Cortical, thalamic, and hypothalamic responses to cooling and warming the skin in awake humans: A positron-emission tomography study

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Contributed by Derek Denton, December 27, 2004

Thermoregulatory mechanisms are remarkably efficient, ensuring minimal temperature variation within the core of the human body under physiological conditions. Diverse afferent and efferent neural pathways contribute to the monitoring of core and skin temperature, generation of heat, and control of thermal exchange with the external environment. We have investigated the cortical, thalamic, and hypothalamic responses to cooling and warming by using positron-emission tomography activation imaging of subjects clad in a water-perfused suit, which enabled rapid change of their skin-surface temperature. Human brain regions that respond to changes in skin temperature have been identified in the somatosensory cortex, insula, anterior cingulate, thalamus, and hypothalamus, with evidence that the hypothalamic response codes for the direction of temperature change. We conclude that signals from thermosensors in the skin providing crucial afferent information to the brain are integrated with signals from central thermosensors, resulting in thermoregulatory responses that maintain core temperature within a remarkably narrow range.

functional neuroimaging | hypothalamus | thermoregulation

The integrity of the human body depends on the maintenance of the internal environment at a relatively constant temperature. Thermoregulatory mechanisms are remarkably efficient, ensuring small temperature tolerances within the core of the body under physiological conditions. Diverse afferent and efferent neural pathways contribute to the monitoring of core and skin temperature, generation of heat, and control of thermal exchange with the external environment. The integration of these processes is a function of the central nervous system within a network that has only been partially described in humans.

The reflex regulation of body temperature is usually considered in the context of a traditional feedback system, with the detection of small changes in internal temperature leading to appropriate effector responses. In humans, the maintenance of a constant internal temperature depends on vasomotor control of the cutaneous circulation and sudomotor control of sweating and shivering, with nonshivering thermogenesis also contributing in neonates. Heart rate is also considered to be a thermoregulatory effector. Results from experiments in animals and inferences from pathological lesions of the human brain suggest that the preoptic region and hypothalamus play an important role in the control of thermoregulatory mechanisms (see ref. 1 for review). Electrophysiological recordings from the preoptic area have identified cells that respond directly to changes in temperature. Almost all the cells described in these studies increase their level of activity in concert with increases in temperature. Cells responsive to cooling of the hypothalamus have been described only infrequently (2).

The capacity of the hypothalamus to integrate cutaneous thermal afferent information in thermoregulatory processes is a matter of debate. Concurrent measurement of the electroencephalography and unit recordings of hypothalamic cells during manipulation of skin temperature in anesthetized animals have raised doubts about the association of hypothalamic activity and cutaneous afferent output in the absence of covarying states of arousal (3), which is a necessary but major drawback of animal studies. Animal experiments have indicated that the central sensors for thermoregulatory responses are located in the hypothalamus, although within this region, the different effector responses may be driven by distinct thermosensitive neurons and mediated by distinct efferent pathways (4). This classical feedback organization has additional sensory input arising from the spinal cord and skin.

In humans, the contribution from skin temperature is important for several reasons. First, it serves in a feed-forward capacity such that regulatory responses can be initiated without the necessity of an error signal from internal (hypothalamic) temperature. Second, and related, the level of skin temperature affects the response pattern with respect to the threshold temperature at which changes in internal (presumably hypothalamic) temperature begin to evoke effector responses. These studies do not indicate the region or regions of the central nervous system in which these thermosensory elements interact in humans. Direct evidence is needed of the organization of these systems in the human brain. Although limited information has been obtained about the cerebral representation of cutaneous thermal sensation in humans (5–9), very few studies have been published on the brain activations associated with the basic processes of thermoregulation. Although the shifts in threshold mentioned above might be taken as suggestive evidence of an action for afferent information from skin temperature at the level of the hypothalamus, such is not necessarily the case. Indeed, this possibility has been doubted based on single-unit records from hypothalamic neurons in anesthetized rats (10).

In addition to physiological mechanisms of thermoregulation, homeotherms have developed a repertoire of behavioral responses that influence body temperature. The impetus for thermoregulatory behavior is the interoceptive experience of thermosensation. Thermal sensations are bimodal (senses of cool and warm) and include a thermoneutral domain that is characterized by the absence of any appreciation of temperature (6). In addition to sensory-discriminative attributes, thermal sensations in humans are invested with a hedonic dimension that motivates actions compatible with maintenance of core temperature (11). Affective responses associated with the experience of

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Abbreviations: PET, positron-emission tomography; rCBF, regional cerebral blood flow.

