Cortical Representation of the Sensory Dimension of Pain

ROBERT K. HOFBAUER,1,2 PIERRE RAINVILLE,3,4 GARY H. DUNCAN,1,2,4,5 AND M. CATHERINE BUSHNELL1,2,5,6
1Department of Neurology and Neurosurgery, McGill University; and 2McConnell Brain Imaging Center, Montreal Neurological Institute, Montreal, Quebec H3A 2B4, Canada; 3Division of Behavioral Neurology and Cognitive Neuroscience, Department of Neurology, University of Iowa Hospitals and Clinics, Iowa City, Iowa 52242; 4Département de stomatologie, Faculté de médecine dentaire et 5Centre de recherche en sciences neurologiques, Université de Montréal, Montreal, Quebec H3C 3J7; and 6Department of Anesthesiology, McGill University, Montreal, Quebec H3A 1A1, Canada

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INTRODUCTION

Pain is a complex sensory and emotional experience that normally signals actual or potential tissue damage. Nevertheless like other sensory modalities, pain can be highly influenced by psychological state or environmental factors. The experience of pain is described along two main axes: the sensory-discriminative dimension of pain processing. Related to, the role of ACC in cognitive processes such as homeostatic regulation (Craig 1996a,b; Davis et al. 1997; Jones et al. 1991; Ploghaus et al. 1999; Talbot et al. 1991). The IC also receives direct thalamocortical nociceptive input in the primate (Dostrovsky and Craig 1996) and has been implicated in autonomic regulation (Augustine 1985, 1996). The IC also receives direct thalamocortical nociceptive input in the primate (Dostrovsky and Craig 1996) and has been implicated in autonomic regulation (Augustine 1985, 1996). The possible implication of IC in the subjective experience of pain is consistent with a function of the IC in higher-order processes relevant to homeostatic regulation (Craig 1996a,b; Craig et al. 2000).

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METHODS

Subjects

Ten normal pain-free subjects (4 males, 6 females; all right-handed) between 20 and 35 yr old (mean = 24.2 yr) participated. All subjects were selected from a larger group (Price et al. 1987; Rainville et al. 1992). For the wrist in a temperature-controlled circulating water bath (Neslab Instruments, Portsmouth, NH) for 60 s. The water temperature was either slightly warm (35°C) or painfully hot (46.0–47.5°C). For the painfully hot condition, the water temperature was individually determined in a pre-experimental session, so that the pain intensity was rated between 40 and 80 on a 100-point magnitude-estimation scale.

Experimental design

Subjects received two trials each of painful heat and slightly warm stimulation during two conditions (alert control and hypnotic control) and received painful heat during the conditions involving hypnotic suggestions for increased- or decreased-pain intensity (Table 1). In the alert-control condition, subjects were instructed to rest quietly. Prior to the hypnotic-control condition, instructions were given to induce a state of hypnosis (see details in following text) without suggestions to alter perception. Subjects then remained in a hypnotic state during subsequent conditions involving suggestions to increase or decrease pain intensity.

Because of possible residual effects of hypnosis and pain-modulation suggestions, the alert control condition was always presented first, followed by the hypnotic-control condition, and finally by the increased- and decreased-pain-intensity conditions (Table 1). The stimulus order of the warm (35°C) and painfully hot (46.0–47.5°C) scans was counterbalanced across subjects within the alert- and hypnotic-control conditions as were the blocks of two trials in the increased- and decreased-pain-intensity conditions.

Hypnotic induction and suggestion procedures

The hypnotic induction and suggestion procedures were adapted from Bourassa and Leclerc (1991) and Kierman et al. (1995) and are described in Rainville et al. (1999). In short, the hypnotic state was induced using a modification of the protocol included in the Stanford Hypnotic Susceptibility Scale, form A (SHSS-A). The hypnotic state was maintained throughout the hypnotic-control and increased- and decreased-pain-intensity conditions; although no instructions were given during the scans, subtests of the SHSS-A were administered between scans to assess hypnotic susceptibility. Before each scan of the increased- and decreased-pain-intensity conditions (Table 1, scans 9–12), subjects were given the additional suggestions to increase or decrease the intensity of the heat pain (Rainville et al. 1999).

