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Pain Processing in Four Regions of Human Cingulate Cortex Localized with Co-registered PET and MR Imaging

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Abstract

Neurosurgical and positron emission tomography (PET) human studies and animal electrophysiological studies show that part of the anterior cingulate cortex (ACC) is nociceptive. Since the contribution of the ACC to pain processing is poorly understood, this study employed PET and magnetic resonance (MR) image co-registration in grouped and individual cases to locate regions of altered relative regional cerebral blood flow (rCBF). Seven right-handed, neurologically intact males were subjects; each received neuropsychological and pain threshold testing. Subjects were scanned during infusion of $H_2[^{15}O]$: four randomized scans during innocuous heat stimulation to the back of the left hand and four scans during noxious but bearable heat to the same place. The averaged rCBF values during innocuous stimuli were subtracted from those during noxious stimuli and statistical parametric maps (SPMs) for the group were computed to identify regions of altered relative rCBF. Finally, single-subject PET images of elevated and reduced rCBF were co-registered with MR images and projected onto reconstructions of the medial surface of the hemisphere. The SPM analysis of the group showed one site with elevated rCBF in the midcingulate cortex and one in the perigenual cortex predominantly contralateral to the side of stimulation. There were bilateral sites of reduced rCBF in the cingulofrontal transitional cortex and in the posterior cingulate cortex (PCC). Co-registered PET and MR images for individuals showed that only one case had a single, large region of elevated rCBF, while the others had a number of smaller regions. Six cases had at least one significant elevation of rCBF in the right hemisphere that primarily involved area 24b′; five of these cases also had an elevation in area 32′, while the seventh case had elevated rCBF in these areas in the left hemisphere. The rostral site of elevated rCBF in the group was at the border of areas 24/24′ and areas 32/32′, although most cases had a site of elevation more rostral in the perigenual cingulate cortex. The ACC site of reduced rCBF was in areas 8 and 32 and that in the PCC included much of areas 29/30 in the callosal sulcus, areas 23b and 31 on the cingulate gyral surface and parietal area 7m. The localization of relative rCBF changes suggests different roles for the cingulate cortex in pain processing: (i) elevated rCBF in area 24′ may be involved in response selection like nocifensive reflex inhibition; (ii) activation of the perigenual cortex may participate in affective responses to noxious stimuli like suffering associated with pain; and (iii) reduced rCBF in areas 8 and 32 may enhance pain perception in the perigenual cortex, while that in the PCC may disengage visually guided processes.

Introduction

Neurosurgical observations over the past four decades have shown that disruption of the anterior cingulate cortex (ACC) and/or its underlying white matter, the cingulum bundle, alleviates affective responses to chronic pain without disrupting the discriminative features of the noxious stimulus (Foltz and White, 1962, 1968; Ballantine *et al.*, 1967). Lidocaine block of the cingulum bundle in experimental animals also reduces responses to chronic noxious stimuli such as formalin injection into the hindlimb (Vaccarino and Melzack, 1989). These interventions disrupt the motivational–affective component of pain (Melzack and Casey, 1968), and recent positron emission tomography (PET) studies of regional cerebral blood flow (rCBF) confirm activity in the ACC during the suffering component of pain (Jones *et al.*, 1991a; Talbot *et al.*, 1991; Casey *et al.*, 1994). These PET studies showed that subtraction of images generated during innocuous heat to the skin from those generated during noxious heat stimuli elevate rCBF in a mid-rostrocaudal part of the cingulate cortex.

Although electrical stimulation of the human midcingulate region

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produces a diffuse numbness widely referred to most of the body surface (Van Buren and Fedio, 1976), primate studies of the connections and functions of this region do not support a primary role in sensation or affect, but rather a major involvement in premotor functions. The cortex in the depths of the mid-rostrocaudal cingulate sulcus has the cytoarchitecture of a motor region (Braak, 1976; Matelli *et al.*, 1991), γ projections to the spinal cord (Biber *et al.*, 1978; Dum and Strick, 1993), motor cortex connections (Morecraft and Van Hoesen, 1992; Bates and Goldman-Rakic, 1992), single-neuron discharges with premotor characteristics (Shima *et al.*, 1991) and electrically evoked motor responses that are somatotopically organized (Luppino *et al.*, 1991). Electrical stimulation of the gyral surface at this level of the ACC in humans usually evokes simple skeletomotor responses, particularly by the fingers, hands, lips and tongue (Talairach *et al.*, 1973), and such stimulation in cats inhibits hypothalamically evoked attack (Siegel and Chabora, 1971). Electrical stimulation of the midcingulate gyrus in a human patient with epilepsy evoked the conscious experience of wanting to leave the room, in contrast to the response evoked from the cortex rostral to this area in the perigenual cortex, which evoked an affective experience of fear (Bancaud and Talairach, 1992). The former response may indicate a behaviourally integrated avoidance response to a potentially threatening experience, but does not appear to engage affect *per se* or the details of premotor planning, while the latter response is an emotional response that may not engage a skeletomotor programme.

The above epilepsy case frames the conundrum of current studies of the contributions of the cingulate cortex to pain. The cingulate nociceptive response has been achieved in all PET studies noted; however, the part of the ACC so activated may not account for the suffering response associated with pain. Since one feature of the PET paradigm requires that the subject should not move during noxious but bearable heat stimuli, response inhibition may be the contribution of the midcingulate region to responses to noxious cutaneous stimuli in PET pain paradigms. It is possible that the contribution of the ACC to affect is due to involvement of another part of the ACC during the suffering response (i.e. the perigenual region including areas 24 and 25). Studies of rCBF before and after angina pectoralis induced with the β1 adrenoceptor agonist dobutamine show elevated rCBF in the perigenual part of the ACC and reduced rCBF in the midcingulate region (Rosen *et al.*, 1994). It is well known that the visceromotor control cortex is located in the rostral and ventral part of the ACC (Neafsey *et al.*, 1993). Finally, the observation of reduced rCBF in the posterior cingulate cortex (PCC) during noxious thermal stimulation (Coghill *et al.*, 1994) may suggest an even broader involvement of the cingulate cortex in pain processing. Thus, different divisions of the cingulate cortex may be engaged in elaborating different aspects of pain perception and responses, and these hypotheses are based on a broader understanding of the functional heterogeneity of the cingulate cortex (Vogt *et al.*, 1992; Devinsky *et al.*, 1995).

Every PET study of cerebral pain processing has reported a mean area of activation in the ACC for a group of subjects (Jones *et al.*, 1991a; Talbot *et al.*, 1991; Casey *et al.*, 1994; Coghill *et al.*, 1994). Although it is important to know the site of statistically significant elevation in rCBF, Watson *et al.* (1993) observed a 27 mm variation in the location of V5 among 12 left hemispheres. In terms of pain research, this distance is significant because it represents two times the depth of the cingulate sulcus and about one-third of the rostrocaudal length of the corpus callosum. If each focus of rCBF is small and concentric, each focus may be limited to a single cytoarchitectural subdivision, such as area 24′ (Vogt *et al.*, 1995a). If, however, the foci are larger and/or eccentric to the mean site, they could easily overlap this area and encroach upon area 24 and/or 23. Since each of these potential outcomes has a different functional consequence, it is necessary to determine the extent to which nociceptive responses vary within the cingulate cortex among individuals and how these variations relate to the midcingulate site.

The present study was undertaken in individuals with co-registered PET and magnetic resonance (MR) images of the medial surface of the hemisphere to evaluate the functional morphology of medial systems that subserve pain processing. The following issues were assessed. First, statistical parametric maps (SPMs) of PET images for the group were used to identify areas with either elevated or reduced relative rCBF during noxious heating of the skin. Since the images are derived from a comparison of images during innocuous heat with those during noxious heat, they represent processes that are likely to be associated with suffering, although this does not mean that all activated areas are engaged in affect. Second, the compared PET images for each case were co-registered with MR images for each case in order to identify which cortical areas are located within each region of elevated or reduced relative rCBF. Individual case analysis showed the full extent of individual sites, the number of sites in single areas, and the extent to which sites in different cases were spatially overlapping. Third, these data were evaluated in the light of human cytoarchitecture and non-human primate connection studies to determine to what extent parallel and distributed cortical processing circuits might contribute to motivational–affective and motor system activities initiated by noxious thermal stimuli.

