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Summary

Frontal lobe activity during pain is generally linked to attentional processing. We addressed the question of whether 'bottom-up' processing and 'top-down' modulation of nociceptive information dissociate anatomically within the frontal lobe by using PET scanning during painful thermal stimulation of normal and capsaicin-treated skin. We showed recently that pain following normally non-painful heat stimuli on chemically irritated skin (heat allodynia) uniquely engages extensive areas of the bilateral dorsolateral prefrontal (DLPFC), ventral/orbitofrontal (VOFC) and perigenual anterior cingulate (ACC) cortices. Here, we applied principal component analysis (PCA) and multiple regression analysis to study the covariance structure of the volumes of interest (VOI) activated specifically during heat allodynia in 14 male healthy subjects and evaluated the relationship of these VOI to ratings of pain intensity and affect. Results yielded a primary principal component (PC) that correlated positively with intensity and unpleasantness and accounted for activity in the medial thalamus, bilateral anterior insula, ventral striatum, perigenual ACC and bilateral VOFC. Activities in the right and left DLPFC loaded on separate PC and correlated negatively with perceived intensity and unpleasantness. The inter-regional correlation of midbrain and medial thalamic activity was significantly reduced during high left DLPFC activity, suggesting that its negative correlation with pain affect may result from dampening of the effective connectivity of the midbrain–medial thalamic pathway. In contrast, right DLPFC activity was associated with a weakened relationship of the anterior insula with both pain intensity and affect. We propose that the DLPFC exerts active control on pain perception by modulating corticosubcortical and corticocortical pathways.

Keywords: pain modulation; capsaicin; functional neuroimaging; prefrontal cortex; effective connectivity

Abbreviations: ACC = anterior cingulate cortex; DLPFC = dorsolateral prefrontal cortex; HPT_c = heat pain threshold on sensitized skin; HPT_n = heat pain threshold on normal skin; PCA = principal component analysis; rCBF = regional cerebral blood flow; VOFC = ventral/orbitofrontal cortex; VAS = visual analogue scale; VOI = volume of interest

Introduction

The CNS is capable of altering sensitivity to painful stimuli. Endogenous pain inhibition is believed to account for the considerable fluctuation of pain that occurs over very short periods of time. The biological significance of endogenous pain control is generally seen in the context of behavioural conflicts in which the individual needs to disengage from pain in order to fight or escape in the presence of body injury (Melzack and Casey, 1968). Analogous human life situations are sporting competition and combat, during which a subject may fail to be aware of even severe tissue damage, which becomes painful when the victim releases engagement in these activities. Whereas the spinal and medullary mechanisms of inhibitory control of nociceptive transmission have been the focus of extensive research since pioneering work by Melzack and Wall (1965), Basbaum and Fields (1978) and Le Bars *et al*. (1979), we have an incomplete understanding of how higher cortical functions contribute to endogenous pain control. Because pain is difficult to ignore and interferes with

Table 1 *Time schedule of events in the PET scanner*

Time (min)	Group A	Group B
–10	HPT_n	HPT_n
0	Rest	Rest
15	$HPT_n - 2°C$	$HPT_n + 2°C$
30	$HPT_n + 2°C$	$HPT_n - 2°C$
45	$HPT_n + 2°C$	$HPT_n - 2°C$
60	$HPT_n - 2°C$	$HPT_n + 2°C$
70–100	Capsaicin treatment	
110	Rest	Rest
115	HPT_c	HPT_c
125	$HPT_n - 2°C$	$HPT_n + 2°C$
140	$HPT_n + 2°C$	$HPT_n - 2°C$
155	$HPT_n + 2°C$	$HPT_n - 2°C$
170	$HPT_n - 2°C$	$HPT_n + 2°C$
175	HPT_c	HPT_c

Average $HPT_n = 45.5 \pm 1.6°C$ (SD); average $HPT_c = 41.1 \pm 1.9°C$.

concurrent activities (Lorenz and Bromm, 1997; Eccleston and Crombez, 1999; Casey and Lorenz, 2000), the involvement of higher cortical functions may constitute a way of resolving cognitive and behavioural conflicts by allowing competing task-relevant stimuli to dominate over pain.

A likely candidate brain area to coordinate pain modulation with goal-directed behaviour is the frontal lobe. Evidence suggests that the dorsolateral prefrontal cortex, comprising Brodmann areas 9 and 46, is important for continuous monitoring of the external world, maintenance of information in short-term memory and governing efficient performance control in the presence of interfering stimuli (MacDonald *et al.*, 2000; Bunge *et al.*, 2001; Sakai *et al.*, 2002). Furthermore, electrical stimulation of fibre connections of the prefrontal cortex to the midbrain mediates antinociceptive effects in rodents (Cooper, 1975; Hardy and Haigler, 1985; Zhang *et al.*, 1998). However, the frontal lobe may not have a unitary role in pain processing, as orbitofrontal and medial frontal lesions diminish pain-related behaviours in animals (Reshetniak and Kukushkin, 1989; Pastoriza *et al.*, 1996).

Non-invasive neuroimaging studies using PET and functional MRI allow us to examine the involvement of the frontal lobe in human pain perception. Various groups describe prefrontal cortex activity following experimental (Casey *et al.*, 1996; Iadorola *et al.*, 1998; Paulson *et al.*, 1998; Baron *et al.*, 1999; Tölle *et al.*, 1999) or clinical (Hsieh *et al.*, 1996; Rosen *et al.*, 1996; Silverman *et al.*, 1997) pain conditions. Frontal lobe activity during pain is generally related to cognitive and attentional processing of painful stimuli (Coghill *et al.*, 1999; Casey, 1999; Peyron *et al.*, 1999; Bornhövd *et al.*, 2002). There is evidence that medial prefrontal areas and the perigenual anterior cingulate cortex (ACC) are activated by expectancy of pain (Ploghaus *et al.*, 1999; Sawamoto *et al.*, 2000), the interaction of pain with anxiety (Ploghaus *et al.*, 2001), placebo cognitions (Petrovic *et al.*, 2002) and cognitively demanding tasks (Petrovic *et al.*, 2000; Bantick *et al.*, 2002).

