Exp Brain Res (2013) 227:185–197
DOI 10.1007/s00221-013-3499-z

RESEARCH ARTICLE

Localization of the primary taste cortex by contrasting passive and attentive conditions

Yuko Nakamura · Kenji Tokumori · Hiroki C. Tanabe · Takashi Yoshiura · Koji Kobayashi · Yasuhiko Nakamura · Hiroshi Honda · Kazunori Yoshiura · Tazuko K. Goto

Received: 3 December 2012 / Accepted: 22 March 2013 / Published online: 19 April 2013

Abstract The primary taste cortex is located in the insula. However, exactly where in the insula the human primary taste cortex is located remains a controversial issue. Human neuroimaging studies have shown prominent variation concerning the location of taste-responsive activation within the insula. A standard protocol for gustatory testing in neuroimaging studies has not been developed, which might underlie such variations. In order to localize the primary taste cortex in an fMRI experiment, we used a taste delivery system to suppress non-taste stimuli and psychological effects. Then, we compared brain response to taste solution during a passive tasting task condition and a taste quality identification task condition to verify whether this cognitive task affected the location of taste-responsive activation within the insula. To examine which part of insula is the primary taste area, we performed dynamic causal modeling (DCM) to verify the neural network of the taste coding-related region and random-effects Bayesian model selection (BMS) at the family level to reveal the optimal input region. Passive tasting resulted in activation of the right middle insula (MI), and the most favorable model selected by DCM analysis showed that taste effect directly influenced the MI. Additionally, BMS results at the family level suggested that the taste inputs entered into the MI. Taken together, our results suggest that the human primary taste cortex is located in the MI.

Keywords Primary taste cortex · Taste coding · Functional MRI · Top-down influence

Y. Nakamura (✉) · K. Tokumori · K. Yoshiura
Department of Oral and Maxillofacial Radiology, Faculty of Dental Science, Kyushu University, 3-1-1, Maidashi, Higashi-ku, Fukuoka 812-8582, Japan
e-mail: nakamura@rad.dent.kyushu-u.ac.jp

H. C. Tanabe
Division of Psychology, Department of Social and Human Environment, Graduate School of Environmental Studies, Nagoya University, Nagoya, Japan

T. Yoshiura · H. Honda
Department of Clinical Radiology, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan

K. Kobayashi · Y. Nakamura
Department of Medical Technology, Kyushu University Hospital, Fukuoka, Japan

T. K. Goto
Oral Radiology, Oral Diagnosis and Polyclinics, Faculty of Dentistry, The University of Hong Kong, Hong Kong, China

Introduction

Primary taste cortex is located in the insula. In primates, the taste pathways project directly from the nucleus of the solitary tract to the taste thalamus, and further on to the primary taste cortex in the anterior insula (AI) (Pritchard 2011). In humans, which part of insula is the primary taste cortex remains unclear.

If the human insula is anatomically and functionally analogous to that of non-human primates, it is possible that the human primary taste cortex is located in the AI. However, primate and human insula demonstrate some anatomical and functional differences. Although the general architectonic plan in the rhesus monkey and human is similar, Mesulam and Mufson (1982) showed that the human insula was much more extensive than that of the rhesus monkey and contains several sulci and at least 2 distinct gyri. A recent study reported another anatomical difference in the insula between humans and non-human primates. Von Economo neurons, which are found in the frontal insular cortex, the

anterior cingulate cortex, and the prefrontal cortex of humans (Fajardo et al. 2008), are most numerous in aged humans, but less numerous in children, gorillas, bonobos, and chimpanzees and nonexistent in macaque monkeys (Craig 2008).

Additionally, a clinical report using invasive electrocortical stimulation of the insula in patients with refractory epilepsy reported that gustatory symptoms occurred after stimulation of electrode contacts in the middle insula (MI), and that the AI did not show reproducible responses to stimulation (Stephani et al. 2011). Therefore, whether the human AI is anatomically and functionally analogous to the non-human primate insula remains unclear.

Previous neuroimaging studies in humans have shown prominent variation concerning the location of taste-responsive activation within the insula (de Araujo et al. 2003a; Faurion et al. 1998; Frank et al. 2008; Grabenhorst et al. 2008; Iannilli et al. 2012; Kobayakawa et al. 1999; Kobayashi et al. 2004; Kringelbach et al. 2004; Nitschke et al. 2006; Schoenfeld et al. 2004; Small et al. 1999; Smits et al. 2007; Veldhuizen et al. 2011; Verhagen and Engelen 2006; Wagner et al. 2006). Based on these results, the location of the primary taste cortex in the human brain has remained a controversial issue. One of the causes of such variation may be that no standard protocol has been developed for gustatory testing in neuroimaging studies. Different methods for delivering taste solutions and different cognitive tasks have been used in each neuroimaging study.

Various methods have been used to present taste stimuli. Some experiments have used a type of taste solution delivery systems that allowed participants to swallow solutions. In these experiments, the primary taste cortex was detected in the anterior to middle insula (de Araujo et al. 2003a; Haase et al. 2007; Iannilli et al. 2012; O'Doherty et al. 2001; Schoenfeld et al. 2004). Other experiments have used a type of taste solution delivery systems that did not facilitate participants to swallow for the presentation of taste solutions. These experiments identified primary taste cortex in the middle to posterior insula (Kami et al. 2008; Kobayakawa et al. 1999, 2012; Nakamura et al. 2011; Ogawa et al. 2005). Such differences in the type of taste delivery system might relate to these slight differences in the location of taste-related areas within the insula.

