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Cortical Responses to Thermal Pain Depend on Stimulus Size: A Functional MRI Study

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Apkarian, A. Vania, Patricia A. Gelnar, Beth R. Krauss, and Nikolaus M. Szeverenyi. Cortical responses to thermal pain depend on stimulus size: a functional MRI study. *J. Neurophysiol.* 83: 3113–3122, 2000. Cortical activity patterns to thermal painful stimuli of two different sizes were examined in normal volunteers using functional magnetic resonance imaging (fMRI). Seven right-handed subjects were studied when the painful stimulus applied to the right hand fingers covered either 1,074-mm^2-area large stimulator or 21-mm^2-area small stimulator. Stimulus temperatures were adjusted to give rise to equivalent moderately painful ratings. fMRI signal increases and decreases were determined for the contralateral parietal and motor areas. When the overall activity in these regions was compared across subjects, increased fMRI activity was observed over more brain volume with the larger stimulator, whereas decreased fMRI activity was seen in more brain volume for the smaller stimulator. The individual subject and group-averaged activity patterns indicated regional specific differences in increased and decreased fMRI activity. The small stimulator resulted in decreased fMRI responses throughout the upper body representation in both primary somatosensory and motor cortices. In contrast, no decreased fMRI signals were seen in the secondary somatosensory cortex and in the insula. In another seven volunteers, the effects of the size of the thermal painful stimulus on vibrotactile thresholds were examined psychophysically. Painful stimuli were delivered to the fingers and vibrotactile thresholds were measured on the arm just distal to the elbow. Consistent with the fMRI results in the primary somatosensory cortex, painful thermal stimuli using the small stimulator increased vibrotactile thresholds on the forearm, whereas similarly painful stimuli using the large stimulator had no effect on forearm vibrotactile thresholds. These results are discussed in relation to the cortical dynamics for pain perception and in relation to the center-surround organization of cortical neurons.

INTRODUCTION

Many laboratories now have described cortical regions activated with thermal painful stimuli (e.g., Apkarian et al. 1992; Casey et al. 1994; Coghill et al. 1994; Davis et al. 1998; Di Piero et al. 1994; Gelnar et al. 1999; Hsieh et al. 1995; Jones et al. 1991; Talbot et al. 1991; Vogt et al. 1996). There are important differences between these studies regarding the cortical regions described to be involved in pain perception, see Apkarian (1995), Gelnar et al. (1999), and Treede et al. (1999) for a discussion on the topic. Differences across laboratories can arise from multiple sources, such as imaging techniques (positron emission tomography, PET; single photon emission tomography, SPECT; or functional magnetic resonance imaging, fMRI), data-processing approaches (filtering, resolution, averaging across subjects), stimulus types used (mechanical, heat, cold, acute vs. chronic pain), and other details. The hypothesis tested in the present study is that a major source of the across-laboratory differences in brain activations for painful thermal stimuli is a consequence of differences in stimulus parameters, such as variations in duration, size, and intensity.

In an earlier brain-imaging study (Apkarian et al. 1992), we demonstrated that painful thermal stimulation of the hand, when presented on a time scale of minutes, results in contralateral somatosensory cortical decreased activity. This result was interpreted to be mainly due to the long duration painful stimulus. Because the somatosensory cortex is critical for vibrotactile perception, its inhibition should translate into decreased ability in vibrotactile perception. This idea was tested in a series of psychophysical experiments where a sustained painful thermal stimulus was applied on the thenar eminence, and vibrotactile thresholds were measured at the same position or at different positions removed from the thermal painful stimulus site (Apkarian et al. 1994; Bolanowski et al. 2000). The results showed increased vibrotactile thresholds and decreased vibrotactile sensitivity during sustained thermal pain for all four tactile channels at the painful site. Moreover the changes in vibrotactile thresholds were a function of body site tested. Vibrotactile thresholds at positions remote from the painful stimulus were unaffected by the presence of thermal pain. These psychophysical results now have been confirmed by studies in another laboratory (Hollins et al. 1996) and provide separate evidence for interpreting the decreased cortical activity we observed earlier (Apkarian et al. 1992).

The present study uses the same strategy as in these earlier studies. fMRI is used to image brain regions activated or deactivated by thermal stimuli that give rise to a similar magnitude of pain but are applied by two different sized stimulators: one large and one small applied to the volar fingers. This tests the hypothesis that cortical response patterns are a function of stimulus parameters. The results indicate that large portions of the upper body representation within the primary somatosensory and motor cortices show decreased activity when the thermal painful stimulus is applied through the smaller stimulator. This in turn generates the new hypothesis that vibrotactile thresholds at a site within the upper body, but remote from the fingers, should demonstrate differential vibrotactile thresholds during pain applied to the fingers through the large or small stimulator. The new hypothesis was tested psychophysically in a separate group of subjects.

Some of this work was in partial fulfillment of the requirements for a PhD dissertation for Patricia A. Gelnar.

METHODS

Seven normal right-handed volunteers participated in the functional imaging study. Another seven normal volunteers participated in the psychophysical study. The general purpose and the procedures were explained to the subjects. All subjects were ≥18 yr of age and signed a consent form. All procedures were approved by the Institutional Review Board.

Functional imaging

All subjects underwent a single scanning session lasting ~1 h. Each scanning session consisted of a high resolution anatomic scan in the sagittal plane, a high-resolution anatomic scan of the entire brain in the coronal plane (6 mm slices, 8 of which corresponded to those imaged in the functional scans), a flow-weighted scan for identification of cortical vessels, and two functional imaging series using Echo Planar Imaging pulse sequences. There were two stimulation tasks in this study, and separate functional series were performed for each task.

During the painful thermal task using the large stimulator, the subject's right hand was attached to the stimulator so that the ventral fingers (digits 2–5) would be in constant contact with the stimulator. The stimulator was heated by circulating water from water baths located outside the imaging suite, and the total stimulating surface area of the thermode was 62 mm in diameter. The large stimulator consisted of a warm (37–38°C) outer annulus (12 mm wide) and a hot (~1°C above the subject's pain threshold) inner cylinder (37 mm diam, 1,074-mm^2 surface area). The inner cylinder was retracted during the control period and forced in contact with the individual's hand for the duration of the stimulus period. The mechanical movements of the inner cylinder were computer controlled. The large stimulator was made of stainless steel and did not cause any detectable MR imaging artifacts.

The small painful thermal stimulator consisted of a platinum-coated ceramic sensor/heating element (3 × 7 mm, 21-mm^2 surface area) that alternated between warm (39–40°C) and painful hot (~1°C above the subject's pain threshold) temperatures. The stimulator temperature was controlled by the supplied current, controlled by a computer. During this task, the tip of the second digit was maintained in constant contact with the stimulator. The small stimulator also did not result in any detectable MR imaging artifacts.

