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# A Unique Representation of Heat Allodynia in the Human Brain

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## Summary

**Skin inflammation causes innocuous heat to become painful. This condition, called heat allodynia, is a common feature of pathological pain states. Here, we show that heat allodynia is functionally and neuroanatomically distinct from normal heat pain. We subtracted positron emission tomography scans obtained during painful heating of normal skin from scans during equally intense but normally innocuous heating of capsaicin-treated skin. This comparison reveals the specific activation of a medial thalamic pathway to the frontal lobe during heat allodynia. The results suggest that different central pathways mediate the intensity and certain qualitative aspects of pain. In making this differentiation, the brain recognizes unique physiological features of different painful conditions, thus permitting adaptive responses to different pain states.**

## Introduction

Noxious heat is encoded by the activity of cutaneous thinly myelinated Aδ and unmyelinated C fibers (Handwerker and Kobal, 1993). However, when skin is inflamed or injured, normally innocuous heat becomes painful, a phenomenon called heat allodynia. The word allodynia is derived from the Greek (*allo odynia* = *other pain*) and was intended to emphasize a change of the pain quality (IASP Subcommittee on Taxonomy, 1979). The neurophysiological differentiation of allodynia from normal pain is important because allodynia is a salient feature of pain under pathological conditions such as inflammation and injury. The appearance of touch-evoked allodynia in normal tissue surrounding a lesion suggests that central mechanisms underlie this type of allodynia (for review, see Raja et al., 1999). Heat-evoked allodynia, however, is typically restricted to the area of a lesion or exposure to a chemical irritant and may be mediated by sensitized peripheral heat nociceptors that have a lower response threshold and activate the same central nociceptive pathways as normal heat pain. If this is so, then the forebrain activity during heat allodynia and normal heat pain should not differ significantly when the pain is perceived to be equally intense.

Despite the similarity of burning sensations evoked by normal heat pain and heat allodynia, there are distinct differences in their underlying peripheral and central mechanisms. Normal heat pain recruits both A and C nociceptors accounting, respectively, for early (first pain) and delayed (second pain) pain components (Raja et al., 1999). Capsaicin-induced heat allodynia may depend largely on the activity of C nociceptors because it persists when the conduction of A fibers is selectively blocked (Torebjörk et al., 1992). However, there is evidence that a unique subgroup of Aδ nociceptors may also become active following capsaicin-induced heat allodynia (Ringkamp et al., 2001). Furthermore, some C nociceptors become exclusively responsive to heat following the application of irritants, such as capsaicin or mustard oil (Handwerker et al., 1994). These nociceptors have a time course of chemogenic sensitization that matches the duration of perceived heat hypersensitivity (Baumann et al., 1991; Schmelz et al., 2000). Thus, heat allodynia following chemical irritants may involve the recruitment of a unique class of nociceptors that are functionally distinct and convey information about the status of pathological tissue rather than the threat of impending heat damage. The functional coupling of chemical and thermal sensing in these afferents is mediated by the vanilloid receptor (VR1) that responds to capsaicin, heat, and low pH (Caterina et al., 1997), and integrates simultaneous exposure to these stimuli (Tominaga et al., 1998). Although the deletion of the VR1 gene in mice reduces the animal's response to noxious heat, the major impairment involves the response to inflammatory pain, suggesting that normal heat pain depends to an important extent on non-vanilloidergic transduction mechanisms (Caterina et al., 2000; Davis et al., 2000; Caterina and Julius 2001).

In addition to these peripheral differences, different spinal mechanisms may mediate heat allodynia and heat pain on normal skin. Unlike normal heat pain, heat allodynia involves the sensitization of spinal cord projection neurons, characterized by the enhancement of their response to heat and enlargement of their receptive fields (Woolf et al., 1988; Hylden et al., 1989; Baumann et al., 1991; for review, see Woolf and Salter, 2000). Whereas lamina V dorsal horn neurons predominantly project Aδ and C nociceptor input directly to lateral thalamic nuclei via the contralateral spinothalamic tract, Lamina I-II dorsal horn neurons of the spinomesencephalic and spinoreticular tracts mainly relay C nociceptor input to parabrachial, midbrain, and medial thalamic nuclei (Hunt and Mantyh, 2001). The sensory-discriminative and affective-motivational aspects of pain differ according to the forebrain targets of ascending pathways (Melzack and Casey, 1968; Price, 2000; Hunt and Mantyh, 2001). Therefore, the central processing of normal heat pain and heat allodynia may differ according to the types of nociceptors and spinal projections mediating these sensations.

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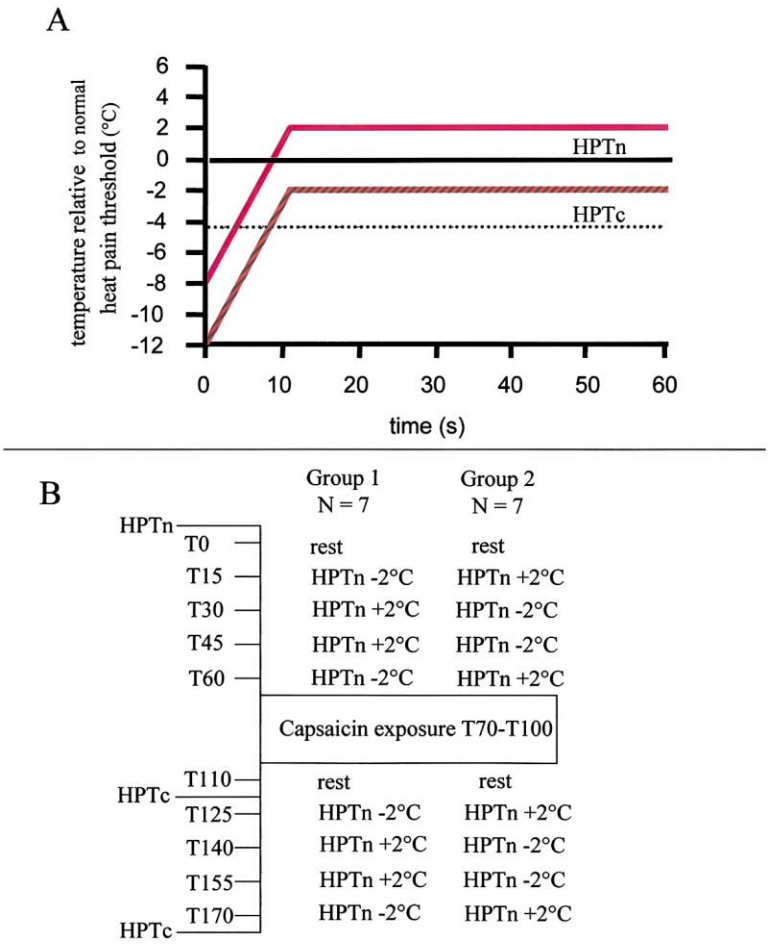


Figure 1. Time Course of Stimuli and Skin Conditions

(A) Time profiles of the two heat stimuli. At the beginning of the scan, the intensity of contact heat was slowly (0.9°C/s) raised to either 2°C below (red + black) or 2°C above (red) the individual heat pain threshold (HPTn) determined on normal skin (solid horizontal line) and kept constant until the end of the scan after 60 s. Treatment of the skin with topical capsaicin (1%, 30 min) reduced the heat pain threshold on average by approximately 4°C (broken horizontal line). Thus, the normally innocuous temperature became painful (heat allodynia; red + black line). (B) Time points of events during the experimental sessions inside the PET scanner (T0 = start of first block).

