Cerebral Processing of Acute Skin and Muscle Pain in Humans

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Svensson, Peter, Satoshi Minoshima, Ahmad Beydoun, Thomas J. Morrow, and Kenneth L. Casey. Cerebral processing of acute skin and muscle pain in humans. J. Neurophysiol. 78: 450–460, 1997. The human cerebral processing of noxious input from skin and muscle was compared with the use of positron emission tomography with intravenous H215O to detect changes in regional cerebral blood flow (rCBF) as an indicator of neuronal activity. During each of eight scans, 11 normal subjects rated the intensity of stimuli delivered to the nondominant (left) forearm on a scale ranging from 0 to 100 with 70 as pain threshold. Cutaneous pain was produced with a high-energy CO2 laser stimulator. Muscle pain was elicited with high-intensity intramuscular electrical stimulation. The mean ratings of perceived intensity for innocuous and noxious stimulation were 32.6 ± 4.5 (SE) and 78.4 ± 1.7 for cutaneous stimulation and 15.4 ± 4.2 and 73.5 ± 1.4 for intramuscular stimulation. The pain intensity ratings and the differences between noxious and innocuous ratings were similar for cutaneous and intramuscular stimuli (P > 0.05).

After stereotactic registration, statistical pixel-by-pixel summation (Z score) and volumes-of-interest (VOI) analyses of subtraction images were performed. Significant increases in rCBF to both noxious cutaneous and intramuscular stimulation were found in the contralateral secondary somatosensory cortex (SII) and inferior parietal lobule [Brodmann area (BA) 40]. Comparable levels of rCBF increase were found in the contralateral anterior insular cortex, thalamus, and ipsilateral cerebellum. Noxious cutaneous stimulation caused significant activation in the contralateral lateral prefrontal cortex (BA 10/46) and ipsilateral premotor cortex (BA 4/6). Noxious intramuscular stimulation evoked rCBF increases in the contralateral anterior cingulate cortex (BA 24) and subessential responses in the contralateral primary sensorimotor cortex (MI/SI) and lenticular nuclei. These activated cerebral structures may represent those recruited early in nociceptive processing because both forms of stimuli were near pain threshold. Correlation analyses showed a negative relationship between changes in rCBF for thalamus and MI/SI for cutaneous stimulation, and positive relationships between thalamus and anterior insula for both stimulus modalities. Direct statistical comparisons between innocuous cutaneous and intramuscular stimulation with the use of Z scores and VOI analyses showed no reliable differences between these two forms of noxious stimulation, indicating a substantial overlap in brain activation pattern. The comparison of noxious cutaneous and intramuscular stimulation indicated more activation in the premotor cortex, SII, and prefrontal cortex with cutaneous stimulation, but these differences did not reach statistical significance. The similar cerebral activation patterns suggest that the perceived differences between acute skin and muscle pain are mediated by differences in the intensity and temporospatial pattern of neuronal activity within similar sets of forebrain structures.

INTRODUCTION

The cerebral processing of cutaneous pain in humans has recently been investigated with positron emission tomography (PET) technique (Casey et al. 1994, 1996; Coghill et al. 1994; Derbyshire et al. 1994; Hsieh et al. 1996; Jones et al. 1991; Talbot et al. 1991). These studies have shown that the contralateral primary sensorimotor cortex (MI/SI) and secondary somatosensory cortex (SII), anterior insular cortex, anterior cingulate cortex, and thalamus participate in the processing of painful cutaneous stimuli. In addition, the prefrontal cortex [Brodmann area (BA) 10/46], parietal lobe (BA 40), lenticular nucleus, premotor cortex, cerebellar vermis, supplementary motor area, and dorsal midbrain have shown pain-related activation in one or more of these studies. In the study by Coghill et al. (1994), the cerebral processing of cutaneous pain was compared with that of vibrotactile stimulation, and it was found that only the anterior insula was significantly more activated with painful stimulation. This suggests that there is a substantial overlap in the cerebral processing of noxious and innocuous stimuli, but also that some cerebral structures may participate uniquely in pain processing (Coghill et al. 1994). Indeed, the cerebral processing of cutaneous innocuous warmth stimuli and noxious heat stimuli has recently been shown to cause distinctly different synaptic activation patterns (Casey et al. 1996). However, in comparing the regional cerebral blood flow (rCBF) changes induced by cutaneous contact heat pain with those induced by deep cold pain, it was found that only the anterior insula was significantly more activated with painful stimulation.

There are no available human data for the cerebral processing of pain from muscles (Mense 1993). Although several techniques can be used to induce experimental muscle pain in humans (Svensson and Arendt-Nielsen 1995), PET activation studies require stimulus paradigms in which the onset and offset of the stimulus can be adequately controlled. We therefore used high-frequency (20-Hz) intramuscular electrical stimulation for selective activation of muscle afferents. For activation of cutaneous nociceptive afferents, a
high-energy CO₂ laser stimulator was used (Bromm et al. 1984; Treede et al. 1995). This device has been used extensively in the investigation of cutaneous nociception, including psychophysical and electrophysiological studies (Beydoun et al. 1993; Bromm and Treede 1991), but not in PET studies.

