Exp Brain Res (1998) 118:52–60

RESEARCH ARTICLE

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Pain and Stroop interference tasks activate separate processing modules in anterior cingulate cortex

Received: 22 July 1996 / Accepted: 28 May 1997

Abstract Investigations of pain using functional imaging techniques have revealed an extensive central network associated with nociception. This network includes the thalamus, insula, prefrontal cortex and anterior cingulate cortex (ACC) as well as the somatosensory cortices. Positron emission tomography (PET) of regional cerebral blood flow (rCBF) has demonstrated activation of the ACC during cognitively challenging tasks such as the Stroop interference task and divided attention. One interpretation of this research is that ACC is involved in the general features of attention and that it does not play a specific role in pain processing per se. Three-dimensional PET imaging provides a method for assessments of rCBF in a single individual during multiple tasks. In addition, coregistration of PET and magnetic resonance (MR) images allows for better localisation of the PET signals so that differences in cortical activation sites can be more accurately determined. This approach was used to assess rCBF during the experience of pain by subtracting images collected during heat from those during noxious heat stimulation. Two regions of the ACC had elevated rCBF, one in the perigenual region and one in the mid-rostrocaudal region (i.e. midcingulate cortex). During the execution of the Stroop task, the group result showed the midcingulate region overlapping with the site seen during the experience of pain. This group result, however, was not confirmed in the individual subject analysis, which revealed widespread and independent areas of ACC response to pain and Stroop. It is concluded that the ACC contributes to multiple cognitive procedures. It is inadequate to describe the primary contribution of ACC to pain processing as "attention" because it is unlikely that the multiple small and independent activation sites produced by pain and Stroop subserve attentive processing throughout the brain.

Key words Affect · Limbic system · Cognition · Functional imaging · Human

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Introduction

Although it has long been known that neurosurgical intervention into cingulate cortex can alleviate affective responses to noxious stimuli such as chronic cancers (Foltz and White 1962), it has been assumed that cingulate cortex itself did not participate specifically in pain-processing functions. This presumption was based in part on the observation that lesions in human cingulate cortex could produce contralateral neglect (Heilman and Valenstein 1972), leading to the suggestion that cingulate cortex was involved in general aspects of attention (e.g. Mesulam 1985). Functional imaging studies using positron emission tomography (PET) to assess regional cerebral blood flow (rCBF) have now demonstrated activation of anterior cingulate cortex (ACC) both during noxious sensory stimuli (Jones et al. 1991; Talbot et al. 1991; Casey et al. 1994; Coghill et al. 1994; Derbyshire et al. 1994; Rosen et al. 1994; Hsieh et al. 1995; Vogt et al. 1996) and during cognitively challenging tasks such as Stroop (1935) interference (Pardo et al. 1990; Bench et al. 1992) and divided-attention (Corbetta et al. 1991) tasks. One interpretation of this growing body of research is that the ACC is involved in the general features of attention and does not play a specific role in pain and other cognitive information-processing functions. It is interesting to note, however, that some PET studies led investigators to alternate conclusions. Pardo et al. (1990) suggested that cingulate cortex is involved in "attention to action" emphasizing its premotor functions, and Corbetta et al. (1991) inferred a role in response selection. Bench et al.

(1992) and Vogt et al. (1992) have argued for the rejection of the concept of ACC as broadly responsible for attention. Instead they suggest that the ACC is a functionally heterogeneous region with functional differences along its rostrocaudal extent.

Heterogeneity of function is supported by the differential afferent and efferent connections of parts of the ACC. The perigenual region of ACC is a projection site of the amygdala (Vogt and Pandya 1987) that appears to be involved in conditioned fear (LeDoux 1991). This region of ACC also has pronounced projections to the periaqueductal grey, which has been implicated in modifying motor responses involved in defence and other emotional behaviours associated with flight and immobility (Hardy and Leichnetz 1981; Holstege 1992). In contrast, the mid-rostrocaudal or midcingulate region that is comprised of area 24' (Vogt et al. 1995) has not been implicated in emotional behaviours and does not have substantial connections with the amygdala or periaqueductal grey. This region has major connections with the parietal cortex (Baleydier and Mauguiere 1980; Vogt and Pandya 1987). Neurological disruption of this region compromises cognitive processes associated with motor or premotor events related to response selection and suggests that ACC can be subdivided structurally according to differential contributions to affect, cognition and premotor functions (Devinsky et al. 1995). Of particular relevance to the present investigation, cingulumotomy lesions in the midcingulate region alleviate chronic pain, possibly because of disruption of nociceptive inputs that travel from the spinal cord via the midline and intralaminar thalamic nuclei to ACC (Vogt et al. 1993).