We recently found substantial prefrontal cortex activation involving bilateral activity of the orbitofrontal, perigenual cingulate and dorsolateral prefrontal cortices using PET during heat stimuli on capsaicin-treated skin (Lorenz *et al.*, 2002). In this study, we compared equally intense pains by adapting the intensity of a thermal contact probe applied to normal skin and the same skin being sensitized by topical capsaicin. Despite equality of perceived intensity, image subtraction revealed a unique activity of a midbrain–medial thalamic pathway to the frontal lobe during pain following normally warm stimuli applied to the sensitized skin (heat allodynia). We generally interpreted the robust frontal activity during heat allodynia as reflecting unique cognitive and emotional responses to nociceptive input from pathological tissue. In the present work we used the PET data from our previous study to determine whether the observed activities within the dorsolateral prefrontal, orbitofrontal and perigenual ACC areas subserve different roles in the processing of pain. We focused on the evaluation of the interregional covariance structure of activity in the volumes of interest (VOI) activated during capsaicin-induced heat allodynia, using the method of principal component analysis (PCA). Furthermore, we used regression analysis to specifically test the hypothesis that the dorsolateral prefrontal cortex (DLPFC) modulates the effective connectivity along the midbrain–thalamic afferent pathway.

Methods

Fourteen right-handed male subjects (mean age 23.9 ± 4.6 years $\pm$ SD) participated in the study. 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 psychophysical model of heat allodynia that resulted in a unique recruitment of frontal lobe activity during $H_2^{15}O$ PET scans is described in detail in our previous paper (Lorenz *et al.*, 2002). Here we limit the description to those aspects of the stimulation and PET protocol that are important for the hypothesis of the present paper.

The capsaicin–heat stimulus and psychophysics

We delivered heat stimuli to the left volar forearm with a digitally controlled feedback contact thermode (Cygnus, Paterson, NJ, USA) that had a gold-plated copper surface contact area of $254\ mm^2$ heated by direct current. The order of scans and sequence of tests and procedures inside the scanner are given in Table 1. We applied one rest condition without stimulation (no probe contact) and two repetitions of two temperature–time profiles to the skin of the left forearm. We performed the first five scans before and the last five scans after the skin was treated for 30 min with 1% topical capsaicin (5×5 cm filter paper saturated with 8-methyl-*N*-vanillyl-6-nonenamid; Sigma, St Louis, MO, USA, diluted in 70% ethyl alcohol). We determined the individual heat pain threshold after positioning the subject inside the scanner. The heat

probe was held on the subject's left forearm. The stimulus started at 30°C and increased at a rate of 0.9°C/s until the subject released a button press to indicate the beginning of pain. The temperature at this instant was noted and the average of five runs was taken as the normal heat pain threshold (HPT_n). We measured the heat pain threshold on sensitized skin (HPT_c) in the same manner after the resting scan following topical capsaicin treatment and after the last scan.

During stimulus scans, the probe was located on the skin at the time of radiotracer injection and kept immobile throughout the 60 s of scanning to avoid mechanical stimulation. The thermal stimulus started at the beginning of PET data acquisition, ~10 s after injection (see below), again using a rise time of 0.9°C/s. The plateau was either 2°C below or 2°C above HPT_n. The location of the stimulated skin was moved between scans in an anticlockwise direction within the area of 5×5 cm. The mild pain and warmth of capsaicin alone declined over the 20–30 min after removal of the patch. Thus, whereas some lingering effect of capsaicin itself was present during the resting scan after treatment, all subsequent scans with thermal stimulation occurred when this sensation had nearly or completely subsided. As determined by continuous ratings in pilot tests outside the scanner (for details see Lorenz *et al.*, 2002), the low-intensity stimulus was felt as warm on normal skin, whereas treatment with capsaicin rendered it as painful as the high-intensity stimulus on the untreated skin. Perceived intensity (0 = no sensation, 10 = maximally painful) and unpleasantness (0 = not unpleasant, 10 = maximally unpleasant) was reported at the end of the stimulus after each scan using an electronic visual analogue scale (VAS) device. The device consisted of a horizontal array of 20 red lights that were displayed to the subject by manipulating a potentiometer with a slider. The experimenter read the value (voltage) on a digital display at the side of the device, not visible to the subject. A marker on this device indicated the pain threshold that served as an anchor for the intensity rating. After becoming familiar with a range of stimulus intensities, subjects located the marker at a certain light to indicate the border between the pre-pain and the pain range. The VAS at normal heat pain threshold was therefore not identical for all subjects and averaged at a value of 4.6 ± 0.85 (SD).

To measure qualitative aspects of the stimulus, we used the short form of the McGill pain questionnaire (Melzack, 1987) after each stimulation scan. This form contains 15 pain descriptors. The subjects answered 'none', 'mild', 'moderate' or 'severe' to indicate how appropriately the words described the perception. We transformed the ranking into numerical values (0–3) and computed sum scores separately for sensory (e.g. hot–burning) and affective (e.g. punishing–cruel) descriptor words.

PET

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 estimating the arrival of radioactivity in the brain and continued for ~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 map) with adjustment for multiple comparisons based on the number of voxels and the smoothness of a random Gaussian model following three-dimensional filtering to increase the signal-to-noise ratio and compensate for anatomical variance (Friston *et al.*, 1991). Spatial resolution was 9 mm according to the full width at half maximum of the Gaussian function. We identified voxels with a significantly increased rCBF compared with the average noise variance computed across all voxels (pooled variance). The critical level of significance was determined by adjusting the type I error ($Z = 4.0$, $P < 0.05$) using this information, which corresponds to an uncorrected P value of 0.0001 (Worsley *et al.*, 1992).

