Exp Brain Res (1997) 117:192–199

RESEARCH ARTICLE

Jesper L.R. Andersson · Anders Lilja · Per Hartvig
Bengt Långström · Torsten Gordh
Hermann Handwerker · Erik Torebjörk

Somatotopic organization along the central sulcus, for pain localization in humans, as revealed by positron emission tomography

Received: 17 October 1996 / Accepted: 12 May 1997

Abstract Regional cerebral blood flow was measured with positron emission tomography (PET) in six healthy volunteers at rest and during experimentally induced, sustained cutaneous pain on the dorsum of the right hand or on the dorsum of the right foot. Pain was inflicted by intracutaneous injection of capsaicin, providing a mainly C-fibre nociceptive stimulus. Statistical analysis showed significant activations along the central sulcus (SI) area when comparing pain in the hand to pain in the foot. Separate comparison of both pain states to a baseline revealed different locations along the central sulcus for hand pain and foot pain. The encountered differences are consistent with what is previously known about the somatotopics of non-painful stimuli. When comparing painful stimuli to baseline, the contralateral anterior cingulate gyrus, the ipsilateral anterior insular cortex and the ipsilateral prefrontal cortex were implicated. The results are consistent with an involvement of SI in the spatial discrimination of acute cutaneous pain.

Key words Pain · Capsaicin · Cerebral blood flow · Positron emission tomography · Somatotopic organization · Human

J.L.R. Andersson · A. Lilja · P. Hartvig · B. Långström
Uppsala University PET Centre, University Hospital, Uppsala, Sweden

J. L. R. Andersson
Department of Radiation Sciences, University Hospital, Uppsala, Sweden

A. Lilja
Department of Diagnostic Radiology, University Hospital, Uppsala, Sweden

T. Gordh
Department of Anaesthesiology, University Hospital, Uppsala, Sweden

H. Handwerker
Department of Physiology I, University of Erlangen/Nürnberg, Erlangen, Germany

E. Torebjörk (✉)
Department of Clinical Neurophysiology, University Hospital, S-751 85 Uppsala, Sweden
Fax: +46-18-55 61 06

Introduction

Despite extensive research efforts, there is still a lack of knowledge and some controversy regarding brain processing of pain. Specifically the role of the primary somatosensory cortex (SI) in human pain perception has been debated (Jones et al. 1991, 1992; Talbot et al. 1991; Apkarian et al. 1992; Duncan et al. 1992a, b; Roland 1992; Stea and Apkarian 1992). One group performed positron emission tomography (PET) studies, comparing painful with non-painful thermal stimuli, and found significant pain-related increases in blood flow in areas corresponding to SI (Talbot et al. 1991), while similar experiments by others failed to show such activations (Jones et al. 1991). The discrepancies were attributed to inadequate subtraction of tactile components of the stimuli (Jones et al. 1992), but no real consensus was reached (Duncan et al. 1992a). To add to the controversy, significant decreases in blood flow in SI in response to painful stimuli were found using SPECT scanning, by yet another group (Apkarian et al. 1992). A tentative explanation for this was offered by electroencephalographic findings indicating that an initial activation of the central cortex by pain was followed by an inhibition (Backonja et al. 1991). More recent PET and SPECT studies pointed towards an activation of SI, both for repetitive noxious heat (Casey et al. 1994) and for tonic pain induced by cold water (Di Piero et al. 1994).

The capacity of normal human subjects to localize with minor error a C-fibre-induced pain on the hand (Ochoa and Torebjörk 1989; Koltzenburg et al. 1993) and on the foot (Jørum et al. 1989) implies that there must be a somatotopic representation for pain localization in the brain. Since the SI area is one of the projections of the somatotopically organized lateral thalamic nuclei, it is well suited for this function. Recent PET findings indicated that the locus of the cortical (SI) response to pain inflicted in the contralateral forearm conformed to cortical responses to vibrotactile stimulation of the same area (Coghill et al. 1994). Furthermore, Tarkka and Treede (1993)

have reported results consistent with a somatotopic organization of responses along the central sulcus in a study modelling evoked potentials arising from laser pulses of painful heat. There is, however, to our knowledge, no actual demonstration of a somatotopic organization of SI responses to painful stimuli in humans using PET. In this study a somatotopic organization of responses along the central sulcus to acute cutaneous pain is shown by comparing PET findings during pain induced on the dorsum of the hand with findings during pain induced on the dorsum of the foot. Pain was evoked by intracutaneous injections of capsaicin, which mainly activates C-nociceptors (Lynn 1990), thus eliminating the problem of confounding non-nociceptive afferent inputs.

