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Human cortical representation of oral temperature

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Abstract

The temperature of foods and fluids is a major factor that determines their pleasantness and acceptability. Studies of nonhuman primates have shown that many neurons in cortical taste areas receive and process not only chemosensory inputs, but oral thermosensory (temperature) inputs as well. We investigated whether changes in oral temperature activate these areas in humans, or middle or posterior insular cortex, the areas most frequently identified for the encoding of temperature information from the human hand. In the fMRI study we identified areas of activation in response to innocuous, temperature-controlled (cooled and warmed, 5, 20 and 50 °C) liquid introduced into the mouth. The oral temperature stimuli activated the insular taste cortex (identified by glucose taste stimuli), a part of the somatosensory cortex, the orbitofrontal cortex, the anterior cingulate cortex, and the ventral striatum. Brain regions where activations correlated with the pleasantness ratings of the oral temperature stimuli included the orbitofrontal cortex and pregenual cingulate cortex. We conclude that a network of taste- and reward-responsive regions of the human brain is also activated by intra-oral thermal stimulation, and that the pleasant subjective states elicited by oral thermal stimuli are correlated with the activations in the orbitofrontal cortex and pregenual cingulate cortex. Thus the pleasantness of oral temperature is represented in brain regions shown in previous studies to represent the pleasantness of the taste and flavour of food. Bringing together these different oral representations in the same brain regions may enable particular combinations to influence the pleasantness of foods.

Keywords: Oral temperature; Flavour; Taste; fMRI; Orbitofrontal cortex; Insula; Anterior cingulate cortex

1. Introduction

Neurophysiological studies in macaques [1–7] and functional neuroimaging studies in humans [8–12] have demonstrated that liquid oral stimuli, including pure water, activate the anterior insula/frontal opercular cortex (primary taste cortex), and the medial orbitofrontal cortex (secondary taste cortex). Activity in the primary taste cortex encodes the identity and intensity of oral stimuli, whereas activity in the orbitofrontal cortex reflects the hedonic value of oral stimuli as shown by reductions in responses when foods are ingested to satiety [2,3,11,13–15]. An unanticipated observation from studies of these cortical taste areas is that many (macaque) neurons receive and process not only chemosensory inputs, but somatosensory (texture/viscosity) and thermosensory (temperature) inputs as well [16,17]. Moreover, some neurons respond only to specific temperatures (e.g., cool vs. warm) suggesting a mechanism for encoding oral temperature independently of taste and texture [7,16].

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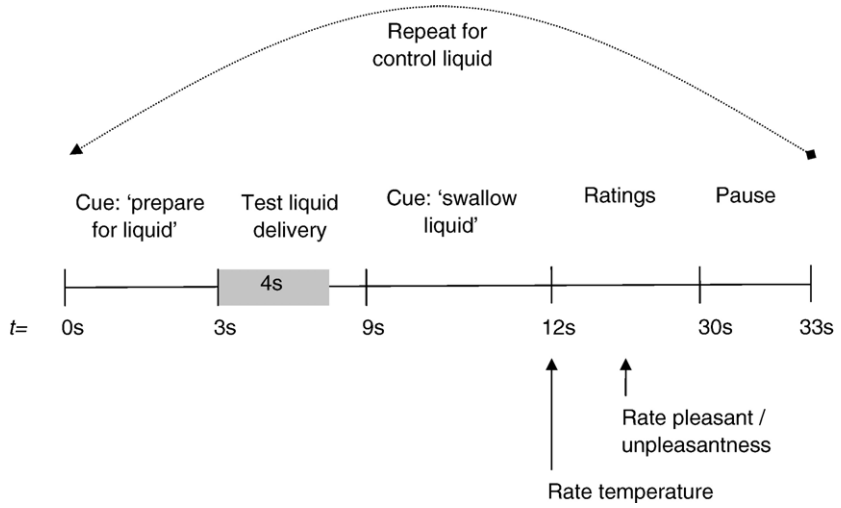

Fig. 1. Schematic of trial sequence. The time line depicts the first half of a single trial. The second half of the trial was identical to the first, except that the liquid delivered was always the tasteless control solution (artificial saliva) at 20 °C (room temperature). A single complete trial lasted 1 min 6 s.

In contrast to the primate neurophysiology used as a model of taste processing in humans, no neuroimaging study to date has investigated whether changes in oral temperature modulate the activity of these areas in humans, or the activity of middle or posterior insular cortex, the areas most frequently identified for the encoding of temperature information from the human hand [18–21]. To this end, we conducted an fMRI study to identify areas of activation in response to temperature-controlled (cooled and warmed) liquid introduced into the mouth. The subjects also provided psychophysical ratings of the subjective temperature of the stimuli as well as their pleasantness to enable investigation of how subjective oral temperature and pleasantness are represented in the brain. Features of this investigation are that a special Peltier device was designed and built to enable the delivery of liquids at different temperatures into the mouth in the fMRI environment [22]; that the temperature stimuli consisted of tasteless liquid so that activation related to temperature and not taste could be imaged; and that a sweet (glucose) taste stimulus was included in the stimulus set to enable identification of taste cortical areas, so that we could determine whether temperature-responsive cortical areas overlapped or were distinct from taste-responsive cortical areas.