Each control and stimulus state was 35 s in duration for both tasks, and the subjects alternated between control and stimulus states for a total of six control-stimulus cycles. With both stimulators, the skin subjected to painful heat had a mean baseline temperature of ~40°C. The temperature at the interface between the stimulators and the skin showed rise rate differences between the two stimulators. Within the first 0.5 s, skin temperature increased at a rate of 16°C/s for the large stimulator and at a rate of 20°C/s for the small stimulator. During a 5-s period, skin temperature increased at an overall rate of 2°C/s for the large stimulator and 1°C/s for the small stimulator. Temperature changes past the first 10 s are very small and depend on the final temperature, which was variable between subjects and stimulators. To determine if these rise rates affect perceived pain, in three subjects pain-perception ratings were measured with each stimulator, using the same procedure as described in Apkarian et al. (1999). For both stimulators, this analysis showed that the time profile of perceived pain was similar to our earlier report (Fig. 3 in Apkarian et al. 1999), where pain perception continuously increases for the duration of the application of the thermal stimulus. The mean time delay to the onset of pain was 4.5 ± 0.5 s (mean ± SD) with a range of 0.9–6.0 s, which was similar for both stimulators. The mean duration of perceived pain was 31.3 ± 2.6 and 33.5 ± 2.8 s, for the large and small stimulators

(significantly different $P < 0.006$), with a range of 25.8–39.0 s. The initial pain perception rise rates were the same for both stimulators with a mean duration of 5.0 s to plateau.

During each scanning session, the subjects underwent two functional imaging series. In one series, painful thermal stimuli were applied with the large stimulator; in the other, painful stimuli were applied with the smaller stimulator. Each functional imaging series lasted 7 min, and the two functional imaging series were separated by ~15 min. All subjects verbally rated the pain at the end of each functional imaging sequence. The pain rating scale was from 0 to 10, with 0 = no pain and 10 = maximum imaginable pain.

For details of the imaging and data analysis software and techniques, see Gelnar et al. (1998, 1999). A brief summary of the imaging parameters and data analysis techniques follows.

SCANNING SEQUENCE. All fMRI experiments were performed on a 1.5 Tesla General Electric (Signa) clinical imaging instrument equipped with an Instascan resonant gradient accessory from Advanced NMR Systems, thus allowing the acquisition of both conventional and echoplanar images. To improve signal-to-noise ratio a single 5-in circular surface receive coil was used.

During each imaging session, the subject was positioned on the scanner bed, and the surface coil was positioned over the parietal cortex, contralateral to the stimulated hand, oriented parallel to the long axis of the magnet. The subject's head and surface coil were immobilized using a vacuum beanbag. Sagittal, high-resolution, and flow-weighted images were obtained with conventional pulse sequences, whereas the functional images were obtained using echo planar pulse sequences. The high-resolution, flow-weighted, and functional scans were all performed at the same slice locations. Scan parameter details were the same as described before (Gelnar et al. 1999). The primary cortical areas of interest were the somatosensory regions, so the middle third of the brain contralateral to the stimulation site was imaged. Eight slice locations were selected for functional scans (each 6.0-mm thick with a 0.5-mm gap between slices). In each study, the first slice was located 6.5 mm posterior to the anterior commissure (AC).

The scanning parameters were as follows. 1) T1-weighted multislice spin echo scout images [TR = 300 ms; TE = 12 ms; 2 NEX number of images averaged; 256 × 256 matrix; field of view (FOV) = 20 × 20 cm] were obtained in the sagittal plane and prescription of subsequent coronal images were performed using the midline sagittal slice. 2) High-resolution coronal multislice spin echo images (TR = 500 ms; TE = 12 ms; 1 NEX; 256 × 256 matrix; FOV = 20 × 20 cm) of the entire brain were obtained with 6.0-mm slice thickness and a 0.5-mm gap between slices. This set included the eight functional slice locations, used for anatomic localization of the areas of functional activation. And 3) functional imaging scans then were performed using echo planar imaging gradient echo acquisition sequence: TR =3,500 ms; TE = 60 ms; flip angle = 90°; NEX = 1; repetitions per slice = 10; matrix = 256 × 128; FOV = 40 cm × 20 cm. This results in a voxel size of 1.56 × 1.56 × 6.00 mm. Six cycles of control and stimulus were performed during a functional imaging series, resulting in the acquisition of 960 images at the eight slice locations in a single functional imaging series. The two functional imaging scans for the two tasks were performed consecutively in a random order.

DATA ANALYSIS. The data analysis entailed the generation of activation maps in individual subjects and for the group of subjects. The individual-subject activation maps followed a procedure outlined in detail in Gelnar et al. (1998). The group activation map was generated using procedures outlined in Gelnar et al. (1999) and in Krauss and Apkarian (1998). A brief summary of these methods is presented in the following text. Because the study used a surface coil, statistical analyses were limited to the cortex underlying the coil including midline structures but excluding the ipsilateral cortex. Only the con-

tralateral one-third of the cortex was studied (approximately the contralateral cortex from 6.0 to 52 mm posterior to AC).

INDIVIDUAL-SUBJECT ACTIVATION MAPS. In-plane head movement was corrected by reregistering all images for in-plane translations. An outlier detection routine was used to discard images with large deviations in mean count that were attributed to artifacts. Individual pixel unpaired t-test values were calculated for the stimulus versus control condition (TR shifted boxcar analysis with 6 cycles of 10 control and 10 stimulus images), using a cutoff criterion level of $P < 0.01$ for all tasks. A minimum cluster-size cutoff criterion of $P < 0.01$ was used to further limit significant activity. The latter defines the minimum number of contiguous pixels that pass the t value cutoff. The cluster threshold was either 3 or 4 pixels in this data set, with an overall false positive rate (P value) estimated in the range of 0.02 and 0.0003 using the method of Xiong et al. (1995). With the Xiong et al. (1995) method, false positive rate for a given cluster cutoff is calculated based on the t value threshold, the smoothness due to the Gaussian filtering, and the total number of pixels in the brain region examined. Pixels that survived both t value and cluster size criteria constituted the individual-subject activity map, i.e., clustered t maps. These maps were superimposed on the anatomic MR images and used to identify the locations of the activation clusters. Significant activation clusters were identified based on the anatomy of the individual high-resolution images.

