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Somatosensory Cortex: A Comparison of the Response to Noxious Thermal, Mechanical, and Electrical Stimuli Using Functional Magnetic Resonance Imaging

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Abstract: In the present study, functional magnetic resonance imaging (fMRI) was used to examine pain perception in humans. Three types of noxious stimuli were presented: electric shock (20.8 mA, 2 Hz), heat (48°C), and mechanical, as well as a control tactile stimulus. The significance of activation at the level of the voxel was determined using correlation analysis. Significant region of interest (ROI) activation was determined by comparing the percentage of active voxels in each ROI to activation in a control ROI in the visual cortex. In response to tactile and shock stimuli, consistent activation was seen in the postcentral gyrus, parietal operculum, and ipsilateral cerebellar cortex. No significant cortical activation was detected in response to noxious heat or mechanical stimulation when compared to nonpainful intensity levels. The data did not indicate adaptation, although further study in this area is necessary. Stationary noxious thermal and mechanical stimulation are ''pure'' noxious stimuli, while electrical stimulation influenced nociceptive and nonnociceptive receptors. Lack of detectable activation in response to pure noxious stimuli supports the idea that nociceptive and nonnociceptive fibers are interspersed in the somatosensory cortex. Conflicting results from recent functional imaging studies of pain perception regarding cortical activation indicate that it is essential to consider both the tactile and nociceptive components of the stimuli used, the spatial extent of stimulation, and the possibility of adaptation to the response. Furthermore, these results suggest that subtractive or correlative methods may not be sufficiently sensitive to image the activity of nociceptive cells, which are sparsely distributed throughout the somatosensory cortex. *Hum. Brain Mapping 6:150–159, 1998.*

Key words: pain; acute; BOLD; human, cortex

INTRODUCTION

Historically, the cerebral cortex was not considered to be involved in the perception of pain. Rather, most investigators in the field believed that the thalamus was principally responsible for processing information

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TABLE I. Summary of previous studies

Stimulus	Imaging method	Cortical activation	Thalamic activation	Cingulate activation	Surface area	Authors
Heat, moving	PET	+	NA	+	14.82 cm^2	Talbot et al., 1991
Heat, moving	PET	+	+	+	15.24 cm^2	Casey et al., 1994
Hot water, moving	SPECT	+↓	NA	NA	Digits	Apkarian et al., 1992
Heat, moving	PET	+	+	+	6.0 cm^2	Coghill et al., 1994
Heat, moving	fMRI	+	NA	+	10.75 cm^2	Gelnar et al., 1996
Electrical	fMRI	+	NA	+	NA	Davis et al., 1995
Electrical	fMRI	+	−	−	NA	Disbrow et al., present study
Heat, stationary	fMRI	+↓	NA	+	3.0 cm^2	Gelnar et al., 1996
Heat, stationary	PET	−	+	+	12.5 cm^2	Jones et al., 1991
Laser, stationary	PET	−	+	+	2.47 cm^2	Derbyshire et al., 1996
Heat, stationary	fMRI	−	−	−	4.0 cm^2	Disbrow et al., present study

↓ = activation out of phase.

about noxious stimuli [Head, 1920; Head and Holmes, 1911; Holmes, 1927; Penfield and Jasper, 1954]. However, the idea that the cerebral cortex was involved in processing nociceptive stimuli came from Marshal [1951], who described a group of patients with superficial wounds to the postcentral gyrus with localized loss of pain perception. Also, more recent work has demonstrated that deficits in the perception of pain and temperature result from cortical lesions in humans [Leijon et al., 1989; Bassetti et al., 1993] and monkeys [Kenshalo et al., 1991].

There is now a wealth of electrophysiological data from several species demonstrating the presence of nociceptive inputs to the postcentral gyrus [Kenshalo and Isensee, 1983; Kenshalo and Willis, 1991; Casey and Morrow, 1983; Chudler et al., 1990. These cells have been shown to respond to noxious thermal and mechanical stimuli. Two general categories of neurons have been described. Wide dynamic range neurons (WDR, also called nociceptive nonspecific) respond to low-intensity stimulation but show a peak response to noxious stimuli. These cells have restricted contralateral receptive fields, encode stimulus intensity, and show no adaptation to noxious heat stimulation. Nociceptive-specific (NS) neurons respond only to noxious stimulus intensities. In monkeys, these cells have been identified along the boarder of Brodmann's areas 3b and 1 [Kenshalo and Isensee, 1983].