We reasoned that similar, near-threshold perceptions of pain intensity caused by different stimulus modalities would maximize the possibility of identifying common cerebral structures with the lowest threshold for nociceptive activation. Differences in activation patterns would then best be explained by physiological differences between the noxious stimuli.

**METHODS**

**Subjects**

Eleven healthy males (30.4 ± 3.5 yr of age, mean ± SE) without pain or neurological diseases participated in the study. Written informed consent was obtained before study inclusion in accord with the guidelines put forward by the Veterans Affairs Medical Center and by the Institutional Review Board for Human Studies at the University of Michigan. All subjects had refrained from smoking and from the consumption of alcohol or caffeine for the 24-h period before the study. None of the subjects were taking analgesics or centrally acting drugs.

**Psychophysics**

The detection threshold was defined as the lowest stimulus intensity required for the subject to report a sensation. The pain threshold was defined as the lowest stimulus intensity required for the subject to report a sensation of pain "just barely painful." Both thresholds were determined with the methods of limits with the use of three ascending and three descending series of stimulation. The pain threshold was anchored as 70 on a 100-point visual scale where 0 denoted "no sensation" and 100 denoted "nearly intolerable pain" (Casey et al. 1993). This intensity scale has also been used in other PET studies (Casey et al. 1994, 1996) and was chosen because it allows scores of both innocuous and noxious stimulus intensities and approximately accommodates the different intensity ranges for innocuous and noxious heat stimuli (30–45° C vs. 45–52°C). All subjects had received training in the use of this rating scale before the PET study.

**Stimulation procedures**

A CO₂ surgical laser (wavelength 10.6 μm, Model 20, Directed Energy) was used for radiant heat stimulation of the skin (Petrovaara et al. 1988). The pulse duration was 50 ms and the beam diameter was adjusted to 10 mm (79 mm²). A pulse generator triggered the laser at 0.5 Hz. The hairy skin overlying the left brachioradialis muscle 5 cm below the elbow (C7 dermatome) was stimulated. To avoid sensitization, the beam location was moved for each stimulus.

An electrical stimulator (Grass S88, Cambridge, MA) with a constant current unit (Model CCU 1A) was used to generate 50-μs square-wave pulses at a frequency of 20 Hz. The electric pulses were applied to the left brachioradialis muscle of the forearm via two disposable 20-mm-long sensory needle electrodes (13R27, 28G; Dantec, Copenhagen, Denmark). The needle electrodes were uninsulated 3 mm at the tip and were inserted 10 mm apart along the muscle fiber direction (Vecchiet et al. 1993). This stimulus frequency caused a steady muscle contraction without any visible movements.

For all subjects two stimulus intensity levels were identified: a level just above the detection threshold and a level just above the pain threshold. The stimulation started 40 s before the start of the scan and continued throughout the 60-s scanning period. The four different stimulus conditions were alternated and repeated twice for each subject; the stimulation sequence was alternated between subjects.

**PET**

A Siemens PET Scanner (ECAT, CTI 931/08-12) was used for data acquisition. The subjects were positioned in the PET scanner parallel to the canthomeatal line with their eyes closed. Before the emission scans, a transmission scan with the use of ⁶⁸Ga ring sources was obtained for attenuation corrections. The subjects then received a total of eight injections of 2–3 ml 50-mCi H₂¹⁵O. The bolus injections in the right antecubital vein were administered over 10 s by a computer-controlled pump. Approximately 12 min elapsed between repeated scans. Each scan provided 15 slices with in-plane resolution of 7 ± 8 mm at full-width half-maximum (FWHM), and axial resolution of 7–8 mm at FWHM. An on-line computer connected to the PET gantry monitored the arrival of the injected tracer in the brain. Image acquisition was started 5 s after arrival and continued for 60 s. A Pranzén filter with cutoff frequency of 0.45 cycles per projection element was used to construct the obtained images. Subsequent analyses were based on the raw cumulative counts from the scans. For each subject, the PET images from the two repetitions of the same condition were averaged. These PET images in a subject were then coregistered with each other (head motion correction) and realigned to a standard stereotactic system (Talairach and Tournoux 1988) by automated procedures described previously (Minoshima et al. 1992–1994). Differences in brain anatomy were minimized by an automated method that incorporated a nonlinear thin plate warping algorithm (Bookstein 1989) as adapted for PET brain images by Minoshima et al. (1994). Image pixel intensities were normalized to global cerebral activity with the use of a linear proportional model to remove baseline differences in cerebral blood flow among scans and subjects (Fox and Raichle 1984). Statistical image analyses and volumes-of-interest (VOI) analyses were performed on those transformed and normalized image sets. The former analysis is based on a pixel-by-pixel analysis without a priori regional hypothesis and thus examines all structures and patterns of brain activation caused by the processing of pain. In this analysis, images were further smoothed with a three-dimensional Gaussian filter to improve signal-to-noise ratio (Friston et al. 1991). Subsequently, the estimated smoothness in the final subtraction images was 15 mm FWHM. Areas of significant activation were determined with the use of a statistical model based on a random Gaussian field model (Worsley et al. 1992). A statistical summation analysis with adjustment for multiple comparisons of intercorrelated pixels was performed by identifying voxels (estimated resels = 725) with increased rCBF compared with the average noise variance computed across all voxels (pooled variance) (Worsley et al. 1992). Because subtraction images were averaged across multiple subjects, and the average noise variance was computed from a large number of pixels, the resultant statistical maps can be well approximated by a standard Gaussian distribution (Worsley et al. 1992). Thus we expressed significance of activation with the use of Z scores. The critical level of significance was set at Z = 4.0 (Coghill et al. 1994).