STATISTICAL COMPARISONS USING INDIVIDUAL-SUBJECT ACTIVATION MAPS. The across subject comparisons of brain activations as a function of task and brain areas involved were based on integrating spatial and intensity parameters defining the statistically significant activation clusters, namely activation index. Total activation index (AI = mean t value × size of each cluster in voxels, summed for all activation clusters in a given region) was used as the dependent variable for significant activation clusters located in regions of interest in the cortex contralateral to the stimulated hand. Seven anatomic regions were examined: somatosensory regions [primary (SI) and secondary (SII)], insula, posterior parietal regions (area 5/7 and area 40), and motor cortical regions [primary (MI) and premotor (PM)]. A two-way ANOVA was performed for the absolute value of total activation index (AI) over all subjects, across regions and tasks, with post hoc evaluation.

GROUP-AVERAGED ACTIVATION MAPS. To generate the group-averaged activation maps the individual-subject unclustered t maps were transformed into Talairach space (Talairach and Tourneaux 1988) and averaged across the population. This was performed using commercial software (MEDx, Sensor Systems). The t maps were resliced to 2 × 2 × 2-mm voxels, spatially filtered with a Gaussian having a 5 × 5 × 5-mm full-width half-maximum (FWHM), and merged across subjects by averaging the t statistics in each voxel. This procedure guards against unequal MR signal variances among subjects (Binder et al. 1997).

The averaged t statistics were thresholded to identify voxels in which the mean change in MR signal between comparison conditions was unlikely to be 0. The average of a set of t deviates is not a tabulated distribution. Binder et al. (1997) use the Cornish-Fisher expansion to select a threshold for rejection of the null hypothesis. However, this approximation is only valid when the number of subjects is larger than eight (personal communication). Therefore we determine this threshold based on the distribution of the averaged t values for each comparison condition (Gelnar et al. 1999). The distribution of the averaged t values in the brain under the coil is tested to ensure that it approximates a normal distribution. Two standard deviations above the mean of this distribution then is considered indicative of the intensity threshold for regions significantly involved in each task, constituting group-averaged t maps. The resultant cutoff t values for increased activity were 0.292 and 0.269 and for decreased activity were -0.306 and -0.289, for the large and small stimulators respectively.

A cluster size threshold also was applied to the group-averaged t map, similarly to that used in the individual-subject activation maps, but with a cluster size appropriately computed to compensate for this averaged data. The cluster cutoff again was calculated based on the method of Xiong et al. (1995), to account for the filtering and resampling. Only pixels with nine or more contiguous activated pixels were included in the clustered map. This corresponds to an effective false positive rate of $P < 0.03$. The resultant activation map is a group-averaged, clustered t map. The group-averaged clustered t map was used to identify cortical regions activated or deactivated in each task, reported in the coordinate system of Talairach and Tourneaux (1988).

Psychophysical measurements

Vibrotactile thresholds and ratings of the level of pain induced by thermal stimuli were measured on the right hand in seven volunteers using a slightly modified version of the methodology we have used earlier (Apkarian et al. 1994; Bolanowski et al. 2000). Three subjects had prior experience in rating thermal pain. Subjects were positioned to allow the application of painful thermal stimuli, through the large or small stimulator, and to be able to simultaneously determine vibrotactile thresholds at the elbow. The tip of the second digit was connected to the small stimulator while the large stimulator was placed on the ventral surface of digits 3–5. The vibratory stimulator was placed just distal to the elbow, ventrally in an area void of hairs. Both thermal stimulators and the vibratory stimulator were fixed on the hand before doing any measurements. This set-up enabled measuring vibrotactile thresholds before the application of thermal stimuli, during thermal pain applied through the large stimulator, and during thermal pain applied through the small stimulator, in a single session. The vibratory stimuli, driven by a waveform generator, were applied through a 3-mm^2 plastic tip surrounded by rigid aluminum annular-shaped surface (33 cm^2). The stimuli were presented around a static indentation of ~0.5 mm to ensure continuous contact between stimulator and the skin. Vibrotactile thresholds were determined for 50-Hz stimuli using a modified ascending and descending method of limits (Apkarian et al. 1994; Gescheider 1985); this permits the evaluation of thresholds within a few minutes. The procedure determines the magnitude of skin displacement that the subject detects as present in the ascending series of vibratory stimulation and as absent in the descending series. A complete typical session lasted ~45 min. In all subjects, vibrotactile thresholds in the baseline condition were determined twice. The first determination was used as a training session and the results were discarded. Baseline thresholds were measured while both thermal stimulators were warm (38–40°C). The inner cylinder of the large stimulator was heated and the subject instructed to verbally rate only the pain intensity (on an analogue scale of 0–10, where 0 is no pain and 10 is worst imaginable pain). This temperature was adjusted until the subject indicated that the pain was at a moderate intensity (4–6 on the analogue scale). Vibrotactile thresholds were obtained throughout the period (5–10 min) during which there was a relatively constant moderate pain. As soon as these measurements were completed, the large stimulator temperature was reset to baseline temperature (in <2 min). Next, the small thermal stimulator was heated slowly until the subject indicated that the pain was of moderate intensity, at which time vibrotactile thresholds were measured again. There was a 7- to 10-min delay from the cessation of the first painful stimulus to the report of pain now applied through the second stimulator. After collecting another set of thresholds (5–10 min), the temperature was returned to baseline (in <1 min) and the session was completed. The sequence for applying painful stimuli through the large and small stimulators was varied between subjects.

In a separate session, the subjects were tested to identify the properties of the pain experienced by using the two stimulators. Both thermal stimulators were placed on the hand as described in the preceding text. Each stimulator temperature was increased to reach a moderate intensity

pain (~5 on a 0–10 scale). The subjects then were questioned regarding 15 descriptors of pain taken from the short form of the McGill Questionnaire (Melzack 1987). For each descriptor, they had to choose one of four categories as best describing the pain being experienced: none, mild, moderate, and severe. The categorizations were converted to numerical values (0–3) and compared between the large and small stimulator.

RESULTS

During functional scanning, the mean intensity of pain reported with the large stimulator was 5.3, and the mean applied temperature for this perception was 47.1°C. In contrast, the mean intensity of pain reported when the functional scans were done with the small stimulator was 6.6 for a mean temperature of 48.3°C. There is no statistical difference in the mean pain rating for the two stimulators ($P > 0.2$), but the applied temperatures are higher for the scans where the small stimulator was used (paired t-test for temperatures, $P < 0.01$).

Figure 1 shows the positive and negative activation maps for both tasks in a single subject. When pain was induced using the large stimulator (Fig. 1, *top*), activations (shown in red) are observed in the midline [supplementary motor (SMA) and cingulate (CING); in slices s1–s7], in PM and MI (s1–s5), insula (s1), SI and SII regions (s2–s4), and in the posterior parietal cortex (areas 5/7 and 40, s6–s8). Decreased activity (shown in blue) is seen scattered in all these cortical subdivisions. When pain was induced using the small stimulator (Fig. 1, *bottom*), increased activity and decreased activity is seen in the same subdivisions, although the decreased activity covers a much larger cortical area as compared with the decreased activity seen with the large stimulator.