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www.pnas.org/cgi/doi/10.1073/pnas.0409753102

temperature are also bivalent. Cooling and warming the skin give rise to pleasant or unpleasant sensory experiences depending on prevailing thermoregulatory requirements. Recent observations (12–14) indicate that the threshold levels of internal temperature at which sweating, cutaneous vasodilation, or shivering are initiated are functions of the skin temperature such that the threshold internal temperature is lowered by elevated skin temperature and raised by cool skin temperature. The impact of the hedonic dimension of thermal sensation suggests that the experience integrates afferent input from the skin and internal thermoreceptors, the latter most probably within the hypothalamus.

The aversive nature of unpleasant thermosensations can be attenuated by behaviors that facilitate thermoregulatory processes, such as seeking shelter from extreme ambient conditions. Conversely, pleasant thermal experiences encourage the persistence of actions that are likely to maintain body temperature, such as remaining close to a radiant source of heat in a cold environment. The mechanisms emergent in poikilotherms (i.e., reptiles may seek and lie in the sun, and body temperature rises) and elaborated in homeotherms parallel those of thirst, hunger for air, hunger, and pain as vegetative regulatory systems with a long evolutionary history. It might be predicted, as has been shown experimentally with some of the systems cited (15–18), that the subjective sensations giving rise to intention to act will be organized in the phylogenetically ancient areas of the brain: the midbrain, hypothalamus, thalamus, allocortex, and transitional cortex. Evidence from functional brain-imaging studies also provides support for the contribution of the ventral posterior thalamic nuclei, insula, and primary somatosensory and associative parietal cortices in cutaneous thermal sensation (5–7). In contradistinction to the linear relationship of thermoregulatory hypothalamic activity and temperature, thermosensory processing in the brain is likely to be focused around the central thermoneutral point. Despite the unique modal qualities and implications of cooling and warming, it is likely that many elements of the thermosensory network will be common to both valences of temperature sensation.

We adopted the working hypothesis that skin temperature acts on the hypothalamic thermoregulatory areas during both heating and cooling. We took advantage of the ability to monitor activity in discrete brain areas by positron-emission tomography (PET) imaging and coupled that with techniques to directly change surface temperature quickly by means of a water-perfused suit. In particular, these changes in skin temperature were nonnociceptive and global, aiming to isolate thermoregulatory responses while avoiding those associated with more discrete but more intense thermal stimuli. Use of the water-perfused suit allowed relatively rapid changes in skin temperature and permitted manipulation of skin-temperature changes separately from changes in internal temperature. Thus, the goals of the present study were to identify the midbrain, hypothalamic, limbic, and cortical network associated with skin-temperature variations. We hypothesized that body heating would cause (*i*) cortical activation associated with cutaneous thermal sensation and (*ii*) thalamic and hypothalamic activation associated with thermoregulatory responses. The present article deals with the regional cerebral blood flow (rCBF) activations resulting from decreases and increases in skin temperature without concomitant changes in core temperature.

Methods

The study included 12 healthy volunteers (10 male and 2 female; age range, 20–44 years; mean age, 28 ± 7 years) who gave consent after verbal and written descriptions of the study, its discomforts, and its risks. The study was approved by the University of Texas Health Science Center Institutional Review Board.

Temperature-Control Procedures. Heating was induced by means of a liquid-conditioned garment (19) similar to those worn by astronauts. The liquid-conditioned garment device was selected because it allowed precise control of body temperature while the subject remained at rest. Temperature-controlled water was circulated through a network of small-diameter tubes sewn into mesh underwear, which covered the torso, upper arms, and legs. The forearms and head were not included. Outer layers were added to prevent heat loss to the environment. The right forearm was instrumented with a laser Doppler blood-flow probe (Moor Instruments, Axminster, U.K.) for the measurement of skin blood flow (20). The probe holder included a capsule covering 0.4 cm^2 that was ventilated continuously with dry air. The relative humidity of the effluent air was measured for the calculation of sweat rate (21). Blood pressure was measured from the right middle finger by the Penaz method (Finapres 3600, Ohmeda, Madison, WI). Skin temperature was measured as the weighted average from six thermocouples placed at representative sites. Oral temperature was registered continuously from a sublingual thermocouple. Subjects were reminded to maintain their mouths closed for several minutes before and during each imaging period to prevent artifactual cooling of the probe.

