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Functional imaging of gustatory perception and imagery: "top-down" processing of gustatory signals

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By recalling gustatory memories, it is possible to generate vivid gustatory perceptions in the absence of gustatory inputs. This gustatory image influences our gustatory processing. However, the mechanism of the "top-down" modulation of gustatory perception in the human is still unclear. Our findings propose a new perspective on the neural basis of gustatory processing. Although gustatory imagery and gustatory perception shared common parts of neural substrates, there was an asymmetrical topography of activation in the insula: the left insula was predominantly activated by gustatory imagery tasks. In addition, the middle and superior frontal gyri were not activated by gustatory perception but they participated in the generation of gustatory hallucinations. These regions in the frontal cortex may mediate the "top-down" control of retrieving gustatory information from the storage of long-term memories.

Keywords: Gustatory perception; Imagery; Top-down modulation

Introduction

The sense of taste is necessary to identify food and forms a taste preference, although the appeal of both sweet- and salty-tasting substances, in large part at least, is innately determined (Beauchamp and Cowart, 1985). Gustatory behaviors, such as neophobia and taste aversion learning, suggest that the gustatory information from the taste buds is compared to gustatory memories at all times during food intake, and thus we avoid ingesting novel or harmful food. Gustatory memories enable us to generate vivid perceptions of taste in the absence of peripheral gustatory inputs. Thus, not only signals from the peripheral gustatory nervous system but also those obtained by recalling gustatory memories play a critical role for gustatory information processing.

To elucidate the mechanism of gustatory perception, the pathway from the peripheral taste receptors to the central nervous system (the "bottom-up" pathway) has been well studied in nonhuman primates. Gustatory afferent fibers in the monkey terminate the nucleus of the solitary tract (Beckstead and Norgren, 1979), from which second-order fibers project to the thalamic ventroposterior medial nucleus (Beckstead et al., 1980). The anterior insula and frontal operculum (AI/FO), which are called the primary gustatory cortex, receive direct projection from the ventroposterior medial nucleus of the thalamus (Pritchard et al., 1986). The properties of AI/FO neurons have been studied using an extracellular unit recording technique. These neurons respond to sweetness, saltiness, bitterness, and sourness, and they code the intensity of stimulus (Scott and Plata-Salaman, 1999; Scott et al., 1986, 1991; Smith-Swintosky et al., 1991; Yaxley et al., 1990). Furthermore, gustatory information is conveyed to the orbitofrontal cortex from the AI/FO (Augustine, 1996; Carmichael and Price, 1994; Cavada et al., 2000). Rolls et al. (Rolls and Baylis, 1994; Rolls et al., 1990) have reported that neurons in the orbitofrontal cortex respond to the visual and/or olfactory stimuli in addition to the gustatory stimulus.

Several classical methods have been used to determine the location of gustatory cortex in the human. Clinical studies have shown that damage in the ventral regions of the central sulcus, including Brodmann area 43 (Bornstein, 1940) or the rostral part of the insula (Motta, 1959), caused gustatory disturbance. Electrical stimulation of the insula in the human elicited gustatory sensations (Penfield and Boldrey, 1937; Penfield and Faulk, 1955). In

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addition, Hausser-Hauw and Bancaud (1987) reported a patient who had an epileptic focus in the frontal operculum, and epileptic activity or electrical stimulation in the focus produced a disagreeable taste. Recent positron emission tomography (PET) studies have revealed that the regional cerebral blood flow (rCBF) in the insula/frontal operculum is increased by gustatory stimulation in the human (Frey and Petrides, 1999; Kinomura et al., 1994; Small et al., 1997a,b, 1999) and the monkey (Kobayashi et al., 2002). Activation in the insula during gustatory stimuli was also shown using functional magnetic resonance imaging (fMRI) in the human (Barry et al., 2001; Cerf-Ducastel et al., 2001; Faurion et al., 1999; Francis et al., 1999). In contrast to the "bottom-up" processing, another gustatory pathway, the "top-down" pathway, which modifies the gustatory information from the peripheral receptors by recalling gustatory memories, remains unclear, although the mechanisms of the "top-down" modification in other sensory systems, such as vision, have been studied in the monkey (Hasegawa et al., 1998; Tomita et al., 1999) and the human (Barcelo et al., 2000; Ishai et al., 2000; Kosslyn et al., 1997; Kreiman et al., 2000).

In addition to the mechanisms of the "top-down" modulation of gustatory perception, the patterns of hemispheric symmetry in gustatory processing are still unknown. Although most of these noninvasive imaging studies have shown that the right insula is more activated by gustatory stimulation than the left (Barry et al., 2001; Cerf-Ducastel et al., 2001; Frey and Petrides, 1999; Small et al., 1997a,b, 1999), some studies have shown that the activation in the left insula is equally (Francis et al., 1999) or more dominant than the right (Kinomura et al., 1994). Faurion et al. (1999) reported that the lateralization of the inferior part of the insula is related to handedness: left insula dominance in right-handed, and right insula dominance in left-handed subjects. In contrast to most reports using PET, studies in patients with corpus callosum resection suggest that gustatory pathways from the tongue to the cerebral cortex are bilaterally distributed with predominance in the left hemisphere (Aglioti et al., 2000, 2001). Another clinical study in the patients with damage to the insula in either cerebral hemisphere showed that damage to the right insula produced ipsilateral taste recognition and intensity deficits, and damage to the left insula caused not only an ipsilateral deficits in taste intensity but also bilateral deficits in taste recognition (Pritchard et al., 1999). Thus, gustatory information seems to be asymmetrically processed in the human cerebral cortex, but the precise pattern of laterality is still controversial.

Here, we present two series of experiments in which whole-brain measurements of blood oxygenation level-dependent (BOLD) responses were performed using a 3.0-T MR scanner to address the following questions: (1) Is there laterality for gustatory processing in the cerebral cortex? (2) Where do gustatory "top-down" signals meet "bottom-up" signals? (3) Where is the source of "top-down" signals during gustatory processing? In the first series of experiments, we examined the regions activated by gustatory perception. Secondly, we designed gustatory and visual imagery tasks to explore the regions activated by "top-down" processing of gustation. We found that the laterality of activity in the gustatory cortex is dependent on the source of inputs: passive inputs from the periphery project to the insula bilaterally, and "top-down" signals are likely to be processed predominantly in the left insula. In addition, the results of the present study suggest that the middle and superior frontal gyri are the candidates for the source of "top-down" signals.

Materials and methods

Subjects

Twenty-five Japanese volunteers were selected after checking for their normal neurological condition and ability of color vision through a diagnostic interview with a neurologist (8 males and 17 females, 21–31 years old, mean age 24.7 years old, right-handed except one subject). Eleven subjects participated in the study of gustatory perception and 18 subjects in the gustatory imagery study. All subjects gave their written informed consent, and the experiment was approved by the research ethic committee in the BF Research Institute.

Gustatory perception

In a pilot experiment, we tested several ways of delivering taste solutions as follows: (1) simple application of the taste solution for various durations, (2) application of taste solution followed by washing with distilled water. These methods of application caused serious head motion when subjects swallowed the solution. In addition, washing out of the taste was incomplete. Therefore, we developed a perfusion system, which was set on the tongue of the subject. The perfusion system consisted of five inlet tubes surrounded by a thick outlet tube with holes and continuous suction (Fig. 1A inset). Using this system, the subject did not have to swallow the solution and did not sense odors during a session. Furthermore, this system improved the efficiency of washing out of the perfused solutions. We measured how long a subject felt gustatory stimuli to determine the duration of ON and OFF blocks. A gustatory stimulus for 2 s induced an immediate onset of sensation and then the offset at 14.9 ± 4.5 s (mean ± SD, n = 10).

The experiment of gustatory perception was divided into a gustatory session and a water session. Each session consisted of eight pairs of alternating tasks, in which 0.8 ml of gustatory solution or water was delivered to the mouth for 2 s followed by no gustatory stimulation for 43 s. According to the latency at the onset of the OFF block mentioned above, we set the ON block for the first 15 s and the OFF block for 30 s (Fig. 1A). In the gustatory session, one of the four stimuli (grapefruit, orange, apple, and grape juice) was delivered in a pseudorandom order to avoid taste adaptation. In the water session, distilled water was delivered in place of the four gustatory stimuli. Both juice and distilled water were maintained at room temperature (18–20°C).

Gustatory imagery

We selected five imagery items for each taste: sweetness, saltiness, bitterness, and sourness. Ten imagery items for each taste were presented to subjects (n = 25), and they were asked to score how effectively they could imagine each taste on the scale of 1 (least imaginable) to 5 (highly imaginable). We selected five highly imaginable items for each taste (total 20) as imagery items (mean score of selected items was 3.7 ± 0.5, mean ± SD, n = 20).