Materials and methods

Subjects

Six right-handed, healthy male volunteers between the ages of 22 and 27 years participated in the study. The experimental protocol was approved by the University Ethics Committee and the University Hospital Isotope Committee, and informed consent was obtained from all subjects according to the Declaration of Helsinki.

Procedure

Each subject lay on his back and was immobilized using a modified version of a stereotactic head fixation (Bergström et al. 1981). After local anaesthesia, a 1.0-mm radial artery catheter (Vigg-Spectramed, Swindon, UK) was inserted at the left wrist, and another catheter was inserted into a vein at the elbow in the same arm. The subjects denied that they felt any ongoing pain from the catheters after insertion. The scanning room was dimly lit, and the subjects had both ears plugged. Two minutes before start of emission scanning, the subjects were instructed to close their eyes and not to move or talk. One baseline scan (BASE) was performed for 2 min in each subject under these conditions without painful stimulation, followed at intervals of 15 (after the baseline) or 30–40 min (after the first pain condition) by two additional scans under similar conditions, except that pain had been induced following capsaicin injection in the right hand (HAND) or foot (FOOT). In three subjects the pain was first inflicted in the foot and then in the hand, and in three subjects the order was reversed.

Preparation and delivery of capsaicin

A sterile colloidal mixture of 1% capsaicin (Sigma; 3.3×10^{-2} M) in Tween-80 and saline was prepared for injection as described previously (Simone et al. 1989) and then passed through a Millipore filter (0.2 μm pore size) into a vial for storage. For intracutaneous injection, a dose of 100 μg of capsaicin in a volume of 10 μl of capsaicin was given through a 27-gauge hypodermic needle (1 ml capacity; Beckton Dickinson, Franklin Lakes, N.J., USA). The injections were performed superficially in skin overlying the first interosseous dorsalis muscle on the dorsum of the right hand and the extensor digitorum brevis muscle on the dorsum of the right foot. The injection produced a bleb of about 4 mm in diameter and induced a red flare with a radius of 2–3 cm around the injection site.

Pain from capsaicin injection

Intracutaneous injection of capsaicin caused immediate, rather intense cutaneous pain that decreased slowly during the next several minutes. The 2-min scanning procedure started 40–60 s after end of injection, and when the scan was over the cutaneous pain was still fairly intense. A cold pack (3 M) with a temperature of about 10°C was then applied on the painful area for 5 min to quickly relieve the pain. No subject had any pain from a previous capsaicin injection when the next scan was started 30–40 min after the previous scan. At that time there was no temperature sensation of warmth or cold from the previous injection site.

Scanner

The studies were performed on a GEMS 2048-15B scanner (Holte et al. 1989). The scanner produces 15 slices with a 6.5-mm slice spacing and has a 6-mm axial and transaxial full width at half maximum (FWHM).

PET scanning

All subjects had a transmission scan, collecting approximately 110 million events, prior to emission scanning. Immediately prior to the emission scan, the arterial catheter extension line was positioned in a blood-activity measurement device (Eriksson et al. 1988) and connected to a syringe pump for withdrawal of blood. An i.v. injection of 800 Mbq of $H_2{}^{15}O$ in 3–4 ml of saline was administered and a PET measurement was commenced. PET data were collected in seventeen 5-s frames followed by two 20-s frames, and the radioactivity concentration of arterial blood was measured with a temporal sampling frequency of 1 Hz throughout the examination. The data from the arterial blood sampling was subsequently not used for the analysis of the data.

Partitioning and reconstruction of PET data

For each scan, the first frame after arrival of bolus to the brain was identified and relabeled as frame 1. Data were then summed into two summation images consisting of data from frames 1, 3, 5, 7, 9 and 11 and from frames 2, 4, 6, 8, 10 and 12, respectively. Hence, each summed data set consisted of two statistically independent estimates of the activity concentration of the brain from time of arrival of bolus and 60 s forth. It has been shown that, by dividing data from each scan in this manner, significant gains in sensitivity may be achieved (Andersson 1997). The summation images were reconstructed using the transmission scan to compensate for attenuation, correcting for scattered radiation (Bergström et al. 1983) and using a 15-mm FWHM Hanning filter. Note that although data were collected for 2 min, only the first 60 s after bolus arrival to the brain were used.