Materials and methods

Subject characteristics

Seven right-handed males with an age of 26.9 ± 1.83 (mean ± SEM) were subjects for these studies. They had no history of pain problems and were medication-free. They were each reimbursed for travel expenses to the Hammersmith Hospital and three were given £50 for participating. Anxiety and depression were assessed using the Spielberger state/trait self-evaluation questionnaire (Spielberger *et al.*, 1970). Their state anxiety was 8.6 ± 2.07, their trait anxiety was 10.9 ± 2.59, and their Beck depression inventory was 3.3 ± 1.71. Only one subject (case 4) had a borderline anxious/depression score; however, the elevations in rCBF in his medial cortex were average for the group in terms of their locations and sizes. Perceptual features of the thermal stimuli were assessed with the McGill Sensory Score for induced acute pain (0.23 ± 0.023), the McGill Affect Score for induced acute pain (0.092 ± 0.049), and a visual analogue score for induced acute pain (62.4 ± 8.01) (Melzack, 1975). Finally, thresholds for innocuous (39.9 ± 0.75°C) and noxious but bearable (43.7 ± 0.66°C) thermal stimulation were determined as outlined below.

Procedure

After the subjects had answered the questionnaires to assess anxiety and depression, they were familiarized with the pain visual analogue scale and the McGill pain questionnaire that were used during the scanning procedure. To determine a measure of sensory intensity, all descriptors selected within the sensory categories of the McGill pain questionnaire were summed by rank value and then divided by the highest possible score. This scoring method yielded values ranging from 0 to 1, a score of 0 indicating that the subject did not select any adjectives from any of the sensory categories and a score of 1 indicating that the subject selected the highest ranked word in each category. This same procedure was used to obtain a quantitative measure of affective descriptors.

The heat stimuli were applied to the dorsal surface of the left hand with a Marstock thermal stimulator (Somedic, Stockholm, Sweden; Thermotest Type 1; Fruhstorfer *et al.*, 1976). This device delivers reproducible intermittent ramps of increasing heat to the skin via a Peltier probe that is 2.5 × 1.5 cm. Prior to the PET studies, thresholds for innocuous and noxious heat stimuli were determined. The subject held one of two control switches that were wired in parallel to the thermal stimulator, and the investigator held the other switch. Once the subject was shown that he could turn the stimulator off, the experimenter began the first ramp of heat. The subject was instructed to switch the heat off as soon as it became just perceptibly painful. This was repeated six times. After the sixth time, without moving the probe, the subject was asked to leave the heat increasing until it became no longer tolerable. It was stressed that the machine would switch off at 50°C and that the subject was not expected to reach a very high temperature. This was repeated three times, giving a total of nine measures. The first three measures were discarded to allow for acclimatization to the procedure, the next three were averaged to give a measure of pain threshold, and the final three recordings were averaged to give a measure of pain tolerance. The 'non-painful hot' temperature used during the scan was 2°C below threshold and the temperature used for 'painful hot' was 2°C below tolerance. These temperatures were confirmed as either non-painful hot or painful hot by the subject and adjusted when necessary.

Scans were obtained with a CTI model 953B (Knoxville, TN) brain tomograph system with 16 detector rings and retractable interplane collimating septa to allow acquisition of data in a high-sensitivity, three-dimensional mode. This allowed for an increase in the acceptance angle and hence the number of photons recorded. The increase in noise is compensated for by the more efficient use of the administered radioactivity (Townsend *et al.*, 1991). Consequently, data can be produced of a quality sufficient for the identification of activated regions in the brains of individual subjects. The axial extent of the scanner was 106 mm, and scans were made with each subject positioned in the scanner so that the axis of the sampling rings was approximately parallel to the glabellar–inion line, which in turn is parallel with the line between the anterior and posterior commissures (i.e. the AC–PC line). The actual camera resolution was 6 mm (full width at half maximum signal, FWHM), whereas the effective resolution for the group analysis was 16 mm (FWHM). A transmission scan was performed using an external ring source of positrons to provide an image of regional tissue density for the correction of emission scans for tissue attenuation effects. Each subject received 16 sequential scans over the course of a single 3 h session, his eyes were open in the dimly lit room, and he was not removed from the scanner once the procedure was initiated. Each scan provided measurements of relative rCBF by recording the distribution of cerebral radioactivity following injection of a bolus of positrons emitting $H_2[^{15}O]$. Arterial sampling was not performed to determine absolute activity because such a procedure is distressing to the subject and increases the time and technical difficulty of an already long procedure. The catheterization itself could confound data collected during the noxious and innocuous stimulations. The 16 scans were composed of four Stroop and four Stroop control scans, which are not reported here. These scans were randomly mixed with eight other scans for assessing pain activation. There were four scans during innocuous heat and four scans during noxious heat stimuli. These latter eight scans are the data sets to be reported in the present analysis. There was 7.2 min between each period of stimulation. Since the stimuli were randomized into 16 sets for each subject, only four stimulus sets were painful, and the stimulation period was 2.45 min; the average delay between noxious stimuli was ~40 min.

Each thermal stimulus commenced prior to the scanning period so that the first three ramps of stimulation allowed the subject to acclimatize to the stimulation. Subjects were warned prior to the start of a stimulation but were not told whether the painful or innocuous temperature was to be applied. The stimuli were randomized from scan to scan to avoid possible order effects. Each scanning period lasted 2.45 min, during which an intermittent and precisely reproducible ramp of increasing heat was applied every 15 s. During the time of stimulation, the lights were dimmed and silence was maintained in order not to contaminate the sensory input. After each scan, verbal confirmation was obtained that subjects had experienced the stimulus appropriately as 'innocuous hot' or 'painful hot'. When applicable, McGill questionnaire responses and visual analogue scale scores for the retrospective acute pain were recorded.

Each subject received MR imaging using a 1 Tesla Picker HPQ Vista system with an RF spoiled volume acquisition that was relatively T1 weighted to give good grey/white contrast and anatomical resolution (TR 24 ms; TE 6 ms; non-selective excitation with a flip angle of 35°; field of view in plane 25 × 25 cm; 192 × 256 in plane matrix with 128 secondary phase encoding steps oversampled to 256; resolution 1.3× 1.3 × 1.5 mm; total imaging time 20 min). There were ~150 slices 1 mm thick sampled in the transaxial plane for each subject. The MR images were aligned parallel with the intercommissural line, and interpolated to yield a cubic voxel size of 1 × 1 × 1 mm, which permitted co-registration with PET images.

Data analysis

These studies were intended to compare relative changes in rCBF between innocuous and noxious heat stimuli as a means of evaluating the sites of altered rCBF associated with the suffering component of pain. A correction for head movement between scans was carried out by aligning them all with the first one using automated image registration software specifically developed for this purpose (Woods *et al.*, 1992). Each realigned set of scans from every patient was reoriented into a standardized stereotaxic anatomical space. A correction was made for global changes in rCBF between scans. These two procedures allow relative rCBF values for each stimulus to be pooled across subjects. A statistical comparison of relative rCBF distributions between conditions and groups was performed to identify sites of significantly changed regional rCBF (Friston *et al.*, 1991). Finally, a principal components analysis was performed and revealed a first principle component contrasting visual Stroop stimuli with the heat stimulations, accounting for 65% of the variance. The second component accounted for 12% of the variance and contrasted the first three scans with the last three scans. Examination of relative CBF changes at particular pixel locations, including the thalamus, anterior cingulate and prefrontal cortices, did not reveal order effects, and previous principle component analysis of pain stimulation data has not revealed anything additional to the cognitive subtraction.

