Differentiation of Visceral and Cutaneous Pain in the Human Brain

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Departments of 1Physiology and 2Anesthesia, McGill University, Montreal, H3G 1Y6; 3Département de Gastroentérologie, Faculté de Médecine, 4Départements de Stomatologie and 5Centre de Recherché en Sciences Neurologiques, Faculté de Médecine Dentaire, Université de Montréal, Montreal, Quebec H3C 3J7 Canada

Submitted 19 November 2002; accepted in final form 9 February 2003

Strigo, Irina A., Gary H. Duncan, Michel Boivin, and M. Catherine Bushnell. Differentiation of visceral and cutaneous pain in the human brain. J Neurophysiol 89: 3294–3303, 2003. First published February 12, 2003; 10.1152/jn.01048.2002. The widespread convergence of information from visceral, cutaneous, and muscle tissues onto CNS neurons invites the question of how to identify pain as being from the viscera. Despite referral of visceral pain to cutaneous areas, individuals regularly distinguish cutaneous and visceral pain and commonly have contrasting behavioral reactions to each. Our study addresses this dilemma by directly comparing human neural processing of intensity-equated visceral and cutaneous pain. Seven subjects underwent fMRI scanning during visceral and cutaneous pain produced by balloon distention of the distal esophagus and contact heat on the midline chest. Stimulus intensities producing nonpainful and painful sensations, interleaved with rest periods, were presented in each functional run. Analyses compared painful to nonpainful conditions. A similar neural network, including secondary somatosensory and parietal cortices, thalamus, basal ganglia, and cerebellum, was activated by visceral and cutaneous painful stimuli. However, cutaneous pain evoked higher activation bilaterally in the anterior insular cortex. Further, cutaneous but not esophageal pain activated ventrolateral prefrontal cortex, despite higher affective scores for visceral pain. Visceral but not cutaneous pain activated bilateral inferior primary somatosensory cortex, bilateral primary motor cortex, and a more anterior locus within anterior cingulate cortex. Our results reveal a common cortical network subserving cutaneous and visceral pain that could underlie similarities in the pain experience. However, we also observed differential activation patterns within insular, primary somatosensory, motor, and prefrontal cortices that may account for the ability to distinguish visceral and cutaneous pain as well as the differential emotional, autonomic and motor responses associated with these different sensations.

INTRODUCTION

Based on the ubiquitous convergence of information from visceral, cutaneous, and muscle tissues, an important dilemma exists concerning how one can distinguish visceral pain from that originating in other tissues of the body. Although primary afferents subserving visceral, cutaneous, and muscle pain are mostly distinct, at the dorsal horn there is much convergence of these pathways so that spinohalamic, spinoreticular, and spinomesencephalic tracts all contain neurons that respond to both somatic and visceral stimuli (McMahon et al. 1995). Recent data suggest that the dorsal column postsynaptic pathway, projecting from the dorsal horn to the thalamus, may be particularly important for visceral pain (Al Chaer et al. 1996; Berkley 1997; Nauta et al. 1997), but even in this pathway, most neurons have both visceral and cutaneous receptive fields (Bradshaw and Berkley 2000). Likewise, the majority of neurons that respond to visceral stimuli in medial, lateral, and posterior thalamus (Berkley et al. 1993, 1995; Bruggemann et al. 1994; Chandler et al. 1992; Kawakita et al. 1993), as well as in primary somatosensory and ventrolateral orbital cortices (Follett and Dirks 1994, 1995; Snow et al. 1992), also respond to cutaneous and other stimulation. Thus although purely somatic cells exist in the CNS, neurons with exclusive visceral inputs are virtually absent (Bradshaw and Berkley 2000; Bruggemann et al. 1994). This ubiquitous viscerosomatic convergence is consistent with the indistinct quality, poor localization, and referral of visceral pain but cannot explain either the ability to identify that a pain originates in the viscera or the contrasting arousal reactions to cutaneous and visceral pain—quick protective reflexes, tachycardia, hypertension, and increased alertness are commonly associated with cutaneous pain, whereas quiescence, bradycardia, hypotension, and loss of interest in the environment are generally associated with visceral pain (Lewis 1942). Ultimately, there must be differences in the cerebral responses to visceral and cutaneous pain that could account for these different perceptual and autonomic reactions.

Human studies of cerebral pain mechanisms have concentrated largely on cutaneous pain and have identified several cortical structures important in cutaneous nociception. These regions include primary and secondary somatosensory cortices (S1 and S2), anterior cingulate cortex (ACC), and insular cortex (IC) (Casey et al. 1996; Coghill et al. 1994; Hsieh et al. 1995; Jones et al. 1991; Talbot et al. 1991). Several studies examining forebrain correlates of visceral pain in normal and pathological conditions have found similar regions to be activated (Aziz et al. 1997; Baciu et al. 1999; Berman et al. 2000; Binkofski et al. 1998, 1999; Mertz et al. 2000). Considering the difficulties of comparing activations across studies and experimental conditions, evidence for the differential involvement of these or other cerebral structures in the processing of visceral and cutaneous pain is still lacking.