The VOI analysis focused on a priori hypotheses that the following structures would be activated by noxious stimuli (Casey et al. 1994, 1996; Coghill et al. 1994; Derbyshire et al. 1994; Jones et al. 1991; Talbot et al. 1991): the contralateral MI/SI, SII, anterior insula, anterior cingulate cortex, thalamus, prefrontal cortex, lentic-
ular nucleus, premotor cortex, and cerebellum. These VOIs are in accord with the VOI defined by Casey et al. (1996). In addition, structures found to be activated by Z score analysis for one type of noxious stimulation (cutaneous or intramuscular) were included as a posteriori VOI only for the other type of noxious stimulation. The size and shape of each VOI was determined within each of the above structures by employing a method similar to that described by Burton et al. (1993). Voxels showing significant peak increases in rCBF between comparison conditions were identified within each of the brain structures of interest. The volume defined by these voxels was then progressively expanded in three dimensions to include only those contiguous voxels that showed rCBF increases that were significantly greater than the global mean change ($P < 0.05$, uncorrected for multiple comparisons). For purposes of comparison, the responses within each VOI are expressed as the average increase in rCBF within the volume of that VOI. If a peak was not present in a selected region, a VOI template derived from previous PET pain activation studies in our laboratory was applied to the images (Casey et al. 1996). To determine the statistical significance of rCBF increases, a paired $t$-statistic was computed for each VOI from the average percentage increase in cerebral blood flow across all subjects. Levels of significance were established based on the Bonferroni correction for multiple comparisons among VOI. Accordingly, the critical level of significance was set at $P = 0.008$ (critical $t_{0.05} = 2.90$, 1-tailed test) for cutaneous stimulation and at $P = 0.006$ (critical $t_{0.05} = 3.14$) for intramuscular stimulation to determine the presence of significant average increases in rCBF within each VOI.

In addition to the described analyses, we also performed direct comparisons of innocuous cutaneous and intramuscular stimulation and noxious cutaneous and intramuscular stimulation with the use of Z score and VOI analyses. The VOI included the nine a priori structures, and the inferior parietal cortex and inferior parietal lobule on a posterior results. The critical level of significance was set at $P = 0.005$ (critical $t_{0.05} = 4.10$, 2-tailed test) because there was no a priori hypothesis that cutaneous stimulation would cause larger or smaller rCBF changes in any given region than intramuscular stimulation.

To investigate the interconnectivity between pain-related cerebral structures a post hoc correlation analysis of the rCBF changes was performed. The following five cortical structures and the thalamus were included in this analysis because neuroanatomic studies have shown that each structure receives direct projections from somatosensory thalamic relay nuclei: the contralateral MI/SI, SII, anterior insular cortex, anterior cingulate cortex, and inferior parietal lobule (Craig et al. 1994; Friedman and Murray 1986; Robinson and Burton 1980; Schmaamhmann and Pandya 1990; Yasui et al. 1988). The anatomic studies have also shown extensive interconnectivity among these cortical structures.

Statistics

Two-way analysis of variance with repeated measures was used for description of psychophysical data. Levels of statistical significance were adjusted for multiple comparisons with the use of the Bonferroni correction. Interconnectivity between the selected VOIs was tested with use of Pearson product-moment correlation in a 6 x 6 table. Significance was accepted at $P < 0.05$. Because of technical problems during one PET scan, data from one subject with intramuscular electrical stimulation was not included in the final analysis.

RESULTS

Psychophysics

The cutaneous CO$_2$ laser stimuli and intramuscular electrical stimuli were perceived differently. At innocuous intensities, the cutaneous stimuli were described as warmth or very faint pricking sensations and at noxious intensities as distinct stinging, pricking sensations followed by a burning sensation from the skin. In contrast, at innocuous intensities the intramuscular stimuli caused a faint vibratory, pulling sensation in the muscle that, at noxious intensities, was replaced by a deep and diffuse aching pain around the site of the stimulation electrodes that occasionally spread to the wrist. Intramuscular stimulation at both intensities caused a steady contraction of the muscle without any visible movements. The mean innocuous and noxious intensities used for CO$_2$ laser stimulation were 4.2 ± 0.2 W and 16.5 ± 0.8 W, respectively; the intensities used for intramuscular electrical stimulation were 1.9 ± 0.6 mA and 10.1 ± 2.3 mA, respectively.

The ratings of perceived intensity were significantly dependent on the stimulus intensity [$F(1,9) = 163.19, P < 0.0001$] and on stimulus modality [$F(1,9) = 22.72, P = 0.001$], with a significant interaction between the factors [$F(1,9) = 6.25, P = 0.0339$; Fig. 1]. The ratings for innocuous cutaneous stimuli were significantly higher than the ratings for innocuous intramuscular stimulation ($P < 0.05$). However, cutaneous and intramuscular stimuli showed similar ratings, near pain threshold, for noxious intensities and for differences between noxious and innocuous ratings ($P > 0.05$).