The AC–PC line was identified directly from the PET image and the data were transformed into standard stereotaxic space of the stereotaxic atlas of Talairach and Tournoux (1988). In order to increase the signal-to-noise ratio and accommodate variability in functional anatomy, each image for the group comparison was smoothed in the x, y and z dimensions with a Gaussian filter of 20 mm (FWHM); images for single-subject analysis were smoothed with a Gaussian filter of 10 mm (FWHM). Differences in global activity were removed following a pixel-by-pixel analysis of covariance (Friston *et al.*, 1990). Elevations in rCBF were those following a subtraction of heat responses from noxious heat responses, whereas reductions were those following subtraction of heat from noxious heat responses. The differences between one condition and another

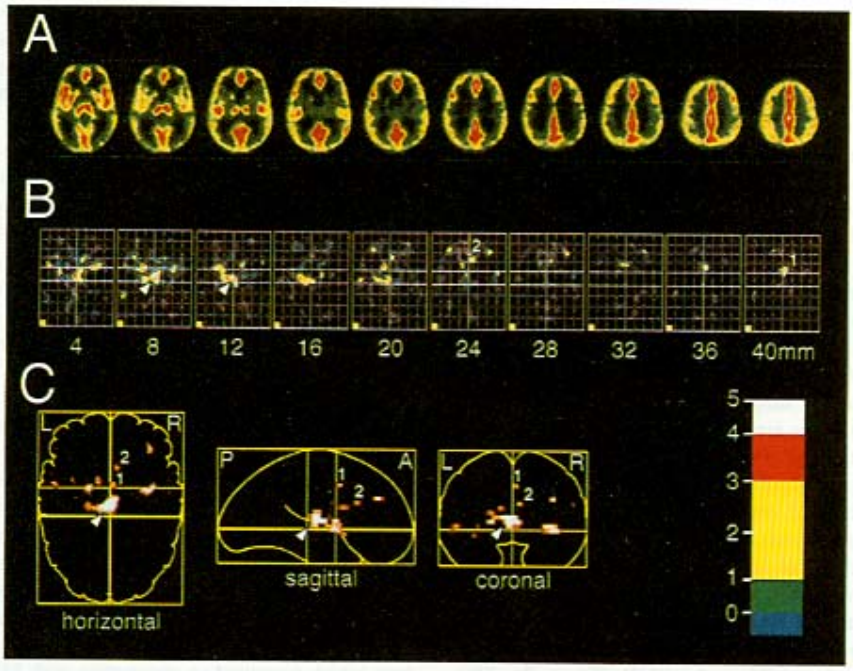

FIG. 1. Group analysis of relative rCBF (A), statistical parametric map (B) and reconstruction of sites with significant elevations in rCBF (C). The colour scale is for z scores. The two medial surface sites of elevated rCBF are numbered in B and C, and the thalamic activation site is identified with arrowheads in each.

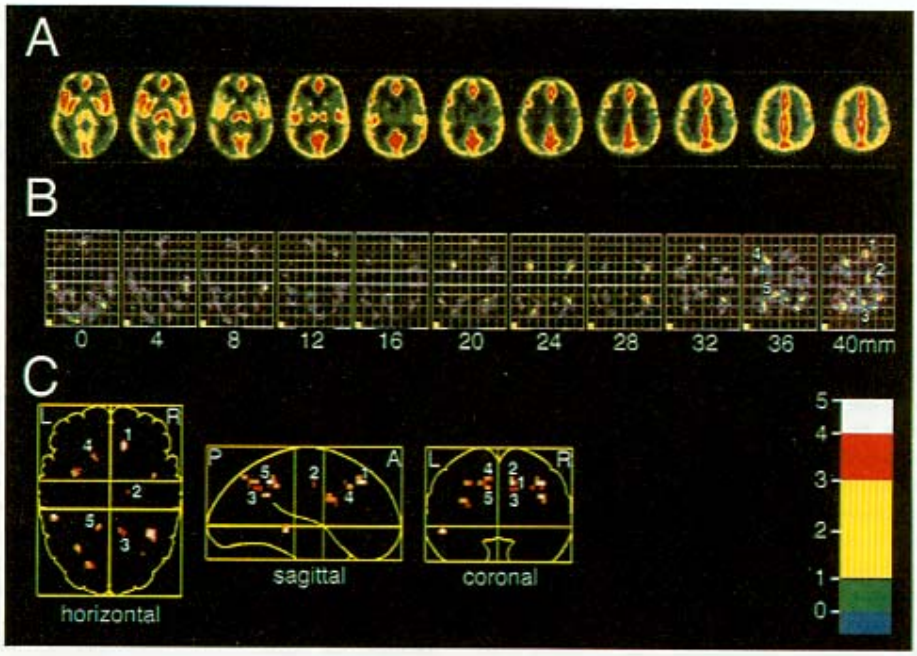

FIG. 2. Group analysis of sites with reduced relative rCBF. Five sites are located on the medial surface.

were assessed with the appropriate contrast (weighting of the eight condition means) using the t statistic. This analysis was performed for each pixel and the resulting set of t values constituted an SPM. The significance of each SPM was assessed by comparing the observed and expected pixels above a specific criterion ($P < 0.001$). The threshold of omnibus $P < 0.001$ was chosen because empirical studies with phantoms have shown that this threshold protects against false positives (Bailey *et al.*, 1991).

Following group analysis, the subjects were examined separately. Initially, the search for areas of significance was conducted in the

same manner as above with an omnibus threshold of $P = 0.05$ to interrogate the whole brain for significant changes in the painful hot condition. This reduced level of significance was employed because the search was restricted to those areas that had altered relative rCBF in the group analysis. This individual SPM procedure was followed with co-registration for each case. For co-registration of SPM and MR images, the stereotaxic image normalization steps were omitted. The subsequent filtering, however, followed by analysis of covariance and the generation of a threshold SPM was identical. The SPM was then co-registered with the subject's own MR scan (Woods *et al.*, 1993). Such superimposition allowed us to determine the position of the region with maximal rCBF changes in relation to the gyral and sulcal pattern of each individual brain. The resolution of this procedure is ~8–12 mm, which is the distance required between two discrete areas to be seen as discrete. This does not mean, however, that (i) differences such as those between the gyral surface and depths of the cingulate sulcus cannot be evaluated between individuals, or (ii) the signal can arise from the cortex 12 mm distant to the site of statistically significant activity. The cartographic activity of plotting regions of altered relative rCBF in seven individuals accurately locates sites of functional changes in the brain. The abbreviation rCBF refers to relative changes in rCBF.

Structure of the cingulate cortex

The distribution of cytoarchitectural areas on the medial surface of the human brain was originally described by Brodmann (1909). Talairach and Tournoux (1988) transposed this map onto reconstructions of MR images and extrapolated this to transverse sections. There are a number of problems, however, with this approach. First, the sulci were not opened by Brodmann and many of the areas he described are not on the surface of gyri as they appear, but rather in the depths of sulci. For example, much of area 32 in the ACC is in the depths of the cingulate sulci and areas 29 and 30 are buried in the depths of the callosal sulcus; they do not appear on the surface of the cingulate gyrus as suggested in the atlas. Second, there are variations in the sulcal patterns that are not considered in the atlas, such as the double parallel pattern of cingulate sulci (Ono *et al.*, 1990). Third, recent advances in relation to the cingulate motor areas in the depths of the cingulate sulcus have required a substantial rethinking of the architecture of the medial surface.

Studies have been published which account for modifications in the Brodmann map and provide for flattening of the cortical surface so that the distribution of areas in the depths of the sulci in the monkey and human cingulate cortices can be assessed (Braak, 1979; Dum and Strick, 1993; Vogt, 1993; Vogt *et al.*, 1995a). These works serve as the basis for the present analysis. The prominent modifications from Brodmann's original map include the following: (i) division of areas 24 and 23 into ventral-to-dorsal a, b and c parts; (ii) subdivision of areas 24 and 32 into two major rostrocaudal divisions where areas 24 and 32 are the rostral parts and areas 24′ and 32′ are the caudal divisions; and (iii) area 31 is associated with the parasplenial lobules but does not extent rostrally into the cingulate sulcus, while area 23c is located in the depths of this sulcus.

Results

Statistical parametric map group analysis of relative changes in rCBF

The SPM analysis of the PET images showed two areas with elevated rCBF in the ACC, each of which is numbered in Figure 1. The first site is the mid-rostrocaudal cingulate site previously reported. It is slightly off the midline in the right hemisphere, 40 mm superior to the AC–PC line, and extends ventrally 32 mm, and it is just rostral to the vertical line through the anterior commissure. The second site of elevated rCBF was also displaced to the right hemisphere, 24 mm superior to the AC–PC line and 20 mm rostral to the VCA line. The large region of elevated rCBF in the thalamus is identified in Figure 1 with arrowheads. Although the ACC sites of elevated rCBF in the group SPM analysis had a slight bias to the right hemisphere, the individual cases discussed below demonstrate that this is a bilateral response. This is an instance where the large site of elevated rCBF in the right hemisphere of the group SPM subsumed an adjacent and smaller site of altered rCBF in the left hemisphere.

There were a number of other cortical areas that had a significant elevation in rCBF and that might be relevant to interpreting changes on the medial surface. These regions of increased rCBF are summarized in Table 1 and included bilateral thalamic and anterior insula sites and right hemisphere dorsolateral prefrontal cortex (DLPF) cortex and left hemisphere area 22. In addition to these regions, there were a few regions with just subsignificant responses, including the left DLPF response at $z = 24$, area 7b and part of area 40 in the left hemisphere ($z = 20$ mm; $y = -22$ mm; $x = -58$ mm) and area 21 in the left hemisphere ($z = 8$ mm; $y = -48$ mm; $x = -58$ mm).