Insula is sensitive to a variety of food-related stimuli, such as odor (Veldhuizen et al. 2010), somatosensation (Cerf-Ducastel et al. 2001), texture (De Araujo and Rolls 2004), mouth temperature (Guest et al. 2007), swallowing (Martin et al. 2001), and chemesthetic stimulus (Rudenga et al. 2010). This feature of the insula is one cause of these differences in taste-related activity within it (Small 2010). In light of this issue, the use of a taste delivery system that does not force participants to swallow any solutions might be preferable to suppress non-taste stimuli (e.g., somatosensory stimulation).

The use of a variety of cognitive tasks in fMRI studies is also one cause of the observed differences in taste-related activity within the insula. Psychological factors, such as top-down attention to taste, affect the location of taste-responsive activation within the insula (Grabenhorst and Rolls 2008; Veldhuizen et al. 2007). Brain responses to a taste solution were greater in the anterior and middle insular taste cortex when attention was focused on to taste intensity than when attention was focused on the pleasantness of a taste stimulus (Grabenhorst and Rolls 2008). To reduce such psychological effects and keep participants in a passive condition, a taste delivery system that does not use any cues may be preferable.

We hypothesized that a passive tasting task would elicit activation in the primary taste cortex, and a cognitive task would elicit activation in the task-related area in addition to the primary taste cortex. We also hypothesized that the cognitive task would have top-down influences on taste coding to modulate connectivity between each taste coding-related region. To test our hypothesis, we conducted an fMRI experiment to localize the primary taste cortex using a taste solution delivery system to suppress non-taste stimuli and reduce psychological effects. Then, we compared brain response to a taste solution during a passive tasting task condition and a taste quality identification task condition (see Materials and methods) to verify whether the psychological task affects the location of taste-responsive activation within the insula. If a brain area responsive to a taste solution differed between the passive tasting and taste quality identification task conditions, we performed dynamic causal modeling (DCM) to verify the neural network of the taste coding-related region as well as random-effects Bayesian model selection (BMS) at the family level to examine which part of insula is the primary taste area.

Materials and methods

Participants

Eighteen healthy right-handed participants (9 women and 9 men, mean age ± SD, 26.1 ± 3.2 years, range, 22–33 years) participated in the present study. They had no history of neurological illness and were not under medication. The participants had not eaten for 2 h before the investigation. The Human Experimentation Committee of Kyushu University approved all experimental procedures, and written informed consent was obtained from all participants.

Taste solutions and delivery

The taste solutions included umami taste (0.1 M monosodium glutamate [MSG]) and salty taste (0.1 M sodium chloride). Both solutions were dissolved in distilled water. A tasteless

and odorless solution containing the main ionic components of saliva (25 mM KCl and 2.5 mM $NaHCO_3$) was used as the control (de Araujo et al. 2003b; O'Doherty et al. 2001), since water has been proposed to stimulate taste cortex (de Araujo et al. 2012; Zald and Pardo 2000). The mean temperature of solutions at the time of the experiment was 22.4 ± 0.9 °C (mean ± SD). The taste solution was delivered by means of a homemade system, with the approved protocol described extensively by Nakamura et al. (2011). The participant perceived the taste stimulus in a passive manner. A continuous suction apparatus, connected to the mouthpiece of the delivery system, prevented participants from swallowing any solution including their own saliva.

Experimental design

To encourage participants to maintain their attention to taste quality during the taste quality identification task event, we designed our experimental procedure using a modification of a task used in a previous study (Buchel and Friston 1997). Buchel and Friston (1997) demonstrated that attention to visual motion could increase the responsiveness of motion-selective cortical area V5 and posterior parietal cortex. In their study, to encourage participants to maintain their attention to visual motion, they asked participants to indicate any change in speed of moving dots in a training session, while during fMRI scanning, they instructed them in the same manner as in the training session but completely eliminated visual motions, so that identical visual stimuli were shown throughout the fMRI session. We asked participants to identify a salty solution in an umami solution in a training session, while during fMRI scanning, we instructed them in the same manner as in the training session but with the salty solution eliminated, so that an identical taste solution (umami solution) was administered throughout this session.

Training session

In the training session, the participants were familiarized with the task and confirmed their ability to perform the experiment comfortably without gagging. The experimental design is depicted in detail in Fig. 1. Each taste solution period lasted 8 s and was followed by a tasteless solution period of 12 s. The fMRI paradigm consisted of 2 events, "identification" and "passive." We presented each event in a random sequence.

In the taste quality identification event, participants were provided a cue in the form of a red cross presented on the screen that was set in front of their faces, and they received the umami solution in their mouth. During this period, we instructed them to identify a salty solution that was administered in the umami solution for less than 1 s. The duration of salty solution administration was gradually shortened

