Anesthesiology 2002; 96:35–44

Early Decay of Pain-related Cerebral Activation in Functional Magnetic Resonance Imaging

Comparison with Visual and Motor Tasks

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Background: **Although pain-related activation was localized in multiple brain areas by functional imaging, the temporal profile of its signal has been poorly understood. The authors characterized the temporal evolution of such activation in comparison to that by conventional visual and motor tasks using functional magnetic resonance imaging.**

Methods: **Five right-handed volunteers underwent whole brain echo-planar imaging on a 3 T magnetic resonance imaging scanner while they received pain stimulus on the right and left forearm and performed visually guided saccade and finger tapping tasks. Pain stimulus on the right and left forearm consisted of four cycles of 15-s stimulus at 47.2–49.0°C, interleaved with 30-s control at 32°C, delivered by a Peltier-type thermode, and visually guided saccade and finger tapping of three cycles of 30-s active and 30-s rest conditions. Voxel-wise *t* statistical maps were standardized and averaged across subjects. Blood oxygenation level–dependent signal time courses were analyzed at local maxima of representative activation clusters ($t > 3.5$).**

Results: **Pain stimulus on the right forearm activated the secondary somatosensory (S2), superior temporal, anterior cingulate, insular, prefrontal cortices, premotor area, and lenticular nucleus. Pain stimulus on the left forearm activated similar but fewer areas at less signal intensity. The S2 activation was dominant on the contralateral hemisphere. Pain-related activation was statistically weaker and showed less consistent signal time courses than visually guided saccade– and finger tapping–related activation. Pain-related signals decayed earlier before the end of stimulus, in contrast to well-sustained signal plateaus induced by visually guided saccade and finger tapping.**

Conclusions: **The authors speculate that pain-related blood oxygenation level–dependent signals were attenuated by the pain-induced global cerebral blood flow decrease or activation of the descending pain inhibitory systems.**

This article is featured in "This Month in Anesthesiology." Please see this issue of ANESTHESIOLOGY, page 5A.

IN the past decade, positron emission tomography studies have yielded substantial insight into the supraspinal substrates of pain experience in humans. Not only the thalamus but also multiple other discrete brain areas are now known to be involved in pain perception,[1] including the primary and secondary somatosensory, anterior cingulate, insular, and prefrontal cortices.[2–7] These cortical areas receive nociceptive information from the thalamus and are considered to mediate either of sensory-discriminative, affective-motivational, and cognitive-evaluative components of pain experience.[1]

Functional magnetic resonance imaging (fMRI) has recently become a popular mode of functional imaging in pain research,[8] offering higher spatial resolution that permits precise anatomic localization and higher temporal resolution on the order of seconds. Instead of radioisotope tracers, fMRI uses blood oxygenation level–dependent (BOLD) contrast to detect neuronal activation. Briefly, neuronal activation is followed immediately by an increase in regional cerebral blood flow (CBF) to a degree that is greater than the increase in oxygen consumption. This causes an enhancement in the ratio of oxyhemoglobin, which is diamagnetic, to deoxyhemoglobin, which is paramagnetic, in the blood vessels neighboring the activated neurons. This phenomenon is detected as a signal intensity increase in T_2^*-weighted magnetic resonance images.[9] Recent fMRI studies have facilitated further understanding of pain-related brain activity, such as the effects of expectation[10,11] and habituation.[12]

Nevertheless, the pain-related brain sites have shown considerable variations among brain imaging studies.[13] Although this may partly be a result of differences in experimental conditions, study design, mode and intensity of pain stimulation, habituation, or attentional state of subjects, some other factors unique to pain perception may be involved as confounders, such as pain-induced suppression of the global CBF[14] and activation of the descending pain inhibitory mechanisms.[15] To solve such uncertainties, more detailed exploration of brain activity changes by pain in well-controlled stimulus conditions are necessary, rather than simple localization by activation mapping.

To this end, the current study was designed not only to localize cerebral activation by a thermal pain stimulus, but also to characterize its signal intensity time courses. A very-high-field MRI scanner was used to enhance sensitivity to pain-related brain activity by BOLD contrasts.[16] A Peltier-type thermal stimulator was used that enabled

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Received from the Department of Anesthesiology and Critical Care Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania. Submitted for publication May 1, 2001. Accepted for publication September 18, 2001. Supported by the International Anesthesia Research Society, Cleveland, Ohio (Clinical Scholar Research Award to Dr. Firestone), grant No. PO1 NS35949 from the National Institutes of Health, Bethesda, Maryland (to Dr. Thulborn), and General Electric Medical Systems, Milwaukee, Wisconsin. Presented in part at the annual meeting of the American Society of Anesthesiologists, San Francisco, California, October 14–18, 2000.

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tightly controlled delivery of thermal pain stimulation.[10,12,17] In contrast to most earlier reports that used only one-sided (right or left) somatic pain stimulus, we stimulated both sides alternately to confirm the reproducibility and the hemispherical laterality of pain-related activation. We also examined cerebral activation by conventional visual and motor tasks[18,19] in the same imaging session. By comparing BOLD signal time courses between the pain stimulus and task paradigms, we tested the hypothesis that pain-related cerebral activation may show weaker, less consistent signal time courses, reflecting possible complication by inhibitory mechanisms.

Methods

Subjects

Written informed consent was obtained from five healthy volunteer subjects (aged 22–47 yr; one woman and four men). All were right-handed with no history of neurologic or psychiatric disorders or medications. Subjects had refrained from taking any psychoactive or analgesic medications for a period of 24 h before the study. The protocol was approved by the Institutional Review Board of the University of Pittsburgh.

