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# Insights into the pathophysiology of neuropathic pain through functional brain imaging

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**Abstract**

We present here an example case of neuropathic pain with heat allodynia as a major symptom to illustrate how the functional imaging of pain may provide new insights into the pathophysiology of painful sensory disorders. Tissue injury of almost any kind, but especially peripheral or central neural tissue injury, can lead to long-lasting spinal and supraspinal re-organization that includes the forebrain. These forebrain changes may be adaptive and facilitate functional recovery, or they may be maladaptive, preventing or prolonging the painful condition, and interfering with treatment. In an experimental model of heat allodynia, we used functional brain imaging to show that: (1) the forebrain activity during heat allodynia is different from that during normal heat pain, and (2) during heat allodynia, specific cortical areas, specifically the dorsolateral prefrontal cortex, can attenuate specific components of the pain experience, such as affect, by reducing the functional connectivity of subcortical pathways. The forebrain of patients with chronic neuropathic pain may undergo pathologically induced changes that can impair the clinical response to all forms of treatment. Functional imaging, including PET, fMRI, and neurophysiological techniques, should help identify brain mechanisms that are critical targets for more effective and more specific treatments for chronic, neuropathic pain.


## Introduction

The Department of Neurology at the University of Michigan has a long tradition of providing clinical service that is based on a contemporary understanding of the basic neurobiology of the nervous system. In the preface to the 1st edition of *The Neurologic Examination*, Russell N. DeJong, the 3rd chairman of our Department, wrote: "The student of the nervous system must understand the basic laws pertaining to it before he can master the intrinsic aspects of nervous function." And in the preface to the 3rd edition of this now classic work, he continued: ". . . if the interpretation of the neurologic examination is to be kept current, it is necessary that it be correlated with the accelerating progress in (the neurosciences)."(DeJong, 1979). Throughout his tenure as (the 4th) Chairman of the Department of Neurology at Michigan, Sid Gilman maintained and amplified this emphasis on grounding the practice of clinical neurology firmly in the basic neurosciences. This has required a continuing and renewed emphasis on basic and clinical research by faculty within the Department. The task has not been easy, given the remarkable acceleration of knowledge in the neurosciences and the current demands on the time and effort of academic clinicians. Nonetheless, the Department has remained among the leaders academic neurology throughout Sid's tenure and shows every promise of continuing in that direction.[1]

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In keeping with our tradition of relating the basic neurosciences to specific clinical problems, we present here the case example of a patient with a clinical problem that is elucidated by the application of a contemporary, neuroscientifically based technology. The purpose here is to demonstrate how an emerging technology, functional brain imaging, can reveal clinically relevant aspects of the pathophysiology of a common neurological condition, painful, post-traumatic neuropathy.

## Case example

A 48-year-old man fractured his left third and fourth metacarpals when a heavy brick fell on his hand at work on a construction site. He complained of "numbness" in the third and fourth fingers and mild grip weakness. Over the next 6 weeks, he noted the development of continuous burning pain and marked sensitivity to touch, heat, and cold throughout the "numb" area; he also suffered from frequent paroxysms of electrical pain radiating down the arm into the fingertips.

On examination, the hand is slightly cool and pale; the patient protects it and is unwilling to participate fully in strength testing. There is sensory loss restricted to the 3rd and 4th fingers. This area shows allodynia to tactile, heat, and cold stimulation, especially when applied repetitively. There is a deficit of the sensation of single stimuli of light touch, cold, heat, and pinprick. Pulses are normal in all arm positions. Shoulder function is normal. There are no myofascial trigger points, but there is marked tenderness to pressure along both injured metacarpals, producing radiating pain into the hand. Limited EMG is normal. X-rays of the hand show good healing of the fractures and no osteopenia. Bone scan shows increased activity at the fracture sites, but normal periarticular uptake.