Although no human imaging studies have directly compared responses to visceral and cutaneous painful stimulation, several have compared the neural processes underlying innocuous...
sensations arising from visceral and somatic tissues, contrasting either distal and proximal esophageal sensation or anal and rectal sensations (Aziz et al. 2000; Furlong et al. 1998; Hobday et al. 2001; Lotze et al. 2001; Schnitzler et al. 1999). Most of these studies describe some differences in somatic and visceral processing, but specific findings differ. Some observed S1 activation for somatic but not visceral sensation, concluding that innocuous visceral sensation is not represented in S1 (Furlong et al. 1998; Lotze et al. 2001; Schnitzler et al. 1999). Other studies found different activation sites in S1 and/or ACC for visceral and somatic stimuli (Aziz et al. 2000; Hobday et al. 2001). Because noxious stimulation was not employed in these studies, it is difficult to speculate whether visceral and somatic pain would show similar differences in the cortical activation pattern. Indeed, numerous studies have shown that innocuous and noxious cutaneous stimulation produce differential cortical activation patterns (Casey et al. 1996; Coghill et al. 1994; Davis et al. 1998).

We recently showed that noxious visceral and cutaneous stimuli, equated for perceived pain intensity, evoke sensations that differ in quality, level of unpleasantness, and spatial distribution (Strigo et al. 2002). These psychophysical findings and previous imaging data suggest the likelihood of both differences and similarities in the neural processing underlying visceral and cutaneous pain. We therefore used functional magnetic resonance imaging (fMRI) in the present study to examine the cortical networks subserving visceral and cutaneous pain resulting from distention of the distal esophagus and contact heat stimulation of the midline chest, respectively. Some of these data have appeared previously in abstract form (Strigo et al. 2001).

**METHODS**

**Subjects**

With the approval of the McGill Institutional Review Board and the Ethics and Research Committee of Montreal Neurological Institute, we studied seven healthy volunteers (4 males, 3 females), ranging in age from 19 to 34 yr (mean age, 25.8). None of the subjects was obese (mean BMI, 23.6) or taking any medication, and all were free of esophageal symptoms. Each subject underwent esophageal manometry (MMS-100, Narco-Bio Systems, Austin, TX) to identify the appropriate position for the stimulation balloon relative to the lower esophageal sphincter. The presence of a strong gag reflex was used as an exclusion criterion. Subjects were all pretrained, and no subject reported nausea or a need to gag.

**Stimulation**

Esophageal stimulation was performed by distending a custom-designed polyethylene balloon (square type, 8 cm in length, 6 cm in diameter, with a maximum volume of 70–80 ml), which was attached to a multilumen polyvinyl esophageal catheter 10 cm above the tip (Mui Scientific, Mississauga, Ontario, Canada). The catheter was attached to a pump via an 800-cm-long tube (the long tube allowed the placement of the pump in an adjacent room outside the MRI environment). One of the three lumens in the catheter was connected to a pressure transducer, the second was attached to the piston on a pump (GandJ Electronics, Toronto, Ontario, Canada) that was used to inflate the balloon with air at a rate of ~50 ml/s, and the third served as the motility port to measure the position of the lower esophageal sphincter. Thermal stimulation of the upper chest was performed with a 9-cm² Peltier-type contact thermode (Medoc, Ramat Yishai, Israel) placed over the approximate position of the esophageal balloon. Cutaneous heat stimulation (rise time = 5°C/s) was chosen to mimic the frequently described “burning” sensations produced by esophageal balloon distention and/or acid reflux (Fass et al. 1998; Katzka et al. 1996; Strigo et al. 2002).

Esophageal balloon distention and cutaneous heat stimulation on the upper chest were presented in separate functional runs conducted during two different sessions for five subjects with the stimulus order counterbalanced across sessions. Two subjects received both esophageal and thermal stimulation during a single session with the catheter present throughout the entire session. No differences in brain activations were observed between the two methods. For each subject, at the start of the visceral experiment, the balloon catheter was passed peri-orally, following the application of local anesthetic [pentobarbital sodium (Xylocaine)], and positioned in the distal esophagus 5 cm above the lower esophageal sphincter; at the start of the cutaneous experiment, the thermode was securely taped onto the upper midline chest. The stimulation sequences for visceral and cutaneous stimulation were identical, consisting of two stimulus intensities—“high,” which produced moderate pain sensation in all subjects, and “low,” which was perceived by all subjects but was not painful. The stimuli were given in quasi-random and counterbalanced order; each stimulus was presented three times and lasted ~36 s (9 whole brain acquisitions). We have previously shown that 30-s stimulation does not lead to habituation or sensitization using the current stimulation parameters (Strigo et al. 2002). Stimuli were interleaved with nonstimulation baseline periods of equal duration (Fig. 1). The stimulation parameters were customized for each subject, to equate the perceived intensities of visceral and cutaneous stimuli (see Fig. 1 legend for details).

**Imaging procedure**

MRI was performed using a 1.5 T Siemens Vision scanner (Siemens AG, Erlangen, Germany) with a standard head coil. Each session consisted of one anatomical scan and four to eight functional scanning runs. The anatomical scans were recorded using a high-resolution T1-weighted anatomical protocol (TR 22 ms, TE 20 ms, flip angle 30°, FOV 256 mm). The functional scans were collected using a blood-oxygen-level-dependent (BOLD) protocol with a T2*-weighted gradient echo-planar imaging (EPI) sequence (TR 4.0 s, TE 51 ms, flip angle 90°) yielding a 5 × 5-mm in-plane resolution.