Experimental Conditions

Each subject was examined with four experimental stimuli or tasks in one imaging session: pain stimulus at the right (PR) and left (PL) forearms; visually guided saccade (VGS); and finger-tapping (FT) tasks. All stimuli and tasks were designed in a "block" paradigm consisting of 15-s (PR, PL) or 30-s (VGS, FT) active phases alternating with 30-s control phases, and given to each subject in a counterbalanced order during the fMRI image acquisition.

Pain Stimulation and Rating of Subjective Sensation

A Peltier-type thermal stimulator (TSA-2001; Medoc, Israel) was used to deliver hot pain stimulus at approximately 46–49°C during the pain experiments.[10,12,17] It was equipped with an fMRI-compatible nonferrous thermode (3×3 cm^2 surface) and a 12-m cable, and was controlled with commercial software (COVAS; Medoc) on a laptop personal computer from outside the scanner room. The thermode was fixed on the subject's volar surface of the right or left forearm with a Velcro belt.

Before the imaging session, the thermode temperature for hot pain stimulus was determined individually by averaging five trials for pain threshold with commercial software (WinTSA; Medoc). While the thermode temperature was being increased gradually from 32°C at a ramp rate of 1°C/s, the pain threshold was determined as the lowest thermode temperature required for the subject to report a sensation as "just painful" by pressing a button to stop the stimulus, which lowered the thermode temperature to 32°C at a ramp rate of −10°C/s. The subject was then asked to rate stimulus intensity and unpleasantness separately with an integer between 0 and 10.[7,11] In this scale, 0 indicated "no sensation" or "not at all unpleasant," and 10 indicated "the most intense pain imaginable" or "the most unpleasant feeling imaginable" for the intensity or unpleasantness, respectively. The score of 5 was anchored to "just painful" sensation or "just unpleasant" feeling. All subjects were trained to rate sensation properly before the imaging sessions.

During the pain stimulus experiments, each subject was examined with four cycles of 15-s hot pain stimulus ("on" phase) at the forearm with intervening 30-s control stimulus at 32°C ("off" phase). The stimulus began and ended with an off phase lasting a total of 210 s. At the beginning of the on phase, the thermode temperature was increased from 32°C to the individually calibrated pain threshold at a ramp rate of 10°C/s, and at the end of the on phase it was decreased to 32°C at the same rate. We limited the duration of the on phase to 15 s to reduce head motion-related artifacts caused by subjects' distress from pain. Immediately after each pain stimulus experiment, the subject was asked to give the scores of pain intensity and unpleasantness verbally through a microphone in the scanner. After the first pain stimulus experiment, the thermode was removed and attached to the other forearm for the second trial.

Visual and Motor Tasks

In VGS and FT, subjects were given visual cues on a projection screen placed above their chest and viewed in an angled mirror fixed to the head coil. The visual cues were presented with in-house stimulus presentation software (CIGAL)[20] on a personal computer.

Visually guided saccade consisted of five cycles of 30-s saccade (on phase) with intervening 30-s control fixation (off phase); it began and ended with the off phase, lasting a total of 330 s. The saccade target was a solid white circle, and the fixation target was a white crosshair; both targets subtended 0.75° of visual angle on a black background. The saccade target was presented at 0°, 3°, or 6° of visual angle to the left or right along the horizontal plane and moved unpredictably with a 0.5 probability to the left or right every 0.75 s in a 3°-step from its previous position. During the off phase, the subject gazed at the crosshair at the center of the screen.

Finger tapping consisted of three cycles of 30-s finger tapping (on phase) with intervening 30-s rest condition (off phase); it began and ended with the off phase, lasting a total of 210 s. During the on phase, a series of Arabic numerals (1, 2, 3, and 4) were presented every 1 s repeatedly at the center of the screen, and the subject responded by tapping the second, third, fourth, and fifth fingers against the thumb in both hands, respectively.

During the off phase, a crosshair was presented for the subject to do nothing but rest.

Image Acquisition

Magnetic resonance imaging scans were conducted using a whole body 3 T scanner (Signa; General Electric Medical Systems, Milwaukee, WI) with a volume head coil. Subjects lay supine in the MRI scanner with their head immobilized by foam padding and pillow. A visual feedback system, providing the subject with information on the head position, further helped the subject to keep a stationary position.[21] Subjects were protected from acoustic noise of the scanner by ear plugs. Functional images were obtained with a T_2^*-sensitive, single-shot, gradient-echo echo-planar pulse sequence with the following parameters: repetition time = 3,000 ms; echo time = 25 ms; flip angle = 90°; imaging matrix = 64 × 64; field of view = 20 × 20 cm; slice thickness = 3 mm; and slice gap = 1 mm. Fourteen slices were acquired, covering the major part of the cerebrum from the primary sensorimotor cortex to the thalamus in an axial orientation. The imaging trials consisted of 70 consecutive scans (210 s) for PR, PL, and FT, and of 110 scans (330 s) for VGS. After all the functional scans were taken, a structural MRI of the whole brain was acquired using a three-dimensional high-resolution acquisition (fast spoiled gradient-recalled acquisition at steady state) for anatomic reference with the following parameters: repetition time = 25 ms; echo time = 5 ms; flip angle = 40°; imaging matrix = 256 × 192; field of view = 24 × 18 cm; slice thickness = 1.5 mm; no slice gap; and 124 axial slices.

