neuroReport

Website publication 21 December 1998

NeuroReport 9, 4179–4187 (1998)

Representation of nociceptive stimuli in primary sensory cortex

Howard H. Berman,[1,2] Karl H. S. Kim,[1,3] Ardesheer Talati[1,2] and Joy Hirsch[1,3,CA]

[1]Department of Neurology, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10021; Departments of [2]Pharmacology and [3]Neuroscience, Cornell University Medical College, 1300 York Avenue, NY 10021, USA

[CA]Corresponding Author

USING fMRI, we observed cortical activity associated with nociceptive hot and cold sensations applied to hand and foot that are not spatially restricted to the corresponding regions of the primary somatosensory cortex (SI). Hot (55–57°C) and cold (0–2°C) tactile stimuli were applied separately to the right hand and foot of eight right-handed subjects. Although somatotopic mapping of hand and foot was observed as expected based on the Penfield homunculus, activations associated with hot during both hand and foot stimulation and subsequently, cold, activated regions unique to each thermal modality irrespective of the body part. This distributed system for thermal information is present at both nociceptive and more neutral thermal intensities (i.e. warm and cool sensations) indicating the presence of distributed sensory processing associated with thermal-related sensations in human primary sensorimotor cortex. *NeuroReport* 9: 4179–4187 © 1998 Lippincott Williams & Wilkins.

Key words: Functional magnetic resonance imaging (fMRI); Nociception; Somatosensory cortex (SI); Somatotopy

Introduction

Although the role of somatosensory cortex (SI) in the mapping of body parts has been well documented,[1–3] its involvement in the processing of thermal (hot and cold) sensations remains poorly defined. Clinical and physiological evidence suggests that SI, which is divided into Brodmann's areas, 1,2, 3a, and 3b, may be involved in thermal and even pain processing.[4–7] Cerebral evoked response studies on humans[6,7] and studies of single cortical units in monkeys[8] and rats[9] support a role for SI in the perception of thermal stimuli. In addition, selective SI ablation studies in rats and clinical studies of humans sustaining damage to SI cortex have shown disturbances in the performance of thermal discrimination tasks.[10] More recently, single unit recording studies in cats, rats, and monkeys have revealed that some neurons in SI receive a nociceptive input.[11] Despite this progress in understanding mechanisms in thermatosensory processing, very little is known about the precise representation in SI for humans. Thus, it is not clear whether thermal information is transmitted within the cerebral cortex as a generalized message or converges on focal areas associated with somesthetic information (somatotopy).

Neuro-imaging techniques have opened new avenues to investigate the central processing of nociceptive input in the awake human. PET studies have identified SI activation during application of painful heat stimuli applied to the contralateral limb[12,13] and recently, SI activation during noxious heat stimulation of the contralateral digits has been shown by fMRI.[14]

In this study, we applied fMRI to investigate the role of SI in higher order processing of nociceptive thermal stimuli using stimulations of two body parts (hand and foot) and two thermal sensations (cool/cold and warm/hot). Our goal is to determine whether representations of thermal sensation are ordered in a somatotopic or a distributed fashion in SI.

Materials and Methods

fMRI: A 1.5T GE MR scanner was employed to obtain T2*-weighted images with a gradient echo pulse sequence (echo time, 60 ms; repetition time, 4000 ms; flip angle, 60°). A GE head coil was employed and 21 contiguous 4.5 mm slices were positioned over the entire cortex with in-plane resolution of 1.5×1.5 mm. Thirty-six images were acquired, one every 4 s; thus, an entire run lasted 144 s and two identical runs were performed for each condition. The initial 10 images (images 4–13 lasting 40 s) of each run were acquired during a baseline (resting) condition, the following 10 images (images

15–24 lasting 40 s) were acquired during tactile stimulation, and the final 10 images (images 27–36 lasting 40 s) were acquired during a post-stimulation (recovery) resting condition. Images 1–3 were excluded to assure a steady state magnetic resonance signal, while images 14, 25, and 26 were excluded to avoid epoch transition periods. Prior to statistical analysis, all brain images were computationally aligned[15] to allow direct spatial comparisons between runs and a two-dimensional gaussian filter was applied. A multistage statistical technique was applied to each volume element, voxel, to identify activity including: comparison of mean baseline and mean stimulation signals, and comparison of mean stimulation and mean recovery baseline signals. All statistical criteria were met on two runs for voxels determined to be active.[16,17] A similar analysis was applied to images acquired from a copper sulphate solution-filled spherical phantom and determined that the empirical probability of a false positive result was $\leqslant 0.0005$.

Subjects and task: Eight healthy subjects (Table 1) were recruited to the study according to institutional guidelines, five receiving a hot (55–57°C) and cold (0–2°C) stimulus separately to the right hand and right foot, two receiving the hot and cold stimuli plus an additional arousal-inducing, but non-painful tactile scrubber stimulus separately to the right hand and right foot, and one receiving both the hot and cold stimuli and warm (30–32°C) and cool (15–17°C) stimuli to the right hand and foot. Prior to entering the scanner, subjects were asked to subjectively quantify the perceived magnitude of the stimulus intensities rated from 1 to 10 where 1 = low intensity and 10 = high intensity. These ratings are presented in Table 1 and confirm that the hot and cold temperatures were of equal perceived magnitude, the perceived magnitude of the scrubber intensity was a similar magnitude to that of the hot and cold stimulus, and the perceived magnitude of the warm and cool stimuli were considerably lower than that of the other stimuli (Table 1).

Stimulation materials and methods: The thermal stimulus consisted of either heated or semi-frozen water packets for the hot and cold stimuli and mildly heated or cooled water packets for the warm and cool stimuli. Temperatures of the packets were recorded before and after stimulation. The scrubber (non-thermal) stimulus consisted of a plastic brush with pointed bristles that was of similar size to that of the water packets. The stimuli were applied intermittently over a total period of 40 s periods of 2 s stimulation alternating with 2 s periods of no stimulation. Thus, 10 on–off cycles of tactile stimulation occurred during the stimulation period.