2. Methods

2.1. Subjects

Subjects were recruited to participate in a single experimental session during which they sampled fluids of different temperatures introduced into their mouths. Because of the difficulty of testing subjects with a bulky Peltier controlled device situated in the magnet, considerable training of the subjects to accustom them to the experiments was provided, and the number of subjects was limited to five. As described below, we performed a group random effects statistical analysis on the data to take into account the within as well as between subjects variability. We note that although with this number of subjects the results cannot necessarily be generalized from this group of subjects in which significant effects were found to the whole population [23], the effects described are statistically significant within this group of subjects, as described below. We further strengthened the statistical analyses by performing conjunction analyses, as shown below, which, indicating convergent activation in some brain areas of oral temperature and taste inputs, provided further evidence that the representations of oral stimuli described in this paper are reliable. Further evidence for the reliability of the findings is that correlations between the psychophysical ratings of temperature and pleasantness obtained for every stimulus delivery, and the fMRI BOLD signals, were found in the same brain regions where contrast analyses showed effects of temperature, as described below. We further note that a sixth experiment was performed, and although not included in the group analyses because the subject was one included in the group, similar results were obtained as in the other five experiments as described below, providing further evidence on the reliability of the experimental procedures and results. In particular, in this sixth experiment, activations to the oral temperature stimuli were confirmed to be present in the orbitofrontal cortex, ventral striatum, and anterior insula ($P<0.05$ svc in all cases). No restrictions were placed on subjects' consumption of food and fluids prior to participation in the study. The study received ethical and safety approval from the School of Dentistry Institutional Review Board at the University of Chapel Hill.

2.2. Oral temperature stimuli and experimental design

Using fMRI, the BOLD (blood oxygenation-level dependent) response was imaged to the introduction of small (1.5 ml) aliquots of temperature-controlled liquids into the mouth. Three temperatures were selected to span the range commonly encountered during ingestion of liquids: 5 °C (cold drink), 20 °C (tap water), and 50 °C (warm tea). The liquid was an almost tasteless solution consisting of the main ionic components of saliva, namely 25 mM

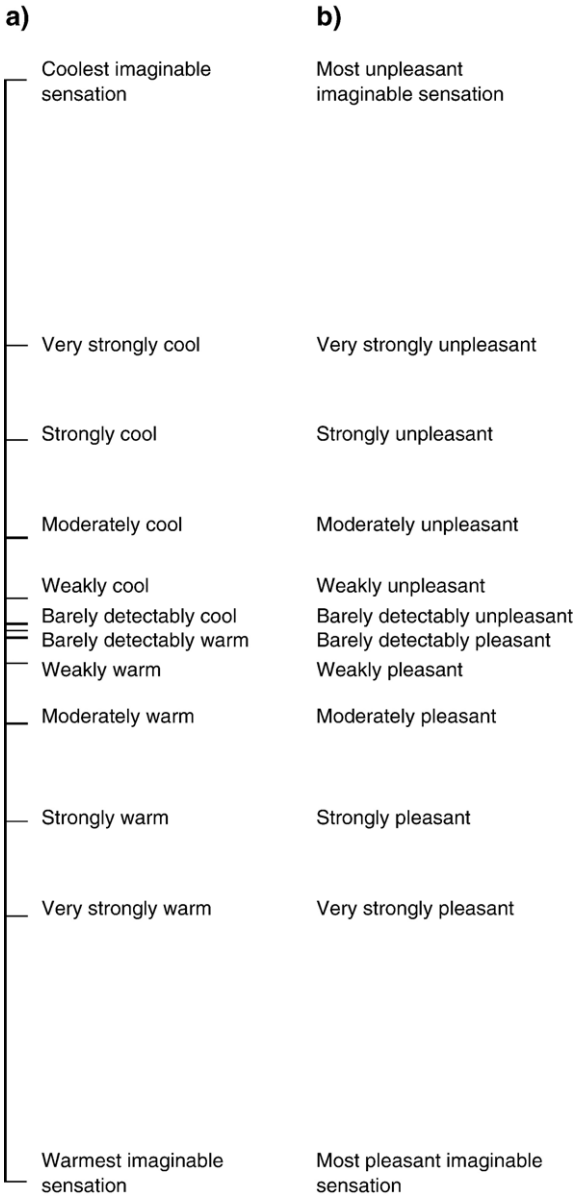

Fig. 2. Response scales used to collect subjective ratings of stimulus temperature and stimulus pleasantness/unpleasantness.

KCl and 2.5 mM $NaHCO_3$, dissolved in water. This 'artificial saliva' was employed instead of pure water to minimize the activation of cortical taste areas, which are activated by water in the mouth [24]. In addition, a 1 M glucose solution (dextrose in the artificial saliva) at 20 °C was included as a test stimulus to differentiate cortical areas encoding temperature from those encoding taste.

The stimuli were delivered in a single event design in a pseudo-randomized permuted sequence, with ten repetitions of each stimulus. Specifically, the order of stimuli was such that the most extreme temperatures (i.e., 5 and 50 °C) were not presented on consecutive trials. This constraint was placed on stimulus presentation so that the liquids would have sufficient time to reach their selected temperatures, given the limitations of the temperature-control system. Each test temperature stimulus (5, 20 or 50 °C) or the glucose stimulus (20 °C) was followed with artificial saliva at 20 °C (the control temperature stimulus and a rinse as well as one of the four test stimuli) during each trial as shown schematically in Fig. 1.