PET

The results from the statistical analyses of rCBF are shown in Table 1. Table 2 provides the stereotactic coordinates of the rCBF peak voxels in the Talairach space. The spatial distribution of the peaks is shown in Figs. 2 and 3. Each of the regions included in the VOI analysis represented a mean of 9.4 ± 1.3 ml brain tissue. Significant increases in rCBF to noxious cutaneous stimulation were found in contralateral SII, anterior insular cortex, thalamus, lateral prefrontal cortex (BA 10/46), inferior parietal lobule (BA 40), and ipsilateral premotor cortex (BA 4/6). Noxious intramuscular stimulation caused significant increases in rCBF in the contralateral SII, anterior cingulate cortex (BA 24), inferior parietal lobule (BA 40), and ipsilateral cerebellum. A subsignificant activation in contralateral MI/SI (BA 4), anterior insular cortex, thalamus, and lenticular nucleus was also observed for intramuscular stimulation. For both
forms of stimuli, a significant decrease in rCBF was observed in the primary and secondary visual cortex (Fig. 4).

The results of the correlation analysis are presented in Table 3. For both cutaneous and intramuscular stimulation there was a significant positive correlation between rCBF increases in the anterior insular cortex and the thalamus (r = 0.792 and r = 0.806, respectively). For cutaneous stimulation there was a significant negative correlation between rCBF changes in MI/SI and the thalamus (r = −0.704) and a positive correlation between the inferior parietal lobule and anterior cingulate cortex (r = 0.691) and between the anterior insular cortex and SII (r = 0.798). Finally, for intramuscular stimulation there was a significant positive correlation between rCBF increases in the anterior insular cortex and the inferior parietal lobule (r = 0.831) and a negative correlation between MI/SI and the inferior parietal lobule (r = −0.639).

In Table 4 the results of the direct comparison of innocuous cutaneous and intramuscular stimulation and noxious cutaneous and intramuscular stimulation are given. There was a complete overlap between the brain activation patterns for innocuous stimulation with the use of both the Z score and VOI analyses. The comparison of noxious cutaneous and intramuscular stimulation also failed to produce a significant Z score (>4). The greatest Z score was 3.12, with a peak located in the dorsal lateral posterior part of thalamus. The VOI analysis revealed that the ipsilateral premotor cortex and, to a lesser degree, the contralateral prefrontal cortex and SII approached the levels of corrected significance indicating more activation in these regions with noxious cutaneous stimulation (Table 4).

**DISCUSSION**

**Comparison of muscle and skin pain**

A comparison of the processing of noxious input from the skin and muscle to the forebrain has not previously been reported in humans. The present study shows multiple distinct cerebral activation foci for these two different stimuli at near pain intensity threshold. The structures with significant rCBF increases in this study may have the lowest threshold for responses to nociceptive activity, because stimulation was near pain intensity threshold in both conditions. All the structures have been shown to be activated in previous PET pain studies (Casey et al. 1994, 1996; Coghill et al. 1994; Derbyshire et al. 1994; Hsieh et al. 1995, 1996; Jones et al. 1991; Talbot et al. 1991). A statistical comparison of the cerebral activation patterns detected no reliable differences between these two forms of noxious stimulation. Overall, both noxious cutaneous and intramuscular stimulation caused significant rCBF increases in the contralateral SII and inferior parietal lobule (BA 40). In addition, comparable levels of rCBF increases were found in the contralateral anterior insular cortex, thalamus, and ipsilateral cerebellum. Both forms of stimulation also caused a significant decrease in rCBF in the occipital lobe.

An overlap between the cerebral processing of skin and muscle pain would be expected because there is a substantial convergence of nociceptive afferents from deep tissues and from skin onto wide-dynamic-range neurons in the spinal cord (Foreman et al. 1977; Mense 1993; Sessle 1995). Furthermore, Berkley and Hubscher (1995) have recently provided evidence in rats that different forms of stimuli such as visceral noxious and cutaneous innocuous touch stimuli converge onto common neurons at higher brain centers. Therefore it is highly likely that skin and muscle pain share some common patterns of neuronal activity within the forebrain.
brain. Analysis of the psychophysical data showed significantly higher ratings of innocuous cutaneous stimulation than of intramuscular stimulation; however, the direct comparison of these two innocuous conditions showed a complete overlap in the brain activation pattern. Thus the small difference in perceived stimulus intensity and the temporal difference between the phasic cutaneous and the tonic intramuscular stimulation could not be detected by the present PET technique.