Image Processing and Statistical Analysis

Image processing and statistical analysis of the functional data sets were performed using customized software (IVANA) on a UNIX workstation. IVANA is an in-house package of AVS (Advanced Visual Systems, Waltham, MA) modules developed to generate voxel (volume element)-wise *t* statistical maps.[18] Before the analysis, low-frequency signal variations, reflecting physiologic fluctuations and inadvertent head motions, were removed by subtracting a smooth low-frequency time course based on a quadratic spline curve fit through four evenly spaced nodes ("detrending").[20] Two data sets of VGS had to be excluded from analysis because of technical difficulties in MRI data acquisition and storage. The data sets from VGS sessions were clipped to 70 volumes (210 s) to equalize the statistical power across all the experiments. The images during the first 6 s of each on and off phase, reflecting hemodynamic transitions of BOLD signal time courses, were excluded from analysis for increased statistical power.[22] A voxel was considered activated if a *t* test comparing on-phase to off-phase signals resulted in $t > 3.5$, which corresponded to a chance probability of $P < 0.001$ without correction for multiple comparisons. For the sake of convenience, such statistical differences are referred to as "activation." The functional activation maps (*t* maps) generated by IVANA were overlaid onto the anatomic reference image and transformed into standardized stereotaxic space (Talairach space) using AFNI software.[23,24] To compensate for normal variation in anatomy across subjects, the unthresholded, stereotaxically resampled three-dimensional *t* maps were smoothed slightly with a Gaussian filter of root-mean-square radius 0.5 mm.[25] The *t* maps were merged across all subjects by averaging the *t* statistics in each voxel to guard against nonequal MR signal variances among subjects.[25] The same threshold of $t > 3.5$ was used for the resultant merged *t* maps. The anatomic brain images were also averaged to produce a "merged" reference image. Activated clusters with a volume less than 0.1 ml, approximately three contiguous voxels, were excluded from analysis.

The voxels of interest for BOLD signal time-course analysis were chosen as voxels showing the highest averaged *t* value (local maxima) in some of most intensely activated clusters. For each voxel of interest, all epochs including one off-on-off cycle were averaged across subjects in an event-related manner. The signal changes over the transitions from on to off phases were examined by repeated-measures analysis of variance and a *post hoc* Fisher protected least significant difference test for multiple comparisons. The maximum percent BOLD signal changes were averaged across all the epochs and were compared among the different experiments by analysis of variance with a *post hoc* Bonferroni test for multiple comparisons.

Table 1. Demographics of Subjects and Pain Rating Scores

Subject	Age	Sex	Thermode Temperature (°C)	Pain Intensity		Pain Unpleasantness	
				Right	Left	Right	Left
1	36	M	48.2	8	8	8	8
2	47	M	49.0	6	6	6	7
3	24	M	47.4	7	8	7	7
4	22	F	47.2	8	9	8	9
5	45	M	46.7	6	7	6	7
Average	34.8 ± 11.6		47.7 ± 0.9	7.0 ± 1.0	7.6 ± 1.1	7.0 ± 1.0	7.6 ± 0.9

Average values are mean ± SD.

Table 2. Cerebral Activation Induced by Painful Thermal Stimulation at the Right and the Left Forearm

Location (Brodmann's Area)	Coordinates x	y	z	*t*
Pain at the right forearm				
Secondary somatosensory cortex				
Right inferior parietal lobule (40)	62	−30	27	7.1
Right inferior parietal lobule (40)	51	−45	34	5.3
Left inferior parietal lobule (40)	−61	−29	16	6.0
Left inferior parietal lobule (40)	−55	−34	38	4.9
Temporal opercular region				
Left superior temporal gyrus (22)	−55	0	5	7.2
Left superior temporal gyrus (42)	−63	−15	9	5.5
Right superior temporal gyrus (22)	48	11	1	6.4
Cingulate cortex				
Right–left anterior cingulate cortex (24)	1	−1	43	6.6
Premotor area				
Right precentral gyrus (6)	47	−1	30	6.6
Right precentral gyrus (4)	39	−12	53	4.6
Left precentral gyrus (6)	−57	0	26	4.9
Insular cortex				
Right insula	−39	5	10	5.3
Left insula	−43	−11	13	4.5
Prefrontal cortex				
Right middle frontal gyrus (10)	42	41	21	5.3
Right middle frontal gyrus (9)	−27	26	36	4.9
Right inferior frontal gyrus (46)	44	34	8	4.8
Other activated areas				
Right lenticular nucleus	22	3	12	4.5
Right lenticular nucleus	19	6	2	4.0
Pain at the left forearm				
Secondary somatosensory cortex				
Right inferior parietal lobule (40)	64	−23	30	5.2
Premotor area				
Right precentral gyrus (6)	52	3	12	5.3
Right precentral gyrus (6)	59	0	33	5.3
Right superior frontal gyrus (6)	8	−10	52	5.2
Insular cortex				
Right insula	40	−6	15	5.2
Left insula	−41	−7	6	4.5

$t > 3.5$ ($P < 0.001$). Boldface locations were used for blood oxygenation level–dependent signal time course analysis.

Results

Stimulus Intensity and Pain Rating Scores

The demographics of subjects and pain rating scores are summarized in table 1. All subjects described the pain stimulus as painful and unpleasant. These pain-rating scores did not differ between PR and PL (paired *t* test, $P = 0.40$ for pain intensity; $P = 0.35$ for pain unpleasantness). There was no correlation between thermode temperatures and pain intensity scores ($r = -0.08$, $P = 0.91$ for PR; $r = -0.51$, $P = 0.43$ for PL) or pain unpleasantness scores ($r = -0.08$, $P = 0.91$ for PR; $r = -0.15$, $P = 0.83$ for PL).

Activation by Pain Stimulation

The most prominent activation by PR was observed bilaterally around the lateral sulcus, *i.e.*, the inferior parietal lobule and superior temporal gyrus, as shown in table 2 and figure 1. The inferior parietal lobule near the lateral sulcus is generally considered the secondary somatosensory cortex (S2) in humans. Other activation clusters appeared in the anterior cingulate (ACC), insular, prefrontal cortices, premotor area, and lenticular nucleus. PL activated similar brain areas but with smaller cluster sizes and less statistical power than those by PR. The ipsilateral S2 and ACC were also activated, as well as the contralateral S2 by PL, but were excluded from analysis because they did not reach the activation volume threshold of 0.1 ml.