Correlations between psychophysics and blood flow responses

Using a method described previously (Casey *et al.*, 1996), we developed VOI from the subtraction image that compared the low-intensity stimulus on capsaicin-treated skin (heat allodynia) against the high-intensity stimulus on normal skin (heat pain). We started at the voxels showing significant peak increases of rCBF in this comparison ($Z > 3.5$) and progressively expanded the volume in three dimensions to include only those contiguous voxels with rCBF increases that were significantly greater than the global mean change ($P < 0.05$, uncorrected for multiple comparisons). We computed correlation coefficients (r) between VOI activity and subjective ratings separately for scans on normal and sensitized skin. As a first step, we removed inter-individual variance by entering subjects as regressors and correlated the standardized residual variance with intensity ratings. Next, we used the residual variance of this computation to calculate the correlation with unpleasantness ratings. This procedure eliminated variance unique to each individual but constant over experimental conditions, and accounted for the strong relationship between perceived intensity and unpleasantness.

PCA of VOI activities

In another step, VOI activities removed from inter-individual variance were subjected to a varimax-rotated PCA, again
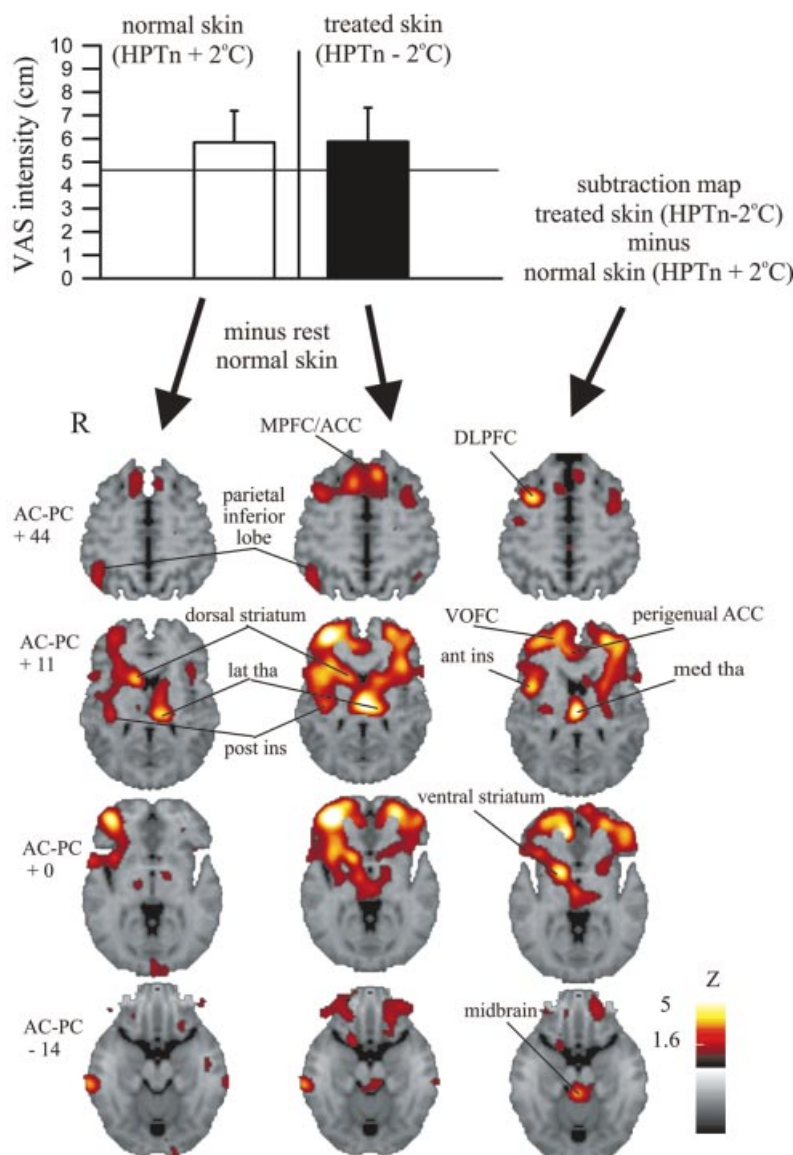
Fig. 1 Regional brain activity during equally intense pain across normal and capsaicin-treated skin conditions. Stimulation of normal skin at high intensity yielded the same pain intensity as low-intensity stimulation on capsaicin-treated skin (top). However, the $H_2^{15}O$ PET images during heat pain (lower part of figure, left column) and equally intense heat allodynia (middle column) were different when compared against the normal rest condition. Similar magnitudes of activity in the dorsal striatum, lateral thalamus (lat tha) and posterior insula (post ins) are removed in the subtraction image of heat allodynia minus heat pain (right column), contrasting activity in the ventral striatum, medial thalamus (med tha), anterior insula (ant ins), midbrain, DLPFC, medial prefrontal cortex, VOFC and perigenual ACC during heat allodynia.

separately for scans during normal and sensitized skin conditions. PCA generally describes the observed data (here VOI activities) as the weighted sum of statistically uncorrelated components and computes principal component (PC) scores that quantify how each extracted component represents a given measurement. The PC scores then allow further statistical analysis (here a correlation with the intensity and unpleasantness ratings). Each component comprises those measurements that are similar to each other, i.e. yield a high covariance. The number of orthogonal components is limited according to a significance threshold determined by the scree