The collective evidence thus suggests that the peripheral and spinal mechanisms of heat allodynia and normal heat pain are different. To determine if normal heat pain and heat allodynia produce different forebrain responses, we performed positron emission tomography (PET) scans of regional cerebral blood flow (rCBF) in healthy volunteers, using topical capsaicin to induce heat allodynia at the same perceived intensity as normal heat pain. We applied the heat stimuli with a slow ramp phase of 0.9°C/s to both normal and capsaicin-treated skin (Figure 1). Slow heating preferentially excites capsaicin-sensitive C nociceptors (Yeomans and Proudfit, 1996).

## Results

### Psychophysics

Fourteen right-handed male subjects (mean age 23.9 ± 4.6 years) underwent 10 PET scans after the injection of radioactively labeled water. The stimulus-time profile and the sequence of events during the PET session are given in Figures 1A and 1B. We determined the heat pain threshold (HPTn) to the slowly ramped stimulus on normal skin (av. 45.5°C ± 1.6 SD) when each subject was in the scanner. During scans, subjects received either no stimulation (resting scan, no probe contact) or slowly ramped (0.9°C/s) contact heat stimulation of the left volar forearm to a constant plateau at either 2°C below or 2°C above individual HPTn. At the time of the injection, we kept the probe immobile to prevent any mechanical allodynia during trials with sensitized skin. The ramp started approximately 10 s later, 5 s after the estimated arrival of the radioactivity in the brain and at the onset of PET data acquisition. We first tested the normal skin followed by the capsaicin-treated skin. The first scan of either skin condition was a resting scan, followed by two repetitions of either temperature in a sequence balanced over two groups of test subjects. The starting temperature for the high intensity stimulus was 4°C above that of the low intensity stimulus, rendering the duration of the ramp phase identical for both intensities. We measured the HPTc on sensitized skin after the resting scan following capsaicin treatment and after the last scan. The average of these two values was 41.1°C (± 1.9 SD). Thus, capsaicin treatment decreased the heat pain threshold by approximately 4°C (dotted line in Figure 1A), which allowed us to elicit a pain response with the low intensity stimulus on capsaicin-treated skin that was similar to that elicited by the high intensity stimulus on normal skin.

We confirmed the match of intensity ratings between these two stimuli over the whole 60 s period by using the same slowly ramped heat stimuli in the same subjects while obtaining continuous VAS recordings in pre-

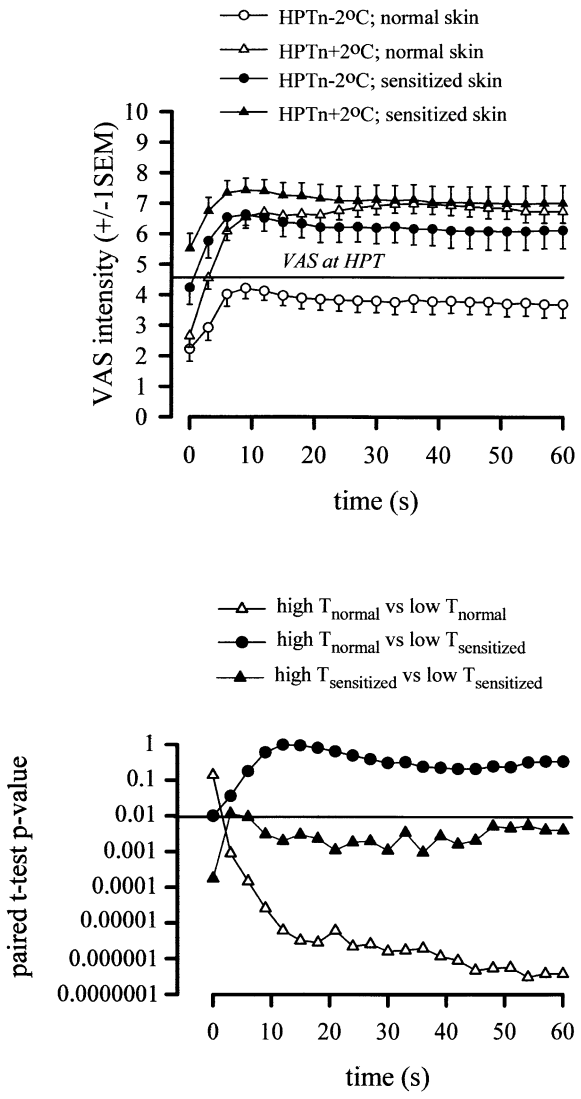


Figure 2. Time Course of Intensity Perception

Top: time course of average perceived intensity during continuous rating in separate sessions outside the scanner. Subjects used a computerized visual analog scale (VAS) device to continuously rate the perceived intensity of the slowly ramped low and high heat stimuli applied on normal and capsaicin-treated skin. The average VAS at heat pain threshold on normal skin (HPTn) is shown as solid horizontal line. Note the similarity of perceived intensity of the high heat stimulus on normal skin (open triangles) and low heat stimulus on sensitized skin (solid circles) especially in the first 20 s during which the blood flow sensitivity of the radiotracer injection is maximal (Beason-Held et al., 1999). Bottom: time course of the statistical significance of differences between continuous intensity ratings of high versus low stimulus intensity on normal skin (open triangles), high stimulus intensity on normal skin versus low stimulus intensity on sensitized skin (filled circles), and high versus low stimulus intensity on sensitized skin (filled triangles).

liminary trials outside the scanner a week earlier (Figure 2, top). The location of the topical capsaicin exposure was also at the left forearm but at a different, more distal skin area than later used during the PET experiment. The bottom graph of Figure 2 presents the time course of the p values derived from paired t tests computed between intensity ratings of the indicated stimuli. Although the VAS value at the starting temperature of the low intensity stimulus on the sensitized skin was significantly higher ($p < 0.01$) than that of the high intensity stimulation on normal skin, the two rating curves converge within 3 s upon further stimulation and are not significantly different throughout the whole stimulation period. In contrast, the pain intensity difference between low and high stimulus intensities is significant throughout the 60 s stimulus period on both normal and sensitized skin.

When reported by single VAS values inside the scanner, the average intensity rating (two repetitions, all test subjects) during the low intensity stimulus on capsaicin-treated skin was also similar to that obtained with the high intensity stimulus on normal skin ($t = 0.13$, $p = 0.90$; Figure 3, top). In addition to the main effects of stimulus intensity ($F = 68.4$, $p < 0.001$) and skin condition ($F = 117.0$, $p < 0.001$) on perceived intensity, skin condition interacted with stimulus intensity due to the greater effect of capsaicin on low compared to high stimulus intensity (condition by intensity: $F = 38.7$, $p < 0.001$). Furthermore, unpleasantness was more enhanced than perceived intensity during sensitization (condition $\times$ VAS dimension: $F = 12.61$, $p < 0.01$; paired t test of the differences: $t = 3.55$; $p < 0.01$; Figure 3, bottom). A short form of the McGill pain questionnaire further examined qualitative differences of pain perception across conditions. Although the sensory score did not differ significantly ($t = 1.4$, $p = 0.17$), the affective score increased during the low intensity stimulus on sensitized skin compared with the high intensity stimulus on normal skin ($t = 2.1$, $p = 0.05$). The effect of capsaicin alone yielded a VAS of 5.4 ($\pm$ 1.6 SD) following the resting scan after capsaicin treatment, which is slightly above the VAS at heat pain threshold (VAS = 4.6; see Experimental Procedures). The spontaneous pain of capsaicin itself decreased gradually to below pain threshold within approximately 30 min after removal of the filter paper. Thus, while some ongoing pain due to capsaicin itself was present when no thermal probe was applied to the skin during the resting scan, all subsequent scans with heat stimulation occurred when pain from capsaicin itself was nearly or completely absent (see Figure 1B).