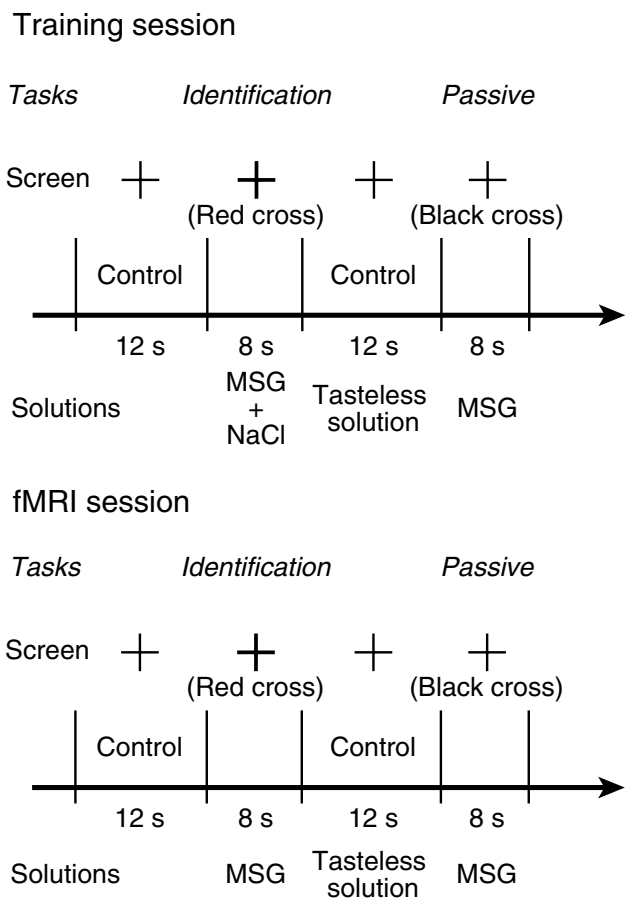

Fig. 1 The experimental design. Each taste solution period was 8 s in length, and following it, each tasteless solution period was 12 s in length. During a taste solution period, a *red cross* ("identification" task) or *black cross* ("passive" task) was presented on the screen set in front of the participant's face, which was followed by a control period of 12 s with a *black cross*. In the training session, a *red cross* was presented, and a salty solution was administrated with the umami solution for less than 1 s in the taste quality identification event. In the fMRI session, the salty solution was not administrated, and we administered only the umami solution in both events. Each event consisted of 12 trials, and the 2 tasks were presented pseudorandomly

in every taste quality identification event, and the shortest periods of salty administration that individual participants could detect were determined. In the passive event, participants were shown a black cross on the screen and received the umami solution. We instructed participants to taste passively in this event. During a control period, a black cross was presented on the screen, and the tasteless solution was delivered. Immediately after the training session, we asked all participants whether they could recognize the umami solution at each event, and whether the umami solution was too weak to recognize or too strong, so as to feel aversive. All participants reported that they could recognize the umami solution, and it was neither too weak to recognize nor so strong as to feel aversive.

fMRI session

In the fMRI experiment, we instructed the participants in the same manner as in the training session, but administered only the umami solution during both passive tasting and taste quality identification events. Therefore, participants tried to identify the salty solution in the umami solution during taste quality identification events although the salty solution was not administered. Each event consisted of 12 trials, and these events were presented pseudorandomly. Visual cues were presented in the same manner as in the training session. No verbal or tactile responses were required of participants.

Behavioral data were obtained immediately after fMRI scanning. We asked the participants to rate the perceived intensity of taste in each event using a visual analog scale ranging from 0 for very weak (no taste) to 10 for very intense ("strongest imaginable taste"). Data were then analyzed by paired-sample t test (SPSS 19.0 software, SPSS Inc, Chicago, USA) with a significance level of $P < 0.05$. We also asked participants to estimate how many times they could identify the salty solution during the fMRI session.

Functional image acquisition

All images were acquired with a 3.0-Tesla whole-body MRI scanner (Achieva TX, Philips Health Care, Best, The Netherlands). Functional scans were obtained using a T2*-weighted echo-planar imaging (EPI) sequence (TR = 3,000 ms, TE = 35 ms, flip angle = 90°, field of view (FOV) = 200 mm, matrix size = 128 × 124 pixels, voxel size = 1.56 × 1.56 × 3.00 mm^3, slice thickness = 3.0 mm, gap = 0 mm). Each EPI volume consisted of 42 axial slices that were acquired in an interleaved mode to reduce the cross-talk of the slice selection pulse. For anatomical reference, T1-weighted three-dimensional turbo field-echo images (TR = 8.2 ms, TE = 3.7 ms, flip angle = 8°, FOV = 240 mm, matrix size = 240 × 240 pixels, voxel size = 1.0 × 1.0 × 1.0 mm^3) were obtained from each participant.

Functional image analysis

Image processing and data analysis were performed using the Statistical Parametric Mapping 8 (SPM8) software package (Wellcome Trust Centre for Neuroimaging, London, UK) implemented in MATLAB 7.4 (The MathWorks Inc., Natick, MA, USA). The first 3 volumes of functional images were discarded owing to unsteady magnetization, and the remaining 160 volumes per run were used for the analysis.

First, the functional images were time acquisition corrected to the slice obtained at 50 % of the TR. Next, all functional images were realigned to the first, and a mean image was created. An anatomical T1-weighted image was co-registered to this mean image. Then, the functional images were normalized (retaining 2 × 2 × 2 mm^3 voxels) to Montréal Neurological Institute (MNI) space and spatially smoothed with a full width at half-maximum isotropic Gaussian kernel of 6 mm. For the time series analysis of all participants, data were high-pass filtered with a cutoff of 128 s to remove confounds created by slow signal drifts with a period exceeding this threshold.

Conventional general linear model (GLM) analysis

Event-specific effects at each voxel were estimated using GLM. In GLM, we included 2 regressors of interest ("passive" and "identification"). We defined each event of interest as an 8-s block. The response to events was modeled by a canonical hemodynamic response function. Since we delivered solutions constantly throughout fMRI scanning, except for the effect of "taste" or "identification task," all conditions (e.g., temperature, texture) during fMRI scanning were supposed to be constant. Therefore, the duration of control was modeled as the baseline. Then, we measured the event baseline difference (Worsley 2001).

Our contrasts of interest were (1) "passive" and (2) "identification" versus "passive." The passive condition reflected the effect of taste in a passive state, and the taste quality identification condition versus passive tasting condition reflected the effect of the taste quality identification task. Contrasts from the first (subject-specific) level were used in a second-level random-effects analysis to test for consistent effects across participants. The insula was included in a region of interest (ROI) based on previous studies showing that the insula formed the core of gustatory perception both in humans (Small et al. 1999; Veldhuizen et al. 2011; Verhagen and Engelen 2006) and the macaque monkey (Yaxley et al. 1990). The prefrontal cortex was also included in a ROI based on its relation to attentional control (Arnsten 2009). Our ROI approach used a WFU PickAtlas (Maldjian et al. 2003, 2004; Tzourio-Mazoyer et al. 2002) to create one unique ROI composed of the prefrontal cortex together with the bilateral insula (number of voxels = 40,425, Fig. 2). The prefrontal cortex portion included bilateral superior frontal gyrus (SFG; dorsolateral, medial, and orbital part), middle frontal gyrus (MFG; lateral and orbital part)/frontal eye field (FEF), and inferior frontal gyrus (IFG; opercular, triangular, and orbital part).

