Anteroposterior somatotopy of innocuous cooling activation focus in human dorsal posterior insular cortex

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THERMAL SENSATIONS IN HUMANS (i.e., sensations of cool, warm, cold, and hot) are important for tactile recognition of objects and for homeostatic control of body temperature, functions that are traditionally differentiated as exteroceptive and interoceptive, respectively (28). The exteroceptive aspect of (innocuous and noxious) thermal sensibility has been regarded as a capacity of the somatosensory system, allied with the sense of touch. Specifically, it has been thought that the haptic abilities to discriminate different temperatures and to localize thermal stimuli on the body must involve the somatotopically well-organized system that represents discriminative cutaneous mechanoreception (23, 43). This has been an explicit presumption at least since Weber's analysis of somatic sensation in 1846 (47).

However, recent findings indicate that the cortical substrate for discriminative innocuous thermal sensation is not part of the somatosensory cortices but, rather, is located in the insula, which is associated with autonomic control (14). This site is the terminus of a spinothalamocortical pathway, phylogenetically distinct to primates and highly developed in humans, that is an expansion of a homeostatic afferent system representing the physiological condition of the body (16). These new findings fundamentally revise our understanding of the neural representation of feelings from the body (16).

To verify and extend these findings, we used functional magnetic resonance imaging (fMRI) to examine thermosensory activation sites in the dorsal posterior insula (dPIns). Our central hypothesis is that if the thermosensory representation in the dPIns participates in the haptic function of localization as well as discrimination, then it should be somatotopically organized. In this initial study, we used cooling stimulation at two body sites. On the basis of the tract-tracing data in the monkey (11), we anticipated finding a somatotopic gradient organized in the anteroposterior direction.

MATERIALS AND METHODS

The data were obtained from 15 healthy, right-handed subjects (6 men and 9 women) between 19 and 41 (mean 27.3) yr of age. All subjects signed consent forms approved by the Barrow Neurological Institute's institutional review board. Before imaging, each subject was screened for the ability to discriminate different innocuous cool temperatures (28, 25, and 22°C).

Imaging procedures. For fMRI data acquisition, subjects lay supine in the 3.0-T magnetic resonance scanner (Signa, General Electric) with eyes closed, ears plugged, and head held firmly in place by foam pads and tape straps. A fiducial was applied to the left forehead. Blankets and scarves were used to minimize thermosensory contamination by the ventilation inside the scanner. During the fMRI session, each subject received stimulation from a large Peltier-type thermode (30 × 30 mm; model TSA-II, Medoc, Ramat-Yishai, Israel) situated on the right thenar hand and with a different thermode (16 × 16 mm) situated on the right lateral neck. Both thermodes were fixed in place with tape.

A single functional scan was collected using hand stimulation, followed by one using neck stimulation. The stimulus sequence during each functional scan consisted of six presentations of an innocuous cooling stimulus that ramped linearly from 33 to 23.25°C at 0.25°C/s (39-s duration, or 13 functional image volumes at TR = 3 s) and then a return to the baseline temperature of 33°C (−1°C/s, 18-s total duration), interleaved with 30-s periods at the baseline temperature; homeostasis; interoception; thermoregulation; functional imaging

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baseline (Fig. 1). A single functional scan using foot brush (block paradigm, 15 s on-15 s off) was collected between the two cooling scans to provide an interval between cooling scans and as an internal control. To ensure that the subjects were attentive to the thermal stimuli, they were verbally alerted 5–10 s before the onset of each cooling stimulus, and they were asked to rate the intensity of each stimulus on a standard scale of 0–10. The ratings were collected at the end of each functional run. In two subjects, the thermode on the neck did not maintain the correct position, and the cooling stimuli were not perceived; those two subjects were excluded from the analysis of neck stimulation.