Experimental Protocol. Skin temperature was brought to 34°C for the control periods. This period included two scans, one after at least 10 min of quiet rest and the other 15 min (average, 14.0 ± 0.4 min) later. Cooling then was instituted by perfusing the suit with cold water at a temperature of ≈4°C. Ten minutes after the onset of cooling (average, 9.6 ± 0.6 min) a third scan was taken. After the thermal-perception interview (see below), the skin temperature was restored to control levels, and 11.0 ± 0.1 min later, the fourth scan was taken. Skin temperature was then raised to 38°C 15.0 ± 0.4 min after the onset of skin warming, and the first of three scans for body heating was taken. The final four scans, which included two additional warm scans and two cool scans, were associated with core temperature changes and will be reported separately. After each scan, the subject was quizzed on the perception of skin temperature on a scale from −4 to +4, for which a reply of −4 indicated feeling very cold, a

Table 1. Group mean physiological and temperature measures for each of the experimental conditions

Scan code*	Cutaneous vascular conductance	Sweat rate	Heart rate, min^{-1}	Mean arterial pressure	Oral temperature, °C	Skin temperature, °C	Skin temperature perception	Thermal comfort perception
C1	1.66 (0.16)	0.05 (0.01)	63.5 (2.2)	98.8 (4.6)	36.7 (0.1)	33.9 (0.1)	−0.5 (0.23)	−0.17 (0.11)
C2	1.50 (0.16)	0.05 (0.01)	60.9 (2.2)	100.9 (4.8)	36.6 (0.1)	33.9 (0.1)	−0.42 (0.23)	−0.33 (0.19)
SC1	1.17 (0.10)	0.05 (0.01)	62.0 (2.6)	114.6 (5.5)	36.6 (0.1)	30.5 (0.2)	−2.83 (0.27)	−2.42 (0.34)
C3	1.35 (0.12)	0.05 (0.01)	59.1 (2.5)	102.1 (5.5)	36.5 (0.1)	33.8 (0.1)	0.09 (0.21)	0.18 (0.12)
H1	2.23 (0.23)	0.07 (0.01)	69.9 (3.7)	95.2 (4.6)	36.6 (0.1)	38.2 (0.1)	2.42 (0.26)	1.58 (0.34)

*See the Fig. 1 legend for definitions of the scan codes.

response of 0 indicated feeling neither warm nor cold, and +4 indicated the skin to be very hot. Thermal comfort was assessed in the same way by asking the subject whether, in terms of thermal comfort, they felt very hot, hot, warm, slightly warm, neutral, slightly cool, cool, cold, or very cold.

Imaging Procedures. Nine PET scans were acquired for each subject. Each subject was supine in a quiet room, with his or her head supported in an hemicylindrical head holder and his or her eyes closed. The scanning methods used at the University of Texas Health Science Center Research Imaging Center have been described (22–25). Briefly, cerebral blood flow was measured by means of $H_2^{15}O$ (half-life 123 s) injected as 8- to 10-ml 60-mCi (1 Ci = 37 GBq) boluses of saline via an i.v. cannula in the left arm. PET scans were performed on a General Electric (Milwaukee, WI) 4096 camera with a 2.0-mm pixel spacing, an interplane center-to-center distance of 6.5 mm, and a *z*-axis field of view of 10 cm. A $^{68}Ge/^{68}Ga$ pin source was used for a transmission scan before the first scan to correct for radiation attenuation. The minimum interscan interval was 10 min, which allowed five half-lives for isotope decay. Image reconstruction was performed by using a Hann filter, yielding images with a spatial resolution of ≈7 mm. Each volunteer also had an anatomical magnetic resonance scan taken for comparison with the PET images. These scans were made with an Elscint (Haifa, Israel) 1.9-T Prestige system and used 3D gradient-recalled acquisitions steady-state acquisition protocol, with a repetition time of 33 ms, an echo time of 12 ms, and a flip angle of 60° to yield a 256 × 192 × 192 volume of data with a spatial resolution of 1 mm^3.