The role of cingulate cortex in processing pain signals, cognitive functions and attention remains a point of contention in studies of brain function. The advent of three-dimensional PET imaging (Townsend et al. 1991; Watson et al. 1993) provides a method for assessments of rCBF in a single individual during multiple tasks. In addition, co-registration of PET and MR images allows for a high resolution of PET signals so that differences in cortical activation sites can be more accurately determined. The present study used noxious and non-noxious heat stimuli randomly alternating with trials of Stroop interference testing on the same subjects to resolve to what extent ACC is involved in general attentional mechanisms or specific cognitive information processing functions. The hypothesis states that, if ACC is involved in attentional processing common to both pain and Stroop, there will be a common region of activation in ACC that both tasks activate. We have already thoroughly analysed rCBF during noxious heat stimuli in the subjects used for this study and found that in most subjects there are two or more sites of elevated rCBF that include the mid-rostrocaudal part of cingulate cortex (i.e. midcingulate cortex) and the perigenual cingulate cortex (Vogt et al. 1996). The present study assesses the extent of overlap between these sites and those produced by Stroop interference testing.

Materials and methods

Subjects

Six right-handed male volunteers (mean age 27 years, SD 5 years) were used for the following study. All subjects gave informed, written consent. This study was approved by local ethics committee and by ARSAC-UK.

Design

Each scanning session consisted of sixteen 2-min 45-s PET scans. During the first 15 s, background data only was collected. Immediately after these 15 s, an $H_2{}^{15}O$ infusion was started. The infusion was at 10 ml/min and continued for 2 min until a total dose of 7 mCi had been administered. This was followed by a 30-s flush of nonradioactive normal saline. Each scan was separated by 7 min to allow decay of radioactivity to less than 5% of the peak value in the preceding scan. Two heat (one painful heat, one non-painful heat) stimulations and two Stroop tasks were each performed four times during the session. The order of the tasks was randomised to control for systematic changes over time due to factors such as arousal and habituation. The two stimulations produced the first within-subject variable, painful heat compared with non-painful heat, and the two tasks produced the second within-subject variable, incongruent colour words (Stroop) compared with congruent colour words (Stroop control). During the heat stimulation scans, subjects received eleven, 15-s ramps of increasing heat, which at their peak were consistently described as either painful (mean temperature 43.3°C, SD 1.6; mean pain rating from 0–100, with 0, no pain and 100, worst pain imaginable, was 67, SD 19) or hot (mean 39.7°C, SD 2.1). The thermode was 2.5 cm×1 cm. Temperatures were ramped from 25° to 43.3° (mean) and back again over a 15-s cycle meaning an average 2.44° change every second for the painful hot stimulation and a 1.96° change every second for the non-painful hot stimulation. Subjects had eyes open during the stimulation and were asked to fixate on the monitor in front of them.

In each Stroop condition the subjects were asked to internally name the ink colour and ignore the word. The coloured words measured 15–32 mm×12 mm and were displayed for 1.5 s with an interstimulus interval of 1 s. The order of the colours presented was varied randomly within and between each task. The experiment was designed such that the cortical areas corresponding to the attentionally demanding or executive component of the Stroop task could be compared with the cortical areas corresponding to the processing of pain within the same group of subjects.

Apparatus

The stimulus for both hot and painful hot conditions was produced by a Somedic thermal threshold stimulator, which delivers reproducible intermittent ramps of increasing heat to the skin via a water-cooled probe (Fruhstorfer et al. 1976).

The software to generate and present the stimuli was written by Professor C. Frith (MRC Cyclotron Unit, Hammersmith Hospital, London, UK) in BASIC on a BBC Microcomputer (Acorn Computers, Cambridge, UK). The coloured words (blue, green, red or yellow) were presented on a 12-inch RGB monitor (KAGA Electronics, Tokyo, Japan) placed approximately 40 cm from each subject. A white cross 5 mm×3 mm presented 5 mm below the coloured stimulus served as a fixation point. Prior to the scan, examples of the Stroop task were shown using a SPARC 2 workstation (SUN Microsystems Europe, Surrey, UK).

PET scans were performed using the ECAT 953B (Knoxville, USA) tomograph system with 16 detector rings and retractable interplane collimating septa to allow acquisition of data in a high-sensitivity, three-dimensional mode. The actual resolution of the PET camera is 6 mm, whereas the effective resolution for the group reported here is approximately 16 mm and for the individuals approx-

imately 12 mm (FWHM). Other physical characteristics of the 953B have been described elsewhere (Townsend et al. 1991). MRI scans were obtained using a 1-T Picker HPQ Vista system.

Procedure

Temperatures that, when applied to the back of the left hand, were reproducibly experienced as non-painful heat or painful heat were established for each subject prior to the scan. In addition, subjects were shown an example of the Stroop conflict task (red printed in green, yellow printed in blue and blue printed in red), and it was explained that everyone finds this task challenging and demanding. Each subject was instructed that during the scanning session they would receive four conflict sessions and four congruent sessions and that for each they should concentrate on the colour of the ink, ignoring the word name, and naming the ink colour internally. Mistakes should be corrected quickly.