2.3. Subject instructions

During each trial, the test and control stimuli were delivered at a constant rate over a 4 s period. The subject was instructed to use the tongue to distribute the liquid around the mouth during the delivery period. For 2 s immediately following delivery of each stimulus, the subject was instructed to hold the liquid in the mouth and not to swallow until cued to do so. After swallowing each liquid stimulus, the subject rated its perceived temperature and pleasantness. Using modifications of the labeled magnitude scale (LMS) described by Green et al. [25], the temperature rating scale consisted of vertically stacked, back-to-back scales for warm vs cool (i.e., a 'butterfly scale'), and also for pleasantness vs unpleasantness (see Fig. 2).

2.4. Apparatus for oral temperature stimulus delivery and psychophysical data collection

Stimulus delivery and psychophysical data collection were controlled by a PC computer located in the scanner room. The two stimulus liquids (artificial saliva and the glucose solution) were held in individual, disposable plastic syringes. Each liquid was forced out of the syringe into a capillary tube (1.59 mm internal diameter) by a separate syringe pump (Type 33, Harvard Apparatus, Holliston, MA) secured 15 ft from the magnet. Each tube terminated in a non-magnetic liquid heating/cooling chamber, 2.6 ml in volume, near the subject's mouth. The chambers were bonded to a Peltier wafer which was electronically controlled via temperature-feedback circuitry, enabling the liquids in the chambers to be heated or cooled according to the experimenter's specifications. The liquid heating/cooling device was custom-designed and built for use in the fMRI environment (Ollie Monbureau, UNC Chapel Hill, School of Dentistry) [22].

The introduction of the liquid stimuli into the mouth was achieved using a customized, silicone-rubber snorkel mouthpiece, fitted to each subject's dentition using fast-setting dental impression material (Regisil 2×, Dentsply International, York, PA). A pair of capillary tubes (0.762 mm internal diameter) joined the outlet of the two liquid storage chambers to a Y-connector embedded in the side of the mouthpiece. The length of the delivery tube, from chamber to tongue tip, was 17.5 cm, corresponding to a volume between tongue tip and the chamber of 0.08 ml. This small volume represents a 'dead space' between the temperature-controlled liquid and the subject's mouth. Thus, the initial 0.08 ml of every liquid stimulus was at (or close to) the ambient temperature. This volume represented just 5.3% of the total volume for the stimulus. A third capillary tube ran directly from one of the syringes to the mouthpiece, bypassing the Peltier device. This tube supplied the control stimulus, i.e., artificial saliva at 20 °C (ambient room temperature), that was delivered during the second half of every trial (Fig. 1).

Table 1
Activations and correlations produced by temperature and taste (activations labeled T were in the insular taste cortex)

Contrast	Coordinates (MNI, peak)	*Z*-score	*P*-Value
Somatosensory cortex			
50−rinse	−50, −34, 30	3.68	0.001 (C)
50–20	−52, −32, 28	4.25	0.000 (C)
50–5	−48, −28, 42	4.83	0.000 (C)
Conjunction (50–20, 5–20)	−56, −24, 32	3.70	0.027 (SVC)
Positive correlation with temperature	−44, −28, 56	4.03	0.000 (C)
Negative correlation with temperature	−44, −36, 56	4.53	0.000 (C)
Negative correlation with pleasantness	64, −22, 42	4.20	0.000 (SVC)
Insula			
Glucose (T)	40, 8, −6	3.32	0.000 (SVC)
	−42, −6, −10	3.77	0.000 (C)
50−rinse (T)	50, 24, 4	3.30	0.030 (C)
	52, −6, 4	3.14	0.011 (SVC)
5−rinse (T)	−36, 20, 0	3.37	0.039 (C)
(T)	40, 14, 6	3.09	0.031 (SVC)
	44, 0, 2	3.41	0.001 (SVC)
5–50	36, −4, 8	2.91	0.006 (SVC)
Conjunction (50−rinse, 5−rinse) (T)	40, 2, −18	4.72	0.040 (C)
Positive correlation with temperature	−36, −8, 16	3.77	0.008 (SVC)
Negative correlation with pleasantness (T)	38, 10, −6	3.07	0.000 (SVC)
Cingulate			
Glucose	6, 32, 26	4.02	0.004 (C)
	12, 30, −20	3.42	0.003 (SVC)
50−rinse	2, 42, −6	4.20	0.007 (C)
5−rinse	0, 50, 14	2.98	0.045 (SVC)
	−2, 16, 44	3.99	0.000 (SVC)
50–5	−6, 20, −4	4.31	0.000 (SVC)
	−6, 38, 10	3.57	0.000 (C)
	4, 34, 32	2.84	0.001 (SVC)
Conjunction (50−rinse, 5−rinse)	2, 44, 16	3.63	0.034 (SVC)
	0, 16, 44	5.09	0.029 (C)
Negative correlation with temperature	2, 44, 8	3.52	0.000 (SVC)
Positive correlation with pleasantness	0, 44, 8	2.94	0.000 (SVC)
Orbitofrontal cortex			
Glucose	24, 18, −26	4.29	0.000 (C)
	10, 28, −12	4.09	0.000 (C)
	−28, 58, −12	3.85	0.000 (C)
50−rinse	2, 42, −6	4.20	0.007 (C)
50–20	10, 36, −20	3.85	0.048 (SVC)
5−rinse	26, 20, −14	3.77	0.000 (C)
50–5	44, 38, −6	3.84	0.004 (SVC)
	−36, 28, −8	3.63	0.000 (SVC)
5–50	30, 22, −26	3.14	0.004 (SVC)
Conjunction (50−rinse, 5−rinse, Glucose)	−48, 28, −10	4.94	0.000 (SVC)
Positive correlation with temperature	54 42 −4	3.74	0.001 (SVC)
Negative correlation with temperature	8, 30, −24	4.44	0.001 (C)
Positive correlation with pleasantness	8, 28, −24	3.44	0.029 (SVC)
Negative correlation with pleasantness	42, 58, −4	3.17	0.001 (SVC)
Ventral striatum			
50−rinse	−14, 14, 2	3.43	0.000 (SVC)
	14, 12, −6	3.66	0.008 (SVC)
50–20	12, 12, −2	3.41	0.001 (SVC)
	−16, 10, 4	3.24	0.002 (SVC)
5−rinse	8, 16, −2	3.35	0.004 (SVC)
	−18, 14, 2	3.50	0.002 (SVC)
Ventral striatum			
Conjunction (50−rinse, 5−rinse)	14, 10, −4	3.12	0.018 (SVC)
Conjunction (50–20, 5–20)	16, 14, −4	5.82	0.000 (C)
Premotor			
Glucose	52, 0, 28	3.61	0.000 (SVC)
50−rinse	46, 4 46	4.23	0.000 (C)
5−rinse	60, 0, 34	3.70	0.000 (C)
50–5	32, −8, 42	4.05	0.000 (C)
Conjunction (50−rinse, 5−rinse)	52, −2, 40	4.44	0.001 (SVC)
Conjunction (50−rinse, 5−rinse, Glucose)	46, 0, 42	3.66	0.025 (SVC)
Positive correlation with temperature	64, −10, 20	3.91	0.000 (C)

