Functional MRI of Pain- and Attention-Related Activations in the Human Cingulate Cortex

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INTRODUCTION

Several lines of evidence support a role of the anterior cingulate cortex (ACC) in pain (Vogt et al. 1993). Anatomical studies have demonstrated projections to the ACC from thalamic midline and intralaminar nuclei (Marini et al. 1996; Musil and Olson 1988; Robertson and Kaitz 1981; Vogt et al. 1979, 1987), and the ventral part of the ventrobasal complex (Yasui et al. 1988). These nuclei receive input from the spinothermal tract and have been shown to contain nociceptive neurons (Albe-Fessard et al. 1985; Apkarian 1995; Craig 1987; Craig et al. 1994). Thus the ACC likely receives information concerning nociception. Electrophysiological recordings in the rabbit (Sikes and Vogt 1992) and human (Hutchison et al. 1993) have located nociceptive neurons in the posterior part of the ACC, a region consistent with posterior area 24 (i.e., 24*). Psychophysical testing has demonstrated hyperpathic-type responses to thermal stimuli in a patient who had undergone cingulotomy (Davis et al. 1994). Surgical cingulotomy has been shown to reduce chronic intractable cancer pain (Bouckoms 1989; Pillay and Hassenbusch 1992) in humans. In rats, analgesia results from interruption of ACC function by lidocaine block (Vaccarino et al. 1989). Positron emission tomography (PET) imaging studies have revealed a high concentration of opiate receptors in the human ACC (Jones et al. 1991b) and have consistently shown ACC activation during application of noxious heat (Casey et al. 1994, 1996; Coghill et al. 1994; Craig et al. 1996; Jones and Derbyshire 1995; Jones et al. 1991a; Talbot et al. 1991) in normal subjects and in patients with chronic pain (Hsieh et al. 1995).

The ACC is thought to be involved in processing many sensory, motor, and cognitive signals (Devinsky et al. 1995; Paus et al. 1993; Vogt et al. 1993). Vogt et al. (1995) delineated the human ACC as Brodmann’s areas 25 and 24 and the cingulofrontal transition area 32. The more caudal parts of areas 23 and 24 can be referred to as 23* and 24*, respectively. Therefore the designation of posterior ACC or posterior area 24 used by some authors would be synonymous with area 24*.

In a review of experimental animal and human studies by Devinsky et al. (1995), the ACC was divided into two broad divisions; a rostral affect division (areas 25, 33, and 24) and a caudal cognition division (areas 24* and 32*). The PET studies compiled by Hsieh et al. (1995) revealed separate pain- and attention-related ensembles within the cognitive division of the ACC. The role of the ACC in cognitive processes has been studied with the use of attention-demanding cognitive tasks such as those that involve response selection. A variety of cognitive tasks in the language (e.g., word generation), sensorimotor (e.g., go/no go), and visual (e.g., Stroop test) domains involves response selection and thus attention. One common finding of imaging studies of attention-demanding tasks is the activation of the ACC (see reviews by Hsieh et al. 1995; Picard and Strick 1996). The exact location of this activation varies among studies, but the more anterior and sometimes dorsal region, areas 32 and anterior 24, seem to be involved.
Most imaging studies of pain and attention have used PET technology in a multisubject design. Some limitations inherent to those studies are avoided with functional magnetic resonance imaging (fMRI). fMRI is a noninvasive technique based on the detection of blood oxygenation (blood oxygenation level detection, bold) and blood flow (Cohen and Bookheimer 1994; DeYoe et al. 1994). fMRI affords relatively high spatial resolution, on the order of 1–2 mm in plane. Because fMRI is fast (a few s per scan), repetitive acquisition of each brain slice in a single session facilitates a single-subject study. We have recently described a technique of transcutaneous electrical nerve stimulation (TENS) of the median nerve to study the somatosensory cortex involvement in pain perception (Davis et al. 1995a). Only brief reports of pain-related ACC activations with the fMRI technique have been published (Davis et al. 1995a; DeLaPaz et al. 1995; Gelhar et al. 1994; Jones et al. 1995). Therefore in the present study we have undertaken an examination of the pain-related activations in the ACC in individual subjects. As a first step toward understanding ACC processing of painful stimuli, TENS of the median nerve was used to evoke pain. Because of the proximity of the ACC attention executive area (Posner and Raichle 1994) to potential pain-related ACC areas within Devinsky’s “cognitive division” (Devinsky et al. 1995), this study also examined the ACC activations during a task that required attention. Some of these findings have been presented in abstracts (Davis et al. 1995b, 1996).