Anatomical normalization

Anatomical standardization of all individuals into a standard brain shape (Greitz et al. 1991) was performed manually by adapting selected atlas brain structures (Thurfjell et al. 1995) to PET data from each subject. Movements between scans were compensated for by software reorientation of scans two and three to match the posistion of the first scan for each individual (Andersson 1995). The reorientation was performed within the same software system as the anatomical standardisation (Andersson and Thurfjell 1997) and hence only one actual resampling of the data had to be performed.

Talairach coordinates

In order to facilitate comparisons to findings by other groups, Talairach coordinates for the activated regions were needed. To achieve this, the Talairach brain (Talairach and Tournoux 1988) was digitized and imported to the software that was used to manipulate the Greitz-atlas (Greitz et al. 1991), and the Talairach brain was transformed to the shape of the Greitz atlas brain. Thus by using the in-

verse of that transform, Talairach coordinates could be evaluated for every point in the volume (L. Thurfjell, personal communication). Due to the extra registration step involved, this estimate of the Talairach coordinates will have somewhat lower precision than if the Talairach atlas had been used directly.

Statistical processing

Data were fitted to a statistical model described by

$$Y_{ijk} = u + \tau_i + \gamma_j + \varepsilon_{ijk} \begin{cases} i = 1,2,3(\text{BASE, HAND, FOOT}) \\ j = 1,2,...,6(\text{subjects}) \\ k = 1,2(\text{data sets for each scan}) \end{cases} \quad (1)$$

where Y_{ijk} denotes observed activity in a given image element (pixel) at state i in subject j and data set k; u denotes mean pixel value averaged over i, j and k; τ denotes effect from stimulation; γ denotes subject (block) effect; and ε denotes residual error (Andersson 1997). The model was solved in a least-square sense for estimates of u, τ, γ, and ε, and t-values were estimated through linear contrasts.

Two contrasts were used; one that was intended to reveal areas pertinent to pain processing in general [–2 1 1] (HAND+FOOT–2×BASE, henceforth referred to as the pain contrast) and one to reveal areas that differed between processing of pain in the hand and the foot, and hence candidates for the somatotopics of pain [0 1 –1] (HAND-FOOT, henceforth referred to as the somatotopics contrast).

The t-maps were converted to z-score maps through a probability-preserving transform (Friston et al. 1991), and the omnibus significance of each t-map was assessed from the mean sum of squares of all intracerebral voxels (Worsley et al. 1995). Estimates of local significance were based on the spatial extent of connected (using a six-connectivity criterion) clusters with z-scores above 2.5 (Friston et al. 1994). The latter method consists of a global search for clusters of voxels with z-score above 2.5, followed by an estimation of the probability that a cluster of the observed extent would occur by chance anywhere in the volume. Hence, a correction for multiple corrections is performed and the stated P-values are per contrast. The smoothness of the z-score maps, used for the assessment of both global and local significance, was estimated from the variance of the partial derivatives of the z-score images.

Anatomical identification

Identification of activated areas was achieved with the aid of the atlas database (Greitz et al. 1991) and software (Thurfjell et al. 1995), which allows for automatic identification of anatomical and cytoarchitectonic areas (Thurfjell et al. 1993). The centre of mass (CM) coordinates for each cluster were used for localization, since this has been shown to yield a higher accuracy than when using the point with the highest z-score (Andersson et al. 1995). The CM coordinates were also used for the translation to the Talairach space. When the extent of a cluster was such that no clear majority, as assessed by visual inspection, of the voxels was located within the same anatomical/cytoarchitectonic area, more than one area was reported.

The main purpose of the present paper was the identification and localization of areas used for somatotopic discrimination of painful stimuli. Their identification was achieved through the somatotopics contrast ([0 1 –1]) described above. If, however, the same contrast had been used for localization, the results might potentially have been biased if there were a partial overlap of the areas activated by hand and foot pain, in which case the distance between the activations would have been exaggerated. Therefore z-score maps for two additional contrasts, [–1 1 0] (HAND-BASE) and [–1 0 1] (FOOT-BASE), were created. These contrasts were used only to achieve proper localisation for the areas indicated by the somatotopics contrast ([0 1 –1]), and no search for other activated areas was performed.