The statistical threshold for imaging analyses was set at P value less than 0.001 at the voxel level without correction for multiple comparison and $P < 0.05$ with family-wise

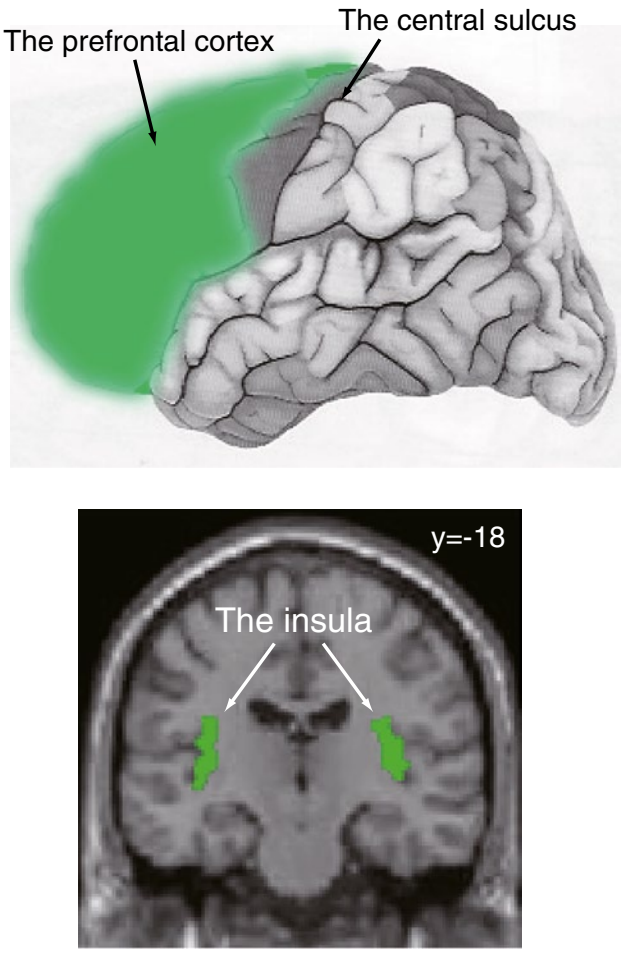

Fig. 2 The ROI location (number of voxels = 40,425). The ROI included bilateral insula, SFG, MFG, and IFG. The *upper figure* is the region of the prefrontal cortex part. The *bottom figure* depicts a coronal slice of the insula part overlaying the canonical anatomical image available in SPM8

error rate (FWE) correction at the cluster level across a ROI for multiple comparisons.

Effective connectivity analysis using dynamic causal modeling

We used DCM (version 10) in SPM8 (Wellcome Trust Centre for Neuroimaging) to examine how the effect of the taste quality identification task modulated brain activation in the taste area and to reveal the optimal primary taste area. DCM is a hypotheses-driven approach to model dynamics in a system of interacting neuronal populations, which are not directly observable with fMRI. DCM parameters include (1) parameters that mediate the influence of extrinsic inputs on the brain regions, that is, "driving input"; (2) parameters that mediate intrinsic coupling among the brain regions, that is, "intrinsic connections"; and (3) bilinear parameters that allow the inputs to modulate that coupling, that is, "modulatory input." The parameters at both neural and hemodynamic levels are adjusted to minimize the differences between predicted and measured blood-oxygen-level-dependent (BOLD) time series (Friston et al. 2003). In this study, the driving input (taste stimulus) directly elicited local responses that were propagated through the embedded system in DCM according to intrinsic connections. The strengths of these connections could be changed by modulatory inputs (the effect of the taste quality identification task).

Volumes of interest (VOIs) for DCM were determined to estimate connectivity among the primary taste areas and to reveal the optimal taste input region, which was activated in our fMRI experiment. According to the results of the group analysis, we defined 3 VOIs. The taste areas were functionally localized to the right AI and right MI. Since the MFG/FEF is activated by an attentional task (Veldhuizen et al. 2007, 2012) and the strong influence coming from the FEF via anterior cingulate cortex indirectly modulates taste processing in the gustatory cortex (Veldhuizen et al. 2012), the MFG/FEF may influence taste processing in the anterior insula. Therefore, the attentional control area was also functionally localized to the right MFG/FEF.

We tested 2 hypotheses: (1) the MI was the primary taste area, because higher activation was observed in the MI than in the AI during the passive event, and (2) although we were unable to observe activation in the AI at the set threshold during the passive event, the AI was the primary taste area because activation in the AI was very low without manipulation of the taste quality identification task. Although other regions participated in the quality identification task (Table 1), we did not need to include other regions to investigate our main hypotheses. Therefore, we did not focus on the cross-hemisphere interactions between regions in this study.