Methods

Subject population

A total of 14 healthy subjects gave informed consent to undergo fMRI during application of painful and cognitive tests. Four of these subjects were not able to hold their heads steady enough to avoid noticeable head motion throughout the imaging session. Therefore, data reported are from only 10 subjects. This subject population comprised 4 males and 6 females with an average age of 31 ± 6 (SD) yr, and all but one male were right handed. All procedures were given ethics approval by the University of Toronto Human Subjects Review Committee. All subjects participated in the TENS pain task (see below), but only eight subjects were additionally tested with the use of the TENS tingling and attention tasks (see Table 1). Before imaging, the details of each experimental task were explained and test TENS stimuli were given to ensure that the electrodes were adequately positioned over the median nerve and to familiarize each subject with the tingling and painful sensations evoked by the stimuli. Subjects were also instructed to verbally rate the intensity of painful stimuli on a scale from 0 (no pain) to 10 (most intense pain imaginable).

Tasks

TENS TASKS (PAIN, TINGLING). TENS of the right median nerve was delivered via a clinical neuromuscular stimulator (Medtronic respond II, model 3128). The stimulator device was connected to two surface electrodes placed on the subject’s volar forearm on the right wrist. Stimulation was applied at 50 Hz, and the intensity was set according to verbal reports of either nonnoxious tingling (tingling task) or pain (pain task) from each subject just before each of the six periods of imaging. Precautions were taken to avoid any inadvertent stimulation due to interaction of the TENS stimulator, leads, and electrodes with the radiofrequency pulses.

<table>
<thead>
<tr>
<th>Subject</th>
<th>Attention task</th>
<th>Tingling task</th>
<th>Pain task</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3.0 ± 0.4</td>
<td>No activation</td>
<td>2.4 ± 0.3*</td>
</tr>
<tr>
<td>2</td>
<td>Not tested</td>
<td>No activation</td>
<td>2.0 ± 0.5</td>
</tr>
<tr>
<td>3</td>
<td>2.5 ± 0.5</td>
<td>No activation</td>
<td>2.6 ± 0.4*</td>
</tr>
<tr>
<td>4</td>
<td>Not tested</td>
<td>No activation</td>
<td>2.8 ± 0.7</td>
</tr>
<tr>
<td>5</td>
<td>2.3 ± 0.4</td>
<td>No activation</td>
<td>1.6 ± 0.4</td>
</tr>
<tr>
<td>6</td>
<td>2.4 ± 0.4</td>
<td>No activation</td>
<td>4.0 ± 0.7*</td>
</tr>
<tr>
<td>7</td>
<td>3.2 ± 0.4</td>
<td>No activation</td>
<td>2.0 ± 0.5</td>
</tr>
<tr>
<td>8</td>
<td>2.7 ± 0.6</td>
<td>No activation</td>
<td>1.6 ± 0.6</td>
</tr>
<tr>
<td>9</td>
<td>3.3 ± 0.4</td>
<td>Not tested</td>
<td>2.9 ± 0.4*</td>
</tr>
<tr>
<td>10</td>
<td>1.3 ± 0.4</td>
<td>Not tested</td>
<td>1.9 ± 0.5</td>
</tr>
<tr>
<td>Means</td>
<td>2.2 ± 0.4</td>
<td>1.9 ± 0.5</td>
<td>2.4 ± 0.2</td>
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Attention task and pain task values are means ± SE. *Omitted trials for which pain ranked as <5/10 did not result in a significant increase in signal intensity.

(see Davis et al. 1995a). Briefly, a DC-powered TENS unit with long leads that did not have loops and with nonmagnetic contacts was used. With these measures in place, there were no adverse effects of TENS stimulation of the median nerve. However, it should be noted that a different electrode orientation, such as is necessary to activate the superficial peroneal nerve, did result in inadvertent interference between TENS stimulation and the radiofrequency pulses and prevented study of TENS of this nerve.

Attention Task. A word generation cognitive task was used to study the effect of attention. In a variant of the category fluency task (Lezak 1995), the subject was requested to generate as many words as possible within a given category of objects (animals, fruits, vegetables, etc.) or proper names (e.g., actors, politicians, etc.). One subject was in addition asked to generate words beginning with a particular letter. Subjects were instructed to perform these cognitive tasks without articulating the words. Each category, proper name, or letter was given to the subject immediately before each of the six imaging periods.