Results

Psychophysical results

When asked after the scanning procedures, the subjects described the pain from capsaicin injection like a sting from a wasp, with a maximal magnitude rated 5–7 on a ratio scale from 0 to 10, in which 0 was no pain and 10 was the worst pain the subjects could imagine. After the injection was completed, the ongoing burning cutaneous pain slowly decreased during the next several minutes. When the 2-min scanning procedure was over, the pain was still rated 4–5 on this scale. Thus, it can be concluded that all subjects perceived considerable ongoing cutaneous pain during the scanning procedures. However, this pain was quickly relieved by local cooling and no subject reported any pain or temperature sensation from a previous capsaicin injection when the next scan was started 30–40 min later.

PET results

The volume for which data were present for all individuals and states extended from 5 mm below the thalamus (Talairach z=0) to the vertex (Talairach z=67), as shown in Fig. 1. Thus, any activations outside this region would not have been detected in this study.

The mean sum of squares indicated highly significant differences in flow pattern between pain and non-pain (S=1.93, n=995, $P<0.00001$) and a smaller but still highly significant difference between hand pain and foot pain (S=1.25, n=995, $P<0.00001$).

Significantly activated peaks ($P<0.05$) for the pain contrast ([–2 1 1]) were found along the contralateral central sulcus, the contralateral anterior cingulate cortex, the

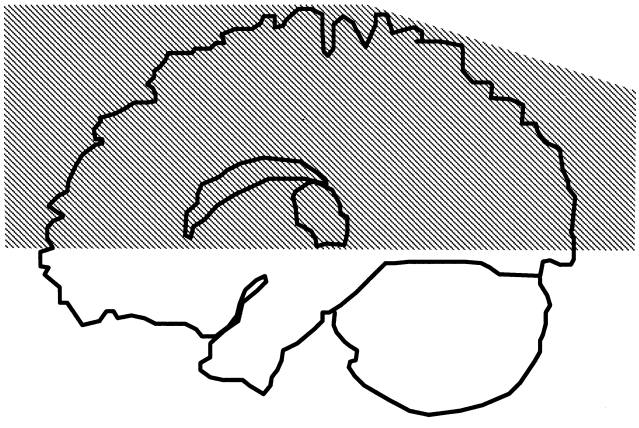

Fig. 1 The *shaded area* demonstrates the area in the cranial-caudal direction for which data were obtained. The *outline* is from the brain atlas database at a level 20 mm lateral of the interhemispheric fissure. *Contours* are shown for the brain outline, the thalamus and the putamen

Table 1 Positron emission tomography results (*BA* Brodmann's area, *Dx* dexter, *Sin* sinister)

Region[a]	Talairach coordinates[b]			*z*-score	Volume (cm^3)	*P*-value[c]
	x	*y*	*z*			
General pain-processing contrast [–2 1 1]						
Post/precentral gyrus, Sin, BA1/4 (SI/MI)	–17	–34	58	5.12	26.84	<0.0001
Middle frontal gyrus, Dx, BA10/46	34	57	14	4.46	3.94	0.0052
Ant. insula/operculum, Dx, BA14/15	41	8	1	3.90	3.67	0.0078
Ant. cingulate gyrus, Sin, BA24/32	–8	–5	37	4.25	2.81	0.0312
Planum temporale, Sin, BA43 (SII)*	–49	–25	11	3.70	2.30	0.0733
Ant. cingulate gyrus, BA24/32*	–1	28	24	4.23	1.91	0.1470
Ant. insula, Sin, BA14*	–36	6	1	3.40	1.46	0.3240
Somatotopics contrast [0 1 –1]						
Post/precentral gyrus, Sin, BA1/4 (SI/MI)	–1	–34	60	–4.50	9.32	<0.0001
Post/precentral gyrus, Sin, BA1/4 (SI/MI)	–43	–32	47	4.22	8.15	<0.0001
Planum temporale, Sin, BA43 (SII)*	–44	–21	5	3.23	1.76	0.1897
Post/precentral gyrus, Dx, BA1/4 (SI/MI)*	53	-26	42	3.95	1.42	0.3446
Hand localization contrast [–1 1 0][d]						
Post/precentral gyrus, Sin	–34	–38	58	4.26	17.50	<0.0001
Foot localization contrast [–1 0 1][d]						
Post/precentral gyrus, Sin	–6	–36	59	5.69	23.40	<0.0001