Instruction cues and response scales were shown to subjects on a projected display, made visible when within the scanner bore via a pair of mirrored lenses attached to the head coil. All psychophysical responses were obtained from subjects using a button box which interfaced with the parallel port on the PC computer that controlled stimulus delivery and psychophysical data collection.

2.5. fMRI data collection

Functional MRI was performed using a Siemens 3T Allegra head-only scanner (Siemens Medical Systems, Erlangen, Germany). A double echo EPI sequence was employed. The first echo was a gradient echo and the second echo was an asymmetric spin echo with a time offset of 15 ms. The asymmetric spin echo reduced the signal loss in the frontal region caused by the susceptibility artifacts, while preserving the signal alteration induced by the functional BOLD contrast. The images were collected in 25 coronal slices of 5 mm thickness to cover the frontal region of the brain. The image resolution within plane was 3 mm in both directions with field of view of 192 mm. TR was 3 s. TEs for the two echoes were 28 ms and 68 ms, respectively.

2.6. Psychophysical data analysis

Psychophysical data were analysed via SAS statistical analysis software using procedure MIXED for a mixed-model ANOVA and related approaches. The data for both of the psychophysical ratings (i.e., subjective temperature and pleasantness) ranged from −1 (the coolest or most unpleasant rating available) to +1 (the warmest or most pleasant rating available). The values were analysed without transformation. Of interest was the extent to which different physical temperatures resulted in different levels of perceived temperature and pleasantness.

2.7. fMRI data analysis

The imaging data were analyzed using SPM5 (Wellcome Department of Imaging Neuroscience, University of London).

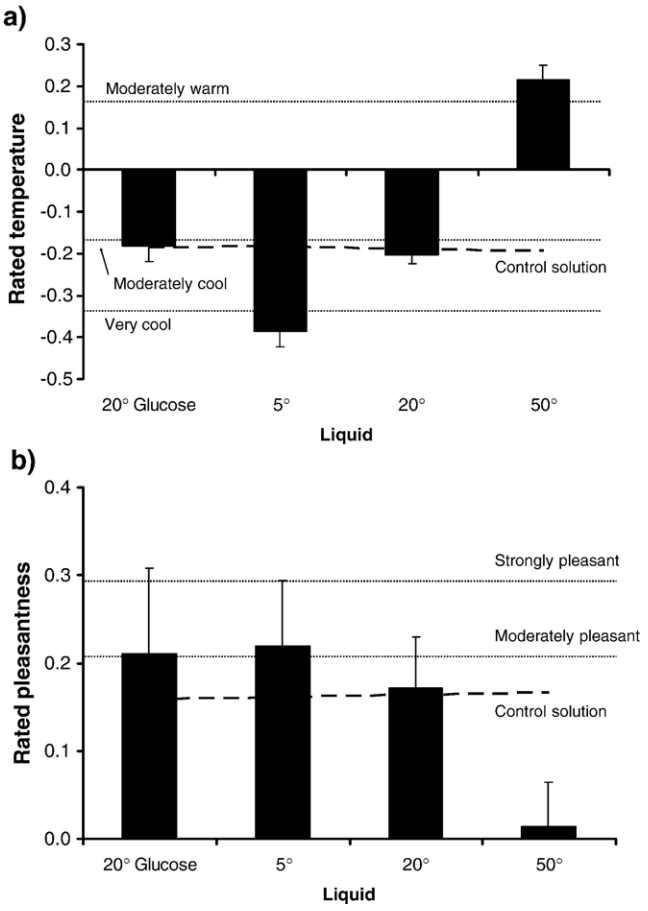

Fig. 3. A. Subjective ratings of the temperatures of the stimulus liquid at different temperatures (bars) and the 20 °C control liquid (broken line). The tasteless liquids had the ionic constituents of saliva, and the glucose solution was dissolved in the tasteless solution. Error bars show+1 SE. B. Subjective ratings of the pleasantness of the test (bars) and control (broken line) oral stimuli made during the scanning. Error bars show+1 SE.