Recently, advances in noninvasive imaging techniques have provided new data in humans on the presence of nociceptive inputs to the neocortex. Although imaging technology is advancing rapidly, the role of the somatosensory cortex in pain perception is still controversial [Roland, 1992; Stea and Apkarian, 1992; Backonja, 1996a,b; Kenshalo, 1996; Caselli, 1996; Apkarian, 1996], and the conclusions drawn using these new methods seem contradictory. Many studies have shown cortical activation in response to painful stimuli [e.g., Talbot et al., 1991; Casey et al., 1994; Coghill et al., 1994; Apkarian et al., 1992], while others have not [Jones et al., 1991; Derbyshire et al., 1996] (see also Table I).

The paucity of nociceptive neurons in primary somatosensory pathways [Casey and Morrow, 1983; Kenshalo and Isensee, 1983] and the somatosensory cortex [Chudler et al., 1990; Kenshalo et al., 1980; Kenshalo and Isensee, 1983], and the conflicting results obtained with new functional imaging techniques, raise questions about the role of the cortex in the perception of pain [Backonja, 1996a,b; Kenshalo, 1996; Caselli, 1996; Apkarian, 1996]. In this study we examine the role of the primary somatosensory cortex, SI, in pain perception by directly comparing patterns of cortical activation in response to pure noxious thermal and mechanical stimuli with electrical and nonnoxious tactile stimuli, using functional magnetic resonance imaging (fMRI). To gain insight into the cortical processing network involved in pain and tactile perception, it is essential to carefully control the various types of stimuli which excite different populations of receptors [reviewed in Willis, 1985].

MATERIALS AND METHODS

Subjects

Twelve volunteers (11 male, 1 female) between ages 18–35 years served as subjects. Subjects with a history of neurologic or psychological disorders were excluded. Following informed consent, subjects were asked to refrain from taking any pharmacologically

active substances, including aspirin, ibuprofen, caffeine, nicotine, or ethanol, for at least 24 hr prior to participation in the study. Heart rate was monitored for 5 subjects during scanning. Blood pressure was not monitored during scanning because the inflation of the blood pressure cuff would have been a significant confounding somatosensory stimulus.

Stimuli

Shock, noxious heat, noxious pinch, and nonpainful brush stimulation were administered in a random order for each subject. Supra- and subpainful electrical, mechanical, and thermal stimuli were alternated during a single scan. In 10 subjects, two levels of electrical stimulation were delivered to the forefinger of the right hand via a peripheral nerve stimulator (DigiStim II, Neurotechnology, Houston, TX) through surface electrodes (i.e., ECG pads). Shock stimulation consisted of a 2-msec duration shock at 2 Hz. Current levels were determined prior to study by each subject. To determine these levels, subjects were asked to adjust the current until it was slightly above threshold. This current level was used for the nonpainful stimulus (mean 6.7 mA, SD 5.7 mA). The level was then slowly increased until subjects indicated that it was no longer tolerable, at which point the current was discontinued. Subjects were then asked to select a current setting that was uncomfortable, but tolerable for the duration of the scan (mean 20.8 mA, SD 10.4 mA). The painful and nonpainful current levels were alternated every 32 sec throughout the imaging procedure.

Heat stimulation was examined in 9 subjects. Again, two intensity levels were determined prior to commencement of the study. A nonpainful level of 38°C was alternated with a mean painful level of 48.5°C (SD = 2°C). Stimulation was delivered to the right forearm using a Peltier thermode (model LTS-3, thermal surface 2 × 2 mm, Thermal Devices). To stimulate a larger number of afferent fibers, the heat stimulus was also delivered to the index finger of the right hand in 3 subjects. The thermode was not moved during the course of the scan.

In 4 subjects, noxious mechanical stimulation was administered to the flesh between the thumb and index finger using a plastic towel clamp called a Surgi-Clamp (Sparta Surgical Corp., Pleasanton, CA), with a surface area of 1.5 × 1.0 cm. Painful but tolerable pinch stimulation was alternated with nonpainful tactile stimulation during which the clamp remained in contact with the skin while the tension was released.