* This area was significant at the $P<0.5$ (contrast-wise type 1 error) level, but not at the $P<0.05$ level

[a] Anatomical identification was performed with the aid of the CBA database (Greitz et al. 1991). When alternative areas (i.e. post/precentral gyrus) are offered, the activated area extended into both areas such that the observer could not, with certainty, decide between them

[b] The Talairach coordinate system is defined with its origin in a point midway between the anterior and the posterior commisure. Axes: *x*, medial-lateral direction, positive values to the right; *y*, anterior-posterior direction, positive values towards the front; *z*, caudal-cranial direction, higher values cranially. The coordinates for the centre of mass of each cluster is reported

[c] The *P*-values are calculated from the observed volume of connected voxels with a *z*-score above 2.5. The resolution of the *z*-score maps was estimated to be 11.4 mm, 12.6 mm and 7.1 mm in the *x*, *y* and *z* directions respectively

[d] This contrast was used only to get an accurate localization for activation along the central sulcus, and no other areas are reported

ipsilateral anterior insular cortex and ipsilateral prefrontal cortex (BA46).

For the somatotopics contrast ([0 1 –1]), a significant increase was found along the central sulcus approximately 40 mm from the vertex, and a significant decrease was found, also along the central sulcus, at the vertex. Hence, the only area where data supports a somatotopical organization is along the contralateral central sulcus.

The results from both contrasts are summarized in Table 1, listing all areas with a *P*-level below 0.5. It may be noted from the table that the most significant (or least insignificant) of the clusters that did not reach the 0.05 level is situated in the SII area for both contrasts.

The somatotopics are illustrated in Fig. 2, showing a coronary slice through a *z*-score image for contrasts [–1 1 0] (HAND-BASE) and [–1 0 1] (FOOT-BASE). The localization of the activation along the central sulcus for the hand pain is compared with those of previous studies in Table 2. Due to lack of previous reports on pain in the foot, the same thing could not be done for the foot pain.

In addition to the SI activations, the localization contrasts ([–1 1 0] and [–1 0 1]) implicated many of the areas encountered in the pain contrast ([–2 1 1]). Furthermore, a significant (P=0.0312) activation was found in the supplementary motor area (SMA) in the HAND-BASE contrast ([–1 1 0]). This is the reason why, in Fig. 2, there seems to be an activation also of the foot area in the HAND-BASE contrast. The centre of this activation (Talairach coordinates: x=18, y=–6, z=60) is located 30 mm frontally of the centre of the SI activation in the FOOT-BASE contrast, and coincides with the superior frontal gyrus rather than with the postcentral gyrus.

Discussion

The main result from this study is the demonstration of a somatotopically organized activation along the human central sulcus in response to acute, intense tonic cutaneous pain. The implications of this and other findings will be discussed in relation to the various regions that we and others have found to be activated during noxious stimulation and pain.

It should be noted that while the statistical methods at hand allow for control of type 1 errors, there is no way to assess the type 2 errors. Hence, while the presence of an