The scanning planes were oriented parallel to the anterior commissure-posterior commissure line and covered the whole brain from the top of the cortex to the base of the cerebellum (27 slices, 5 mm thickness, TR 4.0 s). The individual scans consisted of 126 whole brain volume acquisitions, divided into six cycles. Each cycle consisted of 36 s (9 successive volume acquisitions) without stimulation, followed by 36 s with either visceral or cutaneous stimulation (Fig. 1). Extra baseline (36 s) with no stimulation was added in the beginning and the end of each scanning run. Before being positioned in the scanner, all subjects were instructed to attend to the stimuli and refrain from movement as much as possible. To further prevent movement artifacts, the subject’s head was immobilized with padded earmuffs, a
Psychophysical ratings

After each functional scanning run subjects rated pain intensity and unpleasantness of the stimuli on 10-point scales. The anchors for pain intensity were “no pain sensation” and “extremely intense pain sensation”; for unpleasantness, the anchors were “not at all unpleasant” and “extremely unpleasant.” If the stimulus was rated as zero on the pain intensity scale, the subject was asked to rate the nonpainful sensation using the anchors “no sensation” and “extremely warm/pressure sensation.” Nonparametric statistical analyses were used to compare the psychophysical ratings. Finally, subjects rated pain and/or discomfort from sources other than the experimental stimuli, to evaluate possible confounding discomfort from prolonged inactivity. To avoid head movement, all ratings were nonverbal, using the fingers of one hand to indicate perceptual estimates from 0 to 10.

Image processing and analyses

Functional data were motion corrected and low-pass filtered with a 6-mm FWHM Gaussian kernel to increase the signal-to-noise ratio. All images were resampled into stereotaxic space (Collins et al. 1994). Activation maps were generated using FMRISTAT-MULTISTAT software developed at the Montreal Neurological Institute, Montreal, Canada. This analysis yields t-statistics based on a linear model using random field theory; correlated errors, and Bonferroni correction; data were also corrected for temporal correlation, artifactual drift and random effects. The procedures have been recently described in detail (Worsley et al. 2002) (technical support available at http://www.math.mcgill.ca/keith/fmristat).

In brief, the design matrix for the linear model is based on a regression defined by the external stimuli events convolved with a prespecified hemodynamic response function. The analysis fits the linear model to a single run of fMRI data allowing for spatially varying autocorrelated errors. Statistical output from different runs during a session are then combined using a type of random effects analysis. Thresholds for peak and cluster size detection are set using random field theory (Cao 1999; Worsley et al. 1996).

Analyses presented here involve direct comparisons of high and low visceral or cutaneous stimulus conditions. The resulting t-statistic image reflects the difference in activation between the painful and nonpainful conditions. The volume of the whole brain was estimated to be 1,200 cm$^3$ (150,000 voxels) yielding a threshold value of 4.5 for the global search. Directed searches were performed in S1, S2, IC, and ACC. These areas are significantly activated across normal subjects by similar cutaneous and visceral stimuli (Aziz et al. 2000; Baciu et al. 1999; Derbyshire and Jones 1998; Hobday et al. 2001). The following search volumes were used: S1, 12.1 cm$^3$ (1,512 voxels); S2, 10.1 cm$^3$ (1,260 voxels); IC, 6.2 cm$^3$ (780 voxels); and ACC, 9.6 cm$^3$ (1,200 voxels) as described previously (Olausson et al. 2001). For a directed search within these volumes, the t-values for significant activation were calculated to be 3.3 for S1, S2, and ACC and 3.1 for IC.

To directly compare brain activations produced by visceral and cutaneous stimulation, regions of interest (ROIs) were drawn in each area of the brain that showed significant differential activity in the initial high versus low analysis, namely anterior insula, ventrolateral prefrontal cortex, inferior S1, and primary motor cortex (M1). The original motion-corrected raw data from functional runs of like modality and sequence were then averaged for each subject. Subsequently, the level of activity in the preceding areas was extracted from each subject’s averaged raw data during high and low stimulation conditions, which were then subtracted to obtain the number that corresponded to the activity in the area of interest. Parametric statistical analyses were further used to identify significant differences in the activated signal.

RESULTS

Psychophysical ratings

Figure 2 shows median postscan psychophysical ratings for painful (high) esophageal distension and cutaneous heat stimuli. In agreement with our recent psychophysical study (Strigo et al. 2002), the ratings of unpleasantness associated with noxious esophageal distension were higher than the corresponding ratings of pain intensity ($P < 0.05$, Wilcoxon signed-rank test), whereas there was no difference between the pain intensity and unpleasantness ratings during noxious cutaneous heat stimulation ($P = 0.2$, Wilcoxon signed-rank test). As expected, the pain intensity ratings for the noxious esophageal distension were not significantly different from those associated with the noxious cutaneous heat stimuli (Fig. 2, $P = 0.2$, Wilcoxon signed-rank test). In fact, the median rating for esophageal pain intensity was lower (nonsignificantly) than that for the cutaneous pain intensity, a tendency opposite to the significantly higher unpleasantness ratings. Likewise, the ratings evoked by innocuous (low) esophageal and cutaneous stimuli were statistically indistinguishable (medians: 4.1, nonpainful pressure; 2.4, nonpainful heat; $P = 1.0$, Wilcoxon signed-rank test), indicating that our approach of customizing appropriate stimulus levels for each subject had been successful.