### *Comment*

The history and examination strongly suggest injury to the digital nerves, with possible local neuroma formation. The focal tenderness and the restriction of pain and sensory abnormalities to the territory of sensory loss support this formulation. Because there is evidence for nerve damage, this patient would be considered to have a neuropathic pain syndrome. The protection of the hand, motor dysfunction, and abnormal color and temperature makes complex regional pain syndrome type 1 (CRPS 1; causalgia) a consideration in this case (Allen et al., 1999). The x-ray and nuclear medicine studies did not support this diagnosis, but these tests may be normal in milder cases. Although the prognosis for full recovery in this case is uncertain, all physicians who have attempted to treat painful neuropathies, especially those caused by trauma, know how difficult this can be.

There are many pathological features of this case that deserve additional comment and investigation, but this is beyond the scope of this paper. Accordingly, we select the phenomenon of *allodynia*, and heat allodynia in particular, to illustrate how the functional imaging of pain may provide new insights into the pathophysiology of painful sensory disorders.

## Pathophysiology of heat allodynia: current status

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 (Merskey and Bogduk, 1994). Allodynia is a salient feature of pain under pathological conditions such as inflammation and injury to extraneural or neural tissue. Unlike tactile allodynia, heat-evoked allodynia is typically restricted to the area of a lesion or 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. However, there is substantial evidence that tissue injury of almost any kind can lead to temporary or long-lasting spinal and supraspinal re-organization that includes the forebrain (Kaas et al., 1997). These central changes may be adaptive and facilitate functional recovery, or they may be maladaptive, preventing or prolonging the painful condition and interfering with treatment (Dubner and Ruda, 1992; Woolf and Salter, 2000).

Although the burning sensations of normal heat pain and heat allodynia are similar, 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. However, heat allodynia, following chemical irritants such as topical capsaicin (Petersen and Rowbotham, 1999), recruits 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). Normal heat pain depends in large part on non-vanilloidergic transduction mechanisms (Caterina et al., 2000; Caterina and Julius, 2001; Davis et al., 2000). Capsaicin-induced heat allodynia, however, depends largely on the activity of vanilloid-sensitive C-nociceptors because it persists when the conduction of A-fibers is selectively blocked (Torebjörk et al., 1992). Furthermore, some C-nociceptors become exclusively re-

sponsive to heat following the application of irritants, such as capsaicin or mustard oil (Kilo et al., 1994).

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 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 mainly relay C-nociceptor input to parabrachial, midbrain, and medial thalamic nuclei (Hunt and Mantyh, 2001) that form a gateway to the limbic system. Thus, the sensory-discriminative and hedonic aspects of normal heat pain and heat allodynia will differ according to the types of nociceptors and spinal projections mediating these sensations (Melzack and Casey, 1968; Price, 2000).

The collective evidence 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. Here, we summarize the results of previously $H_2{}^{15}O$ PET published experiments on the analysis of heat allodynia mechanisms (Lorenz et al., 2002; Lorenz et al., 2003)

*Psychophysics of heat allodynia*

We applied contact heat stimuli to 14 right-handed male subjects (mean age 23.9 ± 4.6 years) with a slow ramp of 0.9°C/s to plateau to both normal and capsaicin-treated skin. The plateau temperature was maintained throughout the scan. Slow heating preferentially excites capsaicin-sensitive C-nociceptors (Yeomans et al., 1996). Subjects received either no stimulation (resting scan, no probe contact) or contact heat stimulation of the left volar forearm to a constant plateau at either 2°C below or 2°C above individual HPTn.

The average contact heat pain threshold on normal skin (HPTn) was 45.5°C ± 1.6 s.d.) and, on sensitized skin (HPTc), 41.1°C (±1.9 s.d). Thus, capsaicin treatment decreased the heat pain threshold by approximately 4°C. The spontaneous pain of capsaicin alone decreased gradually so that pain due to capsaicin only was nearly or completely absent during scans with heat stimulation.

The capsaicin treatment allowed us to evoke pain with the low intensity stimulus on capsaicin-treated skin that was similar to that elicited by the high intensity stimulus on normal skin. Visual analog scale pain ratings (VAS) following the low intensity stimulus on capsaicin-treated skin were similar to that obtained with the high intensity stimulus on normal skin (mean VAS 5.8 both conditions; $t = 0.13$, $p = 0.90$). We confirmed the match of intensity ratings between these two stimuli over the whole 60-s scan period in preliminary trials outside the scanner.

