# Pain Intensity Processing Within the Human Brain: A Bilateral, Distributed Mechanism

ROBERT C. COGHILL,[1] CHRISTINE N. SANG,[1] JOSE MA. MAISOG,[2] AND MICHAEL J. IADAROLA[1]
[1]*Pain and Neurosensory Mechanisms Branch, National Institutes of Dental Research and* [2]*Laboratory of Brain and Cognition, National Institute of Mental Health, National Institutes of Health, Bethesda, Maryland 20892*

**Coghill, Robert C., Christine N. Sang, Jose Ma. Maisog, and Michael J. Iadarola.** Pain intensity processing within the human brain: a bilateral, distributed mechanism. *J. Neurophysiol.* 82: 1934–1943, 1999. Functional imaging studies of human subjects have identified a diverse assortment of brain areas that are engaged in the processing of pain. Although many of these brain areas are highly interconnected and are engaged in multiple processing roles, each area has been typically considered in isolation. Accordingly, little attention has been given to the global functional organization of brain mechanisms mediating pain processing. In the present investigation, we have combined positron emission tomography with psychophysical assessment of graded painful stimuli to better characterize the multiregional organization of supraspinal pain processing mechanisms and to identify a brain mechanism subserving the processing of pain intensity. Multiple regression analysis revealed statistically reliable relationships between perceived pain intensity and activation of a functionally diverse group of brain regions, including those important in sensation, motor control, affect, and attention. Pain intensity–related activation occurred bilaterally in the cerebellum, putamen, thalamus, insula, anterior cingulate cortex, and secondary somatosensory cortex, contralaterally in the primary somatosensory cortex and supplementary motor area, and ipsilaterally in the ventral premotor area. These results confirm the existence of a highly distributed, bilateral supraspinal mechanism engaged in the processing of pain intensity. The conservation of pain intensity information across multiple, functionally distinct brain areas contrasts sharply with traditional views that sensory-discriminative processing of pain is confined within the somatosensory cortex and can account for the preservation of conscious awareness of pain intensity after extensive cerebral cortical lesions.

## INTRODUCTION

For the past 30 years, conceptual views of brain mechanisms for the processing of pain have been driven by the elegant proposal that sensory and emotional components of pain are processed in parallel by distinct brain structures (Melzack and Casey 1968). Lateral thalamic nuclei and the somatosensory cortex have been proposed to subserve sensory-discriminative aspects of pain such as quality, location, and intensity processing, whereas medial thalamic nuclei, the prefrontal cortex, and limbic system have been proposed to subserve the affective-motivational dimension of pain.

This model, although importantly emphasizing the affective dimension of pain, does not provide an adequate mechanism for the processing of pain intensity. Multiple, converging lines of evidence indicate that brain regions outside of the traditional "lateral pain system" may also be engaged in the processing of this sensory-discriminative aspect of pain. First, in contrast to the view that the "medial pain system" cannot accurately transmit/process information about sensory features of a painful stimulus, neurons within the parafasicular and center median nuclei of the medial thalamus have been shown to encode pain intensity with accuracy sufficient to support behavioral discrimination (Bushnell and Duncan 1989). Second, although the primary somatosensory cortex is proposed to be the cortical site of sensory-discriminative processing, this structure is not necessary for the processing of pain intensity. Quantitative psychophysical analysis of patients with unilateral lesions of the primary somatosensory cortex reveals that their capacity to evaluate pain intensity is almost completely conserved (Knecht et al. 1996). Similarly, unilateral surgical excision of the postcentral gyrus fails to relieve contralateral chronic pain (White and Sweet 1968). Third, in contrast to the clearly contralateral projections of the "lateral pain system," pain intensity can be processed by brain regions both contralateral and ipsilateral to stimulation. Subjects who have had one cerebral hemisphere surgically removed retain the capacity to be consciously aware of a painful stimulus presented ipsilateral to their remaining hemisphere (Bernier et al. 1997; Gardner 1933; Knecht et al. 1996; Marshall and Walker 1950; Walker 1943). Quantitative psychophysical analysis of these subjects reveals that they have almost no disruption of their capacity to experience and evaluate pain intensity (Bernier et al. 1997; Knecht et al. 1996). Similarly, psychophysical studies of a split-brain patient confirm that both cerebral cortical hemispheres can independently process pain intensity information arising from a unilateral painful stimulus (Stein et al. 1989).

Accordingly, classic concepts of sensory-discriminative processing need to be reformulated. First, to account for the preservation of conscious awareness of pain intensity following damage to the somatosensory cortex, pain intensity processing must be distributed over multiple cerebral cortical regions. Functional imaging studies confirm that multiple cerebral cortical regions are engaged in the processing of pain (Casey et al. 1994; Coghill et al. 1994; Craig et al. 1996; Derbyshire et al. 1997; Hsieh et al. 1996; Iadarola et al. 1998; Jones et al. 1991; Rainville et al. 1997; Talbot et al. 1991; Vogt et al. 1996) and suggest that pain is processed in a distributed fashion (Coghill et al. 1994). However, the extent to which pain intensity information is distributed across these multiple cerebral cortical areas has not yet been evaluated in a fully quantitative fashion. Second, to account for the split-brain and hemispherectomy findings, both cerebral cortical hemispheres

The costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked "*advertisement*" in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

must be engaged (or be capable of being engaged) in the processing of pain intensity information arising from a unilateral noxious stimulus. However, sites responsible for ipsilateral cerebral cortical processing of pain intensity have yet to be identified. Third, to further account for the preservation of conscious awareness of pain intensity in the face of lesions ranging from focal damage to SI to hemispherectomy, significant portions of pain intensity processing must occur in parallel. A highly serial organization would be readily disrupted by lesions, whereas a parallel organization would result in a conservation of intensity information over multiple cerebral cortical areas and would be resilient to disruption by lesions. Anatomic evidence indicates that independent, parallel routes exist for transmission of nociceptive information from the thalamus to brain regions such as SI, SII, anterior cingulate cortex, and insula (Burton and Jones 1976; Burton and Sinclair 1996; Craig et al. 1995; Friedman and Murray 1986; Mufson and Mesulam 1984; Vogt et al. 1987). However, the degree to which pain intensity information is conserved during the transmission from subcortical to cerebral cortical regions remains unknown. To address these issues, we combined positron emission tomography and psychophysical assessment of pain *1*) to determine whether pain intensity–related information is distributed across multiple brain areas, *2*) to quantitatively characterize the relationship between brain activation and perceived pain intensity, and *3*) to identify cerebral cortical regions engaged in the processing of pain intensity evoked by an ipsilateral stimulus.

## METHODS

### *Subjects*

Sixteen right-handed normal volunteers (7 women, 9 men) were recruited to measure brain activation produced by graded painful stimulation. Subjects (1 Pacific Islander, 4 Hispanics, 2 Blacks, 9 Whites) ranged in age from 21 to 46 yr (29 ± 2.15, mean ± SE) and were healthy, pain-free, and had no detectable magnetic resonance imaging (MRI) abnormalities. Negative pregnancy tests were obtained for all female subjects of child-bearing potential. All procedures were approved by the Institutional Review Board of the National Institute of Dental Research and the Radiation Safety Committee of the National Institutes of Health. All volunteers gave written, informed consent acknowledging *1*) that they would receive radioactive tracers, *2*) that they would experience experimental pain stimuli, *3*) that all methods and procedures were clearly explained, and *4*) that they were free to withdraw from the experiment at any time.