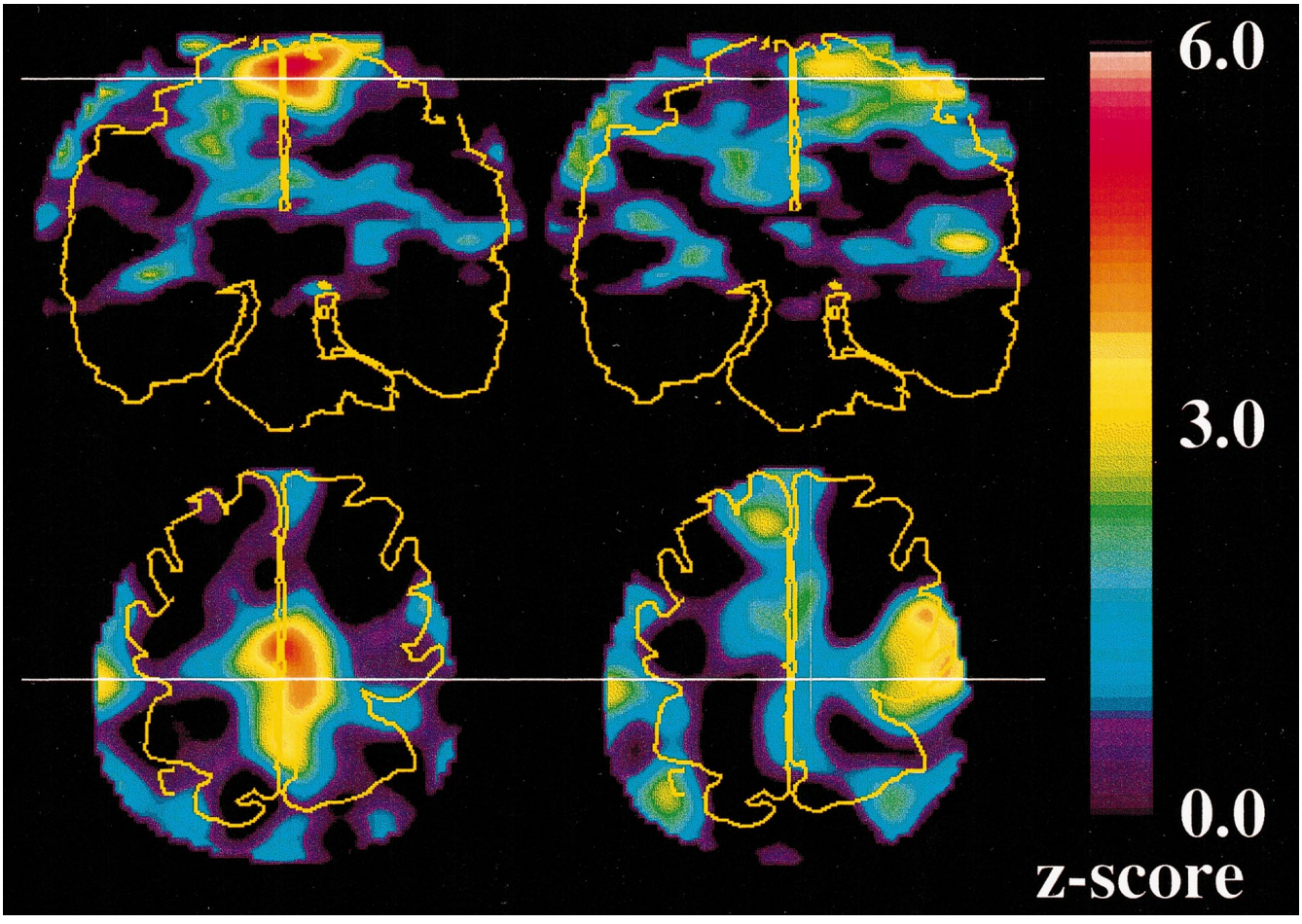

Fig. 2 *z*-Score images of the [–1 0 1] (FOOT-BASE) and [–1 1 0] (HAND-BASE) contrasts at the *left and right*, respectively. In the *upper row* there are two coronal and in the *lower row* two transversal slices. The *solid white lines* in the coronal images demonstrate the level of the transversal slices, and analogously the *white lines* in the transversal slices demonstrate the level for the coronal slices. The *yellow contours* are the brain outline from the brain atlas database (Greitz et al. 1991). Note that *right* corresponds to left in the brain, and that *top* in the transversal slices corresponds to the anterior of the brain. The most cranial activation in the [–1 1 0] (HAND-BASE) contrast, seemingly at the same location as the activation in the [–1 0 1] (FOOT-BASE) contrast, really corresponds to the activation of the supplementary motor area described in the Results section

Table 2 SI activations reported by other groups[a]

Reference	Stimulus location	Tailarach coordinates		
		x	*y*	*z*
Talbot et al. 1991[b, c]	Volar forearm	–31	–31	60
Coghill et al. 1994[b]	Forearm	24	–31	56
Hsieh et al. 1996a	Upper arm	–11	–34	55
Hsieh et al. 1995	Dorsolateral wrist	–32	–30	56
Current	Back of hand	–34	–38	58

[a]Additional groups reporting SI activations without reporting stereotactic coordinates include Casey et al. 1994 and Di Piero et al. 1994
[b]MRI was obtained for each subject and confirmed post-central location
[c]Vibrotactile stimulation activated almost identical area (<5 mm difference)

activation may be discussed with some confidence, the absence of one has little meaning. Therefore the lack of a significant finding in, for example, the thalamus does not indicate with any certainty that it was not activated, merely that it was not detected in the present study.