Statistical comparison of individual-subject activation maps

Figure 2 shows fMRI activity, in total activation index units (this parameter accounts for both intensity and size of activated areas), over the seven regions examined in the contralateral cortex, for both tasks. When the painful stimulus was delivered with the small stimulator (*top left*) positive activations were seen mainly in SI and areas 5/7 and 40, whereas much larger negative activations were observed in PM, MI, SI, and areas 5/7 and 40. In contrast, when the painful stimulus was delivered through the large stimulator (*top right*), positive activations were larger than the negative activations and were seen in more regions: PM, MI, SI, and areas 5/7 and 40. The across-subject and -region mean activation indexes for both tasks are illustrated in Fig. 2, *bottom*, showing that the larger stimulator gives rise to larger positive activation index, whereas the smaller stimulator results in a larger negative activation index. The two-way ANOVA of the absolute value of the activation index showed a significant difference ($F = 6.8$, $P < 0.003$) for the two tasks and for positive and negative activation and a significant difference ($F = 7.8$, $P < 0.0003$) across the seven cortical regions. Post hoc analysis indicated that the negative activation for the small stimulator (-515 ± 59, mean $\pm$ SE) was higher in magnitude than the negative activation for the large stimulator (-178 ± 59), and higher in magnitude than the positive activation for the small stimulator (224 ± 59). Across-region post hoc analysis showed that fMRI activity in SI, MI, and area 40 was higher in magnitude than activity in insula and SII, and SI activity was also higher in magnitude than PM and area 5/7 activity.
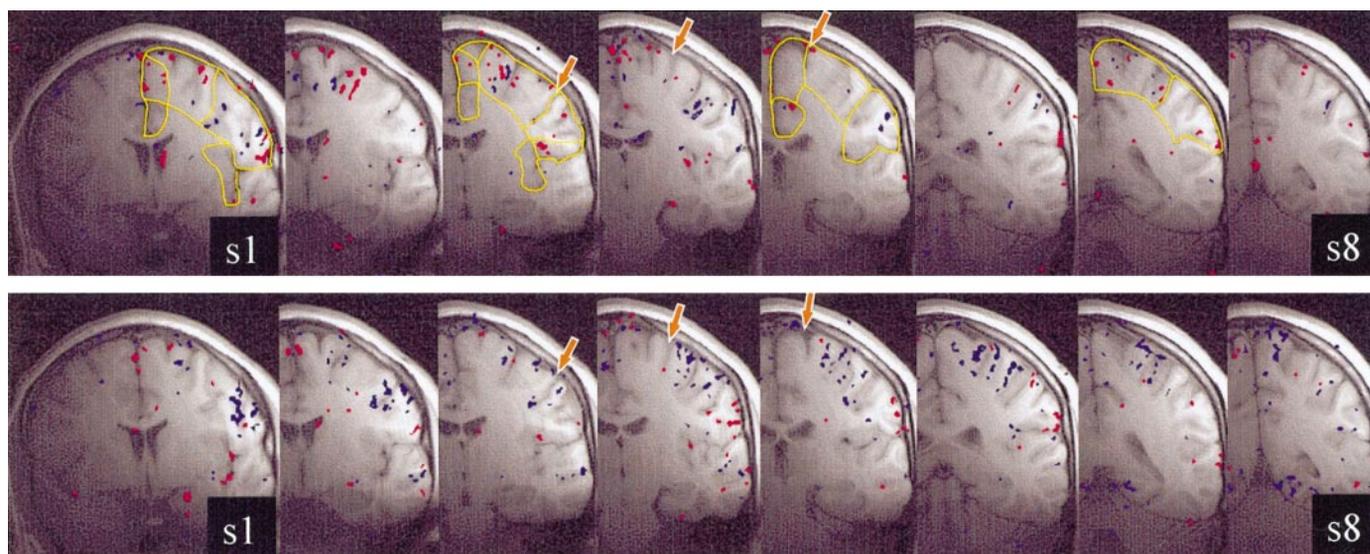