test (Cattel, 1966), which ranks the eigenvalues of the components' eigenvectors derived from the variance–covariance matrix. Components with eigenvalues >1 were regarded as significant in this study. A factor-loading plot displays how a given variable is represented in each component. During varimax rotation, the axes of the extracted components are rotated until the sum of the squared factor loadings reaches a maximum. This procedure usually characterizes a simpler, more easily interpreted structure of the extracted components with only high or low loading values across the variables that are entered. To reasonably minimize the number of variables,
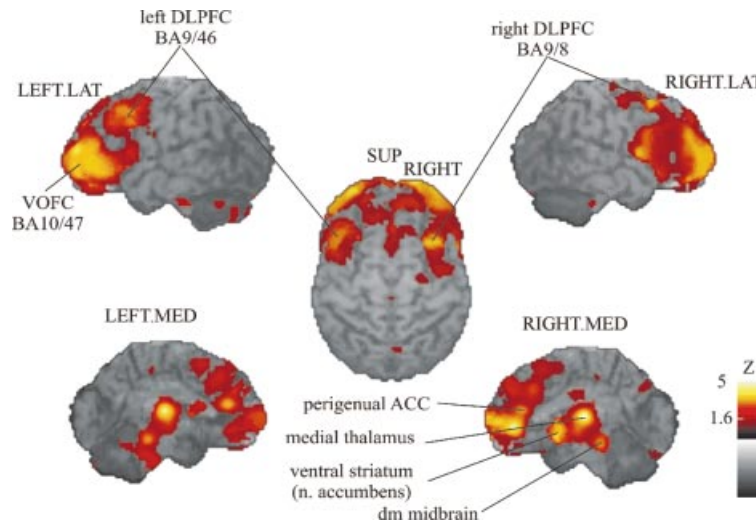
Fig. 2 Surface-rendered images of heat allodynia minus equally intense normal heat pain. Note the extensive recruitment of frontal lobe activity in VOFC and DLPFC regions and the marked activity of the ventral striatum of the basal ganglia involving the nucleus accumbens. LAT = lateral; MED = medial; SUP = superior; dm = dorsomedial.

we averaged the values from ventrolateral, ventromedial and orbitofrontal VOIs of one hemisphere together, subsequently referred to as ventral-orbitofrontal cortex (VOFC). The resulting variance–covariance matrix included 10 VOI for a total number of 70 scans which corresponds to five trials (one resting and two repetitions of low and high stimulus temperature) in 14 subjects during normal or sensitized skin condition.

Finally, we tested the specific hypothesis of whether the DLPFC modulates the coupling between the midbrain and the medial thalamus. We selected these two brain areas because they represent an important pathway linking spinal input with the limbic forebrain (Nauta and Kuypers, 1958; Melzack and Casey, 1968; Price, 2000). The basic assumption was that a region (here DLPFC) modulates the magnitude of correlated neuronal activity between two regions, indicating the strength of flow of neural information between them (Friston *et al.*, 1995; Salinas and Sejnowski, 2001). Using a procedure described by Büchel and Friston (1997), we divided the 70 scans into two sets according to a median half-split of high versus low DLPFC activity, and computed the correlation between midbrain and medial thalamus activities separately for scans with low and high DLPFC activity. We quantified the statistical significance of the influence of DLPFC activity on the correlation of activities between these two regions by computing F statistics and P values for the interaction term (midbrain × DLPFC) in the presence of the two main effects (midbrain + DLPFC) according to the following linear regression model:

Thalamus = $b1$midbrain + $b2$DLPFC + $b3$midbrain × DLPFC

Although we could not determine the direction of the modulating action implied by the interaction term, we base our interpretation on a top-down model of DLPFC function

upon the afferent signal transfer favoured by neurophysiological background information (see Discussion). Regression analysis and PCA were performed using the SPSS 10.0 statistical package (SPSS, Chicago, IL, USA).

Results

Psychophysics and Z score maps of rCBF

The mean VAS of the intensity rating confirms the results of pilot trials that the low-intensity stimulus on capsaicin-treated skin induced a subjective intensity similar to that induced by the high-intensity stimulus on normal skin ($t = 0.13$, $P = 0.90$; Fig. 1, top). Although the VAS unpleasantness rating of these conditions also failed to be statistically different ($t = 1.13$, $P = 0.28$), unpleasantness was generally increased more by capsaicin treatment than intensity, as revealed by a significant skin condition × VAS dimension interaction ($F = 12.61$, $P < 0.01$) in a repeated measures ANOVA (analysis of variance). Furthermore, there was a significantly higher affective score on the McGill questionnaire during low-intensity stimulation of the capsaicin-treated skin compared with high-intensity stimulation of normal skin ($t = 2.1$, $P = 0.05$), whereas the sensory score did not differ ($t = 1.4$, $P = 0.17$).

The PET images in Fig. 1 show in left and middle columns the Z-score maps obtained by subtracting the scans during the normal rest condition from scans during stimulation with the high-intensity stimulus ($HPT_n + 2°C$) on normal skin (i.e. heat pain) and from scans during the low-intensity stimulus ($HPT_n - 2°C$) on capsaicin-treated skin (i.e. heat allodynia). The right-hand column of the lower part of Fig. 1 shows the Z-score map comparing these stimuli against each other. The four rows refer to the different horizontal slice levels relative to the plane of

Table 2 *Multiple regression analysis of rCBF in VOI resulting from image subtraction of scans during low-intensity stimulation on sensitized skin (heat allodynia) minus high-intensity stimulation on normal skin (heat pain)*