In addition, unpleasantness was more enhanced than perceived intensity during sensitization (condition × VAS dimension: $F = 12.61$, $p < 0.01$; paired *t*-test of the differences: $t = 3.55$; $p < 0.01$). A short form of the McGill pain questionnaire also showed that the affective, but not intensity, score increased during the low intensity stimulus on sensitized skin compared with the high intensity stimulus on normal skin ($t = 2.1$, $p = 0.05$).

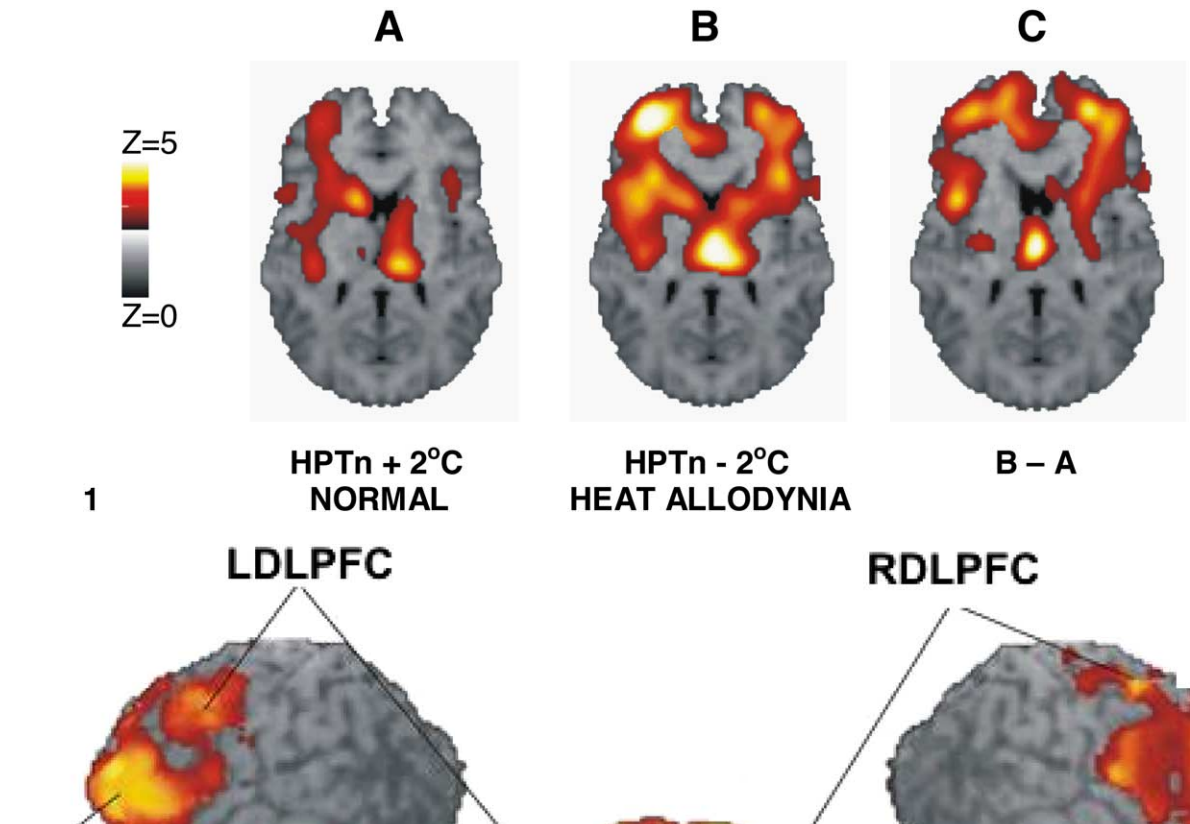
In summary, topical capsaicin enhanced the sensitivity to contact heat such that a normally warm stimulus of approximately 43°C applied to the treated skin became as intense as a noxious heat stimulus of approximately 47°C applied to normal skin. Sensitization had a significantly greater effect on the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

*Forbrain responses during heat allodynia*

Fig. 1 summarizes the Z-score maps obtained from subtracting the normal, non-stimulation resting scans from high-intensity stimulation of normal skin (A), low-intensity stimulations on sensitized skin (B), and the unique activations produced by the capsaicin skin condition during heat allodynia (B-A). Table 1 lists the structures that are uniquely activated during heat allodynia (B-A of Fig. 1).