Each PET brain volume was defined by intensity thresholding at 30% of the maximum voxel value of the image volume, globally normalized by scaling to a mean of 1,000, and corrected for intrasubject movement by using the automated image-registration algorithm (26, 27). Both the magnetic resonance and PET images were spatially normalized to the Talairach atlas (28) with an algorithm developed to use an affine nine-parameter fit and interactive denotation of the anterior commissure–posterior commissure line. Images were transformed into 60 slices by using trilinear interpolation (matrix, 60 × 128 × 128) with isotropic voxels of 2 × 2 × 2 mm^3. Significant changes in rCBF were detected by using image subtraction by means of a validated algorithm (29) in which statistical parametric images are averaged across subjects and the resultant grand averages from chosen pairs of images are contrasted. Local extrema were identified with a 3D search algorithm, and kurtosis and skewness of the histogram of the difference image were used to assess overall significance (24). Anatomical labels were applied automatically by using a 3D electronic brain atlas (30). Regional tests were used to identify the brain areas showing significant differences. Cluster size was based on contiguous voxels within search cubes of 125 mm^3 and *Z* scores computed from the ratio of the image voxel and the average standard deviation of the null distribution. We accepted regional effects only if the *Z* scores were >3.11 ($P < 0.001$) and had at least 25 voxels. Planned comparisons were made between (*i*) the skin-cooling and control conditions (two initial scans) and (*ii*) the skin-warming and control conditions.

Results

Body Temperature and Hemodynamic Responses. Group mean temperature and other physiological data for the control, cooling, and heating phases of the study were obtained (see Table 1 and Fig. 1). By design, oral temperature did not change appreciably through the first two control (36.7 and 36.6°C, respectively), cooling (36.6°C), and early warming (36.6°C) phases. However, a small decrease in core temperature was apparent at the time of the third control scan (36.5°C), compared with the initial control scans [$t(11) = 3.1$; $P < 0.01$]. Consequently, this scan was not averaged with the first two control scans in subsequent comparisons. Cutaneous vascular conductance fluctuated during the protocol [$F(1,10) = 13.7$; $P < 0.004$], decreasing from the mean control scan value of 1.58 mV to the skin-cooling (1.17 mV) and third control (1.35 mV) scans and then increasing during the warming scan (2.23 mV). A significant effect was also apparent for heart rate due to an increase at the warming scan of 69.9 beats per minute, compared with the control scans (62.2 beats per minute) [$F(1,10) = 7.5$; $P < 0.02$]. The mean arterial