Activation by Visual and Motor Tasks

Visually guided saccade activated the bilateral frontal and supplementary eye fields, posterior parietal, primary and secondary visual cortices (table 3, fig. 2). FT activated the bilateral primary motor and somatosensory cortices (M1/S1), premotor and supplementary motor areas, S2, insular and prefrontal cortices, thalamus, and left lenticular nucleus (table 3, fig. 2). Activation by VGS and FT generally showed higher *t* values than pain-related activation.

Blood Oxygenation Level–Dependent Signal Time-course Analysis

Average BOLD signal time courses were analyzed at eight voxels of interests in the most robustly activated clusters by each stimulus or task, *i.e.*, the bilateral S2 and ACC by PR, contralateral S2 by PL, bilateral frontal eye field by VGS, and bilateral S1 by FT (fig. 3). These time courses showed 1–3% of average BOLD signal increases during each stimulus or task with a typical pattern of hemodynamic delay of several seconds both at the beginning and at the end. However, the pain-related signals were rather smaller in amplitude and more irregular than the task-related signals. Although the signal plateaus were well sustained throughout the VGS and FT tasks, pain-related signals tended to decay earlier before the end of stimulus (fig. 4). Although the VGS- and FT-related signals remained above 86% of the maximum until 6 s after the end of task, the pain-related signals decreased to 77% of the maximum before the end of stimulus, down to 56% in 6 s after the stimulus.

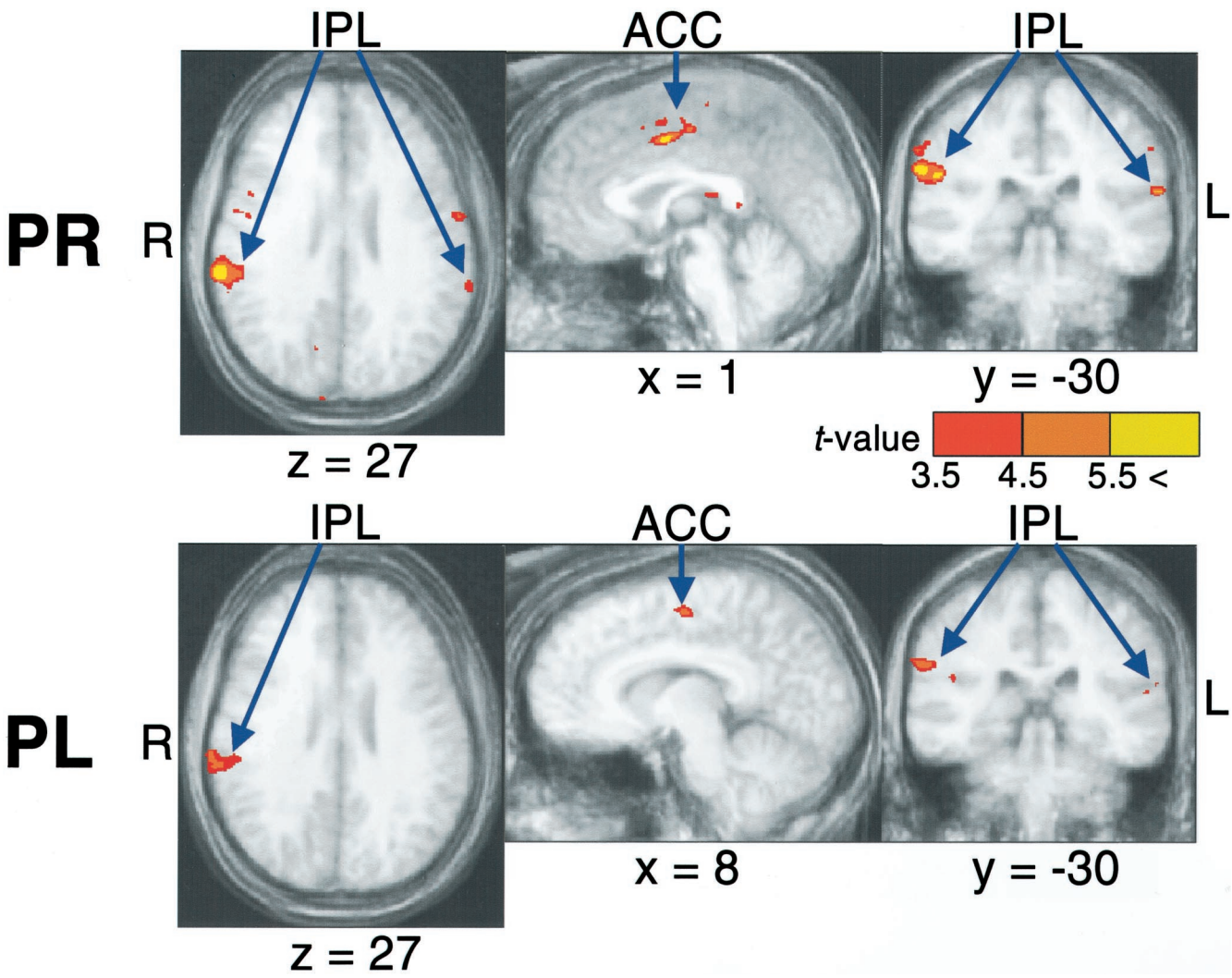

Fig. 1. Averaged activation *t* maps in axial, sagittal, and coronal planes, generated from functional magnetic resonance imaging studies of pain on the right (PR, *top*) or left (PL, *bottom*) forearm. Activated voxels are shown by graded colors indicating *t* values. The x, y, and z values indicate stereotaxic coordinates of each slice in the Talairach space. R = right side; L = left side; IPL = inferior parietal lobule; ACC = anterior cingulate cortex.

The maximum percent BOLD signal changes by pain stimulation in each off-on-off cycle were comparable to those by VGS and FT (fig. 5). In PR, the S2 activation was significantly greater on the contralateral (left) side than on the ipsilateral (right) side. The contralateral S2 activation by PR was significantly greater than that by PL.