Functional magnetic resonance scans using blood oxygenation level-dependent (BOLD) contrast were obtained with a T2*-weighted single-shot gradient echo echo-planar pulse sequence (TR = 3 s, TE = 30 ms, flip angle = 90°, 64 × 64 matrix, field of view = 240 mm, native voxel size = 3.75 × 3.75 mm in plane). Thirty-two contiguous 4-mm-thick slices were acquired in the axial plane, parallel to the anterior-posterior commissure line, covering the whole brain volume. This produced 78 (i.e., 13 × 6) BOLD image volumes during cooling of each body site for each subject. A T1-weighted anatomic (structural) scan with 92 axial slices covering the whole head was obtained at the end of the scanning session.

Analysis methods. The functional images were analyzed using SPM2 (25, 26). The first two frames were discarded to allow for field stabilization. Each series of functional images was corrected for motion and realigned to the first volume in each scan sequence. The series was then spatially coregistered to the echo-planar image (EPI) template in SPM2 in standard Montreal Neurological Institute (MNI) space (24), resampled at 2 × 2 × 2 mm, and smoothed with an 8-mm full-width half-maximum isotropic Gaussian kernel. Signal intensity was globally normalized across each series, high-pass filtered at 128 s, and corrected for serial correlations using the autoregressive model (1).

Statistical analyses were carried out using the general linear model (25). The time series of each voxel was fitted to the stimulus temperature function using a boxcar and 2) a user-specified regressor, convolved with the standard hemodynamic response function (hrf) provided by SPM2. The ON period used in the boxcar analysis was identical to the period of the cooling ramp (excluding the rewarming period), and the OFF period was the asymmetric baseline period. The user-specified regressor was a linearly increasing ramp designed to model the temperature gradation of the cooling ramp on the basis of the hypothesis that this causes a linearly increasing BOLD signal (Fig. 2, top). The results of the regression analysis from the individual subjects were subsequently combined in a second-order random-effects model (1-sample t-test) for group analysis.

To compare directly the somatotopography of loci activated by stimulation of the two different body sites, i.e., hand and neck, we performed directed region-of-interest (ROI) analyses. On the basis of previous imaging results (14), the ROI was defined, using the MarsBar toolbox for SPM2 (4), as a sphere centered in the dpIns (at MNI -38, -24, 14) with a 15.0-mm radius. The results from the ROI analyses for each body locus were superimposed on a single subject anatomic volume to create a somatotopographic image.

Peaks with P < 0.05 and a minimum cluster size of 2 voxels for ROI small-volume analyses were regarded as significant. Exploratory whole brain analyses used a significance threshold of P < 0.001 (uncorrected) and a minimum cluster size of 10 voxels. All significant peaks are reported.

RESULTS

Figure 3 presents the global activation map from the group regressor analysis for hand stimulation, displayed at a threshold of P < 0.001 (t = 3.79, cluster size ≥10). All peaks are described in Table 1. The glass brain clearly shows two strong activation sites: the dpIns (highlighted in the three-dimensional display in Fig. 3, bottom left; t = 6.51, P < 0.0001; centered at MNI -38, -24, 14) and the dorsal medial cortex (highlighted in the three-dimensional display in Fig. 3, bottom right; t = 8.58, P < 0.0001; centered at MNI -8, 18, 58). Smaller, weaker activation clusters were also noted in the right dorso-lateral prefrontal cortex and the right anterior insula.

By contrast, the boxcar analysis (not shown) revealed strong activation mainly in the posterior parietal cortex...
bilaterally (which has been associated with spatial attention) (14) and the cerebellum. Activation in the dpIns and dorsal medial cortex was below statistical threshold. Because a boxcar model does not fully account for dynamic change within epochs of cooling, the contrast between this result and the result from the regressor analysis underscores the direct, linear relation between decreasing cool temperature and increasing BOLD activation in the dpIns and dorsal medial cortex revealed by the regressor analysis.

The time course of the aggregate BOLD signal in the dpIns ROI (defined below) is shown in Fig. 2, bottom, plotted over the convolution product of the linear regressor and the hrf model; these are clearly parallel. In other words, the BOLD signal in the dpIns activation focus showed linearly increasing activation that directly corresponded to the linearly decreasing (cool) stimulus temperature.