There were five sites of reduced rCBF on the medial surface that included the cingulofrontal (i.e. area 32) and cinguloparietal (i.e. area 31) transition cortices in both hemispheres and one that involved the supplementary motor cortex in the right hemisphere. As shown in Figure 2 and Table 1, the five sites included sites 1 ($z = 40$ mm, $y = 14$ mm, $x = 35$ mm) and 4 ($z = 36$ mm, $y = 25$ mm, $x = -21$ mm) in the cingulofrontal transition cortex in the right and left hemispheres respectively, site 2 ($z = 40$–44 mm, $y = -12$ mm, $x = 18$ mm) in the supplementary motor cortex, and sites 3 ($z = 36$–40 mm, $y = 50$ mm, $x = 9$ mm) and 5 ($z = 36$ mm, $y = -39$ mm, $x = -9$ mm) in the cinguloparietal transition cortex in the right and left hemispheres respectively. In addition to the medial surface sites, there were a number of sites with reduced rCBF on the lateral surface. These areas included premotor areas 6d/44 in the right ($z = 24$ mm; $y = 3$ mm; $x = 37$ mm) and left ($z = 24$–28 mm; $y = 3$ mm; $x = -33$ mm) hemispheres, parietal areas 40 and caudal 7b in the right ($z = 40$; $y = -45$; $x = 35$) and left ($z = 40$ mm, $y = -60$ mm, $x = -26$ mm) hemispheres, right parietal area 39 ($z = 28$ mm; $y = -47$ mm; $x = 41$ mm), and left temporal area 21 ($z = 0$ mm; $y = -32$ mm; $x = -50$ mm).

Medial surface morphology

Figure 3 is a schematic diagram of the medial surfaces from the left hemispheres of the first two cases in Figures 4 and 5. They include an example of a double parallel pattern of cingulate sulci (case 1) and a single cingulate sulcus (case 2). In the first case the superior cingulate sulcus is segmented into rostral (Cs1) and caudal (Cs2) parts. The top sections in Figure 3 are midsagittal sections representing a reconstruction of MR images 1–4 mm lateral to the midline. The bottom two sections are parasagittal images representing sections between 5 and 9 mm lateral to the midline. In these latter sections, the depths of the sulci are indicated with dashed lines.

Since the cytoarchitecture and the borders between areas cannot be identified *in vivo*, approximations were made as to the location of particular areas in each brain. Figure 3 shows the approximate locations of cytoarchitectural areas on the medial surface and in a parasagittal section. Each of the recent modifications in the original Brodmann map discussed earlier has been incorporated into these maps. Notice that areas 24c, 24c′, 24c′g and 23c are in the depths of the cingulate sulci and areas 29 and 30 are in the depths of the

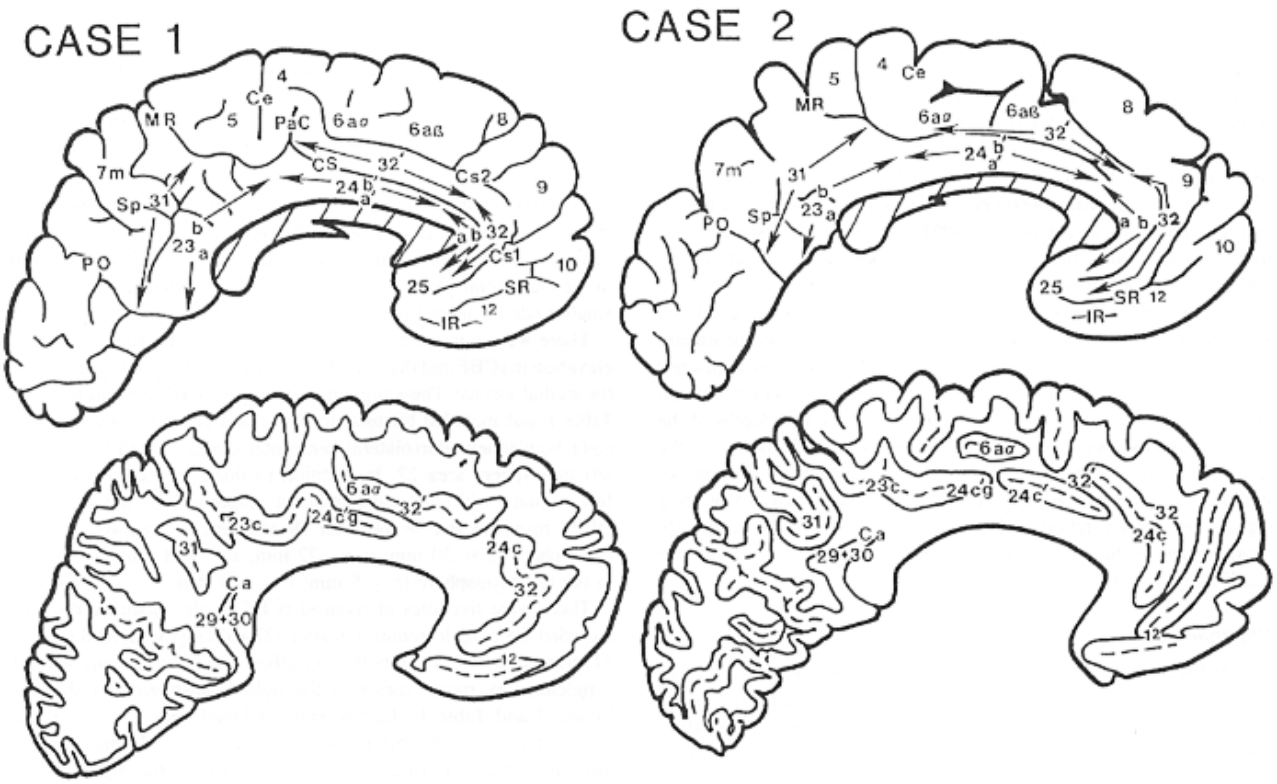

FIG. 3. Two examples of sulcal patterns on the medial surface of the hemisphere: double parallel pattern of cingulate sulci (case 1) and single cingulate sulcus (case 2). The first level in each case is a midsagittal reconstruction of the MR images where the corpus callosum is indicated with hatching, while the second level was derived from images within 5–9 mm lateral to the parasagittal plane and the depths of the sulci are indicated with dashed lines. The approximate locations of cytoarchitectural areas are shown. Ca, callosal sulcus; Ce, central sulcus; CS, cingulate sulcus; Cs1 and Cs2, segments of superior cingulate sulcus; IR, inferior rostral sulcus; MR, marginal ramus of the cingulate sulcus; PO, parieto-occipital sulcus; Sp, splenial sulcus; SR, superior rostral sulcus.

Table 1. Group SPM Analysis of rCBF

ELEVATIONS					REDUCTIONS				
Region	Co-ordinates			Z Score	Region	Co-ordinates			Z Score
	x	y	z			x	y	z	
Right Hemisphere									
ACC #1	2	4	40	3.31	Areas 32/8	35	14	40	3.50
#2	6	20	24	3.31					
DLPF	34	36	28	3.67	Area 6a	18	−12	42	3.47
					6d/44	37	3	24	3.26
Insula	36	0	4	3.69	Area 31	9	50	38	3.14
Thalamus	4	−6	4	3.23	Areas 40/7b	35	−45	40	3.11
					39	41	−47	28	3.21
Left Hemisphere									
Insula	−34	10	−4	3.19	Areas 32/8	−21	25	36	3.10
Area 22	−50	6	4	3.21	Areas 6d/44	−33	3	26	3.49
Thalamus	−2	−14	8	4.66	Area 31	−9	−39	36	3.49
					Areas 40/7b	−26	−60	40	3.09
					Area 21	−50	−32	0	3.67

callosal sulcus around the splenium of the corpus callosum. At rostral levels of the corpus callosum area 24a is located in part of the callosal sulcus, while area 33 is in its depths.

PET and MR co-registration for individual cases: relative rCBF elevations

The group SPM analysis showed that sites of elevated rCBF on the medial surface were primarily in the ACC, and that sites of reduced rCBF were in both anterior and posterior parts of the medial cortex. The SPM analysis does not show the full extent of rCBF changes in individual cases or the number of sites in an individual area that may contribute to a single site in the SPM. In addition, if the sites of altered rCBF do not overlap spatially, they will be overlooked in a group analysis, an effect that has been observed in the ACC in a sequential motor learning task (Schlaug *et al.*, 1994). Co-registered PET and MR images were evaluated for individual cases to determine which cortical areas were involved, the full extent of rCBF in a region, the number of altered rCBF sites in a single area and the extent to which they overlapped for all cases, and the relationships between areas of increased and decreased rCBF in individual cases.