In summary, topical capsaicin enhanced the sensitivity to contact heat such that a normally warm stimulus of approximately 43°C applied to the treated skin became as intense as a noxious heat stimulus of approximately 47°C applied to normal skin. Sensitization had a significantly greater effect on the lower stimulus temperature and produced a relatively greater enhancement of the affective dimension of the evoked pain.

### Regional Blood Flow Responses

Z score maps subtracting the normal, nonstimulation resting scans from the different stimulus conditions are displayed in Figure 4. Table 1 lists the peak voxel coordinates with significant activation as derived from these comparisons. Regions given in parentheses show a peak of activity, but do not reach a Z score value of 4.0 in all image subtractions.

The effect of capsaicin alone (Figure 4, row A; Table

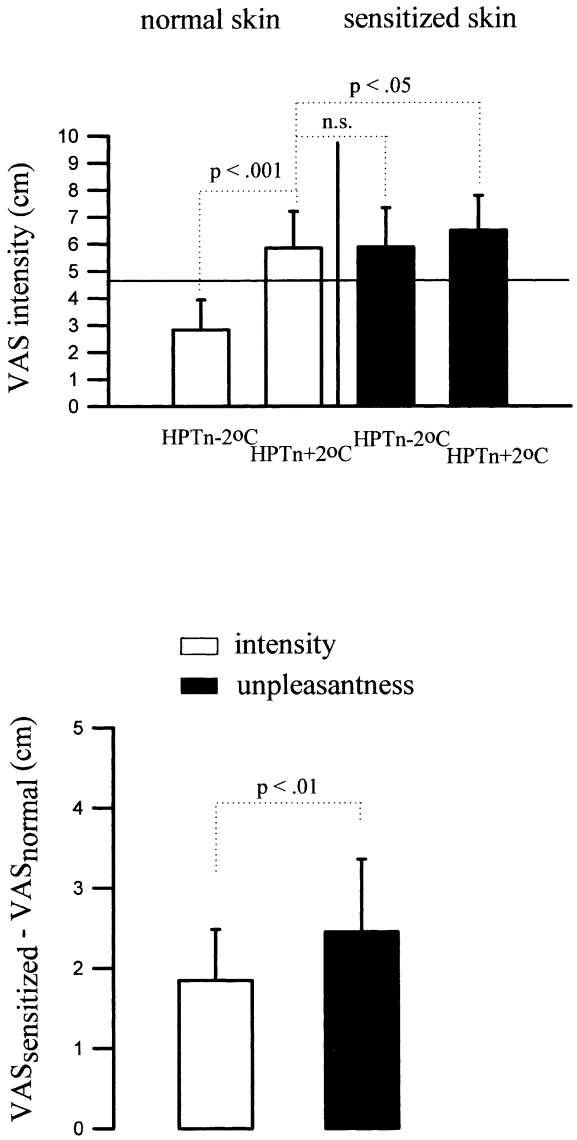


Figure 3. Perceived Intensity and Unpleasantness on Normal and Sensitized Skin

Perceived intensity (±SD) and unpleasantness rated inside the scanner. Top: subjects gave visual analog scale (VAS) ratings of perceived intensity for the two different slowly ramped heat stimuli on normal and sensitized skin. The solid horizontal line indicates the mean VAS at heat pain threshold on normal skin. Note that the high heat stimulus on normal skin induces the same perceived intensity as the low heat stimulus on sensitized skin. Bottom: sensitization of the skin with capsaicin induced a greater increase of unpleasantness compared to intensity (error bars indicate one standard deviation of the difference between VAS at sensitized compared to VAS at normal skin).

1, column A) yields marginally significant activity in the ipsilateral left thalamus, contralateral right perigenual anterior cingulate cortex, right caudate/lenticular nucleus area, left anterior insula, left frontal cortex (BA 10) and the dorsolateral prefrontal cortices of both hemispheres. With low intensity stimulation of the sensitized skin (heat allodynia), the peak activity in each of these structures increases and exceeds or closely approaches a Z score value of 4.0 (Figure 4, row B; Table 1, column B). The peak of thalamic activity shifts from a lateral to a medial position, where it reaches a Z score value of 5.6, and lenticular nucleus activity shifts ventrally, reaching a Z score of 6.7. There is an increase and postero-dorsal movement of peak activity in the anterior cingulate cortex. Marginally significant activity in the left prefrontal cortex shifts dorsomedially. In addition, trends of activation appear in the right secondary somatosensory cortex (SII), merging with that of the mid/posterior insula region and subsignificant activity in the right inferior parietal lobule (BA 40). Thus, the application of normally innocuous heat to sensitized skin amplifies the regional responses to capsaicin alone, shifts the focus of thalamic activity medially, and activates additional regions of the parietal and frontal cortex (compare Figure 4A with 4B). Notably, capsaicin alone does not activate any structures that are not activated by stimulation of the sensitized skin.

On sensitized skin (Figure 4, row C; Table 1, column C), the high and low intensity stimuli activate similar brain regions. However, despite the difference in perceived stimulus intensity (Figures 2 and 3), direct comparison of the two conditions (high minus low; not shown) fails to show any significant activation. Instead, there is a marginally significant *decrease* of rCBF in the medial thalamus (x: −1, y: −10, z: 14; Z score = −3.1), perigenual anterior cingulate cortex (x: −1, y: 35, z: −7; Z score = −3.1), left dorsolateral prefrontal cortex (BA 9/8; x: −39, y: 14, z: 34; Z score = −3.5), and right dorsolateral prefrontal/premotor cortex (BA 9/8 and BA 6; x: 35, y: 14, z: 50; Z score = −3.4). The selective reduction of medial activity within the thalamus shifts the peak activity from medial to lateral portions of the ipsilateral left thalamus. Additionally, the peak activities of the contralateral right anterior insula and right caudate/lenticular nucleus region are reduced while that of the contralateral right SII/midposterior insula region is enhanced during the high intensity stimulus (compare Figure 4B with 4C and column B with column C, Table 1). Thus, on sensitized skin, an increase of applied and perceived stimulus intensity produced a decrease, rather than increase, in the activity of structures uniquely activated during low intensity stimulation. Additional analysis (see below) confirms that the activation pattern of heat allodynia is not due to a difference in stimulus intensity.