### *Functional imaging*

Brain activation was assessed by fully quantitative measurement of cerebral blood flow (CBF) with $H_2{}^{15}O$ positron emission tomography (PET, 33.3 mCi/scan), as described in Coghill et al. (1998b). In brief, subjects were placed in the PET scanner (Scanditronix 2048–15B), fitted with a thermoplastic mask to minimize head movement, and positioned such that the most superior aspect of the cerebral cortex was within the field of view. Across all subjects, the field of view extended ventrally to ~30 mm below the anterior commissure–posterior commissure (AC-PC) line caudally, and 17 mm below the AC-PC line rostrally. Transmission scans were performed for attenuation correction during image reconstruction. For all PET scans, subjects were instructed simply to lie on the bed with their eyes closed and to not move or say anything. Each PET scan was acquired in a dynamic fashion over a 4.5-min period, with a 10-min interval between tracer injections. Before actual PET scanning, a sham scan (saline injection) was carried out to minimize anxiety associated with the PET scan procedure (Talbot et al. 1991). With positioning, a transmission scan, a sham scan, and nine PET scans, each PET session lasted ~2 h.

Subjects received PET scans during rest and graded thermal stimulation (2 scans per temperature). Thermal stimuli were delivered to the upper right arm at levels approximating skin temperature (35°C), pain threshold (46°C), moderate pain (48°C), and substantial pain (50°C). Thermal stimuli were applied via a 1-cm-diam electrically heated probe and were alternated among 6 skin areas (5-s stimulation, 0.5-s interval, 3 cm × 2 cm grid) to avoid habituation or sensitization. Stimulation was initiated 5 s before tracer injection and was continued for 2.5 min. Accordingly, subjects received ~30 heat pulses during the course of a single PET scan. In contrast to the scans of thermal stimuli, the rest scans involved no application of the stimulator. All stimuli were presented in a randomized order. A minimum of 1 day before the PET scans, subjects participated in a training session in which they received a standard series of heat pulses to give them experience rating pain intensity. Subjects also received all stimuli used in the PET session to ensure that the range of temperatures would be well tolerated. At the end of each PET scan, psychophysical ratings of pain intensity and pain unpleasantness were obtained using a numerical scale (integers from 0 to 20) anchored with verbal descriptors (Coghill and Gracely 1996). Within subjects ANOVA was used to identify significant effects of stimulus temperature on psychophysical ratings, and contrast analyses were used to identify differences between adjacent temperature pairs (SAS software, SAS Institute).

### *Image processing*

For intersubject analysis, PET data were transformed into standard stereotaxic coordinates using a linear transform derived by matching individual, high resolution structural MRI scans (Fast gradient recalled echo, 124 × 1.5 mm thick sagittal images with an in-plane resolution of 0.98 mm, extended dynamic range, 256 × 256 matrix, 1 nexus, TE = minimum, Flip Angle = 200) to an average MRI atlas constructed from 305 normal subjects [MNI-Autoreg, provided by the McConnell Brain Imaging Center of the Montreal Neurological Institute (Collins et al. 1994)]. These MRI scans were acquired in a 1-h duration session on a different day than the PET session. PET data were movement corrected and registered with MRI data using the Automated Image Registration (AIR) software (Woods et al. 1992, 1993). To facilitate intersubject analysis and to further minimize variability produced by slight variations in brain structure, PET data were smoothed with a Gaussian filter (full-width, half-maximum resolution, 15 × 15 × 10 mm in mediolateral, anterior-posterior, and superior-inferior dimensions, respectively). To minimize variability produced by global cerebral blood flow changes, each PET scan was normalized to gray matter values by dividing each voxel value by the average of gray matter CBF.

### *Identification of pain intensity–dependent brain activation*

Voxel-by-voxel multiple regression analyses were performed to identify brain regions whose variability was due to subjects' ratings of pain intensity. Multiple regression analyses were performed according to Rencher (1995) using NIH-Functional Imaging Data Analysis Platform [NIH-FIDAP, developed by J. Ma. Maisog. Note that this package has been extensively utilized and validated in functional imaging studies of visual processing (Courtney et al. 1998; Petit et al. 1998)]. Variability unique to individual subjects (i.e., CBF patterns that were constant across all scanning conditions within a given individual, but that differed across different subjects) was first factored out to better characterize effects attributable to psychophysical ratings of pain. Next, the relationship (regression coefficient) between normalized CBF changes and psychophysical ratings of pain intensity

was calculated for each voxel. Wilk's Lambda statistic was used to determine whether each regression coefficient was statistically different from zero. The Wilk's Lambda values were converted to *F* values and then to *z*-scores. The statistical significance of voxels exceeding a *z*-score of 3.09 was then calculated according to the spatial extent of activation (Friston et al. 1994). The volume-wise false positive rate was set at <5% ($P < 0.05$). To visualize changes in normalized CBF across stimulus conditions (i.e., Fig. 2), differences between rest and all stimulated conditions were calculated. Differences in normalized CBF greater than +2 and less than −2 in areas with a statistically reliable relationship with pain intensity are displayed.

The rest scan was included in the pain intensity regression to facilitate identification of effects that were independent of pain intensity (see *Identification of pain intensity–independent brain activation*). One potential complication of this is that pain intensity–independent effects could be falsely identified as pain intensity–related. In a conventional T-statistics analysis, the use of a nonstimulated rest control condition would represent a major concern, because all differences between resting and pain scans would be detected, regardless of their relationship with pain intensity. In contrast, the main strength of the multiple regression analysis is that effects of several different factors (i.e., regressors) can be identified as long as the regressors are orthogonal (i.e., independent). Thus if zero ratings of pain intensity were obtained only within the rest scan, the pain intensity regressor would not have been independent of the state of stimulation (i.e., probe on/off the arm). However, more than 2/3 (33/49) of the zero pain intensity ratings were obtained in stimulated (i.e., nonresting) scans. Accordingly, the brain activation identified in the pain intensity regression is largely independent of activation that is associated with the contact of the stimulator on the arm.

### *Identification of pain intensity–independent brain activation*

To directly characterize brain activation associated with the presence of the stimulator on subjects' arms, effects attributable to perceived pain intensity were factored out, and another multiple regression analysis was performed to identify areas activated by aspects of thermal stimulation that were independent of pain intensity. In other words, this analysis was directed at identifying brain activation that was common to all temperatures of stimulation, but different from the nonstimulated resting condition. This was accomplished by constructing a regressor in which all eight stimulated conditions were weighted at +1 and the rest condition was weighted as −8. This regressor was orthogonal to the pain intensity regressor and therefore provided the capability to obtain an estimate of activity that was independent from that related to pain intensity. Statistical significance of this regression analysis was evaluated as above. To further characterize pain intensity–independent effects, region of interest analyses were performed across all PET scans at the coordinates of the local maxima identified in the regression. Within subjects ANOVA was used to identify significant effects of stimulus condition on normalized CBF, and contrast analyses were used to identify differences between 46°C and all other stimulation conditions.

One additional variable, psychophysical ratings of pain unpleasantness, was also considered for inclusion in the multiple regression analysis. As in most studies of heat pain, these ratings were highly correlated with pain intensity ($r = 0.96$). Because these two variables were not orthogonal, additional analyses with pain unpleasantness as a regressor were not performed, and pain unpleasantness findings are not discussed further.

### *T-statistics analysis*

A T-statistics analysis was performed on a subset of the data to compare the multiple regression results with a more conventional technique. A contrast between 50°C and rest was selected to include both pain intensity–dependent and pain intensity–independent activation components. The T-statistics analysis has been described in detail previously (Chmielowska et al. 1998).