Cerebral activity associated with visceral pain

Table 1 summarizes the regions of increased BOLD responses during noxious esophageal distention relative to innocuous esophageal distension. Directed searches revealed significant activation bilaterally in S2 (which was also significant in a global search), left ACC, right anterior IC, bilateral mid-IC, and left posterior IC. Clusters of global significance were seen bilaterally in cerebellum, inferior intra-abdominal region of S1 (Penfield and Rasmussen 1955), the face area of the primary motor cortex (BA 4; M1), as well as in the supple-

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**FIG. 2.** Median postrun pain intensity and unpleasantness ratings (with ranges) after noxious (high) intensity stimulation. Poststimulus intensity ratings after noxious visceral stimulation were not different from those after noxious cutaneous stimulation ($P = 0.2$), allowing for direct comparison; median ratings of unpleasantness after noxious visceral stimulation were higher than the corresponding pain intensity ratings ($P < 0.05$), while they were not different after noxious cutaneous stimulation ($P = 0.2$; Wilcoxon signed-rank test).
Cortical activity
- R. secondary somatosensory cortex (S2)
- L. secondary somatosensory cortex (S2)
- R. primary somatosensory cortex (S1)-intra-abdominal region
- R. primary somatosensory cortex (S1)-trunk region
- L. primary somatosensory cortex (S1)-intra-abdominal region
- R. anterior insula
- R. mid insula
- L. mid insula
- L. posterior insula
- R. primary motor cortex (M1) — BA 4
- L. primary motor cortex (M1) — BA 4
- SMA (cluster) — BA32/6
- R. posterior parietal cortex — BA 7
- L. posterior parietal cortex — BA 7 (cluster)
- Anterior cingulate cortex (BA 32)

Subcortical activity
- R. cerebellum (cluster)
- L. cerebellum (cluster)
- Cerebellar vermis
- R. basal ganglia (Putamen)
- L. basal ganglia (Putamen)
- R. thalamus
- L. thalamus

Comparison of visceral and cutaneous pain
Comparison of Tables 1 and 2 shows similar levels (t-values differ <1.5 and no difference in direct comparison) of significant activity during visceral and cutaneous pain in a number of areas, including S2, posterior parietal cortex, cerebellum, thalamus and basal ganglia. To identify brain regions that showed differential activity during visceral and cutaneously painful stimulation, ROI analyses were performed in areas that were significantly activated by one condition only or had a large difference (>2) in their respective t-scores of activation (see Table 3). As shown in Fig. 3A, cutaneous pain resulted in a significantly higher activity than did visceral pain in the right (P < 0.01) and a similar tendency on the left (P = 0.1; paired Student’s t-test corrected for multiple comparisons) anterior IC. On the other hand, visceral but not cutaneous pain significantly activated the face area of the M1 on the right (P < 0.05) and showed a similar tendency on the left (P = 0.1; Fig. 3B). In addition, ACC activation during visceral and cutaneous noxious stimulation was spatially distinct (Fig. 3C), with the peak activation for esophageal distension pain being 26-mm rostral to that for cutaneous heat pain (Ma et al. 1999).

Although the inferior intra-abdominal region of S1 was significantly activated by noxious esophageal distension, but not by noxious cutaneous heat (Fig. 4A), this difference in activation levels was not significant in the ROI analysis (P = 0.2, paired Student’s t-test). Similarly, despite a highly significant activation of the right ventrolateral prefrontal cortex during noxious heat stimulation and the paucity of activation during esophageal distention (Fig. 4B), ROI analysis did not confirm a significant difference between the two (P = 0.2, paired Student’s t-test).

Discussion
The present results indicate that, in humans, both visceral and cutaneous pain are associated with a wide cortical and subcortical network of activation sites, consistent with the complex nature of the pain experience and the patterns of activation found in previous pain studies. Further, the within-subject design of the present study demonstrates that noxious stimulation of skin and viscera activates a common neural network, including S2 and posterior parietal cortices, as well as basal ganglia, thalamus and cerebellum. Finally, we show that even when pain intensity is equated for visceral and cutaneous stimuli, the two modalities of stimulation produce differential
activation patterns in S1, IC, and ACC, as well as motor and prefrontal cortices, consistent with the differences in pain quality, affect and behavioral reactions related to visceral and cutaneous stimulation.