Experimental design: A 2×2 contingency table describes the experimental design and analysis strategy (Fig. 1). Somatotopy was evaluated by the conjunction of hot and cold over each body part (Fig. 1 columns). Thus, all thermal stimulations to hand or foot that activated cortical regions associated with the body part were represented. In order to selectively evaluate brain activity specific to thermal sensations and not the body parts stimulated, we isolated regions unique for hot and cold by selecting activity in common over hand and foot stimulations (Fig. 1 rows). In other words, hot activations are those regions active in response to hot stimuli to both the hand and foot. Cold follows a similar logic.

Labeling of the active brain regions in primary sensory cortex: Colored voxels indicate brain activity and were displayed slice by slice on the original T2*-weighted images with a grid indicating actual voxel location. The anatomical identification of the primary sensory cortex was made by inspection of the corresponding T1 (high resolution) images and

Table 1. Subject information

Subject	Age	Handedness	Edinburgh ratio	Temperature intensity ratings[a]									
				Hand					Foot				
				Hot	Cold	Warm	Cool	Scrubber	Hot	Cold	Warm	Cool	Scrubber
CC	26	R	+100	9	9	–	–	–	9	9	–	–	–
MB	35	R	+84.6	8	8	–	–	–	9	8	–	–	–
DR	25	R	+50	10	9	–	–	–	10	9	–	–	–
DV[b]	25	R	+84.6	7	7	4	4	–	7	7	4	4	–
BB	24	R	+60	7	7	–	–	–	8	7	–	–	–
MC	29	AMB	0	8	8	–	–	–	8	8	–	–	–
AF	23	R	+100	–	7	–	–	7	–	7	–	–	7
WT	29	R	+60	7	7	–	–	6.5	7	7	–	–	6.5

[a]Rating scale, 1 = lowest intensity; 10 = highest intensity. Averaged over two tests.
[b]Two separate experimental sessions.

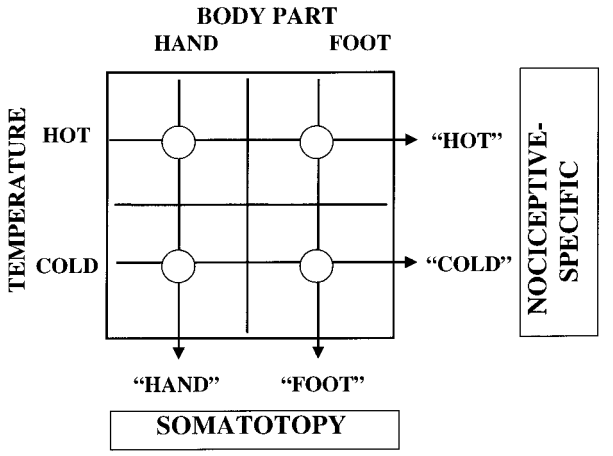


FIG. 1. The strategy for isolating cortical activity associated with somatotopic and nociceptive-specific factors. Circles indicate the four experimental conditions and the horizontal and vertical arrows indicate the factorial partitions that yield nociceptive (rows) and somatotopic (columns) components.

comparison with the human brain atlas.[25] To assign boundaries for the somatosensory cortex, we identified the anterior (central sulcus) and posterior (posterior border of postcentral gyrus) flanking sulci which is the hallmark of the primary somatosensory cortex. Brain activity which lay in the confines of this boundary were recorded and x-y-z Talairach sectors[25] were identified.

Results

As illustrated on three contiguous brain images acquired through primary somatosensory cortex for a typical subject, DR (Fig. 2A), we demonstrate somatotopic mapping of hand and foot as expected based on the Penfield homunculus. The hand (blue) is mapped primarily along the inferior and lateral post central gyrus (c,E,+40) (left, Fig. 2A), while the foot (purple) is mapped along the superior and medial post central gyrus (b,F,+60) (right, Fig. 2A). These activations are bounded anteriorly by the central