Tactile stimulation was applied using a 10 × 10 cm sponge attached to a plastic handle. The palm of the right hand was stimulated in 7 subjects, and in the remaining 5 subjects tactile stimulation was applied only to the right index finger. Thirty-two-second periods of stimulation were alternated with 32-sec periods of no stimulation.

To examine the effects of adaptation, scans on 4 subjects were collected with a shorter (20-sec instead of 32-sec) on / off stimulation cycle for all stimuli. Tactile, noxious thermal, mechanical, and electrical stimuli were identical except for the duration of stimulation.

Imaging protocol

Imaging was performed on a standard clinical GE Signa 1.5 Tesla scanner using a 30.0-cm three-axis balanced-torque head gradient coil designed for rapid gradient switching. It was a shielded, elliptical, end-capped, quadrature transmit / receive birdcage RF (radio frequency) coil designed for high-sensitivity brain imaging. It had a compact annular housing with a 20 × 24 cm internal diameter. The coil fit closely around the patient's head for improved signal to noise, leaving little room for head motion, which is further constrained by thick foam padding on the left and right.

An echo planar (EPI) gradient echo imaging sequence, designed to detect variations in local T2* (repetition time = 2 sec, effective echo time = 40 msec), was used. A total of 144 images was taken of each of 16 brain slices. The field of view was 22 cm, and slice thickness was 6.0 mm (2-mm gap), with a 64 × 64 matrix. For each subject, high-resolution (256 × 512) coronal fast-spin echo images were acquired at the same spatial locations to aid in anatomical localization of the activation. A high-resolution scan for anatomical location of activation was taken with the same slice locations as the EPI scan. The parameters were: fast-spin echo, coronal plane, TR 4,200, effective TE 17 and 136, echo train 8, matrix 512 × 256, FOV 22 cm, slice thickness 6 mm, gap 2 mm, typical slice range posterior 96 mm to anterior 88 mm, 24 slices. Similar images were taken in the axial plane in 4 subjects.

Definition of neural structures and regions of interest

Regions of interest (ROI) were selected based on the results of previous studies [Casey et al., 1994; Jones et al., 1991; Talbot et al., 1991]. These areas included SI (the postcentral gyrus), the parietal operculum (PO), the thalamus, the anterior cingulate, the insula, and the cerebellar cortex. These regions were defined for each

subject based on cerebral anatomy, using the high-resolution anatomical scan and an atlas of cerebral anatomy [Talairach and Tournoux, 1993]. Separate ROIs were created for contralateral and ipsilateral SI, PO, thalamus and cerebellum. The location of all ROIs was confirmed by a Neuroradiologist (HR).

SI was defined in two ways. First, the pre- and postcentral gyri were identified on the high-resolution axial images using the technique described by Kido et al. [1980] and Sobel et al. [1993]. The location of the postcentral gyrus was then functionally confirmed with the data from the nonpainful tactile stimulation of the hand. The hand area of the somatosensory cortex was defined as in nonhuman primates [Mountcastle et al., 1969; Sinclair and Burton, 1991], just caudal to the central sulcus, midway between the sagittal sinus and the lateral sulcus. The location was also confirmed based on the results from the nonpainful tactile stimulation. The motor area, or precentral gyrus, was identified as that gyrus directly anterior to the postcentral gyrus. The lateral sulcus was identified in coronal sections, and the upper bank, including the area immediately overlying the insula, was considered the PO, and was designated as the ROI. The thalamus was easily identifiable from both the coronal and axial high-resolution scans. The anterior cingulate gyrus was defined as that part of the cingulate gyrus anterior to the thalamus. The insula was defined as the cortex in the depth of the lateral sulcus. The anterior boundary was the rostral portion of the third ventricle, and the posterior boundary was the point at which the temporal and frontal lobes appeared as separate structures. The cerebellar cortex was defined as the superior portion of the outer area of the cerebellum. Figure 1 contains examples of the ROIs for one subject.

Statistical analysis

Image processing and display were done with BrainMRI [Buonocore, 1995]. All data were high-pass-filtered to remove low-frequency noise and linear trends resulting from bulk motion, the imaging system, and possibly low-frequency local blood flow changes. A moving average was used with a length of one cycle (64 points) to estimate baseline drift, which was then subtracted from the data to get the filtered, baseline-corrected data. No other correction for motion was done. High-resolution anatomical and functional images were coregistered using BrainMRI [Buonocore, 1995].