We constructed 6 DCMs in the right hemisphere (Fig. 3). The effect of taste was used as a driving input that entered into the MI (Models 1–3) or the AI (Models 4–6). All models were specified to have bidirectional intrinsic connections between all 3 areas. Since a recent neuroimaging study using resting state functional connectivity MRI suggested a functional connection between the AI and MI (Deen et al. 2011), we specified to have bidirectional intrinsic connections between the AI and MI. Since evidence of resting state functional connectivity suggested that dorsal anterior to middle insula was functionally connected with regions implicated in the control of attention including around the FEF (Deen et al. 2011), we specified the existence of bidirectional intrinsic connections between the MFG/FEF and AI and between the MFG/FEF and MI. The effect of the identification task was used as a modulatory input placed on the intrinsic connections from the MI to AI and from the MFG/FEF to AI. The activation in the MI during passive

Table 1 Brain regions showing the effect of each task

Anatomical region	MNI coordinates			*t* value	cluster size	*P*
	x	*y*	*z*			
Passive						
Whole brain						
No significant activation						
ROI						
R middle insula	44	−6	12	5.15	26	0.015
Identification—passive						
Whole brain						
L Cerebellum	−38	−60	−30	8.95	359	0.000
	−10	−74	−20	5.10	50	0.001
R Cerebellum	20	−64	−28	5.58	197	0.000
L Precentral gyrus	−38	−8	46	5.70	38	0.009
R Precentral gyrus	48	0	42	8.09	488	0.000
L Supramarginal gyrus	−54	−48	34	6.36	152	0.000
R Supramarginal gyrus	60	−42	28	7.71	225	0.000
R Superior frontal gyrus	16	8	64	7.44	1,307	0.000
L Anterior insula	−36	18	−2	6.08	226	0.000
R Anterior insula	48	12	0	6.75	189	0.000
L Inferior frontal operculum	−54	10	26	6.00	36	0.012
R Inferior frontal operculum	54	10	28	6.11	172	0.000
R Inferior frontal gyrus	32	26	4	5.21	31	0.028
R Middle frontal gyrus	34	56	16	5.91	56	0.001
	42	34	38	5.04	66	0.000
R Precuneus	8	−72	40	4.82	37	0.010
R Cingulate gyrus	4	−22	28	4.79	49	0.012
ROI						
R Superior frontal gyrus	16	8	64	7.44	131	0.000
R Medial superior frontal gyrus	6	28	40	7.07	105	0.000
R Middle frontal gyrus/FEF	50	10	46	6.96	32	0.005
R Middle frontal gyrus	40	2	62	6.55	98	0.000
	34	56	16	5.91	56	0.000
	42	34	38	5.04	66	0.000
R Inferior frontal operculum	54	10	28	6.11	116	0.000
L Anterior insula	−36	18	−2	6.08	188	0.000
R Anterior insula	48	12	0	6.75	174	0.000
L Inferior frontal gyrus	−40	36	24	5.87	22	0.033
R Inferior frontal gyrus	32	26	4	5.21	28	0.011

MNI coordinate: maximum coordinate *x*, *y*, *z* in MNI-space. Cluster size: number of voxels inside the cluster. *P*: the statistical threshold at $P < 0.05$ FWE corrected at the cluster level

L left, *R* right, *FEF* frontal eye field

tasting task and during the taste quality identification task did not significantly differ ($P = 0.74$) (Fig. 4b). Therefore, we did not place any modulatory inputs on the connections from other areas to the MI.

We then extracted time series across participants by combining anatomical and functional constraints. First, for any VOI of the models, we determined the coordinates of the group maximum in the random-effects analysis (see the results of conventional GLM analysis). Each of these participant-specific local maxima was required to be located within the same anatomical gyrus as the group maximum and not further away than 10 mm. Mean coordinates ([$x \pm$ SE, $y \pm$ SE, $z \pm$ SE]) in MNI-space for the 3 VOIs were as follows: right AI, [40.0 ± 0.65, 13.0 ± 1.00, 1.3 ± 1.10];

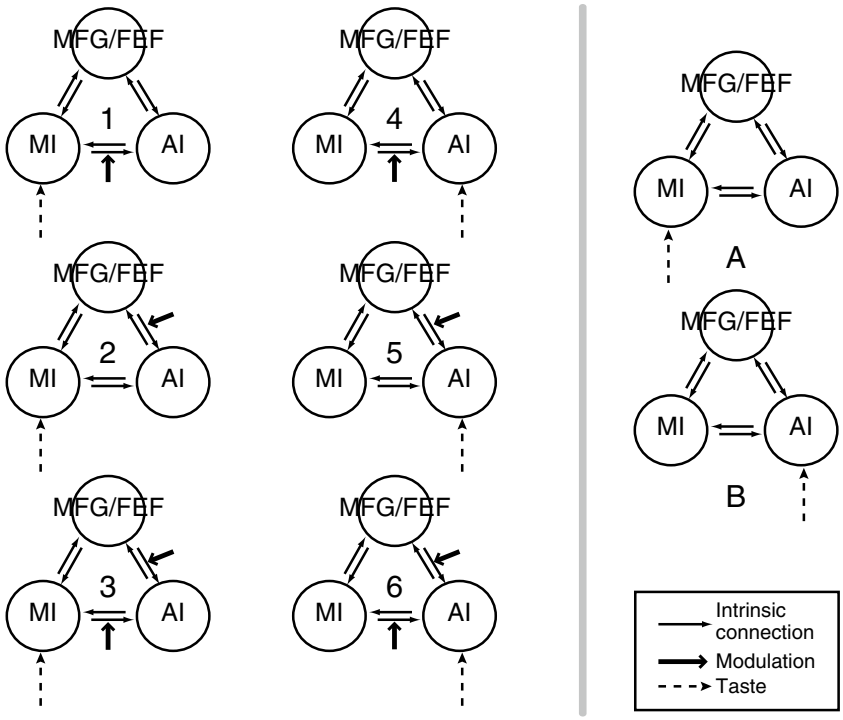

Fig. 3 The basic architecture of the models. The *left side* of a *gray bar*: Illustration of the 6 different models estimated and compared here. Effect of taste was used as a driving input and entered into the MI (Model 1–3) or AI (Model 4–6). All models were specified to have bidirectional intrinsic connections between all 3 areas. The effect of the taste quality identification task was used as a modulatory input that was placed on the intrinsic connections from the MI to AI and from the MFG/FEF to AI. The *right side* of a *gray bar*: Families *A* and *B* differ in driving regions. Family *A* included Models 1–3, and family *B* included Models 4–6