## RESULTS

### *Psychophysical responses*

While undergoing PET scans, subjects' perceptions of pain intensity increased significantly during graded increases in stimulus temperature [single factor within-subjects ANOVA, $F(4,60) = 108.75$, $P < 0.0001$, Fig. 1]. These increases were robust within the noxious range (i.e., temperatures ≥46°C). Statistically reliable differences were evident between all adjacent intensities of noxious stimuli [ANOVA of orthogonal contrast variables, 35 vs. 46°C: $F(1,15) = 18.87$, $P < 0.0006$, 46 vs. 48°C: $F(1,15) = 33.49$, $P < 0.0001$, 48 vs. 50°C: $F(1,15) = 67.19$, $P < 0.0001$].

### *Pain intensity–related responses*

Multiple regression analysis of the functional imaging data revealed that a number of cerebral cortical and subcortical areas exhibited significant, graded changes in activation linearly related to subjects' perceptions of pain intensity (Table 1, Fig. 2, *left panel*). Changes in activity that were positively related to perceived pain intensity occurred in areas previously demonstrated to be responsive to painful stimulation. Bilateral changes in activation were noted in the cerebellum, putamen, thalamus, insula, anterior cingulate cortex, and SII. In contrast, contralateral activation was detected in the dorsal supplementary motor cortex and SI, whereas predominantly ipsilateral activation was noted in the ventral premotor cortex. Changes in activity that were negatively related to perceived pain intensity were also noted. These occurred in occipital, temporal, and parietal areas generally associated with visual processes (Fig. 2).

The findings from the multiple regression analysis are independently supported by comparisons of PET scans at each stimulus temperature with the resting state (Fig. 2, *right panel*). In most areas, innocuous (35°C) and threshold (46°C) stimulation produced minimal differences from rest. However, as stimulus temperature increased to 48 and 50°C, monotonic increases in activation were evident in multiple brain areas

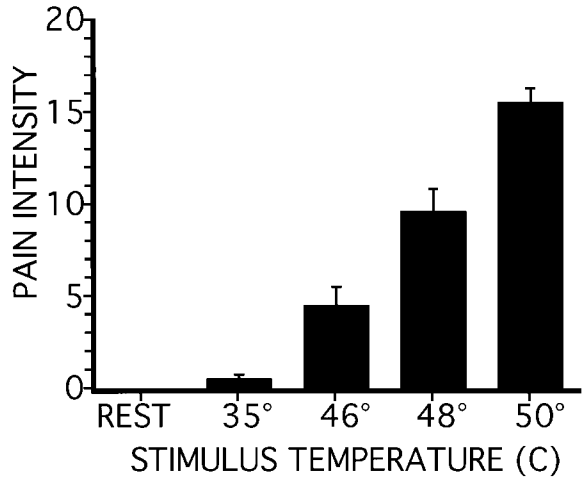


FIG. 1. Subjects' perceptions of pain intensity increased significantly during graded increases in stimulus temperature (means ± SE).

TABLE 1. *Brain activation positively related to perceived pain intensity*

| Region | s | x | y | z | F | $\beta$ | z-Score |
|---|---|---|---|---|---|---|---|
| Cerebellum | | | | | | | |
| Anterior lobe | i | 3.9 | −46.5 | −16.2 | 39.44 | 0.37 | 5.85 |
| Anterior lobe | i | 11.9 | −62.5 | −24.2 | 19.34 | 0.28 | 4.23 |
| Lentiform nuclei | | | | | | | |
| Putamen | c | −28.1 | 9.5 | −0.2 | 26.23 | 0.35 | 4.87 |
| Globus pallidus/putamen | i | 23.9 | −2.5 | −0.2 | 29.09 | 0.39 | 5.11 |
| Thalamus | | | | | | | |
| vpl | c | −20.1 | −18.5 | −0.2 | 17.91 | 0.28 | 4.09 |
| Dorsomedial nucleus | m | −0.1 | −18.5 | −0.2 | 27.08 | 0.50 | 4.94 |
| Centromedian nucleus | i | 9.9 | −14.5 | −0.2 | 35.78 | 0.49 | 5.60 |
| Insula | | | | | | | |
| Mid-insula | c | −38.1 | 1.5 | −4.2 | 33.58 | 0.40 | 5.45 |
| Insula/gts | c | −44.1 | −10.5 | −0.2 | 22.70 | 0.34 | 4.56 |
| Anterior insula | i | 33.9 | 17.5 | −0.2 | 17.56 | 0.32 | 4.05 |
| Frontal operculum | | | | | | | |
| Ventral premotor area | c | −60.1 | 7.5 | 3.8 | 23.54 | 0.34 | 4.64 |
| Ventral premotor area | c | −62.1 | −0.5 | 11.8 | 18.76 | 0.29 | 4.18 |
| Ventral premotor area | i | 49.9 | 9.5 | −0.2 | 49.17 | 0.55 | 6.43 |
| Ventral premotor area | i | 55.9 | 1.5 | 7.8 | 43.29 | 0.44 | 6.09 |
| Parietal operculum | | | | | | | |
| SII | c | −38.1 | −12.5 | 19.8 | 22.52 | 0.24 | 4.54 |
| SII | c | −50.1 | −26.5 | 19.8 | 15.45 | 0.24 | 3.81 |
| SII | i | 49.9 | −12.5 | 15.8 | 26.05 | 0.31 | 4.86 |
| Medial wall | | | | | | | |
| ACC BA 24/32 | m | −0.1 | 11.5 | 35.8 | 31.74 | 0.41 | 5.31 |
| ACC BA 24 | m | −0.1 | −2.5 | 47.8 | 36.22 | 0.42 | 5.63 |
| SMA BA 6 | m | −0.1 | −0.5 | 51.8 | 36.11 | 0.40 | 5.63 |
| Sensory-motor | | | | | | | |
| SI | c | −24.1 | −38.5 | 59.8 | 12.60 | 0.29 | 3.46 |
| SMA BA 6 | c | −18.1 | −14.5 | 59.8 | 26.61 | 0.31 | 4.91 |

Locations (x, mediolateral; y, rostrocaudal; z, dorsal-ventral) are according to the Talairach coordinate system. Only statistically reliable foci ($P < 0.001$) are included. s, side; i, ipsilateral; c, contralateral; m, midline; $\beta$, regression coefficient; vpl, ventroposteriolateral nucleus; gts, superior temporal gyrus; BA, Brodmann's Area; ACC, anterior cingulate cortex; SMA, supplementary motor area.

(Fig. 2, *right panel*). These normalized CBF differences further confirm that the regression coefficient accurately describes the quantitative relationship between brain activation and perceived pain intensity. For example, the regression coefficient of the medial thalamus was 0.5, and the average psychophysical rating of 50°C was 15.6. Accordingly, the predicted activation difference between scans of 50°C stimulation and rest would approximate 0.5 * 15.6 or 7.8 (in units of normalized CBF). The observed activation difference was 7.07 (in units of normalized CBF).

In addition to the quantitative differences evoked during graded increases in painful stimulus intensity, clear qualitative changes were noted in the patterns of activation as well. In both the secondary somatosensory cortex and the thalamus, activation was predominantly contralateral during both 35 and 46°C stimulation. However, as stimulus intensity increased, activation within these areas became progressively bilateral.

### *Pain intensity–independent responses*

When brain activation attributable to perceived pain intensity was factored out, multiple regression analysis revealed that two brain regions were commonly activated during all thermal stimuli, regardless of stimulus temperature. These two regions were located in the right prefrontal cortex (Fig. 3, *top panel;* Table 2). As in the pain intensity regression above, this regression analysis accurately predicts the normalized CBF differences between all stimulated conditions and rest. For example, multiplication of the regression coefficient of the ventral focus (0.73) by the range of the regressor (9, i.e., −8 to + 1) would predict that normalized CBF should increase ~6.5 units above resting levels any time the thermal stimulator contacts the subjects' arms, regardless of its temperature. The observed average of the normalized CBF differences between all stimulated conditions and rest (i.e., 35-rest, 46-rest, 48-rest, 50-rest) was 6.14, closely approximating the predicted value.