Although the low intensity heat stimulus on sensitized skin was perceived as intense as the high intensity heat stimulus on normal skin, the statistical subtraction map comparing the two conditions shows considerable forebrain activation. This comparison shows that, during heat allodynia, 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 and developed volumes of interest (VOI) according to a method described previously (Casey, Minoshima et al. 1996). For each of the seventeen VOI (Table 1), we computed 2-way repeated measures analyses of variance (ANOVA) with stimulus intensity (low



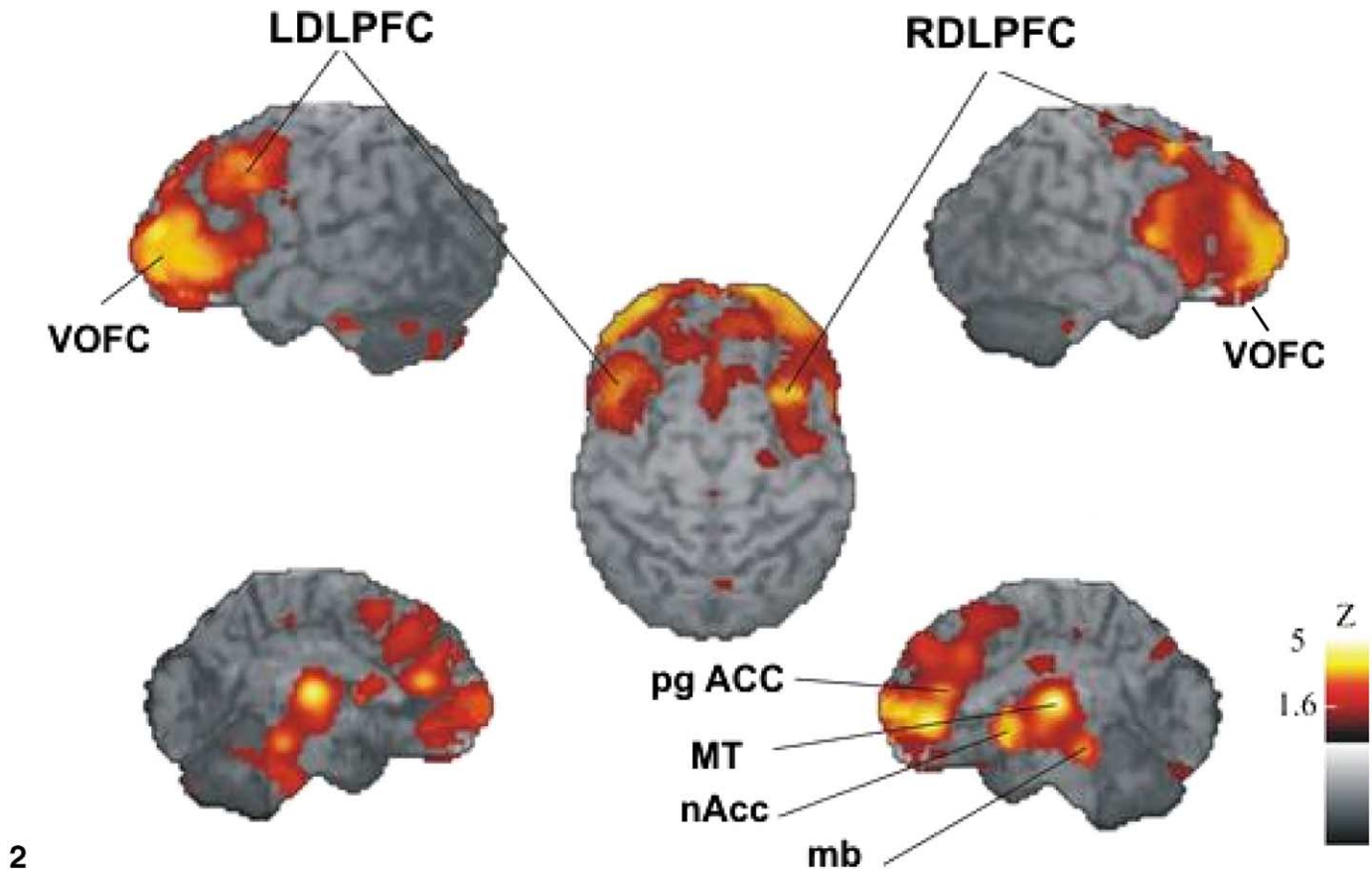




Fig. 1. Heat allodynia compared to normal heat pain at equal perceived pain intensities (av. VAS rating = 5.8; $t = 0.13$, $p = 0.90$). Right hemisphere shown on left. A: Activations during contact heat 2°C above normal heat pain threshold (HPTn) to normal skin of left forearm. B: Activations during contact heat 2°C below normal heat pain threshold (HPTn) to sensitized skin of left forearm (heat allodynia). C: Subtraction image, showing activations due to sensitized skin condition alone.

Fig. 2. Surface-rendered images of heat allodynia minus equally intense normal heat pain. Note the extensive recruitment of bilateral frontal lobe activity in ventral/orbitofrontal (VOFC) and dorsolateral prefrontal cortex (DLPFC) regions and the activity in the perigenual anterior cingulate cortex (pg ACC), medial thalamus (MT), nucleus accumbens (nAcc) of the ventral striatum and the dorsal medial midbrain (mb).

vs high) and skin condition (normal vs sensitized) as effects. Whereas the consistent increase of rCBF due to skin sensitization is expected by selection, the high stimulus intensity yields generally smaller rCBF responses compared to the low stimulus intensity (Table 1). 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.