Six cases are shown in Figure 4; they are numbered beginning with the case with the largest elevation of rCBF in the right hemisphere (case 1) and proceeding to the case with the smallest elevation in rCBF (case 6). Case 7 is not shown in this figure because it had no alterations in rCBF in the right hemisphere, although there were two elevation sites and no reductions in rCBF in the left hemisphere of this case (see Table 2 for this case). The solid black areas in Figures 4 and 5 represent changes in rCBF in sections that were 1–4 mm

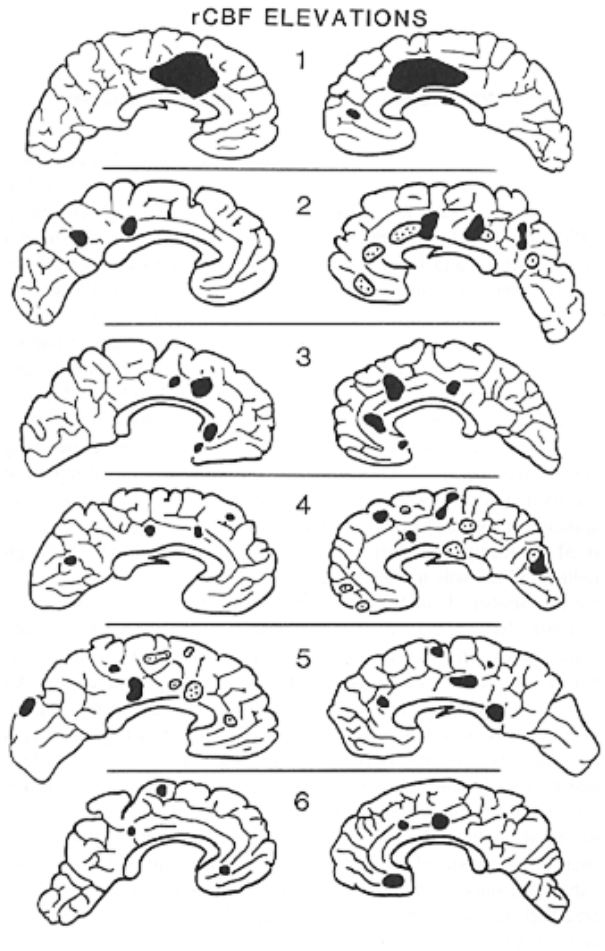

FIG. 4. Reconstructions of co-registered PET and MR images from the medial surfaces of the left and right hemispheres for individual cases. Regions of significantly elevated relative rCBF are shown for midsagittal sections (solid black for slices 1–4 mm lateral to the midline) and parasagittal sections (solid lines with dots for slices 5–9 mm lateral to the midline). The cases are organized in order from that with the largest total cingulate activation in the right hemisphere (case 1) to the case with the least cingulate activation in the right hemisphere (case 6).

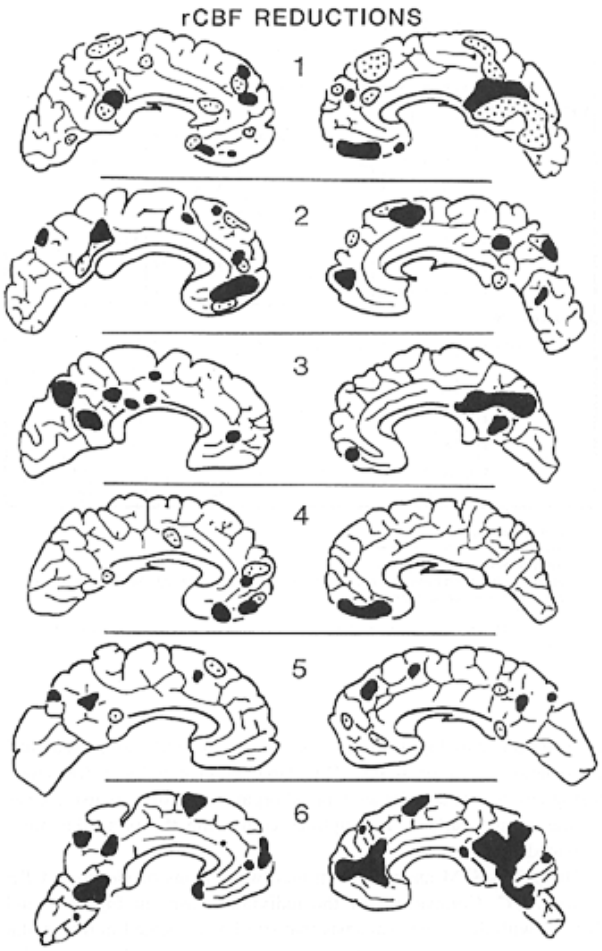

FIG. 5. Reconstructions of co-registered PET and MR images associated with significantly reduced relative rCBF in the same cases as in Figure 4. The solid black and dotted regions apply to midsagittal and parasagittal sections in the same way as in Figure 4.

lateral to the midline, and the solid lines with dots are for elevations in parasagittal sections 5–9 mm lateral to the midline.

Although all cases had elevated rCBF in some part of the cingulate cortex, only case 1 had a single, large site of elevated rCBF in each hemisphere. These sites incorporated the cortex on both the cingulate gyral surface and the depths of the cingulate sulci. Due to this overlap, no dots were used to show regions in the sulcal depths in Figure 4. Cases 2–6 had multiple sites of elevated rCBF in the right hemisphere and case 7 had elevated rCBF only in the left hemisphere. In case 2, for example, the regions of elevated rCBF in the right hemisphere encompassed two regions on the cingulate gyral surface as well as a third in the medial parietal cortex. There were also three regions of elevated rCBF in the depths of the cingulate sulcus in addition to a site in the gyrus rectus and one in the occipital cortex. In the left hemisphere of case 2 there were two sites of elevated rCBF, both of which were in the PCC. Although the SPM analysis had a bias to the right hemisphere, the individual responses showed that in most instances elevations in rCBF were bilateral. This was probably because the large right hemisphere change in rCBF subsumed the smaller and nearby site in the left hemisphere in the group SPM analysis.

With reference to the parasagittal sections for case 1 in Figure 3, rCBF was elevated in the right hemisphere in the following areas in an approximately symmetrical fashion in both hemispheres: 24a′, 24b′, 24c′, 24c′g, 32′, 6aα and a small involvement of 6aβ. There was also a small site in area 32 in the right hemisphere. In the right hemisphere of case 2, parts of the ACC with elevated rCBF included areas 24a′, 24b′, 24a, 24b, 32 and 12. There were also a number of areas in the PCC with elevated rCBF, including areas 23b, 31 and 7m. In the left hemisphere of case 2 the two activation sites were both in the PCC in areas 23a, 23b and 31.

The areas with rCBF changes in the right hemisphere are summarized for all cases in Table 2. Since those in the left hemisphere are essentially a subset of those in the right hemisphere, they are not included in the table for the sake of simplicity. Table 2A, in

Table 2. Changes in rCBF on the Medial Surface

	25	32	24a	24b	24c	6	10	9	8	6aα	6aβ	24c′	24c′g	31	23 & 30	23c	23b	23a	11	2m	5
A. Elevated rCBF																					
Case 1		X								X	X	X	X	X	X						
2		X	X	X		X						X	X		X			X		X	X
3	X	X	X	X	X				X				X	X	X			X			
4						X			X	X	X	X	X			X			X		X
5		X		X							X		X			X	X	X			
6	X	X		X									X	X	X				X		
7	❋	❋	❋	❋	❋								❋	❋	❋						
B. Reduced rCBF																					
Case 1	⊗		○	○	X	⊗		⊗	⊗		X				○	X	⊗	⊗	X	X	○	X
2		○				○	X	X	⊗		⊗				○	⊗	○	⊗		⊗	⊗	
3		○				X				○					X	⊗	⊗			⊗	⊗	
4						⊗	○	○							○	○						
5		X					X		⊗		⊗					⊗				⊗	⊗	
6	○	⊗	X	X	X		⊗	X	⊗		⊗					X	⊗	X		⊗	⊗	
	AF									RS						VS						

X = Right hemisphere
○ = Reduced rCBF in left hemisphere
⊗ = Reductions in both hemispheres
❋ = Elevated rCBF in left hemisphere (case 7 had no elevations in the right hemisphere and no reductions in either hemisphere)

Abbreviations: AF, affect; RS, response selection; VS, visuospatial regions as considered in the Discussion.

conjunction with Figure 4, can be used to identify areas that had consistently elevated rCBF. This table is essentially a frequency histogram that reflects the anatomical organization of responsive areas on the medial surface. It simplifies comparing the particular areas activated in all cases.