right MI, [39.78 ± 0.81, −6.44 ± 0.80, 9.11 ± 1.24]; right MFG/FEF, [48.9 ± 0.90, 7.4 ± 0.93, 44.4 ± 0.91]. Second, in order to extract time series from each participant-specific VOI, we defined GLM for DCM. We recombined regressors that were used to execute the conventional GLM analysis. We set 2 conditions, "taste" and "attention." The "taste" condition included "identification" and "passive" regressors, and the "attention" condition included an "identification" regressor. "Taste" was modeled as a "driving input" able to cause direct responses in primary taste areas. "Attention" was modeled as a "modulatory input" able to change the effective connectivity ("intrinsic connections") in the DCM. Once we had specified and estimated the GLM for DCM, we defined the *F*-contrast that was needed for mean correcting the extracted time series. Finally, we extracted time series from each participant-specific VOI by using GLM for DCM.

To determine the best model to fit the observed data from all participants, we implemented a random-effects BMS at the group level (Stephan et al. 2009). For the best model to fit the observed data from all participants, DCM parameters were obtained for the following effects: (1) the direct influence of taste on regional activity ("driving input"), (2) the intrinsic connections between regions ("intrinsic connections"), and (3) the changes in intrinsic connectivity between regions induced by the effect of the taste quality identification task ("modulatory input") (Friston et al. 2003). One-sample *t*-tests were performed on the parameters. Connections were considered statistically significant if they passed a threshold of $P < 0.05$.

Additionally, to reveal the optimal input region, we performed random-effects BMS at the family level (Penny et al. 2010). We defined 2 families (noted A and B in Fig. 3) that partitioned the whole model space into different families with no overlap. These 2 families of models varied in terms of their driving inputs into the MI or AI. Family A included Models 1, 2, and 3, and Family B included Models 4, 5, and 6. BMS was then used to compare these competing families so that inferences could be made at the family level. An exceedance probability was computed corresponding to the belief that a particular family is more likely than the other, given the data from all participants.

Results

Behavioral data

Ratings of the perceived intensity of taste

The rating of perceived taste intensity in the taste quality identification event was 4.9 ± 0.4 (mean ± SE), and that in the passive tasting event was 4.6 ± 0.4. Ratings did not significantly differ between events ($P = 0.31$).

Debriefings about the taste quality identification event

To confirm whether participants tried to detect a salty solution during the taste quality identification event, all participants were debriefed after the fMRI scanning session, and

all except one reported that they detected the salty solution more than once during the taste quality identification event. In the fMRI scanning session, 18 participants detected salty solution 4.1 ± 0.7 (mean ± SE) times during the "identification" event. All participants were rather surprised when informed that no salty solution had been administered.

Functional imaging data

Conventional GLM analysis

The effect of passive tasting task According to the whole-brain analysis, the passive tasting task did not result in significant activation. Within our ROI, an effect of the task was observed in the right MI ($P < 0.05$, FWE corrected at the cluster level) (Fig. 4a; Table 1).

The effect of the taste quality identification task To determine the regions that represented the effect of the taste quality identification task rather than the effect of the passive tasting task, we contrasted the taste quality identification event and passive tasting event (["identification"]—["passive"]). In the whole-brain analysis, brain activation induced by the effect of the taste quality identification task was observed in multiple brain regions with the statistical threshold of $P < 0.05$ (FWE corrected at the cluster level) (Table 1). In the ROI analysis, significant effects of the task were observed in the AI [taste cortex (Pritchard 2011)] and the MFG/FEF [attentional control area that influences taste processing in the anterior insula (Veldhuizen et al. 2012)] with the statistical threshold of $P < 0.05$ (FWE corrected at the cluster level) (Fig. 4a; Table 1). There was no significant difference between the activation observed in the MI during the passive tasting task and that observed during the taste quality identification task (paired-sample t test, $P = 0.74$) (Fig. 4b).

DCM analysis

DCM analysis was performed to examine how the effect of the taste quality identification task modulated taste areas and then to reveal the optimal taste input region. The best model to fit the observed data across all participants was identified using the random-effects BMS. Then, the most likely family or the winning family across all participants was identified using the random-effects BMS at the family level in order to reveal the optimal input region.

BMS demonstrated significant evidence (exceedance probability, 0.793) in favor of Model 3 (Fig. 5). In Model 3, the direct influence of taste into the MI, the modulation placed on the connection from the MI to AI, and the connection from the MFG/FEF to AI were significantly greater than zero ($P < 0.05$). Means and SEs of all the parameter estimates for the selected model (Model 3) are described in Table 2. All modeled intrinsic connections, except the connection from the AI to MI ($P = 0.053$) and the MFG/FEF to MI ($P = 0.218$), were significantly greater than zero ($P < 0.05$).

We compared the 2 different families (A and B) using the BMS approach to reveal the optimal input region. The winning family was family A (exceedance probability, 0.979), indicating that family A accounted for a total of 0.979 in exceedance probability (Fig. 5a). Our BMS result at the family level suggested that the driving inputs entered into the MI.

Discussion

We performed an fMRI experiment to test the hypotheses that (1) the passive tasting task would elicit activation in the primary taste cortex, while a cognitive task would elicit activation in the task-related area in addition to the primary taste cortex, and (2) the cognitive task would demonstrate top-down influences on taste coding. These effects would modulate connectivity between each taste coding-related region. According to our conventional GLM analysis results, the effect of the passive tasting task was observed in the right MI, and that of the taste quality identification task was observed in the bilateral AI. The effect of the taste quality identification task was also observed in the right MFG/FEF. DCM analysis was performed to examine how the effect of the taste quality identification task modulated taste areas and then to reveal the optimal taste input region. The result of BMS suggested that the effect of the task was modulated by the strength of both intrinsic connections, MI to AI and MFG/FEF to AI. Additionally, BMS results at the family level suggested that the driving inputs entered into the MI. Collectively, our results suggest that the primary taste cortex is located in the MI, rather than the AI.