Central sulcus

Psychophysical experiments in normal human subjects with selective nerve blocks or with the combined techniques of microneurography and intraneural electrical microstimulation have shown that the mean error in localizing a painful cutaneous stimulus from a pure C-fibre input is of the order of 1 cm on the dorsum of the hand (Ochoa and Torebjörk 1989; Koltzenburg et al. 1993) and 2 cm on the dorsum of the foot (Jørum et al. 1989). Such accuracy implies a somatotopic arrangement for pain localization in the brain. Several lines of evidence indicate that this capacity resides in the SI. First, clinical studies on patients with their SI surgically removed have shown that the ability to sense pain was largely unchanged, but that localization was impaired (Penfield and Jasper 1954). Second, there are SI cortical neurons in the monkey that encode the intensity of noxious mechanical and thermal stimulation and have restricted, contralateral receptive fields. Such neurons are thought to be involved in the sensory-

discriminative aspects of pain, including localization (Kenshalo and Isensee 1983).

Several neuroimaging studies support the involvement of the SI in the processing of pain, reporting cerebral blood flow (CBF) increases in this area in response to painful stimuli as measured by PET (Talbot et al. 1991; Casey et al. 1994; Coghill et al. 1994; Hsieh et al. 1995, 1996a) or SPECT (Di Piero et al. 1994). This is further supported by measurements of field potentials in rats (Schouenborg et al. 1986; Kalliomäki et al. 1993) and evoked potentials in humans (Tarkka and Treede 1993). Insufficient intensity of the pain stimulus may be one possible explanation for the negative findings in some studies (Jones et al. 1991; Derbyshire et al. 1994).

The findings of our study, in which possible tactile components of the stimuli were avoided by utilizing capsaicin, point in the same direction. The present design avoids many of the pitfalls present in earlier studies, where, assuming that there is a finite potential for perfusion increases in any given area, the subtraction of non-painful from painful stimulation may lead to underestimation of pain-induced increase in blood flow. Furthermore, it would be reasonable to assume that tonic pain experienced from capsaicin leads to less withdrawal reflexes, and the suppression thereof, than would be the case with a phasic heat stimulus on the skin. Our results indicate that the activations along the central sulcus have both the largest magnitude and spatial extent (these two entities are, however, strongly coupled, owing to the finite resolution of PET data) of all areas detected in the pain contrast. Hence, we conclude that this area plays an important role in the processing of pain, and suggest that it is used for somatotopic discrimination.

Although both the CM coordinates and the coordinates for the peak *z*-score indicate a postcentral localization for the observed activations, both extend well across the central sulcus. Hence, based on the data from the present study only, it cannot be concluded with certainty that some of the signal does not originate precentrally. It is, however, our interpretation that the observed activations take place mainly in the SI.

This is further supported by the comparison with earlier studies, shown in Table 2, where the foci found in the present study is even slightly more posterior than those found by others, where a postcentral origin was confirmed by MRI (Coghill et al. 1994).

Secondary somatosensory cortex

The SII has been implicated in several PET studies on experimental pain (Talbot et al. 1991; Casey et al. 1994; Coghill et al. 1994; Hsieh et al. 1995) as well as in neuromagnetic localization of cortical activity evoked by dental stimulation in man (Hari et al. 1983), in subdural recordings of tooth pulp-evoked potentials in unanaesthetized monkey (Chudler et al. 1986) and in analysis of pain-related somatosensory evoked potentials elicited by a CO_2 laser (Tarkka and Treede 1993). Clinical evidence for its contribution to pain stems from a case study reporting increased thresholds for heat pain, cold pain and mechanical pain caused by a tumour compressing SII (Greenspan and Winfield 1992). It therefore appears that the SII region is involved in pain processing, although the percentage of nociceptive cells among the total population of somatosensory neurons has been reported to be fairly low in this area (Robinson and Burton 1980, Dong et al. 1989). There is a somatotopic organization for neurons in the SII cortex (Nelson et al. 1979), but such neurons have large, poorly demarcated receptive fields, which overlap extensively and sometimes have bilateral representation (Burton and Robinson 1981; Dong et al. 1989).

The SII did not reach significance in any of the contrasts, but was the least insignificant of the remaining clusters in both. Given the relatively low sensitivity of PET activation studies, neither its involvment in pain processing in general or localization in particular may be ruled out based on our data. Indeed, of the areas found in the present study, it is the second most likely candidate for a somatotopic organization.

