for 18.0 °C stimuli (Fig. 2-IA) was -22.3 ± 2.2, -19.8 ± 1.9, and -22.7 ± 1.5 in the $C_{body/Clocal}$, $N_{body/Clocal}$, and $H_{body/Clocal}$ conditions, respectively. When 41.5 °C stimulus was applied to the skin, the rating value of the sensation was 17.3 ± 2.2, 14.6 ± 2.1, and 12.7 ± 2.3 in the $C_{body/Hlocal}$, $N_{body/Hlocal}$, and $H_{body/Hlocal}$ trials, respectively (Fig. 2-IC).

Fig. 2-IB and -ID shows the averaged rating values of the pleasantness/unpleasantness in each condition. ANOVAs revealed a significant main effect of local ($F(1, 15) = 30.589, p < 0.001$) and whole-body interaction ($F(2, 30) = 25.655, p < 0.001$). The values for 18.0 °C stimuli were -19.2 ± 2.7, -9.5 ± 3.1, and 3.7 ± 4.0 in the $C_{body/Clocal}$, $N_{body/Clocal}$, and $H_{body/Clocal}$ conditions, respectively (Fig. 2-IB). The values in the $H_{body/Clocal}$ condition were greater than 0 (i.e., rated as feeling pleasant) and those in the $N_{body/Clocal}$ and $C_{body/Clocal}$ conditions were less than 0 (i.e., rated as feeling unpleasant). Post hoc test demonstrated that the values were significantly smaller in the $C_{body/Clocal}$ and $N_{body/Clocal}$ conditions than in the $H_{body/Clocal}$ condition ($p < 0.001$ and $p < 0.01$, respectively). The values for 41.5 °C stimuli were 17.3 ± 3.2, 13.0 ± 3.1, and -3.3 ± 2.7 in the $C_{body/Hlocal}$, $N_{body/Hlocal}$, and $H_{body/Hlocal}$ conditions, respectively. The value in the $H_{body/Hlocal}$ condition was less than 0 (i.e., rated as feeling unpleasant). The values in the $N_{body/Hlocal}$ and $C_{body/Hlocal}$ conditions were greater than 0 (i.e., rated as feeling pleasant). Post hoc test showed that the values were significantly larger in the $C_{body/Hlocal}$ and $N_{body/Hlocal}$ conditions than in the $H_{body/Hlocal}$ condition ($p < 0.001$ and $p < 0.01$, respectively). Additionally, significant correlations between VAS scores of the thermal sensation and pleasantness ratings were observed only when cold stimulation was applied to the skin surface of the whole body; i.e., $C_{body/Clocal}$ and $C_{body/Hlocal}$ conditions ($p < 0.01$, respectively) (Fig. 2-II).

**fMRI results**

The results of a within-subjects one-way ANOVA revealed no main effect of temperature of local thermal stimulation or whole-body thermal stimulation, and no interaction between temperatures of local and whole-body thermal stimulation. The results of a conjunction analysis showed significant activation of the medial prefrontal cortex (Brodmann area [BA] 8) extending to the anterior cingulate cortex (BA 32), bilateral insula extending up to subcentral area (BA 43) in the right hemisphere, bilateral inferior occipital gyri (BA 18), the right middle frontal cortex (BA 10/46), and the right inferior parietal lobe (BA 40); indicating overlapping brain activity with several right-lateralized regions across the six thermal stimulation conditions (Table 1 and Fig. 3).

The results of pair-wise comparisons revealed that the local cold thermal stimulation elicited greater brain activity in the anterior cingulate gyrus (BA 32) extending to the medial prefrontal cortex (BA 9) and the dorsal part of the medial frontal gyrus (BA 8) under the whole-body cold condition than the whole-body hot condition (i.e., $C_{body/Clocal} > H_{body/Clocal}$) (Table 2 and Fig. 4A). On the other hand, the local hot thermal stimulation induced greater brain activity in the anterior cingulate cortex (BA 32), the dorsal part of the medial frontal gyrus (BA 8), the bilateral caudate nuclei, and the right middle frontal gyrus (BA 10) under the whole-body cold condition than the whole-body hot condition (i.e., $C_{body/Hlocal} > H_{body/Hlocal}$) (Table 2 and Fig. 4B).

