The Journal of Neuroscience, July 1994, 14(7): 4095–4108

Distributed Processing of Pain and Vibration by the Human Brain

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Pain is a diverse sensory and emotional experience that likely involves activation of numerous regions of the brain. Yet, many of these areas are also implicated in the processing of nonpainful somatosensory information. In order to better characterize the processing of pain within the human brain, activation produced by noxious stimuli was compared with that produced by robust innocuous stimuli. Painful heat (47–48°C), nonpainful vibratory (110 Hz), and neutral control (34°C) stimuli were applied to the left forearm of right-handed male subjects. Activation of regions within the diencephalon and telencephalon was evaluated by measuring regional cerebral blood flow using positron emission tomography (^{15}O-water-bolus method).

Painful stimulation produced contralateral activation in primary and secondary somatosensory cortices (SI and SII), anterior cingulate cortex, anterior insula, the supplemental motor area of the frontal cortex, and thalamus. Vibrotactile stimulation produced activation in contralateral SI, and bilaterally in SII and posterior insular cortices. A direct comparison of pain and vibrotactile stimulation revealed that both stimuli produced activation in similar regions of SI and SII, regions long thought to be involved in basic somatosensory processing. In contrast, painful stimuli were significantly more effective in activating the anterior insula, a region heavily linked with both somatosensory and limbic systems. Such connections may provide one route through which nociceptive input may be integrated with memory in order to allow a full appreciation of the meaning and dangers of painful stimuli.

These data reveal that pain-related activation, although predominantly contralateral in distribution, is more widely dispersed across both cortical and thalamic regions than that produced during innocuous vibrotactile stimulation. This distributed cerebral activation reflects the complex nature of pain, involving discriminative, affective, autonomic, and motoric components. Furthermore, the high degree of interconnectivity among activated regions may account for the difficulty of eliminating pathological pain with discrete CNS lesions.

[Key words: pain, vibration, thalamus, positron emission tomography, human, primary somatosensory cortex, insula, secondary somatosensory cortex, heat, cingulate cortex]

An understanding of nociceptive processing in the human brain has remained elusive, perhaps because of the complexity and multiplicity of mechanisms supporting this essential sensory experience. Early observations by neurosurgeons led to the view that pain is a diencephalic phenomenon and that the telencephalon has little to do with pain perception (Head and Holmes, 1911; Penfield and Boldrey, 1937). These observations, however, were founded largely on the results of focal lesions and focal stimulation and did not examine the possibility that activation of multiple brain regions may be essential for the experience of pain. Modern theories of pain processing (Melzack and Casey, 1968; Price, 1988) acknowledge that multiple brain regions may likely play key roles in nociceptive processing and postulate that areas involved in discriminative aspects of tactile sensation, such as ventroposterior thalamus (VP) and primary somatosensory cortex (SI), are also involved in discriminative aspects of nociception, while medial areas of thalamus and their diffuse cortical projection sites—for example, frontal, cingulate, and insular cortices (Jones and Seavitt, 1974; Kaufman and Rosenquist, 1985; Royce and Mourey, 1985; Friedman and Murray, 1986)—are involved in the affective aspects of nociception (Bowsher, 1957; Price and Dubner, 1977; Melzack, 1986).

This functional segregation has been supported by a limited number of lesion and stimulation studies in humans and monkey. Lesions to SI in monkey (Kenshalo et al., 1991) and to the region around secondary somatosensory cortex (SII) in human (Greenspan and Winfield, 1992) lead to deficits in pain discrimination. Further, localized pain has been evoked from microstimulation of the base of VP in humans (Dostrovsky et al., 1990; Lenz et al., 1993). In contrast, lesions to anterior cingulate or insular cortices in humans have been reported to alter affective responses to pain (Foltz and Lowell, 1962; Hurt and Ballantine, 1973; Berthier et al., 1988).

Nevertheless, the conspicuous paucity of nociceptive neurons in primary somatosensory pathways continues to raise doubts about the importance of these areas to pain perception. Although anatomical studies in primates show projections from regions of the dorsal horn that contain nociceptive neurons to parts of VP thalamus (Apkarian and Hodge, 1989; Craig, 1992), most investigations have yielded only a small percentage of neurons in VP that respond to noxious stimuli in the primate (Kenshalo et al., 1980; Casey and Morrow, 1983; Bushnell and Duncan,

Received Aug. 5, 1993; revised Dec. 27, 1993; accepted Feb. 2, 1994.

We thank Sylvain Milot, Peter Neelin, Sean Marrett, and the staff of the McConnell Brain Imaging Centre and the Medical Cyclotron Unit for their technical assistance. This work was supported by the Medical Research Council of Canada. R.C.C. was supported by an MRC fellowship.

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1987; Bushnell et al. 1993). Similarly, although regions of primate thalamus containing nociceptive cells project to SI and SII (Kenshalo et al., 1980; Friedman and Murray, 1986; Gingold et al., 1991; Rausell and Jones, 1991), relatively few nociceptive neurons have been identified in these cortical regions (Kenshalo and Isensee, 1983; Kenshalo et al., 1988; Dong et al., 1989).

Other data question the view that nociceptive processing in "extralemniscal" pathways is restricted exclusively to the affective/motivational aspects of pain perception. In awake monkeys we have found cells in the region of the thalamic nucleus parafascicularis (Pf) that respond differentially to perceptually liminal differences in noxious heat stimuli, and thus could provide a neural substrate for the discrimination of pain intensity (Bushnell and Duncan, 1989). Further, quantitative psychophysical data from a case study involving anterior capsulotomy indicate that lesions which interrupt thalamocortical projections to the anterior cingulate and frontal cortices reduce the perceived intensity of noxious heat stimuli (Talbot et al., 1993).

Recent advances in functional imaging now provide a powerful tool for addressing questions about cerebral mechanisms of pain in normal humans. These techniques allow a simultaneous assessment of activation within multiple brain regions, thereby providing global information unattainable in individual stimulation, lesion, or recording experiments. In an initial study using positron emission tomography (PET) to examine the regional distribution of cerebral blood flow (rCBF), we found that painful heat stimuli activate regions of SI and SII cortices, as well as area 24 in the anterior cingulate cortex—all contralateral to the stimulated arm (Talbot et al., 1991). We concluded that each of these regions may contribute substantially to discriminative aspects of nociception, since the experimental methods employed were designed to minimize the affective dimension of pain perception. Using similar stimulation and imaging techniques, Jones et al. (1991) replicated our finding of anterior cingulate activation and additionally reported contralateral activation at the level of thalamus—an area below the region scanned in our study. They did not, however, detect significant pain-related activation of SI or SII cortex, and thus proposed that one cortical site, the anterior cingulate cortex, is the sole representation of the "suffering" component of pain (Jones et al., 1991). To complicate this issue further, Apkarian et al. (1992) recently argued for a role of SI cortex in pain processing based on their observation of a *de*crease in rCBF in this region during a study of tonic heat stimulation using single photon emission computed tomography (SPECT).

The present study was undertaken, therefore, to address these disparate results by examining in more detail activation within the human brain during painful cutaneous heat stimulation. We sought to confirm the involvement of multiple cerebral cortical regions in the processing of pain and to test the specificity of pain-related activation by comparing it with that produced by robust tactile stimulation. Blood-flow studies have established that regions within SI and SII cortices are activated during vibrotactile stimulation (Fox et al., 1987; Meyer et al., 1991; Seitz and Roland, 1993). Likewise, we have observed activation within the same regions during painful heat stimulation (Talbot et al., 1991). However, without a direct comparison of pain- and vibrotactile-related activity within the same subjects, few conclusions can be drawn concerning the relative locations or strengths of activation evoked by the two stimulus modalities.

A preliminary report of these data has been presented (Coghill et al., 1992).

Materials and Methods

Subjects. Nine right-handed pain-free male subjects between 20 and 35 years old (mean, 27 years) participated in this experiment. Subjects gave informed consent acknowledging that (1) they would be exposed to low doses of radiation and heat-induced pain, (2) the methods to be used and the risks involved were clearly explained and understood, and (3) they were free to withdraw from the experiment at any time without prejudice. All procedures were approved by the Ethics and Research Committee of the Montreal Neurological Institute and Hospital and were in accordance with the Declaration of Human Rights, Helsinki, 1975.

Stimulation procedures. Neutral 34°C thermal (Control), 47–48°C painful heat (Pain), and 110 Hz vibrotactile (Vibration) stimuli were employed as experimental conditions that were presented to the subjects during separate scans. Thermal stimuli were produced by a computer-controlled contact thermode with a rise time of 6°C/sec (Larson et al., 1987), and 110 Hz vibrotactile stimuli were delivered by an electric vibrator (Daito, Osaka, Japan). Each device had a circular stimulating surface of 1 cm^2, that was placed on the skin of the subject's left (nondominant) forearm.