Table 1
Structures activated during heat allodynia and the ANOVA of this activation with stimulus intensity and skin condition as factors

| Heat allodynia (HPTn − 2°C) − (HPTn + 2°C) | | | Stimulus intensity | | Skin condition | |
|---|---|---|---|---|---|---|
| Region | *z*-score | ΔrCBF (%) | p | ΔrCBF (%) | *p* | ΔrCBF (%) |
| med midbrain | (3.6) | 4.1 | .14 | −1.3 | .01 | +2.7 |
| med thalamus | 5.2 | 5.8 | .07 | −1.4 | <.01 | +2.5 |
| R putamen | 4.7 | 5.4 | .05 | −1.6 | .01 | +2.6 |
| L ant insula/putamen | 4.0 | 4.5 | .40 | −.5 | .01 | +3.0 |
| R ant insula | 4.0 | 4.6 | <.01 | −1.5 | .05 | +2.1 |
| perigenual ACC | (3.9) | 4.4 | .05 | −1.0 | <.01 | +3.0 |
| R med frontal | 4.9 | 5.5 | .14 | −1.0 | .01 | +3.2 |
| R sup frontal | 4.6 | 5.2 | .06 | −1.1 | .05 | +3.1 |
| R mid frontal | 4.2 | 4.8 | .11 | −1.0 | .03 | +3.0 |
| R sup frontal | 4.1 | 5.0 | .91 | +.2 | .26 | +3.4 |
| R mid frontal | (3.8) | 4.7 | .14 | −1.5 | .91 | +.3 |
| R mid frontal | (3.9) | 4.4 | .06 | −1.0 | .02 | +2.7 |
| R DLPFC/premotor | 4.4 | 4.9 | .02 | −1.8 | <.01 | +2.6 |
| L mid frontal | 4.6 | 5.2 | .93 | +.1 | .01 | +3.9 |
| L inf frontal | 4.2 | 4.7 | .02 | −1.0 | <.01 | +2.7 |
| L mid frontal | 4.0 | 5.1 | .64 | −.5 | .25 | +4.2 |
| L DLPFC | (3.7) | 4.2 | .01 | −1.3 | <.001 | +2.2 |

The positive rCBF responses with skin condition in these structures is expected during heat allodynia. However, note the lack of positive responses with stimulus intensity during heat allodynia. Indeed, all significant responses are negative, showing that the activations during heat allodynia are not due to increased stimulus intensity.