There was no correlation observed between brain activities and participants’ subjective ratings. The results of a conjunction analysis for the ratings of local thermal sensation and pleasantness/unpleasantness showed widely distributed common activity in several brain regions, including the bilateral middle
The aim of the present study was to develop an experimental procedure to separate the two components of thermal perception, and clarify brain mechanisms involved in the discriminative and hedonic components of thermal perception. Psychophysical assessments during independent thermal stimuli applied to the whole body and forearm demonstrated that the two thermal components were independent and separable. fMRI revealed that the thermal stimuli activated widespread brain regions commonly activated across the six experimental conditions (Table 1).

### Table 1

| Region name (BA) | Hem. | Voxels | Z value | p value | x, y, z (mm) |
|------------------|------|--------|---------|---------|-------------|
| Frontal gyrus (44) | Rt  | 2056   | 6.14    | < 0.001 | 56, 14, 10 |
| Insula (anterior) | Rt  | *      | 5.53    | < 0.001 | 34, 28, 8  |
| Insula (posterior) | Rt  | *      | 4.25    | < 0.001 | 42, 2, 2   |
| Medial frontal gyrus/anterior cingulate gyrus (8/32) | Rt  | 1212   | 6.60    | < 0.001 | 6, 10, 50  |
| Postcentral gyrus (43) | Rt  | 945    | 5.64    | < 0.001 | 64, -22, 18|
| Inferior parietal lobe (40) | Rt  | *      | 3.77    | < 0.001 | 52, -34, 36|
| Insula (anterior) | Lt  | 510    | 5.34    | < 0.001 | 32, 24, 6  |
| Inferior frontal gyrus (44) | Lt  | *      | 3.78    | < 0.001 | -54, 6, 2  |
| Inferior occipital gyrus (18) | Rt  | 354    | 6.41    | < 0.001 | -30, -92, -12|
| Inferior/middle frontal gyrus (10/46) | Rt  | 328    | 5.55    | < 0.001 | 46, 46, 8  |
| Inferior occipital gyrus (18) | Lt  | 245    | 4.73    | < 0.001 | 26, -92, -12|

BA, Brodmann area; Hem., hemisphere; Rt., right; Lt., left. *a peak is included in a large cluster. Coordinates (x, y, z) are of the voxel of local maximal significance in each brain region according to the Montreal Neurological Institute (MNI) template.

In a direct comparison of activation during thermal sensation and thermal pleasantness/unpleasantness ratings, greater activation during thermal sensation ratings was observed in the bilateral anterior insula, lentiform nuclei, thalamus, superior and inferior parietal lobes (BA 7 and 40), inferior occipital gyrus (BA 18) extending to the fusiform gyri (BA 37) and cerebellum, right anterior cingulate gyrus (BA 32) extending to the dorsal part of the medial frontal gyrus (BA 6/8), superior and inferior frontal gyrus (BA 64 and 44), and precuneus (BA 7) (Table 3 and Fig. 5). Additionally, the thermal sensation rating involved the bilateral hippocampus and pons, and the left precentral and postcentral gyri.

In a direct comparison of activation during thermal sensation and thermal pleasantness/unpleasantness ratings, greater activation during thermal sensation ratings was observed in the bilateral anterior insula, lentiform nuclei, thalamus, superior and inferior parietal lobes (BA 7 and 40), inferior occipital gyrus (BA 18) extending to the fusiform gyri (BA 37) and cerebellum, hippocampus and pons, anterior cingulate gyrus (BA 32) extending to the dorsal part of the medial frontal gyrus (BA 6/8), the left precentral and postcentral gyrus (BA 6 and 43), right middle temporal gyrus (BA 39), and superior parietal lobe (BA 7) (Table 4 and Fig. 6). Significantly greater activation during thermal pleasantness/unpleasantness ratings was observed in the anterior cingulate gyrus (BA 32) extending to the bilateral superior and medial frontal gyrus (BA 8 and 10), bilateral inferior parietal lobes (BA 40), right middle temporal gyrus (BA 21), cuneus (BA 18), and cerebellum (Table 4 and Fig. 6).