Visual stimuli were projected onto a screen placed across the bore of the MR magnet 2.8 m from the subject's eyes. Auditory stimuli were 16-bit digitally synthesized tones, and sampled female speech sounds presented biauricularly through headphones at precise intervals using a custom-made computer playback system.

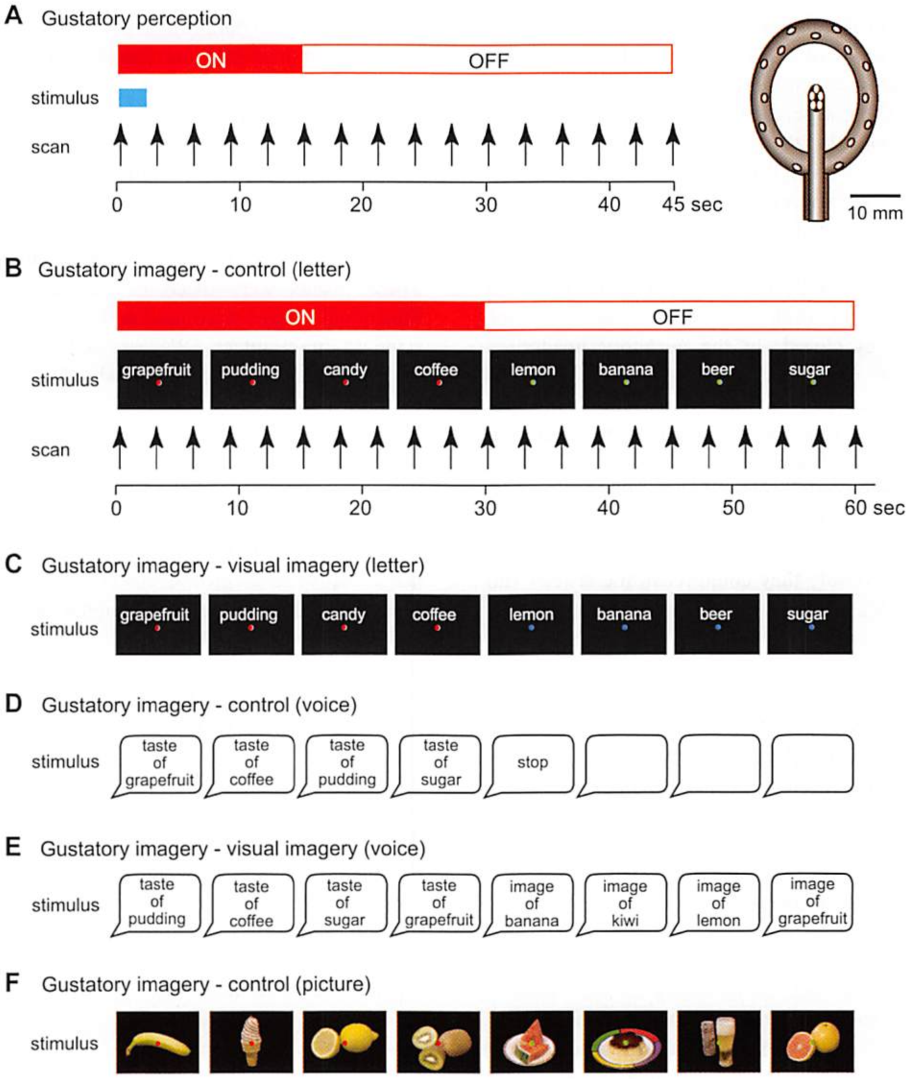

Fig. 1. Experimental designs of the gustatory perception and gustatory imagery tasks. (A) In the gustatory perception task, gustatory stimuli or water stimuli were presented for 2 s (a blue bar), followed by resting period of 43 s. The ON or OFF blocks were repeated eight times. Inset: the liquid perfusion system. (B–F) Experimental design of the gustatory imagery tasks. Each stimulus was presented for 7.5 s. Four gustatory imagery stimuli composed one ON block. Four visual imagery stimuli or no imagery stimuli composed one OFF block. The ON or OFF blocks were repeated five times. (B) Gustatory imagery—control (letter) session. As words with a red fixation point was indicated, the subjects were supposed to recall tasting the indicated food or beverage. When the subjects saw words with a green fixation point, they were supposed to only read them. (C) Gustatory imagery—visual imagery (letter) session. The gustatory imagery task was the same as in (B). As words with a blue fixation point was indicated, the subjects were required to recall the image of the indicated food or beverage. (D) Gustatory imagery—control (voice) session. The subjects were asked to recall the taste of food or beverage when they heard the phrase "taste of food or beverage" through headphones. The subjects were then asked to stop recalling when "stop" was announced. (E) Gustatory imagery—visual imagery (voice) session. The gustatory imagery task was the same as in (D). The subjects were requested to recall the image of food or beverage when the sentence "image of food or beverage" was presented. (F) Gustatory imagery—control (picture) session. As pictures with a red fixation point was indicated, the subjects were supposed to recall tasting the indicated food or beverage. When the subjects saw a green fixation point, they were supposed to only look at them.

We prepared five sessions: (1) gustatory imagery—control (letter), (2) gustatory imagery—visual imagery (letter), (3) gustatory imagery—control (voice), (4) gustatory imagery—visual imagery (voice), and (5) gustatory imagery—control (picture). All sessions consisted of five pairs of ON and OFF blocks alternately. As the duration of each block was 30 s, the total time of one session was 300 s. In the gustatory imagery—control (letter) session (Fig. 1B), words of a food or beverage with a red fixation point were presented four times for 7.5 s each time (ON block). During the presentation of a red fixation point, subjects were supposed to recall the taste of the presented food or beverage. The taste of items included in a block, that is, sweetness, saltiness, bitterness, and sourness, were randomized. Then, words with a green fixation point were presented in the same way as in the imagery task (OFF block). During the presentation of a green fixation point, subjects were asked to only look at it. In the gustatory imagery—visual imagery (letter) session (Fig. 1C), the gustatory imagery task with a red fixation point was presented in the same manner as in the gustatory imagery—control (letter) session (ON block). After that, words with a blue fixation point were presented (OFF block). Subjects were supposed to recall the image of the presented food or beverage during the presentation of a blue fixation point. In the gustatory imagery—control (voice) session (Fig. 1D), four kinds of taste of food or beverage were presented at 7.5 s intervals, which indicate the gustatory imagery condition (ON block). Then, a phrase of "stop" was presented as the nonimagery condition. In the nonimagery condition, the subjects took a rest for 30 s (OFF block). In the gustatory imagery—visual imagery (voice) session, as the gustatory imagery condition was presented in the same manner as in the gustatory imagery—control (voice) session (ON block), the visual imagery condition was presented by four images of food or beverage at 7.5 s intervals (OFF block). Both sessions presented by voice were performed with eyes closed. In the gustatory imagery—control (picture) session (Fig. 1F), four pictures of food or beverage with a red fixation point as the gustatory imagery condition (ON block), and four pictures with a green fixation point as the nonimagery condition were presented, respectively (OFF block). We randomized the order of the sessions for each subject. All verbal stimuli in the sessions using letters or voice were presented in Japanese. After the imagery sessions, subjects were asked to score how vividly they could recall the taste: 1 (no image) to 5 (vivid image). Each gustatory imagery session was performed on 18 subjects, but we excluded the data obtained from four to six subjects because of their low scores on the imagery rating (<3). As a result, the number of the subjects registered to the standardized brain image was as follows: gustatory imagery—control (letter), 12; gustatory imagery—visual imagery (letter), 14; gustatory imagery—control (voice), 12; gustatory imagery—visual imagery (voice), 14; and gustatory imagery—control (picture), 12.

Data acquisition and statistical analysis

The experiments were performed using a 3.0-T Signa VH/i (GE Medical Systems, Waukesha, WI, USA). Subjects lay down in supine position in the scanner, and head motion was minimized by a padded head holder and forehead straps. All experiments were performed in a darkened room. Echo-planner imaging sequence (EPI) with 30 axial slices was used; slice thickness = 5 mm; no gap; matrix = 64 × 64; field of view = 200 × 200 mm; repetition time = 3000 ms; echo time = 30 ms; flip angle = 90°. In addition, T1-weighted, high-resolution anatomical images (matrix = 256 × 256 matrix, thickness = 1.2 mm) and three-dimensional images (matrix = 256 × 256 matrix, thickness = 5 mm) were acquired for each subject.