Control Tasks. For each subject, a rest task was interleaved with the experimental tasks (see below). During this control the subjects were told to relax, and in some cases to just listen to the sound of the magnet. A simple counting task was additionally used for four subjects. During the counting task, the subject was requested to count forward by ones. The starting number was incremented by 100 (i.e., 100, 200, 300, etc.) in successive task periods.

Experimental protocol

Imaging Parameters. A 1.5-T GE Signa Advantage MRI (General Electric Medical Systems, Milwaukee, WI) scanner was used to obtain images of the ACC in the sagittal plane. The subjects were positioned supine on the MRI table with head stabilized in the head coil with pillows and foam padding. Functional images of a single sagittal slice 3–4 mm lateral to midline were obtained with the use of a gradient echo technique with the following parameters: repetition time = 68 ms, echo time = 40 ms, scan time = 28 s per six images (~4.7 s/image), flip angle = 45°, slice thickness = 4 mm, field of view = 48 × 24 cm, data matrix = 256 × 128 for an in-plane resolution of 1.9 mm. Images were collected from the left hemisphere (contralateral to the peripheral stimulus) in all subjects. In addition, the right ACC (contralateral or ipsilateral to the stimulus) was imaged in three laterality experiments. A high-resolution anatomic image T2-weighted fast spin echo or T1-weighted gradient echo of the same slice was then acquired to serve as a background for the activation map.
TASK SEQUENCES. The timing and sequence of image acquisitions are shown schematically in Fig. 1. For each subject, images were obtained during six repetitions each of a rest period and various tasks presented in an interleaved sequence. Because 6 images were obtained in each of the six repetitions, a total of 36 images was obtained for any particular task. A typical experiment would consist of a rest period, followed by the attention task, the TENS tingling task, and the TENS pain task. A transition period of ~10–15 s was maintained between tasks, during which time instructions were given for the next task. Before the TENS tasks, the stimulus intensity was adjusted to achieve the desired sensation. The subject was requested to indicate the presence of nonnoxious tingling, or a very intense level of pain. In eight subjects, the TENS intensity was set at a mild pain level (i.e., a rating of <5/10) for one of the six trials. After the termination of each TENS pain task, the subject was requested to rate the intensity of the evoked pain on a scale from 0 to 10.

Data analysis

Raw data from each experimental subject were checked for misregistration. Of the initial 14 subjects in the study, 4 were omitted from further data analysis because of a significant degree of head movement during the scanning procedure. Data from each subject were analyzed to locate task-related significant increases or decreases in signal intensity. All data were subjected to a pixel-by-pixel analysis of the signal intensity differences between rest (control) and task images with the use of software developed in house and also with the Analysis of Functional Neuroimages (AFNI) software (R. W. Cox, Biophysics Research Institute, Medical College of Wisconsin, 1995). The AFNI software was used to perform statistical analyses and also enabled superposition of functional data onto high-resolution anatomic images. Regions of statistically significant signal intensity changes are referred to as "activations." Each pixel was screened for significant activation with a one-tailed t-test at P < 0.001 for data analyzed with in-house software, or with Pearson’s linear correlation coefficient (r) > 0.3 (1-tailed) for data analyzed with AFNI. All data reported were clusters of two or more pixels, significant at r > 0.4, except for one subject whose pain-related activation was significant at r = 0.32. Statistical maps were superimposed on the high-resolution anatomic image obtained for each subject. The pixels within each region of interest (ROI) were further analyzed to assess task-related changes in signal intensity. The region used for the ROI analysis was the maximum number of the significant pixels in the ROI that were in a contiguous rectangular configuration. Percent changes in signal intensity during a task compared with rest were calculated in two ways: 1) overall mean percent change for the whole session (i.e., typically mean of 36 images during task compared with mean of 36 images during rest) and 2) mean percent change during each task repetition (i.e., mean of 6 images during task compared with overall mean during rest). This latter calculation allowed an assessment of the relationship between stimulus intensity and ACC activation.

RESULTS

Pain-related activations

All subjects were capable of differentiating stimulation-evoked paresthesia from pain. TENS-evoked painful sensations were sensed predominantly in the peripheral distribution of the median nerve. All subjects tolerated the stimuli and were able to provide verbal ratings of the pain intensity evoked during each trial. Typically, subjects provided subjective reports of the quality of pain with the use of descriptors such as deep, achining, cramping, tight, warm, unpleasant, and sharp.