**Limbic System:**

IC. Generally IC is considered to play a major role in visceral as well as somesthetic sensations (Augustine 1996). Our results suggest that there may be a differential response to visceral and somatic pain in IC, particularly in the anterior extent of IC. Although painful esophageal distension produced activation of the right anterior IC, painful cutaneous heat resulted in a bilateral activation of this region that was significantly greater than that produced by the visceral stimuli. The robust anterior IC activation during heat pain is consistent with findings from other PET and fMRI studies (Becerra et al. 1999; Coghill et al. 1994; Davis et al. 1998; Derbyshire and Jones 1998; Ha et al. 1998a,b; Svensson et al. 1997), as well as with electrophysiological findings of thermal nociceptive neurons in IC of primates (Craig 2000; Craig and Dostrovsky 1999). Other data suggest that anterior IC is involved more generally in thermal processing because this region is also activated by innocuous cutaneous warm and cool stimulation (Craig et al. 1996, 2000; Davis et al. 1998; Fulbright et al. 2001). Craig et al. (2000) proposed that activation of anterior IC is related to the subjective evaluation of temperature. This idea is intriguing in relation to our finding of a small, but significant, activation in anterior IC during painful esophageal distension. In a previous psychophysical study, we found that subjects often report a burning sensation in the chest during esophageal distension (Strigo et al. 2002). This heat sensation, in the absence of an actual temperature elevation, could well be associated with the anterior IC activation. In spite of these previous results suggesting a role of the anterior IC in thermal processing, the differences we have observed in the present study may more likely be related to differences in visceral and cutaneous stimulation than to differences in pressure and thermal stimulus modalities because cutaneous pressure pain also has been shown to activate anterior IC (Gracely et al. 2002).

### Table 2. Regions of increased neuronal activity during painful thermal heat stimulation

<table>
<thead>
<tr>
<th>Region</th>
<th>Stereotaxic Coordinates</th>
<th>t-Score</th>
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</thead>
<tbody>
<tr>
<td>R. Anterior insula (cluster)</td>
<td>32 12 8 6.3</td>
<td></td>
</tr>
<tr>
<td>L. Anterior insula (cluster)</td>
<td>32 24 6 6.2</td>
<td></td>
</tr>
<tr>
<td>R. Mid insula</td>
<td>36 -12 6 5.1</td>
<td></td>
</tr>
<tr>
<td>L. Mid insula</td>
<td>-40 2 6 4.4</td>
<td></td>
</tr>
<tr>
<td>R. Posterior insula</td>
<td>36 -20 14 3.6</td>
<td></td>
</tr>
<tr>
<td>L. Posterior insula</td>
<td>-28 -22 6 4.9</td>
<td></td>
</tr>
<tr>
<td>R. Secondary somatosensory cortex (S2)</td>
<td>54 -38 32 4.6</td>
<td></td>
</tr>
<tr>
<td>L. Secondary somatosensory cortex (S2)</td>
<td>-56 -24 16 3.7</td>
<td></td>
</tr>
<tr>
<td>R. Primary somatosensory cortex (S1)—trunk region</td>
<td>18 -37 64 2.0 (n.s.)</td>
<td></td>
</tr>
<tr>
<td>L. Primary somatosensory cortex (S1)—trunk region</td>
<td>-22 -40 64 1.8 (n.s.)</td>
<td></td>
</tr>
<tr>
<td>R. Ventrolateral prefrontal cortex (BA 10)</td>
<td>42 50 2 5.3</td>
<td></td>
</tr>
<tr>
<td>R. Posterior parietal cortex—BA 7</td>
<td>38 -50 42 4.9</td>
<td></td>
</tr>
<tr>
<td>L. Posterior parietal cortex—BA 7</td>
<td>-34 38 3.3</td>
<td></td>
</tr>
<tr>
<td>R. Parietal association cortex—BA 40</td>
<td>54 -36 44 5.0</td>
<td></td>
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<tr>
<td>L. Parietal association cortex—BA 40</td>
<td>-60 -38 38 4.8</td>
<td></td>
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<tr>
<td>Posterior cingulate cortex (BA 23)</td>
<td>-2 -26 28 4.9</td>
<td></td>
</tr>
<tr>
<td>Anterior cingulate cortex (BA 24)</td>
<td>-10 0 42 3.5</td>
<td></td>
</tr>
<tr>
<td><strong>Cortical activity</strong></td>
<td></td>
<td></td>
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<tr>
<td><strong>Subcortical activity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R. Thalamus</td>
<td>12 -12 8 4.3 (n.s.)</td>
<td></td>
</tr>
<tr>
<td>L. Thalamus</td>
<td>-16 14 6 5.4</td>
<td></td>
</tr>
<tr>
<td>R. Cerebellum (cluster)</td>
<td>36 -56 44 5.3</td>
<td></td>
</tr>
<tr>
<td>L. Cerebellum (cluster)</td>
<td>28 -56 30 5.0</td>
<td></td>
</tr>
<tr>
<td>L. Anterior Insula (cluster)</td>
<td>-40 -52 44 4.9</td>
<td></td>
</tr>
<tr>
<td>L. Basal ganglia (Putamen)</td>
<td>-26 -66 32 4.5</td>
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</tr>
<tr>
<td>Cerebellar vermis</td>
<td>4 -58 30 4.5</td>
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<tr>
<td>R. Basal ganglia (Putamen)</td>
<td>26 6 4 4.9</td>
<td></td>
</tr>
<tr>
<td>L. Basal ganglia (Putamen)</td>
<td>-30 -6 6 4.6</td>
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- *Numbers indicate the average (n = 7) of the activity in the areas of interest ± SD calculated as described in METHODS; ** *P < 0.01 (paired Student’s t-test, corrected for multiple comparisons); * *P < 0.05 (paired Student’s t-test, corrected for multiple comparisons).
and anterior cingulate cortex (ACC). These data are consistent with human brain-imaging studies showing tactile-evoked activation in posterior IC, whereas somesthetic sensations were most often evoked by posterior IC stimulation (Ostrowsky et al. 2000, 2002). The predominance of somesthetic responses with posterior IC stimulation is consistent with human brain imaging studies showing tactile-evoked activation in posterior IC (Coghill et al. 1994; Davis et al. 1998; Olausson et al. 2002). Consistent with our human findings, gastric responses in rats have been localized more in mid- and posterior IC than in the anterior IC (Cechetto and Saper 1987). Our findings and those of others suggest a complex relationship between visceral and somatic representation in IC.