During each 60 sec scanning period, one of the three stimulus conditions (Control, Pain, Vibration) was presented to the subject. Stimuli were delivered at six marked locations (3 × 2 matrix with interstimulus distance of 3 cm) on the ventral surface of the forearm. In order to minimize sensitization or habituation that may result from repeated presentations of noxious heat (Price et al., 1983), stimuli were rotated among the six locations, with a 6 sec presentation at each site followed by a 4 sec interstimulus level. The painful heat was presented as a two-step pulse, in which the temperature was held at 47°C for 5 sec and then raised to 48°C for 1 sec (Talbot et al., 1991). This procedure maximizes neuronal responses to noxious heat while minimizing exposure to potentially injurious stimuli (Bushnell and Duncan, 1989; Maixner et al., 1989). The control and vibrotactile stimuli were presented to the same six spots of skin using identical sequencing and timing parameters as those employed during the noxious heat scans.

Quantitative psychophysical response procedures. All subjects participated in a practice session in which they were presented the same stimuli to be used during the PET scans. During this session, subjects were asked to rate all stimuli on a magnitude-estimation scale, with 0 denoting no sensation, 50 denoting pain threshold, and 100 signifying extreme pain (Talbot et al., 1991). Only subjects who showed no withdrawal response to the noxious heat stimuli and who reliably and differentially rated the neutral thermal, vibrotactile, and noxious heat stimuli were retained for the PET study.

PET scans. The relative distribution of cerebral blood flow (CBF) was evaluated using the $H_2{}^{15}O$ bolus methodology of Fox and Mintun (1989) without arterial blood sampling. PET scans were obtained with the Scanditronix PC-2048 system, which provides 15 image slices 6.5 mm apart with a transverse image resolution of 4.6–6.4 mm and an axial resolution of 5.4–7.1 mm (Evans et al., 1989, 1991a,b).

Prior to the PET scan session, the subject's head was firmly secured by a custom-fitted foam headholder (Evans et al., 1991a), eye patches were placed to limit extraneous stimulation, and an infrared pulse oximeter was positioned on the right index finger to monitor heart rate. An intravenous catheter was inserted into the median vein of the right forearm for injection of the $H_2{}^{15}O$ bolus and secured in such a way as to minimize discomfort during the PET scans. Subjects were instructed to remain still, attend to all the stimuli presented during each scan, and rate the mean intensity of those stimuli after each scan was completed. Their heads were then optimally positioned within the PET scanner; the most superior region scanned was never more than 2 mm inferior to the superior extreme of the cerebral cortex. Brain regions included within the scanned areas are displayed in Figure 1.

In order to minimize possible anxiety-related cerebral activation associated with the novelty of the measurement procedures (injection of radioactive tracer and operation of the PET camera), the first scan for each subject was designated a "sham." During these sham scans, physiological saline (0.9%, 9 ml) was injected into the venous catheter, the 34°C control stimulus was applied in the standard fashion, and the scan procedures simulated as closely as possible.

Following the sham scan, six 60 sec experimental scans were conducted, with at least 15 min between each scan to minimize effects of preceding stimuli and to allow the tracer concentration to decay to background levels. Scanning of each stimulus condition (Control, Pain,

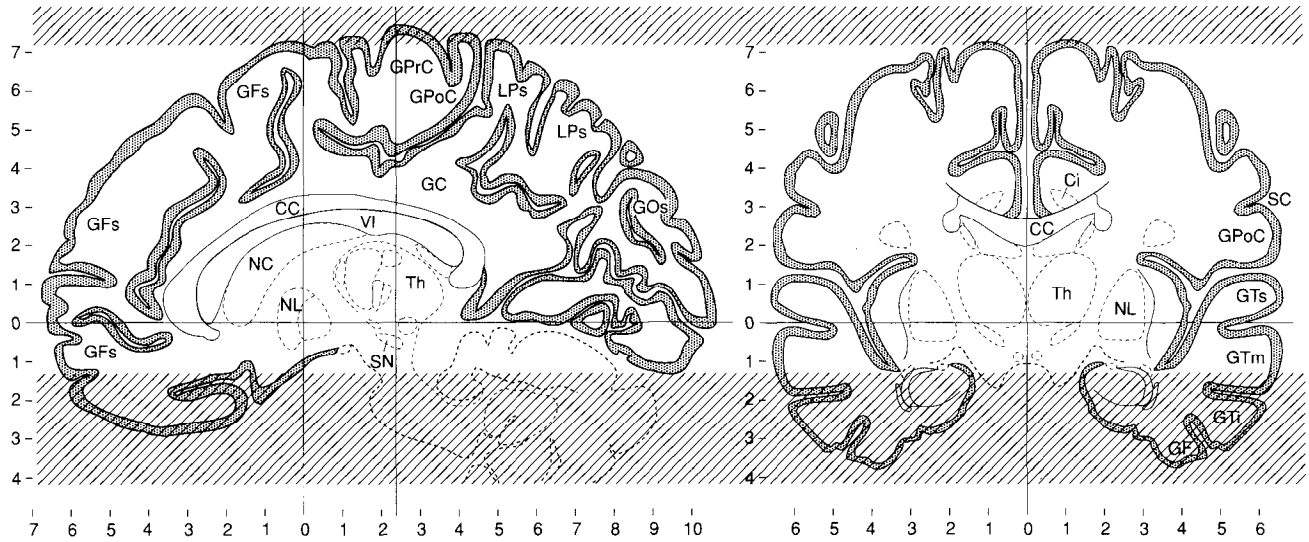


Figure 1. Brain regions examined by positron emission tomography. As can be seen in the sagittal (*left*) and coronal (*right*) sections, cerebral regions from the vertex of the parietal cortex to the inferior portions of the thalamus were scanned in all subjects. Structures within the *hatched areas* were not included in the analysis since not all subjects were scanned at these levels. Structures not fully examined include the amygdala, temporal poles, ventrolateral orbital frontal cortex, cerebellum, superior colliculus, and other inferiorly located regions (after Talairach and Tournoux, 1988). Abbreviations for Figures 1 and 6: *CC,* corpus callosum; *Ci,* cingulum; *GC,* cingulate gyrus; *GFi,* inferior frontal gyrus; *GFm,* middle frontal gyrus; *GFs,* superior frontal gyrus; *Gh,* parahippocampal gyrus; *GOb,* basal orbital gyri; *GOs,* superior occipital gyrus; *GPoC,* postcentral gyrus; *GPrC,* precentral gyrus; *GTi,* inferior temporal gyrus; *GTm,* middle temporal gyrus; *GTs,* superior temporal gyrus; *LPi,* inferior parietal lobule; *LPs,* superior parietal lobule; *NC,* caudate nucleus; *NL,* lenticular nucleus; *SC,* central sulcus; *SN,* substantia nigra; *Th,* thalamus; *VI,* lateral ventricle.

and Vibration) was performed twice, in a pseudorandom order. Heart rates were recorded at 15 sec intervals throughout 1 min periods preceding, during, and following each scan. At the end of each scan, subjects gave a single rating for the mean intensity of the stimuli presented during that scan.

Magnetic resonance image scans. Each subject received an MRI scan during a separate session following the PET portion of the experiment. A Phillips 1.5 T Gyroscan was utilized to obtain 64, 2-mm-thick T_1-weighted multislice spin echo images (repetition time T_R = 550 msec; echo time T_E = 30 msec) for later reconstruction into the three-dimensional MRI volume.

Image processing and analysis. PET images were smoothed with a 20 mm (full width, half-maximum) Hanning filter to minimize the effects of anatomical variability among subjects (Fox and Mintun, 1989). This has the effect of increasing the signal-to-noise ratio in the averaged image, but reduces the spatial resolution. Using a volumetric image registration procedure (Evans et al., 1989, 1991a), the MRI volume from each subject was aligned with the PET volumes. Both MRI and PET data were then remapped into a standardized stereotaxic coordinate system (Evans et al., 1991a), using an orthogonal coordinate frame based on the anterior commissure–posterior commissural line as identified in the MRI volume (Evans et al., 1992).