The explanation for our negative finding may reside either in the actual absence of a somatotopic organization, or in a combination of poor demarcation, the small total extent of SII in comparison with SI and the limited resolution of the PET technique.

Cingulate gyrus

Activation of the anterior cingulate gyrus has been observed in several PET studies on experimental pain (Jones et al. 1991; Talbot et al. 1991; Casey et al. 1994, Coghill et al. 1994; Hsieh et al. 1995, 1996a). Data from the present study show no indication of somatotopic organization of the pain-induced activation in this region, evident from the complete absence of any activations in this area in the somatotopics contrast. This is consistent with single-cell studies in the rabbit showing that neurons in the upper anterior area 24 respond to noxious mechanical and heat stimuli applied over very large parts of the body (Sikes and Vogt 1992). Thus it appears unlikely that the anterior cingulate cortex has anything to do with localization of pain. Many lines of evidence suggest that the anterior cingulate cortex is involved in attention, expression of emotion (anxiety, aggression), vocalization and autonomic reactions, all of which can be triggered by painful stimuli (see Vogt et al. 1992 for a review). Destruction of the anterior cingulate cortex and its underlying white matter in patients with chronic pain has been reported to abolish the affective components of pain, while the patients were still able to localize noxious stimuli (Foltz and White 1962; Ballantine et al. 1975).

Anterior insular cortex

Contralateral activation of the (anterior) insular cortex has been found in response to painful stimuli in previous PET

studies (Casey et al. 1994; Derbyshire et al. 1994; Jones and Derbyshire 1994; Hsieh et al 1995). Coghill et al. (1994) reported a significant activation near the anterior portion of the contralateral insular cortex and a trend toward activation in the ipsilateral anterior region. Similar results were reported by Hsieh et al. (1995), who found a bilateral activation of this area. Our study shows a significant ipsilateral activation and a non-significant (P=0.3240) trend of contralateral activation in this region. Thus we support the suggestion of Coghill et al. (1994) that this area may be activated bilaterally by painful stimuli. Interestingly, lesions of the insular cortex on either the right or the left side have been reported to be associated with asymbolia to pain, i.e. increased pain tolerance and endurance, lack of withdrawal, and absent or inadequate emotional responses to painful stimuli (Berthier et al. 1988).

Middle frontal gyrus (Brodmann areas 46 and 10)

Activation of this region was found as a subsignificant trend by Jones et al. (1991), and significant activation of this area was observed by Derbyshire et al. (1994) and Hsieh et al. (1995). The same area has also been reported to be involved in the perception of itch (Hsieh et al. 1994), and it is conceivable that the frontal activation reported by Di Piero et al. (1994) also corresponds to this region. Hence, there are several studies that report right-sided activation despite differences in the side to which pain was applied. This suggests that the prefrontal cortex is activated on the right, possibly the subdominant side in response to pain. The prefrontal cortex has projections to the anterior cingulate cortex, the basal ganglia and the insular cortex (Groenwegen et al. 1990) and may be involved in a "supervisory attention system" (Shallice 1982), which is lateralized to the right hemisphere (Posner and Rothbart 1991).

Supplementary motor area (Brodmann area 6)

This area was found in the HAND-BASE contrast but not in any of the other contrasts, the reason probably being that it coalesced with the SI activation of the foot area. The SMA has been implicated in previous studies on cutaneous (Coghill et al. 1994; Hsieh et al. 1995, 1996a) and visceral (Aziz et al. 1997) experimental pain and in studies on cluster headache (Hsieh et al. 1996b). It has been suggested that its activation should reflect motor responses to the pain such as grimacing, teeth clenching (Hsieh et al. 1996a) and withdrawal (Hsieh 1995). Given that it is activated also during cluster headache (Hsieh et al. 1996b) and in the present study, where withdrawal would amount to little, the former explanation seems the most likely.

Conclusion

The data from the present study strongly indicate a somatotopic involvement of the contralateral SI in the spatial localization of strong, acute cutaneous C-fibre pain elicited by intracutaneous capsaicin injection. Furthermore, although not statistically significant, it cannot be ruled out based on our data that there is a somatotopic organization of the SII cortex. In the other areas implicated for pain processing, the anterior insular cortex, the anterior gyrus cinguli and the middle frontal gyrus, there is no indication of such organization.

Acknowledgements Supported by the Swedish Medical Research Council, projects 5206 (E.T.) and 9077 (T.G.).

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