Significant voxel activation was determined using the correlation technique described by Bandettini et al. [1993]. The statistical significance of the relationship between the data and a boxcar function was determined. A 2-scan (4-sec) delay was implemented between the initiation of data collection and application of the boxcar. The correlation threshold of 0.4 used in this study corresponds to $P = 2.1 \times 10^{-6}$, which is conservative even after Bonferroni adjustment for alpha inflation [Buonocore and Maddock, 1998]. The average signal change between conditions (i.e., brush and rest) before filtering was 2.7%, which is comparable to that in other studies [Weisskoff et al., 1992].

Significant ROI activation was then determined based on significant voxel activation. For each condition the number of significantly active voxels within each ROI was compared with the number of activated voxels in a control ROI. The use of predetermined areas of activation has been reported in the PET literature [Casey et al., 1994; Jones et al., 1991; Talbot et al., 1991]. Unlike these previous studies, for each scan a separate control ROI of a comparable size (50 voxels = $150 \times 150 \times 6$ mm) was taken from the visual cortex of the occipital poles, an area expected to be uninvolved in processing pain or somatosensory information.

To make the comparison, the percentage of active voxels was calculated for each ROI, and an arcsine transformation of the data was performed, to convert percentages from a binomial to a Gaussian distribution [Zar, 1984]. A repeated-measures analysis of variance (ANOVA) was used to make a within-subjects comparison of the arcsine transform of the percentage of active voxels in each ROI with the control ROI percentage. A separate repeated-measures ANOVA was performed for each stimulus condition. $P < 0.05$ was considered significant for this analysis.

In this way, ROIs hypothesized to be involved in pain perception could be compared to a control region that was subject to the same artifacts during scanning. The activity in the control ROI was assumed to give an estimate of the noise due to bulk motion resulting from respiration or cardiac activity, or to the imaging system.

RESULTS

Significantly active ROIs for the nonpainful tactile stimulus were contralateral SI ($F(1,4) = 58.67$, $P < 0.001$) and PO ($F(1,4) = 40.89$, $P < 0.01$), and ipsilateral SI ($F(1,4) = 8.48$, $P < 0.05$) and PO ($F(1,4) = 13.18$, $P < 0.05$). Activation of SI cortex was located on the postcentral gyrus in a region consistent with the representation of the hand.

For noxious shock stimulation, the contralateral SI ($F(1,9) = 10.23$, $P < 0.02$) and PO ($F(1,9) = 14.86$,