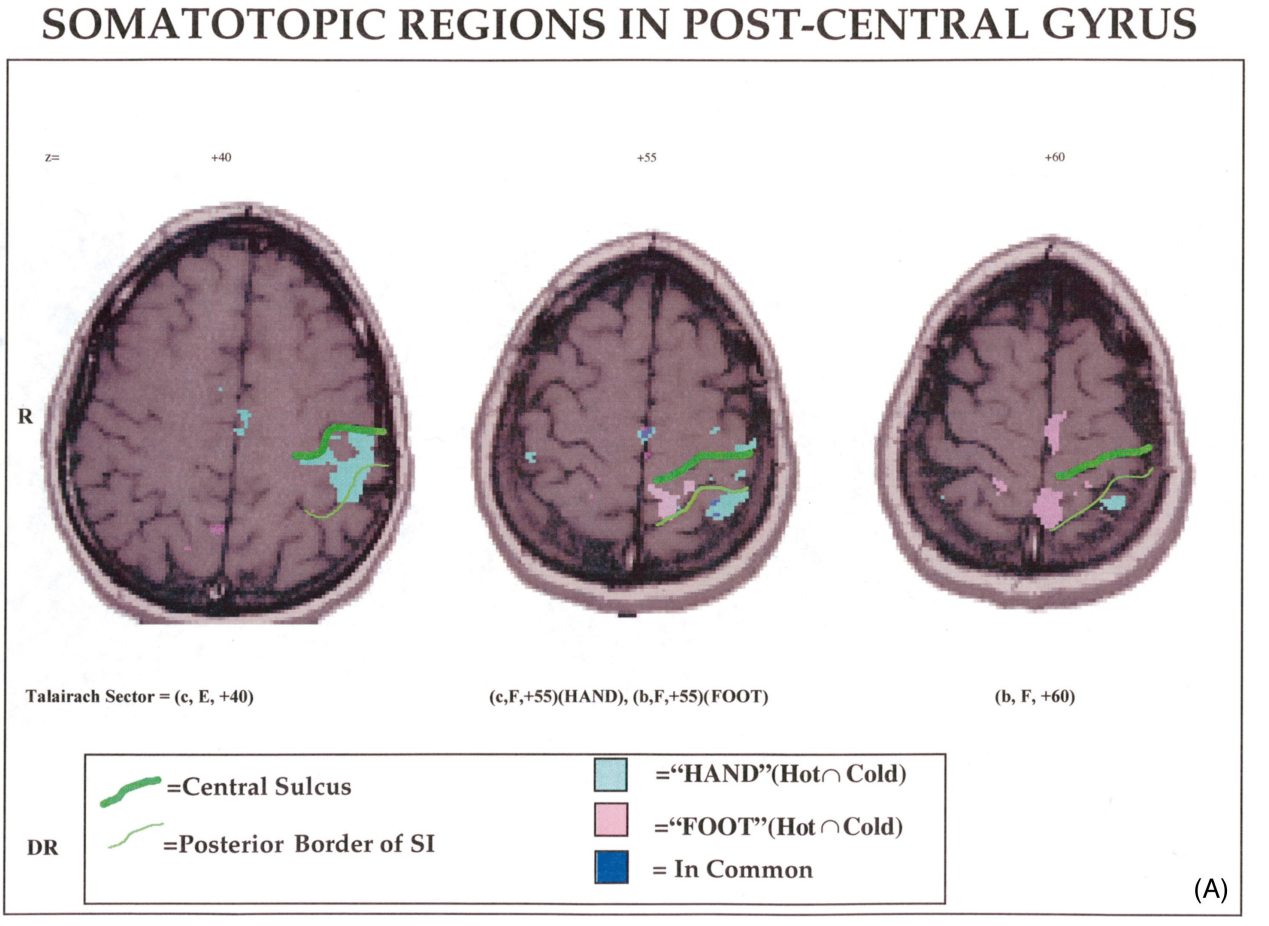


FIG. 2**A**. A somatotopic representation of hand and foot stimulation in postcentral gyrus (SI) for subject DR (columns, Fig. 1). Anatomical axial slices are at levels corresponding to z = +40,+55 and +60 from the Talairach and Tournoux atlas.[25] The Talairach coordinates for hand and foot are illustrated to identify the focal site of activation for each body part in SI. The hand (blue) is mapped along the inferior and lateral post central gyrus, while the foot (purple) is mapped along the superior and medial postcentral gyrus. These activations are bounded anteriorly by the central sulcus (dark green), and posteriorly by the posterior border of SI (light green) which is the hallmark of SI.

sulcus (dark green), and posteriorly by the posterior border of the primary somatosensory cortex (light green) which is the hallmark of the post-central gyrus. The Talairach sectors below each illustration indicate the approximate centroid location of hand and foot in standard stereotactic atlas coordinates[25] and are shown to be localized in distinct sectors with no appreciable overlap. As expected, these focal activations appeared to be predominantly contralateral to the stimulated body part. The somatotopic mapping of body parts is represented for all subjects (Table 2, rows 1 and 2) and demonstrate similar patterns of segregation.

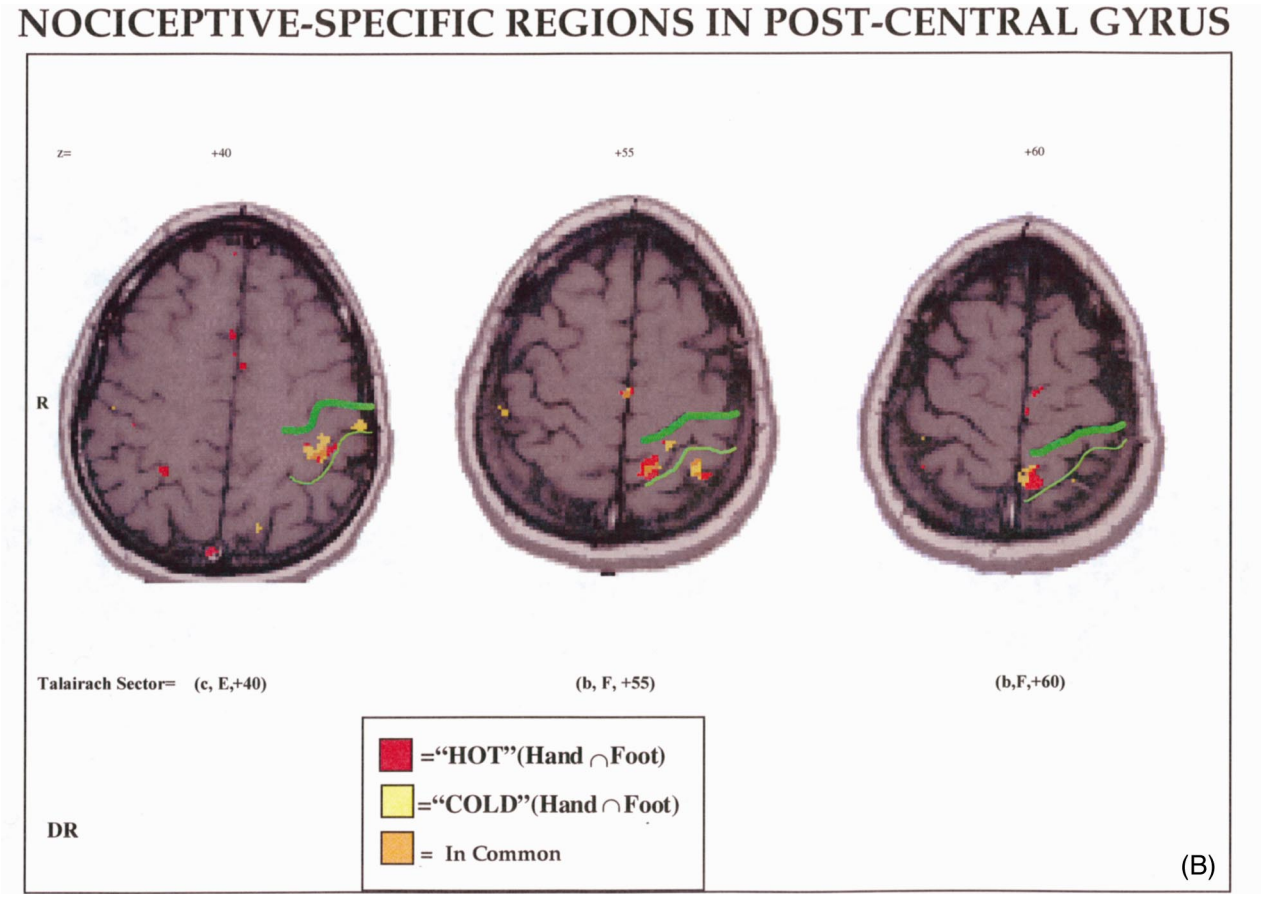
Hot (red) and cold (yellow) regions in primary somatosensory cortex are indicated in Fig. 2B for subject DR and isolate those activations common to hand and foot (Fig. 1, rows). As in Fig. 2A, SI is bounded by the anterior central sulcus and posterior border of SI. We observed a pronounced overlap of hot and cold sensations which is represented as orange in the figure. As seen with the somatotopic activity (Fig. 2A), thermal activation is predominantly contralateral to the stimulated body part.