The direct comparison of noxious cutaneous and intramuscular stimulation also showed a substantial overlap; however, the ipsilateral premotor cortex and to a lesser degree the contralateral prefrontal cortex and SII tended to be more activated with the cutaneous stimuli and the anterior cingulate cortex was more responsive to the intramuscular stimulation (Table 4). These differences are also apparent when the rCBF changes for cutaneous and intramuscular stimulation are compared in Table 1. The perceived intensity of the noxious cutaneous and intramuscular stimuli was identical and the difference between noxious and innocuous ratings was also similar. Thus the observed differences in cerebral activation patterns are most likely due to the type and origin of activated fibers. The processing of skin and

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**FIG. 2.** Color-coded statistical surface maps of regions with increased regional cerebral blood flow (rCBF) during noxious cutaneous and intramuscular stimulation. Maps are superimposed on a brain magnetic resonance image (MRI) of a single subject transformed onto the stereotactic coordinates of the human brain atlas used in this study. Lateral (LAT) view of right (RT) and left (LT) hemispheres and medial (MED) view at midsagittal plan. Stimulation was performed on left arm. Color bar: Z scores (Z > 4.0 is considered significant).

**FIG. 3.** Color-coded statistical maps of regions with increased rCBF. Maps are superimposed on horizontal MRI slices at indicated levels above intercommissural line. PA, parietal cortex; SII, secondary somatosensory cortex; PF, prefrontal cortex; INS, insula; PM, premotor cortex; TH, thalamus; ACC, anterior cingulate cortex; LN, lenticular nucleus.
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FIG. 4. Color-coded statistical surface maps of the regions with decreased rCBF. Medial view of right hemispheres. For further explanation see Fig. 2. Occipital lobe shows significantly decreased rCBF for both forms of stimulation.

Muscle pain has been shown to involve different mechanisms at the peripheral and at the spinal cord level (Dubner 1995; Mense 1993; Sessle 1995). In a review of the topic, for example, Mense (1993) cites evidence for differences in the spinal termination and supraspinal inhibition of nociceptive afferents from muscle as compared with those from the skin. A comparison of somatosensory potentials evoked by innocuous stimulation of cutaneous and muscle afferents has also suggested differences in the strength of projection and/or sites of projection in the pericentral cortex (Gandevia et al. 1984).

SII

SII has been shown to be activated by painful cutaneous contact heat pain (Casey et al. 1994, 1996; Coghill et al. 1994; Talbot et al. 1991), cold pain (Casey et al. 1996),

<p>| TABLE 3. Pearson product-moment correlation between rCBF in six selected VOI |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>SII</th>
<th>Anterior Insula</th>
<th>Anterior Cingulate</th>
<th>Thalamus</th>
<th>Inferior Parietal</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Cutaneous laser (n = 11)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MI/SI</td>
<td>-0.328</td>
<td>-0.432</td>
<td>-0.002</td>
<td>-0.704*</td>
</tr>
<tr>
<td></td>
<td>P = 0.324</td>
<td>P = 0.184</td>
<td>P = 0.993</td>
<td>P = 0.016</td>
</tr>
<tr>
<td>SII</td>
<td>0.798*</td>
<td>0.259</td>
<td>0.410</td>
<td>0.217</td>
</tr>
<tr>
<td></td>
<td>P = 0.003</td>
<td>P = 0.442</td>
<td>P = 0.210</td>
<td>P = 0.556</td>
</tr>
<tr>
<td>Anterior insula</td>
<td>0.252</td>
<td>0.792*</td>
<td>0.200</td>
<td></td>
</tr>
<tr>
<td>Anterior cingulate</td>
<td>P = 0.454</td>
<td>P = 0.003</td>
<td>P = 0.556</td>
<td></td>
</tr>
<tr>
<td>Thalamus</td>
<td>0.225</td>
<td>0.691*</td>
<td>0.143</td>
<td>P = 0.019</td>
</tr>
<tr>
<td></td>
<td></td>
<td>P = 0.506</td>
<td></td>
<td>P = 0.675</td>
</tr>
<tr>
<td>B. Intramuscular electrical (n = 10)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MI/SI</td>
<td>-0.433</td>
<td>-0.519</td>
<td>-0.206</td>
<td>-0.407</td>
</tr>
<tr>
<td></td>
<td>P = 0.211</td>
<td>P = 0.125</td>
<td>P = 0.568</td>
<td>P = 0.243</td>
</tr>
<tr>
<td>SII</td>
<td>0.028</td>
<td>-0.402</td>
<td>-0.086</td>
<td>0.371</td>
</tr>
<tr>
<td></td>
<td>P = 0.994</td>
<td>P = 0.249</td>
<td>P = 0.813</td>
<td>P = 0.292</td>
</tr>
<tr>
<td>Anterior insula</td>
<td>0.245</td>
<td>0.806*</td>
<td>0.831*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>P = 0.495</td>
<td>P = 0.005</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior cingulate</td>
<td>0.349</td>
<td>0.327</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thalamus</td>
<td></td>
<td>P = 0.323</td>
<td></td>
<td>P = 0.356</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>P = 0.525</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>P = 0.119</td>
</tr>
</tbody>
</table>

All regions are contralateral to the stimulated side. For abbreviations, see Tables 1 and 2. * P < 0.05.
TABLE 4. Mean changes in rCBF and t-statistics for VOI analyses