| Region | Stereotactic coordinates: x, y, z (mm))* | Pain intensity | | | | | | Pain unpleasantness | | | | | |
| | | Normal | | | Sensitized skin | | | Normal | | | Sensitized skin | | |
		r	t	P	r	t	P	r	t	P	r	t	P
Dm midbrain	1, –33, –14	0.01	0.11	0.91	**0.35**	**3.05**	**<0.01**	–0.09	–0.74	0.46	–0.02	–0.16	0.87
Dm thalamus	1, –17, 11	0.08	0.62	0.54	0.20	1.72	0.09	–0.13	–1.03	0.31	–0.02	–0.14	0.89
R v striatum	17, 5, –2	–0.01	–0.07	0.94	0.08	0.67	0.50	0.08	0.66	0.51	0.11	0.92	0.36
L ant insula	–24, 10, 7	–0.03	–0.22	0.83	0.17	1.38	0.17	0.18	1.45	0.14	**0.37**	**3.29**	**<0.01**
R ant insula	42, 5, 11	0.00	0.00	1.0	0.02	0.19	0.85	0.10	0.84	0.41	**0.25**	**2.16**	**0.03**
Perig ACC	–1, 37, 16	–0.04	–0.36	0.72	0.08	0.65	0.52	–0.04	–0.34	0.73	–0.01	–0.11	0.91
R VOFC	12, 44, 2	0.01	0.09	0.93	0.22	1.86	0.07	0.00	0.00	1.0	0.15	1.23	0.22
	17, 57, 4	0.03	0.25	0.80	**0.29**	**2.50**	**0.02**	–0.13	–1.10	0.28	0.19	1.55	0.13
	33, 55, 4	**0.23**	**1.96**	**0.05**	**0.23**	**1.96**	**0.05**	0.05	0.41	0.68	0.12	0.97	0.33
	28, 53, –2	–0.04	–0.32	0.75	0.17	1.39	0.17	–0.04	–0.31	0.76	–0.03	–0.21	0.83
	35, 46, 18	0.03	0.24	0.81	–0.06	–0.51	0.62	–0.14	–1.14	0.26	–0.07	–0.62	0.54
	28, 46, –4	–0.09	–0.76	0.45	**0.24**	**2.04**	**0.05**	0.15	1.23	0.22	0.22	1.89	0.06
L VOFC	–28, 50, 7	0.07	0.55	0.58	**0.33**	**2.90**	**<0.01**	–0.01	–0.09	0.93	0.11	0.87	0.39
	–42, 44, 4	0.12	1.00	0.32	**0.26**	**2.21**	**0.03**	0.08	0.65	0.52	**0.27**	**2.32**	**0.02**
	–21, 46, –7	–0.04	–0.29	0.77	**0.35**	**3.04**	**<0.01**	0.07	0.56	0.58	0.20	1.7	0.10
R DLPFC	33, 14, 45	–0.13	–1.05	0.30	–0.22	–1.84	0.07	–0.13	–1.04	0.30	–0.19	–1.61	0.11
L DLPFC	–37, 17, 36	–0.01	–0.09	0.93	–0.13	–1.07	0.29	–0.15	–1.21	0.23	–0.30	–2.62	0.01

Significant correlations are shown in bold. *– = left, posterior and inferior relative to the anterior commissure for *x*, *y* and *z*, respectively. Dm = dorsomedial; v = ventral; Perig = perigenual; ant = anterior; R = right; L = left.
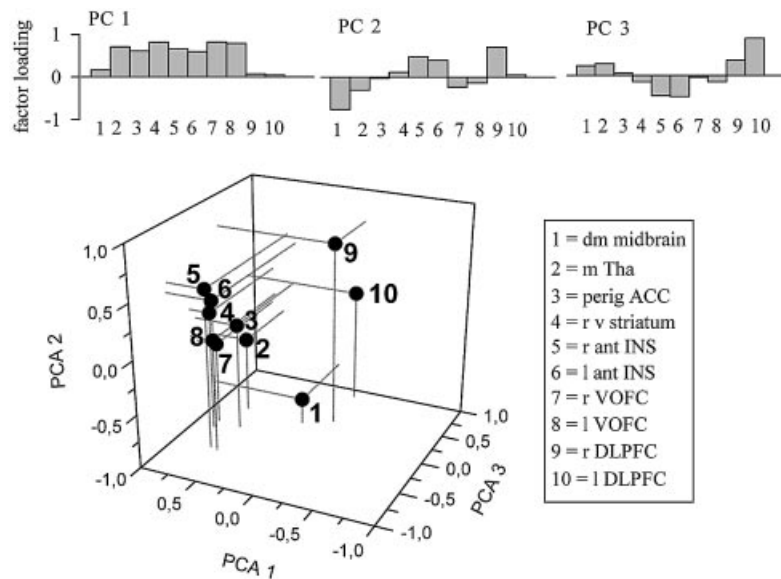
Fig. 3 Factor-loading plots derived from a varimax-rotated PCA of activity during sensitized skin condition in 10 VOI specifically activated by heat allodynia. Note that the DLPFC activity of both hemispheres loads on selective principal component (PC) distinct from PCA 1, accounting for activity in brain regions 2–8. m Tha = medial thalamus; perig ACC = perigenual ACC; r v = right ventral; r ant INS = right anterior insula; l ant INS = left anterior insula; r = right; l = left.

Table 3 *Results of PCA*

Five-factor solution of VOI[1] activity during normal skin condition

Principal component	Eigenvalue	Variance (%)	Cumulative (%)	Regression: intensity		Regression: unpleasantness	
				r	P	r	P
1	3.02	30.21	30.21	–0.01	n.s.[2]	0.06	n.s.
2	1.89	18.86	49.06	–0.05	n.s.	0.06	n.s.
3	1.37	13.67	62.73	–0.01	n.s.	–0.10	n.s.
4	1.12	11.18	73.92	0.01	n.s.	0.14	n.s.
5	1.10	10.89	84.81	–0.06	n.s.	–0.18	n.s.
Three-factor solution of VOI activity during capsaicin-treated skin condition							
1	3.63	36.28	36.28	**0.24**	**0.03**	**0.30**	**<0.01**
2	1.64	16.38	52.66	**–0.33**	**<0.01**	**–0.26**	**<0.01**
3	1.53	15.28	67.95	–0.12	n.s.	**–0.48**	**<0.001**

[1]VOI derived from the image subtraction of scans during low intensity on capsaicin-treated skin (heat allodynia) minus high intensity on normal skin (heat pain); [2]not significant.