The TENS pain task activated a small region within the contralateral ACC in each subject. There were no observable decreases in signal intensity in the ACC during the TENS task. An ROI analysis of the pixels with the greatest statistical significance within each activation revealed the pain-related activation to be a 2–4% increase as compared with the mean resting intensity within those pixels. The activations observed in each subject are shown in Table 1 and yield a grand mean ± SE change across all subjects of 2.4 ± 0.2%. An example of TENS pain-related activation but not painful sensations were sensed predominantly in the peripheral distribution of the median nerve. All subjects tolerated the stimuli and were able to provide verbal ratings of the pain intensity evoked during each trial. Typically, subjects provided subjective reports of the quality of pain with the use of descriptors such as deep, achining, cramping, tight, warm, unpleasant, and sharp.

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activated during moderate to intense pain but not during a mild pain (Fig. 3A, on5). The more anterior ROI appeared to be activated even during mild pain (see Fig. 3B, on5) and did not appear related to the subjective ratings of pain intensity (see below). This double activation was not seen for any of the other subjects.

For eight of the subjects, the TENS stimulation was adjusted to deliver intense pain (≥5/10) for five of the trials and a less intense pain in one trial. The TENS-related activation of four of these eight subjects showed a clear dependence of signal increases on the pain intensity. The example shown in Fig. 3A (also see Fig. 6) indicates that in this subject an intense level of pain was necessary for ACC activation in that ROI. The data for each trial in the TENS pain task for all subjects are shown in Fig. 4. Regression analysis of these data revealed a significant linear relationship \( F(1,58) = 18.356, P < 0.001 \) between the change in signal intensity and perceived pain \( r = 0.49 \). One source of variability in the data as shown is the normalization factor for each subject, that is, the variability (albeit not statistically significant) in the resting signal intensity level used to calculate signal intensity changes during the task. However, despite variability across subjects, the data suggest that very intense pain results in a greater increase in signal intensity than mild pain.

The exact location of the pain-related ACC activation varied among subjects. The pain-related activation in the subject shown in Fig. 2A was in the middle of the cingulate near the posterior part of the ACC. In each subject, the pain activation was typically a small cluster of two to four pixels in this posterior ACC region. In some subjects the activation was on the superior margin of this part of the ACC (see Fig. 5A). The anatomic complexity of the cingulate infolding contributed to the difficulty in precise localization of the

FIG. 2. Example of TENS- and attention-related activations in subject 1. Statistically significant activations \( r \geq 0.5 \) associated with each of 4 tasks, indicated by red pixels, have been overlaid on a high-resolution fast spin echo sagittal image through left cingulate cortex. Each activation map displays signal intensity \( A \) or nonpainful \( B \) intensity or during nonarticulating verbal fluency conditions. Note lack of activation during nonpainful TENS, and 2 regions of interest (ROIs) with painful TENS. Purple arrow: pain-intensity-related ROI. Blue arrows: attention-related ROI (see text for explanation). Also note congruent ROIs activated with either of 2 verbal attention tasks (blue arrows).
mated by relation of the ROI to the anterior border of the fornix, anterior commissure, and corpus callosum. The dorsoventral position of the activation was approximated from the distance of the ROI to the superior border of the corpus callosum and the cingulate sulcus. The group data clearly show a concentration of pain-related activations in the posterior aspect of area 24.

Attention-related activations

Attention-related ACC activation was observed for all eight subjects tested. The signal intensity changes associated with these tasks were always increases in signal intensity. The individual data shown in Table 1 indicate a range of signal intensity increases of $1.3 - 3.3\%$ above resting levels, with an overall mean across subjects of $2.2 \pm 0.4\%$ (mean $\pm$ SE).