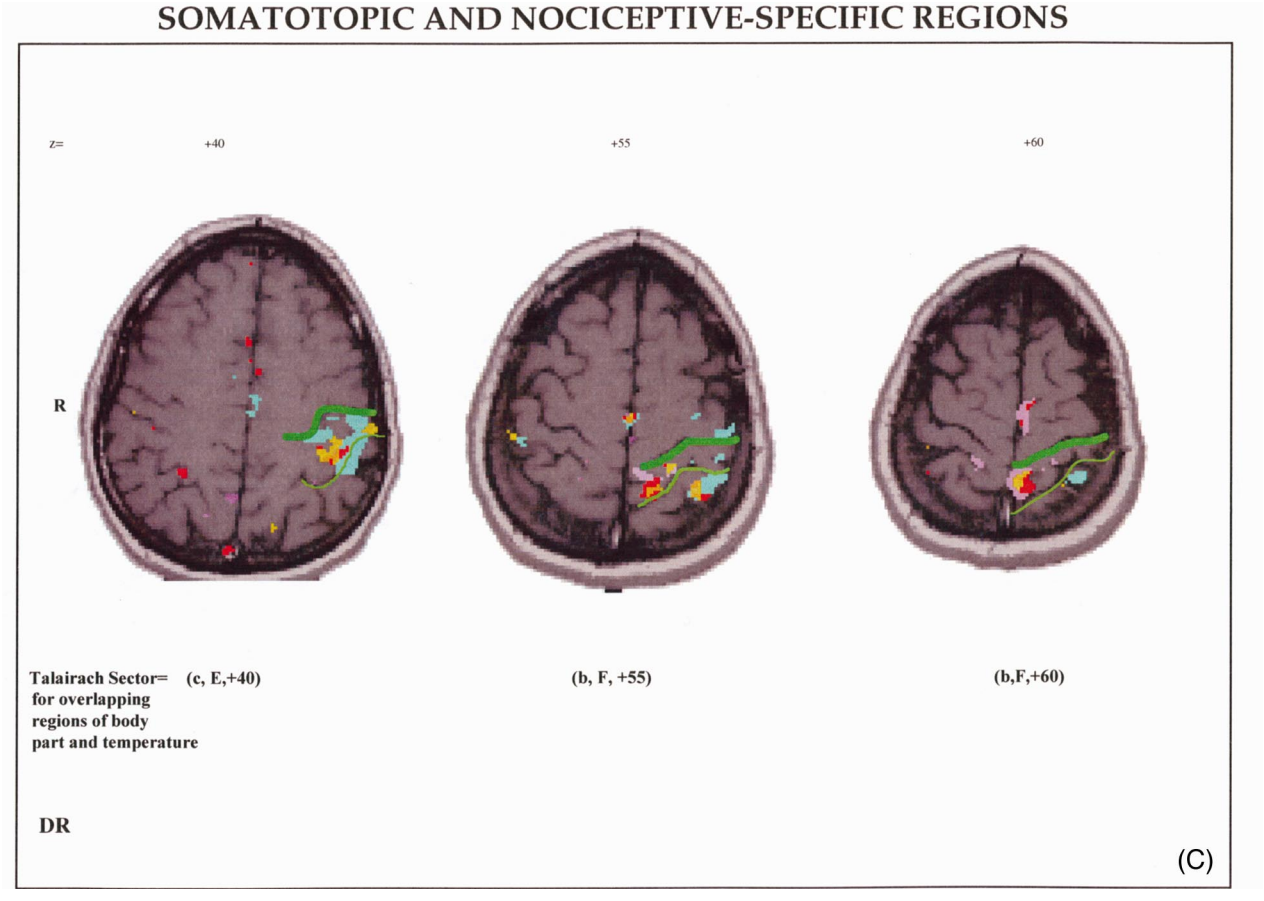
FIG. 2. (**B**) A nociceptive-specific representation of hot and cold stimulation in postcentral gyrus (SI) for subject DR (rows, Fig. 1). Anatomical axial slices are at levels corresponding to z = +40,+55 and +60). As in (A), SI is bounded by the anterior central sulcus and the posterior border of SI. Talairach coordinates for hot and cold document the localization of these modalities in SI. (**C**) Activity from (B) is represented on top of activity from (A), illustrating that the nociceptive thermal modalities hot (red) and cold (yellow) are located in regions adjacent to or superimposed on that of both body parts hand (blue) and foot (purple) on slice +40,+55, and +60.

Table 2. Talairach and Tournoux sectors of activity found in somatosensory cortex