Pre-processing of the data used SPM5 for realignment, re-slicing with generalized interpolation, normalization to the MNI coordinate system (Montreal Neurological Institute), and spatial smoothing with a 8 mm full width at half maximum isotropic Gaussian kernel and global scaling. A high-pass filter with a cut-off period of 128 s was applied.

A general linear model was then applied to the time course of activation where stimulus onsets were modeled as *single impulse response functions* and then convolved with the canonical hemodynamic response function, HRF and a duration parameter of 4 s. Time derivatives were included in the basis functions set. Following smoothness estimation, linear contrasts of parameter estimates were defined to test the specific effects of each condition with each individual dataset.

Voxel values for each contrast resulted in a statistical parametric map of the corresponding *t* statistic, which was then transformed into the unit normal distribution (SPM Z). The statistical parametric maps from each individual dataset were then entered into second-level, random effects analyses accounting for both scan-to-scan and subject-to-subject variability. More precisely, the sets of individual statistical maps corresponding to a specific effect of interest were entered *in a multiple regression model* as implemented in SPM5, and the corresponding group effects were assessed by applying linear contrasts to the (second-level) parameter estimates generating a *t*-statistics map for each group effect of interest. The above allowed us to perform conjunction analyses at the second (group) level to test for example whether taste and temperature activated the same voxels. (This was performed by running the group analysis for each effect separately, and then, at the group level, selecting the conjunction not global selection, in order to test the true conjunction as implemented in SPM5, not the global null hypothesis.) The correlation analyses of the fMRI BOLD signal with given parameters of interest (i.e., physical temperature of the stimuli, subjective ratings of stimulus temperature, and ratings of stimulus pleasantness) were performed at the second-level through applying one-sample *t*-tests to the first-level *t*-maps resulting from performing linear parametric modulation as implemented in SPM5.

Reported *P* values for each cluster as implemented in SPM based on this group analysis are fully corrected (C in Table 1) for the number of comparisons (resels) in the entire volume

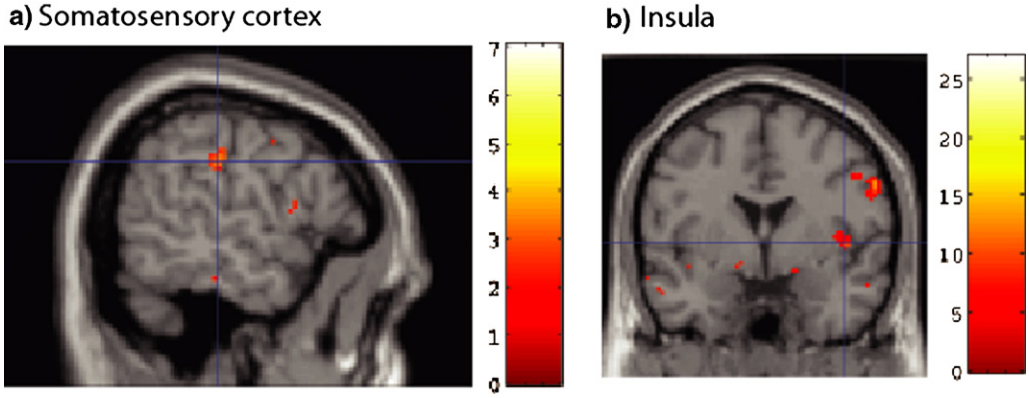

Fig. 4. a. A region of primary somatosensory cortex shown in a parasaggittal section activated by the conjunction of the hot (50–20) and the cold (5–20) stimuli at [−56, −24, 32]. The bar is calibrated to show the *t* value. b. Insula. Activations produced in the insula in the 5−rinse condition at [44, 0, 2]. Activation is also shown above it in the premotor cortex.

["whole-brain" multiple comparisons, [26]]. We supplement these by describing further activations corresponding to clusters of voxels significant when corrected for the number of comparisons made within each region [small volume correction, (SVC) applied with a sphere of 8 mm chosen to be greater than or equal to the spatial smoothing kernel, [26]], in order to provide an indication of effects appearing in further brain areas such as the insular, anterior cingulate, orbitofrontal and somatosensory cortices, and the ventral striatum shown to be of interest because of activations found in prior studies of oral representations in the brain [10–12,14,15,24,27,28].

3. Results

3.1. Psychophysical results

Fig. 3A illustrates the mean ratings of subjective temperature made by the subjects for the control and test solutions, across all four of the experimental conditions. A mixed-model ANOVA indicated that the temperature ratings varied according to the actual temperature of the solution ($F_{3,183}=501.69$, $P<0.0001$). Pairwise tests, corrected for multiple comparisons, demonstrated that solutions at different temperatures were rated differently.

Ratings of the pleasantness of the stimulus liquids are shown in Fig. 3B. Subsequent analyses indicated that the pleasantness of the test solutions varied ($F_{3,183}=29.61$, $P<0.0001$), with post-hoc tests showing that the 50 °C solution was found less pleasant than all other solutions (i.e., 5 °C and 20 °C tasteless solution, and 20 °C glucose solution), which did not differ from each other in their rated pleasantness.

3.2. Functional neuroimaging results

Table 1 shows the MNI coordinates, Z values, and the significance levels of the effects described next.