ACC. Both esophageal distension and cutaneous heat on the chest led to activations in ACC. Whereas many brain-imaging studies of distal painful stimulation (e.g., hand or arm) show a particularly strong ACC activation, we observed a less robust activation with both the cutaneous and visceral proximal stimulation. Little is known about cortical processing of information from the trunk area, but because the trunk region has a small somatosensory representation in S1, it is possible that the processing in ACC is also limited.

The most salient feature of the ACC activation in the current study is that visceral stimulation activated a more anterior part of ACC than did cutaneous stimulation. Other data support this suggestion of a differential representation of visceral and cutaneous sensation in ACC. Silverman et al. (1997) observed during painful rectal distention that the ACC activation was in a region rostral to that most commonly activated by cutaneous pain. A similar relationship was observed by Lotze et al. (2001) during nonpainful visceral and somatic stimulation with visceral stimulation induced by rectal balloon-distention activating a more anterior part of ACC than somatic stimulation induced by the distention of the anal canal.

A number of studies have found attention-related activity in ACC (Bench et al. 1993; Benedict et al. 2002; Derbyshire et al. 1998; Luks et al. 2002; Pardo et al. 1990; Yamasaki et al. 2002). Further, Davis et al. (1998) observed that attention-related ACC activity is generally rostral and/or superior to pain-evoked activity. Thus one interpretation for the topographic differences in ACC activation by visceral and cutaneous pain could be that visceral pain commands more attention.

We also found that both visceral and cutaneous pain are associated with widespread activation in mid- and posterior IC as well as in anterior IC. These data are consistent with human intraoperative stimulation studies that showed both visceral and somatic sensations during stimulation throughout the insular region (Ostrowsky et al. 2000, 2002; Penfield and Faulk 1955). Although Ostrowsky and colleagues (2002) have demonstrated both painful and nonpainful sensations evoked by intracortical electrical stimulation of the posterior IC, they have also observed that visceral sensitive and visceromotor responses were evoked most often by stimulation in the mid- and anterior IC, whereas somesthetic sensations were most often evoked by posterior IC stimulation (Ostrowsky et al. 2000, 2002). The predominance of somesthetic responses with posterior IC stimulation is consistent with human brain imaging studies showing tactile-evoked activation in posterior IC (Coghill et al. 1994; Davis et al. 1998; Olausson et al. 2002). Consistent with our human findings, gastric responses in rats have been localized more in mid- and posterior IC than in the anterior IC (Cechetto and Saper 1987). Our findings and those of others suggest a complex relationship between visceral and somatic representation in IC.

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We also found that both visceral and cutaneous pain are associated with widespread activation in mid- and posterior IC as well as in anterior IC. These data are consistent with human intraoperative stimulation studies that showed both visceral and somatic sensations during stimulation throughout the insular region (Ostrowsky et al. 2000, 2002; Penfield and Faulk 1955). Although Ostrowsky and colleagues (2002) have demonstrated both painful and nonpainful sensations evoked by intracortical electrical stimulation of the posterior IC, they have also observed that visceral sensitive and visceromotor responses were evoked most often by stimulation in the mid- and anterior IC, whereas somesthetic sensations were most often evoked by posterior IC stimulation (Ostrowsky et al. 2000, 2002). The predominance of somesthetic responses with posterior IC stimulation is consistent with human brain imaging studies showing tactile-evoked activation in posterior IC (Coghill et al. 1994; Davis et al. 1998; Olausson et al. 2002). Consistent with our human findings, gastric responses in rats have been localized more in mid- and posterior IC than in the anterior IC (Cechetto and Saper 1987). Our findings and those of others suggest a complex relationship between visceral and somatic representation in IC.

ACC. Both esophageal distension and cutaneous heat on the chest led to activations in ACC. Whereas many brain-imaging studies of distal painful stimulation (e.g., hand or arm) show a particularly strong ACC activation, we observed a less robust activation with both the cutaneous and visceral proximal stimulation. Little is known about cortical processing of information from the trunk area, but because the trunk region has a small somatosensory representation in S1, it is possible that the processing in ACC is also limited.

The most salient feature of the ACC activation in the current study is that visceral stimulation activated a more anterior part of ACC than did cutaneous stimulation. Other data support this suggestion of a differential representation of visceral and cutaneous sensation in ACC. Silverman et al. (1997) observed during painful rectal distention that the ACC activation was in a region rostral to that most commonly activated by cutaneous pain. A similar relationship was observed by Lotze et al. (2001) during nonpainful visceral and somatic stimulation with visceral stimulation induced by rectal balloon-distention activating a more anterior part of ACC than somatic stimulation induced by the distention of the anal canal.