## The pathophysiology of heat allodynia revisited

What accounts for the physiological differences in the forebrain responses to normal heat pain and heat allodynia? 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. For example, (Stucky et al., 2001) have recently reviewed the evidence that isolectin B4 binding and related chemical characteristics may differentiate among nociceptors that are activated by heat or during inflammation. However, we need additional studies to determine the extent to 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. Normal heat-sensitive nociceptors primarily activate the ventral lateral thalamus via lamina V neurons of the lateral spinothalamic tract (Hunt and Mantyh, 2001). The forebrain activity that occurs during both brief and relatively prolonged stimulation of this functional pathway has been extensively studied and is quite distinct from the pattern of activation seen during heat allodynia (Casey, 1999; Casey et al., 2001). Capsaicin, however, sensitizes mechano-, heat-sensitive, and heat insensitive C-nociceptors that innervate lamina 1 neurons of the spinal dorsal hom (Craig and Dostrovsky, 2001), including primate spino-mesencephalic tract cells projecting to the midbrain periaqueductal gray (Dougherty et al., 1999). It is therefore possible that capsaicin-sensitized C-nociceptors preferentially recruit spino-mesencephalic, spinoreticular or spino-parabrachial pathways to the medial and intralaminar thalamic nuclei (Craig 1995; Bernard et al., 1996; Bourgeais et al., 2001). 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; MacLean, 1957). We found a significantly greater 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 involve subcortical and cortical limbic system structures similar to those that are uniquely activated during heat allodynia (Reiman et al., 1997; Lane et al., 1997a; Lane et al., 1997b).

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. Large differences of unpleasantness occur 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 (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 et al., 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. Thus, heat allodynia, and possibly inflammatory pain, cannot be regarded as simply an enhanced normal pain response.

## Forebrain modulation of heat allodynia: a mechanistic analysis

The dorsolateral prefrontal cortex comprising Brodman areas 9 and 46 is important for continuous monitoring of the

Table 2
Multiple regression analysis of rCBF against perceived pain unpleasantness in structures active during heat allodynia [(HPTn − 2°C) on sensitized skin − (HPTn + 2°C) on normal skin]

| Region | Pain unpleasantness | | | | | |
|---|---|---|---|---|---|---|
| | normal | | | sensitized | | |
| | *r* | *t* | *P* | *r* | *t* | *p* |
| Dm midbrain | −.09 | −.74 | .46 | −.02 | −.16 | 0.87 |
| Dm thalamus | −.13 | −1.03 | .31 | −.02 | −.14 | 0.89 |
| r v striatum | .08 | .66 | .51 | .11 | .92 | 0.36 |
| l ant insula | .18 | 1.45 | .14 | .37 | 3.29 | <0.01 |
| r ant insula | .10 | .84 | .41 | .25 | 2.16 | 0.03 |
| perig ACC | −.04 | −.34 | .73 | −.01 | −.11 | 0.91 |
| r VOFC | −.04 | −.31 | .76 | −.03 | −.21 | 0.83 |
| | −.14 | −1.14 | .26 | −.07 | −.62 | 0.54 |
| | .15 | 1.23 | .22 | .22 | 1.89 | 0.06 |
| l VOFC | −.01 | −.09 | .93 | .11 | .87 | 0.39 |
| | .08 | .65 | .52 | .27 | 2.32 | 0.02 |
| | .07 | .56 | .58 | .20 | 1.7 | 0.10 |
| r DLPFC | −.13 | −1.04 | .30 | −.19 | −1.61 | 0.11 |
| *l DLPFC* | −.15 | −1.21 | .23 | *−.30* | *−2.62* | *0.01* |

Note the unique negative correlation of activity in the left DLPFC with perceived pain unpleasantness.

external world, maintenance of information in working memory and governing efficient performance control in the presence of interfering stimuli such as pain (MacDonald III et al., 2000; Bunge et al., 2001; Sakai et al., 2002). Accordingly, we used the PET data of the above study to determine whether the observed activities within specific cortical areas subserve different roles in the processing of pain. We focused on the evaluation of the inter-regional covariance structure of activity in the volumes-of-interest (VOI) activated during capsaicin-induced heat allodynia, using the methods of correlation analysis and principal component analysis (PCA) (Lorenz et al., 2003).