Discussion

The current study showed that the most prominent cerebral activation by thermal pain is found in the bilateral S2, in accordance with earlier fMRI studies using electrical,[26] thermal,[12,17,27] and laser-evoked[11] somatic pain stimulation. Although the *t* values of both sides of S2 activation were comparable, BOLD signal time-course analysis clearly showed the contralateral dominance of S2 activation by pain. This is consistent with earlier electrophysiologic findings that showed a higher amplitude of source potential at the contralateral S2 than at the ipsilateral S2 in response to laser-evoked somatic[28] and trigeminal pain.[29] In humans, S2 is localized in the parietal operculum, lateral and posterior to the face presentation in the primary somatosensory cortex, and anterior and medial to the primary auditory areas.[30,31] Receiving afferent fibers from the ventral posterior nucleus of the thalamus and the ipsilateral and contralateral primary sensory cortex,[32,33] S2 represents somatotopic organization of the bilateral, predominantly contralateral, body parts, and is involved in the integrative aspect of sensation[32] as well as nociception as part of the lateral nociceptive system.[1]

We also observed some pain-related activation clusters in the bilateral temporal opercular region near S2. Although these clusters had the highest intensity on the superior temporal cortex (Brodmann's area 42/22; table 2), they partly overlapped the parietal and frontal lobes

Table 3. Cerebral Activation Induced by Visually Guided Saccade and Finger-tapping Tasks

Location (Brodmann's Area)	Coordinates x	y	z	*t*
Visually guided saccade				
Frontal eye field				
Right precentral gyrus (6)	44	−12	56	13.6
Left precentral gyrus (6)	−50	−14	50	11.9
Posterior parietal cortex				
Left precuneus (7)	−11	−73	50	10.9
Right precuneus (7)	8	−52	51	6.4
Right intraparietal sulcus (7)	29	−55	45	6.0
Left intraparietal sulcus (7)	−39	−54	53	5.4
Visual cortex				
Left calcarine sulcus (17)	−7	−75	10	8.5
Right cuneus (19)	28	−82	25	5.7
Supplementary eye field				
Left–right medial frontal gyrus (6)	−4	−10	52	8.2
Extrastriate visual area				
Left middle temporal gyrus (21)	−53	−53	8	7.0
Right middle temporal gyrus (21)	61	−53	10	6.9
Other activated areas				
Left middle frontal gyrus (8)	−27	44	41	4.8
Left insula	−34	6	16	4.8
Finger tapping				
Primary sensorimotor cortex and premotor area				
Right precentral–postcentral gyrus (1–4, 6)	42	−26	55	22.3
Left precentral–postcentral gyrus (1–4, 6)	−39	−36	50	18.1
Supplementary motor area				
Right–left medial frontal gyrus (6)	5	−11	53	12.4
Secondary somatosensory and insular cortices				
Right inferior parietal lobule (40)	53	−28	23	9.2
Right inferior parietal lobule (40)	60	−41	25	8.3
Right insula	37	−6	17	7.3
Left postcentral gyrus (40)	−63	−18	14	7.4
Temporal–frontal opercular regions				
Right superior temporal gyrus (22)	53	7	0	6.7
Left superior temporal gyrus (42)	−54	−10	12	6.3
Left superior temporal gyrus (20)	−53	−2	5	6.2
Left inferior frontal gyrus (44)	−52	6	8	6.0
Prefrontal cortex				
Right middle frontal gyrus (8)	36	35	47	6.3
Right middle frontal gyrus (9)	46	42	23	5.5
Right middle frontal gyrus (9)	43	15	49	4.9
Left middle frontal gyrus (8)	−30	39	43	4.8
Right superior frontal gyrus (9)	22	62	28	5.2
Left superior frontal gyrus (8)	−12	48	43	5.2
Other activated areas				
Left lenticular nucleus	−26	−9	−1	6.4
Left thalamus	−11	−23	9	6.1
Right thalamus	14	−22	7	5.5

$t > 3.5$ ($P < 0.001$). Boldface locations were used for blood oxygenation level–dependent signal time course analysis.

on the merged anatomic reference, possibly reflecting activation at S2, insular cortex, and premotor area. Activation of the superior temporal cortex by similar thermal stimuli at 46 and 41°C was also reported by Becerra *et al.*[12] This activation may not be involved in pain perception itself, but may be possibly related to shifting of spatial attention to the pain stimulus.[34] Lesion of this area is known to cause spatial neglect in humans and monkeys.[34]

The other activation clusters by pain in the ACC, insular, prefrontal cortices, premotor area, and lenticular nucleus are in accordance with earlier fMRI findings.[10–12,17,27,35,36] ACC has nociceptive neurons[37] and is considered to mediate affective[38] and attentional[39] aspects of pain as part of the medial nociceptive system.[1] The present ACC activation belongs to the midcingular cognitive region[40] that may be involved in attentional orienting reaction[13] or motor response to pain,[27] rather than to the rostral affective region.[40] The insular cortex also receives direct projections from the thalamus and has thermosensory and nociceptive representation.[41] Activation of the prefrontal cortex, premotor area, and lenticular nucleus may reflect judging and planning for movement to avoid injury.[7,32]

On the other hand, S1 was not activated by pain, in contrast to its robust activation by FT. Although the role for S1 in pain perception remains controversial among brain imaging studies, S1 is considered to mediate the sensory-discriminative aspect of pain, such as localization and intensity coding,[42] as part of the lateral nociceptive system.[1] The absence of pain-related S1 activation may be a result of the small size (9 cm^2) of the thermode that may have failed to activate sufficient number of cortical nociceptive neurons, which are sparsely distributed, to establish spatial summation.[13] In addition, because of the highly tuned somatotopy of S1 and individual differences in sulcal anatomy, intersubject averaging may have obscured possible S1 activation in the activation *t* maps.[42]