### Discussion

The aim of the present study was to develop an experimental procedure to separate the two components of thermal perception, and clarify brain mechanisms involved in the discriminative and hedonic components of thermal perception. Psychophysical assessments during independent thermal stimuli applied to the whole body and forearm demonstrated that the two thermal components were independent and separable. fMRI revealed that the thermal stimuli activated widespread brain areas; however, different brain regions may be involved in processing thermal pleasantness/unpleasantness and evaluation of discriminative and hedonic components.

### Table 2

The dissociated effects of temperatures of whole-body thermal stimulations on the perception of local thermal stimulations.

| Region name (BA) | Hem. | Voxels | Z value | p value | x, y, z (mm) |
|------------------|------|--------|---------|---------|-------------|
| Cbody>Clocal > Hbody>Clocal | Lt  | 656    | 3.99    | < 0.001 | -10, 50, 18|
| Anterior cingulate gyrus (32) | Lt  | *      | 3.86    | < 0.001 | 10, 44, 20 |
| Medial frontal gyrus (9) | Rt  | *      | 3.44    | < 0.001 | 10, 52, 24 |
| Caudate nucleus | Lt  | 318    | 4.11    | < 0.001 | -2, 34, 50 |
| Anterior cingulate gyrus (32) | Lt  | 1801   | 4.78    | < 0.001 | -14, 16, 4 |
| Middle frontal gyrus (10) | Rt  | *      | 4.21    | < 0.001 | 6, 38, 8  |
| Caudate nucleus | Rt  | 3.78    | < 0.001 | 26, 46, 4 |
| Medial frontal gyrus (8) | Rt  | 3.63    | < 0.001 | 14, 46, 6 |
| Medial frontal gyrus (8) | Rt  | 3.82    | < 0.001 | 12, 36, 44|

BA, Brodmann area; Hem., hemisphere; Rt., right; Lt., left. *a peak is included in a large cluster. Coordinates (x, y, z) are of the voxel of local maximal significance in each brain region according to the Montreal Neurological Institute (MNI) template.

Previous psychophysiological studies have reported on the relationship between the two thermal components (i.e., discriminative and hedonic components). Thermal sensation of local heat or cold (i.e., discriminative component) is initially determined by the skin temperature or environmental condition (i.e. hot or cold) (Chatonnet and Cabanac, 1965; Cabanac, 1971; Mower, 1976; Attia, 1984; Kuno, 1987; Nakamura et al., 2008, 2013). However, the feeling of warmth or coolness (i.e., thermal pleasantness/unpleasantness) is influenced by the core body temperature or environmental condition (Cabanac, 1971; Mower, 1976). The dissociated effects of temperatures of whole-body thermal stimulations on the perception of local thermal stimulations (Table 2) support this hypothesis.
and a water-perfusion suit for hot or cold environment. Moreover, the hedonic component could be separated from the discriminative component (Figs. 2-IA-D). The skin surface temperature of the whole body changed with the water temperature; however, ear temperature remained unchanged. Thus, regional difference in skin temperature (i.e., skin temperature between the stimulation area and whole body) may be a factor determining thermal feeling.

We used VAS scores to evaluate the rating of the intensity of thermal stimuli and thermal feeling. The results clearly demonstrated that thermal stimuli applied to the forearm induced different thermal feeling depending on whole-body thermal condition: the score was lower in the \( C_{\text{body,local}} > H_{\text{body,local}} \) condition (Fig. 2-ID), and higher in the \( C_{\text{body,local}} > H_{\text{body,local}} \) and \( N_{\text{body,local}} \) conditions than in the \( H_{\text{body,local}} \) condition (Fig. 2-IB). The score for thermal sensation was not influenced by whole-body thermal condition (Fig. 2-IA and -IC). Previous brain-mapping studies of thermal perception using fMRI and PET also used the rating values with digital (Kanosue et al., 2002; Farrell et al., 2011) or analogue scales (Craig et al., 2000; Olausson et al., 2005; Rolls et al., 2008; Grabenhorst et al., 2008, 2010) in the analysis. However, these studies analyzed the data separately, focusing on either perceptual component without considering the influence of the other. In the present study, during whole-body cooling, thermal unpleasantness increased as the thermal sensation of cold at the forearm did (\( C_{\text{body,local}} > C_{\text{body,local}} \) in Fig. 2-II, respectively). The result may indicate that, in some thermal condition of the whole body, ratings of the two components change in a similar manner. Therefore, it is unclear if the brain mapping in previous studies, based on rating of either component of interest, precisely reflects the component.