The group SPM analysis identified two regions of elevated rCBF in the ACC. Comparison of the individual cases in Figure 4 and Table 2 with these sites suggests that site 1 was located in the caudal part of area 24′ and site 2 at the borders of areas 24′/24 and 32′/32. The area in the cingulate cortex with the most consistently elevated rCBF in site 1 was area 24b′. There was variation of activation sites among individual cases, particularly in the perigenual cortex, which could skew statistical analysis yet lead to a similar functional outcome. Thus, the perigenual cortex contains an active site in six of the seven cases, as shown in Table 2 (i.e. areas 25, 32, 24a, 24b and/or 24c). Only case 4 does not contain an active site in this region, while area 32 was involved to some extent in all other cases. Examples of variation within this region include (i) a small site in area 24, as in cases 2 and 5, (ii) a site that extends into area 24 from area 24′, as in case 1, (iii) a site in area 25, as in case 6, and (iv) involvement of areas 24 and 25 together, as in cases 3 and 7.

The cingulate motor areas are located in the depths of the cingulate sulcus and some of them are in areas 24c′ and 24c′g. These areas were inconsistently involved in the regions of elevated rCBF (Table 2). The most complete involvement of these areas occurred in case 1, which had the largest overall activation site in the cingulate cortex. In addition to case 1, three cases had part of area 24c′ involved and no others engaged area 24c′g.

Elevated rCBF in the PCC was inconsistent according to which cases were involved as well as the topography of the areas so engaged. Five of the seven cases had a site of elevated rCBF somewhere in the PCC. The cases with the largest (case 1) and smallest (case 7) overall activation of the cingulate cortex failed to engage the PCC. In the other five cases, four had an involvement of a small part of area 23 and two had an area 31 involvement. Only one case had an area 5 elevation and one an area 7m elevation.

PET and MR co-registration of individual cases: relative rCBF reductions

The same procedure for co-registration of MR and PET images was used to assess reduced rCBF on the medial surfaces of the individual cases, and the results are shown in Figure 5 and Table 2B. The group SPM analysis showed five sites of reduced rCBF on the medial surface: sites 1 and 4 were in the cingulofrontal transition cortex, site 2 was in the supplementary motor cortex, and sites 3 and 5 were in the cinguloparietal transition cortex. In the individual cases shown in Figure 5, case 4 stands out once again as unique, because it had no evidence of reduced rCBF in the PCC in the right hemisphere and only a small site in the left hemisphere. Only case 7 had no reductions in either hemisphere. In three cases (1, 3 and 6), there was a large swathe of cortex with reduced rCBF in the right hemisphere stretching across areas 29, 30, 23a, 23b, 31 and 7m. Since this broad region of inactivated cortex occurred in three of the seven cases, it was not apparent in the SPM analysis that such a broad region of reduced rCBF is an important part of responses to noxious stimuli. Although reduced rCBF was more limited in the PCC in cases 2 and 5, there were a number of smaller sites of reduced rCBF in these same areas.

Table 2B summarizes the areas with reduced rCBF in both hemispheres. The following observations stand out. First, only case 6 had significant reductions in rCBF in the perigenual cortex. All other cases had little or no relative change in rCBF in this region. Second, there were few reductions in rCBF in the midcingulate region (i.e. site 1 for elevated rCBF). The only areas of the medial surface that frequently had reduced rCBF in addition to area 32 were in the prefrontal, paracingulate cortex including areas 12, 10, 9 and 8. Third, the SPM analysis showed that in the right hemisphere there was a small involvement of area 6aβ, and this is apparent in Figure 5 and Table 2B. Since there were also increases in rCBF in some cases in area 6aβ, the rCBF response in this paradigm is complex and may be related to premotor functions associated with different parts of the body surface. Fourth, the PCC contained persistent reductions in rCBF. The areas so involved included four cases each for the following areas: 29/30, 23b, 31 and 7m. Although there were some areas with elevated rCBF in the PCC in these cases, as seen in Table 2A, they were infrequent and limited in size. Finally, the open circles in Table 2B identify reductions in the left hemisphere and the × within a circle those areas that had reductions in both hemispheres. The changes in paracingulate regions were generally bilateral.

PET and MR co-registration of individual cases: summary

In addition to the single case presentations in Figures 3 and 4 and the frequency distribution of rCBF in Table 2, the data from individual cases can be qualitatively summarized so that the overall topography of involved regions can be assessed for the group. Although this method bypasses the statistical rigour of SPM analysis, it shows the full extent of each of four major sites on the medial surface. Figure 6 shows this summary of elevations and reductions in rCBF for the individual cases, which was constructed in the following way. First, the medial surface from case 2 was used as a template to reconstruct each site. A site was included only if it overlapped with one other site, thereby eliminating single sites that had no counterparts in any other case. Second, the SPM analysis showed that there were two sites of elevated and two sites of reduced rCBF that involved the cingulate cortex. These four sites are numbered in Figure 6 under 'Summary of individuals', the numbers 1 and 2 representing elevations

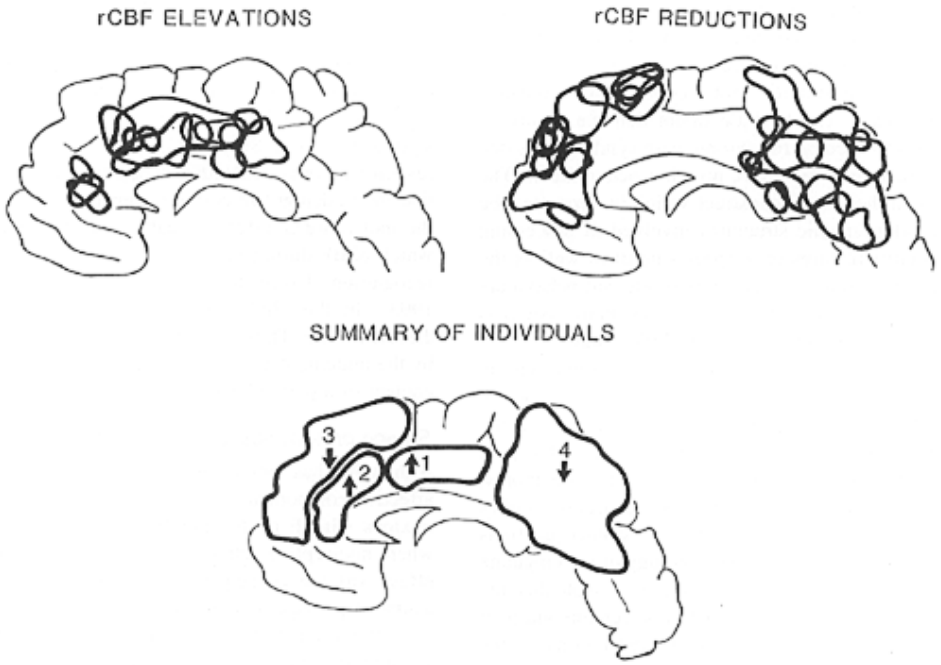

FIG 6. Qualitative summary of individual sites of altered relative rCBF reconstructed onto the medial surface of case 2. Sites were included that overlapped with at least one other site and the summary of individuals was produced with the same standard and some smoothing at the edges. In the summary of individuals the two sites of elevated (1 and 2) and reduced (3 and 4) rCBF identified by the group SPM analysis are indicated with appropriately oriented arrows at their approximate locations on the medial surface.

and 3 and 4 reductions in rCBF. Third, a final drawing around each of the four SPM sites was made such that each line included regions with two or more smaller sites and some smoothing between individual sites. Although the topographical distribution of activation sites looks continuous along cortex dorsal to the corpus callosum, two regions were separated midway between the two sites from the SPM analysis.

In conclusion, there are two regions of elevated rCBF in the ACC that include the perigenual cingulate cortex and midcingulate cortex. In addition, there are two regions of depressed rCBF, including one in the rostral cingulofrontal transition and frontal cortices and another in the posterior cingulate, cinguloparietal transition and medial parietal cortices. The regions of reduced rCBF are larger than the sites of elevated rCBF and involve cingulate and adjacent regions.