The attention tasks generally activated a region in the upper bank of the ACC. These activated regions were larger than the pain-related activations, typically $>4$ pixels. In many cases the activation spilled into more superior regions, considered cingulate motor areas, and sometimes even into the supplementary motor cortex. Interestingly, in the subject that performed two variants of the verbal fluency attention task, activations were indistinguishable (see Fig. 2, C and D). An example of one subject with a very superior activation is shown in Fig. 5B. In this subject, the attention-task-related activation is superior and anterior to the painful TENS activation. This relationship between attention and pain activations was a consistent finding. That is, within each subject the attention-related activations were always

![Figure 3. Signal intensity changes during pain and attention tasks in subject 1. Percent signal intensity (mean $\pm$ SE) changes during TENS stimulation at painful intensities ("on") compared with no TENS stimulation ("off") when the subject is at rest are shown for each of 6 repetitions of TENS and rest for the ROI in posterior area 24 (A; Fig. 2, purple arrow) and in the more anterior ROI (B; Fig. 2, blue arrow). Subject’s pain rating for each TENS applications is also shown. Of note is significant increase in anterior but not posterior ROI during “on,” which was only mildly painful. C: signal increases associated with silent generation of proper names (pn) are shown for the ROI in the anterior cingulate cortex (ACC) (Fig. 2, blue arrow). Proper name categories: pn1, actors; pn2, politicians; pn3, cities; pn4, streets; pn5, countries; pn6, authors.

A composite map of pain-related cingulate activations in all subjects is shown in Fig. 7. The variability in subjects' cingulate anatomy (e.g., double vs. single cingulate sulcus) precludes an exact composite map of all data. However, it was possible to approximate the location of all subjects' activations as projected onto a sagittal section 3 mm from midline according to the atlas of Talairach and Tournoux (1988). This was accomplished by the use of the relative relationship of each subject’s activation to anatomic structures visible in the high-resolution single slice obtained for that subject (e.g., size and position of corpus callosum, fornix, etc.). The length of the corpus callosum gave one index of the relative size of the subject’s brain and the atlas section. The anterior-posterior position of the activation was approximated by relation of the ROI to the anterior border of the fornix, anterior commissure, and corpus callosum. The dorsoventral position of the activation was approximated from the distance of the ROI to the superior border of the corpus callosum and the cingulate sulcus. The group data clearly show a concentration of pain-related activations in the posterior aspect of area 24.
FIG. 5. Example of painful TENS- and attention-related activations in subject 9. Statistically significant activations (r ≥ 0.5), indicated by red pixels, have been overlaid on a high-resolution (T1-weighted gradient echo) sagittal image through left cingulate cortex. A: TENS stimulation at a painful intensity. B: verbal fluency attention (category) task.

anterior and superior to the pain-related activation. The group data for all attention-related ACC activations are shown in Fig. 7.

Another example of the relationship between pain- and attention-related activation is shown in Fig. 2. In this subject, the attention tasks resulted in two major activations, one in the ACC and the other on the dorsal bank of the cingulate sulcus. This latter region is most likely in area 32. Interestingly, the more anterior ACC activations in this subject during either the attention or painful TENS task were similar (see Figs. 2 and 3). A key finding (as mentioned above) is that the TENS activation in this ROI was not related to pain intensity (see Fig. 3B, on5). Therefore this region is likely associated with attentional processes, possibly common to both tasks.

Controls and laterality

The TENS tingling task did not result in activation of the ACC in any of the subjects. Also, in pilot studies it was found that a flexion-type movement such as making a fist also did not activate the ACC. This task was used to control for any occasional muscle contractions that may be evoked by intense TENS stimuli.

Three subjects were scanned in a second session to image the right ACC. Pain-related activation was observed for the subject in which the left (contralateral) median nerve was stimulated, but not for the two subjects with right (ipsilateral) median nerve stimulation. The verbal fluency attention tasks yielded activations similar to those observed in the left ACC sessions.

Counting, for most subjects, is an automatic task that requires little attention. Four subjects were studied in the counting task, and images were obtained of the left ACC for three subjects and in the right ACC for one subject. No activation was observed for the right ACC session or for two of the left ACC sessions. In one subject there was some counting-related activation in the left cingulate. This activation was very weak and, interestingly, overlapped the region activated during the verbal fluency task.

DISCUSSION

In this study we demonstrate that a small region of the posterior part of the ACC is activated during moderate to intense pain evoked by electrical stimulation of the contralateral median nerve. The data also indicate that separate regions of the ACC are activated during a painful task versus a nonpainful, attention-demanding cognitive task. The composite map shown in Fig. 7 illustrates the spatial relationship between the pain-related activations and the more anterior attention-related activations.