FIG. 1. Cortical functional magnetic resonance imaging (fMRI) activity patterns in a single subject for painful thermal stimulation using large and small stimulators. *Top*: cortical activity when the painful thermal stimulus was delivered through the large stimulator. *Bottom*: responses for painful stimulation using the small stimulator. Red are regions of increased fMRI signal. Blue are regions of decreased fMRI signal. Arrows indicate the central sulcus. Slice 1 (s1) is at 6.5 mm posterior to the anterior commissure. Eight consecutive slices (s1–s8) are imaged, each slice was 6.0 mm thick separated by 0.5 mm. On the *top panel* (slices 1, 3, 5, and 7), the borders of the regions studied are outlined in yellow. In slice 1, on the medial bank cingulate, ventrally, and supplementary motor cortex, more dorsally, are shown. Laterally, premotor, motor and insular cortices are situated medio-laterally. In slice 3, the premotor region occupies a small areas wedged on the transition from the medial to the lateral cortical surface and lateral to the central sulcus, primary and secondary somatosensory and insular cortices can be seen. In slice 5, on the medial bank the region ventral to the cingulate is now primary motor cortex. The lateral bank of slice 5 is composed of areas 5/7 and 40. These borders are not shown for the even slices, although they should be apparent from the neighboring slice outlines.
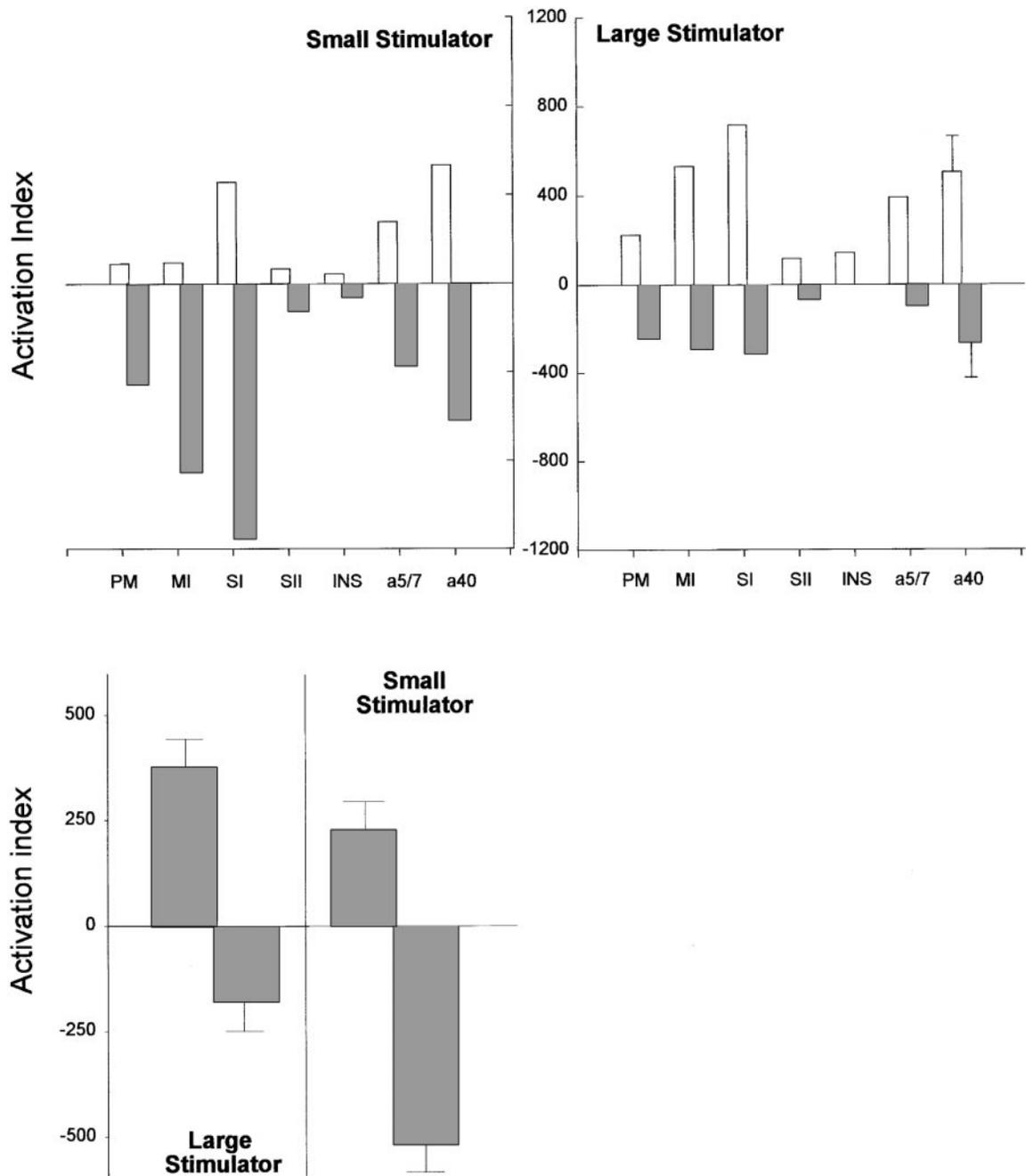
FIG. 2. Brain region and stimulator size dependence of fMRI responses to thermal painful stimuli. Across-subject mean activation index is shown (*top*) for 7 regions of the cortex (PM and MI, pre- and primary motor regions; SI and SII, primary and secondary somatosensory regions; INS, insula; a5/7 and a40, posterior parietal regions) contralateral to the hand stimulated painfully by the small stimulator (*left*) and large stimulator (*right*). Standard errors shown on the *right 2 bars* apply to all bars. *Bottom*: average activation index and SEs across regions and subjects for the large stimulator (*left*) and the small stimulator (*right*).

fMRI activity differences across tasks and brain areas using group-averaged results

The group-averaged and clustered fMRI activity *t* maps for both stimulators are shown in Fig. 3. A more restricted area of the brain region imaged was analyzed in the group-averaged activations (−10 to −28 mm posterior to the anterior commissure) because head position realignment across subjects resulted in a smaller mutually examined volume. As a result the group-averaged analysis does not cover area 5/7 and only

includes the most anterior portion of area 40. The cortical regions with significantly increased activity (red) and with significantly decreased activity (blue) are shown for the group-averaged responses for the large stimulator (Fig. 3, *top*) and the small stimulator (Fig. 3, *bottom*). Consistent with the individual analysis, a larger cortical area showed increased activity when pain was induced through the large stimulator as compared with when pain was induced through the small stimulator. Conversely larger portions of the cortical area studied
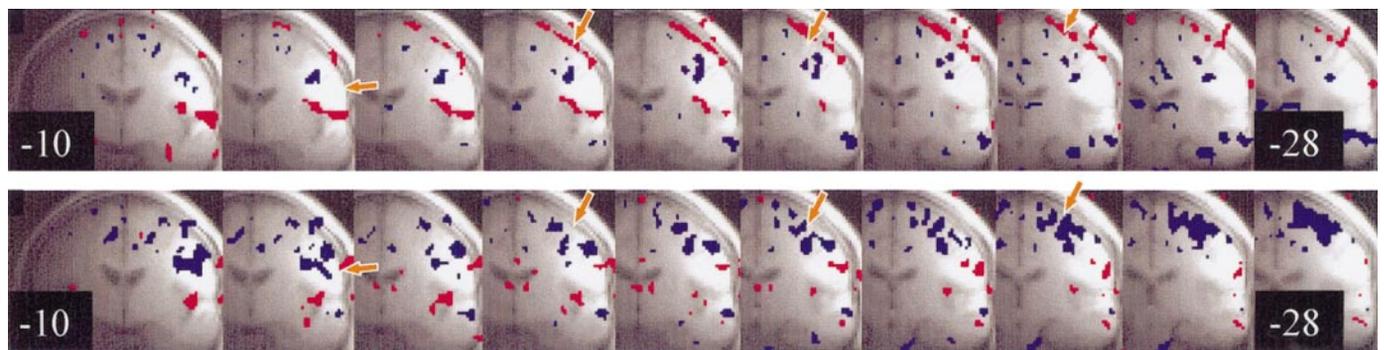
FIG. 3. Group-averaged cortical fMRI activity patterns for painful thermal stimulation using large and small stimulators. *Top*: cortical activity when the painful thermal stimulus was delivered through the large stimulator. *Bottom*: responses for painful stimulation using the small stimulator. Red are regions of increased fMRI signal. Blue are regions of decreased fMRI signal. Arrows indicate the central sulcus. The fMRI activity is superimposed on the group-averaged anatomic MR images, transformed into Tailarach and Tourneaux (1988) coordinates, starting at 10 mm posterior to the anterior commissure (-10), ending at 28 mm posterior to the anterior commissure (-28). Slice thickness is 2 mm, and voxels are $2 \times 2 \times 2$ mm volumes. Lack of anatomic detail is due to the averaging of anatomic images across subjects, indicating the extent of uncertainty regarding anatomic boundaries. Central sulcus was identified by atlas coordinates. Lateral sulcus is better defined. Anatomic regions of interest are defined in relation to both sulci and atlas coordinates.

showed decreased activity when pain was induced with the small stimulator as compared with the large stimulator. With the large stimulator, increased fMRI activity in the cortex contralateral to the stimulated hand was observed mainly in PM and MI, SI, SII and insula; whereas decreased activity was seen in on the midline, including SMA and CING, in PM and MI, SI, and area 40. With the small stimulator, increased activity was limited to SI, insula, and area 40, whereas decreased activity included midline CING, large portions of PM, MI, and SI. Table 1 summarizes these areas indicating the anterior-posterior extent of each area, the volume of the fMRI activity (in mm^3 converted from the number of voxels), and the Talairach coordinates for the maximum fMRI responses. Re-

sponse magnitudes are presented in maximum t values, the corresponding z and P values are also shown (Table 1).