Visually guided saccade and FT reproduced previously reported oculomotor- and motor-related activation[18,19] robustly, with higher *t* values than the pain stimulus. This may reflect consistency of BOLD signal changes and well-sustained signal plateau throughout the tasks. Relatively less robust activation by pain may partly be caused by inconsistent signal time course and early signal decay before the end of stimulus, as shown in figures 3 and 4, in support of our hypothesis. An earlier positron emission tomography study demonstrated that pain stimulus by intradermal injection of capsaicin decreased global CBF by 22.8% in normal human subjects, implying that pain stimulus directly activated the sympathetic innervation of cerebral blood vessels.[14] Such decrease in global CBF could attenuate or eclipse regional CBF increases by pain and may explain early decay of pain-related BOLD signals when compared with the other nonpainful visual and motor tasks, assuming that changes in global and regional CBF are additive.[43] Indeed, hyperventilation-induced hypocapnia, reducing global CBF by cerebrovascular constriction, decreased the BOLD responses to visual stimulus in the visual cortex from 3.97% to 0.77% in normal human subjects.[44] The same inhibitory mech-

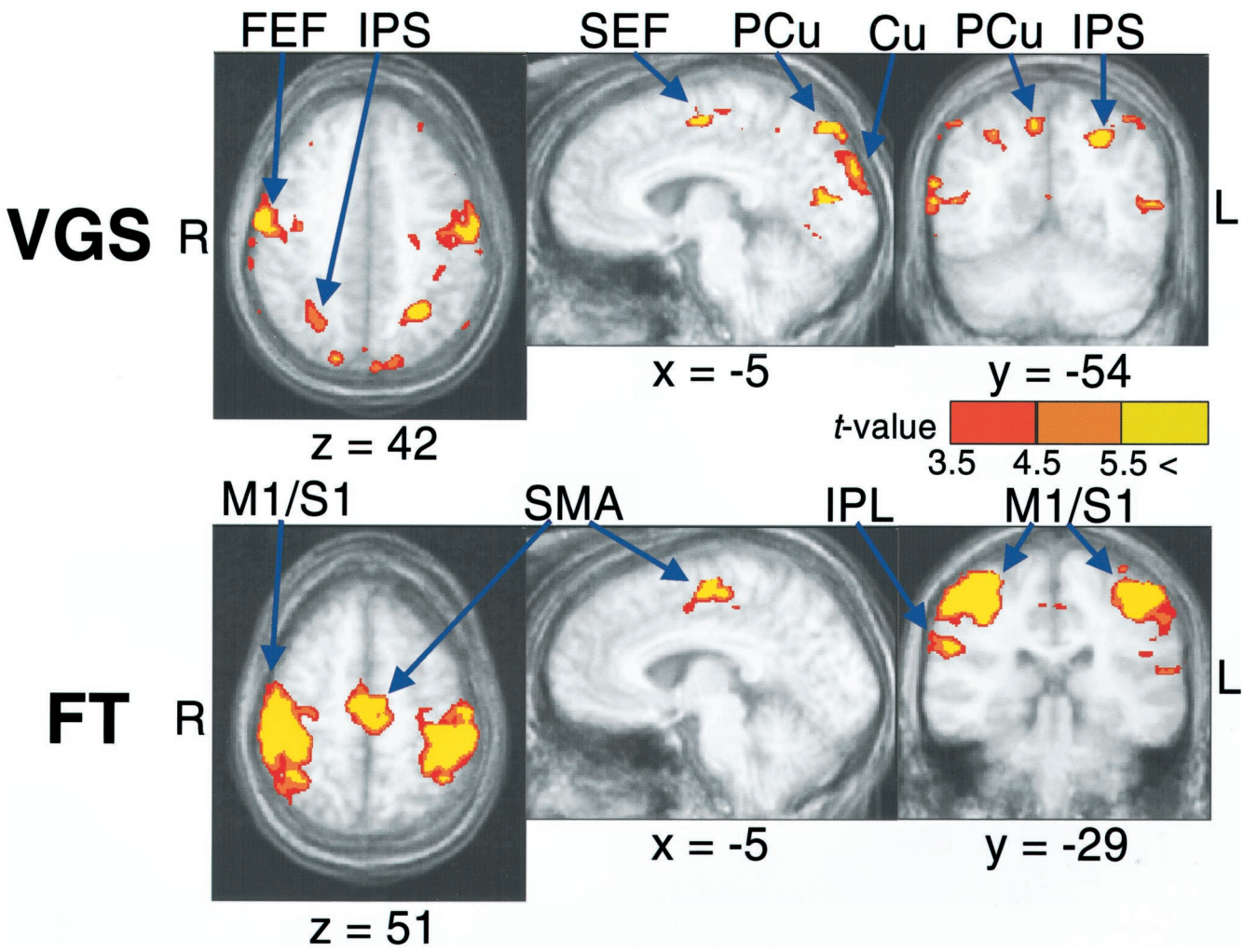

Fig. 2. Averaged activation *t* maps in axial, sagittal, and coronal planes, generated from functional magnetic resonance imaging studies of visually guided saccade (VGS, *top*) and finger tapping (FT, *bottom*) tasks. Activated voxels are shown by graded colors indicating *t* values. The x, y, and z values indicate stereotaxic coordinates of each slice in the Talairach space. R = right side; L = left side; FEF = frontal eye field; SEF = supplementary eye field; IPS = intraparietal sulcus; PCu = precuneus; Cu = cuneus; M1/S1 = primary motor and somatosensory cortices; SMA = supplementary motor area; IPL = inferior parietal lobule.

anism may have resulted in inconsistent pain-evoked BOLD signals that yielded lower statistical intensity of activation. In contrast, conventional cognitive tasks seem to increase global CBF.[45] The visual and motor tasks in the current study also required the subjects' cognitive efforts and may have sustained or increased global CBF, resulting in well-sustained signal plateau.