Discussion

Elevated rCBF in the midcingulate cortex during noxious stimulation of the skin has been observed frequently in PET studies (Jones *et al.*, 1991a; Talbot *et al.*, 1991; Casey *et al.*, 1994; Coghill *et al.*, 1994). The present report used SPM analysis of the group data to confirm this finding, to demonstrate a second site of elevated rCBF anterior to this site, and to characterize two bilateral regions of reduced rCBF in the cingulofrontal and cinguloparietal transition cortices. Using co-registered PET and MR images to assess individual cases it also was shown that the first site of elevated rCBF was primarily in area 24b′ and that the second site was at the border of areas 24/32 and 24′/32′, although elevated rCBF in the perigenual cortex was dispersed beyond the cytoarchitectural border zone identified with SPM group analysis. The sites of reduced rCBF were mainly in rostral area 32 and caudal area 31. A summary of the individual responses showed that reduced rCBF in the PCC was more extensive than indicated by the SPM analysis where reductions occurred in cingulate areas 29/30, 23b and 31 in addition to that in area 7m.

Classical views of nociceptive information processing emphasize the role of the lateral thalamic nuclei (i.e. ventroposterior lateral and medial nuclei) and the primary and secondary somatosensory cortices in somatotopic localization and intensity coding of noxious stimuli (Albe-Fessard *et al.*, 1985; Kenshalo and Willis, 1991). In a PET paradigm where noxious heat stimuli were applied to one of six probe sites 3 cm apart during separate scanning periods (Talbot *et al.*, 1991; Coghill *et al.*, 1994), rCBF is elevated in the somatosensory cortices as well as the supplementary motor cortex on the medial surface. Although these structures are thought to be engaged in the sensory–discriminative components of processing nociceptive information and sensorimotor integration, they have no role in affect and learning processes that mediate long-term avoidance of noxious stimuli.

A slightly larger thermal probe and a single stimulation site on the dorsal aspect of the hand was used in the present and an earlier study (Jones *et al.*, 1991a). Such stimulation avoids activating multiple groups of nociceptors that would provide subjects with information about multiple stimulus locations. The consequent elevation of rCBF in the cingulate cortex but not in sensorimotor areas suggests that the present responses were the result of the suffering component of pain. Since subjects in the present study received noxious heat stimuli during the entire scanning period and the heat stimuli were reported by all subjects as noxious by visual analogue scale rating, alterations in their rCBF were associated with the suffering component of pain. The present paradigm did not engage coding processes associated with the localization or intensity of the stimuli that could require discriminative and/or premotor processing. To the extent that previous studies evoked suffering, they also produced elevated rCBF in the cingulate cortex and other parts of the limbic system.

If the processing of nociceptive information in the limbic cortex is to be understood, a new conceptual framework is required to resolve the contributions of limbic structures to affect (i.e. the suffering response to noxious stimuli), motor control, and avoidance learning and memory. There can be little doubt that the failure of classical 'pain' theories to account for chronic pain syndromes is due to their attention to structures which have no relevance to affect. The medial pain system is a theoretical construct which incorporates the limbic thalamic and telencephalic structures involved in processing the motivational–affective features of noxious stimuli as well as the motor system interactions needed for generating relevant behaviours (Vogt *et al.*, 1993). The formulation of the medial pain system is expanded below with observations from recent PET studies.

The statement that the cingulate cortex is involved in nociception and pain processing does not imply that any part of it is purely nociceptive. Although Figure 6 suggests that large expanses of the medial cortex are implicated in nociception, this cortex is not a 'pain centre'. This is evident from a large body of connectional anatomy, lesion, electrical stimulation and single-neuron recording studies indicating that the cingulate cortex is involved in many other functions as well. It is from the perspective of the neurobiology of the cingulate cortex that studies of nociception can be interpreted such that the specific contributions of the cingulate cortex to nociception and pain processing can be determined. Three essential subdivisions of the cingulate cortex have been identified based on fundamental differences in the cytoarchitecture of these regions and extensive neurobiological studies (Vogt *et al.*, 1992; Vogt and Gabriel, 1993; Devinsky *et al.*, 1995). At the bottom of Table 2 are abbreviations associated with groups of areas that have fundamentally different cytoarchitecture and contribute to the functional heterogeneity in the cingulate cortex. The first region is the affective region, which includes areas 25, 24 and 32 (AF in Table 2), the second is the response selection region, which includes areas 24′ and 32′ (RS in Table 2), and the third is the visuospatial region, which includes areas 29, 30, 23 and 31 (VS in Table 2). Although activation of a cortical region in the PET pain studies cannot be attributed to a specific sensory, motor or other function, activation of the cortex in any of these three regions suggests specific contributions of the cingulate cortex to nociception and pain processing.

Cingulate cortex in affect

Area 25 has direct projections to autonomic brainstem nuclei and has been termed the visceromotor control cortex (Neafsey *et al.*, 1993). Although areas 32 and 24 do not have such direct projections to autonomic centres, electrical stimulation and lesion studies clearly implicate them in autonomic regulation, including classical conditioning (Buchanan and Powell, 1993; Devinsky *et al.*, 1995). Also, electrical stimulation in the perigenual cortex can evoke fear and other emotional responses (Bancaud and Talairach, 1992). An example of an affective response that engages the perigenual cortex has been reported by George *et al.* (1995). These investigators had healthy women recall sad events during PET scanning and showed elevated rCBF in the infragenual cortex. Thus, the main contribution of the perigenual cortex is to affect, and we propose that activation of the cortex in this region in the PET pain paradigms is associated with the motivational–affective component of pain.

Cingulate cortex in response selection

The second functional region is that for response selection (RS in Table 2). This region has been implicated in response selection with the Stroop interference task (Pardo *et al.*, 1990; Bench *et al.*, 1993) and a divided attention task (Corbetta *et al.*, 1991), and has been shown to have a major role in premotor functions, as discussed further below. We do not mean to imply, however, that the midcingulate cortex is not involved in affect. Interestingly, the left midcingulate region is activated in a Stroop task that employs words with affective significance (sad Stroop; George *et al.*, 1994) and the cingulate response is correlated with task performance speed. Another indication that the midcingulate cortex is engaged in responses associated with the motivational–affective features of the environment is a study in which rCBF during visual recognition of faces was subtracted from recognition of faces that expressed emotional content (George *et al.*, 1993). In this PET study the the right midcingulate cortex had elevated rCBF. Thus, one of the contingencies that may be employed by the midcingulate cortex during response selection is the emotional content of a particular stimulus.

Source of nociceptive signals in the cingulate cortex

Although it has long been known that lesions in the ACC abolish the affective components of pain while leaving intact the localization of noxious stimuli (Foltz and White, 1962, 1968), it was not known where nociceptive activity originated and whether or not the surgical effect was the consequence of cingulate cortex damage or due to axons of passage associated with other cortical areas. The origin of nociceptive inputs to the cingulate cortex was first proposed to arise via spinothalamic mechanisms (Vogt *et al.*, 1979). A primary role for the midline and intralaminar thalamic nuclei in transmitting nociceptive signals to limbic cortex is suggested for the following reasons. (i) Thalamic nuclei in the midline and intralaminar regions, including the parafascicular, paraventricular, parataenial, ventromedial and reuniens nuclei, receive spinothalamic input (Craig and Burton, 1981; Giesler *et al.*, 1981) and project to the ACC (Vogt and Pandya, 1987; Vogt *et al.*, 1993). (ii) Since the projections of the midline and intralaminar nuclei are topographically extensive, it is possible that such a system subserves nociceptive responses and pain processing, which also have a wide distribution in the ACC. (iii) Neurons in the midline thalamic nuclei (Casey, 1968; Dong *et al.*, 1978) have many of the same receptive field properties as those in the ACC (Sikes and Vogt, 1992), including large receptive fields with little or no somatotopic organization, rapidly adapting responses, and a high proportion of neurons with responses to both noxious heat and noxious mechanical stimuli. (iv) Lidocaine block of thalamic activity greatly attenuates or abolishes ACC nociceptive responses (Sikes and Vogt, 1992). (v) Casey *et al.* (1994) and the present study showed bilateral thalamic and ACC activations following unilateral noxious stimulation, suggesting functional linkage between these structures.