Psychophysical and physiological measurement procedures

Immediately after each scan, subjects rated both pain intensity and unpleasantness using separate magnitude-estimation scales of 0–100. Verbal descriptor end points were given for each scale. For the intensity scale, “0” was defined as “no burning, prickling, stinging sensation,” the most frequently chosen words describing the sensory aspect of heat pain in an independent study (Morin and Bushnell 1998), and “100” indicated an “extremely intense sensation.” For the unpleasantness scale, “0” was designated as “not at all unpleasant.”

<table>
<thead>
<tr>
<th>TABLE 1. Experimental conditions</th>
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<tr>
<td><strong>Scan</strong></td>
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* Stimulus order in scans 1–4, 5–8, and pain-modulation suggestions order in scans 9–12 are reversed in half the subjects and sessions.
and “100” denoted “extremely unpleasant.” To avoid ceiling effects, subjects were instructed that responses could surpass “100” if larger values were needed to describe sensations relative to previous ratings (Rainville et al. 1992, 1999). If the stimulus was not rated as painful, the subjects rated warmth intensity on a 0–100 magnitude-estimation scale. For the warmth scale, “0” was defined as “no warm sensation,” and “100” indicated “just hot, barely painful.” Psychophysical ratings of stimulus intensity and unpleasantness were compared across the four experimental conditions involving noxious stimuli (ANOVA; alert control, hypnosis control, hypnotic suggestions for increased-pain intensity, and hypnotic suggestions for decreased-pain intensity).

Heart rate was recorded for 1 min before and for 1 min during each of the 12 PET scans. Rates were averaged across the two presentations of each stimulus condition and compared within each experiment (ANOVA) to determine the effects of the stimulation (before and during) and the experimental conditions (alert-control 35°C and hypnosis-control 35°C; alert-control 47°C, hypnosis-control 47°C, increased- and decreased-pain intensity).

**Scanning procedures**

rCBF was measured using three-dimensional high-resolution PET (Siemens ECAT HR+, 63 slices) following bolus injection of H\(^2\)O (10 mCi) without arterial blood sampling (Fox and Mintun 1989; Fox and Raichle 1984; Herscovitch et al. 1983; Raichle et al. 1983). Stimulus onset was simultaneous with bolus injection and 1-min scans started approximately 15 s postinjection. Data were collected in two sequential frames of 40 and 20 s. Results reported here are for the first 40 s of data acquisition, which we found to produce a higher signal-to-noise ratio in preliminary analyses and in previous studies (Coghill et al. 1994; Duncan et al. 1998; Talbot et al. 1991). An inter-scan interval of 12–15 min allowed the tracer to decay to background levels and minimized sensitization to repeated thermal stimulation. Subjects were inserted earphones, through which they received instructions or hypnotic suggestions before each scan, connected to a microphone. During each scan, the microphone was turned off, and subjects remained immobile and kept their eyes closed. After completing the PET sessions, each subject underwent a high-resolution anatomical magnetic resonance imaging (MRI; 160 1-mm slices acquired on a Philips 1.5T Gyroscan system).

**Image processing and analysis**

Each PET- and MRI-volume was automatically transformed into a stereotaxic space similar to that of Talairach and Tournoux, using the method published by Collins et al. (1994) to allow for inter-subject averaging and localization of rCBF changes. PET volumes were smoothed with a 14-mm (full-width, half-maximum) Hanning filter and normalized to the average brain count. Data were analyzed using the following three complementary methods.