All statistical analyses were performed by Statistical Parametric Mapping (SPM99, Wellcome Department of Cognitive Neurology, London, UK) implemented in Matlab (Mathworks, Sherborn, MA, USA) where statistical inferences were based on the theory of random Gaussian fields. To compensate for artificial signal intensity changes that were caused by head movement, image realignment was applied to register the EPI images within the mean image of each time series. We excluded the results obtained from one subject in the experiment of gustatory perception because his images showed motion of more than 10% of the pixel size. To perform intersubject averaging, individual images were then transformed into the standard stereotaxic space of Montreal Neurological Institute (MNI; Collins et al., 1994). This procedure involves, first, transforming the anatomical image of each subject into standard stereotaxic space, and then, applying this parameter to EPI images to transform these images into the standard space. EPI images were finally smoothed with a Gaussian kernel of 8 mm full width at half maximum to increase the signal to noise ratio.

Statistical parametric maps were generated for each experiment by a general linear model (fixed effect model) with a delayed boxcar function, convolved with the hemodynamic response function. A part of data were also analyzed by a random effect model for the comparison of previous studies in which the same model was used to generate statistical parametric maps. These results were listed in Supplementary Tables 1 and 2. Functional images were masked by the image made by the binary standard brain image. We assessed statistical significance at a criterion of a single-voxel threshold of $P < 0.05$ corrected for multiple comparisons (SPM99 default) across the brain volume examined. The t maps were then registered to the anatomical standardized brain image. Of the data set of imagery experiments, the percentage change in the time course of the BOLD signal of the maximally activated voxel within the cluster was measured. To evaluate the BOLD signal increase in the gustatory imagery tasks relative to control or visual imagery tasks, we excluded the first three values of the BOLD signals of the ON and OFF blocks and calculated the mean percentage of the BOLD signal increase in a stable state in each block. The values of the BOLD signal increase in the ON and OFF blocks were compared using a paired t test, and the level of $P < 0.05$ was considered statistically significant.

Conjunction analyses were performed over contrasts from the sessions of gustatory perception and gustatory imagery to detect the regions commonly activated for these sessions (Price and Friston, 1997). Similar analyses were also performed to find the commonly activated regions throughout the sessions of gustatory imagery—control, and throughout the sessions of gustatory imagery—visual imagery. Concerning conjunction analyses, we report regions that achieve $P < 0.001$, uncorrected.

Results

Gustatory perception

Both gustatory and water stimulation (Fig. 1A) commonly activated the superior frontal, middle frontal, inferior frontal, precentral, and postcentral gyri, insula/frontal operculum, inferior parietal lobe, and cerebellum (Table 1, Fig. 2A). Besides these regions, gustatory stimulation activated the thalamus and the region including the putamen (Table 1). We also listed the activated regions obtained from statistical parametric map generated by a random effect model in Supplementary Table 1. Similar regions including the insula/frontal operculum were activated in the analysis using a random effect model, except the thalamus in the gustatory and water sessions and the superior frontal and postcentral gyri and putamen in the water session.

It was found that water stimulation activated the same part of the insula/frontal operculum that was activated by passive gustatory stimulation (Figs. 2B and C). The volume of activated regions in the left and right insula/frontal operculum during passive gustatory stimulation was 1336 and 3744 mm^3, respectively (Table 2). The maximum t value in the left and right insula or frontal operculum was almost the same (5.99 vs. 6.02, respectively).

Table 1
Activated regions by passive gustatory and water stimulation

	Gustatory stimulation (fruit juice)				Water stimulation			
	x	y	z	t value	x	y	z	t value
Superior frontal gyrus	6	10	56	7.22	4	12	54	4.92
Middle frontal gyrus	54	24	28	4.88	40	56	12	5.33
Inferior frontal gyrus	32	20	−6	6.42	32	22	−6	5.08
Precentral gyrus	56	10	8	6.70	56	10	8	6.29
Postcentral gyrus	−64	−18	26	6.58	−62	−16	24	5.92
Insula	36	20	0	6.02	46	12	−2	5.53
Inferior parietal lobe	−56	−38	26	6.45	−54	−52	44	5.91
Cerebellum	−14	−58	−40	5.15	34	−64	−42	5.53
Thalamus	6	−30	2	5.42				
Putamen	14	12	−6	5.22				

x, y, z: Stereotaxic coordinates of peak of activated clusters.

Gustatory imagery

We designed five sessions of imagery tasks to explore regions that correlate to gustatory imagery (Figs. 1B–F, see Materials and methods).

In the session of gustatory imagery—control (letter), the following regions were activated: the insula, orbitofrontal gyrus, putamen, globus pallidus, lateral thalamus, precentral, and inferior/middle/superior frontal gyri (Fig. 3). The session of gustatory imagery—control (letter) includes at least two major processes, the imagery process itself and the perception of taste. To exclude the regions activated by the imagery process, another session was executed: gustatory imagery—visual imagery (letter), which was composed of gustatory imagery tasks as the ON block and visual imagery tasks as the OFF block. As this session includes imagery processes in both blocks, we may assume that the regions

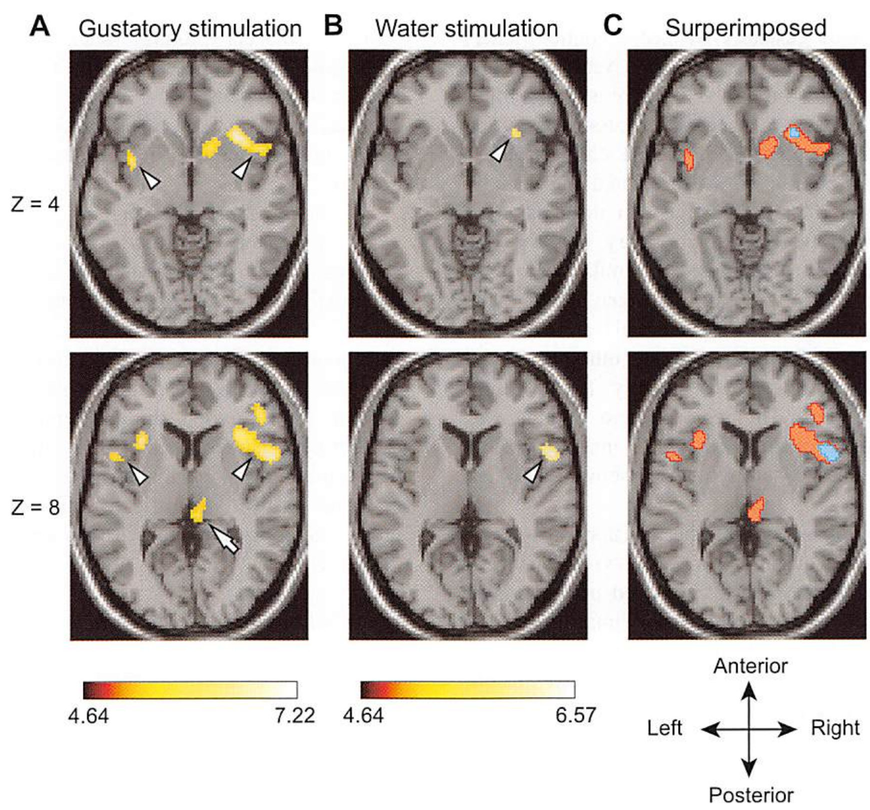

Fig. 2. Activated regions during passive gustatory perception superimposed on the standard brain. (A) Passive gustatory stimulation using fruit juice activated the insula/operculum (arrow heads), caudate nucleus, and thalamus (arrow). (B) Water gustatory stimulation activated the insula/operculum (arrow heads). (C) Regions activated by water stimulus (blue) are superimposed on those activated by passive gustatory stimulation with fruit juice (red). Note that the regions activated by passive gustatory stimulus include those by water stimulus. Scale bars indicate t values of passive gustatory stimulation (A) and water gustatory stimulation (B). Z values on the left indicate the z-axis values of the standard brain according to the MNI coordinate system. The orientation arrows are applied to all slices.

