CALL FOR PAPERS | Physiology and Pharmacology of Temperature Regulation

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

Le H. Hua,1 Irina A. Strigo,1 Leslie C. Baxter,2 Sterling C. Johnson,3 and A. D. (Bud) Craig1

1Atkinson Research Laboratory and 2Neuropsychology Neuroimaging Laboratory, Barrow Neurological Institute, Phoenix, Arizona; and 3University of Wisconsin Medical School, William S. Middleton Memorial Veterans Affairs Hospital, Madison, Wisconsin

Submitted 17 February 2005; accepted in final form 29 March 2005

Hua, Le H., Irina A. Strigo, Leslie C. Baxter, Sterling C. Johnson, and A. D. (Bud) Craig. Anteroposterior somatotopy of innocuous cooling activation focus in human dorsal posterior insular cortex. Am J Physiol Regul Integr Comp Physiol 289: R319–R325, 2005. First published March 31, 2005; doi:10.1152/ajpregu.00123.2005.—Prior data indicate that graded activation by innocuous thermal stimuli occurs in the dorsal posterior insular (dIns) cortex of humans, rather than the parietal somatosensory regions traditionally thought necessary for discriminative somatic sensations. We hypothesized that if the dIns subserves the haptic capacity of localization in addition to discrimination, then it should be somatotopically organized. Using functional magnetic resonance imaging to detect activation in the dIns by graded cooling stimuli applied to the hand and neck, we found unimodal foci arranged in an anteroposterior somatotopographic pattern, consistent with participation of the dIns in localization as well as discrimination. This gradient is orthogonal to the mediolateral somatotopy of parietal somatosensory regions, which supports the fundamental conceptual differentiation of the interoceptive somatic representation in the dIns from the parietal exteroceptive representations. These data also support the suggestion that the poststroke central pain syndrome associated with lesions of the dIns is a thermoregulatory dysfunction. Finally, another focus of strongly graded activation, which we interpret to represent thermoregulatory behavioral motivation elicited by dynamic cooling, was observed in the dorsal medial cortex.

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 (dIns). Our central hypothesis is that if the thermosensory representation in the dIns 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 cost of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

http://www.ajpregu.org
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 \( \geq 10 \)). All peaks are described in Table 1. The glass brain clearly shows two strong activation sites: the dplns (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 dorsolateral 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) 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, 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 $38, 18, 14$). 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>Talaracch 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>(BA46)</td>
<td>$55, 32, 21$</td>
<td>4.45</td>
<td>94</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

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.
hand cooling focus in red. Clearly, these are arranged in a contiguous anteroposterior relation, with the neck focus centered ~8 mm anterior to the center of the hand focus. The spatial relation of the hand and neck cooling sites revealed by these data is valid and reliable, because the data were obtained in the same subjects in single scanning sessions. Foci separated by at least the width of the Hanning window can be regarded as statistically distinct (35). In addition, a paired t-test comparison of the hand and neck data showed that the activation in the more posterior dpIns focus was significantly higher during hand than during neck stimulation \((t = 4.89, P < 0.001, n = 13)\).

**DISCUSSION**

The present data provide significant support for our hypothesis that the innocuous thermosensory representation in the dpIns 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 sensitivity 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 neural representation of discriminative thermal sensation in the human cortex is located in the insula, the limbic sensory cortical region classically associated with autonomic control and homeostasis, rather than in the parietal somatosensory cortical regions (14, 29). The present data underscore the fundamental distinction that thermal sensation is represented in the central nervous system as one aspect of the physiological condition of the body.

**Central representation of discriminative thermal sensation.** Whereas considerable evidence on the precise coding properties of specific cutaneous thermoreceptors was gathered in the 1960s and 1970s (28), investigators who sought thermosensory neurons in portions of thelemniscal somatosensory system found only neurons with convergent properties (so-called “T + M” cells) that showed discharges with a nonlinear relation to temperature that originated from slowly adapting mechanoreceptors (6, 7, 42). Specific thermoreceptive neurons in the central nervous system were first discovered by Christensen and Perl (9) in lamina I of the spinal dorsal horn. Thermoreceptive lamina I trigeminothalamic and spinothalamic tract (STT) neurons that are specifically responsive to cooling or warming have subsequently been well characterized in cats and monkeys (1, 13, 15, 22). These neurons appear to constitute the only ascending pathway for discriminative thermosensory activity. Their linear responses to temperature directly parallel psychophysical measurements of human thermosensory capacities. These lamina I neurons are distinct morphologically as well as functionally and biochemically, so they can be viewed as a virtual “labeled line” for thermal sensation (17).

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.

Anterograde tracing data in the monkey indicate that the VMpo nucleus projects to the dpIns cortex with an anteroposterior topography (11). The available lesion, stimulation, and functional imaging data in humans are consistent with this cortical projection. Thus only lesions of this region reduce or eliminate contralateral thermal sensation in humans (2, 27, 45). Electrical stimulation of the dpIns in awake humans can result in specific thermal sensations (39). A laser-evoked potential study provided evidence that selective warming specifically activates the dpIns (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 dpIns by noxious cold (8, 12, 36).

Direct evidence indicating that discriminative thermal sensation is represented in the dpIns 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 dpIns 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 dpIns 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 dpIns to participate in discriminative cooling sensation. The recognition that the discriminative thermosensory cortex lies in the dpIns is striking because of the association of the insular cortex with autonomic control, rather than somatosensation. 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 representation 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 pri-mates (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.

**ACKNOWLEDGMENTS**

We thank M. Auldridge, L. Brady, A. Godinez, K. Krout, and P. Puppe for technical assistance. A preliminary report of this work was presented at the 2004 Meeting of the Society for Neuroscience.

**GRANTS**

This work was supported by National Institute of Neurological Disorders and Stroke Grant NS-40413 and the Barrow Neurological Foundation.

**REFERENCES**