**DIRECTED SEARCHES OF PAIN-RELATED ACTIVITY IN S1, S2, ACC, AND IC.** To obtain peak-activation maps of pain-related changes in rCBF for each subject, we subtracted normalized PET data recorded during the warm (35°C) condition from those of the painfully hot (46.0–47.5°C) condition during alert-control and hypnosis-control states. Resulting volumes of pain-related changes in rCBF were averaged across sessions, and statistical t-maps were derived using the methods of Worsley et al. (1992). Directed searches of rCBF changes were performed on the right cortex, contralateral to the stimulus, in regions previously shown to be involved in pain processing: S1 (postcentral gyrus), S2 (ventral aspect of the parietal operculum), ACC, and IC. The anatomical coordinates used for each directed search were derived by averaging the stereotaxic coordinates across the four experimental conditions from Rainville et al. (1997) and searching for significant peaks within a 15 mm radius of these coordinates. The significance threshold for these directed searches was \( t = 4.5 \) (\( P < 0.05 \)), suggesting that the hypnotic state itself did not affect pain perception. However, pain ratings were highly modulated by the hypnotic suggestions. Consistent with the hypnotic suggestions themselves, intensity ratings differed between the high- and low-intensity conditions...
Heart rate increased when the noxious thermal stimulus was applied ($P < 0.005$; Table 2), whereas heart rate was not altered on application of the warm stimulus ($P > 0.15$). Furthermore, there was no significant effect of experimental condition on heart rate ($P > 0.19$).

### Pain-related changes in rCBF during the alert-control condition

To assess the effects of thermal stimulation on rCBF, the 47°C pain stimulation data were compared with those of the 35°C nonpainful stimulation. Results of directed searches performed on the right contralateral S1, S2, ACC, and IC are summarized in Table 3. In the alert-control condition, there were significant pain-related increases in rCBF within all four areas. A global search of the scanned brain regions revealed additional significant increases in rCBF within the ipsilateral parietal cortex (association area 7; Table 4, alert control).

### Pain-related changes in rCBF during the hypnosis-control condition

To assess the effects of hypnosis, itself, on pain-related activation, scans were performed after subjects received hypnotic induction but before any suggestions were given for pain modulation. Pain-related activation within this hypnotic state was then determined by comparing rCBF observed during the 47°C pain stimulation condition with that of the 35°C nonpainful stimulation condition. Results of this comparison demonstrated significant pain-related activation in right contralateral S1, S2, ACC, and IC, analogous to that observed in the alert-control condition (Table 3). Furthermore a direct comparison of the hypnosis-control 47°C condition to the Alert-control 47°C condition did not reveal significant differences in these areas. These data suggest that hypnosis alone had no effect on cortical pain-related activation. The global search revealed no additional pain-related increases in rCBF during the hypnosis-control condition (Table 4).

### Effects of hypnotic suggestions to modulate pain perception

As in the alert- and hypnosis-control conditions, pain-related activation continued to be a prominent feature of the hypnotic suggestion conditions. A subtraction of the 35°C hypnosis control condition from each of the 47°C hypnotic suggestion conditions revealed significant pain-related activity in S1, S2, ACC, and IC (Table 3). A direct contrast analysis of the increased- and decreased-pain-intensity conditions revealed, however, a differential effect of hypnotic suggestions on pain-evoked activation within these cortical areas (Table 5).

### MODULATION OF S1 ACTIVITY

Pain-related activity within S1 was larger in response to hypnotic suggestions for increased-pain intensity, compared with that observed following hypnotic suggestions for decreased-pain intensity (Table 3 and Fig. 2). Direct comparison of the two suggestion conditions (increased- vs. decreased-pain intensity) confirmed the significantly higher rCBF in S1 during the increased-pain-intensity condition (Table 5 and Fig. 2). This contrasts with data from Rainville et al. (1997), that data demonstrated a nonsignificant tendency for lower rCBF in S1 in response to suggestions for increased pain unpleasantness (compared with that seen during the decreased-pain-unpleasantness condition; see Fig. 2). In the present study, increased-pain intensity–hypnosis control 35°C; * decreased-pain intensity–hypnosis control 35°C.