With both stimulators, the depth of the central sulcus, area 3a of SI at the border of MI, showed decreased activity. Most of the hand-shoulder representation in MI showed decreased activity (regions just medial to the lateral sulcus, slices at -10 to -22 mm posterior to AC) when pain was induced with the small stimulator. However, this decreased activity did not extend to MI regions subserving the face or the lower body. In contrast, when pain was induced with the large stimulator most of hand MI was activated (-16 to -22). Within SI, the postcentral gyrus just lateral to the central sulcus (mainly area 1 of SI, -14 to -24) was activated for pain induced with the

TABLE 1. *Activity in cortical regions in the group-averaged fMRI responses when thermal painful stimuli are applied*

Area	Mediolateral*	Anteroposterior	Superior Inferior	Range, mm		Maximum t Value	Maximum z Value	P Value	Volume, mm^3
Large stimulator									
Increased fMRI activity									
INS/SII	-58	-10	10	-10	-22	0.51	3.54	0.00021	1360
PM/MI	-36	-22	62	-12	-24	0.51	3.54	0.00021	1232
SI	-56	-18	46	-14	-28	0.48	3.34	0.00022	840
Decreased fMRI activity									
PM	-26	-10	56	-10	-12	-0.32	-2.14	0.017	88
MI, anterior	-38	-14	34	-10	-14	-0.41	-2.73	0.0034	376
SI	-38	-16	34	-16	-24	-0.42	-2.79	0.0027	832
MI, posterior	-18	-20	64	-20	-28	-0.34	-2.27	0.012	144
CING	-4	-44	24	-20	-28	-0.34	-2.27	0.012	352
PP (40)	-38	-26	34	-26	-28	-0.35	-2.33	0.01	152
Small stimulator									
Increased fMRI activity									
INSULA	-46	-10	6	-10	-24	0.39	2.97	0.0015	816
SI	-58	-20	28	-14	-20	0.30	2.30	0.0107	264
PP (40)	-50	-22	32	-22	-26	0.30	2.30	0.0107	368
Decreased fMRI activity									
PM	-26	-10	60	-10	-12	-0.29	-2.07	0.019	144
MI	-16	-22	60	-10	-24	-0.34	-2.42	0.008	2424
CING	-8	-12	42	-10	-28	-0.29	-2.07	0.019	288
SI	-32	-26	56	-14	-28	-0.46	-3.25	0.00041	4496

Talairach coordinates are shown for the activation cluster with peak activity, its anteroposterior spread (range), maximum t value, the corresponding z and uncorrected P values, and the total volume of the cluster. INS/SII, secondary somatosensory and insular regions; PM/MI, premotor and primary motor regions; SI, primary somatosensory cortex; CING, cingulate cortex; PP (40), posterior parietal cortex; fMRI, functional magnetic resonance imaging. * Negative mediolateral values are left brain responses, contralateral to the stimulated hand. Talairach coordinates are in mm/s from the anterior commissure, where superior, anterior, and right are positive.

large stimulator. In contrast, this area showed decreased activity when pain was induced with the small stimulator, and instead a SI region more lateral (area 2, −16 to −22) was activated.

Comparing the individual-subject analysis to the group-averaged results

The individual-subject analysis (Fig. 2) was presented in terms of the activation index. This parameter is the product of the intensity of a given response (*t* value that is related to the magnitude of change in fMRI signal) and its spatial extent (number of voxels). The group-averaged results are presented quantitatively (Table 1) in terms of response intensity (maximum *t* value) and spatial extent (volume). The overall patterns of change are similar between the two results. Table 1 shows that both intensity and spatial extent are largest for the increased fMRI responses to thermal painful stimuli using the large stimulator. On the other hand, the largest decreased fMRI signal both in intensity and in spatial extent are found in SI in response to the thermal painful stimuli using the small stimulator. Table 1 also shows that the main parameter changing between the two stimulators is the spatial extent of decreased fMRI signal and not its intensity. The same result was seen in the individual-subject analysis when the activation index was subdivided into a mean *t* value and number of voxels.

Psychophysics

EFFECT OF STIMULUS SIZE ON THE GATING OF TOUCH BY THERMAL PAIN. The size effects of painful thermal stimuli applied to the fingers were tested psychophysically by measuring vibrotactile thresholds at a site removed from the thermal stimuli, the ipsilateral volar forearm. In these psychophysical studies, the mean intensity of pain reported with the small stimulator was 5.46 and the mean applied temperature for this perception was 49.7°C. In contrast, the mean intensity of pain reported with the large stimulator was 5.5 for a mean temperature of 44.8°C. There is no difference in the mean pain rating for the two stimulators ($P > 0.9$), although there is a difference in the applied temperatures ($P < 0.001$).

Figure 4A shows the group averaged vibrotactile thresholds in the control baseline state, during the report of a moderately intense pain induced by the large thermal stimulator and during the same intensity pain induced by the small stimulator. Figure 4B shows the same results as a percent change from baseline thresholds. There was no significant difference between control thresholds and thresholds measured when the pain was induced with the large stimulator (paired *t*-test, $P > 0.2$). However, there was a significant increase in vibrotactile thresholds when pain was induced with the small stimulator as compared with the baseline thresholds (paired *t*-test, $P < 0.02$).