Table 2
Volume of activated regions by passive gustatory stimuli and gustatory imagery (mm^3)

	Ins/FO		OFG		PrG		IFG		MFG		SFG	
	L	R	L	R	L	R	L	R	L	R	L	R
Gustatory stimulation												
Fruit juice	1336	3744	0	0	1128	2792	0	256	0	688	0	2624
Distilled water	0	64	0	0	1112	2296	0	208	4232	552	0	208
Imagery												
Gustatory imagery—control (letter)	184	0	224	0	3912	264	2888	0	5952	0	5744	0
Gustatory imagery—visual imagery (letter)	440	0	0	0	3672	1224	0	0	0	0	0	0
Gustatory imagery—control (voice)	824	0	528	0	14,000	3448	3432	80	2720	0	11,904	2000
Gustatory imagery—visual imagery (voice)	0	0	0	0	280	0	0	0	0	0	0	0
Gustatory imagery—control (picture)	72	0	336	0	888	936	0	0	464	0	1360	0

Ins/FO: insula/frontal operculum; OFC: orbitofrontal gyrus; PrG: precentral gyrus; IFG: inferior frontal gyrus; MFG: middle frontal gyrus; SFG: superior frontal gyrus; L: left; R: right.

activated by imagery are canceled and specific regions for gustatory perception are activated. In the gustatory imagery—visual imagery (letter) session, only the insula and precentral gyrus were activated (Fig. 3). Although activation in the orbitofrontal gyrus fell below the statistical criterion, it probably represents a true increase in BOLD signal, given that the BOLD signal displayed a similar time course to that of other activated regions (Fig. 3B). The time course of the BOLD signal in the activated area showed a signal pattern that increased and reached a plateau in the ON block and then decreased to a baseline in the OFF block.

Tasks in the sessions of gustatory imagery—control (letter) and gustatory imagery—visual imagery (letter) were performed by visual presentation of words on a screen. There is a possibility that some regions for gustatory imagery processing may be masked because they are also activated by visual stimuli in these sessions. To exclude this possibility, we presented the task by voice through headphones (Figs. 1D and E). In the session of gustatory imagery—control (voice), the gustatory imagery was associated with increased neural responses in similar regions to those in the gustatory imagery—control (letter) session: the insula, orbitofrontal gyrus, putamen, precentral, and inferior/middle/superior frontal gyri (Table 2). On the other hand, the session of gustatory imagery—visual imagery (voice) only activated the precentral gyrus. The region where t value was not significant in the gustatory imagery—visual imagery (voice) session, the insula, and orbitofrontal gyrus, also showed a boxcar like pattern.

Using the same scans obtained from the gustatory imagery—visual imagery (letter) and gustatory imagery—visual imagery (voice) sessions, we set the ON block composed of four visual imagery tasks and the OFF block of four gustatory imagery tasks as the session of visual imagery—gustatory imagery (letter) and visual imagery—gustatory imagery (voice), respectively. In both sessions, we observed the activation of the secondary visual cortex (Brodmann areas 18 and 19), suggesting that the visual imagery—gustatory imagery sessions reveal the area specific to visual imagery.

There is a possibility that linguistic processes may influence activated areas since tasks presented by letters or voice are designed using words. To exclude the possibility, another approach for gustatory imagery was performed: gustatory imagery—control (picture) (Fig. 1F). The gustatory imagery—control (picture) session enhanced the BOLD signal in the insula, orbitofrontal gyrus, precentral, and middle/superior frontal gyri (Table 2). Table 3 summarizes the stereotaxic coordinates and t values of peak voxels in consistently activated regions throughout the gustatory imagery sessions.

We also listed the results obtained from statistical parametric map generated by a random effect model in Supplementary Table 2. The analyses using a random effect model revealed that the insula and superior frontal gyri were commonly activated in the sessions of gustatory imagery—control (letter, voice, and picture), and the middle frontal gyrus was activated in gustatory imagery—control (letter and voice) sessions. On the other hand, the analyses using a random effect model showed that similar regions were activated to those detected by the analyses using a fixed effect model except the superior frontal gyrus in the session of gustatory imagery—visual imagery (voice).

To demonstrate the regions active in any sessions of gustatory imagery compared to control or visual imagery tasks, we performed the conjunction analyses. Table 4 lists the commonly activated regions obtained from the conjunction analysis among the gustatory imagery—control (letter, voice, and picture) sessions. The regions activated consistently throughout these sessions were the insula, orbitofrontal, and middle/superior frontal gyri in the left hemisphere and precentral gyrus in both hemispheres. On the other hand, the conjunction analysis between the gustatory imagery—visual imagery (letter and voice) sessions showed significant activation in the insula and precentral gyri, but not in the middle/superior frontal gyri (Table 4).

Commonly activated regions between gustatory perception and imagery tasks

The above results have revealed that passive gustatory stimulation and gustatory imagery commonly activated a part of the insula. Indeed, the activated regions by each gustatory imagery task, except for the gustatory imagery—visual imagery (voice), overlapped in a part of the left insula activated by passive gustatory perception (Fig. 4). The overlapped volume is as follows: gustatory imagery—control (letter), 120 mm^3; gustatory imagery—visual imagery (letter), 144 mm^3; gustatory imagery—control (voice), 184 mm^3; gustatory imagery—control (picture), 24 mm^3.

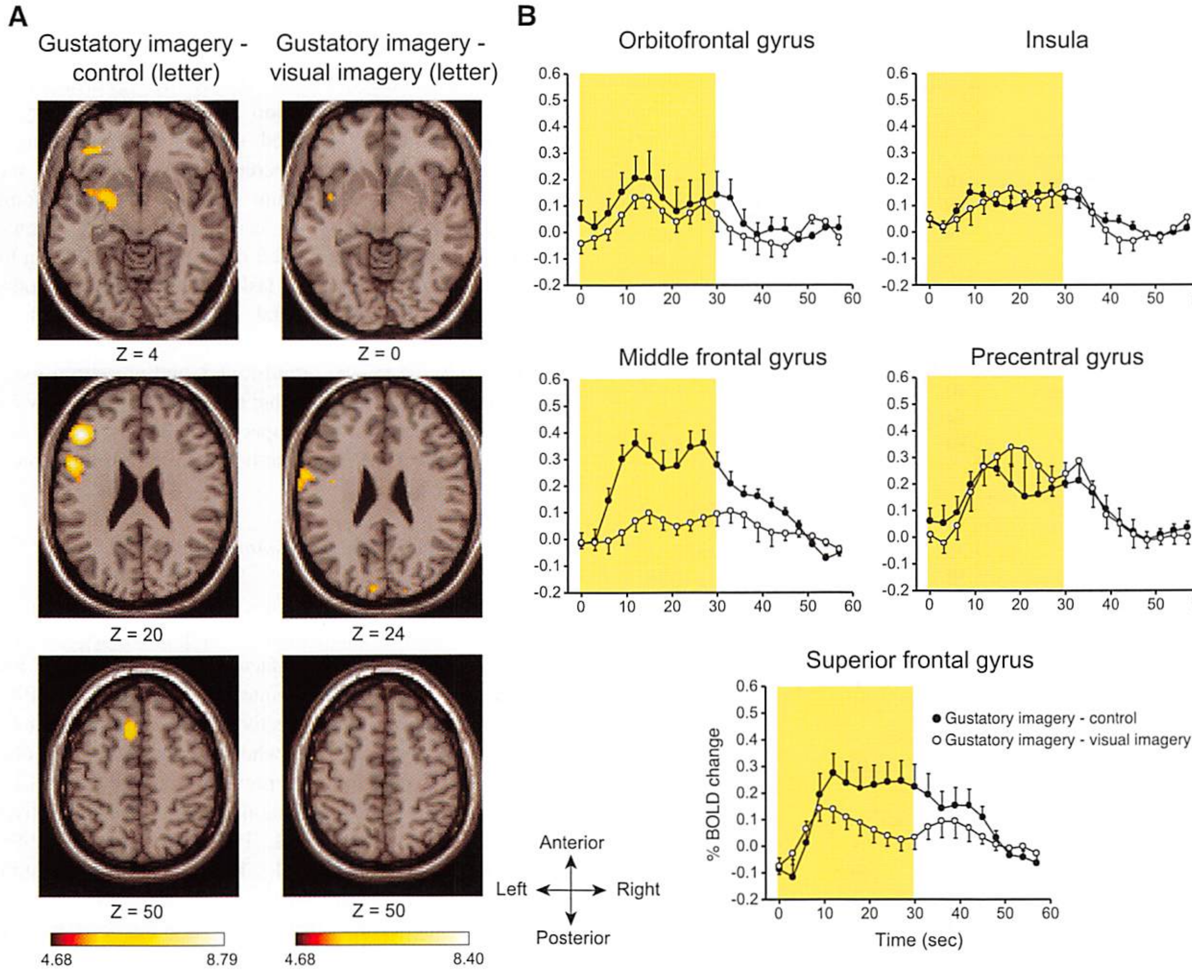

Fig. 3. Activated regions through gustatory imagery tasks shown in letters. (A) Activated regions in the gustatory imagery—control (letter) session (left panels) and the gustatory imagery—visual imagery (letter) session (right panels) superimposed on the standard brain. Top: The inferior frontal gyrus and insula were activated in the gustatory imagery—control (letter) session. In the gustatory imagery—visual imagery (letter) session, only the insula was activated. Middle: The middle frontal gyrus and precentral gyrus were activated in the gustatory imagery—control (letter) session, while only the precentral gyrus was activated in the gustatory imagery—visual imagery (letter) session. Bottom: The superior frontal gyrus was activated in the gustatory imagery—control (letter) session, but no activated region was found in the gustatory imagery—visual imagery (letter) session. Scale bars indicate t values of the gustatory imagery—control (letter) and gustatory imagery—visual imagery (letter) sessions. Z values at the bottom indicate the z-axis values of the standard brain according to the MNI coordinate system. The orientation arrows are applied to all slices. (B) Time course of BOLD signals of the maximally activated voxels within the clusters: the orbitofrontal and middle/superior frontal gyri, insula, and precentral gyrus. Closed and open circles indicate the values of the gustatory imagery—control (letter) and gustatory imagery—visual imagery (letter) sessions, respectively. Yellow shades indicate the period of gustatory imagery tasks. Error bars indicate SD across the subjects.