### TABLE 2. Heart rate across experimental conditions

<table>
<thead>
<tr>
<th>Condition</th>
<th>Before*</th>
<th>During†</th>
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<tbody>
<tr>
<td>Alert control 35°C</td>
<td>64.4 ± 3.3</td>
<td>64.8 ± 3.9</td>
</tr>
<tr>
<td>Alert control 47°C</td>
<td>65.0 ± 3.4</td>
<td>68.9 ± 4.0</td>
</tr>
<tr>
<td>Hypnosis control 35°C</td>
<td>66.2 ± 4.6</td>
<td>66.1 ± 4.6</td>
</tr>
<tr>
<td>Hypnosis control 47°C</td>
<td>66.2 ± 4.4</td>
<td>69.5 ± 4.4</td>
</tr>
<tr>
<td>Increased-pain intensity</td>
<td>67.1 ± 4.2</td>
<td>70.9 ± 3.8</td>
</tr>
<tr>
<td>Decreased-pain intensity</td>
<td>65.8 ± 3.8</td>
<td>69.4 ± 3.7</td>
</tr>
</tbody>
</table>

Values are expressed as heart rate in beats per minute as means ± SD. * One-minute period immediately before application of pain stimulus; † one-minute period of hand in water bath.

### TABLE 3. Pain-related activation in directed search sites

<table>
<thead>
<tr>
<th>Region</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>t-Scores</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alert control</td>
<td>34</td>
<td>−18</td>
<td>57</td>
<td>4.13</td>
</tr>
<tr>
<td>S2</td>
<td>42</td>
<td>−16</td>
<td>17</td>
<td>4.49</td>
</tr>
<tr>
<td>ACC</td>
<td>12</td>
<td>−2</td>
<td>44</td>
<td>3.04</td>
</tr>
<tr>
<td>IC</td>
<td>8</td>
<td>3</td>
<td>32</td>
<td>2.72</td>
</tr>
<tr>
<td>Hypnosis control</td>
<td>39</td>
<td>−25</td>
<td>57</td>
<td>3.35</td>
</tr>
<tr>
<td>S1</td>
<td>39</td>
<td>−19</td>
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<tr>
<td>ACC</td>
<td>0</td>
<td>3</td>
<td>45</td>
<td>3.11</td>
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<tr>
<td>IC</td>
<td>32</td>
<td>13</td>
<td>3.41</td>
<td></td>
</tr>
<tr>
<td>Increased-pain intensity</td>
<td>42</td>
<td>−26</td>
<td>59</td>
<td>5.04</td>
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<tr>
<td>S2</td>
<td>40</td>
<td>−12</td>
<td>14</td>
<td>3.10</td>
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<tr>
<td>ACC</td>
<td>8</td>
<td>5</td>
<td>48</td>
<td>3.11</td>
</tr>
<tr>
<td>IC</td>
<td>31</td>
<td>20</td>
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<tr>
<td>Decreased-pain intensity</td>
<td>36</td>
<td>−25</td>
<td>57</td>
<td>3.90</td>
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<tr>
<td>S2</td>
<td>47</td>
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<td>2.64</td>
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<tr>
<td>ACC</td>
<td>12</td>
<td>17</td>
<td>30</td>
<td>2.81</td>
</tr>
<tr>
<td>IC</td>
<td>31</td>
<td>15</td>
<td>5</td>
<td>3.69</td>
</tr>
<tr>
<td>Putamen</td>
<td>28</td>
<td>−6</td>
<td>59</td>
<td>4.67</td>
</tr>
<tr>
<td>Medial frontal gyrus</td>
<td>25</td>
<td>56</td>
<td>4.79</td>
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</table>