Stimulation of the normal skin activates fewer brain regions than stimulation of the sensitized skin (Figure 4, rows D and E; Table 1, columns D and E). Again, despite a significant difference in perceived intensity (Figures 2 and 3), there is no significant rCBF difference when the two intensities are compared directly in a subtraction map (not shown). Yet, as on sensitized skin, the high intensity stimulus accentuates responses in lateral portions of the ipsilateral thalamus (x: −17, y: −19, z: 16; Z score = 2.8) while decreasing the activity in the medial thalamus (x: 3, y: −10, z: 9; Z score = −2.4) and contralateral right anterior insula (x: 46, y: 23, z: 0; Z score = −3.7) when compared with the low intensity stimulus.

To compare heat allodynia directly with normal heat pain, we performed the subtraction analysis shown in Figure 4 (bottom row, B minus E) and Figure 5 (top row)

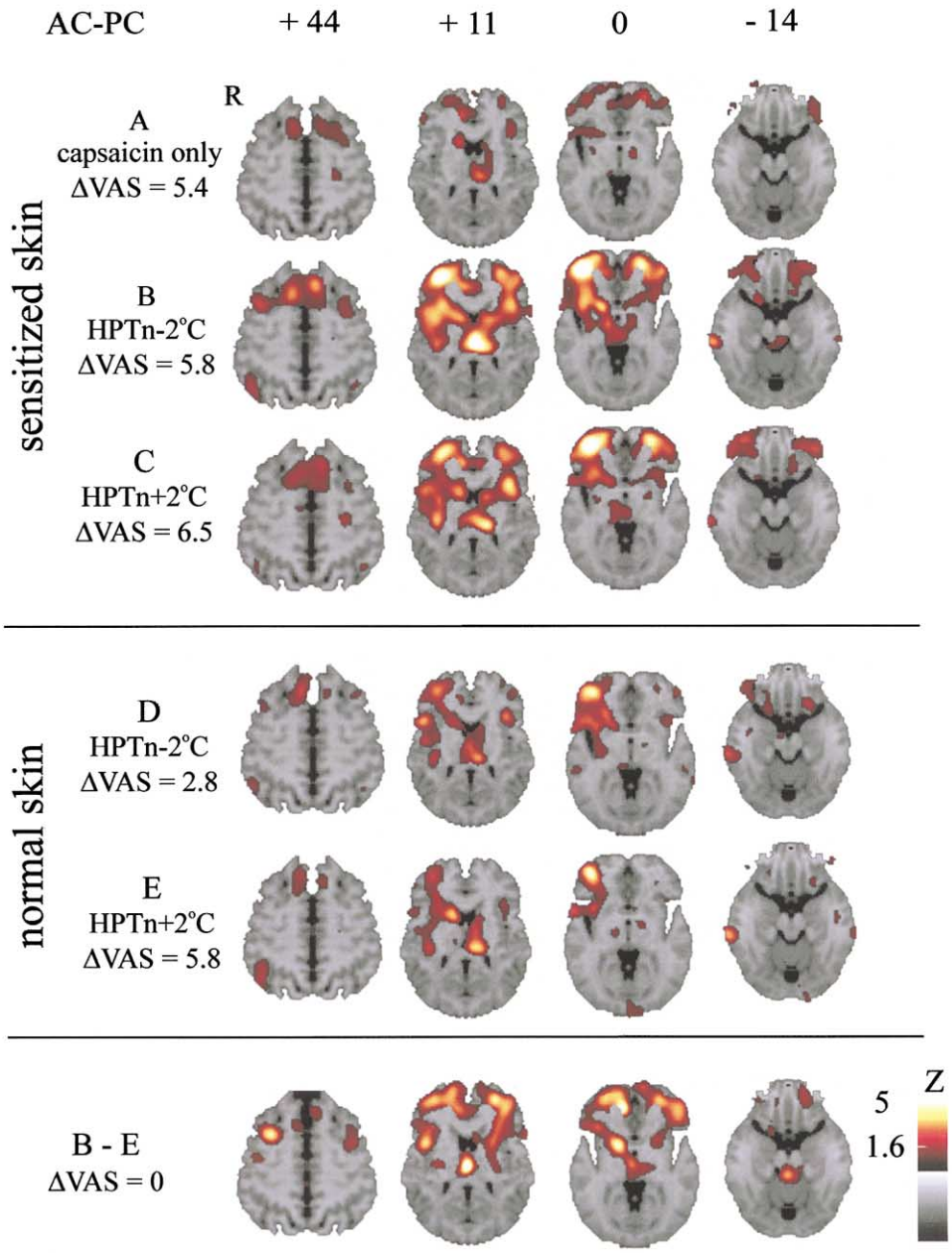


Figure 4. Statistical Maps of Brain Responses to Stimulation of Normal and Sensitized Skin

Z score maps of regional cerebral blood flow (rCBF) increases from six different image subtractions (14 subjects). Row A: normal resting scans (no stimulation; normal skin) are subtracted from resting scans with the left forearm treated by capsaicin without thermal stimulation. Row B: heat allodynia. Same as above except that the left forearm is stimulated with a slowly ramping contact heat stimulus to sensitized skin 2°C below each individual's heat pain threshold on normal skin (HPTn). Row C: same as above except that the stimulus is applied to sensitized skin 2°C above HPTn on normal skin. Rows D and E: same as rows B and C with stimuli applied to the normal skin. Bottom row: The subtraction map of row B minus row E representing the difference between sensitized and normal skin during equally intense pain intensities. Responses of rCBF are superimposed on transverse (right hemisphere to the left) slices at four levels relative to the line connecting anterior and posterior commissure (AC-PC) of a magnetic resonance imaging (MRI) brain scan anatomically transformed to stereotactic atlas coordinates (Minoshima et al., 1994). Despite the same level of perceived intensity, the difference in skin conditions (B–E) is represented by strong activation of the medial thalamus, anterior insula/putamen (right > left), perigenual cingulate cortex, bilateral orbitofrontal and dorsolateral prefrontal cortices, and the dorsomedial midbrain (see Table 2, column A). Note that activity in ventrolateral thalamus, mid/posterior insula, and parietal inferior lobule (BA 40) is present in both conditions (rows B and E) and therefore eliminated in the subtraction shown in the bottom row.

(see also Table 2, column A). Although the low intensity heat stimulus on sensitized skin was perceived as intense as the high intensity heat stimulus on normal skin (Figures 2 and 3), the statistical subtraction map comparing the two conditions shows considerable forebrain activation. This comparison shows that, during heat allo-