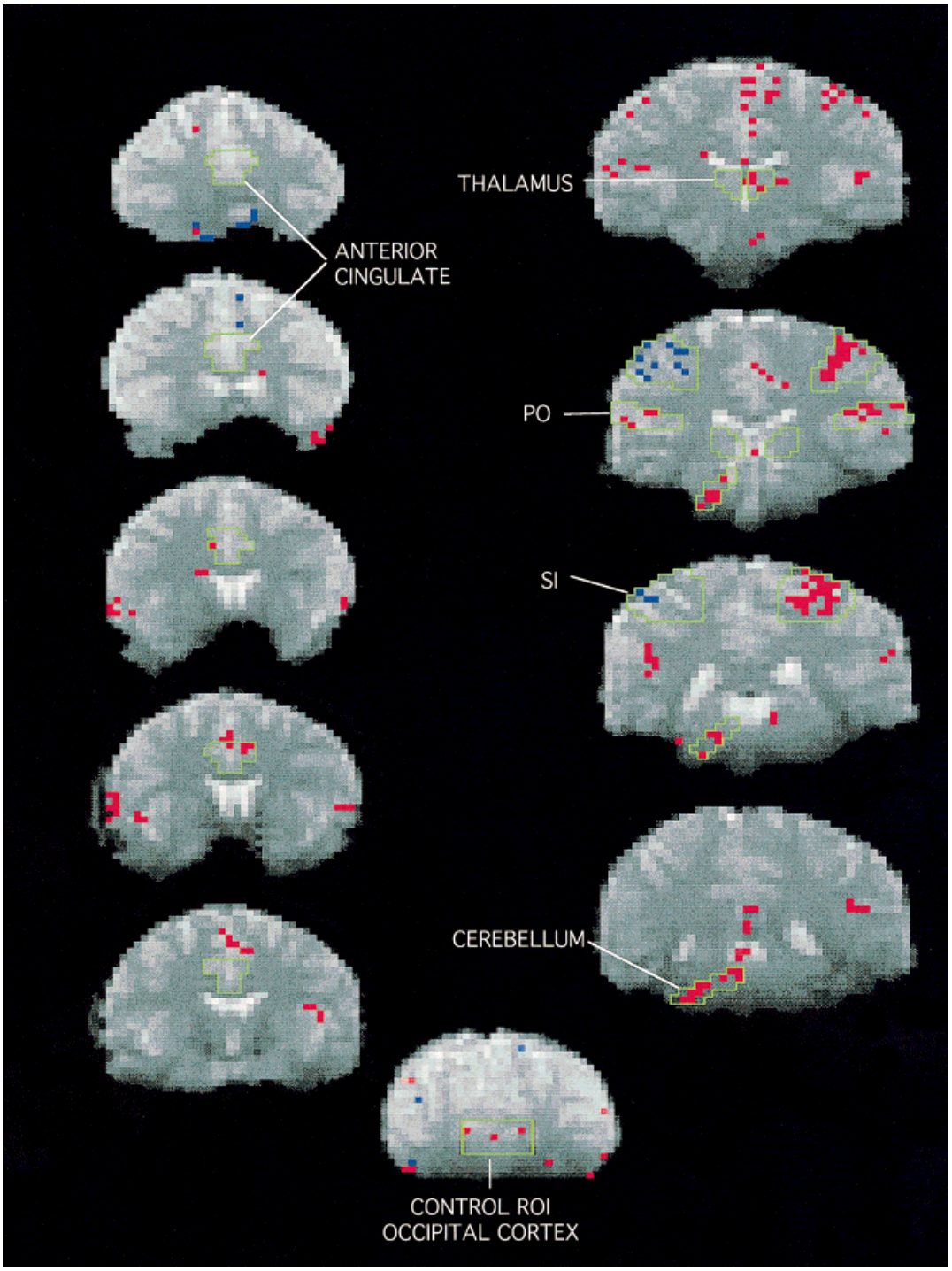

Figure 1.

Consecutive coronal EPI images (top left = rostral) from a typical subject, showing the response to noxious electrical stimulation. Green lines delineate predetermined regions of interest. Red voxels indicate significant activation in phase with the noxious stimulus. Blue voxels represent significant activation that is 180° out of phase.

$P < 0.004$), ipsilateral PO ($F(1,9) = 8.34$, $P < 0.02$), and ipsilateral cerebellum ($F(1,9) = 5.67$, $P < 0.04$) were significantly different from the control ROI (Fig. 1). Although activation of the primary motor cortex (MI) was not significant, MI activation was seen in 4 of 10 subjects who received electrical stimulation.

Although ipsilateral SI activation for noxious shock stimulation was not significant, it is interesting to note that in 6 of the 10 subjects the small response was 180° out of phase with respect to stimulus presentation (Fig. 1), i.e., signal intensity was lower during the stimulation period than during the rest period. In one subject, all cortical responses were out of phase with respect to painful shock stimulation.

No significant cortical activation was seen in response to noxious heat stimulation of the forearm. Further, no significant activation was seen in response to thermal stimulation of the more densely innervated fingertip. Noxious mechanical stimulation also yielded no significant activation. No activation was significant in the anterior cingulate, thalamus, or insula during any stimulus conditions.

Heart rate increased significantly during both noxious heat (mean (SD), before: 67 (2), during: 71 (2)) and shock (before: 66 (2), during: 74 (2)) stimulation ($P < 0.01$).

Because of the lack of activation in response to noxious thermal and mechanical stimulation, these data were also analyzed for adaptation to response. Adaptation of response to noxious thermal stimulation has been reported by others [Tracey et al., 1997]. However, cortical responses for the 20-sec stimulus cycle were not significantly different from those obtained with a 32-sec stimulus cycle; therefore, these data were combined for the ROI analysis. The possibility of adaptation was further examined by analyzing the data from the 20-sec-cycle thermal and mechanical stimulations using a boxcar function that represented a 10-sec on and 30-sec off stimulation cycle. Again, no cortical region had statistically significant levels of activation, although 2 of the 4 subjects did show some active voxels in the somatosensory cortex.