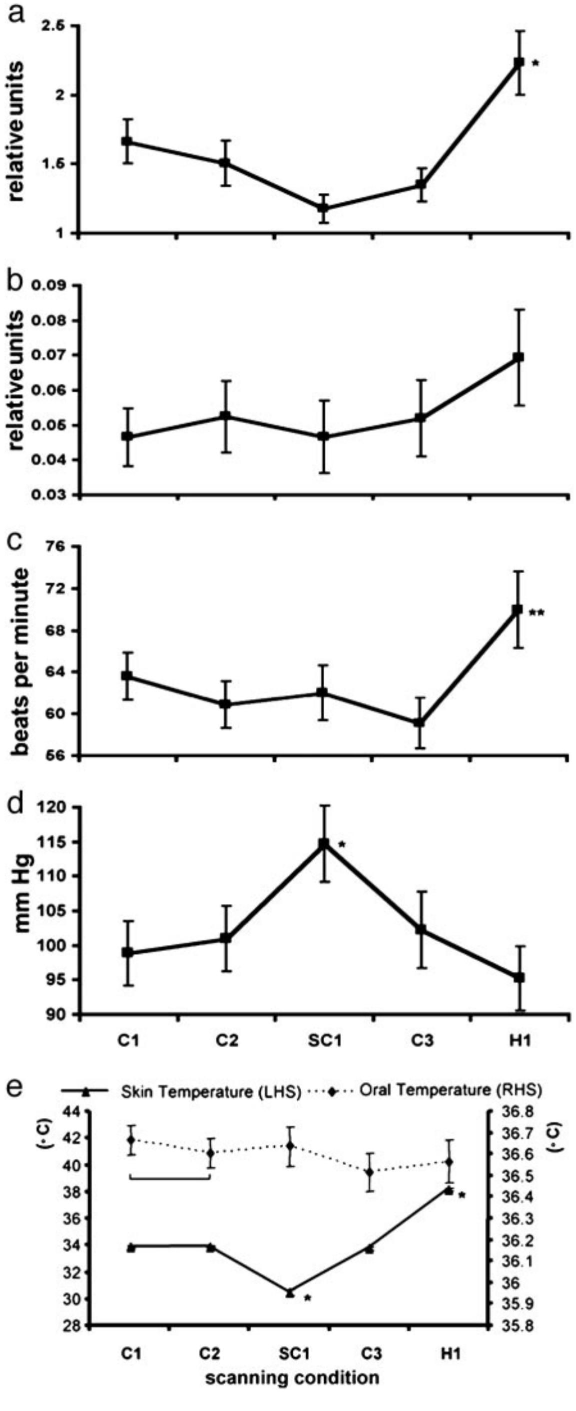

Fig. 1. Physiological and temperature measurements acquired during the bodysuit water-temperature manipulation. (*a*) Cutaneous vascular conductance. (*b*) Sweat rate. (*c*) Heart rate. (*d*) Mean arterial blood pressure. (*e*) Skin and oral temperature. Scan codes: C1, control scan 1; C2, control scan 2; SC1, skin-cooling scan 1; C3, control scan 3; H1, skin-heating scan 1.

Table 2. Brain activations observed when comparing normal skin and core temperatures

			Skin cooling (SC1)					Skin warming (H1)				
Region	Brodman area	Hemisphere	*x*	*y*	*z*	Size	*Z* score	*x*	*y*	*z*	Size	*Z* score
Pre/post central gyrus	4/5	Left	0	−32	58	39	3.11	−4	−32	58	45	4.25
	4/5	Right						6	−34	58	45	3.39
	4/3	Left	−16	−34	54	96	3.78					
	4	Right	16	−22	56	77	3.43	16	−26	60	25	3.27
	3	Right	24	−28	48	87	3.92	22	−30	46	79	3.55
		Left						−30	−30	32	83	3.41
		Right	34	−24	34	76	3.34					
	3/4	Left	−42	−11	32	82	3.34					
Supplementary motor area	6	Left	−2	−26	60	33	3.14	−4	−32	58	45	4.25
	6	Left	−14	−18	50	51	3.27					
Anterior cingulate cortex	24		0*	−14*	34*	55*	2.96*					
	31	Right	6	−14	42	77	3.43	16	−16	40	51	3.27
	24	Right						3	−8	25	62	3.43
	24	Right						2	−6	36	60	3.48
	32	Left	−3	8	44	41	3.09					
	24	Right	7*	12*	28*	53*	2.80*	6	10	26	56	3.18
	24	Left	−6	−10	36	63	3.07					
	24	Right						2	−6	36	60	3.48
	24	Right						8	0	36	77	3.87
Posterior cingulate cortex	31	Left						−14	48	26	46	3.09
	31	Right	12	−48	28	54	3.58	10	−32	30	67	3.30
	23	Right	4	−24	24	62	3.25	6	−24	28	67	3.27
	23	Right	2	−36	22	76	3.54					
Prefrontal cortex: inferior frontal gyrus	47	Left	−32*	28*	−13*	41*	2.89*	−31	26	−13	43	3.23
Posterior parietal cortex: inferior parietal lobule	40	Right	38*	−48*	30*	25*	2.56*	32	−42	48	46	3.39
Insula	13	Left	−38*	−26*	2*	65*	2.93*	−41*	−23*	−41*	42*	2.75*
	13	Right	30	3	−2	34	3.16	29	2	0	27	3.00
Parahippocampal gyrus	36	Left	−26	−26	−30	65	5.39	−28	−22	−28	61	4.87
Midbrain: hypothalamus		Right						8	−20	−4	30	3.00
		Right						4	−10	−16	46	3.07

Shown are brain activations observed when comparing normal skin and core temperatures (conditions C1 and C2) with skin cooling to 30.5°C while maintaining a constant core temperature (condition SC1), and skin heating to 38.2°C with a constant core temperature (condition H1). Significant activations are reported with cluster sizes >25 voxels and a Z score > 3.11 ($P < 0.001$) except for those regions shown with an asterisk, which are trends to significance ($P < 0.005$).

pressure rose during cooling [114.6 mmHg (1 mmHg = 133 Pa)] and decreased during warming (95.2 mmHg) [$F(1,10) = 13.1$; $P < 0.006$]. Ratings of thermal sensations also changed during the course of the protocol in keeping with the manipulation of skin temperature [$F(1,10) = 44.5$; $P < 0.0001$].