Each subject was positioned in the scanner so that the axis of the scanner was approximately parallel to the glabellar-inion line. 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. All subjects underwent 16 sequential scans over the course of a single 3-h session. Each thermal stimulus and each task was commenced 5 s prior to the start of the scan. After each measurement, verbal confirmation was obtained that subjects had experienced the stimulus or task appropriately. MRI scans were acquired for each subject within 2 weeks of their PET study.

PET data analysis

PET images were analysed using statistical parametric mapping (SPM software; MRC cyclotron unit, UK) and interactive image display software (Analyze, Biomedics Research Unit, Mayo Clinic) on a SPARC 2 workstation. Calculations and matrix manipulations were performed in PRO MATLAB (Mathworks, New York, USA). The object of the analysis of these studies was to compare changes in blood flow between the different stimulation conditions so that the effect of heat intensity without pain could be contrasted with the effect of painful thermal stimulation and the effect of colour naming without interference (Stroop control) could be contrasted with the effect of colour naming with interference (Stroop). In order to complete these comparisons, the following procedures were carried out. Correction for head movement between scans was completed computationally by aligning them all with the first one, using Automated Image Registration (AIR) software specifically developed for the purpose (Woods et al. 1992). The AC-PC line was identified directly from the PET image and the data transformed into standard stereotactic space of the stereotactic atlas of Talairach and Tournoux (1988). In order to increase the signal-to-noise ratio and accommodate variability in functional anatomy, each image was smoothed in x, y and z dimensions with a Gaussian filter of 10 mm (FWHM). A correction was made for global changes in blood flow between scans. These two procedures allow flow values for each stimulus condition to be pooled across subjects. Finally a statistical comparison of blood flow distributions between conditions was performed to identify sites of significantly changed regional flow (Friston et al. 1991).

The differences between one condition and another were assessed with the appropriate contrast (weighting of the eight condition means) using the t-statistic. This analysis is performed for each pixel and the resulting set of t-values constitutes a statistical parametric map (SPM{t}). The significance of each SPM{t} was assessed by comparing the observed and expected pixels above a specific criterion ($P<0.001$). The threshold of $P<0.001$ was chosen because empirical studies with phantoms have shown that this threshold protects against false positives (Bailey et al. 1991).

In order to individually assess changes in rCBF, the above procedure was repeated for each individual separately. The search for areas of significance, however, was restricted to the region of the ACC and guided by the group result. This constrained search allowed the use of a lower threshold for significance ($Z>1.65$; $P<0.05$: Friston et al. 1991).

PET-MRI coregistration – individuals

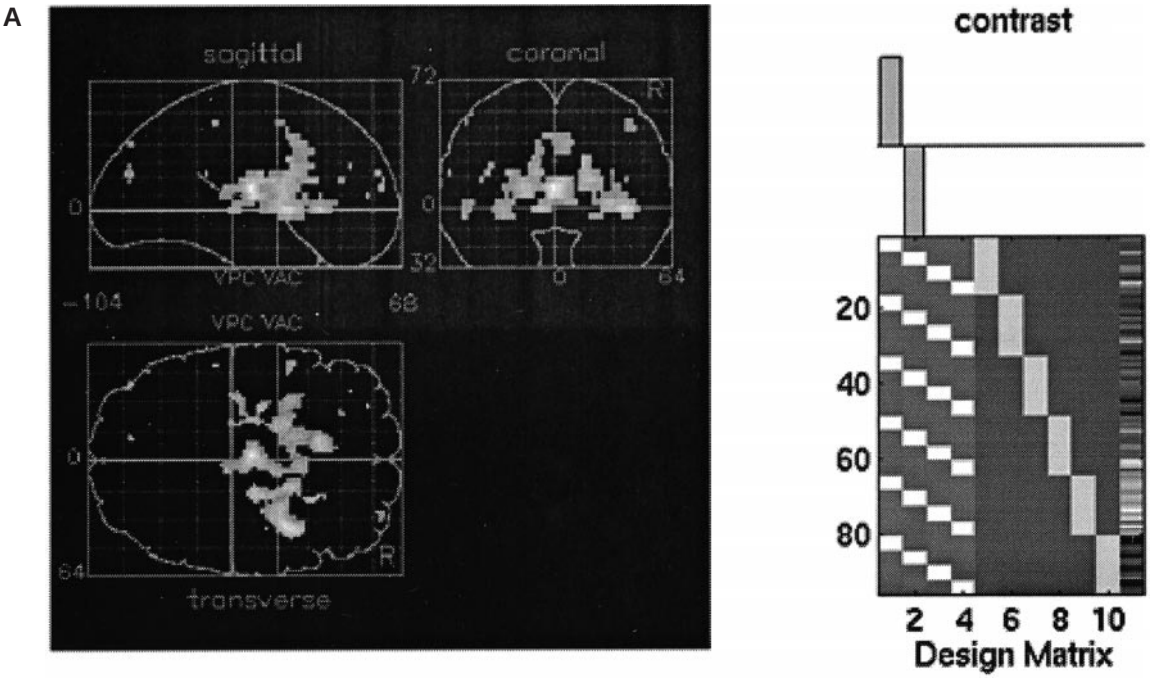
For each of the individual subjects an MRI was obtained using a 1-T Picker HPQ Vista system using an RF spoiled volume acquisition that is relatively T1-weighted to give good grey/white contrast and anatomical resolution (TR 24 ms; TE 6 ms; non-selective excitation with a flip angle of 35°; field of 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). After reconstruction, the MR images were also aligned parallel with the intercommisural line and interpolated to yield a cubic voxel size of 1.00×1.00×1.00 mm, which permitted coregistration with PET images.