DISCUSSION

Somatosensory cortex activation

It is not surprising that no cortical activation was found in response to noxious heat stimulation. These data are consistent with the idea that nociceptive neurons are interspersed with nonnociceptive neurons in SI [Casey and Morrow, 1983; Chudler et al., 1990; Kenshalo et al., 1988; Kenshalo and Isensee, 1983]. They are often difficult to isolate from neighboring nonnociceptive neurons, using electrophysiological recording techniques [Kenshalo, 1996]. With the current spatial resolution capabilities of fMRI and PET, blood oxygenation level-dependent (BOLD) signal or blood flow-related signal used in these types of imaging may not look significantly different for the response to a noxious vs. a nonnoxious stimulus because of the intermixed organization of the responding fibers in the cortex. Therefore, an analysis based on the subtraction or correlation of a nociceptive and nonnociceptive condition would indicate a lack of activation. Although a BOLD or a blood flow signal can be used effectively to identify the cortex where the areas consist of large groups of neurons processing a common aspect of a stimulus [e.g., Tootell et al., 1995; Menon et al., 1996], this signal may not be appropriate for distinguishing the activity of a diffuse group of neurons from their more numerous neighbors, as is the case with nociceptive and nonnociceptive fibers in SI. This problem has even been described while using invasive electrophysiological techniques to isolate action potentials from nociceptive neurons in monkey SI cortex [Kenshalo, 1996].

Furthermore, nociceptive wide dynamic range neurons, i.e., cells that respond to low-intensity stimulation but show a peak response to noxious stimuli, often respond to painful and nonpainful stimuli in a graded fashion [Chudler et al., 1990; Kenshalo et al., 1988]. Therefore, a significant portion of neurons may have been active during both conditions. Because fMRI can only be used to detect signal *change* between two conditions, this pattern of activation would not be detected.

However, an increasing number of neuroimaging studies on the perception of pain are being performed with conflicting results regarding the involvement of the somatosensory cortex. These differences may be due to several factors, including the type and extent of stimulation, the imaging technique, and the data analysis method being used.

Regarding thermal stimulation, several PET studies of cerebral blood flow have been done with varying results. Jones et al. [1991] reported activation of the contralateral thalamus and contralateral cingulate cortex. No increases in regional cerebral blood flow were seen in the somatosensory cortex on either side. As in the present study, a thermode was used to present the stimuli, and the position remained constant throughout the scan. In a similar PET study, Derbyshire et al. [1996] reported no activation of anterior parietal fields during painful laser stimulation when compared to nonnoxious levels of stimulation. In both of these

studies, the thermal stimuli contained no mechanical component.

Talbot et al. [1991] used a contact thermode to present a noxious heat stimulus to the forearm. In this study, the thermode was moved over six locations on the forearm, producing a combination of noxious (heat) and nonnoxious (mechanical) input. To control for this confounding factor, stimuli for control scans were also presented with a thermode that was moved over six sites on the forearm. Results indicated activation in the contralateral SI arm representation of the postcentral gyrus, in the contralateral SII, and in the contralateral anterior cingulate gyrus. Similarly, Casey et al. [1994] and Coghill et al. [1994] presented heat pulses to six sites on the forearm. Areas of significant activation included the contralateral SI, the thalamus, and the cingulate cortex, as well as the bilateral SII cortex. All scans of noxious stimulation were subtracted from scans of similarly presented nonnoxious stimulation to determine areas of significant activation.

In both Talbot et al. [1991] and Casey et al. [1994], the mechanical aspect of the stimulus was identical in both conditions and should therefore have had no effect once the images were subtracted. However, it is striking that studies using thermal stimulation with a restricted area of stimulation and no mechanical component showed no cortical activation, and that studies using thermal and mechanical stimulation of a large area did show cortical activation (Table I). Other imaging studies of heat pain have shown a similar pattern.

Another example of a study where a combination of painful and mechanical stimulation was used was described in Apkarian et al. [1992], using single-photon emission computed tomography (SPECT). They studied the cortical blood flow response to a circulating hot-water bath (46°C) vs. tepid circulating water bath. Results indicated one significantly active area, i.e., the contralateral SI cortex. The interesting finding in this study was that the change in blood flow was 180° out of phase with the stimulus. The authors concluded that this decrease during painful stimulation was indicative of a net neural inhibition in the SI cortex.