Each PET volume was then normalized by dividing every voxel count by the mean value for all intracerebral voxels. For individual subjects, the normalized images from the two repetitions of the same stimulus condition were averaged to reduce variability. Different stimulus conditions were then subtracted from each other (voxel by voxel), and the relative mean state-dependent change (ΔCBF) volume was obtained by averaging these subtraction images across subjects. Identical stimulus conditions were also subtracted ($Pain_2 - Pain_1$, $Vibration_2 - Vibration_1$, and $Control_2 - Control_1$) to assess the intrasubject reliability of ΔCBF imaging and to evaluate effects attributable to stimulus order.

Once subtractions were completed, the average ΔCBF volume was converted to a t statistic volume by dividing each voxel by the standard error of the mean (SEM). The SEM was computed, in turn, by dividing the mean standard deviation in ΔCBF for all intracerebral voxels by the square root of the number of subjects (Worsley et al., 1992).

Individual MRI images were subjected to the same averaging procedure, such that composite stereotaxic image volumes (128 × 128 × 80 voxels, with dimensions of 1.34 mm, 1.72 mm, 1.5 mm in the x; y; and z-planes, respectively) were obtained for both t statistic and MRI volumes. The average MRI and t statistic volumes were then merged to allow anatomical localization of the t statistic peaks.

The significance of a given CBF activation was assessed by thresholding the t statistic images at levels dictated by the Gaussian random field (GRAFT) model of Worsley et al. (1992). The GRAFT model predicts the likelihood of a single voxel in a three-dimensional random field exceeding a given magnitude. It incorporates the correlation among adjacent voxels and corrects for multiple comparisons when searching CBF subtraction volumes for significant activation peaks. This is achieved by replacing the voxel as the unit of volume with the "resel," a volume with dimensions equal to the image resolution in each direction (x = 20 mm, y = 20 mm, and z = 8 mm, with a 20 mm filter), and by considering the number of resels within a given search volume to represent the number of independent tests of the null hypothesis. The number of simultaneous tests being performed is proportional to the volume being searched, so that a directed search in a well-defined subvolume, for example, temporal lobe, will have fewer resels that an exploratory search over the whole brain.

When the GRAFT model is applied to a 200 resel volume, corresponding approximately to the gray matter volume of the human brain, a threshold of 4.0 will yield a volume-wise false positive rate of 0.12. In other words, there is only a 12% probability that one resel in the 200 resel volume will exceed that threshold by chance. Thus, one would have to repeat the same experiment (with 8–12 subjects per experiment) eight times (8 × 0.12 = 0.96) before one could expect a single false positive peak to be detected. Furthermore, the probability of a given resel exceeding the threshold of t = 4.0 by chance (e.g., uncorrected for multiple comparisons) is equivalent to $p < 0.0005$. Thus, the threshold of t = 4.0 is set conservatively. For smaller volumes, the false positive rate would be proportionately smaller and the threshold value can be relaxed.

To appraise further the reliability of identified peaks, post hoc directed searches were performed at every significant site in each individual's subtracted volume. Regional standard deviations were utilized to compute a local t statistic from the mean of individual ΔCBF values. Using this method of analysis, all points displayed a t value of 3.21 or greater, corresponding to $p < 0.025$.

Analysis of heart rate and psychophysical ratings of stimulus intensity. Heart rates were examined in three 1 min periods before, during, and after each of the six PET scans. Rates were averaged across the two presentations of each stimulus condition, and these averages utilized

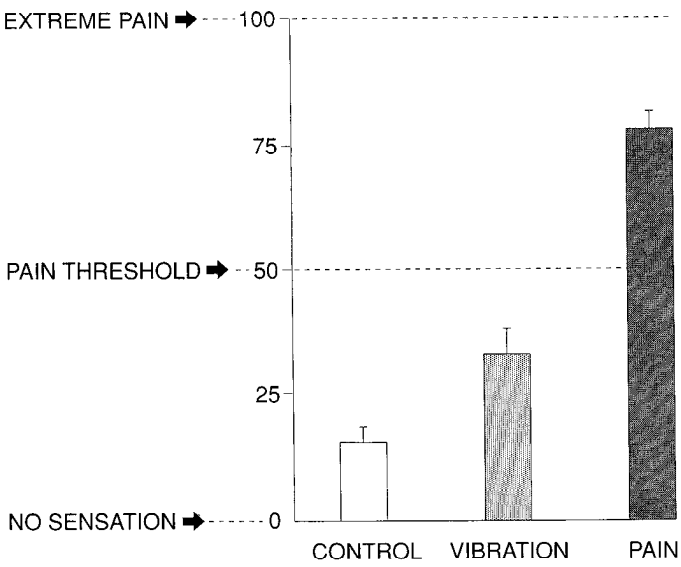


Figure 2. Mean psychophysical ratings (±SEM) of stimulus intensity. Subjects rated the vibrotactile stimulus as significantly more intense than the neutral temperature (34°C), but below pain threshold. The 47–48°C heat stimulus was rated as painful and significantly more intense than the vibratory stimulus.

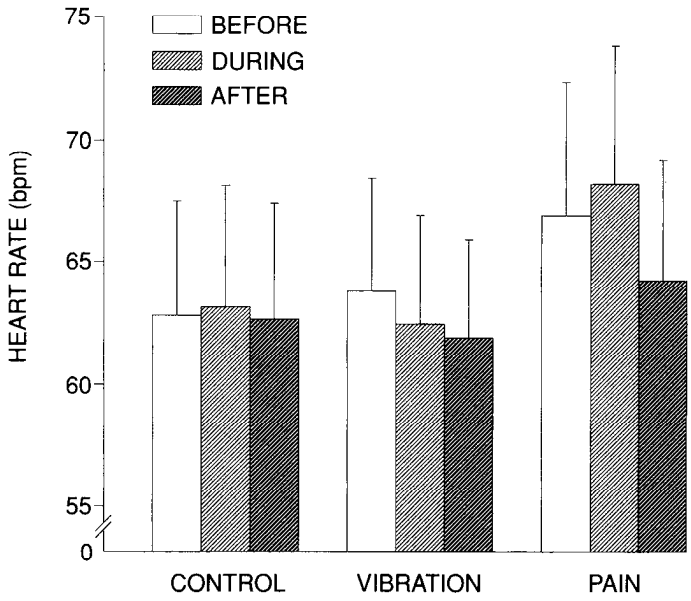


Figure 3. Mean heart rates (±SEM) for nine subjects before, during, and after the 34°C control stimulus, the vibratory stimulus and the 47–48°C painful heat stimulus. Heart rate "before" the Pain condition was significantly greater than that measured "before" either the Control or Vibration conditions; however, no further significant increases were observed during the application of the noxious heat.

for subsequent analyses. A two-factor analysis of variance (ANOVA) repeated within subjects was employed to determine significant effects of time (before, during, after stimulation) and stimulus condition (Control, Vibration, Pain) on heart rate. Psychophysical ratings of stimulus intensity were analyzed by a single-factor (stimulus) ANOVA repeated within subjects.

Analysis of the relationship of heart rate and CBF. In order to evaluate the possible relationship between heart rate and local CBF distribution, pain-induced rCBF changes were tested for their correlation with heart rate changes. Each subject's heart rate during painful stimulation was expressed as a percentage of that during control stimulation, and then compared with that subject's contribution to the significant ΔCBF peaks observed in the mean Pain − Control subtraction volume.

Results

Psychophysical ratings and heart rate

Subjects' ratings of stimulus intensity were dependent on the modality of stimulation presented (Fig. 2; ANOVA, $p < 0.001$) and indicate that they were able to discriminate among the three stimuli using a single scale that included both painful and non-painful sensations. As expected, the 47–48°C stimuli were rated as painful by all subjects and significantly more intense than the vibrotactile stimuli ($p < 0.001$). In turn, subjects rated the vibrotactile stimuli as significantly more intense than the 34°C control ($p < 0.001$).

Heart rates were also significantly influenced by testing condition (ANOVA, $p < 0.04$; Fig. 3), with rates being highest during the noxious heat trials. Interestingly, however, these heart rate increases associated with the Pain condition may have been due predominately to anxiety. An analysis of these data for the 1 min period preceding each test condition revealed that heart rate was elevated *before* the noxious stimuli were actually applied (ANOVA comparison of "before" periods for Control, Pain, and Vibration, $p < 0.03$; Fig. 3), and did not show any further significant increase during the application of the noxious heat (ANOVA contrasts, before Pain vs during Pain, $p = 0.45$).

Effects of stimulus order on CBF distribution

Comparisons of the first and second presentations of the Control, Vibration, or Pain conditions showed no significant focal changes in rCBF, indicating an absence of detectable habituation or sensitization in the current paradigm. In addition, these data indicate that intervening stimulus conditions had no discernable effect on the observed distribution of CBF. The lack of significant differences between the two Control conditions further indicates that following activated (Pain, Vibration) conditions, CBF returned to basal levels within the 15 min interim preceding the second Control condition. Thus, in order to reduce variability and maximize statistical power, data were averaged across the two presentations of each stimulus condition for all subsequent analyses.