Stereotaxic coordinates (x = medial-lateral, y = anterior-posterior, z = superior-inferior) based on the Talairach and Tournoux (1988) atlas. S1 and S2, primary and secondary somatosensory cortices; ACC, anterior cingulate cortex; IC, insular cortex. Two-sample $t$-tests (see METHODS); $^a$ alert control 47°C–alert control 35°C; $^b$ hypnosis control 47°C–hypnosis control 35°C; $^c$ increased-pain intensity–hypnosis control 35°C; $^d$ decreased-pain intensity–hypnosis control 35°C.
separate comparisons of each suggestion condition to the hypnosis-control 47°C condition did not yield significant changes in S1 activity, thereby limiting our ability to clarify whether the observed suggestion-related modulation of S1 activity was the result of increased activity in the increased-pain condition, decreased activity in the decreased-pain condition, or both.

MODULATION OF S2 ACTIVITY. Pain-related activity within S2 was observed in both suggestion conditions (Table 3). As was observed in S1, the direct contrast analysis showed a greater pain-related activity following suggestions for increased-pain intensity compared with that seen for decreased-pain intensity; however, this difference in S2 did not reach significance (Table 5). However, rCBF levels in S2 were significantly lower in the decreased-pain condition compared with those observed in the hypnosis-control 47°C condition (t = -2.6), whereas no significant differences were observed between the increased-pain and hypnosis-control 47°C conditions.

MODULATION OF ACC ACTIVITY. Pain-related activity was evident in ACC during hypnotic suggestion conditions for both increased- and decreased-pain intensity (Table 3 and Fig. 2). However, in contrast to the significant modulation of pain-related activity observed within S1 during suggestions to alter perceived pain intensity, such suggestions did not significantly alter pain-related activity within the ACC (Table 5). Whereas in the Rainville et al. (1997) study, the direct contrast analysis revealed greater pain-related activity following suggestions for increased-pain unpleasantness, there was no significant difference in ACC activity between suggestions for increased-pain intensity and decreased-pain intensity (Fig. 2).

MODULATION OF IC ACTIVITY. Pain-related activation was observed in IC during suggestions for increased- and decreased-pain intensity (Table 3). The direct contrast of the increased- and decreased-pain-intensity conditions revealed a mixed pattern of activation, suggesting higher rCBF in the middle IC in the increased-pain-intensity condition and higher rCBF in the
most rostral part of the IC in the decreased-pain-intensity condition (see Table 5).

Global search analysis

A comparison of the hypnotic suggestion conditions for increased or decreased pain to the hypnosis-control 35°C condition revealed a few additional pain-related activation sites (Table 4). Using the more stringent criterion of global searches, we found significant S1 activation only in the increased-pain intensity condition (Table 4). This is consistent with the results described in the preceding text showing modulation of S1 related to suggestions for increased or decreased pain intensity. A single additional peak was found in the right putamen in the increased-pain intensity condition, and peaks were observed in the frontal cortex during the decreased-pain intensity condition. Some significant pain-related decreases in rCBF were observed in this study but are not addressed in this report.

DISCUSSION

Results of the present experiments and those of previous human brain imaging studies increasingly point toward a cerebral substrate for pain perception that involves a distributed network of cortical and subcortical regions that participate in the processing of noxious stimuli. The present findings, in agreement with our previous studies and those of others, show that this cerebral nociceptive network includes such regions as S1 and S2, ACC, and IC, in addition to subcortical regions, such as thalamus and basal ganglia. Data from the present study and those of Rainville et al. (1997) extend those findings by providing experimental evidence in healthy human subjects for a preferential treatment of sensory-discriminative and affective dimensions of pain perception within somatosensory and limbic structures, respectively.