Region of interest analyses of the original, normalized PET data (i.e., no variability factored out) confirmed that both areas exhibited a relatively constant degree of activation during all stimulated conditions, despite progressive increases in stimulus temperatures. In the ventral prefrontal focus, however, brain activation tended to peak at 46°C, the temperature closest to pain threshold (Fig. 3, *bottom panel*). Region of interest analysis confirmed the existence of a statistically significant effect of scan condition at this locus [ANOVA, $F(4,60) = 4.60$, $P < 0.0026$]. However, contrast analyses revealed that normalized CBF during 46°C stimulation was significantly greater than that of only the rest condition [$F(1,15) = 15.31$, $P < 0.0014$], although trends toward greater activation were noted when compared with the 35°C [$F(1,15) = 3.09$, $P < 0.0990$] and 48°C [$F(1,15) = 3.74$, $P < 0.0722$] conditions.

### *Multiple regression versus T-statistics analysis*

A T-statistics analysis examining differences between scans of 50°C and rest identified statistically reliable activation of structures demonstrating both pain intensity–dependent and pain intensity–independent activations as identified in the mul-

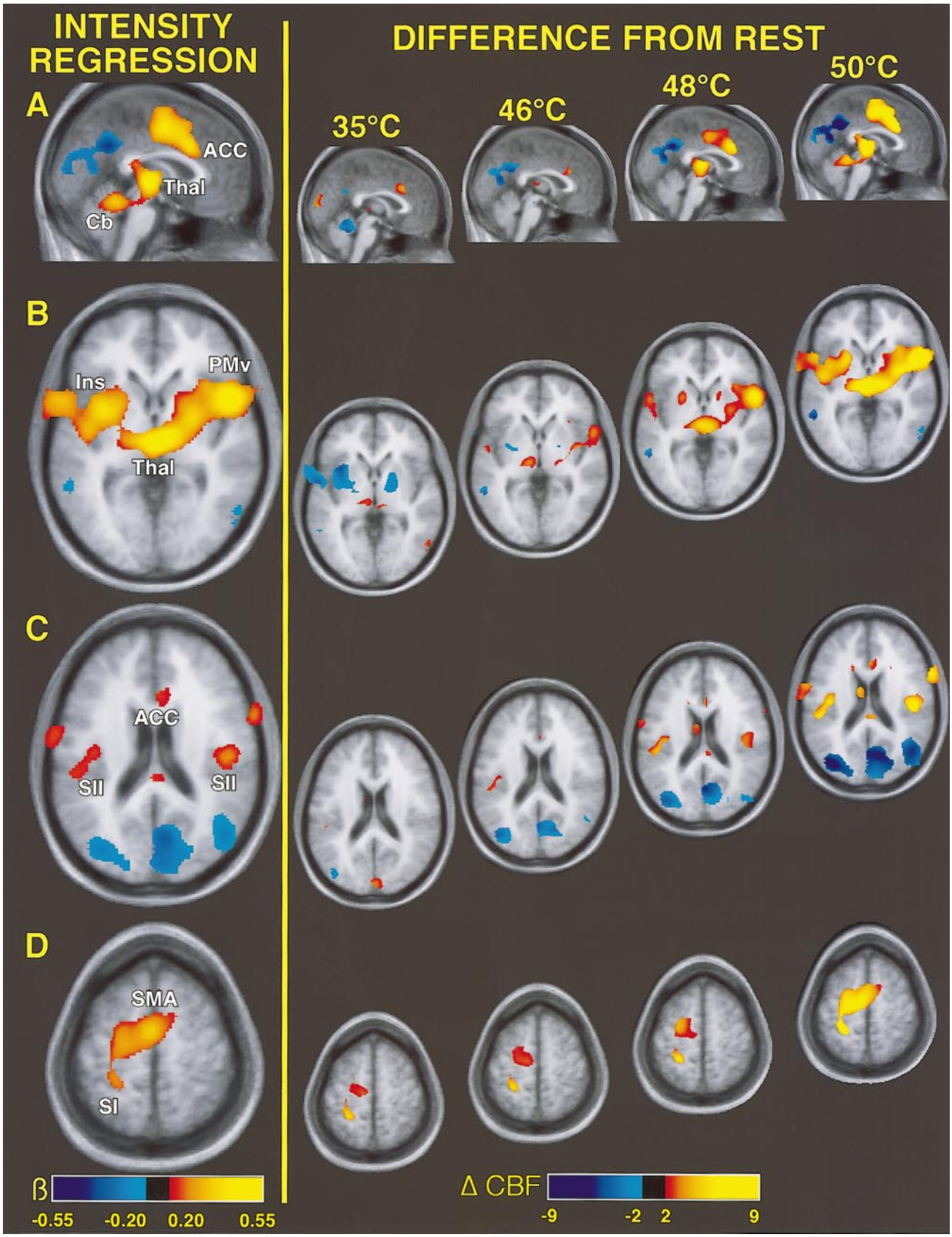


FIG. 2. Multiple regression analysis reveals that activation within a diverse array of brain areas is significantly related to subjects' perceptions of pain intensity (*left panel*, regression coefficients ($\beta$) are color coded such that red-yellow voxels are positively related with pain intensity, whereas blue-violet voxels are inversely related to pain intensity, $P < 0.001$). Progressive increases in activation are evident within these areas as stimulus temperature increases [*right panel*, cerebral blood flow (CBF) difference between each temperature and rest]. Functional data are displayed on the averaged structural magnetic resonance imaging (MRI) data of all subjects. The left side of the image corresponds to the subjects' left. ACC, anterior cingulate cortex; Thal, thalamus; Cb, cerebellum; Ins, insula; PMv, ventral premotor cortex; SII, secondary somatosensory cortex; SI, primary somatosensory cortex; SMA, supplementary motor area

tiple regression analysis. There was a striking degree of similarity between the two different analytic techniques for both the pain intensity–dependent (Fig. 4, *A–D*) and pain intensity–independent (Fig. 4*E*) findings, with the multiple regression technique demonstrating somewhat greater sensitivity. Nevertheless, the T-statistics analysis identified activation in areas with pain intensity–dependent responses including the following: bilateral portions of the putamen, thalamus, and SII; midline portions of the anterior cingulate cortex and supplementary motor cortex; contralateral portions of the insula, dorsal SMA, SI; and the right frontal operculum. Only two regions, the cerebellum and the left frontal operculum, were detected by the regression analysis, but not the T-statistics analysis (Fig. 4, *A* and *B*).

The T-statistics analysis also detected activation within the right prefrontal cortex, an area shown to have pain intensity–independent effects in the multiple regression analysis (Fig. 4*E*). This finding underscores the utility of the multiple regression approach in that the pain intensity–dependent regression analysis did not falsely identify this activation as being pain intensity related. In contrast, the use of a nonstimulated rest condition in the T-statistics analysis provides no information as to whether this area was activated by the contact of the probe or by the pain elicited by 50°C stimulation.