Fig. 2 is a surface-rendered version of the subtraction shown in C of Fig. 1. We computed correlation coefficients (*r*) between the activity of heat allodynia VOI and subjective ratings separately for scans on normal and sensitized skin. As shown in Table 2, the left DLPFC has a unique negative correlation with perceived pain unpleasantness only during heat allodynia. The right DLPFC also shows a trend for a negative correlation with perceived intensity and unpleasantness. In addition, PCA demonstrates that bilateral DLPFC activity varies independently from activity in other areas specifically engaged during heat allodynia (Lorenz et al., 2003). The functional asymmetry of the right and left DLPFC in the correlation analysis may be related to inter-hemispheric differentiation or to the fact that we restricted our analysis to medial thalamic VOI of the heat allodynia subtraction map, which eliminated the lateral thalamus.

Based on the above analysis, we tested the specific hypothesis that the left DLPFC modulates the coupling between midbrain and medial thalamus. These two brain areas represent an important pathway linking spinal input with the limbic forebrain (Nauta and Kuypers, 1958; Price, 2000). The basic assumption is that a region (here left DLPFC) modulates the magnitude of correlated neuronal activity between two regions indicating the strength of flow of neural information between them (Salinas and Sejnowski, 2001; Friston, 2002). We used a procedure described by Büchel and Friston (1997) (Büchel and Friston, 1997), dividing the scans into two sets according to a median half-split of high versus low left DLPFC activity. We then computed the correlation between midbrain and medial thalamus activities separately for scans with low and high left DLPFC activity. Fig. 3 shows the result of this analysis, which is consistent with the hypothesis that increased activity in the left DLPFC contributes to reducing the perceived unpleasantness of heat allodynia by attenuating the ascending connectivity between the midbrain and medial thalamus.

Although the results of this study are compatible with a key role of the left DLPFC in cortical mechanisms of pain modulation, this interpretation is based on correlation analysis. We cannot rule out the possibility that our experimental conditions differentially influenced the DLPFC through ascending mechanisms. An interventional approach is needed to test further the association between DLPFC activity and pain suppression.

## Implications for neuropathic pain

Our functional imaging studies show that: (1) the forebrain activity during heat allodynia is different from that during normal heat pain and, (2) during heat allodynia, specific cortical areas can attenuate specific components of the pain experience, such as affect, by reducing the functional connectivity of subcortical pathways.

In the case example given above, there is no doubt that some of the forebrain responses shown here participate in processing information ascending via the spinothalamic tract and that this information leads to an elaboration of the pain this patient experiences. However, it is at least equally relevant clinically to recognize that the forebrain is a powerful source of descending modulatory influences that directly affect the transmission and encoding of ascending nociceptive information, especially in pathological pain states. Forebrain modulation is clinically relevant in neuropathic pain because: (1) changes in the physiology of the forebrain will alter the effectiveness of descending analgesic mechanisms, and (2) therapy directed at enhancing forebrain analgesic modulation will complement and perhaps amplify therapies that directly reduce ascending input from nociceptors.

Because of the large volume of the human forebrain in relation to that of the spinal cord (77%:2% of CNS volume), these descending modulatory influences assume greater importance in humans than in other species, such as the laboratory rat where the forebrain is less anatomically dominant (31%:35% of CNS volume) (Swanson, 1995). The human spinothalamic tract, for example, contains an estimated $2–5 \times 10^3$ fibers while the corticospinal tract, which