Table 1. Results of Image Subtractions from the Resting Scans with Normal Skin

| | | | | Sensitized Skin | | | | | | Normal Skin | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Rest (A) Capsaicin Only | | | HPTn − 2°C (B) | | | HPTn + 2°C (C) | | | HPTn − 2°C (D) | | | HPTn + 2°C (E) | | |
| Region | Coordinates x,y,z[a] | Z score | %Δ rCBF | Coordinates x,y,z | Z score | %Δ rCBF | Coordinates x,y,z | Z Score | %Δ rCBF | Coordinates x,y,z | Z Score | %Δ rCBF | Coordinates x,y,z | Z Score | %Δ rCBF |
| dm Thal | | | | 1, −17, 11 | 5.6 | 8.5 | | | | 3, −24, 7 | (3.6) | (4.7) | | | |
| L Lateral Thal | −6, −24, 11 | (3.3) | (5.5) | | | | −12, −24, 14 | 4.5 | 6.8 | −8, −26, 11 | (3.6) | (4.6) | −10, −24, 11 | 4.1 | 5.7 |
| R Caud/LN | 15, 12, 11 | (2.9) | (4.9) | 19, 10, 4 | 4.5 | 6.7 | 15, 10, 9 | (3.7) | (5.5) | 19, 17, −9 | (2.8) | (3.6) | 15, 10, 11 | (3.9) | (5.4) |
| R Ant Ins | | | | 33, 19, 4 | 4.6 | 6.9 | 33, 21, 4 | (3.6) | (5.4) | 53, 12, 7 | (3.8) | (4.9) | 35, 12, 2 | (3.0) | 4.2 |
| L Ant Ins | −39, 21, 9 | (2.5) | (4.2) | −37, 19, 9 | 4.1 | 6.1 | −37, 14, 9 | 4.3 | 6.6 | −37, 19, 9 | (3.5) | (4.5) | −39, 17, 7 | (2.5) | (3.4) |
| R SII/Post Insula | | | | 39, −19, 14 | (3.4) | (5.2) | 37, −19, 14 | 4.1 | 6.2 | 48, −28, 22 | 4.0 | 5.2 | 51, −28, 25 | 4.0 | 5.5 |
| R Inf Par Lob | | | | 46, −55, 45 | (2.7) | (4.1) | | | | 55, −44, 32 | 4.0 | 5.2 | 48, −62, 38 | (3.1) | 4.3 |
| Anterior CC | 12, 41, 18 | (3.2) | (5.4) | 10, 30, 34 | 4.2 | 6.2 | 10, 39, 18 | 4.3 | 6.6 | 10, 28, 38 | (3.5) | (4.5) | 15, 30, 38 | (2.6) | (5.4) |
| R Med Front (B 10) | | | | 37, 48, 2 | 6.7 | 10.0 | 37, 48, 0 | 6.2 | 9.3 | 39, 46, 2 | 4.5 | 5.9 | 39, 48, 0 | 4.7 | 6.5 |
| R DLPFC (B 8/9) | 42, 23, 36 | (3.5) | (5.8) | 44, 23, 34 | 4.0 | 6.1 | 33, 44, 18 | 4.3 | 6.6 | 44, 23, 24 | 4.5 | 5.8 | | | |
| L Med Front (B 10) | −26, 50, 0 | (3.0) | (5.0) | −24, 50, 4 | 4.9 | 7.6 | −24, 53, −4 | 4.7 | 7.7 | | | | | | |
| L DPFC (B 8/9) | −12, 30, 27 | (3.4) | (5.6) | −10, 30, 47 | (3.7) | (5.5) | −33, 48, 18 | (3.9) | (5.9) | −51, 17, 22 | (3.1) | (4.1) | | | |

dm = dorsomedial; lat = lateral; perig = perigenual; inf = inferior; ant = anterior; post = posterior; thal = thalamus; caud = caudate nucleus; LN = lenticular nucleus; ins = insula; par lob = parietal lobule; R = right; L = left; CC = cingulate cortex; SII = secondary somatosensory cortex; med = medial; DLPFC = dorsolateral prefrontal cortex; DPFC = dorsal prefrontal cortex.

[a] Minus denotes left, posterior and inferior relative to the anterior commissure for x, y and z mm, respectively.

dynia, there is significantly enhanced activity in the medial thalamus, bilateral anterior insula, right ventral putamen, bilateral orbital and medial frontal (BA 10/11) and right dorsolateral prefrontal (BA 9/8) cortices. Strong trends of activation appear in the dorsomedial midbrain, perigenual anterior cingulate cortex (BA 32), and the left dorsolateral prefrontal cortex. Activations that are present at similar magnitudes during both conditions are removed by the subtraction; this includes responses in ipsilateral ventrolateral thalamus, SII/posterior insula, dorsal portions of the right putamen, and in the inferior parietal lobule (BA 40).

The above findings reveal a dissociation of the effect of perceived intensity from the effect of skin sensitization. To examine this observation in more detail, we used the peak voxel coordinates determined by activity (peak voxel Z score $>$ 3.5) during heat allodynia when compared with equally intense normal heat pain (Table 2, column A; see also B–E of Figure 4) and developed volumes of interest (VOI) according to a method described previously (Casey at al., 1996). For each of the seventeen VOI (Table 2, column A), we computed 2-way repeated measures analyses of variance (ANOVA) with stimulus intensity (low versus high, column B of Table 2) and skin condition (normal versus sensitized, column C of Table 2) as effects. Whereas the consistent increase of rCBF due to skin sensitization is expected because the VOI have been identified according to this effect (column C, Table 2), the high stimulus intensity yields generally smaller rCBF responses compared to the low stimulus intensity (column B, Table 2). These decreases in rCBF response reach statistical significance in six VOI (dorsolateral prefrontal (BA 9/8) and medial/orbital (BA 10) cortices of both hemispheres, the right anterior insula, the perigenual anterior cingulate cortex (BA 32), and the right ventral putamen). Marginally significant decreases of rCBF appear in the medial thalamus and the right superior and mid frontal cortex. In none of these VOI is there a significant interaction of intensity with skin condition. Thus, activity in these regions is associated with skin condition and is not dependent on stimulus intensity. Indeed, normally nonpainful stimulus intensities activate these particular structures more than normally painful stimulation of normal or capsaicin-treated skin. These results are consistent with the fact that we obtained a statistical image (Figures 4B–4E) following the subtraction of images acquired during heat allodynia from those acquired during normal heat pain that was perceived as equally intense (Figures 2 and 3).

## Discussion

This study shows that the forebrain activity during capsaicin-induced cutaneous heat allodynia is physiologically different from normal cutaneous heat pain at equal levels of perceived pain intensity. During heat allodynia, there is a unique activation of the medial thalamus, the contralateral right ventral putamen, the dorsal midbrain, and limbic brain structures of both hemispheres such as the right anterior insula, perigenual cingulate cortex, and the prefrontal and orbitofrontal cortices. This observed difference between heat allodynia and normal heat pain cannot be attributed to differences in per-