PAIN DESCRIPTOR DIFFERENCES WHEN INDUCED BY THE LARGE OR SMALL STIMULATOR. To identify whether there were differences in the detailed properties of the pain experienced beyond its intensity, the severity of 15 descriptors were examined for the same intensity pain experienced through the large or small stimulator. The overall rating of the severity of the pain experienced across 15 descriptors was not different between the two stimulators (paired *t*-test). This was also true when the descriptors were grouped into the sensory and affec-
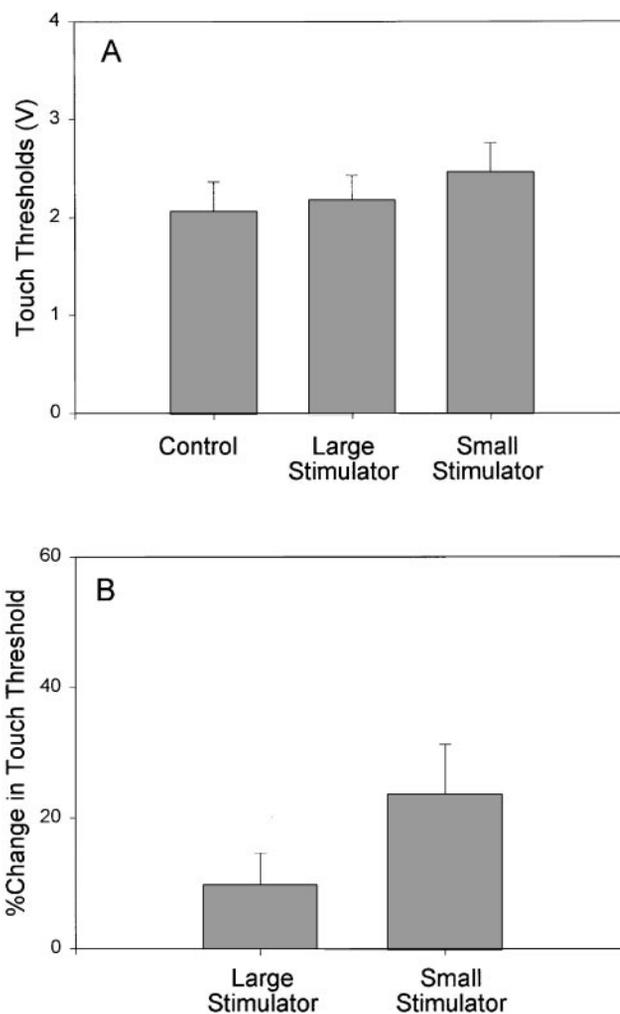

FIG. 4. Effect of the size of painful thermal stimuli on vibrotactile thresholds. Mean and SE of thresholds ($n = 7$ subjects) for detecting a 50-Hz vibration on the volar forearm are shown when the large and small thermal stimulators, placed on the fingers, are kept warm (control), when the large stimulator is heated to a temperature that induces moderate pain (large stimulator), and when the small stimulator is heated to induce moderate pain (small stimulator). In *B*, the same results are shown as percent change relative to the baseline control thresholds.

tive components [in the short form of the McGill Pain Questionnaire (Melzack 1987) first 10 descriptors are sensory, the rest are affective]. When individual categories were examined, two descriptors showed systematic differences for the two stimulators: splitting and shooting. Both were rated more severe with the small stimulator than the large stimulator. Splitting was rated as none in all seven subjects when pain was induced with the large stimulator and as mild or moderate by five subjects when pain was induced with the small stimulator (paired *t*-test, $P < 0.03$). Shooting also was rated slightly more severe when pain was induced through the small stimulator (borderline significance, paired *t*-test, $P < 0.06$).

D I S C U S S I O N

The main result of this study is the demonstration that cortical responses to painful thermal stimuli critically depend on the spatial properties of the stimulus. This demonstrates that cortical fMRI activity patterns for seemingly constant percep-

tions are not necessarily constant. The implication is that the brain can arrive to the same constant sensory perception through various internal configurations, which in this example are dictated by the afferent load. A large number of earlier studies regarding the cortical circuitry underlying pain perception have been interpreted based on anatomic plausibility, i.e., using the known thalamocortical projection patterns as the means with which the cortical activations are functionally labeled (see Treede et al. 1999). Given that we show here that the extent of increased and decreased activity seen in the contralateral sensorimotor cortex dramatically changes with the body surface area stimulated painfully, the relative roles of the components of the cortical network underlying pain needs to be evaluated parametrically as a function of stimulus properties. This approach should reveal the dynamics of the cortical network underlying pain and pinpoint functional differentiations beyond those formulated by anatomic connectivity.

Generally the distribution of increased fMRI activity with painful thermal stimulation in the cortex examined is similar to our earlier results (Gelnar et al. 1999) and to those reported by other groups (reviewed in Apkarian 1995; Gelnar et al. 1999). The pattern of increased activity for the large stimulator is more similar to our earlier study (Gelnar et al. 1999), although the overall increased activity was larger and there was a larger spatial extent in the earlier study. This is consistent with the present results because the thermal stimulator used in the earlier study was larger and covered about twice as large surface area on the fingers compared with the large stimulator used in this study. Thus the two studies together consistently imply that the larger the skin area where thermal pain is felt the larger the cortical increased activity. In the Gelnar et al. (1999) study, decreased cortical fMRI activity was not reported because very few and very small regions showed significantly decreased activity. Therefore that study is also consistent with the present study and extends the present results by agreeing with the observation that the larger skin area where thermal pain is felt the smaller are the motor and parietal cortical decreased activity.

The psychophysical results show that the inhibition observed in the cortex can generate hypotheses regarding the impact of the inhibition on perception. The vibrotactile thresholds were tested for a body region remote enough from the site of painful stimulation where our earlier studies have shown that using a large surface thermal stimulator would not show significant changes in vibrotactile thresholds (Bolanowski et al. 2000). The results in this study agree with the former and show no significant change in vibrotactile thresholds on the forearm when thermal pain was induced on the fingers by the larger stimulator but do show significantly increased vibrotactile thresholds at the forearm when the same intensity of pain is induced through the smaller stimulator. This is consistent with the interpretation that the decreased fMRI signal in the cortex is due to a decrease in information processing ability for that region of cortex, which would occur when neuronal activity in the region is inhibited. Moreover it illustrates that thermal painful stimulus size dynamically modulates the spatial extent of the inhibition of vibrotaction by pain.

The extent of similarity of the pain perceived by the two stimulators, across 13 of the 15 dimensions of the descriptors tested, was surprising. The differences seen for two descriptors, splitting and shooting, were also minimal. Thus we cannot attribute the differences in cortical activity seen for the two stimulators to the higher dimensional properties of the pain experienced. Moreover the large decreased activity seen during pain perception with the small stimulator seems to be limited to this sensory modality because similar, or even smaller sized, vibrotactile stimuli result primarily in increased fMRI signal (Gelnar et al. 1998, 1999).