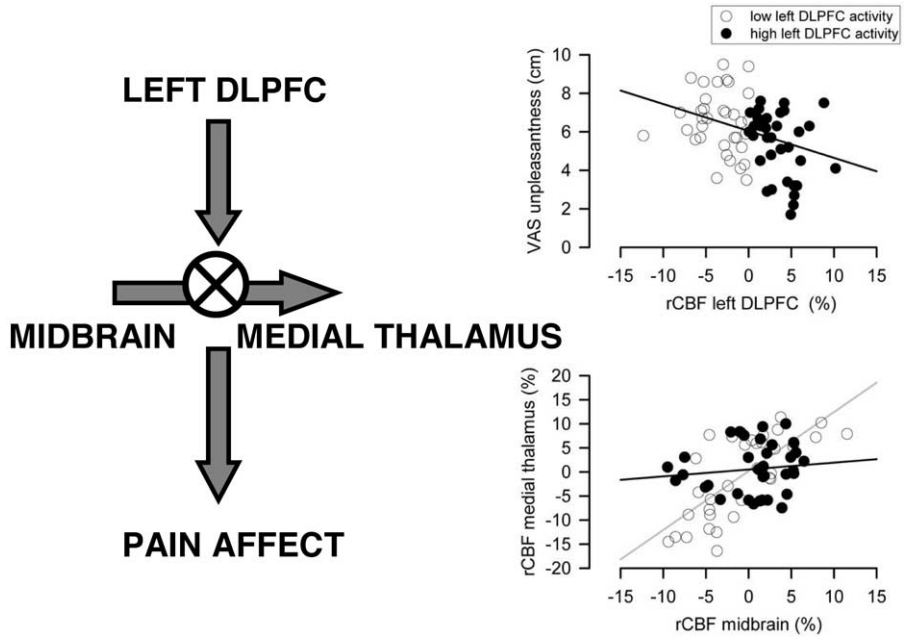



Fig. 3. The influence of left dorsolateral prefrontal cortex (DLPFC) on the correlated activity between the dorsomedial midbrain and medial thalamus during heat allodynia. Upper right graph shows the negative correlation between activity in the left DLPFC and each subject's rating (VAS) of pain unpleasantness during heat allodynia. A median split of DLPFC activity defines high (filled circles) and low (open circles) activity levels. The lower right graph shows the strong positive midbrain-thalamic correlation when DLPFC activity is low and a lack of significant correlation when DLPFC activity is high. The diagram (left) summarizes one interpretation of this relationship. Midbrain and medial thalamic activity are uniquely activated during heat allodynia, which is associated specifically with increased pain unpleasantness (compared to normal heat pain). The left DLPFC, while also activated in this condition, is negatively correlated with pain unpleasantness. Our analysis of these results is consistent with the interpretation that the left DLPFC actively reduces pain unpleasantness (affect) by reducing the activity ascending from the midbrain to medial thalamus during heat allodynia.

includes fibers terminating in the superficial layers of the dorsal horn (Cheema et al., 1984; Ralston and Ralston III, 1985), contains an estimated $500 \times 10^3$ to $1 \times 10^6$ fibers (Blinkov and Glezer, 1968; Towe, 1995). Corticothalamic influences are also likely to be dominant in the human because, in the cat, approximately 50% of the estimated 5–9000 synapses on thalamocortical projection neurons are presumed to be of cortical origin whereas only 15% are formed by ascending afferent fibers (Liu et al., 1995).

Common experience and clinical observation outside the psychophysical laboratory shows that the perception of all components of pain, including intensity, intrinsic unpleasantness, and the emotional and cognitive elaboration of the painful experience, can be greatly modified by the environment in which the noxious stimulus is applied. In the clinical setting, the placebo effect, produced by suggestions, expectancy, and the environment, has been so well documented and measured that the efficacy of treatments, especially analgesics, must be measured against a placebo control (Levine et al., 1978; Levine et al., 1979; Turner et al., 1994; Amanzio and Benedetti, 1999). In the case of experimentally induced pain, the placebo effect can result in as much as a 30% decrease in perceived pain intensity (Price et al., 1999).

Because both exogenous (pharmacological) (Casey et al., 2000; Petrovic et al., 2002) and endogenous analgesia (Zubieta et al., 2001), including the placebo effect, activate forebrain pain control mechanisms, pathologically induced forebrain changes are likely to alter the clinical response to drugs or any other form of treatment. There is now ample evidence that the forebrain undergoes major functional changes following injury to extraneural and to peripheral and central neural tissue (Kaas, 1991; Flor et al., 1995; Jones and Pons, 1998; Woods et al., 2000). In our studies, it is evident that the forebrain physiology of heat allodynia is very different from the forebrain physiology of normal heat pain. It is therefore likely that the forebrain of patients with chronic neuropathic pain undergoes similar changes. As shown here, functional imaging, including PET, fMRI, and neurophysiological techniques, should eventually enable us to identify those brain regions and regional interconnections that are critical targets for more effective and more specific treatments.

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