To show the regions active in common across the gustatory perception and imagery sessions, the conjunction analyses between gustatory perception and gustatory imagery—control sessions, or gustatory perception and gustatory imagery—visual imagery sessions, were performed. As shown in Table 5, the conjunction analyses demonstrated commonly activated regions, that is, the insula and precentral gyrus, throughout the sessions of gustatory perception and gustatory imagery. The activated clusters of the left insula in each session were overlapped or quite close to each other (Fig. 4). This finding suggests that the gustatory imagery tasks and a passive perception share a common region, a part of the insula.

BOLD signal increases in gustatory imagery sessions

We found five regions that showed significantly enhanced responses during gustatory imagery in all of three gustatory imagery—control sessions: the insula, orbitofrontal, precentral, and middle/superior frontal gyri in the left hemisphere (Tables 2 and 3). In each session, we set the region of interest (ROI) in the peak voxels of these five regions, all of which existed in the left hemisphere. In the session of gustatory imagery—visual imagery (voice), we found no activated clusters in the insula, orbitofrontal, and middle/superior frontal gyri. The ROIs of these unactivated regions were therefore set in the same voxel of the gustatory imagery—control (voice) session. The gustatory imagery—visual imagery (letter) session also showed no activation in the orbitofrontal and middle/superior frontal gyri. In this case, the ROIs of these regions were set in the same voxel of the gustatory imagery—control (letter) session.

We calculated the mean percentage of BOLD signal increase in gustatory imagery tasks, relative to control or visual imagery tasks. The first three BOLD signals of the ON and OFF blocks were

Table 3
Activated regions by gustatory imagery

	Peak coordinates			t value
	x	y	z	
Gustatory imagery—control (letter)				
L Insula/frontal operculum	−40	2	6	5.99
L Orbitofrontal gyrus	−36	36	−12	5.72
R Precentral gyrus	64	0	30	5.20
L Precentral gyrus	−62	−14	32	5.54
L Middle frontal gyrus	−44	30	24	8.64
L Superior frontal gyrus	−8	14	66	7.66
Gustatory imagery—visual imagery (letter)				
L Insula/frontal operculum	−40	0	−6	5.43
R Precentral gyrus	54	−6	36	4.92
L Precentral gyrus	−60	2	20	5.58
Gustatory imagery—control (voice)				
L Insula/frontal operculum	−34	22	2	6.27
L Orbitofrontal gyrus	−25	36	−14	5.73
R Precentral gyrus	52	−6	36	7.59
L Precentral gyrus	−52	10	10	8.83
L Middle frontal gyrus	−52	4	46	9.06
R Superior frontal gyrus	4	6	66	9.09
L Superior frontal gyrus	−8	6	66	10.38
Gustatory imagery—visual imagery (voice)				
L Precentral gyrus	−64	−10	30	5.19
Gustatory imagery—control (picture)				
L Insula/frontal operculum	−38	−4	16	4.96
L Orbitofrontal gyrus	−26	40	−16	5.00
R Precentral gyrus	64	−2	32	5.98
L Precentral gyrus	−54	2	38	6.04
L Middle frontal gyrus	−46	36	18	5.51
L Superior frontal gyrus	−6	−2	68	6.36

x, y, z: Stereotaxic coordinates of the peak of activated clusters. L: left; R: right.

excluded from the calculation because these signals were during the rise and fall periods, respectively. The result is summarized in Fig. 5. BOLD signals in the insula, orbitofrontal, and precentral gyri were increased by gustatory imagery tasks in both the gustatory imagery—control and gustatory imagery—visual imagery sessions, except the orbitofrontal gyrus in the gustatory imagery—control (letter) and gustatory imagery—visual imagery (voice) sessions, and the precentral gyrus in the gustatory imagery—visual imagery (voice) session (Figs. 5A–C). On the other hand, no statistically significant change of BOLD signals was observed in the middle and superior frontal gyri during the gustatory imagery—visual imagery sessions (Figs. 5D and E).

Laterality of activated areas by gustatory processing

To examine the laterality of gustatory processing in the cerebral cortex, we measured the volume of activated area in the insula, orbitofrontal, precentral, and inferior/middle/superior frontal gyri. As shown in Table 2, the activated volume in these regions by each imagery task was predominantly clustered in the left hemisphere, although passive gustatory stimulation dominantly activated the right insula. This finding suggests that gustatory information is asymmetrically processed in the primary gustatory cortex.

Discussion

In the present study, we investigated the organization of neural systems for gustatory perception and gustatory imagery. Passive gustatory stimulation activated several cerebrocortical regions including the insula/frontal operculum. The pattern of activation in the insula/frontal operculum was bilateral. We found that gustatory imagery tasks also activate the insula, showing the predominant activation in the left hemisphere. In addition to insula activation, gustatory imagery tasks, contrasted with nonimagery tasks, activated the orbitofrontal, precentral, and middle/superior frontal gyri. Gustatory imagery contrasted with visual imagery activated only the insula, orbitofrontal, and precentral gyri. These results suggest the possibility that the source of "top-down" signals may be in the middle and superior frontal gyri, and that these signals may affect the neural activities in the insula, orbitofrontal, and precentral gyri.

Activation in the insula by gustatory stimulus

Non-invasive imaging studies for gustatory sensation in the human have revealed that intraoral stimuli involve several types of processing: gustatory, olfactory, somatosensory, and oral movements. This complex interaction makes it difficult to identify the brain regions selectively processing gustation. Thus, it remains an open question whether a gustatory stimulus itself activates the insula. Indeed, previous studies using PET have reported that intraoral application of water evoked activation in the insula (Frey and Petrides, 1999; Small et al., 1999; Zald and Pardo, 2000; Zald et al., 1998). Our present study also showed that water stimulation activated the insula/frontal operculum, suggesting that these regions certainly process somatosensation such as tactile. This idea is supported by electrophysiological evidence in the monkey that a quarter of the neurons in the AI/FO respond to the mouth and jaw movements and only 4–9% neurons respond to taste (Scott and Plata-Salaman, 1999).

While several PET studies have reported that results obtained by the subtraction of water stimuli from taste stimuli did not show the activation in the insula (Frey and Petrides, 1999; Zald et al., 1998), other studies have shown the insula activation (Kinomura et al., 1994; Small et al., 1997a,b, 1999). Barry et al. (2001)

Table 4
Activated regions by gustatory imagery (conjunction analysis)

	Peak coordinates			t value
	x	y	z	
Gustatory imagery—control (letter/voice/picture)				
L Insula/frontal operculum	−30	0	12	3.05
L Orbitofrontal gyrus	−40	36	−14	2.20
R Precentral gyrus	50	−6	32	3.90
L Precentral gyrus	−50	−4	34	4.44
L Middle frontal gyrus	−42	32	18	4.48
L Superior frontal gyrus	−4	4	66	4.21
Gustatory imagery—visual imagery (letter/voice)				
L Insula/frontal operculum	−40	8	6	1.95
R Precentral gyrus	62	−4	28	2.55
L Precentral gyrus	−60	2	28	3.30

x, y, z: Stereotaxic coordinates of the peak of activated clusters. L: left, R: right.