Pain processing in the ACC

The overall experience of pain can be divided into sensory-discriminative, motivational-affective, and reflexive components (Willis 1985). The classic spinoholamocortical pathway that terminates in somatosensory cortex has been associated with the sensory-discriminative aspects of pain, whereas the medial thalamus and limbic areas associated with nociception are assumed to be involved in the motivational-affective aspects of pain (Bushnell 1995). The ACC is generally considered part of the motivational-affective pain system, mainly because it receives input from medial thalamic nuclei. Typically, designation of a nucleus as a sensory-discriminative rather than motivational-affective center is based on the presence of neurons with properties such as small receptive fields and steep stimulus-response functions. Although the rabbit nociceptive ACC neurons (Sikes and Vogt 1992) do not fit this definition, a small number of human ACC neurons clearly has the ability to encode the intensity of noxious thermal stimuli (Hutchison et al. 1993). Therefore the role of the ACC in intensity coding of pain is
not clear. In the present study, we found that the ACC was not activated by stimuli perceived as mildly painful, but was activated during pain rated as moderate or intense. Although our study was not designed to construct detailed stimulus-response functions, the data suggest that the ACC is involved in severe pain. Further studies are underway to specifically address the issue of intensity coding in the ACC.

Data emerging from imaging studies of pain suggest that processing of nociceptive inputs may be affected by the type of pain experience. Blood flow changes in the ACC may vary depending on the quality of pain evoked, whether it is steady or intermittent, and whether it is acute or chronic. Cortical activations have been reported with PET or single photon emission computed tomography (SPECT) for noxious heat (Casey et al. 1994, 1996; Coghill et al. 1994; Craig et al. 1996; Jones et al. 1991a; Talbot et al. 1991) or cold (Craig et al. 1996) stimuli with a contact thermode and for tonic cold immersion pain (Casey et al. 1996; Di PIERO et al. 1994). However, a SPECT study of tonic hot water bath pain found cortical decreases (Akparian et al. 1992). In a recent study by Casey et al. (1996), there was a greater increase in the ACC regional cerebral blood flow associated with noxious tonic cold stimuli compared with noxious repetitive heat stimuli, and the peak voxels due to the two stimulus modalities were in slightly different parts of the posterior ACC. Furthermore, Hsieh et al. (1995) found right ACC activation in patients with painful neuropathy, regardless of the laterality of chronic neuropathic pain. The present findings did not bring to light any evidence for this laterality with acute TENS-evoked pain, suggesting a difference in the processing of acute versus chronic pain in the ACC.

Specificity of function and location of pain activations

Had all our paradigms activated the ACC, it could be hypothesized that the function of the ACC is merely a nonspecific sensory-cognitive integration center. However, ACC activation was not observed during the TENS tingling task, the ipsilateral pain task, or many of the mild pain or counting tasks. These findings are consistent with recent PET studies (Casey et al. 1996; Craig et al. 1996) that reported ACC activation during noxious but not nonnoxious thermal stimuli. Furthermore, the pain-related and attention-related activations were nonoverlapping within individual subjects. Therefore the data indicate discrete functional regions within the ACC.

One advantage of fMRI is its spatial resolution in the order of 1–2 mm. With this precision, we were able to locate pain-related signal intensity changes in a very small region in the posterior part of the ACC. This region is consistent with Brodmann’s area 24. Vogt et al. (1995) divided area 24 into several subregions by constructing a flat map of the human cingulate. Because of the limitation of our single slice technique, we cannot precisely place our activation in any one of the regions, although activations appear to reside in area 24*. Previous PET imaging studies of pain have found a similar location of pain-related activations (Casey et al. 1994; Coghill et al. 1994; Hsieh et al. 1995, 1996; Jones et al. 1991a; Talbot et al. 1991). On the basis of these previous findings, we chose our slice to span most of area 24 (i.e., from 2 to 6 mm lateral to midline). Although we likely obtained most of the pain-related ACC activation, additional more medial or lateral activations could have been missed. Therefore this study cannot define the exact size of pain-related activations in the ACC. Similarly, limitations inherent to the PET technique restrict comparison of the size of pain-related activations with PET studies and the present fMRI study. The seemingly much larger region of activation reported in PET studies may be affected by image manipulations. Therefore the size of the region within ACC devoted to pain-related function cannot be resolved with these data alone. A small pain-related region might seem at odds with the proposed significance of the ACC in pain processing. However, it would not be surprising given the small numbers of cortical nociceptive neurons located in the human ACC (Hutchison et al. 1993).