For the coregistration of SPM and MR images, the steps of image realignment to the intercommisural line and anatomical standardization were omitted. However, the subsequent filtering, followed by ANCOVA and the generation of a thresholded SPM{t} were identical. The SPM{t} was then coregistered with the subjects own MRI scan. Such superimposition allowed us to determine the position of the region of maximal rCBF change in relation to the gyral and sulcal pattern of the ACC. Because the search for significance was constrained to the medial surface, SPM{t} thresholded at $P<0.05$ were accepted as significant (Friston et al. 1991).

Table 1 Activation foci in the anterior cingulate cortex (ACC) – Group. Sixteen PET scans were collected from each of the six subjects and separated into the two experiments: pain and stroop activation. Coordinates of the pixels where the most significant increases in blood flow were identified in the ACC for each group comparison are shown. Coordinates refer to the stereotaxic atlas of Talairach and Tournoux (1988). The Z-score is a measure of the degree of significance of the difference between the conditions and is the number of SDs from the mean t-value in the (t) statistical map illustrated in Figs. 1, 2

Stroop vs Stroop Ctrl				Noxious heat vs innocuous heat			
Coordinates			Z-score	Coordinates			Z-score
x	y	z		x	y	z	
−2	14	40	3.46	−10	32	0	3.22
0	2	48	3.42	4	10	36	3.01

Fig. 1 **A** Comparison of noxious heat with non-noxious heat. The display format is standard, with three orthogonal views of the brain from the top, from the right and from the back (the largest voxel along any line of view is shown). The stereotactic space is that defined by the atlas of Talairach and Tournoux (1988). Voxels are thresholded at $P<0.01$ ($Z>2.33$). The grey scale is arbitrary; white is maximum. The *top right panel* shows the design matrix of the general linear model used to partition the data (six blocks corresponding to the six subjects, 16 scan effects and global activity as a covariate of no interest). **B** Selected axial slices derived from the analysis shown in **A**. The activations are shown as statistical parametric maps (SPM) that show the areas of rCBF increase with a Z-value coded according to the colour bar (*right*). The SPM is superimposed on an anatomical reference image derived from a T1-weighted MR image. The *numbers* above each axial slice refer to the relative distance to the AC-PC line (joining the anterior and posterior commisures), which is situated at 0 mm. The anterior part of the brain corresponds to the *top* of the image, the posterior parts to the *bottom*. The *left* side of each image is the left side of the brain. The areas showing significant increases in blood flow are bilateral lentiform nucleus, thalamus and caudate, contralateral insula and midline ACC. The perigenual cingulate activation (A24) and the midcingulate activation (A24') are indicated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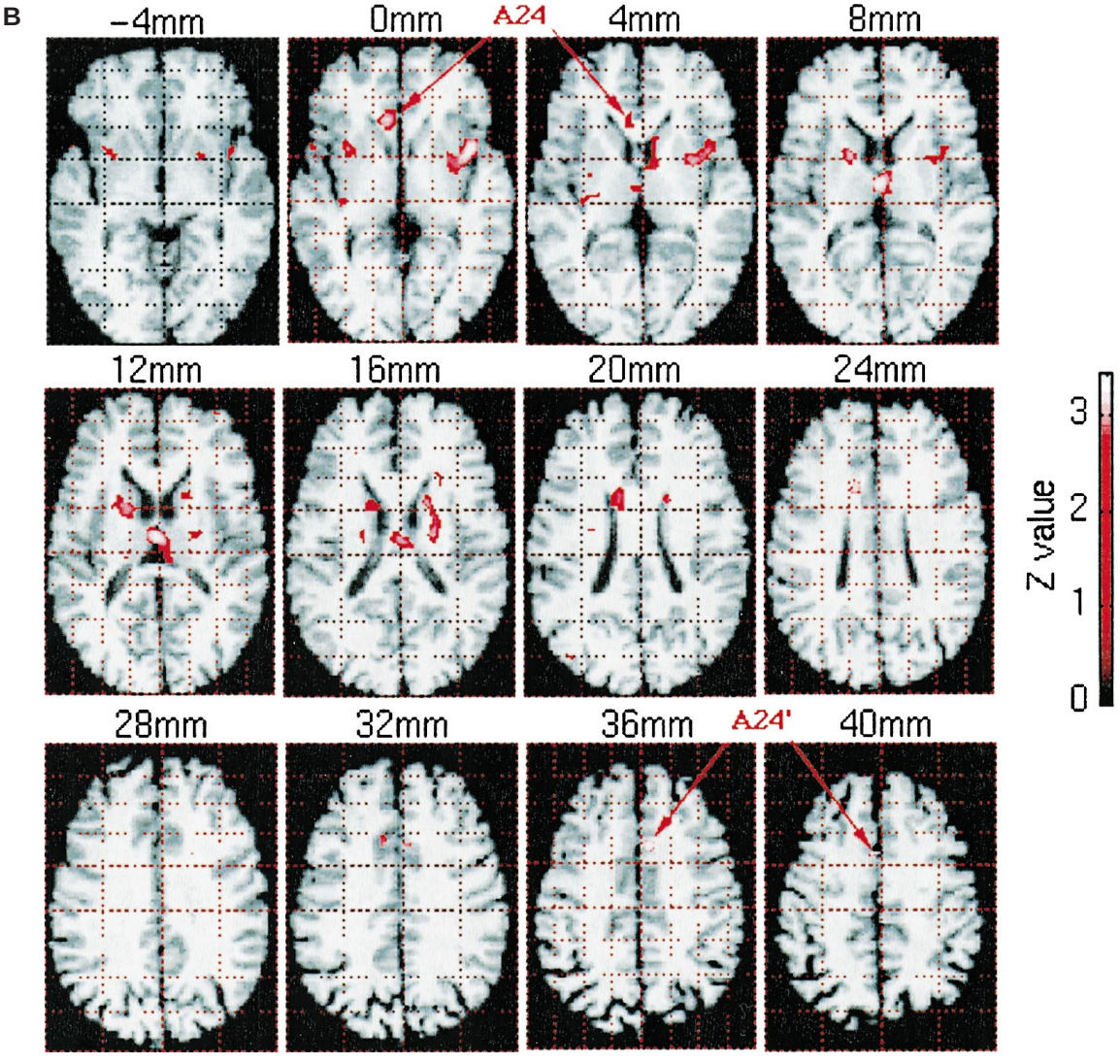
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Fig. 1A, B