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than does cutaneous pain and thus activates ACC attention circuitry. Although this is possible, it seems unlikely because the subjects were required to attend to the heat pain in the same way as the esophageal distention to rate the different aspects of the stimulus. Further such an interpretation would suggest that visceral pain produces two activation foci—one in a pain-related portion of ACC and another in an attention-related area, whereas we observed only one ACC activation site during visceral pain.

The possible segregation of visceral and somatic input to the ACC could parallel that observed in the periaqueductal gray matter (PAG). Keay et al. (Keay and Bandler 1993; Keay et al. 1994) demonstrated in rats that noxious stimulation of the skin increases c-fos labeling in the lateral PAG, whereas stimulation of the viscera increases c-fos labeling in the ventrolateral PAG (Keay and Bandler 1993; Keay et al. 1994). Correspondingly, behavioral reactions in rats evoked by microstimulation in the lateral and dorsolateral PAG are similar to those produced by cutaneous pain, whereas behavioral reactions evoked by microstimulation in the ventrolateral PAG are similar to those produced by visceral pain (Bandler and Shipley 1994; Bandler et al. 2000). The ACC has been shown in animal studies to be interconnected with the PAG in a columnarily ordered fashion (Bandler and Shipley 1994). In primates, cingulate areas 32, 25, and 24, as well as posterior cingulate regions, project to PAG, and projections from these distinct cortical areas terminate primarily in individual longitudinal PAG columns (An et al. 1998). The specific relationship between ACC and PAG columns is not fully explored, but our data suggest the possibility that the differential response selection related to visceral and cutaneous pain may be subserved at least in part by column-specific ACC-PAG connections. Such response selection could be related to active versus passive emotional coping, which Bandler and colleagues have suggested is mediated by different PAG-medial prefrontal circuits that include ACC (Bandler et al. 2000).

The more rostral ACC activation by visceral pain in our study is also interesting in terms of the higher affective response to the visceral than to the cutaneous pain. The activation is close to the perigenual region, which has been implicated in visceromotor control, vocalization and affect (Devinsky et al. 1995; Vogt et al. 1996). Electrical stimulation of the ventral part of the perigenual region (i.e., infragenual or BA 25), just anterior to the activity seen in our study, produces various visceral responses including nausea, vomiting, salivation, and others (Lewin and Whitty 1960; Pool and Ranshoff 1949). The important role perigenual cortex plays in affect is also suggested by reactions to electrical stimulation of human cingulate, which include emotional responses such as fear, pleasure, and agitation (McGraw et al. 1976; Meyer et al. 1973); likewise, human brain imaging studies implicate rostral ACC in the emotional experience associated with guilt, anger, and recollection of traumatic events in trauma-exposed individuals (Dougherty et al. 1999; Shin et al. 1999, 2000).

Somatosensory system

Visceral and cutaneous pain resulted in similar activity in S2 cortex. This activation is consistent with other studies of both visceral and somatic pain (Aziz et al. 1997; Binkofskii et al. 1998; Coghill et al. 1994; Talbot et al. 1991). Although animal data suggest that <3% of S2 neurons respond to noxious stimulation (Robinson and Burton 1980), a recent human evoked-potential study using cutaneous laser stimulation argues for the existence of direct nociceptive input into S2 (Lenz et al. 1998). Furthermore, data from fMRI and MEG studies suggest that S2 is the primary cortical target for esophageal afferent fibers (Binkofskii et al. 1998; Schnitzler et al. 1999) and likewise that S2 is a predominant site of activation resulting from innocuous distension of the rectum (Aziz et al. 2000; Binkofski et al. 1998; Hobday et al. 2001; Kern et al. 1998).

Distal esophageal distention activated the inferior part of S1 cortex, which represents the intra-abdominal region in the sensory homunculus (Penfield and Rasmussen 1955). A recent histological study in rats showed that this area has extensive vagal inputs and most likely is a visceral part of S1 (Ito 2002).

Similar activation has been observed after nonpainful distension of the distal esophagus and the rectum (Aziz et al. 2000; Hobday et al. 2001), suggesting that it is indeed a site of visceral representation. Interestingly, esophageal distention resulted in a subthreshold activity in the trunk area of S1 (r = 2.8), suggesting a possible substrate for the referral of esophageal pain to the chest, which we observed psychophysically (Strigo et al. 2002). The finding that esophageal stimulation tended to activate trunk S1, whereas cutaneous heat did not activate the esophageal S1 area, is consistent with the observation that visceral pain can be referred to the skin but not visa versa.

M1 and SMA

Painful visceral stimulation resulted in bilateral activity in M1, whereas painful cutaneous stimulation did not activate this area. The area of M1 activated by esophageal distention most likely corresponds to the area responsible for vocalization and salivation (Penfield and Rasmussen 1955) and has been shown to be activated by nonpainful distal esophageal distention (Aziz et al. 2000). Increased M1 activity found in our study after visceral pain is not surprising because esophageal balloon distension induces salivation and peristaltic contractions (Yamamoto et al. 1998). Moreover, a similar area of M1 is activated by swallowing (Hamdy et al. 1999), and an urge to swallow is induced by balloon distension. On the other hand, because the BOLD signal reflects predominantly presynaptic activity, the motor cortex activation may represent sensory afferent input to motor cortex that may or may not have an immediate influence on the motor response (for review, see Strick and Preston 1983).