the anterior and posterior commissure (AC–PC level, third row). Despite the equality of perceived intensity, heat allodynia yielded significantly enhanced activity in the medial thalamus, bilateral anterior insula, right ventral striatum, perigenual ACC)/medial prefrontal cortex, bilateral DLPFC and VOFC and the dorsomedial midbrain. Activations that are present at similar magnitudes during both conditions are removed by the subtraction; this includes responses in the ipsilateral ventrolateral thalamus, SII/posterior insula, dorsal portions of the right striatum and the right parietal inferior lobule (Brodmann area 40). The surface-rendered lateral and superior views and paramedian sagittal slices in Fig. 2 demonstrate the

extensive recruitment of the VOFC and DLPFC of both hemispheres by heat allodynia compared with equally intense normal heat pain. It also illustrates the marked activity in the ventral striatum of the basal ganglia involving the nucleus accumbens of the right hemisphere. Significant deactivation of rCBF in this comparison appeared in the bilateral lingual and fusiform gyri of the occipital lobe and the posterior cingulate cortex (not shown). These deactivations were due to the high blood flow in these brain areas during the normal rest condition being significantly more reduced during heat allodynia compared with normal heat pain. Similar deactivation of the visual system has been observed in numerous PET
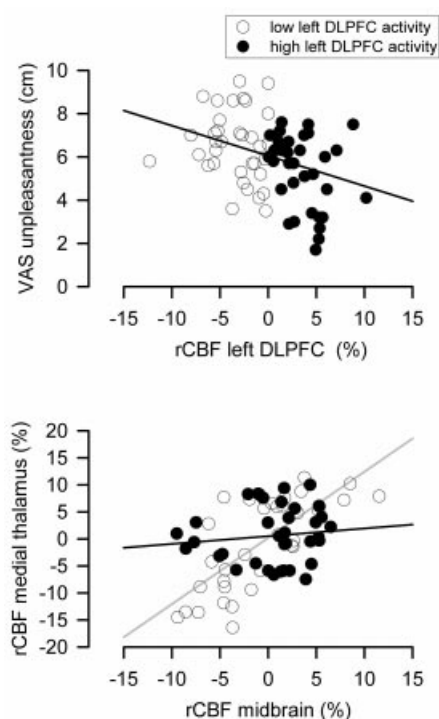
Fig. 4 Regression of unpleasantness ratings on VOI activity in the left DLPFC (top). Note the inverse association of pain affect with activity in the left DLPFC ($r = -0.30$, $P < 0.01$) during trials ($n = 70$) on sensitized skin. Median half-split of data yielded significantly greater unpleasantness during low (open circles) than high (filled circles) DLPFC activity. Dependency of correlation of activity between midbrain and medial thalamus on left DLPFC activity (bottom). There was a significantly lower correlation of activity in the midbrain with that in the medial thalamus during high (filled circles; black regression line) compared with low (open circles; grey regression line) left DLPFC activity.

studies during a variety of stimulus and task conditions and is interpreted as a non-specific shift from a default mode of brain activity (awake resting) to mental engagement (Raichle *et al.*, 2001).

The anatomical coordinates of the 17 VOI that exceeded a Z score of 3.5 in the comparison of heat allodynia with equally intense normal heat pain, and their correlation with perceived pain and unpleasantness, are given in Table 2. Activation of only one region, in the right VOFC ($x = 33$, $y = 55$, $z = 4$), correlated significantly with perceived intensity when the normal skin was stimulated. However, on stimulation of sensitized skin there was a positive correlation with perceived intensity in seven regions and with unpleasantness in three regions. The rCBF in the dorsomedial midbrain, various regions of the right and left VOFC and marginally in the medial thalamus correlated with perceived intensity only. The left and right anterior insula showed a selective correlation with unpleasantness. One region in the left VOFC ($x = -42$, $y = 44$, $z = 4$) showed a positive correlation with both perceived intensity and unpleasantness. Although the perigenual ACC was activated during heat allodynia, there was no correlation with either perceived intensity or

unpleasantness ratings. Notably, the left DLPFC showed a significant negative correlation with unpleasantness and an insignificant negative correlation with perceived intensity. The right DLPFC also yielded a marginally significant negative correlation with perceived intensity ($P = 0.07$) during scans on sensitized skin.

PCA

We performed the varimax-rotated PCA on the data for 10 VOI derived from the subtraction map of scans with low intensity on sensitized skin (heat allodynia) minus high intensity on normal skin (heat pain) separately for scans during normal and sensitized skin conditions. The reduction to 10 from the original 17 VOI is due to averaging of the various subregions within the VOFC (see Methods). PCA extracted five components from the scans during the normal skin condition and three components from the scans during the sensitized skin condition. Table 3 lists the eigenvalues, the percentages of variance explained and the correlation coefficients of the factor scores with perceived intensity and unpleasantness. The amount of cumulatively explained variance from these components was 84 and 68% for normal and sensitized skin conditions, respectively. Notably, only for scans during the sensitized skin condition did the PC scores yield a relationship with subjective ratings, PC 1 being positively and PC 2 negatively correlated with both intensity and unpleasantness ratings. PC 3 had a unique negative correlation with unpleasantness.

The factor-loading plot of the 10 VOI over the three PC dimensions derived from the data during the sensitized skin condition is presented in Fig. 3. It displays a cluster of areas that load positively on PC 1 and involve the medial thalamus, right ventral striatum, bilateral anterior insular cortices, perigenual ACC and bilateral VOFC. PC 2 and PC 3 accounted primarily for activity in the right and left DLPFC, respectively. The midbrain loaded negatively on PC 2 and weakly positively on PC 1 and PC 3. Factor analysis therefore demonstrated that bilateral DLPFC activity varied independently of activity in other areas specifically engaged during heat allodynia. Moreover, regression on the psychophysical data suggested an inverse relationship of DLPFC with the magnitude of perceived pain. Right and left DLPFC had different factor loadings and showed relative differences regarding correlations with intensity and unpleasantness ratings.