Condition	(CC) (x,y,z)	(MB) (x,y,z)	(MC) (x,y,z)	(WT) (x,y,z)	(DR) (x,y,z)	(EB) (x,y,z)	(DV*) (x,y,z)	(AF) (x,y,z)	(DV)* (x,y,z)
Somatotopy									
Hand (Hot∩cold)	(c,F,+50)	(d,E,+28) (d,E,+32) (d,E,+35) (c,E,+40) (c,E,+45)	(c,E,+45) (c,F,+55)	(c,E,+45)	(d,E,+32) (d,E,+35) (c,E,+40) (c,E,+45) (c,E,+50)	(d,E,+32) (d,E,+35) (c,E,+40) (c,E,+45) (c,F,+50) (c,F,+55)	(d,E,+28) (d,E,+32) (c,E,+35) (c,E,+40) (c,E,+45)	(d,E,+32) (d,E,+35) (c,E,+40) (c,E,+45) (c,F,+50) (c,F,+55)	–
Foot (Hot∩cold)	(a,F,+65)	(b,F,+60)	(a,F,+65)	(a,F,+60) (a,F,+65)	(d,E,+32) (b,F,+50) (b,F,+55) (b,F,+60)	(d,E,+32) (d,E,+35) (c,E,+40) (a,F,+65)	(d,E,+28) (d,E,+32) (c,E,+35) (c,E,+40) (a,F,+60)	(d,E,+32) (d,E,+35) (b,F,+55) (a,F,+60) (a,F,+65)	–
Nociceptive-Specific									
Hot (Hand∩foot)	(c,E,+55) (c,F,+50)	(d,F,+55) (d,F,+60)	(c,E,+45)	(c,E,+35)	(d,E,+32) (c,F,+35) (c,E,+40) (b,F,+50) (b,F,+55)	(d,E,+32) (d,E,+35) (c,E,+40) (c,E,+45) (c,F,+55) (c,F,+60)	(d,E,+28) (d,E,+32) (c,E,+35) (c,E,+40) (c,E,+45)	–	–
Cold (Hand∩foot)	(b,F,+65)	(d,E,+28) (d,E,+35) (c,E,+45) (b,F,+55) (b,F,+60)	(c,E,+45) (c,F,+55)	(c,E,+40) (a,F,+60)	(d,E,+32) (c,E,+40) (c,E,+45) (b,F,+55)	(d,E,+32) (d,E,+35) (c,E,+40) (c,E,+45) (c,F,+55) (c,F,+60)	(d,E,+28) (d,E,+32) (c,E,+35) (c,E,+40) (c,E,+45)	(d,E,+32) (d,E,+35) (c,E,+45) (c,F,+50)	–
Warm (Hand∩foot)	–	–	–	–	–	–	–		(c,E,+35) (c,E,+40) (c,E,+45)
Cool (Hand∩foot)	–	–	–	–	–	–	–		(c,E,+35) (c,E,+40) (c,E,+45)
Scrubber (Hand∩foot)	–	–	–	–	(c,E,+45)	–		(d,E,+32) (d,E,+35) (c,E,+45) (c,F,+50)	–

*Two separate experimental sessions for DV


NOCICEPTIVE-SPECIFIC REGIONS IN POST-CENTRAL GYRUS
z=
+40
+55
+60
R
Talairach Sector= (c, E,+40)
(b, F, +55)
(b,F,+60)
="HOT"(Hand ∩Foot)
="COLD"(Hand ∩Foot)
= In Common
DR
(B)


SOMATOTOPIC AND NOCICEPTIVE-SPECIFIC REGIONS
z=
+40
+55
+60
R
Talairach Sector= (c, E,+40)
for overlapping
regions of body
part and temperature
(b, F, +55)
(b,F,+60)
DR
(C)

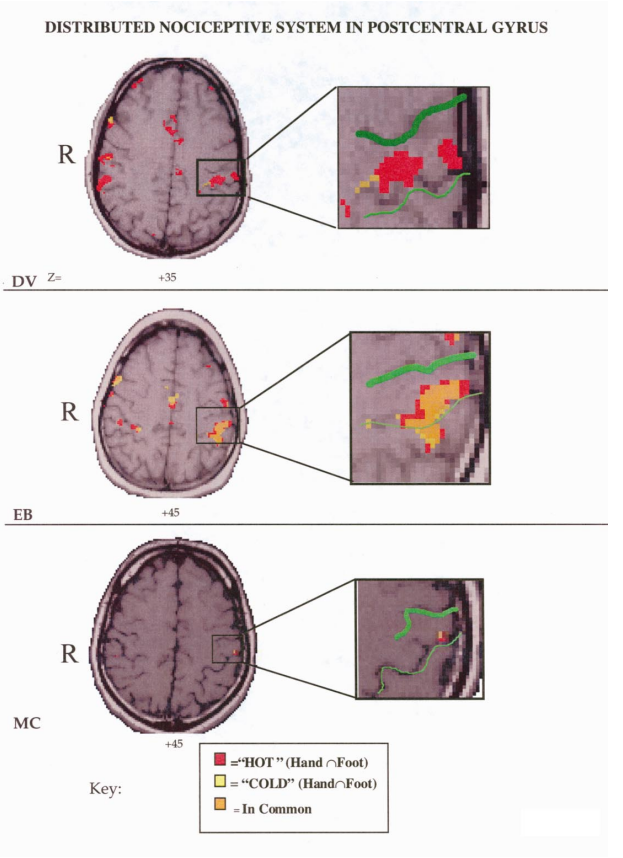


FIG. 3. Illustrations of the distributed nociceptive system for hot and cold in postcentral gyrus for three subjects. Anatomical axial slices are illustrated for each subject (DR = +55, EB = +45, DV = +35). The thick dark green line indicates the central sulcus boundary and the thin light green line indicates the posterior border.

To compare the spatial and functional relationship of the somatotopic and nociceptive-specific activations for subject DR, we combined Figs. 2A and 2B for each of the 3 slices (Fig. 2C). For each slice, hot and cold activations are found in a similar spatial localization to that of the body parts; however, there is not a complete overlap. Both hot and cold activations are found in the hand and foot representations, illustrating diffuse activation of thermal sensation that is not specific for the body region directly stimulated. For example, the hand representation (z = +40) overlaps both hot and cold activations. Similarly, the foot representation (z = +55,+60) overlaps with these same thermal modalities. Similar findings were observed for all eight subjects: three are illustrated in Fig. 3, and all Talairach and Tournoux coordinates[25] are represented in Table 2. By comparing the sectors of hand and foot, illustrated in the somatotopy rows in Table 2, it is evident, with only a few exceptions, that there is no overlap between each body region (a focal activation). However, the representations of hot and cold seen in the nociceptive-specific rows, are not specific to a body region (a distributed activation), residing both within and adjacent to the hand and foot representations.

In order to examine the effect of intensity on the distributed thermal phenomenon seen in the primary somatosensory cortex, we compared a mild thermal stimulus (warm and cool) with a perceived magnitude of stimulation of 4 compared to 7 for hot and cold for subject DV (Table 1). Figure 4 compares the cortical representations for two intensities of thermal stimuli, hot and warm and cold and cool. Two slices (z = +35 and +50) are selected to illustrate the main findings. Even though separate experimental sessions were run for each thermal intensity, the activity for hot and cold stimulation was spatially very similar to that of warm and cool stimulation confirming the expected reproducibility of the data. It is evident, however, that the higher intensity thermal stimuli elicited a larger activation (more area). Fig. 5 compares the number of voxels in the primary cortex activated during low and high intensity stimulations for each thermal sensation (Fig. 1 rows, 5a) and body part (Fig. 1 columns, 5b). Hot and cold (black bar, 5a) nociceptive-specific activations were significantly larger in area than that of warm and cool (white bar, 5a) activations indicative of an intensity effect. However, there was no such proportional increase in magnitude for each body part (hand and foot) corresponding to the nociceptive (black bar) and neutral (white bar) thermal conditions (Fig. 5b).