Visceral pain also significantly activated SMA, and cutaneous pain showed a similar tendency (r = 4.2). This area is thought to be responsible for motor control, motor planning and execution (for review see Picard and Strick 1996). Moreover, its activation has been observed in other pain studies and is probably the result of a desire to avoid noxious stimulus (Becerra et al. 1999; Coghill et al. 1994; Iadarola et al. 1998; Kwan et al. 2000), which is consistent with the slightly higher activity therein after visceral stimulation.

Subcortical activation

Both visceral and cutaneous pain resulted in activation loci in the thalamus, basal ganglia, and cerebellum, suggesting that
both types of information are transmitted through these regions. Single-unit studies of neurons in the thalamic ventro-posterior region in animals show convergence of visceral and cutaneous information (Bruggemann et al. 1994; Chaudhury et al. 1992; Kawakita et al. 1993), consistent with the similar thalamic activation by these two stimulus modalities.

A similar multifocal and bilateral cerebellar activation was evoked by visceral and cutaneous pain, consistent with the existence of multiple somatotopic maps in this brain structure (Bower and Kassel 1990; Bushara et al. 2001; Shamas et al. 1978). The cerebellum has been implicated in the control of various functions, including motor, sensory, cognitive, and, according to the recent evidence, nociceptive activities (Bower 1997; Ekerot et al. 1991; Gao et al. 1996; Saab et al. 2000). Several previous human and animal imaging studies reported activity in the cerebellum after painful somatic and visceral stimulation (Becerra et al. 1999; Casey et al. 1994; Derbyshire and Jones 1998; Iadarola et al. 1998; Mertz et al. 2000; Saab et al. 2000; Svennson et al. 1997). Furthermore, in a recent study, electrical and chemical stimulation of cerebellar cortex suggested that the cerebellum plays a role in the modulation of visceral and somatic nociceptive responses (Saab and Willis 2001; Saab et al. 2001), and it is likely that this modulatory role is similar during pain arising from both skin and viscera.

**Prefrontal cortex**

Cutaneous but not visceral pain activated the right ventrolateral prefrontal cortex (area 10). Only three of seven subjects showed activity in this region during painful cutaneous heat stimulation, suggesting that this activation may not be directly linked to nociceptive processes. Prefrontal activity similar to that evoked by cutaneous stimulation in this study has been previously observed in a number of human pain studies (Chartron et al. 2001; Coghill et al. 1999; Hsieh et al. 1999; Iadarola et al. 1998). However, Coghill et al. (1999) noted that the prefrontal pain-evoked activity does not show the same systematic relationship to perceived pain intensity seen in other regions but instead shows the highest activity when a stimulus just becomes painful with lower activation associated with higher levels of pain. These findings suggest that the prefrontal pain-evoked activity is related to a cognitive variable, possibly episodic memory associated with rating the stimulus, spatial features of stimulation evaluation, or escape behavior induced by “escapable” stressors, such as cutaneous pain. The latter is consistent with interconnectivity of this area with dorsolateral PAG in macaque monkey mediating active (cutaneous pain) but not passive (visceral pain) emotional coping strategies (Bandler et al. 2000).

**Caveats**

In the preceding discussion, we argue that visceral and cutaneous stimuli produce differential patterns of cerebral activation consistent with differences in quality, affect, and behavioral reactions evoked by these two modalities of noxious stimulation. An alternative explanation could be that differences in cerebral activation are simply due to differences in the unpleasantness attributed to visceral and cutaneous stimuli. While certain characteristics of cerebral activation evoked by visceral stimuli may well be due to the distinct unpleasantness that characterizes this stimulus modality, such an explanation would suggest that a similar pattern of activation would have been observed for cutaneous stimuli if the level of stimulation had been increased enough to evoke a greater degree of unpleasantness. Previous data, however, argue against such a direct influence of increasing unpleasantness on changing patterns of activation. Coghill et al. (1999) showed that with different levels of cutaneous noxious heat, which produce different ratings unpleasantness (as a function of pain intensity), the degree of activation in ACC, S1, S2, and IC varied, but the location remained constant. In the present study, subjects’ ratings of absolute unpleasantness evoked by cutaneous heat pain were somewhat lower, but not significantly different from that evoked by visceral stimulation. Although this absence of significance may reflect some “noise” inherent to such behavioral measures, we feel that a simple difference in the degree of unpleasantness attributed to the two stimulus modalities is not the most parsimonious explanation for the distinctly different patterns of cerebral activation that we observed for visceral and cutaneous noxious stimulation.

**Conclusion**

Results of the present study demonstrate that visceral and cutaneous pains of similar intensity have differential representation in somatosensory, motor, and limbic areas of the brain that could underlie the differential perceptions and reactions associated with stimulation of skin and viscera. On the other hand, the similar activations within S2 and posterior-parietal cortices, as well as thalamus, basal ganglia, and cerebellum suggest the existence of a common cortical and subcortical network that identifies a stimulus as painful, independent of the nature of that pain.

Special thanks to Dr. G. J. Bennett for useful comments on the manuscript. This research was supported by Canadian Institute of Health Research.

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