**Brain areas activated by thermal stimulation**

Based on the psychological assessments of thermal perception, the brain areas responsible for the hedonic component could be evaluated based on the rating of the intensity of thermal sensation. For example, the thermal sensation in the \( N_{\text{body,local}} \) and \( H_{\text{body,local}} \) conditions induced the same intensity of heat sensation. However, pleasant feelings were observed in the \( N_{\text{body,local}} \) condition but not the \( H_{\text{body,local}} \)

### Table 3

A conjunction analysis for the perception of thermal stimulations.

| Region name (BA) | Hem. | Voxels | Z value | p value | x, y, z (mm) |
|-----------------|------|--------|---------|---------|-------------|
| Fusiform gyrus (37) | Rt | 10921 | 7.10 | < 0.001 | 54, -52, 18 |
| Inferior occipital gyrus (18) | Lt | * | 7.01 | < 0.001 | 12, -92, -10 |
| Cerebellum | Lt | * | 6.99 | < 0.001 | -34, 70, -28 |
| Cerebellum | Rt | * | 6.32 | < 0.001 | 34, -74, -26 |
| Inferior occipital gyrus (18) | Rt | * | 6.30 | < 0.001 | 14, -90, -10 |
| Fusiform gyrus (37) | Lt | * | 5.82 | < 0.001 | -44, -56, -18 |
| Insula (anterior) | Rt | 7254 | 6.99 | < 0.001 | 44, 16, -4 |
| Inferior frontal gyrus (44) | Rt | * | 6.32 | < 0.001 | 48, 18, 24 |
| Anterior cingulate gyrus (32) | Rt | * | 6.25 | < 0.001 | 6, 34, 28 |
| Superior frontal gyrus (6) | Rt | * | 5.78 | < 0.001 | 32, 0, 64 |
| Middle frontal gyrus (46) | Rt | * | 5.78 | < 0.001 | 40, 38, 20 |
| Thalamus | Rt | * | 5.44 | < 0.001 | 16, -4, 0 |
| Medial frontal gyrus (6/8) | Rt | * | 4.89 | < 0.001 | 4, 20, 56 |
| Lentiform nucleus | Rt | * | 3.75 | < 0.001 | 18, 4, 0 |
| Superior parietal lobe (7) | Rt | 5090 | 7.20 | < 0.001 | 52, -46, 54 |
| Inferior parietal lobe (40) | Rt | * | 7.08 | < 0.001 | 52, -38, 46 |
| Precuneus (7) | Rt | * | 6.16 | < 0.001 | 16, -64, 40 |
| Superior parietal lobe (7) | Lt | 2384 | 6.61 | < 0.001 | -24, 48, 60 |
| Inferior parietal lobe (40) | Lt | * | 6.17 | < 0.001 | -38, -44, 34 |
| Insula (anterior) | Lt | 1049 | 5.23 | < 0.001 | -34, 22, 6 |
| Thalamus | Lt | 220 | 4.31 | < 0.001 | -22, 4, 2 |
| Lentiform nucleus | Lt | * | 3.74 | < 0.001 | -18, 10, 2 |
| Middle frontal gyrus (46) | Lt | 204 | 4.47 | < 0.001 | -50, 34, 26 |

BA, Brodmann area; Hem., hemisphere; Rt., right; Lt., left. *a peak is included in a large cluster. Coordinates (x, y, z) are of the voxel of local maximal significance in each brain region according to the Montreal Neurological Institute (MNI) template.
inferior parietal lobe (Fig. 3 and Table 1). In addition, neither the cingulate cortex, bilateral insula, right middle frontal cortex, and right thermal conditions in the present study, many brain regions were ac-