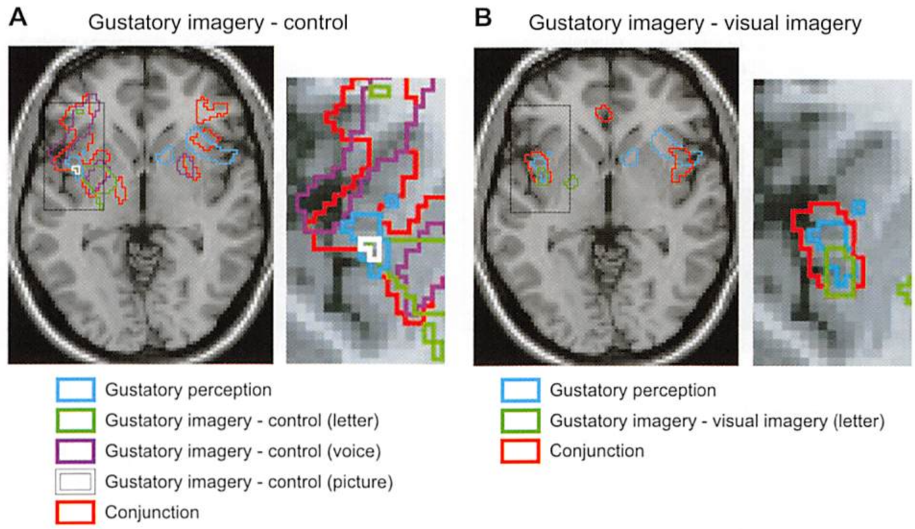

Fig. 4. Spatial relationship among the activated regions obtained from the sessions of gustatory perception and gustatory imagery. (A) The activated regions of the insula are outlined in colors: gustatory perception, blue; gustatory imagery—control (letter), green; gustatory imagery—control (voice), purple; and gustatory imagery—control (picture), white. The commonly activated regions obtained from the conjunction analysis over these sessions were shown in red. Inset: a magnified view of the black square. (B) The activated regions of the insula are outlined in colors: gustatory perception, blue; and gustatory imagery—visual imagery (letter), green. In the gustatory imagery—visual imagery (voice) session, the insula was not significantly activated. The commonly activated regions obtained from the conjunction analysis over these sessions were shown in red. Inset: a magnified view of the black square. The z-axis value of the standard brain was 4 according to the MNI coordinate system.

developed a method using electric taste stimulation, which was used during fMRI and avoided the effect of somatosensation, and they showed that electrical taste stimulation certainly activated the insula. The present study may explain these inconsistent results. Our results showed that the volume of activated regions in the insula/frontal operculum by gustatory stimulation was larger than that by water stimulation. Furthermore the region activated by water application in the insula/frontal operculum was within those activated by gustatory stimulation, suggesting that gustatory stimulation activates a larger population of cerebrocortical neurons in the insula/frontal operculum than water. However, the outer region of activation in the insula/frontal operculum might be weakly activated by water stimulation, though it is under statistical significance. Therefore, the subtraction of water stimulation from gustatory stimulation reveals a lower amplitude of activation in the insula/frontal operculum, which might mistakenly appear as if the insula/frontal operculum were not activated by gustatory stimuli.

Table 5
Activated regions by gustatory perception and imagery (conjunction analysis)

	Peak coordinates			t value
	x	y	z	
Gustatory perception and gustatory imagery—control (letter/voice/picture)				
L Insula/frontal operculum	−36	24	2	3.38
L Orbitofrontal gyrus	−32	40	−16	3.23
R Precentral gyrus	66	6	10	2.50
L Precentral gyrus	−58	4	34	3.53
L Middle frontal gyrus	−52	20	40	2.33
Gustatory perception and gustatory imagery—visual imagery (letter/voice)				
R Insula/frontal operculum	46	6	0	2.73
L Insula/frontal operculum	−40	−2	4	4.02
R Precentral gyrus	64	−6	24	3.61
L Precentral gyrus	−60	0	26	3.65

x, y, z: Stereotaxic coordinates of the peak of activated clusters. L: left; R: right.

Response in the orbitofrontal gyrus to gustatory stimulus

There is a dense axonal projection from the insula/frontal operculum to the orbitofrontal cortex (Cavada et al., 2000; Morecraft et al., 1992). Several imaging studies have shown that gustatory stimulation activates the orbitofrontal cortex, the secondary gustatory cortex (Small et al., 1997a,b; Zald et al., 1998; Zald et al., 2002). These studies required the subjects to discriminate the kind of taste or rate the stimulus for pleasantness–unpleasantness. On the other hand, the present study did not require higher brain processes, such as identification of the taste in the sessions of the passive gustatory or water stimulations, and the orbitofrontal gyrus was not activated. These findings suggest that the region in the orbitofrontal gyrus responding to gustatory stimuli may process identification of food, satiety, and preference of food, but a passive gustatory stimulus may not be sufficient to activate it. Indeed, not only gustatory information but also olfactory and/or visual information converge on neurons in the orbitofrontal cortex of the monkey (Rolls and Baylis, 1994), and they may be involved in decoding primary reinforcers such as taste and olfaction and in learning and reversing associations of visual and other stimuli to these primary reinforcers.

Gustatory imagery activates the insula

A part of activated area in the insula during passive gustatory perception is also activated by gustatory imagery, suggesting that the insula is not a simple passive gustatory processing area but that it also processes higher gustatory information by receiving a "top-down" signal. This hypothesis is supported by several

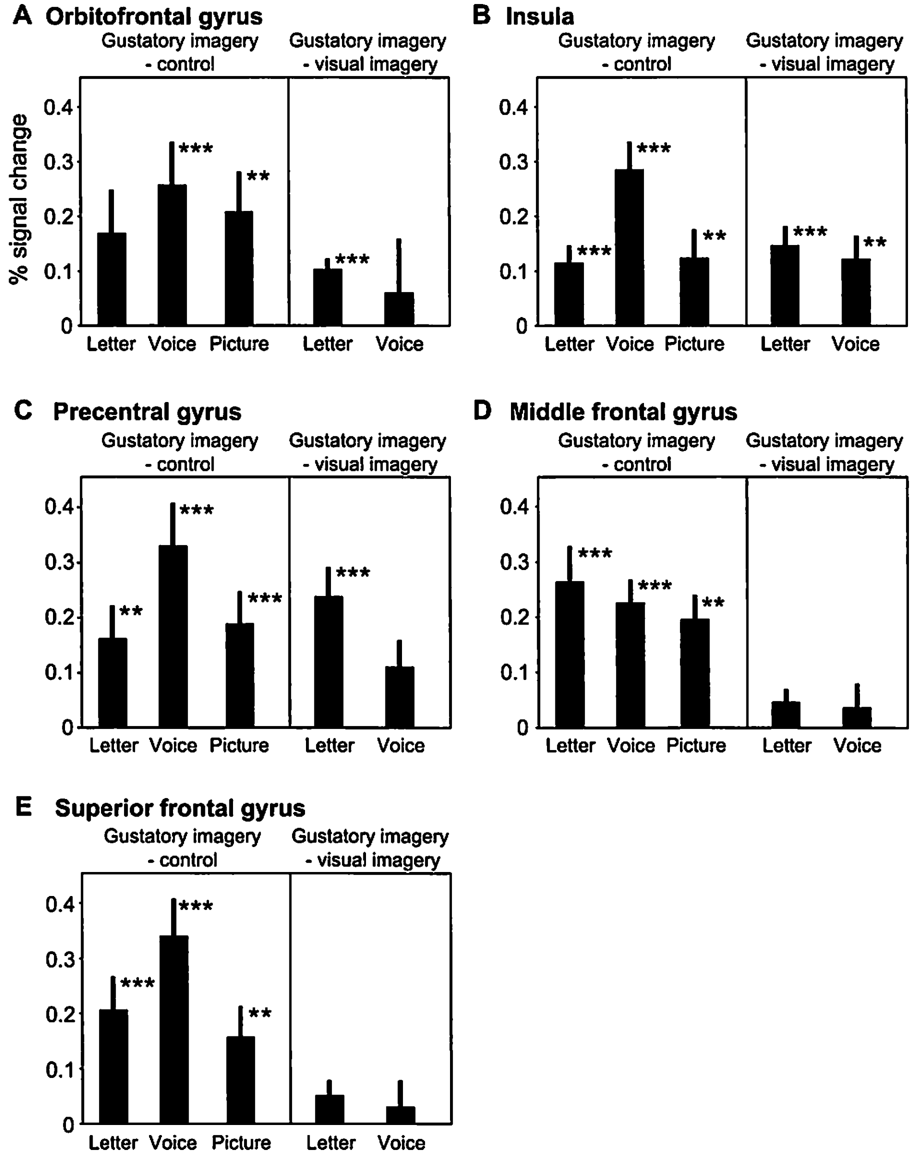

Fig. 5. BOLD signal changes (%) in the orbitofrontal gyrus (A), insula (B), precentral gyrus (C), middle frontal gyrus (D), and superior frontal gyrus (E) during gustatory imagery tasks relative to control or visual imagery tasks. Left three columns in each graph indicate the BOLD signal increase in the gustatory imagery—control (letter), gustatory imagery—control (voice), and gustatory imagery—control (picture) sessions. The right two columns indicate the BOLD signal increase in the gustatory imagery—visual imagery (letter), and gustatory imagery—visual imagery (voice) sessions. Note that only little BOLD signal increase was observed in the middle and superior frontal gyri during the gustatory imagery—visual imagery (letter and voice) sessions. Error bars indicate SD. $^{**}P < 0.01$, $^{***}P < 0.001$.