Anterior insula and affect

This study and earlier ones (Casey *et al.*, 1994; Coghill *et al.*, 1994) had elevated rCBF in the anterior insula. A number of studies have reported connections between the anterior insula and cingulate cortex (Vogt *et al.*, 1979; Pandya *et al.*, 1981; Mesulam and Muffson, 1982; Vogt and Pandya, 1987). Taken together, it appears that area 24′ has the most pronounced connections with posterior parts of the insula, while the anterior insula has only limited connections with perigenual parts of the cingulate cortex. Due to the limited interconnections between these areas, it is possible that the anterior insula and the perigenual cingulate cortex are engaged simultaneously in a parallel distributed network that is involved in affective responses to noxious stimuli.

Motor control: area 24b′ and DLPF cortex

One of the questions considered in the individual co-registered cases was whether or not the cingulate premotor areas in the depths of the

cingulate sulcus along with their spinal projections might be directly engaged in the midcingulate activation site; they were not consistently involved in this response. It appears that the contribution of the cingulate cortex to motor regulation in this PET pain paradigm is one step removed from the cingulate premotor areas, since area 24b′ on the gyral surface was the most consistently engaged area at this level of the ACC. Reports of intracingulate circuitry (Van Hoesen *et al.*, 1993) have shown that area 24b′ has major and reciprocal connections with the cingulate premotor areas, and it is therefore in a position to influence the outputs of these sulcal areas.

Area 24b′ may operate in concert with the DLPF cortex in response inhibition during noxious stimulation, since the latter region had significantly elevated rCBF in the right hemisphere in the present study and has been implicated in response inhibition (Goldman-Rakic, 1987). Area 24b′ receives projections from area 46 in the DLPF region (Barbas and Mesulam, 1985; Vogt and Pandya, 1987; Bates and Goldman-Rakic, 1993) and these connections are bilateral (McGuire *et al.*, 1991). In addition, area 46 is devoid of direct spinal cord projections, as is true for area 24b′. One brainstem pathway of each of these regions that may contribute to the response inhibition function is the projection to the bulbar reticular formation (Keizer and Kuypers, 1989). It has been postulated by Goldman-Rakic (1987) that the DLPF cortex regulates behaviours that are guided by internal representations of reality, and that it is not needed for behaviours that are guided by external stimuli. Further support for this idea is provided by PET studies which suggest that the ACC and DLPF are involved in willed action (Frith *et al.*, 1991) and non-motor learning (Raichle *et al.*, 1994). An important behavioural aspect of the present PET paradigm is the need to restrain movement in spite of a noxious but bearable somatic stimulus. The study by Siegel and Chabora (1971) showed that electrical stimulation of the ACC in cats can inhibit hypothalamically evoked attack. Thus, it is possible that area 24b′ and DLPF are engaged together for response inhibition, including that required in the PET pain paradigms.

Motor control: visual guidance by areas 7b/7m and 23/31

Visuomotor activity associated with active avoidance and nocifensive responses, particularly those guided by visual stimuli (Dong *et al.*, 1994), may be guided by sensorimotor associations in area 7b of inferior parietal cortex. Projections of area 7b to area 23b on the cingulate gyral surface and area 23c in the cingulate sulcus have been reported (Neal *et al.*, 1990). Since the PCC has been implicated in visuospatial functions, including postsaccadic information processing (VS in Table 2; Sikes *et al.*, 1988; Musil *et al.*, 1993; Olson *et al.*, 1993), it is likely that dorsal parts of the PCC and area 7b are involved in visually guided nocifensive responses. In the present experiments, however, the subject was in a dimly lit room and was not required to make visually guided movements. Furthermore, parts of area 7b and the PCC had prominent reductions in rCBF, suggesting that there was an inhibition of visually guided movements. A possible corollary of these findings is that, since the subjects experienced pain in the presence of reduced rCBF in area 7b and the PCC, these areas may not be involved in the affective responses to noxious stimuli that require elevated cortical activity.

Although the specific functions of area 7m are not known, it has pronounced connections with the cingulate cortex (Vogt and Pandya, 1987; Cavada and Goldman-Rakic, 1989) and is probably involved to some extent in sensorimotor processing, although not specifically related to pain processing. Interestingly, the connections of area 7m with the cingulate cortex are mostly associated with the cingulate motor areas. In the present task area 7m had reduced rCBF, as did much of areas 31 and 23b. Thus, the reduction in rCBF in the PCC and medial parietal areas may enhance the inactivation of cingulate motor areas in a task that requires response inhibition.

Hemispheric specialization in affective responses

The goal of the present study was to identify which areas in the cingulate cortex might subserve different aspects of pain processing. Although the alterations in relative rCBF were essentially bilateral, this does not require that each hemisphere plays an equivalent role in pain perception, processing and responses. An alternative hypothesis is that the cingulate cortex in each hemisphere is engaged in different aspects of motivational–affective pain processing.

It is well known that the two hemispheres contribute differentially to language (Joanette *et al.*, 1990). A report by Heilman *et al.* (1984), for example, suggested that individuals with right hemisphere damage had decreased comprehension of emotional prosody, while those with left hemisphere damage were more impaired in comprehension of propositional prosody than control cases. In terms of emotion and the cingulate cortex consider the following observations. (i) Extracting the emotional content in a visual facial recognition task elevates rCBF in the right ACC (George *et al.*, 1993). (ii) The emotional Stroop task that employs words with affective content elevates rCBF in the left ACC (George *et al.*, 1994). (iii) Complex emotions (i.e. those not restricted to simple visual images like faces or words), such as sadness, elevate rCBF in the ACC in both hemispheres (George *et al.*, 1995). It is possible that affective responses in the cingulate cortex associated with different types of pain are processed differently in each hemisphere.

Opiate regulation of cortical responses

Morphine blocks the affective features of acute and chronic noxious stimuli while leaving the sensory–discriminative component of pain intact (Price *et al.*, 1985; Kupers *et al.*, 1991), and it produces an elevation in mood over a period of 2 h (Kaiko *et al.*, 1981). While some of these actions are probably associated with binding to receptors at subcortical sites, much evidence suggests a powerful regulation of the ACC by opiate compounds. Morphine elevates rCBF in the anterior and ventral part of the perigenual ACC (Jones *et al.*, 1991b), a region that is similar to the one activated by sadness in healthy women in the study of George *et al.* (1995). The midcingulate region that is associated with elevated rCBF during noxious stimuli has a range of diprenorphine binding capacities from low to high, while binding in rostral perigenual areas of the ACC is high (Vogt *et al.*, 1995b). These localizations may indicate a more powerful regulation of affect and mood in the perigenual region of the ACC than of the gyral midcingulate regions.

Conclusions

The cingulate cortex does not appear to be engaged in the somatotopic coding of noxious stimuli and it is not a 'pain centre'. Instead, we propose that different parts of the cingulate cortex are engaged in at least three levels of processing of nociceptive information: (i) midcingulate area 24b′ is involved in response selection and other premotor functions which can include response inhibition or visual guidance of responses to noxious stimuli via the PCC; (ii) rostral area 24′ and perigenual areas 24, 25 and 32 encode the affective content of a noxious stimulus; and (iii) the ACC, possibly via thalamic and PCC interactions, may be involved in the acquisition of appropriate avoidance responses to stimuli which are predictably noxious. Thus, depending on the required behavioural outcome, studies will probably engage different parts of the cingulate cortex. In the present study no visual cues or motor response inhibition was possible for avoidance

behaviour. Therefore, in this paradigm the PCC and parietal visuospatial areas had reduced rCBF, probably as a result of inhibition of visually guided movements, while midcingulate and DLPF had elevated rCBF, probably associated with response inhibition. Additionally, activation of the perigenual cingulate cortex may have been involved in defining the affective content of the noxious heat stimuli.

These studies confirm our early expectations that co-registration techniques provide a high level of spatial resolution of the PET signal and new insights into the contributions of different medial cortical areas in pain processes. The further elaboration of models of cortical pain processing in the human brain will require better techniques for evaluating the temporal coding of such events and a greater flexibility in behavioural paradigms. Finally, the failure of classical models of pain processing to explain chronic pain syndromes probably reflects the bias towards areas engaged in the sensory–discriminative processing of noxious information rather than areas specifically engaged in pain affect and learning and memory. Understanding the contributions of different components of the limbic system to pain, including the medial and intralaminar thalamic nuclei, will shed new light on chronic pain syndromes and provide more effective means of therapeutic intervention.

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Abbreviations

ACC	anterior cingulate cortex
AC–PC line	reference line through anterior and posterior commissures
DLPF	dorsolateral prefrontal cortex
FWHM	full width at half maximum signal
MR	magnetic resonance
PCC	posterior cingulate cortex
PET	positron emission tomography
rCBF	relative regional cerebral blood flow
SPM	statistical parametric map

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