The insular taste cortex

The results of conventional GLM showed that passive tasting resulted in activation of the right MI, which has been proposed as a component of early taste cortex (Small et al. 1999; Small 2010; Veldhuizen et al. 2011; Verhagen and Engelen 2006). BMS results suggested that the most favorable model is Model 3 (exceedance probability = 0.793). In this model, the driving input to the right MI was significantly greater than zero. Additionally, BMS results at the family level revealed that family A, with set driving inputs into the MI, accounted for a total of 0.979 in exceedance probability. Taken together, these results indicate the possibility that the primary taste cortex is located in the MI.

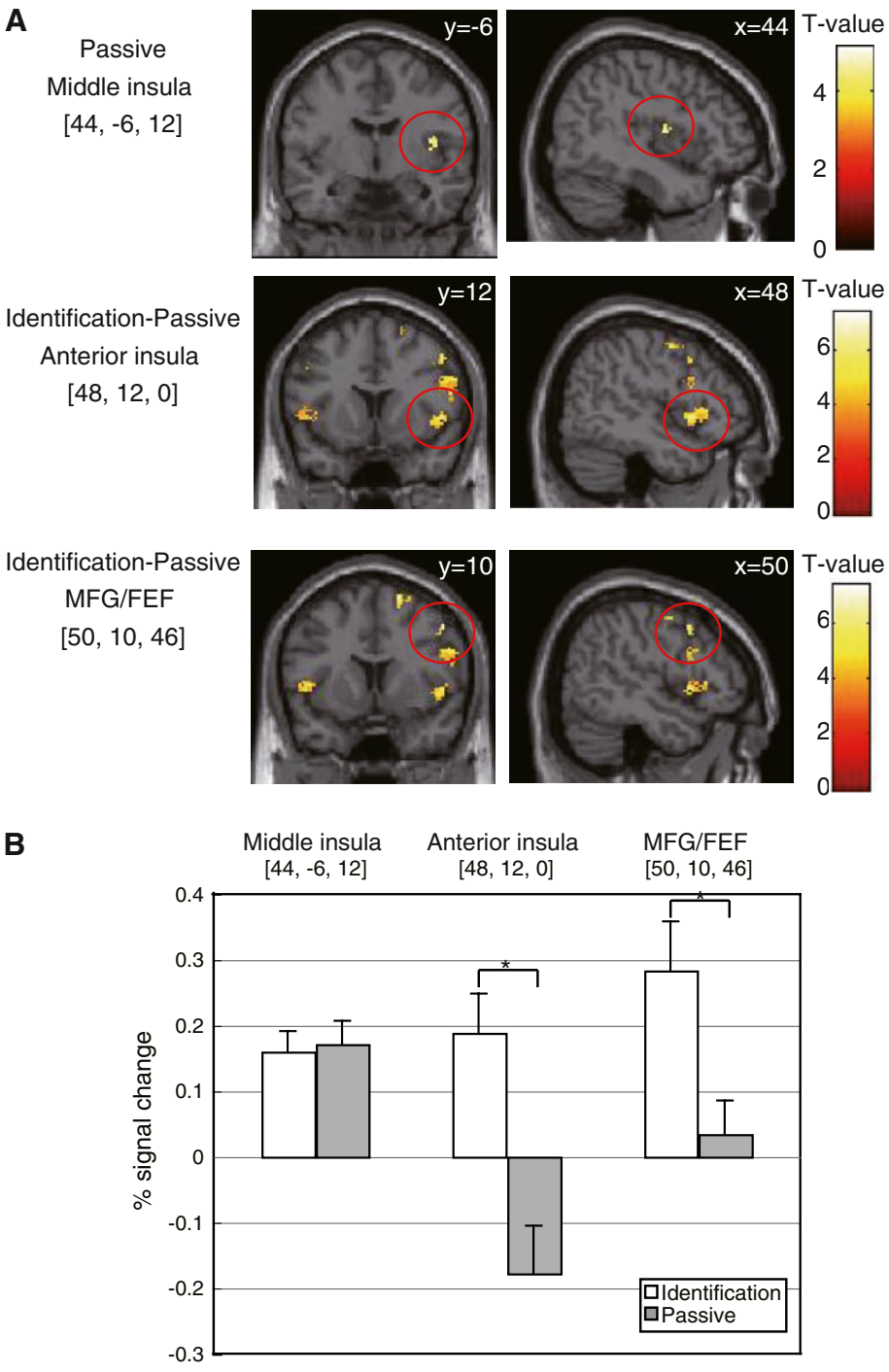

Fig. 4 Brain activation in the ROI analysis. **a** An effect of taste in the passive tasting event was observed in the right MI ($P < 0.05$, FWE corrected at the cluster level; *top row*), and significant effects of the taste quality identification task were observed in the AI (taste cortex; *middle row*) and MFG/FEF (the attentional control area; *bottom row*) with the statistical threshold of $P < 0.05$, FWE corrected at the cluster level. The *colored bar* depicts *T* values. [*x*, *y*, *z*] = MNI coordinate. **b** The *bar graphs* show (on the *y*-axis) the percentage signal change for the taste quality identification event (*white bars*) and passive tasting event (*dark gray bars*) (±SEM), averaged over participants. MNI coordinates [*x*, *y*, *z*] of the voxel that responded maximally within the significant cluster are shown on the *x*-axis. The response was taken from the significant cluster, as identified in the fMRI analysis. *Significant difference was observed between % signal changes in each event (paired-sample *t* test, $P = 0.000$)

A previous study demonstrated that the primary taste cortex in the primate is located in the AI (Pritchard 2011). Petrides et al. (1996) reported a close correspondence in the architectonic features of the anterodorsal insula and adjacent frontal opercular cortex in the human and macaque brains. Additionally, some human neuroimaging studies have reported responses to taste stimuli in the AI (Grabenhorst et al. 2008; McCabe and Rolls 2007; Small and Prescott 2005). Thus, primary taste cortex has been considered likely to demonstrate good correspondence between monkeys and humans (Rolls 2007).