clinical studies. Penfield et al. (Penfield and Boldrey, 1937; Penfield and Faulk, 1955) showed that electrical stimulation in the insula evokes gustatory perceptions. In addition, a study of patients with parietal and/or temporal lobe epilepsy found that seizures included gustatory hallucinations (Hausser-Hauw and Bancaud, 1987). Patients with insular lesions showed deficits of taste recognition and intensity (Bornstein, 1940; Motta, 1959; Pritchard et al., 1999; Shenkin and Lewey, 1944). Our results taken together with these studies suggest that peripheral information from taste buds ("bottom-up" signals) and stored information such as gustatory memories ("top-down" signals) converge dominantly onto the left insula, and these signals are processed by neurons in the insula to generate gustatory recognition.

Recent imaging studies have examined brain responses to food or its pictures in the human. Gordon et al. (2000) reported that the visual perception of food decreases regional cerebral blood flow (rCBF) in the left temporoinsular and right inferior temporoparietal cortices. However, several fMRI studies have shown that food-related visual stimuli elicit no responses in the insula (Killgore et al., 2003; LaBar et al., 2001). In addition, PET studies by Karhunen et al. (1997, 2000) have reported that the food exposure has little effect on the rCBF in the brain of normal subjects. These findings suggest that exposure to food itself is not enough to yield significant activation in the insula. Combining the present findings, it is likely that gustation, including hallucinatory gustation, is an essential factor to activate the insula.

Asymmetrical activation in the insula

Gustatory imagery and gustatory perception evoked asymmetrical activity in the insula. Passive gustatory perception activated the insula bilaterally, whereas gustatory imagery evoked responses mainly in the left insula. This asymmetry raises the question of whether the role of the left insula is different from that of the right. Several functional brain imaging studies have reported the asymmetrical localization for mental imagery processing. Visual image generation causes greater activation in the left posterior temporal site (Farah, 1989), the left inferior temporal lobe (D'Esposito et al., 1997), or the left ventral temporal cortex (Ishai et al., 2000). Pritchard et al. (1999) reported that damage to the right insula produced deficits of taste recognition ipsilaterally, whereas damage to the left insula caused bilateral taste deficits, suggesting that taste information from both sides of the tongue passes through the left hemisphere. This hypothesis agreed with the result in the present study in that the gustatory imagery session activated mainly the left insula. Complex gustatory behaviors, such as discrimination of taste, may be processed mainly in the left insula.

Where are gustatory memories stored?

Regarding the regions that store gustatory memories, our results suggest that there are at least two candidates: the insula and the precentral gyrus, which were activated in both the gustatory imagery—control, and gustatory imagery—visual imagery sessions. Considering previous studies that showed the precentral gyrus is the center of the motor function, the activity in the central gyrus may be due to the imagery of oral movement and/or swallowing accompanied with the gustatory imagery (Zald and Pardo, 1999). The insula is therefore likely to store gustatory memories. In addition to the insula, the orbitofrontal gyrus is also a candidate for gustatory memory storage, though there was no significant activation in the orbitofrontal gyrus during the gustatory imagery—visual imagery sessions. As Rolls (1996) suggested, neurons in the orbitofrontal gyrus play an executive function in controlling and correcting reward- and punishment-related behavior and in emotion. Thus, there is a possibility that several neurons are involved in the visual processing in addition to encoding gustatory memories. This possibility may account for the result of less activation in the orbitofrontal gyrus during gustatory imagery—visual imagery sessions.

Candidate regions for the source of "top-down" signals

We have another important question: What region is the source of the "top-down" signals? Our results obtained by gustatory imagery, compared with control or visual imagery conditions, may have an interesting implication. Gustatory imagery tasks in combination with control tasks evoked activation in the insula, orbitofrontal, precentral, and middle/superior frontal gyri regardless of the way the task was presented. On the other hand, gustatory imagery, contrasted with visual imagery, activated merely the insula and precentral gyrus, and the responses in the middle and superior frontal gyri were negligible. It is likely that the generation of gustatory hallucinations and visual images requires activation in the middle and superior frontal gyri. Indeed, similar results were obtained in studies of visual imagery (Ishai et al., 2000) and motion imagery tasks (Goebel et al., 1998). The prefrontal cortex including the middle and/or superior frontal gyri has been shown to play an important role for "top-down" control of visual processing using event-related potential recording (Barcelo et al., 2000), PET (Buckner et al., 1996), and fMRI (Hopfinger et al., 2000). In addition, behavioral and electrophysiological studies in the monkey support the idea (Hasegawa et al., 1998; Tomita et al., 1999). Therefore, the middle and superior frontal gyri seem to play an essential role for generating the imagery without the specificity of sensory modality and might be candidates for the source sending "top-down" signals to the various regions that contain modality specific memories.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.neuroimage.2004.08.002.

References

Aglioti, S., Tassinari, G., Corballis, M.C., Berlucchi, G., 2000. Incomplete gustatory lateralization as shown by analysis of taste discrimination after callosotomy. J. Cogn. Neurosci. 12, 238–245.

Aglioti, S.M., Tassinari, G., Fabri, M., Del Pesce, M., Quattrini, A., Manzoni, T., Berlucchi, G., 2001. Taste laterality in the split brain. Eur. J. Neurosci. 13, 195–200.

Augustine, J.R., 1996. Circuitry and functional aspects of the insular lobe in primates including humans. Brain Res. Rev. 22, 229–244.

Barcelo, F., Suwazono, S., Knight, R.T., 2000. Prefrontal modulation of visual processing in humans. Nat. Neurosci. 3, 399–403.

Barry, M.A., Gatenby, J.C., Zeiger, J.D., Gore, J.C., 2001. Hemispheric dominance of cortical activity evoked by focal electrogustatory stimuli. Chem. Senses 26, 471–482.

Beauchamp, G.K., Cowart, B.J., 1985. Congenital and experiential factors in the development of human flavor preferences. Appetite 6, 357–372.

Beckstead, R.M., Norgren, R., 1979. An autoradiographic examination of the central distribution of the trigeminal, facial, glossopharyngeal, and vagal nerves in the monkey. J. Comp. Neurol. 184, 455–472.

Beckstead, R.M., Morse, J.R., Norgren, R., 1980. The nucleus of the solitary tract in the monkey: projections to the thalamus and brain stem nuclei. J. Comp. Neurol. 190, 259–282.

Börnstein, W.S., 1940. Cortical representation of taste in man and monkey. II. The localization of the cortical taste area in man and a method of measuring impairment of taste in man. Yale J. Biol. Med. 13, 133–156.

Buckner, R.L., Raichle, M.E., Miezin, F.M., Petersen, S.E., 1996. Functional anatomic studies of memory retrieval for auditory words and visual pictures. J. Neurosci. 16, 6219–6235.

Carmichael, S.T., Price, J.L., 1994. Architectonic subdivision of the orbital and medial prefrontal cortex in the macaque monkey. J. Comp. Neurol. 346, 366–402.

Cavada, C., Company, T., Tejedor, J., Cruz-Rizzolo, R.J., Reinoso-Suarez, F., 2000. The anatomical connections of the macaque monkey orbitofrontal cortex. A review. Cereb. Cortex 10, 220–242.

Cerf-Ducastel, B., Van de Moortele, P.F., MacLeod, P., Le Bihan, D., Faurion, A., 2001. Interaction of gustatory and lingual somatosensory perceptions at the cortical level in the human: a functional magnetic resonance imaging study. Chem. Senses 26, 371–383.

Collins, D., Neelin, P., Peters, T., Evans, A.C., 1994. Automatic 3D intersubject registration of MR volumetric data in standardized Talairach space. J. Comput. Assist. Tomogr. 18, 192–205.

D'Esposito, M., Detre, J.A., Aguirre, G.K., Stallcup, M., Alsop, D.C., Tippet, L.J., Farah, M.J., 1997. A functional MRI study of mental image generation. Neuropsychologia 35, 725–730.