CBF distribution during pain

A comparison of CBF during Pain (47–48°C) with that during Control (34°C) revealed a number of cortical, subcortical, and extracerebral sites that were differentially activated during the presentation of the noxious heat stimuli (Table 1).

Cerebral cortex. As we had previously observed (Talbot et al., 1991), painful stimulation produced significant activation in regions approximating SI and SII (Table 1). SI cortex was activated contralateral to stimulation, in a region consistent with the cutaneous representation of the arm (Fig. 4*A*), as defined by single-unit (Mountcastle et al., 1969; Hyvärinen et al., 1980; Sinclair and Burton, 1991) and evoked-potential (Allison et al., 1989, 1991; Joseph et al., 1991) recordings in the primate. Activation observed in the region of SII cortex (near the posterior insula/parietal operculum) also was focused in the right hemisphere, contralateral to stimulation (Fig. 4*B*).

Painful heat stimulation also produced significant activation near the anterior portion of the insular cortex and/or the frontal

Table 1. Pain-related foci of activation

Region	Coordinates M-L	A-P	S-I	% Change rCBF	*t* Value
SI	24	−31	56	4.75	4.02
SII	36	−6	18	5.44	4.57
Ant. insula	38	6	9	6.70	5.65
Ant. cingulate	1	1	42	4.93	4.15
SMA (inferior)	1	−4	54	5.95	5.00
SMA (superior)	5	−6	66	4.78	4.02
Thalamus	11	−19	−3	5.36	4.53
Putamen (ipsi.)	−25	1	−8	5.46	4.57
Putamen (ipsi.)	−23	−7	6	4.99	4.23
Extracerebral (temporal)	75	15	−3	5.03	4.23
Extracerebral (temporal)	68	17	8	6.01	5.05
Extracerebral (ipsi. temporal)	−71	22	−3	6.03	5.09
Extracerebral (ipsi. temporal)	−70	15	−13	5.78	4.87
Extracerebral (frontal)	34	53	30	4.77	4.02
Post. cingulate	1	−50	29	−6.08	−5.14
Orbital gyrus	20	67	−11	−4.70	−3.99[a]
Ant. insula (ipsi.)	−31	5	5	4.43	3.72[a]

Coordinates of peak activation are expressed in millimeters. M-L, medial-lateral relative to midline (positive = right); A-P, anterior-posterior relative to anterior commissure (positive = anterior); S-I, superior-inferior relative to commissural line (positive = superior). Negative *t* values indicate that blood flow was less during the Pain condition than during the Control condition.

[a] Below the threshold of statistical significance.

Table 2. Vibration-related foci of activation

Region	Coordinates M-L	A-P	S-I	% Change rCBF	*t* Value
SI	28	−31	57	6.02	5.21
SII	42	−21	15	6.68	5.78
SII (ipsi.)	−55	−26	21	4.65	4.04
Post. insula	38	−13	−5	5.10	4.39
Post. insula (ipsi.)	−32	−7	−8	4.70	4.04
Middle frontal gyrus	44	32	22	−5.21	−4.51
Middle frontal gyrus	44	20	31	−4.84	−4.21
Orbital gyrus	20	65	−11	−4.92	−4.25
SMA	5	−19	47	4.31	3.69[a]
Ant. cing.	3	3	39	4.52	3.38[a]
Thalamus	11	−23	−3	3.42	2.95[a]

Coordinates of peak activation are expressed in millimeters. M-L, A-P, and S-I are defined in Table 1. Negative *t* values indicate that blood flow was less during the Vibration condition than during the Control condition.

[a] Below the threshold of statistical significance.

operculum (Table 1, Fig. 4*C*). A trend toward activation (t = 3.72) was observed in the ipsilateral anterior insular region, suggesting that this area may be activated bilaterally (Table 1, Fig. 4*C*).

Three pain-related regions of activation were also observed along the medial wall of the right frontal cortex, contralateral to stimulation. The most inferior of these medial foci was in area 24 of the anterior cingulate cortex (Table 1, Fig. 5*A*), a region previously observed to be activated in the human during painful stimulation (Jones et al., 1991; Talbot et al., 1991). Superior to the anterior cingulate activation, two foci were detected within the supplementary motor area (SMA). Both SMA foci occurred within area 6 of the superior frontal gyrus, with one being situated superior to the other (Table 1, Fig. 5*A*).

Two cortical regions demonstrated a *decrease* in rCBF during the Pain condition, compared to the Control (negative *t* values of Table 1). One of these foci was located medially in the posterior cingulate gyrus in a position approximating area 31 (Fig. 6*D*). The other focus was located in area 10 near the anterior tip of the orbital gyrus (Fig. 6*A*). Both of these pain-related sites of decreased rCBF were situated in the right hemisphere, contralateral to the stimulated forearm (Fig. 6*A*).

Subcortical regions. Pain-related increases in rCBF were observed in the area of basal thalamus (Table 1, Fig. 5*B*), contralateral to the stimulated arm. Activation of any or all of a number of adjacent thalamic nuclei, including VP, Sm, and Pf, could have contributed to this focus, since the PET imaging technique is unable to distinguish among structures of such close proximity. In the ipsilateral hemisphere, painful stimulation produced a significant increase in rCBF only in the region of the putamen (Table 1, Fig. 4*C*).

Extracerebral regions. In addition to the intracerebral changes in rCBF, significant increases in *extra*cerebral blood flow were detected on both sides of the head when the Pain condition was compared to the Control (Table 1, Fig. 4*C*). These extracerebral increases in rCBF occurred in areas adjacent to the temporalis muscle and superficial temporal artery.

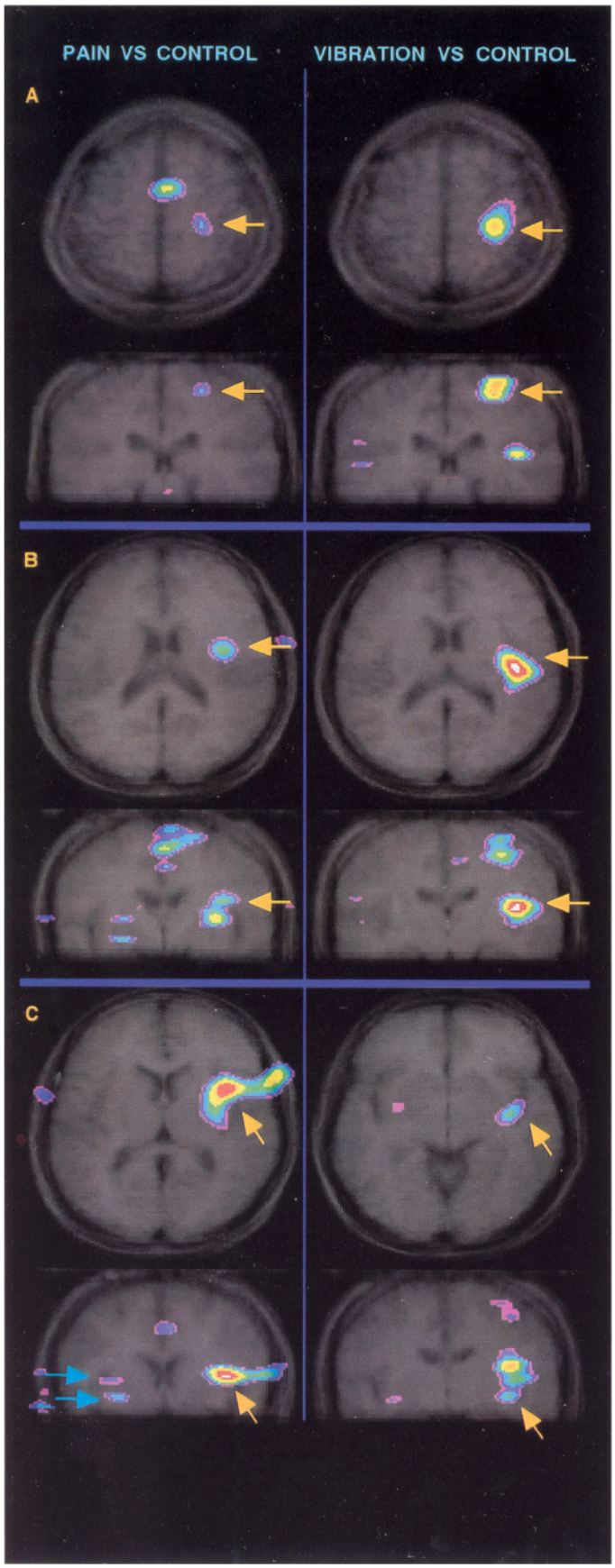
Relationship between CBF and heart rate changes. None of the intracerebral blood flow changes related to painful stimulation were significantly correlated with either heart rate increases or extracerebral blood flow changes. In contrast, extracerebral increases in blood flow, ipsilateral to stimulation, were strongly correlated with increases in heart rate that occurred during painful stimulation ($r = 0.91$, $p < 0.001$). Contralateral extracerebral blood flow changes, however, were not significantly related to changes in heart rate ($r = 0.44$, $p = 0.232$).