Brain regions involved in the pleasant feeling. However, across six parametric mapping [SPM] between the two conditions may re

Table 4

| Region name (BA) | Hem. | Voxels | Z value | p value | x, y, z (mm) |
|------------------|------|--------|---------|---------|-------------|
| Thermal sensation rating > Pleasantness rating |
| Middle frontal gyrus (6/8) | Lt | 13505 | 6.82 | < 0.001 | -4, 2, 56 |
| Precentral gyrus (6) | Lt | * | 6.26 | < 0.001 | -40, -16, 64 |
| Inferior parietal lobe (40) | Lt | * | 6.00 | < 0.001 | -44, -34, 42 |
| Anterior cingulate gyrus (32) | Lt | * | 5.93 | < 0.001 | -4, 10, 40 |
| Postcentral gyrus (43) | Lt | * | 5.49 | < 0.001 | -58, -20, 20 |
| Postcentral gyrus (1/2/3) | Lt | * | 5.41 | < 0.001 | -38, -28, 52 |
| Inferior occipital gyrus (18) | Lt | * | 3.45 | < 0.001 | -26, -90, 4 |
| Cerebellum | Lt | * | 3.13 | < 0.001 | -30, -72, -20 |
| Fusiform gyrus (37) | Lt | * | 3.12 | < 0.001 | -42, -56, -18 |
| Thalamus | Rt | 8484 | 5.56 | < 0.001 | 12, 12, 2 |
| Insula (anterior) | Lt | * | 5.53 | < 0.001 | -32, 22, 6 |
| Inferior frontal gyrus (44) | Rt | * | 5.23 | < 0.001 | 60, 10, 16 |
| Thalamus | Lt | * | 5.18 | < 0.001 | -10, -14, 0 |
| Insula (anterior) | Rt | * | 4.76 | < 0.001 | 34, 18, 6 |
| Hippocampus | Rt | * | 4.74 | < 0.001 | 20, 26, -4 |
| Lentiform nucleus | Lt | * | 4.73 | < 0.001 | -18, 8, 4 |
| Hippocampus | Lt | * | 4.57 | < 0.001 | -22, -30, -2 |
| Lentiform nucleus | Rt | * | 4.40 | < 0.001 | 18, 10, 0 |
| Pons | Rt | * | 3.34 | < 0.001 | 6, -18, -14 |
| Inferior frontal gyrus (44) | Lt | * | 2.95 | < 0.001 | -58, 8, 18 |
| Cerebellum | Rt | 2981 | 5.24 | < 0.001 | 22, -48, -24 |
| Fusiform gyrus (37) | Rt | * | 4.77 | < 0.001 | 36, -58, -16 |
| Inferior occipital gyrus (18) | Rt | * | 4.37 | < 0.001 | 32, -84, 0 |
| Inferior parietal lobe (40) | Rt | 841 | 4.52 | < 0.001 | 68, -40, 22 |
| Postcentral gyrus (1/2/3) | Rt | * | 4.19 | < 0.001 | 50, -28, 46 |
| Middle temporal gyrus (39) | Rt | 647 | 4.23 | < 0.001 | 32, -80, 26 |
| Superior parietal lobe (7) | Rt | * | 3.70 | < 0.001 | 26, -58, 52 |
| Pleasantness rating > Thermal sensation rating |
| Superior frontal gyrus (8) | Rt | 5635 | 5.67 | < 0.001 | 40, 18, 52 |
| Medial frontal gyrus (10) | Lt | * | 5.11 | < 0.001 | 6, 52, 14 |
| Medial frontal gyrus (10) | Rt | * | 5.09 | < 0.001 | 2, 58, 22 |
| Anterior cingulate gyrus (32) | Lt | * | 4.91 | < 0.001 | -12, 48, 12 |
| Superior frontal gyrus (8) | Lt | * | 4.68 | < 0.001 | -30, 22, 52 |
| Cuneus (18) | Rt | 1827 | 4.80 | < 0.001 | 8, -92, 22 |
| Inferior parietal lobe (40) | Rt | 1584 | 5.49 | < 0.001 | 48, -58, 38 |
| Inferior parietal lobe (40) | Rt | 1255 | 5.61 | < 0.001 | -46, -58, 34 |
| Middle frontal gyrus (11) | Lt | 1021 | 5.81 | < 0.001 | -26, -18 |
| Cerebellum | Rt | 760 | 5.20 | < 0.001 | 36, -74, -42 |
| Middle frontal gyrus (11) | Rt | 420 | 3.95 | < 0.001 | 42, 38, -14 |
| Middle temporal gyrus (21) | Rt | 301 | 4.62 | < 0.001 | 62, -32, -18 |

Table 4: Dissociated brain regions involved in the two subjective ratings.