PET Imaging. Contrasts between the control images and the image taken during the period of skin cooling revealed (Table 2, left-hand columns, and Fig. 2) bilateral activation of the somatosensory cortex [Talairach coordinates $(x, y, z)/Z$ scores: (−42, −11, 32)/3.3 and (24, −28, 48)/3.9], the anterior cingulate cortex [(−3, 8, 44)/3.1 and (6, −14, 42)/3.4], and the insula [(−38, −26, 2)/2.9 and (30, 3, −2)/3.2]. There was a trend toward significant deactivation by skin cooling in the hypothalamus, and activation in the left parahippocampus [(−26, −26, −30)/5.4] and thalamus [(14, −16, 5)/2.9].

The skin-heating image when contrasted with the two initial control images produced a similar pattern of cortical activation responses (Table 2, right-hand columns, and Fig. 2). The somatosensory cortices demonstrated bilateral activation very similar to that seen with cooling [(−30, −30, 32)/3.4 and (22, −30, 46)/3.6)]. Similarly, the insula showed bilateral signal increase relative to the initial control images [(−41, −23, −4)/2.8 and (29, 2, 0)/3.0], whereas the anterior cingulate showed activation in the right hemisphere [(16, −16, 40)/3.3]. Activation was observed also in the right side of the hypothalamus [(4, −10, −16)/3.1] and in the left parahippocampus [(−28, −22, −28)/4.9].

Individual time-series plots for normalized rCBF responses in the somatosensory cortices, the insula, the anterior cingulate, and the thalamus show increases for both the skin-cooling and skin-heating conditions (Fig. 3). Conversely, the hypothalamus shows a reduction during the skin-cooling condition and an increase in the skin-heating condition. The skin-temperature change and hypothalamic rCBF change were highly correlated ($R = 0.79$; $P < 0.001$).

Discussion

The present study has identified regions in the cortex, thalamus, and hypothalamus that may be influenced by skin-temperature changes independently of changes in core temperature. We monitored oral temperature during both external cooling and warming sequences without detecting significant changes in core temperature. It is important to note that the cutaneous thermal stimuli administered in the present study covered a large proportion of the skin surface rather than localized regions as used in some earlier studies (5–7). This stimulus therefore approximates normal environmental changes.

Furthermore, for each subject a number of key physiological variables were measured to ascertain the nature and magnitude