CBF distribution related to vibration

A comparison of CBF during Vibration with that during Control stimulation revealed significant peaks at several loci, as detailed in Table 2.

Cerebral cortex. As observed for pain, vibrotactile stimulation produced significant increases in rCBF within the areas of SI and SII (Table 2, Fig. 4*A,B*). The stereotaxic coordinates of the Vibration-related SI focus were indistinguishable from those associated with the SI activation observed in the Pain condition. In contrast, the Vibration-related SII focus, centered deep within the lateral sulcus near the posterior insula, was localized somewhat posterior to that observed during the Pain condition (Fig. 4*C*). Additional sites of activation observed during the Vibration condition were an ipsilateral region in the vicinity of SII (Table 2, Fig. 4*B*), as well as a *bilateral* activation within the insular cortex, anterior to SII (Table 2, Fig. 4*C*).

No statistically significant changes in rCBF related to Vibration were detected in the anterior cingulate gyrus or SMA. Nevertheless, trends toward significant activation were identified in both regions (with *t* values of 3.38 and 3.69, respectively; Table



2), suggesting that those areas that showed increases in rCBF during Pain may also be activated to some extent during Vibration.

Although most differences between the Vibration and Control conditions involved *increases* in rCBF during Vibration, two foci within the contralateral middle frontal gyrus showed *decreased* rCBF during Vibration relative to Control (Table 2, Fig. 6*B,C*). In addition, a significant vibration-related decrease in rCBF was also observed in the anterior tip of the contralateral orbital gyrus (area 10), an area that exhibited a similar decrease in rCBF during the Pain condition (Fig. 6*A*).

Subcortical regions. No statistically significant rCBF changes were observed in the subcortical structures examined, when Vibration was compared to Control. Activation within thalamus fell far short of meeting our statistical criteria for reliability ($t = 2.95$, Table 2).

Comparison of pain- and vibration-induced changes in rCBF

Pain and Vibration conditions produced similar changes in rCBF in several areas of the cerebral cortex. Increases in rCBF produced by Pain overlapped extensively with those produced by Vibration within SI, and to a lesser extent in SII. In addition, as indicated above, *de*creases in rCBF were also noted in both Pain and Vibration conditions within the same area of the orbitofrontal gyrus, contralateral to the stimulated arm.

Relative to the control condition, significant increases in rCBF during the Pain condition, but not during the Vibration condition, were noted in a number of cortical and subcortical areas—including anterior cingulate cortex, SMA, anterior insula, and basal thalamus—all contralateral to the stimulated arm. Nevertheless, a direct statistical comparison of Pain versus Vibration revealed that the only intracerebral region showing significantly increased rCBF during Pain, relative to either Control or Vibration, was the anterior portion of the contralateral insular cortex (Table 3, Fig. 5*C*). Two of the extracerebral activation sites also showed significantly greater rCBF during Pain than during Vibration (Table 3, Fig. 4*C*). In contrast, no site showed reduced rCBF during Pain relative to Vibration.

Discussion

The present results show that, in normal human subjects, cutaneous heat pain produces contralateral activation in a number of cortical and subcortical sites, including SI, SII, anterior cingulate, anterior insula, SMA, and thalamus. In addition, our data suggest that this pattern of pain-related activation is distinct

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Figure 4. Merged PET-MRI horizontal and coronal slices averaged across nine subjects, showing the distribution of cerebral blood flow during painful heat and vibratory stimulation, relative to the 34°C control stimulus. The range of t values for PET data is coded by color (see color bar, Fig. 5). *A,* Both painful (*left*) and vibrotactile (*right*) stimulation produced significant activation within contralateral SI cortex (denoted by *arrows*). *B,* Both painful and vibrotactile stimulation produced contralateral activation within SII and adjacent regions (denoted by *arrows*). *C,* Both painful and vibrotactile stimulation produced activation within the insula. However, pain-induced insular activation occurred anterior and superior to that produced by vibrotactile stimulation. Painful stimulation also produced activation on the border of the ipsilateral claustrum and putamen (*blue arrows*). The coronal sections also show that bilateral extracerebral increases in blood flow were produced by painful, but not vibrotactile, stimulation. The averaged MRI data reflect the underlying anatomical variability between subjects, and hence are not as detailed as individual images.

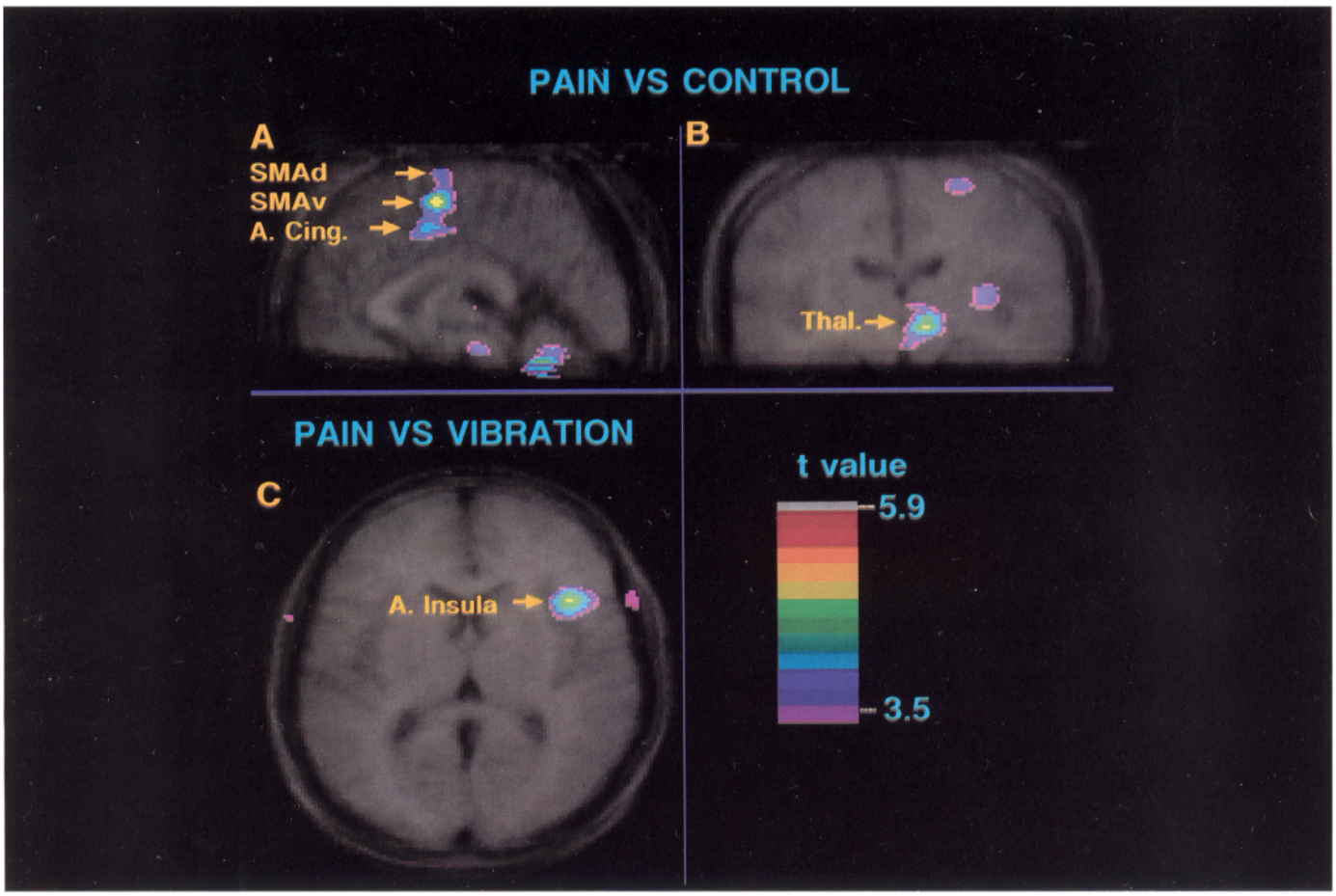

Figure 5. *A,* Painful stimulation produced significant blood flow changes along the medial wall of the contralateral hemisphere. These loci included area 24 of the anterior cingulate cortex (*A. Cing.*), and inferior and superior regions of the supplementary motor cortex (*SMAv, SMAd,* respectively). *B,* Painful stimulation produced significant activation within the contralateral thalamus (*Thal.*). *C,* A direct comparison of pain and vibrotactile stimulation revealed significantly greater activation during pain than during vibration in the anterior portion of the contralateral insular cortex and in a contralateral extracerebral region.