Figure 4 presents the global result of the group regressor analysis for neck stimulation in 13 subjects (2 were excluded). Neck stimulation resulted in graded activation of the dpIns ($t = 2.44, P = 0.015$, centered at MNI $38, -16, 14$). The neck activation data show considerable noise, presumably due to movement-related artifact. The contrast between these data and the hand cooling data emphasizes the benefits obtained with use of a larger thermode and a larger sample size in the hand data. (We do not suspect that the reduced activation in the dpIns was due to the fixed order of presentation, because in preliminary trials, serially repeated scans with hand stimulation at comparable intertrial intervals produced similar results.) Notably, graded activation was not observed in the sensorimotor cortices in the

Table 1. Activation loci correlated with dynamic hand cooling regressor

<table>
<thead>
<tr>
<th>Brain Region</th>
<th>Talarach Coordinate</th>
<th>MNI Coordinate</th>
<th>t-Statistic</th>
<th>Cluster Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>L dorsal medial</td>
<td>−8, 20, 52</td>
<td>−8, 18, 58</td>
<td>8.28</td>
<td>235</td>
</tr>
<tr>
<td>L posterior insula</td>
<td>−38, −22, 14</td>
<td>−38, −24, 14</td>
<td>6.51</td>
<td>137</td>
</tr>
<tr>
<td>R dorsolateral prefrontal</td>
<td>55, 32, 21</td>
<td>56, 32, 24</td>
<td>4.45</td>
<td>94</td>
</tr>
<tr>
<td>(BA46)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R anterior insula</td>
<td>38, 17, −8</td>
<td>38, 18, −8</td>
<td>4.35</td>
<td>93</td>
</tr>
<tr>
<td>R orbitofrontal (BA10)</td>
<td>44, 51, 5</td>
<td>44, 52, 8</td>
<td>4.52</td>
<td>59</td>
</tr>
<tr>
<td>L temporal lobe (BA22)</td>
<td>−63, −9, 6</td>
<td>−64, −10, 6</td>
<td>5.19</td>
<td>32</td>
</tr>
<tr>
<td>L anterior insula</td>
<td>−42, 13, −14</td>
<td>−42, 14, −14</td>
<td>4.76</td>
<td>27</td>
</tr>
<tr>
<td>R middle insula</td>
<td>44, −6, −5</td>
<td>44, −6, −6</td>
<td>4.60</td>
<td>22</td>
</tr>
<tr>
<td>R inferior parietal (BA40)</td>
<td>63, −22, 23</td>
<td>64, −24, 24</td>
<td>4.34</td>
<td>12</td>
</tr>
<tr>
<td>R caudate</td>
<td>10, 8, 3</td>
<td>10, 8, 4</td>
<td>4.31</td>
<td>10</td>
</tr>
</tbody>
</table>

L, left; R, right, MNI, Montreal Neurological Institute.
Rolandic area (S1/M1) or parietal operculum (S2/PV) in the global analyses using hand or neck stimulation.

The neck cooling data can be didactically masked with an ROI over the dpIns, because a directed search in the dpIns is justified by the evidence from the previous PET imaging study (14). The ROI mask used a 15-mm-radius sphere centered at MNI $-38, -24, 14$ (Fig. 4, right). The activation in the neck cooling data within the dpIns ROI survives the significance cutoff of $P < 0.05$ used for small-volume corrections.

By masking the neck and the hand cooling statistical parametric mapping data with the same dpIns ROI and simultaneously superimposing the results on a standard single subject anatomic volume, the composite image shown in Fig. 5 was obtained. The neck cooling focus is shown in green and the

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**Fig. 4.** Left: SPM plots showing activation in the dpIns and other sites by graded neck cooling. Right: ROI plotted on a standard anatomic volume.

**Fig. 5.** Somatotopographical organization of hand (red) and neck (green) activation foci in the dpIns superimposed on a standard anatomic volume.
DISCUSSION

The present data provide significant support for our hypothesis that the innocuous thermosensory representation in the dPlns is somatotopographically organized with an anteroposterior gradient. These data indicate that this cortical thermosensory representation can subserve localization as well as discrimination.