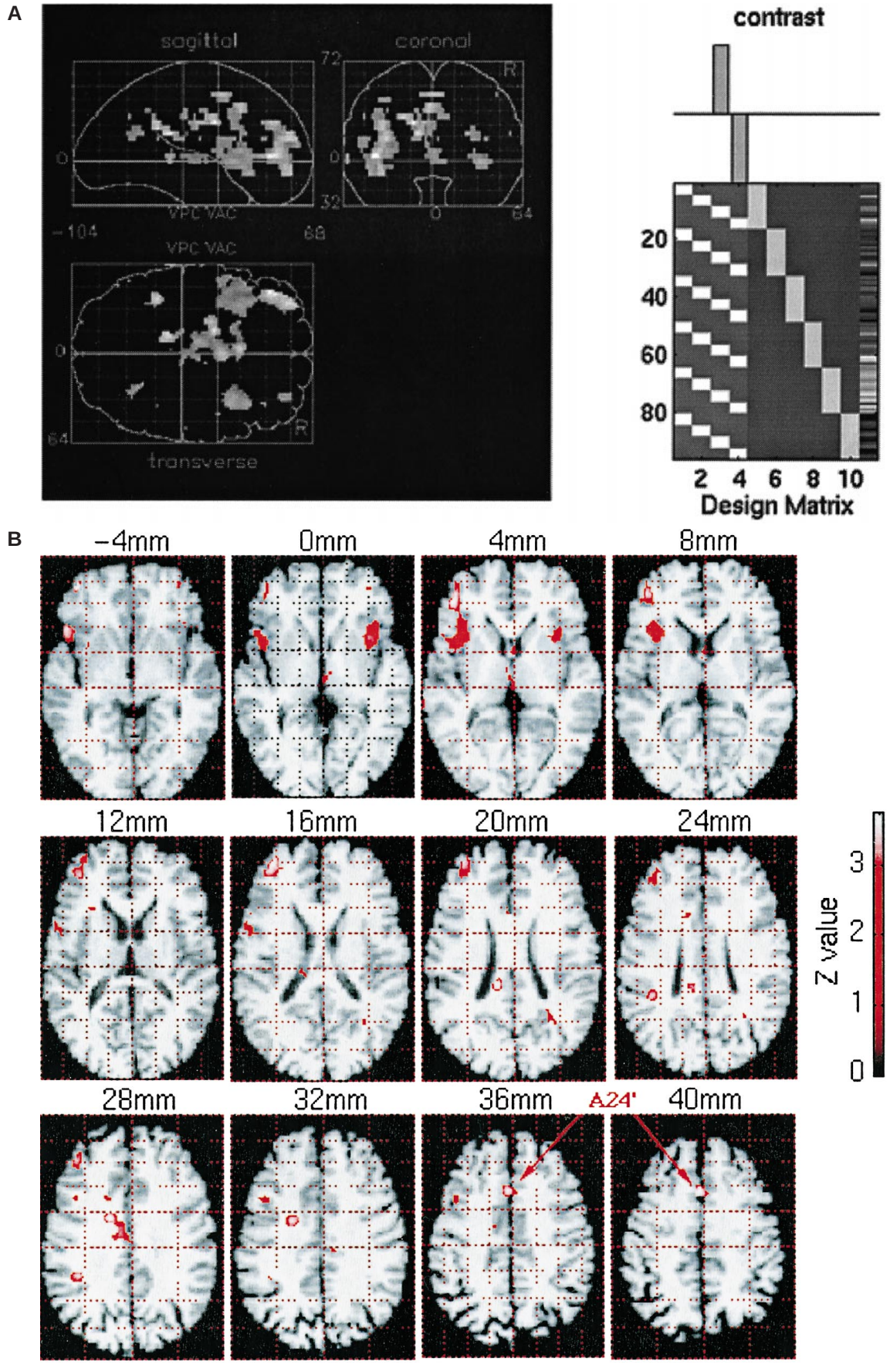
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Fig. 2A, B