Few fMRI studies exist in which perception of thermal pain was examined. Gelnar et al. [1996] compared three types of noxious heat stimuli: 1) moving the hand between two surfaces of different temperatures, one warm and one painful, 2) an annulus with a heated inner core that was put in contact with the skin during stimulation periods and removed during rest periods, and 3) a thermode that was in constant contact with the skin. The first two showed increases in BOLD signal intensity in SI, while the third showed a decrease in this area. Unfortunately, the first two conditions contained unmatched contaminating stimulation from motor and mechanical inputs, rendering the results difficult to interpret.

The differences in results of imaging studies of noxious thermal stimulation (Table I) may be due to several factors. One possibility is that the mechanical component of some of the stimulus methods may have been influential in spite of the careful controls used. It has been suggested that moving the stimulus over several sites on the skin may have manipulated attention [Jones et al., 1995]. Attention has been shown to significantly affect changes in signal intensity in response to somatosensory stimulation [Roland, 1981; Meyer et al., 1991].

Another possible explanation for the varying results may be related to the spatial extent of the thermal stimulation. The stimuli that were moved over several skin sites contained a mechanical component, but they also stimulated a larger group of receptors, resulting in a larger and more easily detectable cortical signal. Similarly, the body part stimulated, e.g., the hand vs. the forearm, would also influence the size of the signal due to differential innervation density of these two structures.

Furthermore, in a recent study using optical intrinsic signal imaging, a method yielding higher spatial and temporal resolution than fMRI and PET, Tommerdahl et al. [1996] compared the response to mechanical and noxious thermal stimuli. They showed that mechanical stimuli activated area 3b and noxious heat stimuli activated area 3a. When the two stimuli were combined, both areas were active. This result suggests that activation in area 3a alone (i.e., response to stationary noxious thermal stimulation) would not be as large or easily detectable, while the use of mechanical and noxious thermal stimulation which simultaneously activates both 3b and 3a would generate a larger region of activation and thus be easier to detect. Additional research is needed to explore this possibility.

It has also been suggested [Tracey et al., 1997] that adaptation may result in a diminished signal. Those studies in which the stimulus was stationary would be more likely to suffer from this confounding factor. However, electrophysiological recording results suggest that adaptation should not be a factor [Kenshalo and Isensee, 1983], and the results of the present study do not show a marked adaptation effect, although the results were not conclusive. Further, in the PET study by Derbyshire et al. [1996] where laser stimulation was

used, 1-msec heat pulses were delivered every 2 sec, reducing the likelihood that adaptation had occurred.

Electrical stimulation has also been used to evaluate the cortical response to noxious stimuli. Because this stimulus results in activation of a variety of local receptors, it is not a pure nociceptive stimulus. Davis et al. [1994] reported cortical activation in response to noxious electrical stimulation. In a subsequent study, Davis et al. [1995] compared noxious and nonnoxious electrical stimulation. They found that SI was activated in both conditions, but that the anterior cingulate cortex was activated only during stimulation that subjects reported as painful. The results regarding SI cortex agree with those from the present study.

Electrical stimulation indiscriminately activates all local receptors, both nociceptive and nonnociceptive. Nonpainful levels of electrical stimulation were used during the control condition. However, by increasing the stimulus intensity or energy, a larger area of receptors would be affected. Davis et al. [1995] reported an increased area of activation as well as an increase in signal change from baseline with increased electrical stimulus intensity. This increase in active cortical area with increase in stimulus energy would account for the SI activation reported in response to electrical stimulation. Indeed, the presentation of all noxious stimuli where a noxious and nonnoxious level are compared are at risk for this confounding factor.

The signal changes in ipsilateral SI in response to painful shock stimulation were primarily 180° out of phase, indicating that signal intensity was higher during the nonpainful electrical stimulation period than it was during the painful one. This out-of-phase signal change may be due to a decrease in signal intensity in response painful stimulation. A recent study by Drevets et al. [1995] showed a related result. Anticipation of painful stimulation led to a significant decrease in signal intensity in the ipsilateral SI cortex. However, they found a similar result in response to cutaneous stimulation while we did not. It has also been suggested that this out-of-phase response may be related to inhibition [Jueptner and Weiller, 1995; Apkarian, 1992].