ACC regions involved in attention and pain

The ACC is thought to be involved in many aspects of cognition, including attention. Posner and Raichle (1994) refer to the ACC as the executive area for attention on the basis of PET imaging and lesion studies. The functional subdivisions of the medial wall as proposed by Picard and Strick (1996) suggest that the more dorsomedial aspect of...
the ACC may be involved in novelty. This is consistent with a designation of this area as an “executive attention” zone, because the ability to selectively attend to a stimulus is likely related to the novelty of the stimulus.

Our results provide evidence that at least two ACC areas are involved in pain and attention-demanding cognitive tasks. The attention tasks activated areas 32’ and 24/24’, which is consistent with previous reports in which PET was used to study word retrieval (Damasio et al. 1996; Warburton et al. 1996) or other attention-demanding tasks (Pardo et al. 1990; Raichle 1994). Devinsky et al. (1995) suggested that area 32’, which is cytoarchitectonically a frontocingulate transition area (Vogt et al. 1995), may be more involved in ‘‘tasks requiring target assessment and attention for linguistic and other features of the sensory environment,’’ whereas area 24’ may be involved in ‘‘cognitively demanding tasks that may or may not require a movement.’’ Rather than one central executive attention system, our results support the idea that the ACC contains several spatially distinct systems. The concept of separate functional areas has also been proposed by Picard and Strick (1996), who subdivided the medial wall into at least four areas on the basis of motor task complexity. Not addressed in this review is the laterality of attention-related activations. The present study located ACC activation in both the left (8 subjects studied) and right (3 subjects studied) hemispheres. Some studies employing word generation tasks have found ACC activation confined to the left hemisphere (for review see Warburton et al. 1996). Other studies of attention employing the stroop task reported right (Pardo et al. 1990) or left (George et al. 1994) ACC activation. However, given the proximity of these activations to the midline and the spatial resolution of PET, it is possible that the right ACC may contribute to these activations.

The ACC seems to be involved in attention-demanding language tasks regardless of articulation. For example, a recent PET investigation showed ACC activation with a verb generation task even though the subjects did not articulate the words (Warburton et al. 1996). This is in agreement with extensive clinical studies that demonstrate that lesions confined to the ACC do not result in akesia or mutism (Devinsky et al. 1995). In another PET study of word generation where participants did articulate, the ACC was activated when the task was novel (i.e., effortful) but not when the task was practiced (Raichle 1994). When there is articulation, automatic or nonarticulation language tasks such as reading are associated with little if any ACC activation (Petersen et al. 1988). Similarly, in the current study, the attention-demanding word generation task activated ACC whereas the less attention-demanding counting task did not activate the ACC in most instances. These findings are interesting in light of a recent PET study by Murtha et al. (1996) that found that ACC activation associated with various cognitive tasks depended on an anticipatory state and not the task itself. In this study, the region activated during the anticipatory state is consistent with the activation we obtained during attention-demanding tasks. Therefore these neuroimaging studies converge on an attentional rather than a motor role for the ACC in language. Similarly, the TENS pain task was unlikely to be greatly influenced by motor effects. Although most painful stimuli evoke a strong escape behavior, subjects questioned about the stimuli in this study did not report a desire to move during painful TENS. This may be a result of the subject’s knowledge that the pain felt in the hand was actually due to the electrical stimulation via the electrodes taped to the wrist. So, unlike the urge to remove the hand from a painful hot plate, for instance, subjects appreciate that they cannot really escape the pain due to the TENS.

The study of pain in the awake, behaving human is a challenge because many cognitive processes can accompany pain perception. Electrophysiological studies in the medullary dorsal horn and thalamus and psychophysical studies have demonstrated task-related responses such that a behavioral state can enhance nociceptive neuronal responses and task performance (Bushnell and Duncan 1989; Bushnell et al. 1985; Dubner et al. 1981; Duncan et al. 1987). In these studies, when a subject was attending to a painful stimulus (via an appropriate cue), there was an enhanced response. These studies demonstrate the contribution of the behavioral state, and in particular attention, to nociception. In imaging studies, it is essential to control for as many variables as possible because one can never know with absolute certainty what a subject is thinking, feeling, or experiencing. In the present study, we compared ACC activation associated with a pain task with ACC associated with an attention-demanding task. However, this comparison is complicated by the use of separate pain and attention tasks in different domains (i.e., somatic vs. verbal, cognitive). Furthermore, because subjects were instructed to provide ratings of pain intensity at the end of each stimulus trial, they likely attended to the stimulus for at least part of the stimulus duration. Therefore, although we found separate regions of activation during the attention and pain tasks, we cannot accurately assess the attentional component of pain per se. To better address the attentional component of pain, one would need to employ a task that involves selective attention or distraction during application of painful stimuli. The findings do reveal that these two tasks activate separate regions of the ACC even though both may have attentional demands, suggesting that the attentional component of the two tasks may differ.