from that produced by innocuous cutaneous stimuli. Painful stimuli produced significantly greater activation of the anterior insular cortex than did vibrotactile stimulation. In contrast, vibrotactile stimulation led to a bilateral activation of the posterior insula that was not observed for painful stimulation. Vibrotactile stimulation did activate regions of SI and SII, but did not produce statistically significant changes in rCBF in the other sites activated by pain. These findings indicate that the pain-related activation of SI and SII observed in our previous study (Talbot et al., 1991) and the thalamic activation observed by Jones et al. (1991) are reliable, reproducible phenomena. Further, these results confirm that multiple cerebral cortical regions are involved in the pain experience.

Comparison with previous studies

In addition to confirming the areas of pain-related activation observed in Talbot et al. (1991) and Jones et al. (1991), the present results revealed additional cortical areas (i.e., SMA and anterior insular cortex) that were activated during the presentation of noxious cutaneous heat. There are several possible reasons for the increased number of regions showing significant activation. Technical differences, such as a larger number of subjects (nine vs eight) and a higher average dose of radioactive tracer (39.4 vs 30.8 mCi) reaching the brain, may have led to an increased sensitivity in the present study compared to our previous report (Talbot et al., 1991).

At least three differences in study design may also have contributed to the increased number of activation sites observed in the present study. First, the present study utilized a neutral

Table 3. Foci of activation related to comparison of pain and vibration

Region	Coordinates M-L	A-P	S-I	% Change rCBF	*t* Value
Ant. insula	42	15	9	5.17	4.69
Extracerebral (ipsi. temporal)	−71	17	0	5.29	4.82
Extracerebral (temporal)	68	13	−11	5.44	4.96

Coordinates of peak activation are expressed in millimeters. M-L, A-P, and S-I are defined in Table 1.

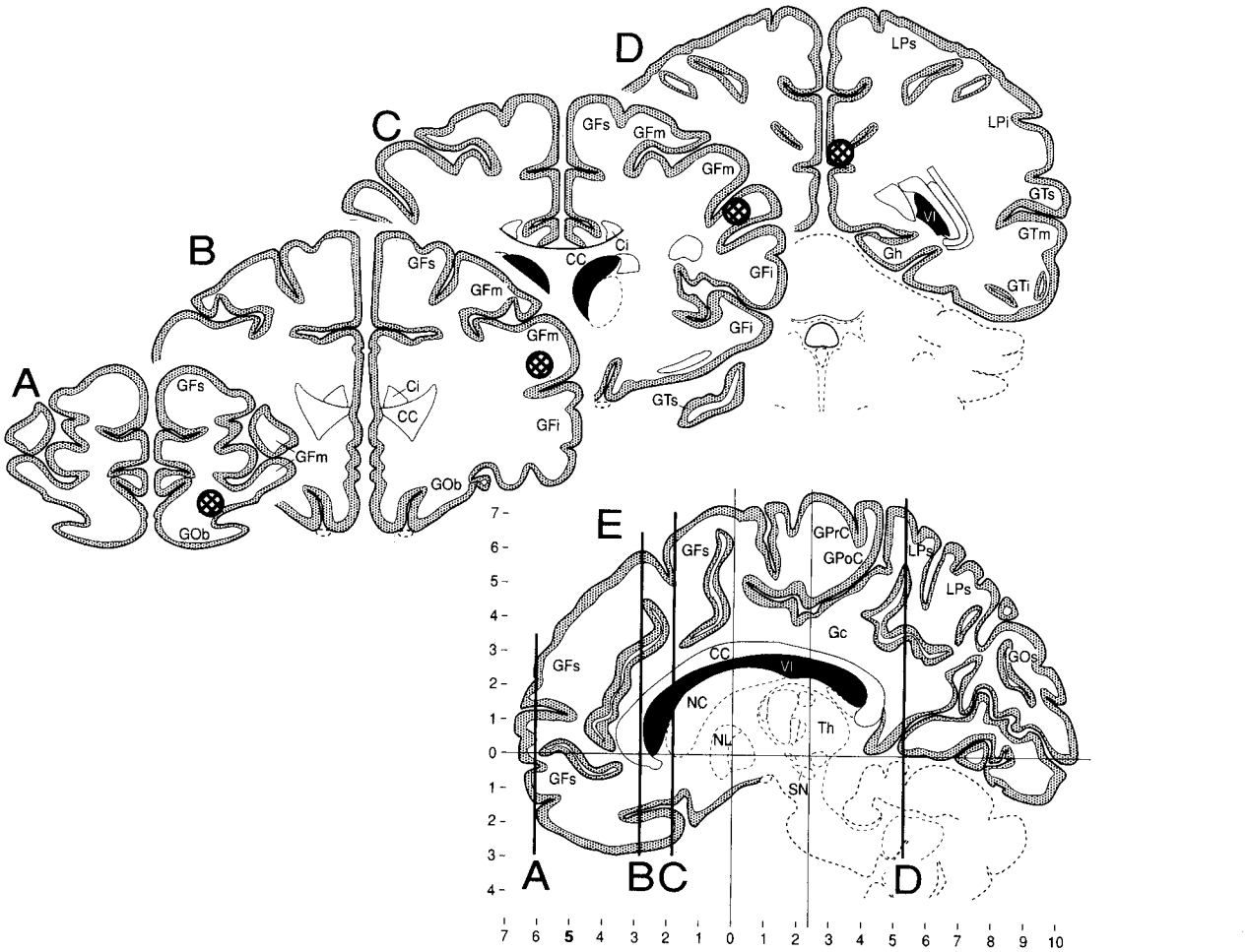

Figure 6. Regions in which painful or vibrotactile stimulation produced less activation than did the control stimulation. *A*, Both painful and vibrotactile stimulation produced less activation than control stimulation in the contralateral orbital gyrus of the prefrontal cortex (area 10). Although stereotaxic coordinates placed these activation sites near the border of the brain, MRI data confirmed that this activation is within the brain. *B* and *C*, Vibrotactile stimulation produced significantly less activation than control stimulation at two loci within the middle frontal gyrus. *D*, Painful stimulation produced significantly less activation than control stimulation in the posterior cingulate cortex. See Figure 1 for abbreviations (after Talairach and Tournoux, 1988).

(34°C) control, whereas our previous study and that of Jones et al. (1991) used a warm (41–42°C) control; thus, the present activation might reflect a combined representation of pain and warmth. However, warm fiber activity is suppressed by noxious heat, so that with repeated heat pulses, the warm fiber input probably contributed little to the observed cerebral activation (Duclaux and Kenshalo, 1980). Second, a thermally neutral control stimulus would undoubtedly produce less activation than a maximally warm control stimulus; thus, subtractions between neutral and painful stimuli would be predicted to yield a greater magnitude of differences than subtractions between warm and painful stimuli. Finally, the preliminary practice sessions of the present experiment may not have been as effective as those of our previous study in reducing pain-related anxiety, since this study's subjects showed increased heart rates before and during the noxious heat conditions, while those in our previous study did not. Although several PET studies indicate that high levels of anxiety are not associated with any specific regional increases in neuronal activation (Reiman et al., 1989; Drevets et al., 1992), it is possible that high levels of anxiety may modulate or enhance pain-evoked neural responses, particularly in brain regions involved in affective responses to pain.

Activation in SI cortex

Both noxious heat and vibrotactile stimuli led to an increased blood flow in the contralateral postcentral gyrus in a region consistent with the arm representation of the primary somatosensory cortex. The vibrotactile-induced activation of SI is not surprising, in that other blood-flow studies in humans and monkeys have consistently observed such activation (Fox et al., 1987; Meyer et al., 1991; Perlmutter et al., 1991; Seitz and Roland, 1993). These PET results are also consistent with findings of single-unit studies in monkeys, which show that vibration induces highly focal increases in neuronal activity in SI cortex (Mountcastle et al., 1969; Hyvärinen et al., 1980).