The aforementioned speculation is limited by the lack of direct CBF measurement that may reveal interactions between global and regional CBF changes. Indirect nature of BOLD signals does not allow simple translation of negative BOLD contrast to a CBF decrease. It is also unknown whether such fluctuation of global CBF occurs rapidly enough to affect BOLD signals in response to acute thermal pain as well as to capsaicin-evoked pain that persists much longer.[14]

Alternative physiologic factors modifying pain-related BOLD signals may include the effects of acute habituation of pain sensation, diminished attention to a pain stimulus, and descending inhibition of pain.

Behavioral habituation to pain, as was observed with a laser-evoked pain stimulus,[7] could parallel attenuation of cerebral activation. We did not measure possible gradual changes in pain sensation over time during each cycle of pain stimulus. Two earlier fMRI studies, however, support our assumption that such behavioral habituation was not likely in the current study. Becerra *et al.*[12] measured pain-rating scores for each of four 46°C-stimuli in a similar block-design paradigm with the same thermal stimulator as ours and found no habituation in pain sensation, despite a progressive decrease in BOLD signal amplitudes toward the end of imaging sessions, which may imply attenuation of neuronal or hemodynamic responses. In contrast, they showed that nonpainful stimulus at 41°C resulted in a decreasing trend of pain sensation. Apkarian *et al.*[46] observed continuous pain-rating

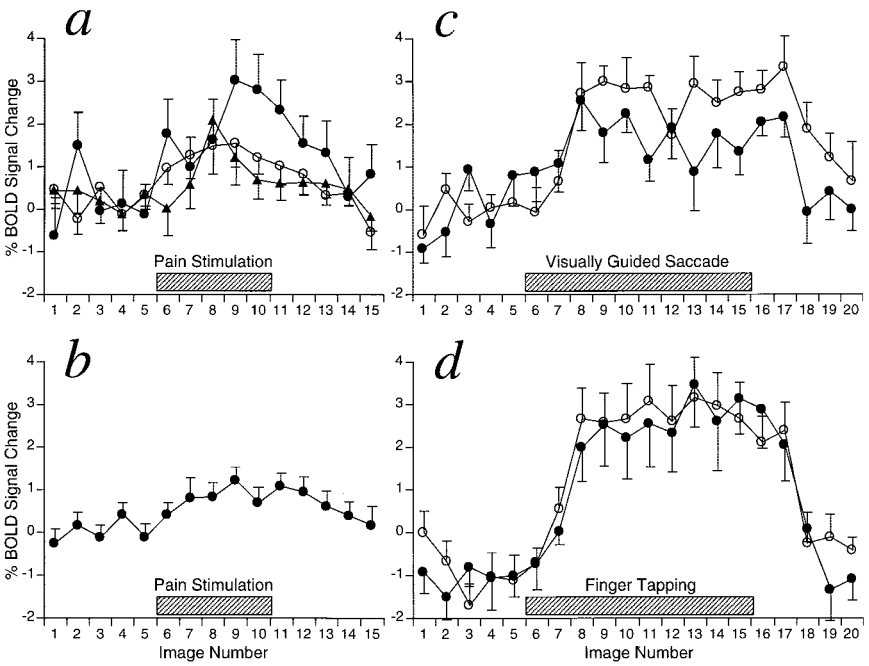

Fig. 3. (*a*) Averaged blood oxygenation level–dependent (BOLD) signal time courses of representative voxels activated by pain stimulation on the right forearm. Open circles represent the voxel at the Talairach coordinate of (62, −30, 27) in the right secondary somatosensory cortex (S2); filled circles at (−61, −29, 16) in the left S2; and triangles at (1, −1, 43) in the right anterior cingulate cortex. (*b*) An averaged BOLD signal time course of a representative voxel activated by pain stimulation on the left forearm. The voxel was localized at (64, −23, 30) in the right S2. (*c*) Averaged BOLD signal time courses of representative voxels activated by a visually guided saccade task. Open circles represent the voxel at (44, −12, 56) in the right frontal eye field, and filled circles at (−50, −14, 50) in the left frontal eye field. (*d*) Averaged BOLD signal time courses of representative voxels activated by a finger tapping task. Open circles represent the voxel at (42, −26, 55) in the right primary sensorimotor cortex, and filled circles at (−39, −36, 50) in the left primary sensorimotor cortex. Bars represent SEM.

responses of subjects using a "potentiometer" while six cycles of 35-s hot pain stimulus were applied and observed an increasing trend of pain sensation during each cycle, and even a gradual increase of the maximum over cycles (sensitization to pain) after the second cycle. The intensity of pain stimulus in our study, averaging 47.7°C, was high enough to avoid acute behavioral habituation, the pain-rating scores being consistently in the "painful" range of 6–9 out of 10 (table 1), although we calibrated the thermode temperature at each subject's pain threshold. The 15-s stimulus may have been more painful than the brief calibration stimulus of the same temperature that was terminated immediately on button pressing. In addition, slow conduction of nociception *via* C fibers, and delay between the subjects' judgment and button-pressing action, may have resulted in calibration at higher temperatures than actual pain thresholds.

Attention directed toward a pain stimulus was shown to enhance pain-related cerebral activation.[39] Because the subjects were asked to rate pain sensation for each stimulus session, the level of attention toward the pain stimulus was most likely sustained in the current study. Possible gradual enhancement of pain sensation over time[46] would also exclude the factor of diminished attention.