<table>
<thead>
<tr>
<th>VOI</th>
<th>Innocuous (Cutaneous-Intramuscular)</th>
<th>Noxious (Cutaneous-Intramuscular)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contralateral</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MI/SI (BA 4)</td>
<td>$0.3 \pm 1.9^*$</td>
<td>$-1.1 \pm 1.4^*$</td>
</tr>
<tr>
<td>$t = 0.14$</td>
<td>$t = -0.75$</td>
<td></td>
</tr>
<tr>
<td>SII</td>
<td>$1.0 \pm 0.9^*$</td>
<td>$1.8 \pm 0.7^*$</td>
</tr>
<tr>
<td>$t = 1.14$</td>
<td>$t = 2.89$</td>
<td></td>
</tr>
<tr>
<td>Anterior insula</td>
<td>$-0.4 \pm 1.8^*$</td>
<td>$1.1 \pm 1.6^*$</td>
</tr>
<tr>
<td>$t = -0.23$</td>
<td>$t = 0.74$</td>
<td></td>
</tr>
<tr>
<td>Anterior cingulate (BA 24)</td>
<td>$-0.7 \pm 0.8^*$</td>
<td>$-3.2 \pm 1.2^*$</td>
</tr>
<tr>
<td>$t = -0.08$</td>
<td>$t = -2.6$</td>
<td></td>
</tr>
<tr>
<td>Thalamus</td>
<td>$-1.2 \pm 1.9^*$</td>
<td>$1.2 \pm 2.3^*$</td>
</tr>
<tr>
<td>$t = -0.67$</td>
<td>$t = 0.52$</td>
<td></td>
</tr>
<tr>
<td>Prefrontal (BA 10/46)</td>
<td>$-1.4 \pm 0.9^*$</td>
<td>$2.7 \pm 1.0^*$</td>
</tr>
<tr>
<td>$t = 0.14$</td>
<td>$t = 2.67$</td>
<td></td>
</tr>
<tr>
<td>Inferior parietal (BA 40)</td>
<td>$1.4 \pm 1.1^*$</td>
<td>$-1.2 \pm 1.5^*$</td>
</tr>
<tr>
<td>$t = 1.40$</td>
<td>$t = -0.78$</td>
<td></td>
</tr>
<tr>
<td>Lenticular nucleus</td>
<td>$2.2 \pm 1.6^*$</td>
<td>$-0.6 \pm 0.9^*$</td>
</tr>
<tr>
<td>$t = 1.42$</td>
<td>$t = -0.61$</td>
<td></td>
</tr>
<tr>
<td>Ipsilateral</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Premotor cortex (BA 4/6)</td>
<td>$1.8 \pm 1.3^*$</td>
<td>$3.6 \pm 1.0^*$</td>
</tr>
<tr>
<td>$t = 1.14$</td>
<td>$t = 3.44$</td>
<td></td>
</tr>
<tr>
<td>Cerebellum</td>
<td>$-0.3 \pm 0.9^*$</td>
<td>$3.4 \pm 1.4^*$</td>
</tr>
<tr>
<td>$t = -0.31$</td>
<td>$t = 2.36$</td>
<td></td>
</tr>
</tbody>
</table>

Values for changes in rCBF (%) are means ± SE. No regions reached the levels of significance for Z score analysis ($Z > 4.0$) or the Bonferroni corrected t-statistics ($t_b = 4.10$). For abbreviations, see Tables 1 and 2.

* Template from Casey et al. (1996).
† Cutaneous template (see Table 2).
‡ Intramuscular template.

The contralateral inferior parietal lobule has not previously been found to be activated during acute noxious stimulation. However, Derbyshire et al. (1994) reported an increase in rCBF in BA 40 ipsilateral to the side of noxious cutaneous heat stimulation in normal subjects. Furthermore, Hsieh et al. (1995) demonstrated a significant bilateral activation of this region in patients with ongoing neuropathic pain. Lesions in BA 40, which is strongly linked to associative functions with intracerebral connections to BAs 18, 19, and 22 and association bundles to the temporal and frontal lobes, have been shown to cause an acute impairment in discrimination and sensation of pain (Bassetti et al. 1993). Furthermore, there is evidence of direct connections between medial thalamic nuclei and SII and the rostral inferior parietal lobule (Schmahmann and Pandya 1990). A disruption of these connections has been suggested as the cause of spontaneous pain in parietal pseudothalamic pain syndrome (Schmahmann and Leifer 1992). Thus several lines of evidence suggest an important role of the inferior parietal lobule in the processing of pain (Dong et al. 1994, 1996). It has been proposed that this region participates in hypervigilance and superattentiveness to nociceptive information (Hsieh et al. 1995). It is possible that the present experimental conditions with stimulation at near pain intensity threshold may have increased the attention because of difficulties for the subjects in choosing a rating and determining whether the stimulus was indeed painful.

**Thalamus**

Increased rCBF in the contralateral thalamus during noxious heat stimulation of the skin has been observed in other PET activation studies (Casey et al. 1994, 1996; Coghill et al. 1994; Jones et al. 1991). The cutaneous noxious laser stimulation in the present study also caused a significant increase in rCBF in the contralateral thalamus. The intramuscular stimulation caused a mean rCBF increase of ~3.6% in the thalamus but, because of large intersubject variability, this was not significant. Because the thalamic nuclei carry nociceptive information to the cortex (Albe-Fessard et al. 1985; Casey and Morrow 1983; Craig et al. 1994; Lenz et al. 1995), one would expect to see a response in this structure. However, PET studies in chronic pain patients have shown a significant decrease in rCBF in the thalamus (DiPiero et al. 1991; Hsieh et al. 1995; Iadarola et al. 1995). Chronic changes such as degenerative processes, inhibition of nociceptive inputs, learning, and uncoupling of blood flow from neuronal metabolism have been suggested as causes for the difference in thalamic activation between acute and chronic pain conditions (Iadarola et al. 1995). In the present study, the rCBF increases in the thalamus showed a significant negative correlation with the rCBF in MI/SI during noxious cutaneous stimulation. This result may reflect the presence of inhibitory thalamocortical interactions.