3.2.1. Somatosensory cortex

Activations of somatosensory cortex areas by oral temperature were found in a number of mutually consistent contrasts. For example, the contrast hot '50−rinse' showed activation in part of the primary somatosensory region, as did '50–20', and so did cold '5−rinse' and '5−20', as shown in Table 1. The activations produced by all these stimuli overlapped, and were in a region that was centered bilaterally near $y=-30$ and $z=34$. These findings are supported by a conjunction analysis for areas activated by both hot and cold. An example of the conjunction analysis is shown in Fig. 4a, which indicates a region of primary somatosensory cortex activated by the conjunction (50–20 in conjunction with 5–20). Interestingly, this area was not activated by glucose-rinse, indicating that this is a somatosensory cortical area not involved in taste processing, though the new evidence we present here shows that it is involved in oral temperature processing. (During the rinse period shown in Fig. 1 the tasteless control solution was delivered as a rinse, and this is therefore a useful control period used in some of the contrasts.)

3.2.2. Insula

As expected, anterior regions of the insula, at for example [40, 8, −6] and [−42, −6, −10] were activated by the taste of glucose (see Table 1). This is in a region shown in previous studies to be activated by taste stimuli, and is probably the primary taste cortex [8,11,24]. In macaques, some neurons in the primary taste cortex are known to be activated by oral temperature stimuli [7]. Nearby parts of the insula were activated by the temperature stimuli. For example, activations in this anterior insula region were found for the contrasts hot '50−rinse' and cold '5−rinse', and cold–hot '5–50' (see Table 1). An example of activations produced in the insula in the '5−rinse' condition at [44, 0, 2] is shown in Fig. 4b, and this is part of the primary taste cortex. The same diagram shows activation described later in the premotor cortex. The activations for the oral temperature conditions were in a region of the insula extending from $y=20$ to $y=-6$, and $z=6$ to $z=-18$. A conjunction analysis between temperature hot '50−rinse' and cold '5−rinse' revealed a significant effect centered at [40, 2, −18]. Overall, the region of the insula activated by oral temperature included at least part of the insular region that is the primary taste cortex.

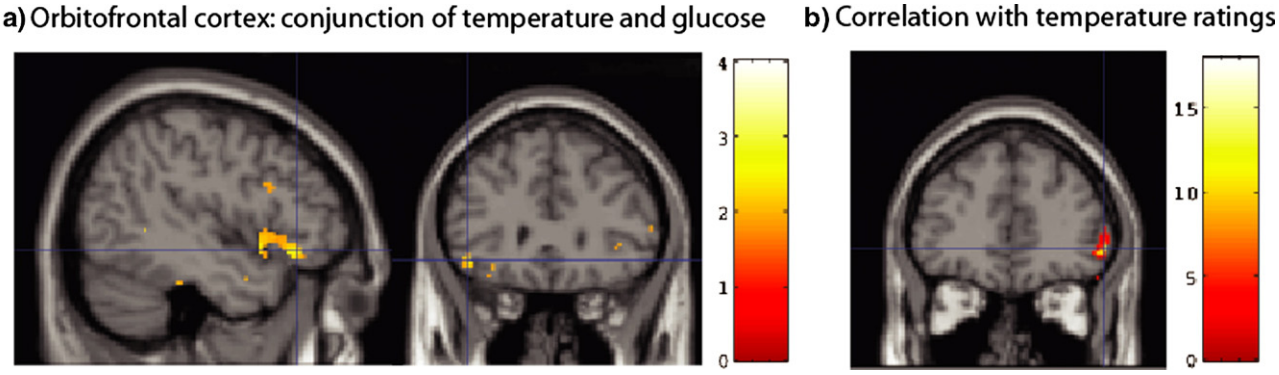

Fig. 5. Orbitofrontal cortex. a. A conjunction of temperature and glucose (50−rinse, 5−rinse, and glucose-rinse) activated the orbitofrontal cortex at [−46, 29, −10]. This activation extends up to and is continuous with activations in the anterior insula. b. Positive correlation of the BOLD signal with the subjective ratings of temperature of the temperature series in the caudal orbitofrontal cortex [−30, 24, −16]. A positive correlation reflected a higher BOLD signal with increasing temperature. The activation extended forwards as far $y=31$.

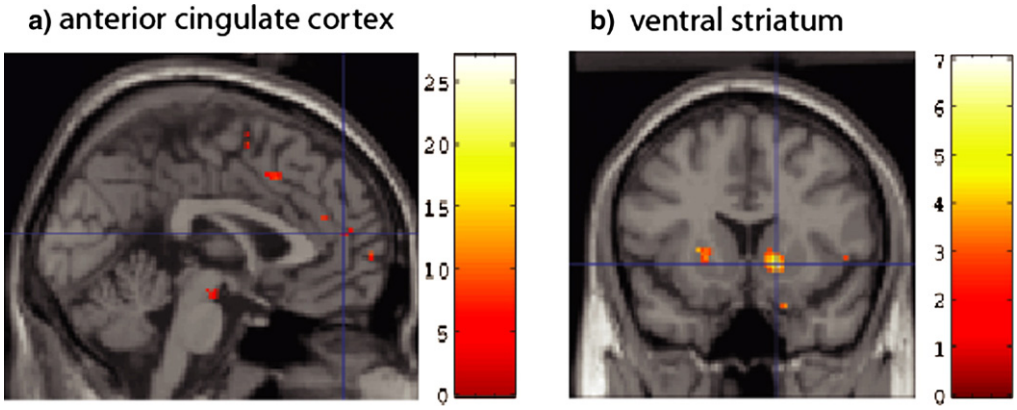

Fig. 6. a. Anterior cingulate cortex. An activation by cold (5–rinse) is shown in the pregenual cingulate cortex at [0, 50, 14] (marked by crosshairs), together with activation in a more dorsal area of the anterior cingulate cortex produced by the same cold stimulus at [−2, 16, 44]. b. Ventral striatum. A conjunction between hot (50–20) and cold (5–20) produced bilateral activation (e.g. [16, 14, −4] on the right).