The haptic capacities of discrimination and localization that are such perceptually obvious aspects of human thermal sensation have traditionally been regarded as its primary characteristics; therefore, thermal sensation has been categorized conceptually with the discriminative sense of cutaneous touch and has been thought to involve the somatosensory cortices. By contrast, the homeostatic functions of thermal sensibility have traditionally been relegated to “lower” portions of the central nervous system, e.g., the hypothalamus and brain stem. However, the primal role of temperature sensation throughout evolution (to enable adaptive responses to the effects of temperature on metabolism) is an essential capacity for all animals. Amoebas, worms, fish, and reptiles thermoregulate. In mammals, the maintenance of core temperature is absolutely critical for homeostasis and survival. The deep significance of this evolutionary perspective is substantiated by the finding that the discriminative thermosensory cortex of the dpIns to participate in discriminative cooling sensation. The recognition that the discriminative thermosensory cortex lies in the dPlns is striking because of the association of the insular cortex with autonomic control, rather than somatosensory functions. Yet, this finding is consistent with the emerging view that ascending lamina I projections serve as a general homeostatic afferent pathway conveying activity that represents nutritive afferents (2, 27, 45).

The thermoreceptive-specific lamina I STT neurons project by way of the lateral STT, and lesions of this pathway in cats and humans selectively eliminate contralateral thermal sensation (17, 33, 37). In monkeys, anatomic and physiological findings indicate that thermoreceptive-specific lamina I neurons project to the posterior part of the ventral medial (VMpo) nucleus in the posterolateral thalamus with an anteroposterior (head-to-foot) topography (13, 17, 22). Recordings of thermoreceptive-specific VMpo units in monkeys confirm these observations (10, 13). Furthermore, similar units have been recorded in the region of the human VMpo (also called the “posterior-inferior region of the ventral caudal nucleus), and graded microstimulation at such recording sites produced graded, well-localized specific thermal sensations in awake humans (19, 34, 38). Notably, thermoreceptive-specific neurons have not been identified in any other portion of monkey or human thalamus.

A laser-evoked potential study provided evidence that selective warming specifically activates the dPlns (29), and recent fMRI studies provided supplemental data supporting activation of the insular cortex by cooling and “paradoxical heat” (3, 18, 20). Notably, imaging evidence also indicates strong activation of the human dPlns by noxious cold (8, 12, 36).

Direct evidence indicating that discriminative thermal sensation is represented in the dPlns was first provided by our earlier PET imaging study in humans (14), in which a graded series of tonic cool stimuli was presented on the right hand and a global regression analysis across these temperatures was performed. The dPlns was the only site in the contralateral cortex in which graded activation that correlated directly with the stimulus temperature was observed. The present data confirm that activity in the dPlns is directly correlated with cooling stimuli, and when combined with the preceding functional, anatomic, and clinical evidence on the ascending thermosensory pathway, this finding strongly supports the unique ability of the dPlns to participate in discriminative cooling sensation. The recognition that the discriminative thermosensory cortex lies in the dPlns is striking because of the association of the insular cortex with autonomic control, rather than somatosensory functions. Yet, this finding is consistent with the emerging view that ascending lamina I projections serve as a general homeostatic afferent pathway conveying activity that represents numerous aspects of the physiological condition of the body (16). This finding is consistent also with accumulating functional imaging data indicating that the dorsal insular cortex is activated by several interoceptive modalities, including exercise, cardiorespiratory activation, itch, sensual touch, hunger, thirst, taste, and “air hunger” (16), as well as muscle pain (32), heat pain (5), and cold pain.
However, this finding contrasts with the traditional view that discriminative thermal sensation is allied with the sense of touch. The haptic capacities of discrimination and localization are usually thought to require the somatotopically well-organized somatosensory representations in the parietal cortex (23). The conclusion that discriminative thermal sensation does not require participation of the somatosensory cortex begs the question as to whether the dpIns may subserve localization as well and, thus, whether the dpIns is itself somatotopically organized. The present observations provide significant support for the conclusion that the dpIns participates in the discrimination and localization of thermal stimuli, consistent with the clinical lesion data.