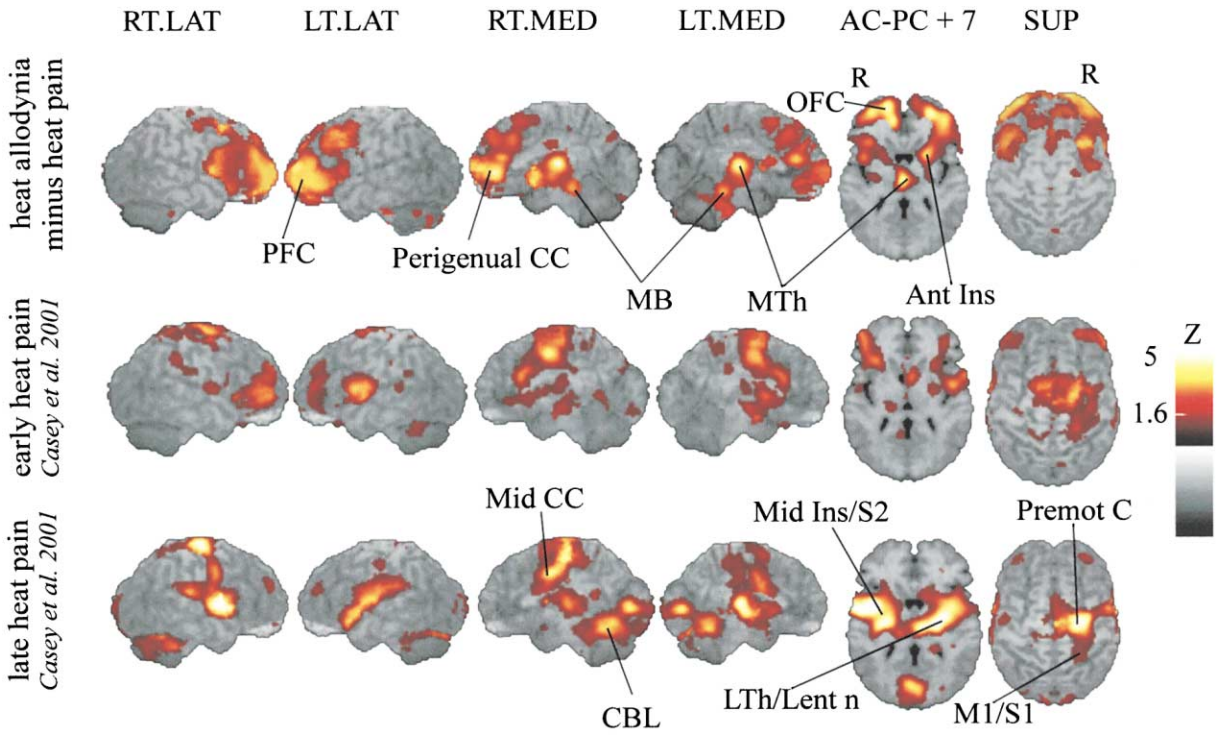


Figure 5. Comparison of Brain Responses during Normal Heat Pain and Heat Allodynia

Comparison of image subtractions from the present study with results from a recent study on normal heat pain of our group (Casey et al., 2001). 1st row: low intensity stimulus on sensitized skin (heat allodynia) minus equally intense high intensity stimulus on normal skin using constant slowly ramped heat. 2nd row: early phases (scanning start at beginning of stimulation) of heat pain (50°C) minus warmth (40°C) using repeated preset contact heat stimuli on normal skin. 3rd row: late phases (scanning starts 40 s after beginning of stimulation) of heat pain (50°C) minus warmth (40°C) using repeated preset contact heat stimuli on normal skin. Note that during late scanning of normal heat pain (3rd row), peak activation appears in the lateral thalamus merged with activity of the lenticular nuclei (left: x = −21, y = −15, z = 9; Z score = 5.3; right: x = 28, y = −13, z = 7; Z score = 4.9) and mid/posterior regions of the insula (left: x = −35, y = 3, z = 4; Z score = 4.4; right: x = 39, y = 1, z = 11; Z score = 6.6). In addition, there is significant and borderline activity in sensorimotor (BA 4: x = 24, y = −17, z = 58; Z score = 4.8) and premotor cortex (BA 6: x = 51, y = −4, z = 38; Z score = 3.4) contralateral to the stimulated left forearm, best seen in the superior view (right hemisphere on the right). Early differs from late phases of heat pain mainly by less thalamic, mid/posterior insula, sensorimotor cortex, and cerebellar activities and by more anterior insula and prefrontal activity. In contrast, the medial thalamus is maximally active during heat allodynia. Although the anterior insula is activated by both early normal heat pain and heat allodynia, the latter yields much stronger prefrontal and orbitofrontal cortex activity in both hemispheres. Abbreviations: RT = right; LT = left; LAT = lateral; MED = medial; SUP = superior; ant = anterior; PFC = prefrontal cortex; OFC = orbitofrontal cortex; CC = cingulate cortex; MB = midbrain; mTh = medial thalamus; LTh = lateral thalamus; Lent n = lenticular nucleus; premot C = premotor cortex; CBL = cerebellum.

ceived intensity because much greater and more sustained differences in the perceived intensities of heat applied to either normal or sensitized skin (Figures 2 and 3) did not reveal significant differences in brain response. Furthermore, increasing the intensity of heat applied to sensitized skin *reduced*, rather than increased, the activity in those structures that are uniquely activated during heat allodynia (compare A, B, and C of Figure 4; note column B, Table 2).

Several conditions of our experiment could affect the results. First, the small perceived intensity difference (VAS = 1.8) during the first 20 s of the scan, when the blood-flow sensitivity of the bolus injection is maximal (Beason-Held et al., 1999), may explain why we failed to demonstrate the brain regions known to be involved in normal heat pain. Previous imaging studies used greater intensity differences (range of VAS differences = 6.0–6.8) of repeated, rapidly ramped contact heat stimuli (Casey et al., 1996; Paulson et al., 1998; Coghill et al., 1999), compared early and late phases of normal heat pain (Casey et al., 2001), and consequently evoked a PET activation pattern that is strikingly different from that of heat allodynia. Second, a greater anticipation of pain upon stimulating sensitized skin could activate the anterior insular and perigenual cingulate cortex during heat allodynia (Ploghaus et al., 1999). Finally, the generally greater ipsilateral thalamic activity during slowly ramped painful heat could be related to the tonic nature of the elicited pain (Derbyshire and Jones, 1998), because repeated rapidly ramped noxious heat stimuli typically activates the thalamus bilaterally (Casey et al., 1994, 1996; Coghill et al., 1999).

### Unique Aspects of Heat Allodynia Activation

As illustrated in Figure 5, neither the effects of heat intensity nor the temporal characteristics of the stimulus (Casey et al., 2001) can account for the difference between heat allodynia and normal heat pain. As shown in the comparison analysis (top row), heat allodynia is associated with unique activity in the medial thalamus,