Modulation of effective midbrain–thalamus connectivity by the DLPFC

To test the hypothesis that the DLPFC exerts a top-down modulation of the effective connectivity along the midbrain–thalamic pathway, we divided the 70 scans during the capsaicin trials into those with low and high activity in left- and right-hemisphere DLPFC by a median-half-split of the
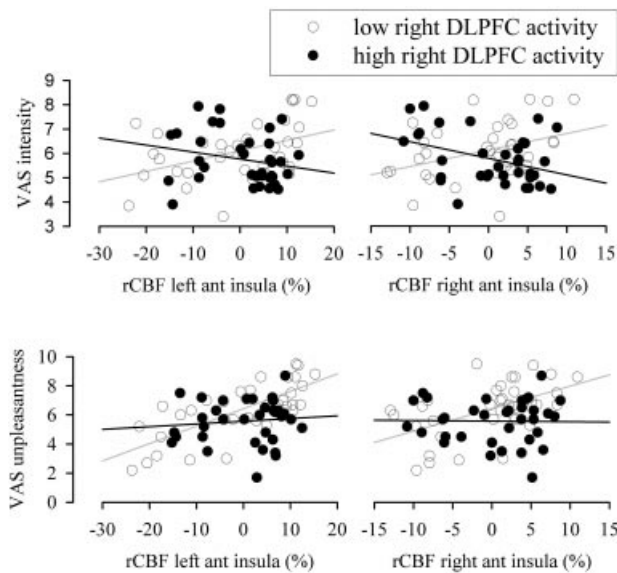
Fig. 5 Correlation of activity in left and right anterior insula with VAS ratings of intensity (top) and unpleasantness (bottom) during low (open circles) and high (filled circles) right DLPFC activity.

VOI data. Figure 4 (top) illustrates the inverse relationship of the unpleasantness rating with activity in the left DLPFC. The VAS for unpleasantness was significantly higher during low compared with high DLPFC activity ($t = 4.25$, $P < 0.001$). The bottom diagram shows that the correlation of midbrain and medial thalamus activity was also significantly higher between scans during low left DLPFC activity ($r = 0.72$, $P < 0.001$) compared with scans during high left DLPFC activity ($r = 0.12$, $P = 0.49$). The F value of the interaction between left DLPFC and midbrain on medial thalamus activity was highly significant ($F = 19.3$, $P < 0.0001$). A similar but weaker modulatory effect of the left DLPFC was observed for the correlation between midbrain and perigenual ACC activities ($F = 5.9$, $P = 0.02$). Notably, the relationship of the perigenual ACC activity with unpleasantness was also dependent on left DLPFC activity. Whereas the correlation was positive during low left DLPFC activity, it was negative during high left DLPFC activity, rendering the F value of the interaction (DLPFC × perigenual ACC) on VAS for unpleasantness significant ($F = 4.9$, $P = 0.03$). This effect may explain why we failed to observe a correlation of perigenual ACC with unpleasantness independent of left DLPFC activity.

Although the right DLPFC failed to significantly alter the correlation between midbrain and thalamus activities, the relationship of activities in the anterior insulae of both hemispheres with pain intensity and unpleasantness appeared strikingly dependent on the magnitude of right DLPFC activity (Fig. 5). Positive correlations were observed during low right DLPFC activity but not during high right DLPFC activity. The F statistic for the interaction between right DLPFC and right anterior insula on both VAS for intensity

($F = 9.7$, $P < 0.01$) and VAS for unpleasantness ($F = 10.8$; $P < 0.01$) was significant. Similarly, there was a significant interaction between right DLPFC and left anterior insula on VAS for intensity ($F = 5.9$, $P < 0.05$) and VAS for unpleasantness ($F = 13.3$, $P = 0.001$).

Discussion

This study shows that the presence of nociceptor sensitization following topical treatment with capsaicin strongly enhances the engagement of the frontal lobe during painful heat stimulation. In our companion paper (Lorenz *et al.*, 2002) we addressed in detail the issue that pain in response to a normally warm stimulus after capsaicin treatment (heat allodynia) is not simply a leftward shift of the stimulus–response function of thermal nociception. Instead, when compared with equally intense normal heat pain, heat allodynia involves relatively greater recruitment of the medial thalamic pathways, which convey greater affective reactions and probably other contextually important qualitative information related to the perceived tissue pathology. By using further statistical methods (PCA, regression analysis), the present study demonstrates a dissociation of subregions within the frontal lobe regarding pain and pain modulation. A network of 17 distinct anatomical areas specifically activated during heat allodynia showed the bilateral DLPFCs to be exclusively negatively correlated with perceived intensity and/or unpleasantness. The right and left DLPFC accounted for unique PCA factors of the variance–covariance matrix across the repeated scans after capsaicin treatment, distinct from a PCA factor that comprised areas such as the medial thalamus, perigenual ACC, right ventral striatum, bilateral insulae and VOFC, and that correlated positively with pain intensity and unpleasantness. The region-by-region correlation of activities between midbrain and medial thalamus, as well as between midbrain and perigenual ACC, was significantly higher during scans with low compared with high activity in the left DLPFC. High correlation is thought to indicate strengthened flow of neural information, i.e. high effective connectivity (Salinas and Sejnowski, 2001). The approach of using regression analysis to detect changes in effective connectivity has been described for PET and functional MRI of the visual system (Friston *et al.*, 1995; Büchel and Friston, 1997). Although the direction of the modulating action cannot be determined this way, our result may indicate a top-down mode of inhibition of neuronal coupling along the ascending midbrain–thalamic-cingulate pathway through descending fibres from the prefrontal cortex. This hypothesis is consistent with invasive studies in animals. Hardy and Haigler (1985) demonstrated that electrical stimulation of the prefrontal cortex in rats depressed the midbrain response to noxious stimuli (foot pinch). In cats, electrical stimulation of the periaqueductal grey matter or the frontal (pericruciate) cortex suppresses the medial thalamic response to noxious stimuli (Andersen, 1986). The existence of a pain modulation pathway involving the rodent midbrain,

medial thalamus and prefrontal cortex is also suggested by the studies of Condes-Lara *et al*. (1989).