There are almost no other data available on the topographic organization of the dpIns. Vogel et al. (46) reported one case in which laser-evoked potentials associated with pricking pain from the face seemed to originate from a dipole located more anteriorly in the dpIns than from the dipoles associated with pain from the hand or foot. In the data reported by Ostrowsky et al. (39), sites in the dpIns at which stimulation in awake humans produced pain sensations in the face seemed to be more anterior than those that produced pain sensations in the limbs. Our present data provide the first direct evidence of somatotopy in the dpIns representation of innocuous thermal sensation. Whereas further fMRI evidence is needed to map the complete thermosensory representation, the anteroposterior somatotopic gradient indicated by our observations is consistent with the tracing evidence in the monkey on the somatotopographic organization of the input to the dpIns from the VMPo nucleus. Notably, this gradient is orthogonal to the mediolateral somatotopy of the neighboring parietal somatosensory regions (21). This distinction supports the fundamental conceptual differentiation of the interoceptive somatic representations in the dpIns from the exteroceptive somatosensory representations in parietal cortices (16, 17). This organization reflects the differentiation of afferent activity important for autonomic control of smooth muscle from activity important for sensorimotor control of skeletal muscle established during spinal ontogeny (17).

Activation of the dorsal medial cortex. The graded thermosensory activation in the dorsal medial cortex is a novel finding; it was not seen with graded tonic stimulation in our earlier PET study (14). This region does not coincide with the supplementary motor cortex but, rather, appears to be in Brodmann’s area 8, anterior and superior to the cingulate motor regions (41). We interpret this as activity related to the increasing behavioral thermoregulatory motivation caused by a dynamic cooling ramp.

Thermoregulation, which includes autonomic, neuroendocrine, and behavioral responses, has traditionally been relegated to the hypothalamus and brain stem. Our analysis of the homeostatic afferent lamina I pathways and of imaging studies of emotion (16) led to the view that the lamina I pathway has phylogenetically distinct thalamocortical projections in primates (especially well-developed in humans) that generate sensory and motivational activity in parallel. This means that not only painful, but also innocuous, thermal stimuli should produce activation of the anterior cingulate, or limbic motor cortex, associated with motivation. Such activation was not observed in our earlier PET study, perhaps because we used stable, tonic cool stimuli, but in the present study, in which we used dynamic cooling stimuli, there was very strong correlative activation in the dorsal medial cortex. Our interpretation that this activity represents the homeostatic motivation associated with thermoregulatory behavior is supported by the observation that thermoregulatory behavior is not blocked by lesions of the hypothalamus (44), whereas motivation by painful stimuli (i.e., aversive conditioning) is blocked by lesions of the anterior cingulate (30). The identification of thermosensory activation in this region of the dorsal medial cortex [which many reviewers nevertheless view as associated with “cognitive,” rather than “emotional,” behavior (40)] is a second major result of this study. Direct examinations of thermoregulatory processing by other physiologists have not yet identified this region, but further work is clearly needed (31).

Role of the dpIns in central pain. Finally, these studies also impact our understanding of the effects of lesions of the dpIns, which have been directly associated with the central pain syndrome (45). Our earlier PET identification of the dpIns as the site of the discriminative thermosensory cortex was interpreted as support for the hypothesis that thermosensory dysfunction might be the cause of the ongoing burning pain in this syndrome by disinhibition. That is, thermosensory dysfunction would impair the normal inhibition of pain by cooling, resulting in pain by the release of ongoing inhibition. This hypothesis thus suggests that central pain is actually a thermoregulatory dysfunction (14). It incorporates anatomic findings indicating that the dpIns has a major role in the control of homeostatic integration, including direct projections to critical sites in the brain stem. A cardinal (and nearly universal) feature of this syndrome is that such burning pain occurs in the region of the body where the thermosensory dysfunction is most profound (3, 16). In order for this cross-modal topographic correspondence to occur, the thermosensory representation in the dpIns (and its forebrain and descending connections) must be somatotopically organized. The present study provides direct evidence supporting this organization.

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References