The present study and that of Rainville et al. (1997) took the unique approach of using hypnotic suggestions as a cognitive manipulation to modulate, and therefore separate, the unpleasantness and intensity of the pain evoked by an experimental stimulus. In the Rainville et al. (1997) experiment, hypnotic suggestions directed toward altering the affective dimension of pain sensation produced significant changes in the perceived unpleasantness of painful heat stimuli without commensurate changes in its perceived intensity. Correspondingly, this manipulation produced significant modulation in pain-evoked activity within ACC but no significant changes in the activity within somatosensory structures, S1 or S2. In the current experiment, hypnotic suggestions directed toward pain sensation produced significant changes in S1 (with a similar trend in S2 cortex) but not in the ACC. This double dissociation of the modulation of nociceptive processing provides direct experimental evidence in support of the hypothesis that activity in classical limbic cortices and somatosensory systems contribute differentially to the pain experience.

In the Rainville et al. (1997) study, hypnotic suggestions led to selective changes in perceived pain unpleasantness and modulation of pain-related activity in ACC but not in S1; correspondingly, pain unpleasantness ratings were significantly correlated with rCBF in ACC but not in S1. By contrast, in the current study, although the suggestions targeted only pain sensation, subjects reported perceptual changes in both pain sensation and pain unpleasantness. A similar modulation of pain affect, secondary to changes in pain sensation, was observed by Rainville et al. (1999) and supports a successive-stage model of pain processing (Wade et al. 1996) in which pain unpleasantness is highly (but not exclusively) dependent on pain sensation. In the current study, the high correlation between pain intensity and pain unpleasantness ratings precludes the use of regression analysis to distinguish cortical areas involved in each dimension of pain. However, the observation of significant modulation of ACC activity associated with direct suggestions for altered unpleasantness (Rainville et al. 1997), but only a smaller nonsignificant modulation of ACC activity when affect is changed indirectly following suggestions for altered sensation, indicates that primary modulation of affect may involve both direct and indirect modulatory influences on ACC, whereas secondary modulation of affect, such as that observed in the present study, may involve only a subset of modulatory circuits without a predominant (significant) influence on ACC activity.

Role of somatosensory cortices in the sensory dimension of pain

The indication by the present data that S1 and maybe S2 participate in processing the sensory dimension of pain is consistent with findings from clinical studies that show deficits in pain sensations after lesions to somatosensory cortices (Greenspan et al. 1999; Ploner et al. 1999). For example, Ploner et al. (1999) observed that a patient who suffered a stroke that encompassed S1 and S2 did not experience a painful sensation when a hot laser stimulus was applied to the affected arm, indicating that intact somatosensory cortices are necessary for the normal experience of pain sensation. However, the patient reported an ill-localized and ill-defined unpleasant feeling in the absence of a clear pain sensation, suggesting that pain affect was present in the absence of pain sensation. The role of S1 cortex in pain processing has been disputed, and a number of brain-imaging studies have failed to detect pain-related S1 activation (see Bushnell et al. 1999). A recent study by Peyron et al. (1999) concluded that S1 does not code pain intensity. These investigators point out that many of the studies that report pain-related S1 activity used a painful stimulus that is moved from spot to spot during the scanning session and suggest that the S1 activation is related to the touch component of the stimulus. Such a concept has been suggested previously by Jones et al. (1992) and refuted by Duncan et al. (1992). The current study used a tonic stationary stimulus throughout the pain conditions, as well as the nonpainful control conditions, and thus does not support such an interpretation of S1 pain-evoked activity. However, pain-evoked activity in S1 appears to highly modulated by cognitive factors. Directing attention away from a painful stimulus reduces S1 pain-evoked activity (Bushnell et al. 1999) as do hypnotic suggestions to reduced perceived pain intensity (current study).