3.2.3. Orbitofrontal cortex

Hot, cold, hot–cold, and cold–hot contrasts showed activation in the orbitofrontal cortex, as shown in Table 1. As expected from previous studies [11,12], glucose taste activated the orbitofrontal cortex. Of particular interest was that a conjunction of temperature and glucose (50−rinse, 5−rinse, and glucose-rinse) showed activation in the orbitofrontal cortex. The region where this particular conjunction showed a significant result was in the lateral orbitofrontal cortex [−46, 29, −10] as shown in Fig. 5a, and can be clearly shown extending up to and continuous with activations in the anterior insula.

3.2.4. Cingulate cortex

Activations by oral temperature and glucose taste were found in nearby parts of the anterior cingulate cortex. The contrasts hot '50−rinse', cold '5−rinse' and hot–cold '50–5' each showed activation of the pregenual cingulate (e.g. 5−rinse shown in Fig. 6a at [0, 50, 14]) and a more dorsal area of the anterior cingulate cortex (e.g. 5−rinse shown in Fig. 6a at [−2, 16, 44]). This result was supported by the conjunction analyses between hot '50−rinse' and cold '5−rinse' (see Table 1, pregenual at [2, 44, 16] and dorsal cingulate at [0, 16, 44]). A medial orbitofrontal cortex/subgenual part of the cingulate was activated by hot oral temperature '50−rinse' [2, 42, −6] and glucose taste [12, 30, −20], but not by cold '5−rinse'.

3.2.5. Ventral striatum

Another region for which activations were found for oral temperature contrasts is the ventral striatum. Activations were found for hot '50−rinse' and '50–20', cold '5−rinse', and for a conjunction between hot and cold (see Table 1). Fig. 6b shows a conjunction between 50–20 and 5–20, with bilateral activation ([16, 14, −4] on the right). No significant activation in the ventral striatum was found for the glucose taste condition in this group of subjects.

3.2.6. Premotor cortex

Activations in the premotor cortex were found in overlapping areas for taste and oral temperature contrasts. Glucose taste activated the premotor cortex at [52, 0, 28] while hot '50−rinse' and cold '5−rinse' activated nearby areas, as shown in Table 1. This result is supported by a conjunction analysis between 50−rinse and 5−rinse, which showed an activated area at [52, −2, 40], as well as by a conjunction analysis which included the oral temperature stimuli (50–rinse, 5–rinse) and the glucose taste stimulus, which showed an activated area at [46, 0, 42]. An example of the activation in the premotor cortex by oral temperature (contrast 5–rinse) (centered at [60, 0, 34]) is included in Fig. 4b.

3.2.7. Correlation analysis of fMRI data with subjective temperature ratings

For these correlation analyses, the three temperature stimuli 5, 20 and 50 °C were used. Positive correlations of the BOLD signal with this temperature series were found in the lateral orbitofrontal cortex (area 47/12 l as defined by Price [29]), as illustrated in Fig. 5b, and in the premotor cortex, as shown in Table 1. (The positive correlation in the lateral orbitofrontal cortex may be related to the fact that the higher temperatures were rated as less pleasant, as shown in Fig. 3.) Negative correlations (i.e. greater activations for colder temperatures) were found in the medial orbitofrontal cortex, in the pregenual cingulate cortex, and in the somatosensory cortex, as shown in Table 1. (The negative correlation in the medial orbitofrontal and pregenual cingulate cortex may be related to the fact that the lower temperatures were rated as more pleasant, as shown in Fig. 3.) The correlation analyses not only provide confirmation of the evidence described above based on contrasts of different temperatures, but also show how the subjective feeling of temperature is correlated with activations in these different areas.

3.2.8. Correlation analysis of fMRI data with hedonic ratings

For these correlation analyses, the three temperature stimuli 5, 20 and 50 °C were also used. Positive correlations of the BOLD signal with the pleasantness ratings of this temperature series was found in the medial orbitofrontal cortex, for example at [8, 28, −24] (see Table 1). Positive correlations with pleasantness were not evident in the primary taste cortex and in

the somatosensory cortex. Negative correlations (i.e. greater activations for temperatures rated as unpleasant) were found in the primary taste cortex (for example at [38, 10, −6]), in the lateral orbitofrontal cortex ([42, 58, −4]), and in the somatosensory cortex (e.g. [64, −22, 42], as shown in Table 1; and in the amygdala ([30, 12, −24] Z=3.43 P=0.000 SVC). The correlation analyses provide confirmation of the evidence described above based on contrasts of different temperatures, but also show that pleasantness was correlated with activations in the medial orbitofrontal cortex, and that the subjective feeling of unpleasantness was correlated with activations in a number of areas, including the lateral orbitofrontal cortex (see Table 1). Correlations with unpleasantness were also found in or near the taste insula and in the somatosensory cortex. These could be related to the fact that the warmer temperatures were less pleasant as shown in Fig. 3B, and these brain areas may have responded more to the warmer vs the cold temperature.