Farah, M.J., 1989. The neural basis of mental imagery. Trends Neurosci. 12, 395–399.

Faurion, A., Cerf, B., Van De Moortele, P.F., Lobel, E., Mac Leod, P., Le Bihan, D., 1999. Human taste cortical areas studied with functional magnetic resonance imaging: evidence of functional lateralization related to handedness. Neurosci. Lett. 277, 189–192.

Francis, S., Rolls, E.T., Bowtell, R., McGlone, F., O'Doherty, J., Browning, A., Clare, S., Smith, E., 1999. The representation of pleasant touch in the brain and its relationship with taste and olfactory areas. NeuroReport 10, 453–459.

Frey, S., Petrides, M., 1999. Re-examination of the human taste region: a positron emission tomography study. Eur. J. Neurosci. 11, 2985–2988.

Goebel, R., Khorram-Sefat, D., Muckli, L., Hacker, H., Singer, W., 1998. The constructive nature of vision: direct evidence from functional magnetic resonance imaging studies of apparent motion and motion imagery. Eur. J. Neurosci. 10, 1563–1573.

Gordon, C.M., Dougherty, D.D., Rauch, S.L., Emans, S.J., Grace, E., Lamm, R., Alpert, N.M., Majzoub, J.A., Fischman, A.J., 2000. Neuroanatomy of human appetitive function: a positron emission tomography investigation. Int. J. Eat. Disord. 27, 163–171.

Hasegawa, I., Fukushima, T., Ihara, T., Miyashita, Y., 1998. Callosal window between prefrontal cortices: cognitive interaction to retrieve long-term memory. Science 281, 814–818.

Hausser-Hauw, C., Bancaud, J., 1987. Gustatory hallucinations in epileptic seizures. Electrophysiological, clinical and anatomical correlates. Brain 110, 339–359.

Hopfinger, J.B., Buonocore, M.H., Mangun, G.R., 2000. The neural mechanisms of top-down attentional control. Nat. Neurosci. 3, 284–291.

Ishai, A., Ungerleider, L.G., Haxby, J.V., 2000. Distributed neural systems for the generation of visual images. Neuron 28, 979–990.

Karhunen, L.J., Lappalainen, R.I., Vanninen, E.J., Kuikka, J.T., Uusitupa, M.I., 1997. Regional cerebral blood flow during food exposure in obese and normal-weight women. Brain 120, 1675–1684.

Karhunen, L.J., Vanninen, E.J., Kuikka, J.T., Lappalainen, R.I., Tiihonen, J., Uusitupa, M.I., 2000. Regional cerebral blood flow during exposure to food in obese binge eating women. Psychiatry Res. 99, 29–42.

Killgore, W.D., Young, A.D., Femia, L.A., Bogorodzki, P., Rogowska, J., Yurgelun-Todd, D.A., 2003. Cortical and limbic activation during viewing of high-versus low-calorie foods. NeuroImage 19, 1381–1394.

Kinomura, S., Kawashima, R., Yamada, K., Ono, S., Itoh, M., Yoshioka, S., Yamaguchi, T., Matsui, H., Miyazawa, H., Itoh, H., Goto, R., Fujiwara, T., Satoh, K., Fukuda, H., 1994. Functional anatomy of taste perception in the human brain studied with positron emission tomography. Brain Res. 659, 263–266.

Kobayashi, M., Sasabe, T., Takeda, M., Kondo, Y., Yoshikubo, S., Imamura, K., Onoe, H., Sawada, T., Watanabe, Y., 2002. Functional anatomy of chemical senses in the alert monkey revealed by positron emission tomography. Eur. J. Neurosci. 16, 975–980.

Kosslyn, S.M., Thompson, W.L., Alpert, N.M., 1997. Neural systems shared by visual imagery and visual perception: a PET study. NeuroImage 6, 320–334.

Kreiman, G., Koch, C., Fried, I., 2000. Imagery neurons in the human brain. Nature 408, 357–361.

LaBar, K.S., Gitelman, D.R., Parrish, T.B., Kim, Y.H., Nobre, A.C., Mesulam, M.M., 2001. Hunger selectively modulates corticolimbic activation to food stimuli in humans. Behav. Neurosci. 115, 493–500.

Morecraft, R.J., Geula, C., Mesulam, M.M., 1992. Cytoarchitecture and neural afferents of orbitofrontal cortex in the brain of the monkey. J. Comp. Neurol. 323, 341–358.

Motta, G., 1959. I centri corticali del gusto. Bull. Sci. Med. 131, 480–493.

Penfield, W., Boldrey, E., 1937. Somatic motor and sensory representation in the cerebral cortex of man as studies by electrical stimulation. Brain 60, 389–443.

Penfield, W., Faulk, M.E., 1955. The insula. Further observations on its function. Brain 78, 445–470.

Price, C.J., Friston, K.J., 1997. Cognitive conjunction: a new approach to brain activation experiments. NeuroImage 5, 261–270.

Pritchard, T.C., Hamilton, R.B., Morse, J.R., Norgren, R., 1986. Projections of thalamic gustatory and lingual areas in the monkey, Macaca fascicularis. J. Comp. Neurol. 244, 213–228.

Pritchard, T.C., Macaluso, D.A., Eslinger, P.J., 1999. Taste perception in patients with insular cortex lesions. Behav. Neurosci. 113, 663–671.

Rolls, E.T., 1996. The orbitofrontal cortex. Philos. Trans. R. Soc. Lond. B 351, 1433–1443.

Rolls, E.T., Baylis, L.L., 1994. Gustatory, olfactory, and visual convergence within the primate orbitofrontal cortex. J. Neurosci. 14, 5437–5452.

Rolls, E.T., Yaxley, S., Sienkiewicz, Z.J., 1990. Gustatory responses of single neurons in the caudolateral orbitofrontal cortex of the macaque monkey. J. Neurophysiol. 64, 1055–1066.

Scott, T.R., Plata-Salaman, C.R., 1999. Taste in the monkey cortex. Physiol. Behav. 67, 489–511.

Scott, T.R., Yaxley, S., Sienkiewicz, Z.J., Rolls, E.T., 1986. Gustatory responses in the frontal opercular cortex of the alert cynomolgus monkey. J. Neurophysiol. 56, 876–890.

Scott, T.R., Plata-Salaman, C.R., Smith, V.L., Giza, B.K., 1991. Gustatory neural coding in the monkey cortex: stimulus intensity. J. Neurophysiol. 65, 76–86.

Shenkin, H.A., Lewey, F.H., 1944. Taste aura preceding convulsions in a lesion of the parietal operculum. J. Nerv. Ment. Dis. 100, 352–354.

Small, D.M., Jones-Gotman, M., Zatorre, R.J., Petrides, M., Evans, A.C., 1997a. A role for the right anterior temporal lobe in taste quality recognition. J. Neurosci. 17, 5136–5142.

Small, D.M., Jones-Gotman, M., Zatorre, R.J., Petrides, M., Evans, A.C., 1997b. Flavor processing: more than the sum of its parts. NeuroReport 8, 3913–3917.

Small, D.M., Zald, D.H., Jones-Gotman, M., Zatorre, R.J., Pardo, J.V., Frey, S., Petrides, M., 1999. Human cortical gustatory areas: a review of functional neuroimaging data. NeuroReport 10, 7–14.

Smith-Swintosky, V.L., Plata-Salaman, C.R., Scott, T.R., 1991. Gustatory neural coding in the monkey cortex: stimulus quality. J. Neurophysiol. 66, 1156–1165.

Tomita, H., Ohbayashi, M., Nakahara, K., Hasegawa, I., Miyashita, Y., 1999. Top-down signal from prefrontal cortex in executive control of memory retrieval. Nature 401, 699–703.

Yaxley, S., Rolls, E.T., Sienkiewicz, Z.J., 1990. Gustatory responses of single neurons in the insula of the macaque monkey. J. Neurophysiol. 63, 689–700.

Zald, D.H., Pardo, J.V., 1999. The functional neuroanatomy of voluntary swallowing. Ann. Neurol. 46, 281–286.

Zald, D.H., Pardo, J.V., 2000. Cortical activation induced by intraoral stimulation with water in humans. Chem. Senses 25, 267–275.

Zald, D.H., Lee, J.T., Fluegel, K.W., Pardo, J.V., 1998. Aversive gustatory stimulation activates limbic circuits in humans. Brain 121, 1143–1154.

Zald, D.H., Hagen, M.C., Pardo, J.V., 2002. Neural correlates of tasting concentrated quinine and sugar solutions. J. Neurophysiol. 87, 1068–1075.