Ascending nociceptive information activates supraspinal analgesic mechanisms mediated by the descending inhibitory systems, which modulate the transmission of nociception at the spinal and medullary dorsal horn *via* descending fibers through the midbrain periaqueductal gray.[15] Such top-down-regulation may possibly attenuate pain-related cerebral activation indirectly by suppressing nociceptive transmission at the dorsal horn level, or directly by unknown interactions among the cortical and subcortical structures that may be involved in cognitive and motivational processes.[15] Although we did not observe the behavioral attenuation of pain sensation, activation of top-down pain control systems may have affected the BOLD signals at the neuronal and hemodynamic levels.

Despite the equal perceived intensity and unpleasantness by PR and PL, PL induced less brain activation than PR, both in the number of activated clusters and in the maximum BOLD signal change at the contralateral S2. Such weaker responses by PL than by PR may imply hemispherical asymmetry in somatosensory representation and support the findings by magnetic source imaging that the representation of the dominant hand was larger than that of the contralateral one in the corre-

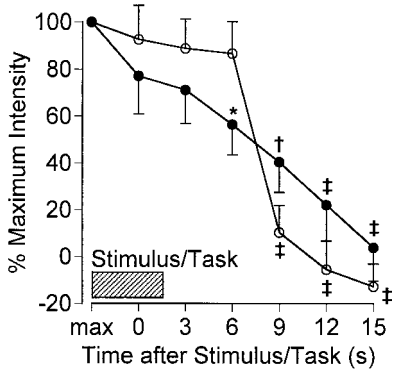

Fig. 4. Decay of blood oxygenation level–dependent signals after the end of stimulus or task. Pain-related signals (filled circles; n = 79) decayed more rapidly than visual and motor task-related signals (open circles; n = 48). Signal intensities were averaged and compared with the maximum (max) during the on phase across all the voxels of interest in all subjects. Bars represent SEM. *P < 0.05; †P < 0.005; ‡P < 0.0001 against the maximum by repeated-measures analysis of variance and a *post hoc* Fisher protected least significant difference test for multiple comparisons.

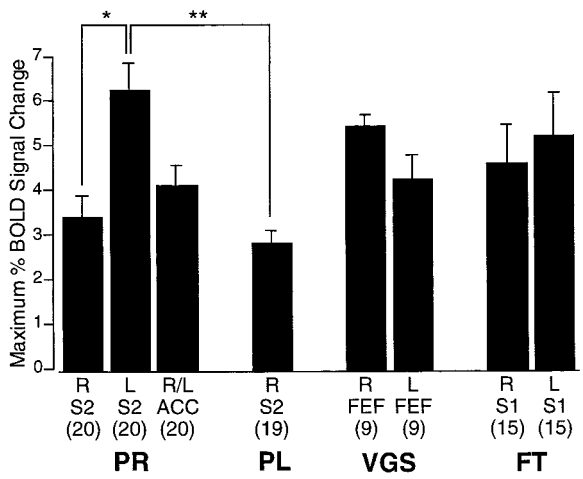

Fig. 5. Comparison of maximum percent blood oxygenation level–dependent (BOLD) signal changes among representative activated voxels by pain stimulation on the right (PR) and left (PL) forearm, visually guided saccade (VGS), and finger tapping (FT) tasks. The activation at the contralateral secondary somatosensory cortex (S2) by PR was greater than that at the ipsilateral S2 (*P = 0.0003 by analysis of variance and a *post hoc* Bonferroni test for multiple comparisons). The contralateral S2 activation was greater in PR than that in PL (P < 0.0001). Bars represent SEM. R = right side; L = left side; ACC = anterior cingulate cortex; FEF = frontal eye field; S1 = primary somatosensory cortex. Numbers in parentheses indicate numbers of off-on-off cycles from which maximum BOLD signal changes were sampled.**

sponding hemispheres in right-handers, but not in left-handers.[47]

The current study has the following limitations. First, the conventional block design involved repetition of identical stimuli with fixed duration and intervals, which may have confounded the results with the effects of expectation by subjects.[10] This problem could be avoided by using event-related study designs with randomized stimuli.[11,48,49] Second, pain stimulus lasting more than 15 s might have been more appropriate to detect early signal decay. However, our preliminary studies with pain stimulus lasting 30 s or longer resulted in significant head motion from distress, which prevented proper fMRI data analysis. Therefore, we chose shorter, 15-s duration of pain stimulus, which eventually resulted in fMRI data that could be analyzed. More sophisticated techniques to correct head-motion artifacts, rather than time-course detrending, might permit longer duration of pain stimulus. Lastly, the functional scans of the current study did not include the lowest part of the cerebrum, such as the hippocampus and amygdala, and the cerebellum. These parts have been studied in relation to pain perception, but not in detail.[7,10] To better characterize activation of each brain site involved in pain perception, further fMRI studies with fewer focused brain slice selection and rapid event-related designs will be needed in the future. Such studies will not only facilitate physiologic insight into cerebral pain processing, but will also provide novel methods to evaluate subjective pain experience and the effects of therapeutic interventions or drugs in an objective manner, as was done using positron emission tomography.[50–52]

In summary, we have demonstrated that the bilateral S2 was most robustly activated by somatic thermal pain in BOLD-contrast fMRI. Such activation was dominant on the contralateral hemisphere and more robust during the right-sided stimulation in right-handed subjects. The pain-related activation showed lower statistical intensity and early signal decay in contrast to robust and well-sustained activation by visual and motor tasks. Such attenuation of pain-related BOLD signals may result from the pain-induced global CBF decrease or activation of the descending pain inhibitory systems.

The authors thank Denise Davis, B.S., R.T. (Research Instructor, Department of Anesthesiology and Critical Care Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania), for technical assistance during magnetic resonance imaging scanning; James Voyvodic, Ph.D. (Assistant Research Professor, Department of Radiology, Duke University, Durham, North Carolina), for providing paradigm presentation and data processing software; and Stuart W. G. Derbyshire, Ph.D. (Research Assistant Professor, Department of Anesthesiology and Critical Care Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania), for helpful comments on the manuscript.

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