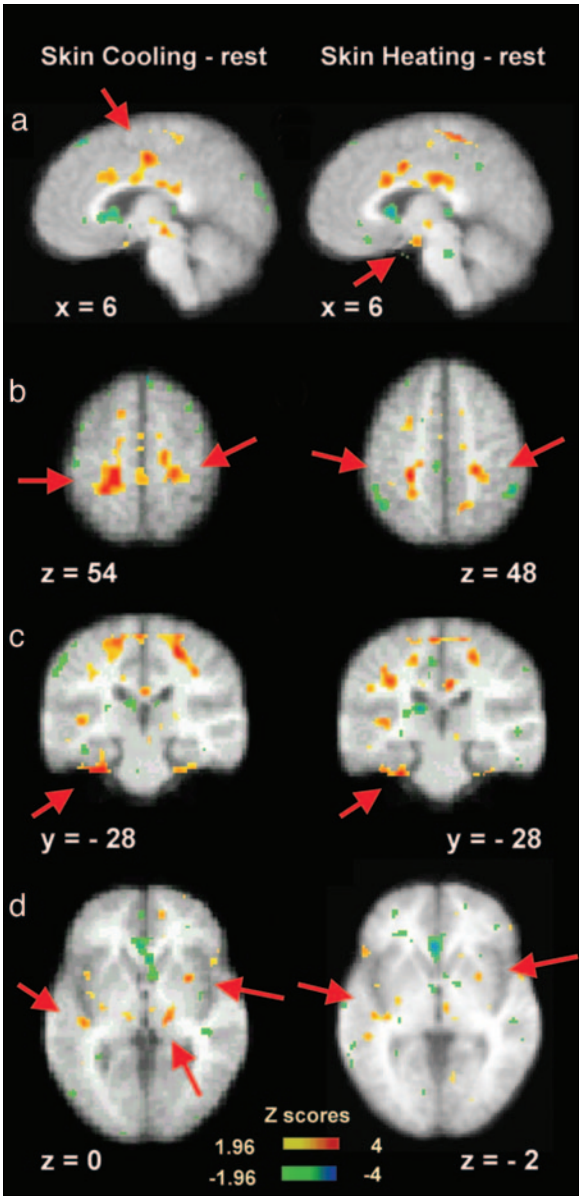

Fig. 2. Activations and deactivations for the skin-cooling (*Left*) and skin-heating (*Right*) scans, compared with the control scans displayed on the average magnetic resonance brain image of the 12 subjects. (*a*) Sagittal sections ($x = 6$) showing extensive activation in the right anterior cingulate during cooling and warming (arrows) and in the hypothalamus. (*b*) Axial sections ($z = 54$ and 48) showing extensive bilateral somatosensory activation for both conditions. (*c*) Coronal sections ($y = -28$) showing left parahippocampal activation. (*d*) Axial sections ($z = 0$ and -6) showing left posterior and right anterior insula and right thalamus activation. The positive and negative *Z*-score color coding is shown.

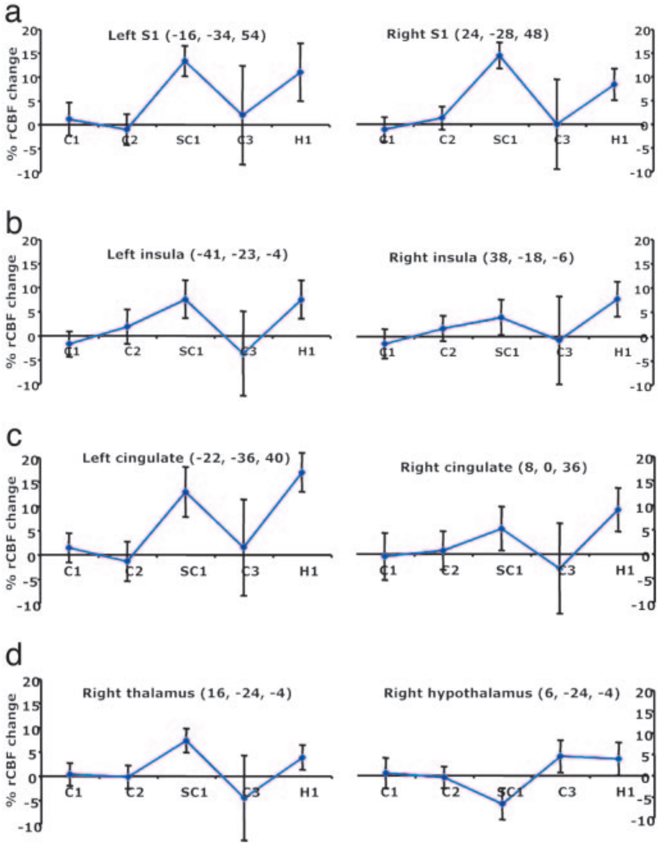

Fig. 3. Plots of percent rCBF change in the cortical and subcortical regions highlighted in Fig. 2: bilateral responses in somatosensory cortex (*a*), insula (*b*), anterior cingulate (*c*), and right thalamus (*d*) as a function of scan condition showing increased signal change during both the skin-cooling and skin-heating conditions, compared with the average control rCBF signal. (*d*) The percent rCBF signal change in the right hypothalamus showing reduced response for the skin-cooling condition [skin-cooling scan 1 (SC1)], compared with the average control rCBF signal, and increased response when the skin temperature is raised and a disequilibrium exists between the skin and oral temperatures [control scan 3 (C3) and skin-heating scan 1 (H1)].

of any homeostatic responses caused by thermal stimuli. Expected but small changes in skin vascular conductance, arterial pressure, and heart rate indicated that appropriate homeostatic responses to cooling and warming (±4°C) were engaged in the subjects. An increase in sweat rate was observed with warming, consistent with the increase in skin temperature.