Table 2. Results of Volume-of-Interest (VOI) Analysis

| Regions Activated during Sensitized Skin at HPT −2°C versus Normal Skin at HPT + 2°C (A) | | | | | Effect of Intensity on VOI Activity (B) | | | Effect of Skin Condition on VOI (C) | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Peak Coordinates | | | MANOVA | | | MANOVA | | |
| No. | Region | x, y, z (mm) | Z Score | ΔrCBF (%) | F | p | ΔrCBF (%)[a] | F | p | ΔrCBF (%)[b] |
| 1 | dm midbrain | 1, −33, −14 | (3.6) | 4.1 | 2.5 | .14 | −1.3 | 8.9 | .01 | +2.7 |
| 2 | dm thalamus | 1, −17, 11 | 5.2 | 5.8 | 3.8 | .07 | −1.4 | 10.1 | <.01 | +2.5 |
| 3 | R putament | 17, 5, −2 | 4.7 | 5.4 | *4.6* | *.05* | *−1.6* | 9.2 | .01 | +2.6 |
| 4 | L ant insula/putamen | −24, 10, 7 | 4.0 | 4.5 | .8 | .40 | −.5 | 8.8 | .01 | +3.0 |
| 5 | R ant insula (BA13) | 42, 5, 11 | 4.0 | 4.6 | *9.9* | *<.01* | *−1.5* | 5.5 | .05 | +2.1 |
| 6 | perigenual ACC (BA9/32) | −1, 37, 16 | (3.9) | 4.4 | *4.6* | *.05* | *−1.0* | 9.6 | <.01 | +3.0 |
| 7 | R med frontal (BA10/32) | 12, 44, 2 | 4.9 | 5.5 | 2.5 | .14 | −1.0 | 8.4 | .01 | +3.2 |
| 8 | R sup frontal (BA10) | 17, 57, 4 | 4.6 | 5.2 | 4.4 | .06 | −1.1 | 4.7 | .05 | +3.1 |
| 9 | R mid frontal (BA10) | 33, 55, 4 | 4.2 | 4.8 | 3.0 | .11 | −1.0 | 6.4 | .03 | +3.0 |
| 10 | R sup frontal (BA10) | 28, 53, −2 | 4.1 | 5.0 | .01 | .91 | +.2 | 1.4 | .26 | +3.4 |
| 11 | R mid frontal (BA10) | 28, 46, −4 | (3.8) | 4.7 | 2.5 | .14 | −1.5 | .01 | .91 | +.3 |
| 12 | R mid frontal (BA10) | 35, 46, 18 | (3.9) | 4.4 | 4.1 | .06 | −1.0 | 6.9 | .02 | +2.7 |
| 13 | R DLPFC/premoter (BA9/6/8) | 33, 14, 45 | 4.4 | 4.9 | *7.4* | *.02* | *−1.8* | 10.4 | <.01 | +2.6 |
| 14 | L mid frontal (BA10) | −28, 50, 7 | 4.6 | 5.2 | .01 | .93 | +.1 | 8.8 | .01 | +3.9 |
| 15 | L inf frontal (BA46/10) | −42, 44, 4 | 4.2 | 4.7 | *7.0* | *.02* | *−1.0* | 16.5 | <.01 | +2.7 |
| 16 | L mid frontal (BA11) | −21, 46, −7 | 4.0 | 5.1 | .19 | .64 | −.5 | 1.5 | .25 | +4.2 |
| 17 | L DLPFC (BA9/8) | −37, 17, 36 | (3.7) | 4.2 | *8.7* | *.01* | *−1.3* | 30.4 | <.001 | +2.2 |

For abbreviations see Table 1.

[a,b] Plus signs reflect greater rCBF during high than low stimulus intensity[a] or greater rCBF during sensitized than normal skin condition[b].

ventral putamen, dorsomedial midbrain, and prominent bilateral frontal lobe involvement. Early scanning (middle row) during normal heat pain evokes bilateral prefrontal and anterior insula activity, but these structures do not respond as the stimulus continues (bottom row) as in the present study. During the late phase of normal heat pain, there is maximal activity in the mid/posterior insula and lateral thalamus. These structures show significant intensity dependency over a range of stimulus temperatures during normal heat pain (Coghill et al., 1999). However, they are active also during heat allodynia, so do not appear in the statistical image comparison of these two conditions (Figures 4B–4E). In contrast, the right anterior insula is active (Figures 4B–4E), consistent with current evidence for functional specialization within the insula. Ploghaus et al. (1999) showed that activity in the anterior, but not posterior, insula correlates with the anticipation of pain. In addition, Craig et al. (2000) noted a stronger relationship of right (ipsilateral) anterior insula and orbitofrontal activation with perceived, compared to applied, stimulus intensity. The primary sensory-motor and premotor cortices (BA 6) and the bilateral cerebellum respond during the late phases of normal heat pain but not during heat allodynia. In addition, activity in the cingulate cortex during normal heat pain appears caudal (BA 24) to the perigenual areas (BA 32) that are active during heat allodynia.

We also observed that activity in the putamen is more ventral during heat allodynia than during normal heat pain (Figures 4B, 4E, and 4B–4E; Table 1, columns B and E; Table 2, column A). This result may reflect a functional differentiation within the basal ganglia. Nakano et al. (2000) reviewed evidence separating the striatum into a dorsal sensorimotor loop, which connects the ventrolateral thalamus and sensorimotor cortex, and a ventral associative-limbic loop that includes the medial thalamus, orbito-/prefrontal cortex, and perigenual cingulate cortex (BA 32). In addition, Becerra and colleagues (2001) revealed an overlap of pain and reward circuits within the frontal lobe and ventral striatum. The results suggest that heat allodynia engages motor mechanisms that are influenced strongly by motivational and emotional context.

Normally noxious temperatures reduced the activation of some brain areas specifically responding during heat allodynia (Table 2, column B). The mechanism of this suppressive effect is unknown. It is possible that the neuronal mechanisms that mediate normal heat pain intensity impair the activation of pathways mediating heat allodynia, but this hypothesis remains to be tested in other experiments.

### Mechanisms of Heat Allodynia

As noted in the Introduction, a number of chemical and anatomical characteristics are associated with physiological differences among nociceptors, but it is not yet possible to identify those that are uniquely associated with heat allodynia. Stucky et al. (2001) have reviewed the evidence that isolectin B4 binding and related chemical characteristics may differentiate among nociceptors that are activated by heat or during inflammation. Andrew and Craig (2001) recently showed that histamine excites specific spinothalamic projection neurons, suggesting a unique chemogenic pathway. Therefore, it is possible that topical capsaicin activates a chemogenic pain pathway that is exaggerated by heat. In contrast, intense heating of normal skin could activate the capsaicin-insensitive VRL-1 receptor (Caterina et al., 1999) and a different central pathway. However, we need additional studies to determine which particular biochemical characteristics of afferent fibers can account for the unique forebrain responses during heat allodynia.

It is possible that different spinal pathways mediate normal heat pain and heat allodynia. Capsaicin sensitizes mechano-, heat-sensitive, and heat-insensitive C nociceptors (Handwerker et al., 1994) that innervate lamina I neurons of the spinal dorsal horn (Craig and Dostrovsky 1999). The time course of capsaicin-induced

heat hypersensitivity in these "silent" nociceptors matches the duration of burning pain more closely than that of polymodal C nociceptors (Schmelz et al., 2000). Intradermal capsaicin also sensitizes primate spino-mesencephalic tract cells projecting to the midbrain periaqueductal gray (Dougherty et al., 1999). Thus, capsaicin-sensitized C nociceptors may preferentially recruit spino-mesencephalic, spinoreticular or spino-parabrachial pathways to the medial and intralaminar thalamic nuclei (Craig, 1995; Bernard et al., 1996; Westlund and Craig, 1996; Bourgeais et al., 2001) whereas normal heat-sensitive nociceptors give relative emphasis to activity in the ventral lateral thalamus primarily via lamina V neurons of the lateral spinothalamic tract (Hunt and Mantyh, 2001).

### Functional Aspects of Forebrain Activity during Heat Allodynia

The ventral posterior thalamus relays nociceptive information to the primary and secondary somatosensory cortices and mid/posterior portions of the insula (Craig and Dostrovsky, 1999). These brain areas encode the intensity of nociceptive stimuli and are important for the sensory-discriminative evaluation of pain (Melzack and Casey, 1968; Price and Dubner, 1977; Price, 2000). In contrast, the medial thalamus is densely connected with the frontal lobe and relays nociceptive information to the prefrontal cortex, the anterior cingulate gyrus, and anterior insula. These structures are components of the "limbic system," which has long been associated with emotional reactions and motivated behaviors (MacLean, 1955, 1957). We found a significantly greater rating of affect induced during heat allodynia in comparison with normal heat pain, which is consistent with the role of medial thalamic pathways in mediating affective and cognitive determinants of pain (Melzack and Casey, 1968; Price, 2000). Emotions, either self-generated or triggered by other sensory modalities, involve limbic system structures similar to those that are uniquely activated during heat allodynia (George et al., 1995; Lane et al., 1997; Reiman et al., 1997).