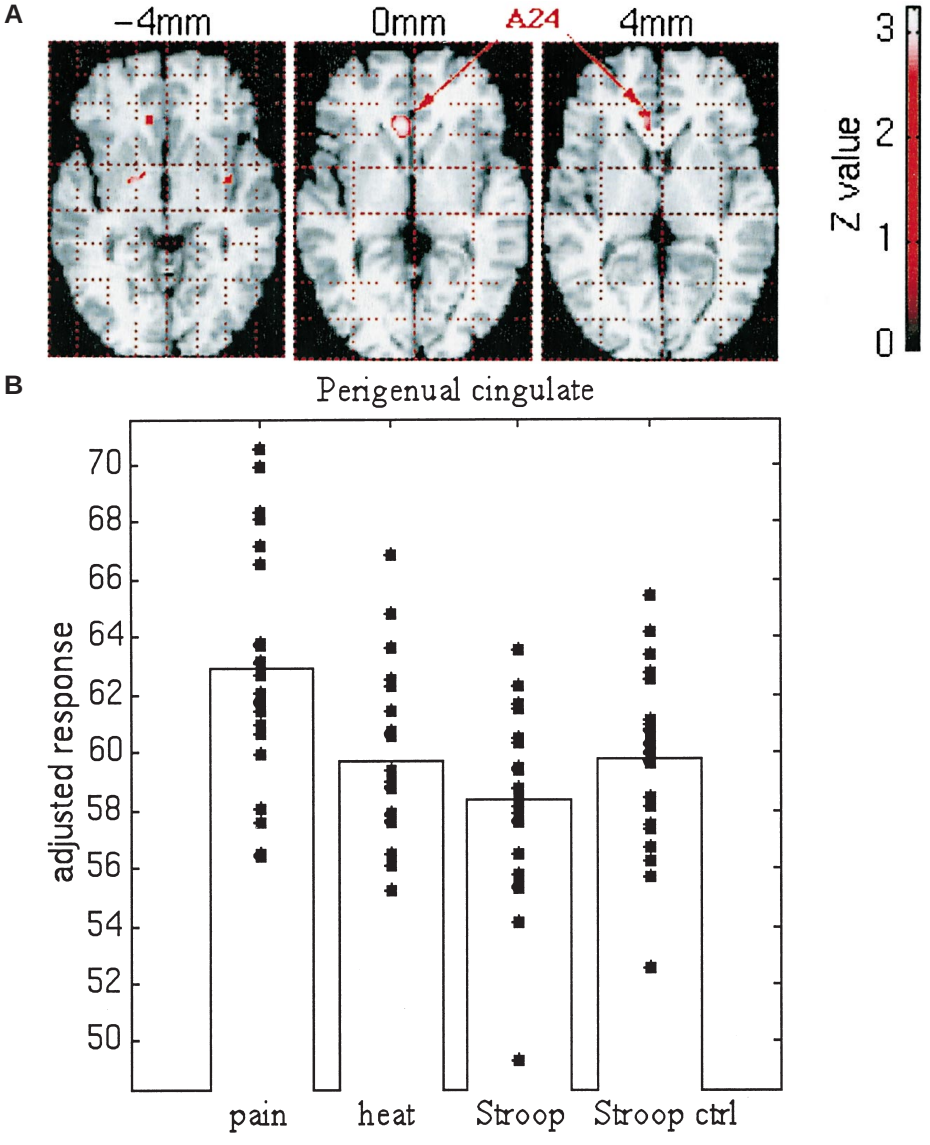

Fig. 3 **A** The perigenual activation as an increase greater than that seen during the Stroop task. **B** The change in blood flow in the perigenual region shown in **A**