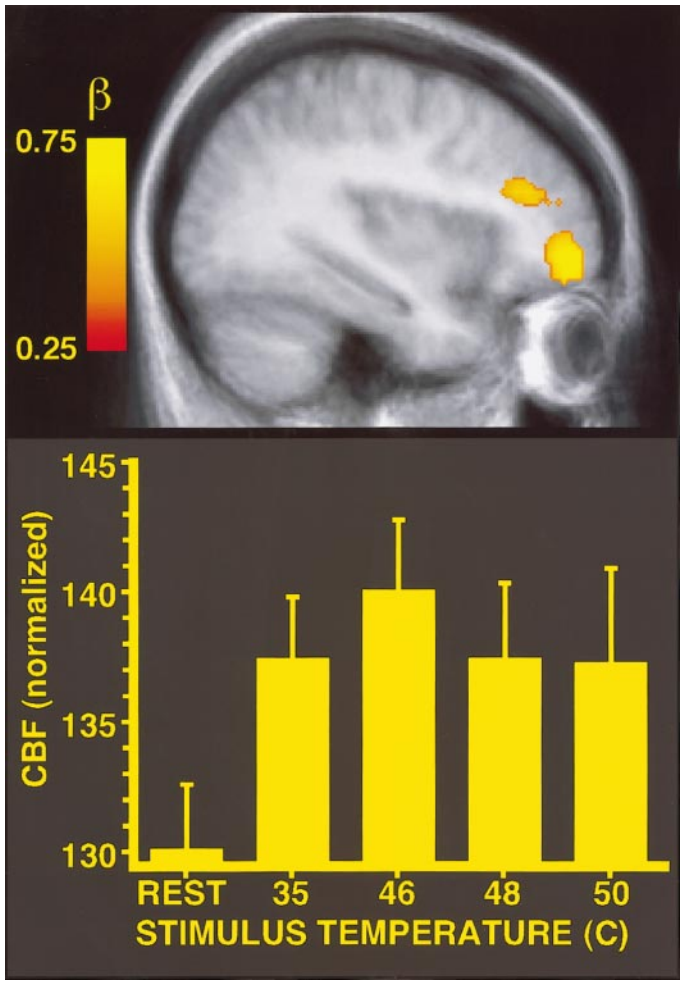


FIG. 3. Two regions of the right prefrontal cortex were differentially activated during thermal stimulation (as compared with rest) in a manner not linearly related to perceived pain intensity (*top panel*, $P < 0.03$). In the ventral focus, region of interest analysis indicates activation peaked during stimulation approximating pain threshold (46°C, *bottom panel*, means ± SE).

TABLE 2. *Brain activation independent of perceived pain intensity*

| Region | x | y | z | *F* | β | z-score |
|---|---|---|---|---|---|---|
| BA 10 | 35.9 | 51.5 | −8.2 | 17.80 | 0.73 | 4.07 |
| BA 9 | 27.9 | 39.5 | 23.8 | 17.15 | 0.52 | 4.00 |

See Table 1 for abbreviations.

## DISCUSSION

The significant relationship between perceived pain intensity and the activation of a diverse array of brain regions provides a new level of insight into the organization of brain mechanisms of pain processing. Pain intensity processing is distributed across multiple cerebral cortical and subcortical regions and is not confined to areas classically thought to be engaged in sensory-discriminative processing. This information processing occurs in regions both contralateral and ipsilateral to stimulation in a fashion that is quantitatively related to subject's perceptions of pain intensity. Therefore each cerebral hemisphere is independently capable of supporting conscious awareness of this specific feature of a painful stimulus. Moreover, the finding of pain intensity–related responses in regions important in motor control, affect, and attention suggests that intensity-related processing can be utilized in functions other than those involved in the conscious awareness of sensory features of a painful stimulus.

### *Distributed mechanism for the processing of pain intensity*

The present findings confirm in a fully quantitative manner that pain intensity is processed in a highly distributed fashion. This distributed mechanism encompasses a number of functionally distinct regions that all exhibit activation that is closely related to perceived stimulus intensity. These include brain areas typically thought to be important in *1*) somatosensory processing: SI, SII, and the posterior insular cortex; *2*) motor processing: cerebellum, putamen/globus pallidus, supplementary motor cortex, ventral premotor cortex, and the anterior cingulate cortex *3*) affective processing: anterior cingulate cortex and insular cortex; *4*) attentional processing: anterior cingulate cortex, primary somatosensory cortex, and the ventral premotor cortex; and *5*) autonomic function: anterior cingulate cortex and anterior insular cortex (Casey et al. 1994; Coghill et al. 1994; Craig et al. 1996; Derbyshire et al. 1997; Hsieh et al. 1996; Hutchison et al. 1999; Iadarola et al. 1998; Jones et al. 1991; Rainville et al. 1997; Talbot et al. 1991; Vogt et al. 1996).

Multiple, converging lines of evidence indicate that this distributed processing of pain intensity information rests on a parallel infrastructure of nociceptive transmission. First, anatomic evidence indicates that information about noxious stimulus intensity may be transmitted independently from thalamic sites to cerebral cortical areas such as SI, SII, the insular cortex, the anterior cingulate cortex, the supplementary motor cortex, and the ventral premotor cortex (Burton and Jones 1976; Burton and Sinclair 1996; Craig et al. 1995; Dum and Strick 1998; Friedman and Murray 1986; Mufson and Mesulam 1984; Vogt et al. 1987). Second, neurological