Our finding that strengthened coupling between the midbrain and medial thalamus is associated with increased unpleasantness ratings during low left DLPFC activity is consistent with the role of these areas in mediating affective reactions to pain (Nauta and Kuypers, 1958; Melzack and Casey, 1968; Price, 2000). Left DLPFC activity was additionally associated with a reduction in the correlation of the perigenual ACC with perceived unpleasantness. The perigenual ACC receives major input from the medial thalamus and is densely connected with the nucleus accumbens of the ventral striatum (Kunishio and Haber, 1994), which was also prominently active when the capsaicin-treated skin was stimulated. These two brain areas appear to represent nodes of an overlap between pain and reward circuitries (Becerra *et al*., 2001). Interestingly, the nucleus accumbens exerts antinociceptive effects following noxious capsaicin and thermal stimuli (Gear *et al*., 1999). In contrast, the right DLPFC primarily reduces the correlation of the bilateral anterior insulae with both perceived intensity and unpleasantness. The insula participates in the intensity decoding of thermal stimuli (Coghill *et al*., 1999; Craig *et al*., 2000) and receives sensory input from lateral thalamic nuclei (Craig and Dostrovsky, 1999). The failure to observe a reduction in the effective midbrain–thalamus connectivity during high right DLPFC activity may be due to the fact that we restricted our analysis to the medial thalamic VOI developed from the subtraction map of heat allodynia minus equally intense normal heat pain, which markedly reduced activity in the lateral thalamus (Fig. 1). It remains unclear whether the described differences between left and right DLPFC in the PCA and regression analysis may be related to an interhemispheric differentiation of prefrontal pain modulation mechanisms.

Because the primary goal of this study was to demonstrate that heat allodynia recruits a supraspinal network different from that recruited by equally intense normal pain, our instructions given to the subjects were not intended to manipulate pain perception. It is conceivable that the subjects, nonetheless, engaged greater cognitive control over pain during stimulation of their capsaicin-treated skin, which they perceived to be irritated and more sensitive. Hypnosis selectively alters affective reactions to pain in correlation with changes in orbitofrontal and midcingulate areas (Rainville *et al*., 1997). Likewise, a mentally demanding task diminishes the perception of pain, consistent with reduced activity in the thalamus, insula and midcingulate and with increased activity in the perigenual cingulate and frontal cortex (Bantick *et al*., 2002). Activity in these latter brain areas is also enhanced and more strongly correlated with midbrain activity during placebo analgesia (Petrovic *et al*., 2002). We observed a stronger correlation of midbrain and perigenual ACC activity during scans with low left DLPFC activity, during which the degree of coupling between perigenual ACC and unpleasantness was significantly higher

than during scans with high left DLPFC activity. It is possible that a functional dissociation within the midbrain can account for both facilitating and inhibitory influences on pain and affect (Hirakawa *et al*., 2000).

Activity in the VOFC differed from that in the DLPFC by being positively correlated with pain in our study. This observation is consistent with reports of activity in these areas during expectation of pain (Ploghaus *et al*., 1999; Sawamoto *et al*., 2000) or its exacerbation by anxiety (Ploghaus *et al*., 2001). Furthermore, animals with orbitofrontal (Reshetniak and Kukushkin, 1989) and medial frontal (Pastoriza *et al*., 1996) lesions show diminished pain behaviours. Functional dissociation of the ventromedial/orbital and lateral PFC has also been described in studies of abnormal brain chemistry in chronic pain patients (Grachev *et al*., 2000, 2002), differential representations of negative versus positive emotions (Northoff *et al*., 2000), and shifts of affective versus cognitive–attentional response settings (Dias *et al*., 1996). Notably, target areas of descending projections from the frontal lobe to the midbrain dissociate anatomically in the rat with respect to medial versus lateral origins in the PFC (Hardy, 1986). A role of the DLPFC in the control of pain is, furthermore, consistent with studies that demonstrate this region to be associated with efficient performance in the presence of conflicting stimuli (MacDonald *et al*., 2000; Bunge *et al*., 2001). Working memory tasks that require a high degree of executive control are typically associated with DLPFC activity (Smith and Jonides, 1999; Funahashi, 2001). The DLPFC may protect the maintenance of momentary behavioural goals by rendering working memory operations resistant to distractive stimuli (Sakai *et al*., 2002). Lorenz and Bromm (1997) found that the ability to maintain performance accuracy in a short-term memory task during experimental painful muscle ischaemia correlates positively with frontal lobe activity measured by event-related brain potentials elicited by the memory stimuli. The interaction of the prefrontal cortex with midbrain, thalamic, striatal and cingulate structures of the limbic system may thus reflect the active manipulation of the behavioural dominance of pain dependent upon motivational and emotional context. The presence of abnormal tissue status, such as inflammation, might engage prefrontal mechanisms of pain modulation robustly because it requires behavioural flexibility and the ability to suppress prepotent response tendencies to guarantee optimal adaptation. Notably, descending inhibition is more efficiently recruited during acute compared with chronic states of inflammation of the rodent joint even when the nociceptive test stimulus induces similar intensities of pain reactions in either condition (Danziger *et al*., 1999). It is therefore conceivable that cognitive mechanisms of pain control, governed by the prefrontal cortex, synergistically interact with autonomous mechanisms of descending inhibition, governed by subcortical structures, during acute stages of injury and inflammation. In contrast, acute pain from normal tissue requires less flexible, more habitual reactions to the threat of impending tissue damage. Activity originating in

the faster-conducting Aδ-nociceptors and projection within the lateral thalamic pathway to association areas of the sensory and motor cortices and the recruitment of dorsal basal ganglia and cerebellum appear appropriate to achieve this function and can explain why these brain areas are predominantly activated by acute heat pain on normal skin (Casey *et al*., 2001).

Although the results of this study are compatible with a key role of the 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 this brain region through ascending mechanisms. An interventional approach is needed to further test the association between DLPFC activity and pain suppression. Future studies could examine the effects of interactions between different pain intensities and different degrees of working memory load or use transcranial magnetic stimulation to reversibly and selectively interfere with prefrontal function during pain stimulation.

Acknowledgements

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