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

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Hua, Le H., Irina A. Strigo, Leslie C. Baxter, Sterling C. Johnson, and A. D. (Bud) Craig. Anteroposterior somatotomy 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 (dplns) cortex of humans, rather than the parietal somatosensory regions traditionally thought necessary for discriminative somatic sensations. We hypothesized that if the dplns 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 dplns 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 dplns 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 dplns from the parietal exteroceptive representations. These data also support the suggestion that the poststroke central pain syndrome associated with lesions of the dplns is a thermoregulatory dysfunction. Finally, another focus of strongly graded activation, which we interpret to represent thenergulatory behavioral motivation elicited by dynamic cooling, was observed in the dorsal medial cortex.

Temperature; homeostasis; interoception; thermoregulation; functional imaging

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 sensation 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 (dplns). Our central hypothesis is that if the thermosensory representation in the dplns 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

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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 \( = 90^\circ \), \( 64 \times 64 \) matrix, field of view = 240 mm, native voxel size = \( 3.75 \times 3.75 \) 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., \( 13 \times 6 \)) 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 \( 2 \times 2 \times 2 \) 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 1) 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 dplns (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 \( \geq 10 \)). 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 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 dIns 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 dIns and dorsal medial cortex revealed by the regressor analysis.

The time course of the aggregate BOLD signal in the dIns 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 dIns 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 dIns ($t = 2.44, P < 0.015$, 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 dIns 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
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

topographic composite
(neck = green, hand = red)

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 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 in which graded activation that correlated directly with cooling and “paradoxical heat” (3, 18, 20). Notably, imaging evidence also indicates strong activation of the human dpIns by noxious cold (8, 12, 36).

Electrical stimulation of the dpIns in awake humans can result in specific thermal sensations (39). A laser-evoked potential stimulating 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 somatosensory. 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-orga-
nized 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 sup-
port 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 so-
matotopic gradient indicated by our observations is consistent
with the tracing evidence in the monkey on the somatotopo-
graphic organization of the input to the dpIns from the VMPo
nucleus. Notably, this gradient is orthogonal to the mediolat-
eral somatotopy of the neighboring parietal somatosensory
regions (21). This distinction supports the fundamental con-
ceptual differentiation of the interoceptive somatic representa-
tions in the dpIns from the exteroceptive somatosensory rep-
resentations 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 ther-
mosensory 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, neuroendo-
crine, and behavioral responses, has traditionally been rele-
gated 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 corre-
lative activation in the dorsal medial cortex. Our interpretation
that this activity represents the homeostatic motivation associated
with thermoregulatory behavior is supported by the observa-
tion 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 ante-
crior cingulate (30). The identification of thermosensory activa-
tion 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 process-
ing 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 inter-
preted as support for the hypothesis that thermosensory dys-
function 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, result-
ning in pain by the release of ongoing inhibition. This hypo-
thesis thus suggests that central pain is actually a thermoregu-
laratory dysfunction (14). It incorporates anatomic findings indi-
cating 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 corre-
cspondence to occur, the thermosensory representation in
the dpIns (and its forebrain and descending connections) must
be somatotopically organized. The present study provides di-
rect evidence supporting this organization.

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