**Anterior insular cortex**

In the present study, the contralateral anterior insular cortex showed a significant increase in rCBF during noxious cutaneous stimulation and a trend of activation during noxious tooth pulp stimulation (Hari et al. 1983), and painful stimulation of the nasal mucosa (Huttunen et al. 1986). It is noteworthy that brain electrical source analyses and magnetoencephalographic recordings both have indicated neuronal activity in an area compatible with the contralateral SII, but not in primary somatosensory cortex (SI), with noxious cutaneous laser stimulation (Chen and Bromm 1995; Kakigi et al. 1995; Laudahn et al. 1995). The significant activation of SII with cutaneous laser and intramuscular electrical stimulation agrees with these previous findings. It has been suggested that SI and SII receive and process nociceptive information in a parallel fashion and it is possible that, unlike tactile sensations, SII may not require serial transmission from SI for the processing of pain (Coghill et al. 1994). The exact role of SII in the processing of skin and muscle pain is not known. Few (<3%) neurons recorded from SII respond to noxious stimulation (Robinson and Burton 1980). However, on the basis of clinical observations (Greenspan and Winfield 1992), neuroanatomic data (Friedman and Murray 1986), neurophysiological data (Dong et al. 1994), and behavioral data (Dong et al. 1996) it has been argued that SII and cortical areas within or adjacent to the lateral sulcus are important for the integration of sensory-discriminative aspects of pain and for providing a common circuity to neuronal networks involved in the affective-motivational aspects of different forms of pain and in the spatially directed attention to noxious stimulation (Kenshado and Douglass 1995).
ious intramuscular stimulation. These results are in accord with the consistent activation of anterior insular cortex in other studies of cutaneous pain (Casey et al. 1994, 1996; Coghill et al. 1994). The anterior insular cortex seems to be strongly connected to the processing of cutaneous pain, because only this structure was significantly activated when scans with noxious heat pain and vibrocutaneous stimulation were subtracted from each other (Coghill et al. 1994). The anterior insular cortex also receives input from several areas associated with the processing of pain such as SI, SII, and anterior cingulate cortex (BA 24), and from the posterior portion of the ventromedial thalamic nucleus (Craig et al. 1994; Friedman and Murray 1986; Friedman et al. 1986). In accord with these anatomic projections, we found significant positive correlations between rCBF increases in the anterior insular cortex and the thalamus, SII, and the inferior parietal lobule (Table 3). Because neurons in the anterior insular cortex project to various limbic structures, it is possible that this region is essential for the integration of ongoing pain with previous experiences of pain and the motivational and affective components of pain (Coghill et al. 1994; Hsieh et al. 1995).

Cerebellum

The noxious intramuscular stimulation caused a significant increase in rCBF in the cerebellum. In addition, there was a trend for a cerebellar activation during the noxious cutaneous stimulation. This is a confirmation of previous results of Casey et al. (1994, 1996) and Hsieh et al. (1995). The cerebellar activity may be considered a part of motor planning during the perception of noxious stimulation and may also be related to direct nociceptive projections to the cerebellum (Ekerot et al. 1991a,b; Jie and Pei-Xi 1990). Recent evidence has linked the cerebellum not only to motor functions but also to higher cognitive functions. The cerebellum and basal ganglia have access to the prefrontal cortex (BA 46) (Kim et al. 1994; Middleton and Strick 1994). Chudler and Dong (1995), after reviewing the literature of the basal ganglia and pain, concluded that the basal ganglia may be involved in both the sensory-discriminative, affective, and cognitive dimension of pain in addition to providing modulation and sensory gating of nociceptive information to higher motor areas. Consistent with these conclusions and previous PET pain studies, we also noted a strong trend for activation in the lenticular nucleus during intramuscular stimulation (Casey et al. 1996; Coghill et al. 1994; Jones et al. 1991).

Occipital lobe

Another common feature for skin and muscle pain in the present study was the significant deactivation in the primary and secondary visual cortex. The reason for this reduction in rCBF is not known, but similar observations have been presented in other PET pain studies (Derbyshire et al. 1994; Hsieh et al. 1995, 1996). Involuntary ocular oscillation in the absence of visual input has also been shown to cause a significant decrease in rCBF in the occipital lobe (Wenzel et al. 1996), but the relation of this finding to pain remains unclear.