We are not able to directly compare the present results with our earlier SPECT study (Apkarian et al. 1992) because of multiple technical differences: spatial resolution was very poor in the SPECT study, stimulus duration was six times longer, and the stimulus encompassed a much larger body surface including glabrous and hairy hand. Moreover a recent PET study examined SI activity for tonic painful thermal stimulation (Derbyshire and Jones 1998). The results were inconclusive because in different subjects either increased or decreased activity was observed in SI. Because of technical difficulties we have not been able implement the paradigm used in our SPECT study with fMRI. Until the latter is achieved, the exact correspondence between the results of our SPECT study to the current study and to other functional imaging studies of pain remains uncertain.

Technical issues

Consistent with earlier studies (Defrin and Urca 1996; Douglass et al. 1992; Price et al. 1989), we observe that stimulus temperature for a given pain perception magnitude shows spatial summation. Because threshold was determined for each stimulator, our results are in agreement with the observation that pain thresholds show spatial summation (Defrin and Urca 1996).

In both the brain imaging and psychophysical studies, the large stimulator temperature was significantly lower from that of the smaller stimulator. However, there seems to be a substantial difference in the mean temperature used during scanning versus in psychophysical experiments. This difference may be a reflection of individual subject threshold differences because the two studies used separate groups of subjects and the applied temperatures were relative to each subject's threshold. Also, for technical reasons, the skin temperature measurements performed in the scanner are less reliable, especially for the small stimulator.

The design of this study emphasized equating the magnitude of perceived pain between the two stimulators as much as possible. We achieved this better in the psychophysical study than in the brain-imaging study. There are a number of small differences between the two stimulators besides the applied painful temperature: presence of an outer annulus for the large stimulator, the sensation of warmth being different because of differences in body area subjected to the warm temperature, differences in rise rates and in the total duration of pain perceived between the stimulators, and the presence of a mechanical component in the large stimulator. However, it is unlikely that these differences can account for the cortical fMRI activity patterns observed, especially because the results obtained with the large stimulator correspond to the results seen earlier with a stimulator that was a fixed surface of constant temperature (Gelnar et al. 1999).

It should be emphasized that the psychophysical study was designed to test a hypothesis derived from the brain-imaging

study; as such it simply tests the validity of our interpretation of the brain-imaging results. Our interpretation is based on the assumption that decreased fMRI signals indicate decreased neuronal activity within that region. The latter has been a point of disagreement in the past (see e.g., Jueptner and Weiller 1995). BOLD-based fMRI is sensitive to tissue deoxyhemoglobin content, which is determined by the rates of oxygen consumption and cerebral blood flow. During increased local neuronal activity, it is accepted that regional blood flow increases without a commensurate increase in oxygen consumption (Fox and Raichle 1986; Fox et al. 1988). The resultant decrease in regional deoxyhemoglobin generates susceptibility gradients giving rise to the blood-oxygen-level-dependent (BOLD-fMRI) signal increase. BOLD has been found to be consistent with cerebral-blood-flow-based functional maps generated by PET (Ojemann et al. 1998) or by perfusion-based magnetic resonance imaging techniques (Kim 1995). A number of studies recently have been able to identify and quantify the specific cellular molecular mechanisms of neuronal activity that are coupled to the BOLD-fMRI signal (Kennan et al. 1998; Magistretti et al. 1999; Van Zijl et al. 1998). The study by Van Zijl et al. (1998) correctly predicts the magnitude of BOLD-fMRI signal intensity changes on brain activation, thereby providing a sound physiological basis for these studies. The paper by Magistretti et al. (1999) outlines the direct metabolic pathway between energy demand (mainly glucose) and neuronal activity (mainly glutamate). It shows that 80–90% of the energy demand to be directly related to the energy consumption by glutamatergic neurons. A corollary to the latter is that decreased BOLD-fMRI signal, similar to PET cerebral-blood-flow studies, translates into inhibition of activity in cortical glutamatergic neurons (e.g., Vandenberghe et al. 1995). Our psychophysical study was formulated with this assumption and provides indirect confirmation of the assumption.

Physiological implications of the observed activation patterns

The observed pattern of increased and decreased fMRI signal with the two sizes of thermal painful stimuli suggests a distinct center-surround organization for neurons in the areas examined. In both SI and MI, the small stimulator resulted in inhibitory responses that spread throughout the upper body representation, implying that this defines the size of the nociceptive inhibitory surround for neurons in these regions. Moreover in both regions, increasing the size of the thermal stimulus to cover most of the fingers diminished the spread of the inhibitory response, implying that the excitatory receptive fields of the nociceptors are large enough to extend from the arm to the fingers or that the majority of the cells in the region receive some excitatory nociceptive input from the fingers or more likely some combination of both effects. Such an organization would be consistent with the role ascribed to SI in the sensory discriminative dimension of pain because it results in increasing the localization of noxious stimuli by changing the regional signal-to-noise ratio. This also may be part of the mechanisms underlying attentional shifts with pain (e.g., Drevets et al. 1995). The electrophysiological data show that nociceptive cells in SI have small excitatory receptive fields, arranged in a somatotopic pattern along the postcentral gyrus (Kenshalo and Isensee 1983; Lamour et al. 1983). To our

knowledge, their inhibitory surround receptive fields have not been described. Surround inhibition has been described for SI cells for innocuous stimuli because the earliest electrophysiological studies of the region (e.g., Mountcastle 1957). A recent elegant study by DiCarlo et al. (1998) described the receptive fields of area 3b cells in the alert monkey. The excitatory and inhibitory receptive fields for neurons with inputs from the distal fingerpads were studied. More than 94% of the cells examined in response to random dot tactile stimuli showed well-defined center-surround type receptive field organization. To our knowledge, responses of such neurons to noxious stimuli have not been characterized. Thus the organization of nociceptive inhibitory responses for cells coding tactile stimuli remains to be determined.

In contrast to SI and MI, the fMRI responses in SII and insula suggest that nociceptive neurons in these regions do not have a prominent center-surround excitatory-inhibitory relationship and that the responses in these regions simply reflect the excitatory responses related to the size of the skin stimulated. The suggested differential organization for SI and MI versus SII and insula implies a number of testable hypotheses, especially in relation to the spatial summation properties of thermal pain and in relation to pain localization and intensity discrimination, which remain to be explored.

Conclusions

The present study indicates that the cortical responses during pain perception have a critical dependence on the spatial properties of thermal painful stimuli. In our earlier SPECT and psychophysical studies (Apkarian et al. 1992, 1994) we concluded that the temporal properties of thermal painful stimuli are also critical in determining cortical responses to pain. Taken together, the studies imply that spatiotemporal properties of thermal painful stimuli need to be systematically studied to fully define the cortical dynamics underlying thermal pain perception.

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