The S2 cortex is usually activated by painful stimuli in PET and fMRI studies (Coghill et al. 1994; Ha et al. 1998; Svensson et al. 1997). This activation was confirmed in all phases of the current experiment, but was absent during the hypnotic suggestion conditions in the Rainville et al. (1997) study. In that report, we postulated that the absence of S2 activation could be caused by a habituation of S2 activity to repeated stimulation...
Role of ACC in the affective dimension of pain

Data from our previous study (Rainville et al. 1997) showed a selective modulation of ACC pain-evoked activity after hypnotic suggestions for changes in pain unpleasantness. This modulation of pain-related activity in ACC by suggestions to alter pain affect and the significant correlation between ACC activity and subjects’ ratings of pain unpleasantness strongly implicate the involvement of this region in the affective dimension of the pain experience. These observations are consistent with results of lesion studies suggesting that patients who have undergone a cingulotomy show a reduction in pain-related emotional responses (Corkin and Hebben 1981; Foltz and Lowell 1962; Foltz and White 1968). The findings are also generally consistent with those of Tolle et al. (1999), who used a regression analysis to show that pain-evoked activation of ACC is more related to affective than to sensory components of the pain experience. The peak of affective-related pain activation in ACC was somewhat more anterior in the Rainville et al. (1997) study than in the Tolle et al. (1999) study. Tolle et al. suggest that the more rostral peak of the Rainville et al. study may be related to the influence of the cognitive demands of the hypnotic suggestion task. The location of ACC pain-related activity in the current study was less anterior than that of Rainville et al. (1997), suggesting that hypnotic suggestions in themselves may not explain the small differences in response locations between studies.

As indicated in the preceding text, in the current experiment, there was a secondary modulation of pain affect when suggestions were given to modify pain sensation. This secondary pain-affect modulation was not accompanied by a significant change in pain-evoked ACC activity. The finding that the changes in pain unpleasantness were not associated with significant modulation in the ACC indicates that secondary changes in pain affect may have a different neural substrate than those associated with the direct and specific modulation in pain unpleasantness. This combination of primary and secondary modulatory mechanisms suggests that the contribution of ACC to pain affect may be most determinant when pain unpleasantness is highly dependent on cognitive factors associated with the meaning of pain and largely independent of variations in pain intensity. On the other hand, when pain unpleasantness is strongly determined by pain intensity, the level of pain affect may be at least partially related to activity in other cortical areas. This would be consistent with the model proposed by Price (2000) that emphasizes the interactions between sensory and classical “limbic” cortices for the experience of pain unpleasantness, especially when it is tightly linked to pain intensity.

Recent observations from lesion and brain-imaging studies in humans suggest that S1, S2, and the IC may contribute to some aspects of emotions (Adolphs et al. 2000; Damasio et al. 2000). These intriguing findings raise the possibility that somatosensory areas may contribute to pain affect. These results, together with those of the present experiments, suggest that the relative magnitude of pain unpleasantness experienced may be encoded through different levels of activation within areas such as S1 and the ACC as a function of the factors contributing to pain affect.

Role of IC in pain processing

Our findings of both significant positive and negative differences in IC activation during suggestions for increased and decreased pain intensity suggest that there may be a complicated role of IC in pain intensity coding. Craig et al. (2000) observed a significant correlation between IC activity and intensity of cold stimuli, further suggesting that IC may be involved in coding of noxious and innocuous temperature. Nevertheless other data indicate that IC activity may be important in pain affect. Neuroanatomical studies demonstrate a direct projection from nociceptive regions of thalamus to the insular cortex (Dostrovsky and Craig 1996), thus indicating that the region receives information regarding noxious stimuli. Behavioral consequences associated with disrupting the flow of this information are revealed following insular lesions and are characterized by the condition of pain asymbolia or Schilder-Stengel syndrome in which pain sensations appear to be normal but behavioral and physiological responses to the offending stimulus are atypical (Berthier et al. 1988; Ogden et al. 1959; Winklemann et al. 1962). Patients do not realize that a stimulus is painful nor see a need to escape possibly because the affective component of the stimulus is not conveyed.