Our findings of SI activation during painful stimulation were less predictable. Early human lesion and stimulation data had suggested a minimal role of SI cortex in pain processing. Head and Holmes (1911) observed that pain perception remained generally intact despite widespread injury to the cerebral cortex, and White and Sweet (1969) reported that SI lesions provide only temporary relief from chronic pain. Similarly, Penfield and Boldrey (1937) also discounted the possible role of the SI cortex in the perception of pain based on the paucity of painful sen-

sations produced by electrical stimulation during neurosurgical procedures. More recently, however, Young and Bloom (1983) have reported that some patients with epileptic foci involving SI cortex do experience pain during seizures.

Although we had previously observed pain-induced activation of SI (Talbot et al., 1991), other groups have not observed significant increases in rCBF in SI cortex (Jones et al., 1991; Apkarian et al., 1992). One factor that may have contributed to the absence of SI and SII activation in the Jones et al. study (1991) is that their heat stimulus (46.4°C) only approximated the theshold for nociceptive activity in primary somatosensory neurons (Kenshalo et al., 1988), and thus may not have been sufficiently intense to produce a statistically detectable blood flow change. In addition, their use of only one stimulation site would not have evoked the spatial summation of pain intensity (Price et al., 1989; Douglass et al., 1992) that has been observed with multiple stimulation sites, as employed in our two studies.

The present results and those of our previous study (Talbot et al., 1991) indicate that, despite the difficulty of identifying pain-related activity in the human SI cortex with lesion and stimulation methods, a contralateral representation of pain-related activity clearly coexists with the tactile representation. Single-unit investigations in monkeys support these human data. Kenshalo and co-workers have identified a small population of SI nociceptive neurons that encode the intensity of noxious thermal stimulation (Kenshalo and Isenesee, 1983; Kenshalo et al., 1988; Chudler et al., 1990); the responses of these neurons correlate with both the monkey's ability to detect changes in noxious stimulus intensity (Kenshalo et al., 1988) and with humans' ratings of pain intensity evoked by identical noxious stimuli (Chudler et al., 1990). Since the majority of these SI nociceptive neurons have convergent or wide-dynamic-range (i.e., respond to both painful and nonpainful stimuli in a graded fashion) response properties (Kenshalo et al., 1988; Chudler et al., 1990), it is likely that a significant proportion of neurons contributing to the pain-induced activation in the present study also contribute to the vibrotactile activation. These findings, along with additional evidence that bilateral ablation of SI in monkeys disrupts their ability to discriminate intensities of noxious heat (Kenshalo et al., 1991), suggest that this region is involved in the sensory-discriminative component of pain perception. However, given the equivocal stimulation and lesion results in humans, it appears that although this region may contribute to pain perception, other regions must necessarily be activated for the full experience of pain.

Activation of SII and posterior insula

Noxious heat and vibrotactile stimulation each produced a significant increase in rCBF near the contralateral inferior face of the parietal operculum, in the region defined in the monkey as SII (Roberts and Akert, 1963; Friedman and Murray, 1986), and the Vibration condition activated a similar region *ipsi*lateral to the site of peripheral stimulation. These results confirm previous findings of increased rCBF in human SII related to both noxious heat (Talbot et al., 1991) and vibrotactile stimulation (Fox et al., 1987; Seitz and Roland, 1992).

The present study also revealed a bilateral activation within the posterior insular cortex, probably in the granular subdivision (Ig), during vibrotactile but not noxious heat stimulation. Anatomical data in monkeys showing a projection to Ig from ventroposterior inferior (VPI) thalamus (Friedman and Murray, 1986), a nucleus with strong pacinian input (Herron and Dykes, 1987), is consistent with vibrotactile activation in the posterior insula.

The finding that vibrotactile stimulation produced bilateral activation in the region of SII and Ig is consistent with single-unit recordings in rhesus monkeys. Although receptive fields of monkey SII neurons are mostly contralateral, those in the neighboring 7b region are generally bilateral (Robinson and Burton, 1980a,b). Thus, the present activation may include contributions from both of these areas. Similarly, receptive fields of Ig neurons are generally large and bilateral (Robinson and Burton, 1980b). Only a few nociceptive neurons have been identified in the region of SII/posterior insula in the monkey (Robinson and Burton, 1980c; Dong et al., 1989) and most of these had bilateral receptive fields. Nevertheless, our finding of a preferentially contralateral representation of pain in SII is supported by the observation of Greenspan and Winfield (1992) that a tumor compromising SII resulted in higher pain thresholds on the hand contralateral to the tumor than on the ipsilateral hand. This psychophysical difference was reduced after the tumor was removed, suggesting a predominantly contralateral representation of pain in SII.

The exact role that SII cortex plays in the processing of tactile and pain information is not certain. Data in rhesus monkeys showing that SII somatosensory responsiveness is dependent on an intact SI cortex (Pons et al., 1992), as well as observations in humans and monkeys that lesions of SII lead to deficits in both tactile and pain discrimination (Murray and Mishkin, 1984; Greenspan and Winfield, 1992), suggest that SII and SI may function together to process discriminative aspects of somatosensation. However, since lesions of SI only temporarily alleviate chronic pain (White and Sweet, 1969) and since SII receives direct thalamic input sufficient to transmit nociceptive information (Friedman and Murray, 1986), SII may not necessarily be dependent on serial transmission of information from SI for the processing of pain.

Anterior insular cortex

Noxious heat, but not vibrotactile, stimulation was found to activate a region of the contralateral anterior insular cortex, probably in the disgranular portion (Id). This was the only brain region in which we observed significantly greater blood flow during pain than during vibrotactile stimulation (see Table 3). No study has yet shown nociceptive neuronal activity in Id; nevertheless, this region has connections with a number of cortical areas implicated in nociception, such as SI, SII, and area 24 of the anterior cingulate cortex (Mufson and Mesulam, 1982; Friedman et al., 1986). Similarly, it receives input from the posterior portion of the ventromedial thalamic nucleus (Friedman and Murray, 1986), an area recently shown to receive a strong projection from lamina I of the spinal cord (Craig, 1992) and to contain a high concentration of nociceptive neurons (Bushnell and Craig, 1993).

Several lines of evidence suggest that the pain-related activation in anterior insula may reflect circuitry involved in the affective and reactive components of pain. First, Id has been shown to project to various limbic structures, such as the amygdaloid complex and perirhinal cortex (Friedman et al., 1986). Second, although stimulation in the anterior insular cortex produces predominantly visceral sensations, it also evokes unusual somatic sensations, movements, and sometimes a sense of fear (Penfield and Rasmussen, 1955; Feindel, 1961; Penfield and Faulk, 1984). Finally, Berthier et al. (1988) reported one patient

with an anterior insular lesion who showed inappropriate emotional responses to painful stimuli or to threatening gestures. Insular links with the limbic system may be essential for integrating ongoing pain with memory, allowing full appreciation and evaluation of the meaningfulness of the stimulus in light of previous experience. Such a process would be a key component of pain affect (Price, 1988).

Anterior cingulate gyrus

Area 24 of the anterior cingulate cortex, contralateral to the stimulated arm, was significantly activated by noxious heat stimuli in the present study. This result confirms findings of previous blood flow studies (Jones et al., 1991; Talbot et al., 1991), and shows that this activation is not lateralized to one hemisphere.

In addition to the consistent activation of area 24 in blood-flow studies, several other lines of evidence implicate this region in pain processing. Area 24 receives input from thalamic nuclei containing nociceptive neurons, such as (Pf), Sm, and the base of VP (Craig et al., 1982; Vogt et al., 1987, 1993; Musil and Olson, 1988; Yasui et al., 1988). Surgical lesions of area 24 in humans have been shown to relieve chronic pain (Foltz and Lowell, 1962; Hurt and Ballantine, 1973), and lesions to the cingulum bundle in rats reduce nociceptive behaviors elicited by subcutaneous injection of formalin (Vaccarino and Melzack, 1989). More recently, nociceptive neurons have been identified in anterior cingulate area 24 of rabbits (Sikes and Vogt, 1992).