Fig. 5. Brain regions commonly activated among the thermal sensation and pleasantness ratings were rendered on the medial and lateral surfaces of a brain (A) and superimposed onto axial sections (Z = -4 and 36 mm) of an SPM standard brain (B). The statistical threshold was set to uncorrected p < 0.001 at the voxel level and p < 0.05 FWE-corrected for multiple comparisons at the cluster level. Lt indicates the left side of brain.

Fig. 6. Brain regions that showed greater activity during thermal sensation rating as compared with the pleasantness/unpleasantness rating (A) and during pleasantness/unpleasantness rating as compared with the thermal sensation rating (B). In the upper figures (A), the activation patterns were rendered on the medial and lateral surfaces of a brain (a) and superimposed onto axial (z = 24, 0, and 48 mm) sections of an SPM standard brain (b). In the lower figures, the activation patterns were rendered on the medial and lateral surfaces of a brain (a) and superimposed onto axial (z = -24, 0, and 48 mm) sections of an SPM standard brain (b). The statistical threshold was set to uncorrected p < 0.001 at the voxel level and p < 0.05 corrected for multiple comparisons at the cluster level. Lt indicates the left side of brain.

condition (Figs. 2–IC and –ID). Therefore, the contrast of the statistical parametric mapping [SPM] between the two conditions may reflect the brain areas involved in the pleasant feeling. However, across six thermal conditions in the present study, many brain regions were activated, including the medial prefrontal cortex extending to anterior cingulate cortex, bilateral insula, right middle frontal cortex, and right inferior parietal lobe (Fig. 3 and Table 1). In addition, neither the...
anterior cingulate cortex. It has been reported that the intensity ratings of both cooling and warming are correlated with activation of the insula (Craig et al., 2000; Olausson et al., 2005). We also found activation in the anterior cingulate cortex and insula in the present study; however, we did not observe such correlations with the rating scores. One possible reason for the difference may be a lack of consideration of hedonic component. We showed that, in the $N_{body}$ trials, $C_{local}$ induced unpleasantness and $H_{local}$ pleasantness (Fig. 2-ID). Thus, the intensity of thermal sensation might be just reflected by the activation of brain areas involved in thermal feeling such as the anterior cingulate cortex, not those involved in the thermal sensation per se (Fig. 4).

**Brain areas associated with thermal hedonic component**

Greater activity was observed in the medial frontal cortex and pre-supplemental motor area during local cold stimulation under the whole-body cold than whole-body hot condition; i.e., $C_{body}C_{local} > H_{body}C_{local}$ (Fig. 4A and Table 2). The data suggest that these brain regions may be associated with unpleasantness, because $C_{body}C_{local}$ induced greater unpleasant feelings with a similar cold sensation (Fig. 2). On the other hand, greater activity was observed in the anterior cingulate cortex, pre-supplemental motor area, bilateral caudate nucleus, and right middle frontal gyrus during local hot stimulation under the whole-body cold than whole-body hot condition; i.e., $C_{body}H_{local} > H_{body}H_{local}$ (Fig. 4B and Table 2). The data imply that these brain regions may be related to pleasantness, because $C_{body}H_{local}$ induced greater pleasant feelings with a similar hot sensation (Fig. 2).