In addition to the possible role of IC in pain affect, other studies implicate this area in autonomic control. Studies in rat show that the insula is involved in cardiovascular regulation (Verberne and Owens 1998). In humans, exercise can lead to activation of the insular cortex (Williamson et al. 1997), and cardiac autonomic activity is disrupted by lesions to the insular cortex (Oppenheimer et al. 1996). In the present study, we observed pain-evoked change in heart rate that may be related to the pain-evoked activation in the IC observed during all experimental conditions. In a previous psychophysical experiment, we showed that the hypnotic modulation of pain affect was accompanied by small but significant changes in the pain-evoked heart rate response (Rainville et al. 1999). However, in the present study, the effect of the suggestion on heart rate responses did not reach significance, and correspondingly, the activity level within the IC was not modulated consistently.
In the present experiment and in that of Rainville et al. (1997), the peak of IC activation was more anterior in the suggestion conditions in the alert- and hypnotis-control conditions (see Table 3). This anterior shift in the peak IC activation may reflect a contribution of anticipation to the pain-evoked IC activity because more anterior activation in IC has been suggested to reflect the anticipation of pain (Chu et al. 1999; Ploghaus et al. 1999). In the suggestion conditions, the suggestions themselves alerted the subjects that the upcoming stimulus was to be painful, whereas in the control conditions warm and painful stimulation were presented in a pseudo-random order. Moreover, this anterior shift was most pronounced in the increased-pain affect condition of the Rainville et al. (1997) experiment, consistent with a contribution of anticipatory processes to the affective dimension of pain.

**Possible participation of ACC in the sensory dimension of pain**

The preferential treatment of affective aspects of pain by the ACC discussed in the preceding text does not exclude this structure from a potential participation in some sensory-discriminative aspects of the experience. Although there is no evidence for a somatotopic organization of nociceptive response within the ACC, which may limit its specific contribution to spatial discrimination, other data suggest that the ACC (and, indeed, other “limbic medial pain pathways”) receives nociceptive information relevant to the encoding of the sensory-intensity aspects of pain perception. Electrophysiological evidence supporting this possible role of ACC in pain intensity has been reported by Sikes and Vogt (1992), who identified ACC neurons coding for the intensity of noxious stimuli in anesthetized rabbit. Similar high-resolution coding of intensity has also been reported in the medial thalamus of awake monkeys performing a task requiring the fine discrimination of the intensity of noxious thermal stimuli (Bushnell and Duncan 1989). These intensity-coding neurons were found within an area where thalamocortical projections to the ACC originate (Apkarian and Shi 1998; Craig 1990). More recently, Hutchinson et al. (1999) identified similar single neurons in human ACC that code the intensity of noxious heat. Furthermore changes in pain-intensity ratings of noxious thermal stimuli have been reported following an anterior cingulotomy (Davis et al. 1994) and following the disruption of thalamocortical input to the frontal lobe by a capsulotomy including the ACC (Talbot et al. 1995). These observations suggest that although the activity of the ACC evoked during pain may be more closely related to its affective dimension, the properties of ACC neurons and the effects of lesions affecting this area suggest that the ACC may contribute, to some extent, to the sensory aspects of the experience.

**Conclusion**

It has been well accepted for many decades that pain is a multidimensional experience, and, likewise, it has become increasingly evident that multiple brain regions are activated during the experience of pain. The task thus moved from describing regions activated by pain stimuli to defining what functional significance those regions might have in the various aspects of pain perception. However, the normally strong corelation between sensory and affective components of pain perception has made it difficult to identify potential cerebral correlates for these different pain dimensions. The present experiment and that of Rainville et al. (1997) use a cognitive strategy to manipulate sensory and affective dimensions of pain perception and thus demonstrate a double dissociation of cortical activity related to the perception of pain intensity and pain affect within somatosensory cortices and ACC, respectively. Further, results of these studies speak against a simple dichotomous description of brain areas underlying pain sensation and pain affect. The association between pain unpleasantness and ACC activity was observed when pain affect was directly modulated, independently from pain sensation. In contrast, changes in pain unpleasantness secondary to changes in pain intensity did not lead to a significant modulation of ACC activity. These results indicate that the cortical representation of pain affect depends on the specific factors that contribute to this dimension of the experience.

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