Discussion

The somatotopic organization of the human primary somatosensory cortex is well understood.[1,19,20] The dorsal column-medial lemniscal system, which relays tactile information, ascends within a brain stem pathway, the medial lemniscus, to eventually synapse on the ventral posterior nucleus of the thalamus.[20] These neurons project, in an orderly somatotopic fashion, to the primary somatosensory cortex (SI), to encode the intensity, duration, and location of the external stimulus.[21] Consistent with this projection pattern, a tactile stimulus applied to the hand or foot in this study elicited a focal, non-overlapping signal in the respective contralateral hand or foot region of SI.

The results from the current experiment show that thermal sensations are indeed represented in the somatosensory cortex; however, in a pattern that extends beyond somatotopy. For example, a thermal stimulus applied to the hand or foot elicits an overlapping signal in both the contralateral hand and foot representations of SI. This distribution of thermal sensations over both hand and foot body representations (Fig. 2c) in SI suggests that while somesthetic information ascends via discrete fibers to its unique

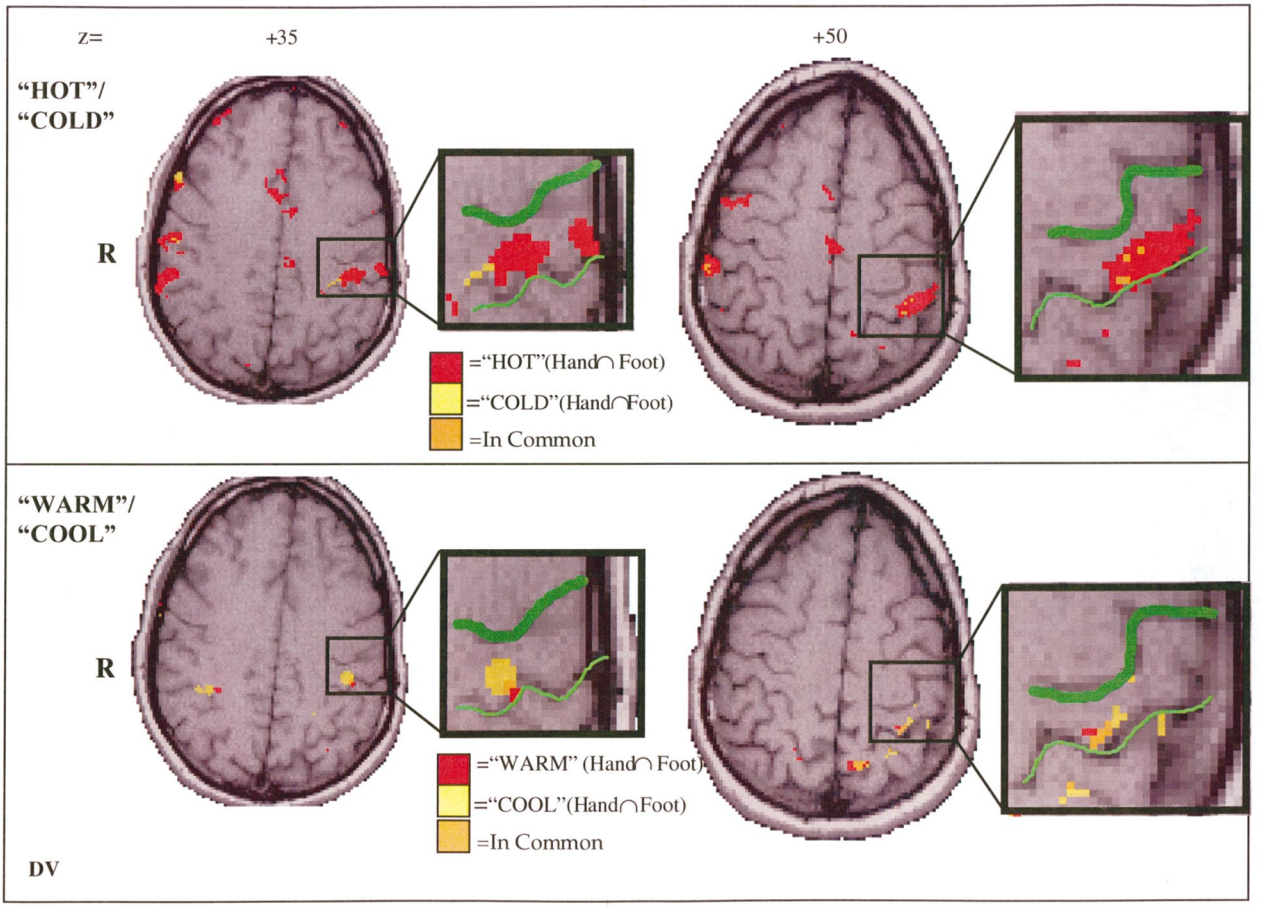


FIG. 4. A comparison of two intensities of thermal stimuli in subject DV (hot 56–58°C/cold 0–2°C; and warm 30–32°C/cool 15–20°C). Two slices are selected (z =+35 and z = +50) to illustrate the main finding that both thermal intensities are distributed in SI relative to the somatotopic condition.

body area, thermal sensations may show diffuse connectivity. These results are in agreement with a preliminary fMRI report which illustrates overlapping hand and foot representations in response to thermal pain.[18]

Our findings indicate that the distributed SI representation of thermal sensation is not dependent on temperature intensity as both nociceptive (hot/cold; Figs. 2b,3) and neutral (warm/cool) thermal conditions had a non-somatotopic distribution in SI (Fig. 4). Activations during the less intense conditions were not as extensive in SI than during the nociceptive stimulation and appear to vary according to the perceived stimulus magnitude (Fig. 5). These observations are consistent with the recent results of another fMRI study where a similar correlation between painful stimuli and non-painful stimuli was observed and these magnitudes paralleled the pain rating VAS score.[22] The cortical response to higher intensity stimuli depicted in the nociceptive-specific condition (distributed; Fig. 5a), was considerably larger than that seen in the somatotopic condition (local; Fig. 5b), and suggests a thermal intensity effect that is differentiated for distributed and focal processing.