Results

Group

Table 1 shows the coordinates of the pixels where the most significant increases in blood flow were identified in each comparison for the area of the ACC. There were two areas of ACC activation in response to pain, a midcingulate response and a perigenual cingulate response. Only a midcingulate region gave increased rCBF during Stroop activation. The results from Table 1 are displayed as SPM{t} in Figs. 1 and 2. These figures suggest the possibility that there is functional overlap between pain and Stroop in the midcingulate cortex as hypothesized. Interaction analysis (pain–heat)–(Stroop–Stroop control) confirmed the additional activation of perigenual cingulate during pain and the activation of midcingulate during pain and Stroop. The results of the interaction analysis are displayed in Fig. 3.

Fig. 2 **A** Comparison of Stroop with Stroop control. Display format and detail as in Fig. 1A. **B** Selected axial slices derived from the analysis shown in **A**. Display format and detail is as for Fig. 1B. The areas showing significant increases in blood flow are left prefrontal (areas 47/ 10/ 46/ 45/ 44/ 9), inferior parietal, and posterior (area 29/ 30) cingulate cortices, bilateral anterior insula and midline anterior cingulate cortex. The midcingulate response at 36 and 40 mm, indicated as in Fig. 1B, can be seen to have a bilateral spread and shows overlap with the pain midcingulate site shown in Fig. 1B

Individuals

It is possible that the group results are misleading and there is actually little or no overlap of activation sites in individual subjects. In order to further investigate this, ACC activation sites were analysed for both tasks for each individual subject.

Table 2 Activation foci in the anterior cingulate cortex (ACC). Coordinates of the pixels within the ACC where the most significant increases in blood flow were identified in each individual comparison. Detail is as for Table 1. All cases were co-registered with their own high resolution anatomy as defined by MRI and three cases (n1175, n1233 and n1246) are illustrated in Fig. 4

Subject	Stroop vs Stroop ctrl				Noxious heat vs innocuous heat			
	Coordinates			*Z*-score	Coordinates			*Z*-score
	x	*y*	*z*		*x*	*y*	*z*	
n1175	−22	8	32	3.366	−12	4	36	2.499
					4	−8	40	2.560
n1183	18	4	28	3.149	12	42	12	3.222
n1194	−16	2	28	3.129	28	−2	44	3.148
n1233	−20	−4	36	3.261	−2	16	28	5.992
	0	14	40	3.387	8	−20	48	3.476
n1246	0	6	28	2.032	2	10	32	2.539
	−2	6	36	1.881				
n1248	0	16	20	5.490	−14	22	28	3.569
	22	10	36	4.193				
	−4	−14	48	3.287				

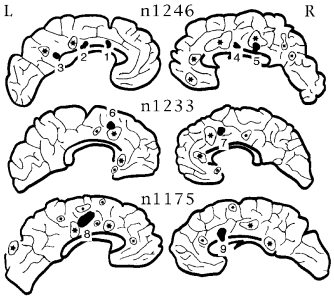

Fig. 4 Drawings derived from parasagittal MR images co-registered with PET associated with pain (*starred regions*) and the Stroop tasks (*black regions*). Three subjects and nine Stroop sites (*numbered*) are displayed as representative of the sites seen in the six individuals studied. Only minimal overlap is apparent in the individual sites processing pain and Stroop interference (namely sites 5 and 6). All sites reported are significant at $P<0.05$ ($Z>1.65$)

Table 2 displays the maximum *Z*-score for rCBF increases in ACC for each subject. For pain it can be seen that there is a range of 42 mm in the *x* plane, 62 mm in the *y* plane and 36 mm in the *z* plane. For Stroop there is a range of 44 mm in *x*, 38 mm in *y* and 20 mm in *z*. Between the two conditions, there is no overlap in peak rCBF, the centre of the Stroop cingulate activation always differs from a subject's pain cingulate activation. These estimates were based on the individual SPM analysis registered to the atlas of Tailarach and Tournoux (1988). Three subjects were selected for display as SPM{*t*} co-registered onto the subject's MRI scan and are shown in Fig. 4.