4. Discussion

A major finding of this investigation is that the temperature of what is in the mouth produces activation in the anterior part of the insula, in a region which was shown in this study was also activated by the taste of glucose. This region is probably the primary taste cortex, based on its correspondence with the anterior taste insula in macaques which receives taste inputs directly from the taste thalamus [30] and contains taste neurons [1–5,31], and on the fact that it has been shown in previous functional neuroimaging studies in humans to be responsive to taste stimuli [8–12]. The representation of oral temperature in the taste insula has been established by an investigation in which some single neurons in the macaque primary taste cortex were found to be tuned to oral temperature, some to taste, and some to both oral temperature and taste [7]. The present findings indicate that a similar situation holds in humans, in that both oral temperature and taste activate this anterior part of the insula.

The activations in the insula by oral temperature were mainly at the anterior end of the insula, in a region which at least largely overlapped with the primary taste cortex. There was no strong evidence for oral temperature representations more posteriorly in the insula. However, consistent with our finding of oral temperature representations in the insula, representations of temperature on the body surface, for example the hand, are found in the insula, but further posteriorly [19,32,33], that is behind the primary taste cortex. Taken together, these investigations show that temperature is represented in the human insula, with the oral representation in the taste insula, where it can potentially be combined with taste representations; and the temperature of other parts of the body is represented in more posterior parts of the insula that have somatosensory representations of other parts of the body.

We note that Craig has referred to the representation of the temperature of parts of the body surface as “interoception” [32]. However, this is puzzling, for at least touch to the body surface might normally be considered as exteroceptive sensing, and the temperature of the hand does not appear to be conceptually more interoceptive than this. However, the temperature of what is in the mouth might be thought to be closer to true interoceptive sensing, and perhaps the term interoceptive sensing would apply to oral temperature sensing somewhat better. Indeed the epithelium of much of the gastrointestinal tract is of endodermal origin [34], and interoceptive might apply to this. However, we note that embryologically the mucous membranes of the lips, cheeks, gums, part of the floor of the mouth, and the palate have their origin in tissue that is of ectodermal origin [34], so even perhaps oral temperature sensing has its origins in part in external sensors.

Part of the advantage of having a representation of oral temperature (and also oral texture [7]) in the taste cortex may be that neurons can then encode combinations of taste, texture and oral temperature, which in particular combinations may have significance, both in modern times and in evolutionary history. These combinations may provide the basis for particular combinations of temperature, taste, texture and odor to be especially pleasant, and also provide a basis for sensory-specific satiety, by allowing a reduction of firing of neurons that respond to particular combinations [27]. An additional part of the evolutionary adaptive value of oral temperature sensing may be that this could give an indication of the potentially damaging consequences for thermal regulation of the ingestion of large quantities of cold fluid.

In contradistinction to the anterior insular representation of oral temperature, primary somatosensory cortex (areas 1, 2 and 3) also represents oral temperature, but not oral taste, as shown by the findings of this investigation. Thus oral temperature (and we surmise also body surface temperature) has a representation that is independent of the insula, and in primary somatosensory areas. Thus not all temperature representations are in the “interoceptive insula” [19,32].

The taste insula projects into the orbitofrontal cortex in macaques [35], and corresponding to this, in the present investigation activations by oral temperature were also found in the orbitofrontal cortex, and in the pregenual cingulate cortex, which receives projections from the orbitofrontal cortex and contains taste neurons [36,37]. Activations in the medial orbitofrontal cortex and cingulate cortex were correlated with the pleasantness ratings of the temperature stimuli provided on every trial of the functional imaging, consistent with much other evidence that the hedonic value of many stimuli is represented in these regions [27,28,38–42]. Activations in the lateral orbitofrontal cortex were negatively correlated with the pleasantness ratings of the temperature stimuli provided on every trial of the functional imaging, consistent with other evidence that unpleasant stimuli tend to be represented in this region [27,28,38,43,44]. However, the present study also revealed that with the temperature stimuli used there was also a negative correlation with pleasantness in the anterior insula, and this may have been related to the fact that with the temperature stimuli used, any difference in activations to different temperatures was also potentially related to hedonics, as shown by the data in Fig. 3.

A region to which the orbitofrontal cortex projects, the ventral striatum, also had activations that reflected oral

temperature, as shown in Table 1. This region in implicated in conditioned incentive effects [27,45], and the activations by oral temperature might be part of a system for responding to rewarding or punishing conditioned temperature stimuli.

In addition, a part of ventral premotor cortex area 6 was activated in this study by the oral temperature stimuli (and in previous studies with taste/oral somatosensory stimuli including water in the mouth [24]). This region is known to receive inputs in macaques from the insular (primary) taste cortex [46]. This region also receives somatosensory inputs from much of the length of the fronto-parietal opercular cortex [46], so may reflect activations in these areas to oral stimuli.

In conclusion, in this fMRI study we have shown that oral temperature is represented in the human primary taste cortex in the anterior insula, and in regions to which it connects such as the orbitofrontal cortex. Part of the advantage of having a representation of oral temperature in these regions is that neurons can then encode combinations of taste, texture and oral temperature [7,16]. These combination-responsive neurons may provide the basis for particular combinations of temperature, taste, texture and odor to be especially pleasant [27,47].

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