### Study design and limitations

This study was undertaken to apply a newly developed imaging technique, fMRI, to the study of pain. The impetus was to examine the involvement of the ACC in pain with the use of an imaging tool that has finer spatial resolution than previous imaging technologies such as PET. Another advantage of fMRI is the ability to perform comparative studies of different cognitive processes in a single subject during a single experimental session. This design eliminates the variability imposed by repeated testing (i.e., possible daily fluctuations, etc.) and the potential loss of information imposed by averaging across subjects. However, the cost of improved spatial resolution is that fMRI studies must deal with potential sources of motion artifact. To minimize such artifacts, subjects were told to refrain from speaking during image acquisition. Because this required subjects to perform the word generation tasks silently, we could not monitor the performance of the subjects during these tasks. But, the subjects appeared to have been properly performing the task.
FIG. 7. Composite map of all pain- and attention-related activations in ACC. Data were pooled for all subjects and projected onto sagittal section 3.0 mm lateral to midline according to Talairach and Tournoux (1988). Approximate locations of each subject’s pain-related (P) and attention-related (A) activations in ACC are indicated and reveal A and P clusters across subjects. Within each individual subject, attention-related activation was anterior and/or superior to pain activation (not shown; see text).

on the basis of subject interviews during training and after imaging sessions. This limitation precluded correlation analyses of ACC activation with word generation performance.

One potential limitation of our methodology was imposed by the mode of stimulation. To study the dependence of TENS-related activation on pain intensity, one of the six repetitions of TENS was kept at a mild level of pain. If we had delivered more repetitions of different levels of pain, we would have had to either increase the overall length of the session or replace some of the more intense stimuli with mild stimuli, thereby reducing the number of intense pain stimuli. Longer sessions with more TENS stimuli tend to decrease the compliance of the subject to tolerate the painful stimuli and increase the likelihood of head movement. Therefore the design chosen was intended to ensure that sufficient data were collected during intense pain while still enabling a study of the pain intensity-activation relationship.

In fMRI, the desire to localize neuronal activations to within 1- to 2-mm spatial resolution causes a significant problem in statistical analysis of the data. In each imaging slice there are typically ~10,000 pixels within the brain. If one chooses to set the individual pixel false positive rate at $P < 0.05$, a Bonferroni correction for multiple comparisons would yield a very conservative $P$ value of $5 \times 10^{-6}$ (i.e., 0.05/10,000). In practice, this $P$ value is not workable because of the low effect size in typical fMRI experiments. Therefore, to reduce the contamination by false positive pixels, in the present study we excluded single-pixel ROIs. Further constraints on the data (e.g., large clusters) could not be imposed in this study because of the small region of ACC activation during the pain task.

Imaging techniques such as fMRI do not directly measure neuronal activity, but rather measure vascular changes such as oxygenation and flow. These measured changes are related to metabolic and neuronal activity (Fox et al. 1988; Magistretti and Pellerin 1996; Malonek and Grinvald 1996; Narayan et al. 1995), although the exact relationship of this coupling is not known. Also, little is known concerning the underlying neuronal locus of fMRI activations (e.g., cell bodies or synapses) or the effect of excitatory versus inhibitory synapses. The energy requirement for excitatory and inhibitory synaptic activity may be similar although the resultant postsynaptic consequences of events of excitatory synaptic events may involve greater energy expenditure. These considerations must be kept in mind when making conclusions about neuronal activation or deactivations during fMRI tasks.

Significance of findings

Our findings shed light on pain- and attention-related cognitive processes. A strength of our study methodology is the ability to assess functionality in multiple tasks within individual subjects. The data clearly distinguish separate re-
regions of the ACC activated during the pain and attention tasks. These findings are consistent with those of Hsieh et al. (1995), whose review across many PET studies showed that pain activations lie in an adjacent ACC ensemble posterior to attention-related cognitive activations. This distinction may have implications in the choice of the optimal cingulotomy lesion site in patients with psychiatric versus chronic pain conditions.

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