The anterior cingulate cortex is, however, by no means exclusively involved in nociception. PET studies in humans indicate that portions of the anterior cingulate may be involved in visual attention (Pardo et al., 1990; Corbetta et al., 1991), while animal behavior data show its involvement in avoidance learning (Thomas and Slotnick, 1963; Gabriel et al., 1991). Area 24 of monkey has been shown to contain movement-related foci (Luppino et al., 1991; Shima et al., 1991) and to have corticospinal projections (Hutchins et al., 1988). The anterior cingulate cortex may also be involved in autonomic responses to external stimuli. Stimulation in this region produces changes in respiration and cardiovascular function in animals and man (Lofving, 1961; Hoff et al., 1963), and single neurons with a discharge frequency related to cardiac or respiratory cycle have been identified in cats (Frysinger and Harper, 1986). Such data suggest a broad role of area 24 in modulating behavioral reactions to external stimuli. The consistent activation of this region in blood-flow studies involving painful stimulation may reflect the importance of nociceptive input in this modulatory process.

Supplemental motor area

Noxious heat, but not vibrotactile, stimuli produced significant activation in the region of SMA in the frontal cortex. This region is thought to be involved in motor control (see Wise and Strick, 1984, for review). Single-unit studies in monkeys show activity of SMA neurons during a waiting period in preparation for movement (Kurata and Wise, 1988; Dao-fen et al., 1991). Further, electrical stimulation of SMA in humans frequently produces an urge to move or evokes an actual movement (Penfield and Rasmussen, 1955). Finally, human blood-flow studies using PET have shown activation of SMA during tasks involving the planning and execution of movement (Roland et al., 1980a,b; Deiber et al., 1991). Thus, the SMA activation of the present study may indicate a preparation and readiness to move the stimulated arm in the avoidance of danger, despite our subjects' denial of any urge to withdraw from the noxious stimuli.

Thalamus

In the present study and in the study by Jones et al. (1991), there was a significant blood-flow increase in the thalamus during noxious heat stimulation. In contrast, we did not observe a significant activation of thalamus during vibrotactile stimulation. These findings are somewhat surprising, in that vibrotactile information is known to be processed in the thalamus (Herron and Dykes, 1987; Ghosh et al., 1992). Nonetheless, other investigators measuring cerebral blood flow have also failed to detect vibrotactile-induced increases in the thalamus (Fox et al., 1988; Seitz and Roland, 1993), although combinations of sensory and motor tasks do produce reliable activation (Seitz et al., 1991).

At least two factors could contribute to these findings of significant thalamic activation during noxious heat but not vibrotactile stimulation. First, although noxious tactile stimuli activate only a small percentage of neurons recorded in the primate somatosensory (VP) thalamus (Perl and Whitlock, 1961; Kenshalo et al., 1980; Casey and Morrow, 1983; Lenz et al., 1990; Bushnell et al., 1993; Tremblay et al., 1993), these stimuli are quite effective in activating neurons distributed throughout a larger area within the thalamus, including the ventromedial posterior nucleus, Pf, Sm, centralis medialis, and the posterior nucleus (Casey, 1966; Dong et al., 1978; Andersen and Dafny, 1983; Dostrovsky and Guilbaud, 1988, 1990; Bushnell and Duncan, 1989; Miletic and Coffield, 1989; Bushnell and Craig, 1993). Second, medial thalamic nociceptive neurons have larger receptive fields than thalamic low-threshold neurons (Casey, 1966; Dong et al., 1978; Andersen and Dafny, 1983; Dostrovsky and Guilbaud, 1988, 1990; Bushnell and Duncan, 1989; Miletic and Coffield, 1989), so a larger proportion of these neurons would be activated by a noxious stimulus on the arm. The effect of larger receptive field size on metabolic activity is seen in 2-deoxyglucose studies of the rat spinal cord, in which a noxious heat stimulus to the foot activates five segments of the lumbar spinal cord, while vigorous brushing activates only one segment (Coghill et al., 1991, 1993). Thus, the more widespread activation of nociceptive cells within a larger number of thalamic nuclei would produce a substantial target of pain-related activity readily detectable by PET.

Areas with decreased blood flow during pain or vibration

In addition to the CBF increases observed during pain and/or vibration relative to the neutral control temperature, we observed a small number of *decreases* in CBF during the experimental conditions. During pain there was a decrease in CBF in the posterior cingulate cortex, and during vibration in the middle frontal gyrus. For both conditions, there was a decrease in CBF to the orbital frontal gyrus (area 10). In a study comparing vibration with a rest condition, Seitz and Roland (1993) reported a number of regional decreases in CBF, suggesting that they reflect a shift away from information processed in these structures.

The functional significance of rCBF decreases in the present study is less clear since an active (34°C) control condition, rather than a nonstimulated baseline condition, was employed. Thus, decreased rCBF may indicate areas that exhibit increased activation during the control condition, relative to the experimental condition, reflecting some unexpected cognitive or sen-

sory differences across the subtraction pair. Conversely, these regional decreases in CBF may indicate a real reduction in activity (from the normal baseline levels of processing within these structures) consequent to the specific demands of the experimental condition.

The neuronal mechanisms underlying decreases in rCBF are not well understood, especially at the level of the cerebral cortex. A reduction in rCBF cannot be interpreted unequivocally as a local inhibitory process, since the release of inhibitory neurotransmitters is considered an energy-demanding event likely to evoke *in*creases in rCBF (Sokoloff, 1991). However, in a cortical area rich with intrinsic neurons, this direct metabolic demand associated with the release of an inhibitory neurotransmitter might be inconsequential, compared to a larger reduction in the activity of the local modulatory processes. An equally plausible explanation for a local decrease in CBF is a diminished input to the region that results from active inhibition occurring at a preceding level of processing. In addition, reductions in rCBF might result from the passive shunting of blood to nearby activated areas. Thus, a clear explanation for the observed decreases in rCBF awaits a better understanding of the relationship between the blood flow and metabolic demands of the different components within the local circuitry of the regions involved.

Extracerebral blood flow and heart rate changes

Pain but not Vibration produced bilateral increases in extracerebral blood flow as well as increases in heart rate. Several lines of evidence suggest that anxiety may have played an important role in modulating these two dependent measures. Similar extracerebral changes have been observed during cholecystokinin-induced anxiety (Benkelfat et al., 1991) and during anxiety produced by the anticipation of pain (Reiman et al., 1989; Drevets et al., 1992). These extracerebral changes could reflect increased perfusion of the temporalis muscles if the subjects were clenching their jaws, or could represent increased flow in the superficial temporal artery that might result from the elevated heart rates observed during the Pain condition. The significant correlation observed between the magnitude of CBF increases in some of the extracerebral foci and changes in heart rate lends support to their possible interactions.

The fact that heart rate was elevated *before* the painful stimuli were actually administered further suggests a role of anxiety in producing these changes. This apparent anticipatory anxiety was observed despite counterbalancing the stimulus order and maintaining a single-blind paradigm design. Since only three stimulus conditions were utilized across the six scans, some subjects may have anticipated the presentation of the painful condition after completion of Control and Vibration scans.

Significance of multiple sites of nociceptive processing

The multiple brain regions activated by noxious stimulation reflect the complex nature of the pain experience, which involves sensory-discriminative and affective components, and may include fear and anxiety, as well as autonomic and motoric reactions. Anatomical connectivity suggests that certain activated regions, such as anterior insular cortex, may be involved in pain affect by integrating somatosensory information with memory. Other regions, such as the SMA and anterior cingulate cortex, may involve modulation of motoric and/or autonomic reactions to pain. Finally, certain areas, such as SI and SII cortices, may contribute primarily to spatial, temporal, and intensity discrimination of painful stimuli. Although each region mentioned above may be preferentially involved with some specific task, the number of different brain regions activated by painful stimulation and high degree of connectivity between these areas strongly suggest that pain is processed by complex cortical and subcortical networks.

A distributed pain system would explain the difficulty of eliciting painful sensations by cortical stimulation, since simultaneous activation of several regions could be necessary for pain. Similarly, a distributed pain system would explain why discrete cortical lesions seldom lead to a complete reduction in pain, but may alter certain aspects of the pain experience or behavioral reactions to pain (Foltz and Lowell, 1962; Hurt and Ballantine, 1973; Berthier et al., 1988; Stein et al., 1989; Kenshalo et al., 1991; Talbot et al., 1993), and why chronic pain may initially be alleviated by lesions at different levels of the neuraxis, but usually returns after a period of months (White and Sweet, 1969; Vierck and Luck, 1979; Vierck et al., 1990). This resilience of chronic pain may involve a plasticity in pain pathways, whereby functions usually performed by one region are taken over by another. Such redundancy and resiliency are of obvious evolutionary value, since nociception is essential for survival (Melzack, 1973). Further studies in which the perception of and behavioral reactions to noxious stimuli are precisely measured and correlated with regional cerebral activation will help define the role of various brain regions in the experience of pain.

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