Cerebral Cortex. Bilateral activation in the vicinity of the central sulcus suggested that the primary somatosensory cortex was activated by both cooling and warming. Comparison of each of these two conditions with the initial thermoneutral state identified similar activated regions for both cooling and warming, suggesting that rather than coding for temperature, this region of the brain provides anatomical specificity in regard to the surface area on which temperature is changing. In the recent study by Craig *et al*. (6), it was suggested that thermal sensation is represented in the insula cortex rather than parietal somatosensory cortex. Although Craig *et al*. observed activation of the left and right parietal cortices with hand cooling, they attributed this response to attention that was directed to the hand being cooled. The widespread area of activation we observed in the parietal primary somatosensory cortex region may reflect the larger bodily surface distribution of the stimuli that were applied in the current study.

We also observed that cooling activated discrete regions in the left posterior and right anterior parts of the insula cortex, and similar sites were also activated by warming. The insula has been shown to respond to painful stimuli as well as to a range of other somatosensory stimuli. If both cooling and warming were activating the same neurons, it would cast doubt on specific temperature coding by such neurons in the insula. It is possible, however, that thermally coding neurons lie close together in this region and the spatial resolution of PET imaging is unable to resolve the separate responses from these adjacent populations of neurons. Major activations were also observed in mid- and posterior cingulate regions. The anterior cingulate has been implicated in tasks requiring an executive role, whereas regions of the midcingulate have been activated in tasks having an affective component such as thirst, pain, and fear. It has been suggested that neural input to the cingulate from ascending spinothalamic pathways that signal afferent information from pain and thermal sensors may provide an affective component of the thermal sensation (31). These ascending pathways may also provide information related to skin temperature to the insula (32). Activations were observed in the right thalamus, consistent with activation of such spinothalamic pathways. However, the spatial resolution of PET imaging is also insufficient to differentiate whether the specific thalamic nucleus activated was the posterior part of the ventromedial nucleus, which has been shown to relay spinothalamic signals to the insula and cingulate cortices.

Hypothalamus. The hypothalamus and preoptic regions play a crucial role in integrating and initiating autonomic thermoregulatory mechanisms such as skin vasomotor responses, sweating, salivation, and shivering (4). Neurophysiological studies in experimental animals show that various sites such as the medial preoptic area, dorsomedial hypothalamus, paraventricular nucleus, and posterior hypothalamus may play roles in mediating these responses (33–36). Both activation and deactivations were observed within this region with thermal stimuli, but unlike the other brain regions discussed, warming and cooling stimuli did not both cause activation of the same region of the hypothalamus. Rather, significant activation was seen in the right ventral hypothalamus with warming and deactivation of the region with cooling. It was surprising that we did not observe significant activation and deactivation in the left ventral hypothalamus, probably because of the limited spatial resolution of PET and the spatial normalization method, which resulted in a better image registration for the right ventral hypothalamus. Although the particular hypothalamic nuclei activated by cooling and warming the skin could not be localized, it is feasible that the above-mentioned diencephalic nuclei drive different thermoregulatory pathways.

In the study by Kanosue *et al*. (8), body exposure to cold air caused activation of the amygdala. We did not observe such activation with skin cooling in the present study. However, the stimulus we used was of shorter duration and strength, resulting in less thermal stress, which could explain the difference between the two findings.

Conclusions

That a stable core body temperature is maintained in mammals despite relatively large variation in ambient temperature attests to the effectiveness of their thermoregulatory mechanisms. Information from thermosensors in the skin provides crucial afferent information to the brain that is integrated with signals from central thermosensors to initiate compensatory thermoregulatory response that maintain core temperature within a remarkably narrow range. Physiological studies in animals have shown that the hypothalamus and adjacent preoptic region probably integrate the afferent information from peripheral and central thermosensors. Human brain regions that respond to change in skin temperature to regulate homeostatic responses to changes in environmental temperature include the somatosensory cortex, insula, anterior cingulate, thalamus, and hypothalamus. Thus, the subjective thermoregulatory sensations giving rise to intention to act are predominantly organized in the phylogenetically ancient areas of the brain, including the midbrain, hypothalamus, thalamus, and elements of the limbic system. The network of cortical and subcortical activations that we identified in humans shows striking similarities to those of pain (15), thirst (16), hunger (17), and hunger for air (18), all being exemplars of vegetative regulations with a long evolutionary history.

This work was supported by National Institutes of Health Grant HL 059166, the benefactors of the Research Imaging Center, the National Health and Medical Research Council of Australia, the Howard Florey Biomedical Foundation of the United States, the Harold G. and Leila Y. Mathers Charitable Foundation, and the Robert J., Jr., and Helen C. Kleberg Foundation.

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