The lower BOLD signal intensity during painful stimulation relative to nonpainful stimulation may also be due to an increase in signal intensity during nonpainful stimulation. Perhaps more cortical SI neurons are active during nonpainful stimulation, leading to increased flow during this condition. This hypothesis is supported by the fact that there are relatively more nonnociceptive vs. nociceptive responsive neurons in the cortex [Chudler et al., 1990; Kenshalo et al., 1988; Kenshalo and Isensee, 1983]. Furthermore, Apkarian et al. [1992] reported a relative decrease in signal intensity using a circulating hot water bath vs. a control bath of 36°C. Perhaps the tactile stimulation of the control bath of circulating water activated more cortical neurons than the painful stimulus. Apkarian et al. suggest that out-of-phase activation was due to the duration of the stimulus, a hypothesis that is supported by the fact that several studies using shorter phasic noxious stimuli have not reported relative decreases in signal intensity in the somatosensory cortex [Casey et al., 1994; Coghill et al., 1994, 1995; Davis et al., 1995].

Other structures

While significant activation was seen in some structures known to be involved in sensory processing, e.g., the cerebellum, several structures known to be involved in pain perception were not active. Several studies [Talbot et al., 1991; Jones et al., 1991; Casey et al., 1994; Coghill et al., 1994; Davis et al., 1995] showed activation of the anterior cingulate. In addition, the thalamus is known to process nociceptive stimuli [Craig et al., 1994], and many PET studies [Casey et al., 1994; Coghill et al., 1994; Jones et al., 1991] reported activation of the contralateral thalamus. In the present study, very little activity was seen in the cingulate or the thalamus.

These differences may be due, in part, to the data analysis techniques employed in the different studies. In this study we used fairly rigorous criteria for evaluating the significance of activation in a given ROI. Not only did we analyze the data on a voxel by voxel basis, but we then compared the extent of activation in each area to an estimate of signal variance due to noise. This technique worked well for areas where a fairly large focus of activation was expected in a large portion of the ROIs. However, it was problematic when only a small portion of a structure was expected to be active, as in the case of the thalamus [Craig et al., 1994]. We outlined the entire thalamus as an ROI, and consequently the percentage of active voxels was quite low. With our current imaging capabilities we were not able to reliably subdivide the thalamus into nuclei to more precisely define this ROI.

The differences in thalamic and cingulate results may also be related to the imaging technique. Both fMRI and PET are used to map local changes in blood flow due to neural activity. However, detection of activity using fMRI requires that blood flow signal changes oscillate over time in relation to changes in stimulus intensity, e.g., at noxious and nonnoxious levels, over the course of one scanning session. There-

fore, with fMRI any structure that is active in both conditions will not be designated as active. Variables such as anxiety or anticipation are problematic. Affect has been shown to influence anterior cingulate activation in response to immersion of the hand in a hot water bath [Rainville et al., 1997]. Anticipation has been shown to lead to increases in blood flow to the anterior cingulate [Murtha et al., 1996]. These conditions may be present throughout the scan, whereas in PET, a control scan is collected separately from an activation scan and then subtracted, and the subject generally knows what the stimulus will be, e.g., noxious or nonnoxious.

This difference could account for the lack of activity in the anterior cingulate, which may be involved in the emotional component of pain perception [Jones et al., 1991; Casey et al., 1994; Coghill et al., 1994]. However, Davis et al. [1995] did show anterior cingulate activation with fMRI in response to painful electrical stimulation. A surface coil was used, which does yield a higher signal-to-noise ratio than the whole-head coil used in this study. Similarly, the thalamus may be active during both nociceptive and nonnociceptive conditions. Although different nuclei of the thalamus would be expected to be involved in the processing of painful and nonpainful inputs [Craig et al., 1994], it may not be possible to discern these differences with the present spatial resolution capabilities.

CONCLUSIONS

In this study we attempted to clarify the role of SI in pain perception by comparing responses to several types of noxious stimuli. While the tactile and electrical stimuli reliably resulted in cortical activation, the thermal and mechanical stimuli did not. These results support the finding that nociceptive neurons are interspersed in the somatosensory cortex. A lack of standardized stimuli, as well as of standardized duration and spatial extent of stimulation, may account for the discrepancies seen in the results of pain studies using functional imaging techniques. Further, the diffuse organization of SI nociceptive cells compared to nonnociceptive cells in SI may render subtraction or correlation of blood flow imaging ineffective for distinguishing nociceptive activation in SI.

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