Prefrontal cortex

We observed a significant activation in the lateral prefrontal cortex (BA 10/46) during noxious cutaneous laser stimulation. Prefrontal activation has been seen in previous studies with noxious cutaneous heat stimulation (Casey et al. 1996; Derbyshire et al. 1994; Jones et al. 1991). The functional significance of this region in the processing of pain is not known, but it has been suggested that the lateral prefrontal cortex participates in pain-related cognitive processes (Hsieh et al. 1995). A recent neuroanatomic study has provided evidence for a direct connection between the prefrontal cortex and both the basal ganglia and cerebellum (Middleton and Strick 1994), which are areas shown to be activated by painful stimuli (Casey et al. 1994, 1996).

Premotor cortex

The premotor cortex was significantly activated during noxious cutaneous laser stimulation. Noxious contact heat has been shown to activate this region (Casey et al. 1994, 1996). The functional significance of this region in the processing of pain has not been established. It could not be related to actual movement of the arm, because all subjects remained silent and immobile during the PET scans. Rather, this activation could represent an urge to move the arm during the noxious stimulation, because the urge to scratch an itch causes bilateral premotor responses (Hsieh et al. 1994), as does either the imagining or execution of hand movements (Stephan et al. 1995).

Anterior cingulate cortex

The anterior cingulate cortex is a region in which all previous PET pain studies have found increases in rCBF (Casey et al. 1994, 1996; Coghill et al. 1994; Derbyshire et al. 1994; Jones et al. 1991; Talbot et al. 1991). The activation in the anterior cingulate cortex during noxious intramuscular stimulation is consistent with these findings. The Z score analysis indicated a subsignificant activation in the ipsilateral anterior cingulate cortex during noxious cutaneous stimulation (rCBF = 3.4%, Z = 3.14, see Figs. 2 and 3). The reasons for the lack of a significant activation in the contralateral structure are not known, but could be related to a large coefficient of variation in rCBF in this region (Table 1). Bilateral activation of the anterior cingulate cortex has been demonstrated previously during cold pain (Casey et al. 1996). The anterior cingulate cortex is a defining structure of the limbic system that is implicated in the processing of affective and reactive components of pain (Melzack and Casey 1968). Anatomic studies have shown direct projections from thalamic nuclei (Yasui et al. 1988). Furthermore, anterior cingulate neurons respond to noxious stimulation (Sikes and Vogt 1993). The anterior cingulate cortex is, however, not uniquely associated with perception of pain but is activated by various attention and motor tasks not related to pain (Hsieh et al. 1994, 1995; Paus et al. 1993; Stephan et al. 1995).

MI/SI

A recent PET pain study has shown that cold pain causes significant activation in a region overlapping both MI/SI
(BA 3) and the primary motor cortex (BA 4), with the actual peak activation located in BA 4 (Casey et al. 1996). Thus we use the term MI/SI. MI/SI seems primarily to be involved in the ability to detect and discriminate changes in the intensity of the painful stimulus (Kenshalo and Douglass 1995). This is supported by both clinical lesion studies (Kenshalo and Willis 1991; Sweet 1982) and direct single-neuronal recordings in animals (Chudler et al. 1990; Kenshalo et al. 1988; Lamour et al. 1983a,b). Although some PET studies have found significant activation in MI/SI in response to noxious cutaneous heat stimuli (Casey et al. 1994; Coghill et al. 1994; Talbot et al. 1991), other studies have not (Derbyshire et al. 1994; Jones et al. 1991). This discrepancy may be due to the use of different stimulus paradigms, some of which may produce spatial and temporal summation that favors MI/SI activation. Attentional factors related to different paradigms may also play a role, because distraction has been demonstrated to reduce the blood flow response to vibrotactile stimulation in SI (Meyer et al. 1991). Furthermore, the number of nociceptive responding neurons in SI is low compared with innocuous responding neurons (Kenshalo et al. 1988; Lamour et al. 1983a,b), which implies that smaller changes in rCBF may occur in response to noxious stimuli than to innocuous stimuli. Finally, there may be substantial intersubject variability in the processing of noxious cutaneous heat stimuli by SI (Jones and Derbyshire 1994). The exact role of MI/SI in the processing of pain needs further elaboration in PET studies.

Of the relatively few nociceptive driven neurons in SI (Kenshalo et al. 1988; Lamour et al. 1983a,b), a low number are driven specifically from deep tissues. Thus Iwanuca et al. (1981) found that <10% of the SI neurons with deep input from the contralateral limb were responsive to nociceptive input from muscle. There seems to be a functional segregation between the input of type I and type II and III muscle afferents, so that type I input mainly activates neurons in SI (BA 3a, 3b) whereas type II and III input projects to BA 4 and SII (Hanson 1985; Hore et al. 1976; Sirisko and Seslik 1983; Wiesendanger 1973). This agrees with the present finding of subsignificant activation in MI/SI and significant activation in SII with intramuscular electrical stimulation, which has been shown to activate both type III and type IV nociceptive afferents at high stimulus intensities (Simone et al. 1994).

In conclusion, the present study shows a distinct pattern of increases in rCBF in response to noxious cutaneous and intramuscular stimulation. The activation patterns exhibited similarities probably reflecting the structures with the lowest threshold for nociceptive activation, because stimulation was near pain intensity threshold. The differences in cerebral activation patterns suggest that variations in the intensity and temporospatial pattern of neuronal activity within similar sets of forebrain structures are responsible for the perceived differences between skin and muscle pain.

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