Previous neuroimaging studies have shown that the hedonic component of thermal perception is associated with several brain regions such as the orbitofrontal, medial prefrontal, and cingulate cortices (Rolls et al., 1996). The discriminative and hedonic components of thermal sensation, as well as thermal stimulation included different brain networks. In addition, the evaluation of the discriminative component involved activation of the medial frontal cortex extending to anterior cingulate cortex, insula, middle frontal cortex, and parietal lobes; whereas that of the hedonic component involved activation of the medial prefrontal cortex, posterior cingulate cortex, and inferior parietal lobes. These results demonstrate that different neural substrates are implicated in the discriminative and hedonic components of thermal sensation, as well as the evaluation of these components in response to thermal stimulation.

**Brain regions involved in evaluation processes of thermal stimuli**

We also compared more activated regions between the rating processes of thermal sensation (discriminative) and pleasantness (hedonic) components (Fig. 6 and Table 4). The medial prefrontal cortex extending to anterior cingulate cortex, bilateral insula, bilateral middle frontal cortex, and bilateral parietal lobes were activated when the discriminative component was evaluated (Fig. 6A and Table 4). The medial prefrontal cortex, posterior cingulate cortex, and bilateral inferior parietal lobes were activated when the hedonic component was estimated (Fig. 6B and Table 4). The former regions are similar to those activated when visual attention is directed; i.e., “dorsal attention network” (Corbetta and Shulman, 2002). The latter regions are included in those activated during resting periods, also known as the “default mode network” (Buckner et al., 2008). This network is related to self-generated thought (Andrews-Hanna et al., 2014) and becomes less activated when attention is directed to external stimulation (Gusnard and Raichle, 2001). These studies suggest different roles for these two brain networks in the process of thermal perception. Chikazoe et al. (2014) investigated the involvement of these networks in the processes of visual perception or taste. They reported that the posterior part of these regions, including the insula, is unique to the sensory modality of origin. Conversely, the anterior part, including the orbitofrontal cortex, affords translation across distinct stimuli and modalities. Skerry and Saxe (2014) suggested that the medial frontal cortex is involved in transforming stimulus-bound inputs into abstract representation of emotion. Pain is also divided into two categories: sensory discrimination and evaluation (Melzack and Casey, 1968). Sensory discrimination of pain is processed in the somatosensory cortices and parietal lobe, whereas pain evaluation is mediated by the cingulate (Vogt, 2005) and orbitofrontal cortices (Kulkarni et al., 2005). In this regard, the discriminative and hedonic components of thermal perception may be processed in the insula and medial prefrontal cortex, respectively.

It has been reported that recalling previous stimuli can evoke activation in the brain regions involved in the processing of each modality such as olfaction (Gottfried et al., 2004), vision (Wheeler et al., 2000), audition (Stark et al., 2010), and pain (Fairhurst et al., 2012). Johnson and Rugg (2007) also showed that several brain regions involved in encoding and recollecting (memory retrieval) overlap with the occipital cortex, anterior fusiform gyrus, and ventromedial frontal cortex in sentence tasks. In the present study, the insula may be the key region for encoding and recollecting thermal information.

**Conclusion**

The present study clarified that local thermal stimulation activates specific brain regions such as the anterior cingulate cortex, insula, and inferior parietal lobe; irrespective of the temperature of local or whole-body stimuli. Brain regions associated with unpleasantness and unpleasantness elicited by specific combination of local and whole-body thermal stimulation included different brain networks. In addition, the evaluation of the discriminative component involved activation of the medial prefrontal cortex extending to anterior cingulate cortex, insula, middle frontal cortex, and parietal lobes; while that of the hedonic component involved activation of the medial prefrontal cortex, posterior cingulate cortex, and inferior parietal lobes. These results demonstrate that different neural substrates are implicated in the discriminative and hedonic components of thermal sensation, as well as the evaluation of these components in response to thermal stimulation.

**Conflicts of interest**

None

**Author contributions**

S.N. and K.N. supervised the entire project. A.Y., T.H., H.N., and K.N. designed the study. A.Y., T.H., M.T., and K.N. performed the experiments. A.Y., T.H., and K.N. analyzed the data. A.Y., T.H., H.N., and K.N. wrote the manuscript.

**Acknowledgements**

This study was supported by the Cooperative Study Program of National Institute for Physiological Sciences, and by a Japan Society for the Promotion of Science KAKENHI Grant-in-Aid for Scientific Research B-25280101 (to K. Nagashima).

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