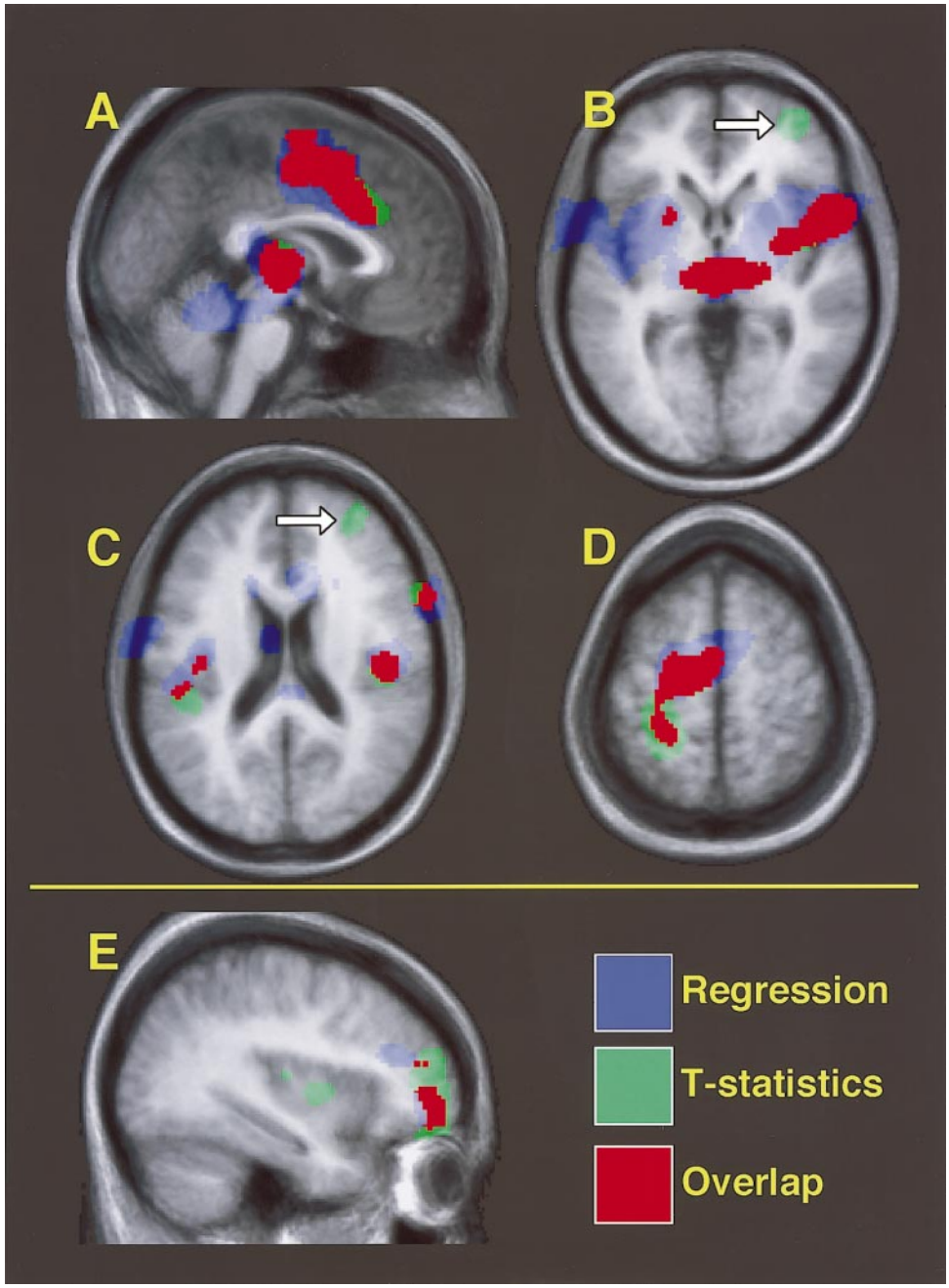


FIG. 4. Results from the multiple regression analysis overlap extensively with findings from a T-statistics comparison of 50°C and rest. Regression results in *A–D* are pain intensity dependent, whereas those in *E* are pain intensity independent. Arrows in *B* and *C* denote T-statistics results in areas that were not pain intensity related and did not overlap with the pain intensity–dependent regression results.

evidence confirms that these multiple thalamocortical pathways are functionally relevant. Discrete injuries of either SI, SII, anterior cingulate cortex, or the insula fail to abolish conscious awareness of pain intensity, although other aspects of processing may be disrupted somewhat. Thus serial transmission of nociceptive information through any one of these cerebral cortical areas is not obligatory for a conscious awareness of the intensity of a painful stimulus (Berthier et al. 1988; Davis et al. 1994; Greenspan and Winfield 1992; Knecht et al. 1996; White and Sweet 1968). Finally, the consistent monotonic increases in activation observed in the present study further suggests a parallel component of pain intensity processing in that intensity information is conserved across a functionally diverse set of brain regions, such as the thalamus, SI, SII, anterior cingulate cortex, supplementary motor cortex, insula, and the ventral premotor cortex. Electrophysiological evidence further confirms that responses to stimulus intensity are highly conserved throughout the neuraxis. Neurons in the spinal cord, various thalamic nuclei, primary somatosensory cortex, secondary somatosensory cortex, and anterior cingulate cortex all exhibit monotonic increases to increasing noxious stimulus intensities (Dong et al. 1994; Kenshalo et al. 1988; Robinson and Burton 1980; Sikes and Vogt 1992; Willis 1985).

Therefore cerebral cortical regions including SI, SII, anterior cingulate cortex, insula, and the premotor cortices, together with their subcortical connections, likely constitute a highly parallel, distributed mechanism that is utilized for pain intensity processing.

Although pain intensity processing has been classically thought to be confined to brain areas contralateral to stimulation, the present findings indicate that intensity information from a unilateral painful stimulus is processed in both cerebral cortical hemispheres (Fig. 2, Table 1). Bilateral pain intensity–dependent activations were identified in SII, the insular cortex, and the anterior cingulate cortex. Ipsilateral activation of these bilaterally responsive areas may support the ipsilateral cerebral cortical processing of pain that has been demonstrated in both hemispherectomized patients and in a split-brain subject (Bernier et al. 1997; Gardner 1933; Knecht et al. 1996; Marshall and Walker 1950; Stein et al. 1989; Walker 1943). Data from the present study confirm that bilateral processing of pain intensity occurs in normal subjects who have not experienced brain trauma. Furthermore, these bilateral areas may also be closely involved with the bilateral spread of pathological pain resulting from a unilateral injury (Livingston 1943; Mitchell 1897; Mitchell et al. 1864; Veldman and Goris 1996).

Thermal stimulation also produced predominantly ipsilateral activation of the right ventral premotor cortex of the frontal operculum (BA 44/BA 6). Of all brain regions examined, the ventral premotor cortex exhibited the most pronounced increases in activation as intensity ratings increased (Table 1, Fig. 2). Most neurons within this area have both tactile and visual receptive fields. The visual receptive fields, however, are organized in a manner related to the body surface and are spatially contiguous with the tactile receptive fields. As such, the ventral premotor cortex has been postulated to play an important role in spatial attentional processing and in encoding the locations of objects in peripersonal space (Fogassi et al. 1996; Graziano et al. 1994). Activation of such a spatial attention system in proportion to pain is not surprising given that increasingly painful stimuli become increasingly effective at attracting attention.

One previous investigation has examined brain activation evoked during graded pain by using laser stimulation designed to manipulate pain sensation into three categories (Derbyshire et al. 1997). Their findings differ substantially from those of the present study in that they did not detect pain category-related activation in the hand/arm area of SI, ipsilateral or contralateral areas of SII, the mid-cingulate cortex, the medial supplementary motor area (SMA), or the cerebellum. Data from that study were acquired on two substantially different types of PET instruments using varied amounts of laser energy to manipulate subjects' pain perceptions to a given level. Both factors may have introduced a significant amount of variability, minimizing their ability to detect pain category-related activation. In another difference from the present findings, Derbyshire et al. detected pain category-related activation in prefrontal areas in which we have demonstrated to be clearly not related to perceived pain intensity [both presently and in a subsequent investigation (Coghill et al. 1998a)]. These differences between our findings and those of Derbyshire et al. may result from significant differences in stimulation paradigms and/or their use of less stringent statistical criteria ($z = 2.33$) than the present investigation ($z = 3.09$ + spatial extent analysis).

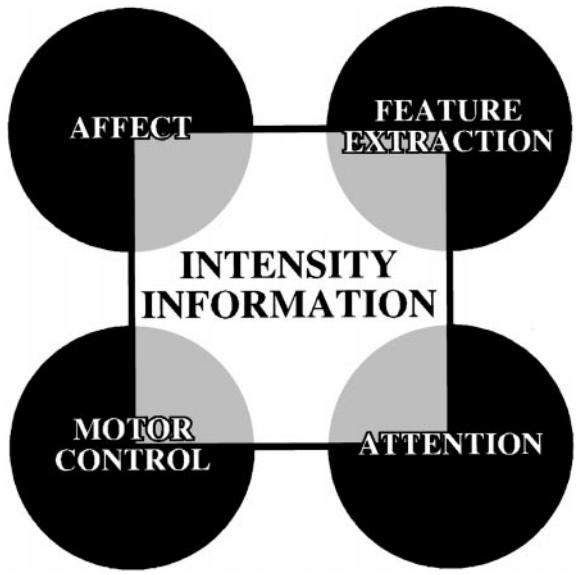


FIG. 5. Pain intensity information (square) is both a critical precursor and an integral component of other individual processes (circles) of the pain experience. Note that all of these aspects of pain are subject to significant modulation by top-down factors.

*Pain intensity–independent responses*

In addition to the distributed responses related to pain intensity, a second pattern of activity largely independent from pain intensity was also evident during painful and innocuous thermal stimulation. Two regions of the right (ipsilateral) prefrontal cortex thought to participate in spatial attention and memory were activated any time the stimulator was in contact with the subject (Table 2, Fig. 3) (Buckner et al. 1996; Fuster 1997). In the present study, subjects had been exposed to the thermal stimuli before the PET session and were required to formulate a psychophysical rating of pain intensity at the end of each scan. As such, subjects were faced with an episodic memory task, evaluating a stimulus in the context of previously experienced stimuli. The observation that the ventral prefrontal focus demonstrated a tendency to peak at 46°C, a temperature approximating pain threshold, further supports this possibility (Fig. 3). Evaluation of stimuli near threshold is generally more difficult than evaluation of frankly supra- or subthreshold stimuli and would be anticipated to place greater demands on brain networks involved in episodic memory, attention, and the cognitive evaluation of somatosensory stimuli. Such a role is further suggested by the observation that subjects with prefrontal lobotomies or leukectomies have severe disruption of their abilities to cognitively assess the meaning and implications of chronic pain. However, these subjects have normal or even lowered pain thresholds and retain their ability to experience both sensory and early affective components of pain (Barber 1959; Freeman and Watts 1948; Hardy et al. 1952; King et al. 1950). Thus the more caudally localized regions demonstrating pain intensity–related responses are sufficient to subserve basic elements of conscious awareness of pain intensity without involvement of the prefrontal cortex.