The observation that the representation of thermal information in SI is not strictly somatotopically arranged suggests that while this region may not serve a primary role in localizing temperature to a specific body part, it does mediate the flow of thermal information. The spinothalamic pathway (STT) is a major direct pathway mediating pain and temperature sensation to the thalamus.[23] The cells within the ventrobasal complex project heavily to SI; however, the topography and spatial mapping of these connections to the cortex and beyond remains unknown as few anatomical studies have focused on this issue. In order to further understand the flow of thermal information, further anatomical work is required.

It has been proposed that one role of the paleospinothalamic tract is to mediate arousal.[20] We observed a similar distribution pattern over multiple body regions in SI for a tactile scrubber stimulus. This suggests that a high-threshold tactile stimulus can feed into the paleospinothalamic system to arouse the sensory cortex and affect a modifying behavior.

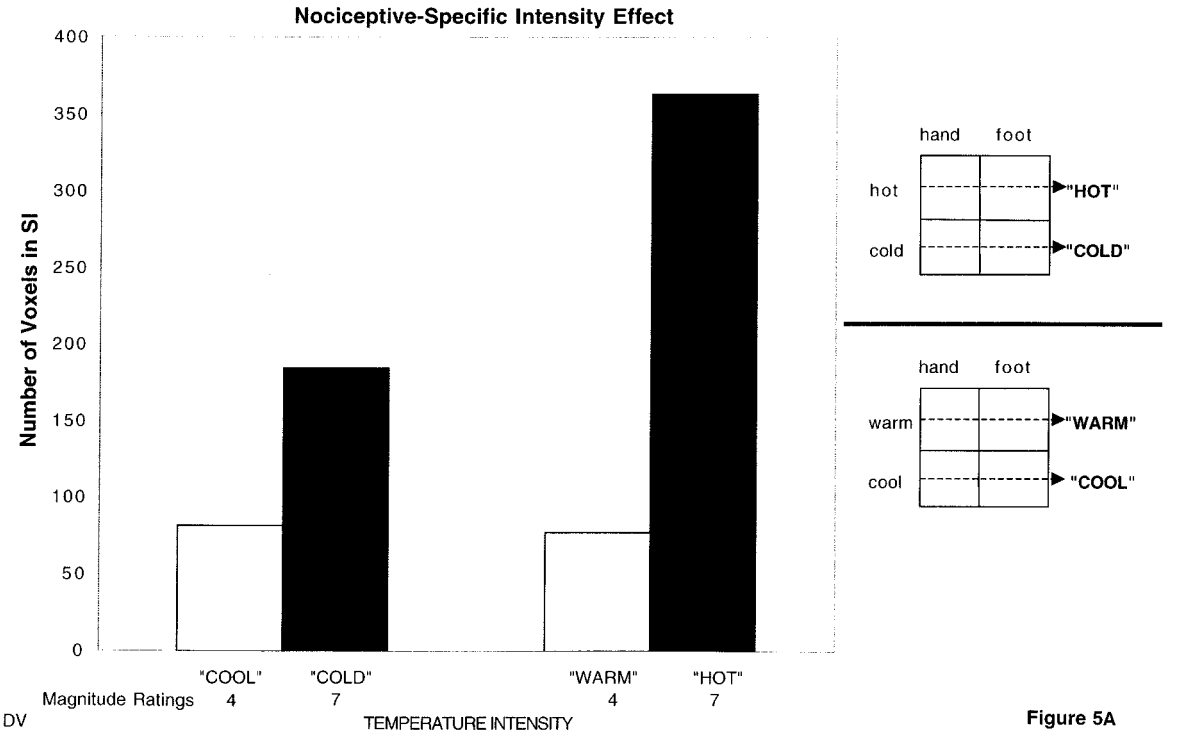


Figure 5A

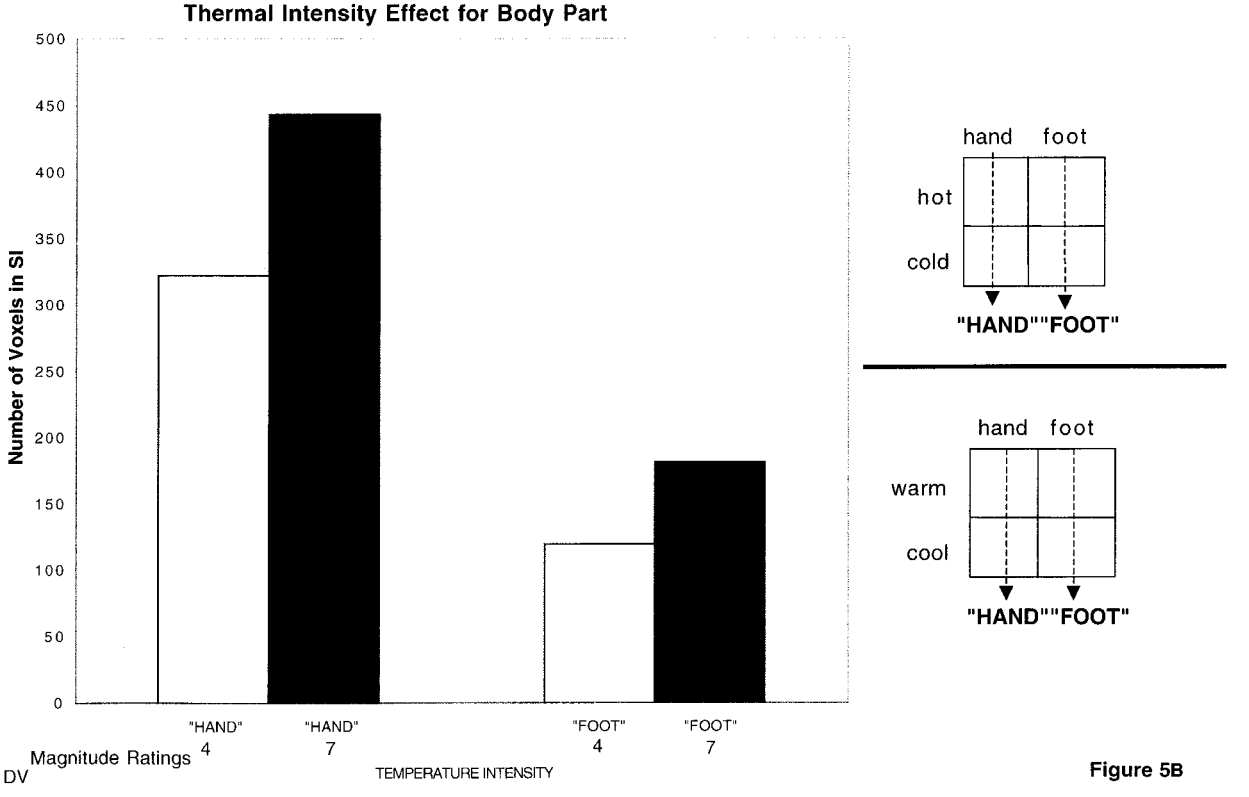


Figure 5B

While some thermal stimuli may have an arousal component (i.e. nociceptive), others clearly do not (i.e. thermal neutral stimuli) suggesting that the distribution of thermal sensations in SI is not exclusively due to an arousal response; instead it may be part of a normal mechanism in the processing of thermal information.

Conclusion

We show that SI plays a unique role in both nociceptive and low intensity thermal processing. A distributed thermal processing system that overlays a focal somesthetic system is demonstrated in humans. These data suggest that thermal qualities are not processed in a strict somatotopic arrangement, in contrast to the mapping of body parts. Instead, a distributed system for thermal stimulation exists in SI that is not spatially restricted to the stimulated body part. This finding furthers the conventional model of somatotopy and may contribute to understanding the complex nature of thermatosensory processing in the brain.

References

1. Penfield W and Rasmussen. *The Cerebral Cortex in Man*, 1st edn. London: Macmillan, 1950.
2. Reivich M, Gur R and Alavi A. *Hum Neurobiol* **2**, 25–33 (1983).
3. Fox PT, Miezen FM, Allman JM *et al. J Neurosci* **7**, 1913–1922 (1987).
4. Head H and Holmes G. *Brain* **34**, 102–254 (1911).
5. Penfield W. *Brain* **60**, 389–343 (1937).
6. Duclaux R, Franzen O, Chatt AB *et al. Brain Res* **78**, 279–290 (1974).
7. Chatt AB and Kenshalo DR. *Exp Brain Res* **28**, 449–455 (1977).
8. Kreisman NR and Zimmerman ID. *Brain Res* **25**, 184–187 (1971).
9. Hellon RF and Provins KA. *J Physiology* **224**, 477–487 (1972).