These cases were chosen as representative of the spread and size of Stroop and pain ACC activation sites seen in the six volunteers. The sites shown indicate activity on the left and right medial surface up to a depth of 9 mm lateral to the midline. This analysis allows representation of all the regions of the medial surface, including the motor regions of the ACC. The techniques for this representation are described in detail in our previous paper (Vogt et al., 1996). The starred areas represent the increases in rCBF during pain, the solid black areas represent increases during the Stroop task. The Stroop responses are bilateral and can be seen to extend from the posterior cingulate (area 31) through the midcingulate (area 24') and to the anterior portion of the cingulate cortex (areas 24 and 25). This individual analysis demonstrates that the overlap in cingulate areas responding to pain and Stroop is quite minimal. Other active regions on the medial surface are also shown including frontal and motor cortices and the juncture of occipitto-parietal cortex. There is no overlap in these additional medial regions.

Discussion

The growing recognition of acute pain as involving attentional and motivational as well as sensory and localisation components suggested a possible functional overlap in the region of the ACC during the performance of Stroop and the experience of pain. Selection of the ACC as a specific region of interest was motivated by previous PET investigations of pain (e.g. Jones et al. 1991; Talbot et al. 1991) the Stroop task (Pardo et al. 1990; Bench et al. 1992) and other cognitive tasks (Petersen et al. 1988; Corbetta et al. 1991). The present study measured rCBF in six volunteers while they experienced: noxious heat to the back of the left hand; innocuous heat to the back of the left hand; the Stroop task (colour words printed in a colour incongruent with the word); and a Stroop control task (colour words printed in the colour congruent with the word). In the group analysis, the midcingulate region (36–40 mm to the AC-PC line) shows overlap of activation sites associated with both tasks. Although this appears to support the hypothesis that ACC is involved in an attentional process common to both Stroop and pain, the individual analysis demonstrated that the overlap in cingulate areas associated with pain and Stroop interference is minimal. The hypothesis of functional overlap in an area of ACC is thus contradicted by the individual results. The reason for this contradiction is likely to be due to the large variation in individual responses shown in Fig. 4. That there is minimal overlap on the medial surface for the individual analyses between Stroop activation and pain activation indicates that the group result is misleading. The lack of common localisation of Stroop and pain processing in the cingulate cortex suggests that the function of the ACC cannot be described under the general single rubric of attention. This does not mean excluding an attentional component from either task but does exclude attention as a major common component.

Individual variation may also explain why different studies of the Stroop effect have different localisations. The Stroop activation of ACC seen in the group studied here is more posterior than that seen in Pardo et al.

(1990) and more superior than that of Bench et al. (1992). This variation is a probable result of the arbitrary grouping of individual variation. However there are a number of task differences between the three studies, which may also account for at least some of the localisation differences in the cingulate responses. Pardo et al. used a display period of 1.3 s, an off period of 0.35 s and a scan procedure lasting 95 s. Thus, during each scan, Pardo presented 58 words, which were displayed for a total time of 75 s. Bench et al. used a display period of 1 s, an off period of 1 s and a scan procedure lasting 120 s. Thus, during each scan, Bench presented 60 words displayed for a total time of 60 s. In a second experiment, Bench et al. replicated the procedure of Pardo et al. During the study reported here, a display period of 1.5 s, an off period of 1 s and a scan procedure of 165 s were used. Thus we presented 66 words for a total period of 99 s. In addition, Bench used a series of baseline conditions including crosses, congruent words and neutral words, during two experiments consisting of six scans each, and most of Bench's significant results came from the comparison of Stroop with crosses. Pardo et al. used only congruent and incongruent conditions, as we did, and only carried out two scans for each subject, one congruent scan followed by an incongruent, raising the possibility of an order effect. Our study involved 16 scans, with the Stroop conditions spread randomly throughout. These differences in design may lead to variability in the relative degree of word processing, preparation for, or suppression of, verbalisation and response selection.

Nevertheless, the variability between the group studies cannot explain the variability observed between the subjects in this study. The Stroop sites 1, 2, 4 and 5 in subject n1246 and site 9 in subject n1175 are in close accordance with those reported in previous studies (Pardo et al. 1990; Bench et al. 1992), suggesting a similar functional response. Sites 6 and 7 in subject n1233 and site 8 in subject n1175, however, are distant from those previously reported, suggesting functional heterogeneity between subjects performing the same task.

The integration of thought, motivation and emotion is the critical aspect of ACC function that is liable to be engaged during many tasks. This report suggests that subserving this integrative function under the general rubric of "attention" is inadequate for both psychological and neuroanatomical investigation. Instead, it is likely that the Stroop task involves many sub-functions, such as response suppression, colour recognition and emotional responses associated with annoyance or frustration, which may involve more than one region of the ACC. This study emphasises the multiple independent roles of ACC engaged during both pain processing and cognitively challenging tasks.

Acknowledgements S.W.G.D. is supported by the Medical Research Council (ROPA award); B.A.V. is supported by the Burroughs Wellcome Fund. We would like to thank Prof. Richard Frackowiak for his support and for the use of the excellent facilities at the MRC Cyclotron Unit, Hammersmith Hospital, London W12 OHS, and Tom Nichols, University of Pittsburgh Medical Center, for his generous help and guidance with the statistics.

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