### *Pain intensity information as an integral component of other aspects of pain*

The widespread distribution of pain intensity–related activation observed in the present investigation indicates that many functionally distinct brain regions are capable of processing pain intensity–related information and can utilize this information for processes distinct from those associated with cognitive evaluation of features of a painful stimulus. Based on these results, we propose that intensity processing is both a critical precursor and an integral component of the many processes comprising the pain experience (Fig. 5). Such processes include cognitive evaluation of features of a painful stimulus (feature extraction), affect, attention, and motor control. This organization provides a neurophysiological basis for the high degree of covariance between discrete aspects of the pain experience (i.e., feature extraction, affective, attentional, motor components) and perceived pain intensity.

In conclusion, the demonstration that one aspect of sensory processing (pain intensity) is so highly distributed across a diverse array of functionally distinct regions is in sharp contrast to other sensory systems (i.e., visual system) in which afferent information undergoes marked changes as it is transmitted from one cerebral cortical area to the next. However, pain is one sensory experience essential for survival. Individuals born without the ability to perceive pain frequently die from injuries and infections they have never felt (Baxter and Olsezewski 1960). The distributed processing of pain intensity within the human brain ensures that this critical ability to detect tissue injury can be spared in the face of extensive CNS damage.

We thank S. Marrett, I. Gilron, and R. Caudle for helpful comments on this manuscript, the staff of the PET Section of the National Institutes of Health Clinical Center for smoothly run studies, and our subjects for their participation.

This research was supported by the intramural research program of the National Institute of Dental Research.

Address for reprint requests: R. C. Coghill, Dept. of Neurobiology and Anatomy, Wake Forest University School of Medicine, Winston-Salem, NC 27157-1010.

Received 29 March 1999; accepted in final form 17 June 1999.

## REFERENCES

BARBER, T. X. Toward a theory of pain: relief of chronic pain by prefrontal leucotomy, opiates, placebos, and hypnosis. *Psychol. Bull.* 56: 430–460, 1959.

BAXTER, D. W. AND OLSEZEWSKI, J. Congenital universal insensitivity to pain. *Brain* 83: 381–393, 1960.

BERNIER, J., BUSHNELL, M. C., PTITO, M., PTITO, A., AND MARCHAND, S. Touch, pain and temperature perception in hemispherectomized patients. *Soc. Neurosci. Abstr.* 23: 440, 1997.

BERTHIER, M., STARKSTEIN, S., AND LEIGUARDA, R. Asymbolia for pain: a sensory-limbic disconnection syndrome. *Ann. Neurol.* 24: 41–49, 1988.

BUCKNER, R. L., RAICHLE, M. E., MIEZIN, F. M., AND PETERSEN, S. E. Functional anatomic studies of memory retrieval for auditory words and visual pictures. *J. Neurosci.* 16: 6219–6235, 1996.

BURTON, H. AND JONES, E. G. The posterior thalamic region and its cortical projection in new world and old world monkeys. *J. Comp. Neurol.* 168: 249–302, 1976.

BURTON, H. AND SINCLAIR, R. Somatosensory cortex and tactile perceptions. In: *Pain and Touch,* edited by L. Kruger. San Diego, CA: Academic, 1996, p. 105–177.

BUSHNELL, M. C. AND DUNCAN, G. H. Sensory and affective aspects of pain perception: is medial thalamus restricted to emotional issues? *Exp. Brain Res.* 78: 415–418, 1989.

CASEY, K. L., MINOSHIMA, S., BERGER, K. L., KOEPPE, R. A., MORROW, T. J., AND FREY, K. A. Positron emission tomographic analysis of cerebral structures activated specifically by repetitive noxious heat stimuli. *J. Neurophysiol.* 71: 802–807, 1994.

CHMIELOWSKA, J., COGHILL, R. C., CARSON, R. E., ISHII, K., CHEN, R., HALLETT, M., AND HERSCOVITCH, P. Comparison of PET [15O]water studies with 6-min and 10-min interscan intervals: single subject and group analyses. *J. Cereb. Blood Flow Metab.* 18: 433–444, 1998.

COGHILL, R. C., GILRON, I., GUTIERREZ, C., AND IADAROLA, M. J. Hemispheric lateralization of somatosensory processing. *Soc. Neurosci. Abstr.* 28: 445.16, 1998a.

COGHILL, R. C. AND GRACELY, R. H. Validation of the combined numerical/verbal descriptor scale for pain. *Am. Pain Soc. Abstr.* 15: A86, 1996.

COGHILL, R. C., SANG, C. N., BERMAN, K. F., BENNETT, G. J., AND IADAROLA, M. J. Global cerebral blood flow decreases during pain. *J. Cereb. Blood Flow Metab.* 18: 141–147, 1998b.

COGHILL, R. C., TALBOT, J. D., MEYER, E., GJEDDE, A., EVANS, A. C., BUSHNELL, M. C., AND DUNCAN, G. H. Distributed processing of pain and vibration in the human brain. *J. Neurosci.* 14: 4095–4108, 1994.

COLLINS, D. L., NEELIN, P., PETERS, T. M., AND EVANS, A. C. Automatic 3-D intersubject registration of MR volumetric data in standardized Talairach space. *J. Comput. Assist. Tomogr.* 18: 192–205, 1994.

COURTNEY, S. M., PETIT, L., MAISOG, J. M., UNGERLEIDER, L. G., AND HAXBY, J. V. An area specialized for spatial working memory in human frontal cortex. *Science* 279: 1347–1351, 1998.

CRAIG, A. D., KROUT, K., AND ZHANG, E.-T. Cortical projections of VMpo, a specific pain and temperature relay in the primate thalamus. *Soc. Neurosci. Abstr.* 21: 456.8, 1995.

CRAIG, A. D., REIMAN, E. M., EVANS, A., AND BUSHNELL, M. C. Functional imaging of an illusion of pain. *Nature* 384: 258–260, 1996.

DAVIS, K. D., HUTCHISON, W. D., LOZANO, A. M., AND DOSTROVSKY, J. O. Altered pain and temperature perception following cingulotomy and capsulotomy in a patient with schizoaffective disorder. *Pain* 59: 189–199, 1994.

DERBYSHIRE, S.W.G., JONES, A.K.P., GYULAI, F., CLARK, S., TOWNSEND, D., AND FIRESTONE, L. L. Pain processing during three levels of noxious stimulation produces differential patterns of central activity. *Pain* 73: 431–445, 1997.

DONG, W. K., CHUDLER, E. H., SUGIYAMA, K., ROBERTS, V. J., AND HAYASHI, T. Somatosensory, multisensory, and task-related neurons in cortical area 7b (PF) of unanesthetized monkeys. *J. Neurophysiol.* 72: 542–564, 1994.

DUM, R. P. AND STRICK, P. L. Thalamic inputs to the lateral premotor areas and the primary motor cortex of the cebus monkey. *Soc. Neurosci. Abstr.* 28: 644.2, 1998.