10. Marshall J. *J Neurol Neurosurg Psychiatry* **14**, 187–204 (1951).
11. Iwata K, Tsuboi Y, Muramatsu H and Sumino R. *J Neurophysiology* **64**, 822–834 (1992).
12. Talbot J, Marrett S, Evans A *et al. Science* **251**, 1355–1357 (1991).
13. Svennson P, Minoshima S, Beydoun A *et al. J Neurophysiol* **78**, 450–460 (1997).
14. Morin C, TenBokum L and Bushnell MC. *Soc Neurosci Abstr* **20**, 127 (1994).
15. Woods RP, Mazziotta IC and Cherry SR. *J Comput Assist Tomogr* **17**, 336–346 (1993).
16. Hirsch J, DeLaPaz, Relkin N *et al. Proc Natl Acad Sci USA* **92**, 6469–6473 (1995).
17. Kim K, Relkin N, Lee KM *et al. Nature* **388**, 171–174 (1997).
18. Darbar A, Krauss BR, Szeverenyi NM *et al. Neuroimage Poster Sessions* s423 (1998).
19. Sakai K, Watanabe E, Onodera Y *et al. Magn Reson Med* **33**, 736–743 (1995).
20. Kandel E, Schwartz J and Jessell T. *Principles of Neural Science* 3rd edn. Amsterdam: Elsevier, 1991.
21. Bear M, Connors B and Paradiso M. *Neuroscience, Exploring the Brain*. New York: Williams & Wilkins, 1996.
22. Oshiro Y, Fuijita N, Tanaka H *et al. NeuroReport* **9**, 2285–2289 (1998).
23. Fitzgerald MJT. *Neuroanatomy Basic and Clinical*, 3rd edn. Philadelphia: WB Saunders, 1996.
24. Oldfield RC. *Neuropsychologia* **9**, 97–113 (1971).
25. Talairach J and Tournoux P. *Co-planar Stereotaxic Atlas of the Human Brain*. New York: Thieme, 1988.

ACKNOWLEDGEMENTS: We are grateful to our colleagues Dr Norman Relkin, Dr Maximillian Ruge, Ray Cappiello, Steve Chun, and Diana Rodriguez-Moreno for intellectual and technical contributions. Supported by the William T. Morris Foundation Fellowship, NIH MSTP grant GM07739, the Cornell/Rockefeller/Sloan-Kettering Tri-Institutional M.D.-Ph.D. Program (KHSK); the Charles A. Dana Foundation, Johnson & Johnson Focused Giving Foundation, Cancer Center Support Grant NCI-P30-CA-08748 (JH).

Received 23 September 1998; accepted 22 October 1998

FIG. 5. (**A**) A comparison of the total number of voxels activated during low (warm/cold, white bars) and high (hot/cold, black bars) intensity stimulations for each thermal sensation (Fig. 1, rows). An intensity effect is demonstrated in which the total number of voxels in the hot condition exceeded the warm state by a factor of 4.7; similarly, the number of cold voxels exceeded the number of cool voxels by a factor of 2.3. (**B**). A comparison of the total number of voxels activated for each body part (hand and foot) corresponding to nociceptive (black bar) and neutral (white bar) thermal intensities. There was only a slight intensity increase in which the total number of voxels in hand and foot (hot/cold state) exceeded the number of voxels in the warm/cool state by a factor of only 1.4 and 1.5 respectively. However, the proportional increase of voxel intensity was not as large as in (A).