Although skin sensitization caused greater increases of unpleasantness than pain intensity, factors other than unpleasantness probably contribute to the unique forebrain activations during heat allodynia. The unpleasantness of normal heat pain correlates with activity in the mid/anterior portions of the cingulate cortex (BA 24) (Rainville et al., 1997; Tolle et al., 1999), but the cingulate activity during heat allodynia localizes to the more ventral and rostral BA 32 (Table 2; Figure 5, top). Furthermore, large differences of unpleasantness occur also during noxious heat stimulation of normal skin (Price et al., 1994; Coghill et al., 1999) without producing the frontal lobe responses seen during heat allodynia. The prefrontal responses to painful heating of normal skin are much less extensive than in heat allodynia in both genders (Paulson et al., 1998) and, when tested over a range of intensities, do not correlate with pain intensity or unpleasantness (Coghill et al., 1999). Rather, the prefrontal cortex is activated consistently when painful experiences occur in the context of tissue alterations resulting from capsaicin treatment (this study; Iadarola et al., 1998; Baron et al., 1999), in response to trauma (Hsieh et al., 1996), underlying visceral pains, such as angina pectoris (Rosen et al., 1996), abnormal intestinal pain (Silverman and Munakata, 1997), or neuropathic pain (Hsieh et al., 1995). Allodynia and visceral pain also share similarities with neuroimaging results of air hunger (Liotti et al., 2001) or extreme thirst (Denton et al., 1999). These conditions are associated with cognitive, emotional, and motivational adaptive responses that are more comprehensive than the experience of unpleasantness. Because heat allodynia is usually a symptom of a pathological pain state, the prefrontal and orbitofrontal cortical activity during this condition probably reflects cognitive and emotional responses to perceived tissue pathology. These regions are involved in a variety of sensory and cognitive tasks that include working memory, planning, decision making, response conflicts, or the integration of information about rewards and punishments (Becerra et al., 2001; for reviews, see Fuster, 1997; Miller and Cohen, 2001; Funahashi, 2001). Thus, heat allodynia, and possibly inflammatory pain, cannot be regarded as simply an enhanced normal pain response.

## Conclusions

Noxious heat applied to normal skin evokes a heat pain sensation that is subjectively and physiologically different from the pain produced by the application of normally innocuous heat to skin sensitized by topical capsaicin (heat allodynia). The difference between normal heat pain and innocuous warmth includes activity in the cerebellum, bilateral lateral thalamus, contralateral dorsal putamen, contralateral sensorimotor and premotor cortex, bilateral anterior and midposterior insula, and in the midanterior cingulate cortex. In contrast, the difference between normal heat pain and equally intense heat allodynia consists of activity in the medial thalamus, contralateral ventral putamen, contralateral anterior insula, perigenual anterior cingulate cortex, and extensive bilateral areas of the dorsolateral and orbital frontal cortex. This unique pattern of brain activity is due in part to the greater unpleasantness of heat allodynia, but probably also to the specific activation of peripheral afferent and brain mechanisms mediating responses to pain caused by inflammation, tissue damage, and similar pathological conditions. The brain recognizes the unique physiological features of different painful conditions, thus permitting adaptive responses to different pain states.

### Experimental Procedures

The local institutional review boards of both the Ann Arbor Veterans Affairs and University of Michigan Medical Centers approved the protocol before the study began. The scanner used in this study was a Siemens/CTI 931/08-12 with 15 tomographic slices covering an axial field of view of 10 cm. For each of 10 scans, each subject received a 50-mCi bolus injection of $H_2{}^{15}O$ into the antecubital vein of the right arm. At least 15 min elapsed between each scan. Data acquisition began 5 s after detecting the arrival of radioactivity in the brain and continued for approximately 60 s. After normalizing each image set to whole brain counts (Fox and Raichle, 1984), mean radioactivity concentration images estimating regional cerebral blood flow (rCBF) were created for each experimental condition across all subjects by stereotactic anatomical standardization techniques (Minoshima et al., 1994). We made subtraction images for each subject according to our experimental variables (rest, two

intensities, two skin conditions). We performed a voxel-by-voxel statistical subtraction analysis (Z score) with adjustment for multiple comparisons by estimating the smoothness of subtraction images (Friston et al., 1991) following three-dimensional Gaussian filtering (FWHM = 9 mm) to enhance signal-to-noise ratio and compensate for anatomical variance. We identified voxels with a significantly increased CBF compared to the average noise variance computed across all voxels (pooled variance) (Worsley et al., 1992). The critical level of significance (Z = 4.0) was determined by adjusting p = 0.05 using this information (Adler and Hasofer, 1976).

We delivered heat stimuli to the left volar forearm with a digitally controlled feedback contact thermode (Cygnus, Paterson, NJ) that has a gold-plated copper surface contact area of 254 $mm^2$ heated by direct current. The probe was placed on the skin before the injection, and the temperature stimulus profile was initiated at the start of PET data acquisition. Stimulation at the skin site continued during the total scanning time of 60 s; the probe was not moved during stimulation. Location of the stimulated skin was changed between scans in a counterclockwise manner within an area of 5 × 5 cm. Capsaicin (8-Methyl-N-Vanillyl-6-Nonenamid, Sigma) was diluted in 70% ethyl alcohol to give a 1% solution. After control scans, a filter paper (5 × 5 cm) saturated with this solution was taped firmly to the left volar forearm for 30 min. Another 10 min after removing the skin patch, we performed the next set of scans. Any residuals from the capsaicin solution were removed from the skin by a gauze pad.

Heat pain threshold was tested three times, after positioning the subject inside the scanner, after the resting scan with capsaicin-treated skin, and at the end of the session. The heat probe was held on the subjects' left forearm. The stimulus started at 30°C and increased at the same slow rate of 0.9°C/s as used later for stimulation. Subjects held down a button that they released with the beginning of pain. The temperature displayed at this instant during the first measurement was noted and the average of five test runs was documented as normal heat pain threshold (HPTn). We asked subjects to attach a marker on an electronic visual analog scale (VAS) device to indicate the beginning pain between no thermal sensation (0) and maximum pain (10). Thus, the VAS at heat pain threshold was not identical across all test subjects and yielded a mean value of 4.6 (±0.85 SD). Between scans, subjects rated the perceived intensity and unpleasantness, acknowledging the pain threshold anchor for the former but not for the latter rating. Additionally, the short form of the McGill pain questionnaire (Melzack, 1987) was used after each stimulation scan. This form contains fifteen pain descriptors. Subjects answered with none, mild, moderate, or severe to indicate how appropriate the word describes the perception of the stimulation. We transformed rankings into numerical values (0–3). For each scan, we computed sum scores separately for sensory and affective descriptor words.

In preliminary trials outside the scanner a week earlier, we tested the same subjects in order to achieve continuous intensity ratings every 3 s during the same slowly ramped heat stimuli. The protocol was identical to the one described in Figures 1A and 1B. Capsaicin application was done on the same (left) forearm, but on a more distal location than later used in the scanner. We did not obtain unpleasantness ratings or McGill pain questionnaire responses during these sessions.

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