FOGASSI, L., GALLESE, V., FADIGA, L., LUPPINO, G., MATELLI, M., AND RIZZOLATTI, G. Coding of peripersonal space in inferior premotor cortex (area F4). *J. Neurophysiol.* 76: 141–157, 1996.

FREEMAN, W. AND WATTS, J. W. Pain mechanisms and the frontal lobes: a study of prefrontal lobotomy for intractable pain. *Ann. Intern. Med.* 28: 747–754, 1948.

FRIEDMAN, D. P. AND MURRAY, E. A. Thalamic connectivity of the second somatosensory area and neighboring somatosensory fields of the lateral sulcus of the macaque. *J. Comp. Neurol.* 252: 348–373, 1986.

FRISTON, K. J., WORSLEY, K. J., FRACKOWIAK, R.S.J., MAZZIOTTA, J. C., AND EVANS, A. C. Assessing the significance of focal activations using their spatial extent. *Hum. Brain Map.* 1: 210–220, 1994.

FUSTER, J. M. *The Prefrontal Cortex.* Philadelphia, PA: Lippincott-Raven, 1997.

GARDNER, W. J. Removal of the right cerebral hemisphere for infiltrating glioma. *J. Am. Med. Assoc.* 101: 823–826, 1933.

GRAZIANO, M. S., YAP, G. S., AND GROSS, C. G. Coding of visual space by premotor neurons. *Science* 266: 1054–1057, 1994.

GREENSPAN, J. D. AND WINFIELD, J. A. Reversible pain and tactile deficits associated with a cerebral tumor compressing the posterior insula and parietal operculum. *Pain* 50: 29–39, 1992.

HARDY, J. D., WOLFF, H. G., AND GOODELL, H. *Pain Sensations and Reactions.* Baltimore, MD: Williams & Wilkins, 1952.

HSIEH, J. C., STAHLE-BACKDAHL, M., HAGERMARK, O., STONE-ELANDER, S., ROSENQUIST, G., AND INGVAR, M. Traumatic nociceptive pain activates the hypothalamus and the periaqueductal gray: a positron emission tomography study. *Pain* 64: 303–314, 1996.

HUTCHISON, W. D., DAVIS, K. D., LOZANO, A. M., TASKER, R. R., AND DOSTROVSKY, J. O. Pain-related neurons in the human cingulate cortex. *Nature Neurosci.* 2: 403–405, 1999.

IADAROLA, M. J., BERMAN, K. F., ZEFFIRO, T. A., BYAS-SMITH, M. G., GRACELY, R. H., MAX, M. B., AND BENNETT, G. J. Neural activation during acute capsaicin-evoked pain and allodynia assessed with positron emission tomography. *Brain* 121: 931–947, 1998.

JONES, A. K., BROWN, W. D., FRISTON, K. J., QI, L. Y., AND FRACKOWIAK, R. S. Cortical and subcortical localization of response to pain in man using positron emission tomography. *Proc. R. Soc. Lond. B Biol. Sci.* 244: 39–44, 1991.

KENSHALO, D. R., JR., CHUDLER, E. H., ANTON, F., AND DUBNER, R. SI nociceptive neurons participate in the encoding process by which monkeys perceive the intensity of noxious thermal stimulation. *Brain Res.* 454: 378–382, 1988.

KING, H. E., CLAUSEN, J., AND SCARFF, J. E. Cutaneous thresholds for pain before and after unilateral prefrontal lobotomy. *J. Nerv. Ment. Dis.* 112: 93–96, 1950.

KNECHT, S., KUNESCH, E., AND SCHNITZLER, A. Parallel and serial processing of haptic information in man: effects of parietal lesions on sensorimotor hand function. *Neuropsychologia* 34: 669–687, 1996.

LIVINGSTON, W. K. *Pain Mechanisms.* New York: MacMillan, 1943.

MARSHALL, C. AND WALKER, A. E. The electroencephalographic changes after hemispherectomy in man. *Electroencephalogr. Clin. Neurophysiol.* 2: 147–156, 1950.

MELZACK, R. AND CASEY, K. L. Sensory, motivational, and central control determinants of pain. In: *The Skin Senses*, edited by D. R. Kenshalo. Springfield, IL: Thomas, 1968, p. 423–435.

MITCHELL, S. W. Clinical Lessons on Nervous Diseases. Philadelphia, PA: Lea Brothers, 1897.

MITCHELL, S. W., MOREHOUSE, G. R., AND KEEN, W. W. *Gunshot Wounds and Other Injuries of Nerves.* Philadelphia, PA: Lippincott, 1864.

MUFSON, E. J. AND MESULAM, M. M. Thalamic connections of the insula in the rhesus monkey and comments on the paralimbic connectivity of the medial pulvinar nucleus. *J. Comp. Neurol.* 227: 109–120, 1984.

PETIT, L., COURTNEY, S. M., UNGERLEIDER, L. G., AND HAXBY, J. V. Sustained activity in the medial wall during working memory delays. *J. Neurosci.* 18: 9429–9437, 1998.

RAINVILLE, P., DUNCAN, G. H., PRICE, D. D., CARRIER, B., AND BUSHNELL, M. C. Pain affect encoded in human anterior cingulate but not somatosensory cortex. *Science* 277: 968–971, 1997.

RENCHER, A. C. *Methods of Multivariate Analysis.* New York: Wiley, 1995.

ROBINSON, C. J. AND BURTON, H. Somatic submodality distribution within the second somatosensory (SII), 7b, retroinsular, postauditory, and granular insular areas of *M. fascicularis. J. Comp. Neurol.* 192: 93–108, 1980.

SIKES, R. W. AND VOGT, B. A. Nociceptive neurons in area 24 of rabbit cingulate cortex. *J. Neurophysiol.* 68: 1720–1732, 1992.

STEIN, B. E., PRICE, D. D., AND GAZZANIGA, M. S. Pain perception in a man with total corpus callosum transection. *Pain* 38: 51–56, 1989.

TALBOT, J. D., MARRETT, S., EVANS, A. C., MEYER, E., BUSHNELL, M. C., AND DUNCAN, G. H. Multiple representations of pain in human cerebral cortex. *Science* 251: 1355–1358, 1991.

VELDMAN, P.H.J.M. AND GORIS, R. J. Multiple reflex sympathetic dystrophy. Which patients are at risk for developing a recurrence of reflex sympathetic dystrophy in the same or another limb. *Pain* 64: 463–466, 1996.

VOGT, B. A., DERBYSHIRE, S., AND JONES, A. K. Pain processing in four regions of human cingulate cortex localized with co-registered PET and MR imaging. *Eur. J. Neurosci.* 8: 1461–1473, 1996.

VOGT, B. A., PANDYA, D. N., AND ROSENE, D. L. Cingulate cortex of the rhesus monkey. I. Cytoarchitecture and thalamic afferents. *J. Comp. Neurol.* 262: 256–270, 1987.

WALKER, A. E. Central representation of pain. *Res. Publ. Ass. Nerv. Ment. Dis.* 23: 63–85, 1943.

WHITE, J. C. AND SWEET, W. H. *Pain and the Neurosurgeon: A Forty Year Experience.* Springfield, IL: Thomas, 1968.

WILLIS, W. D. *The Pain System.* New York: Karger, 1985.

WOODS, R. P., CHERRY, S. R., AND MAZZIOTTA, J. C. Rapid automated algorithm for aligning and reslicing PET images. *J. Comput. Assist. Tomogr.* 16: 620–633, 1992.

WOODS, R. P., MAZZIOTTA, J. C., AND CHERRY, S. R. MRI-PET registration with automated algorithm. *J. Comput. Assist. Tomogr.* 17: 536–546, 1993.