However, the results of other studies have not supported the hypothesis that the human primary taste cortex is located in the AI. One neuroimaging study suggested that the most anterior section of insula in humans might not be a functionally homologous region to the most anterior section of insula in monkeys, which is the putative primary taste cortex in the monkey brain. Veldhuizen and

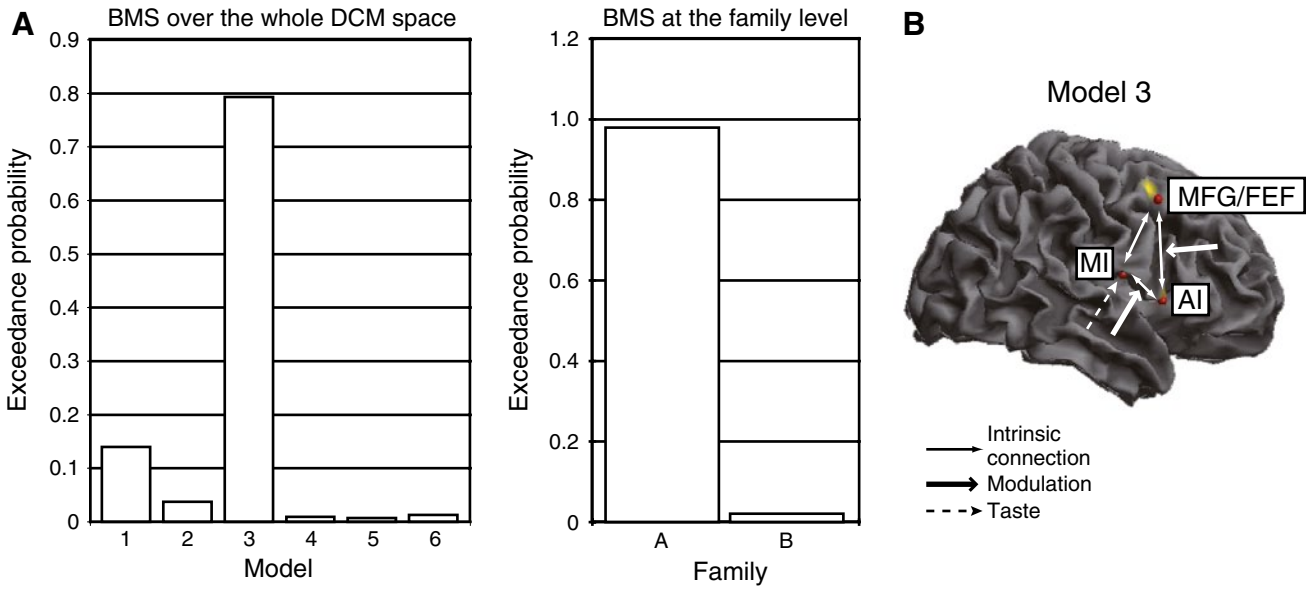

Fig. 5 The result of DCM. **a** The *left graph*: the exceedance probabilities of 6 models. BMS demonstrated significant evidence (exceedance probability, 0.793) in favor of Model 3. The *right graph*: the exceedance probability for families *A* and *B*. Family *A* has higher evidence (exceedance probability, 0.979) than family *B*. **b** The architecture of Model 3. The direct influence of taste into the MI as well as the modulation placed on the connection from the MI to AI, and the connection from the MFG/FEF to AI were significantly greater than zero ($P < 0.05$)

Table 2 Means and SEs of all the parameter estimate for the selected model (Model 3)

	Mean	SE	*P*	*T*
Intrinsic connections				
AI → MI	0.0279	0.0163	0.0532	1.7
MI → AI	0.0708	0.0281	0.0110	2.5
AI → MFG/FEF	0.1265	0.0596	0.0243	2.1
MFG/FEF → AI	0.0698	0.0336	0.0267	2.1
MFG/FEF → MI	0.0094	0.0118	0.2183	0.8
MI → MFG/FEF	0.1574	0.0484	0.0023	3.3
Modulatory parameters				
MI → AI	0.1148	0.0519	0.0205	2.2
MFG/FEF → AI	0.0586	0.0324	0.0443	1.8
Driving input	0.0179	0.0047	0.0006	3.8

One-sample *t* tests were performed on the connection parameters

SE standard error

Small (2011) reported the existence of a multimodal region in far anterior insular cortex in humans that is sensitive to directed attention to taste and smell. In addition, the result of a study by Veldhuizen et al. (2007) supported the notion that the human primary taste cortex is not likely located in the AI. These authors tried to identify the primary taste cortex based on the ability of attention to alter the responsivity of early sensory cortex. They hypothesized that trying to taste in the absence of taste should increase the response of primary taste cortex. Their results indicated that attention to taste increased the response in the MI, supporting the hypothesis that the primary taste cortex is located more caudally in humans than in monkeys. This result is consistent with the results of our conventional GLM analysis showing that a passive tasting event, which elicited a response to taste solution in the primary taste cortex, resulted in activation of the right MI.

Several studies have indicated that the MI has several features of the primary taste cortex. Cauda et al. (2011) used resting state functional connectivity to confirm the existence of a functional tripartition of the AI, transitional zone (MI), and posterior insula. They also reported that the MI demonstrated maximum correlations with the ventral posterior medial nucleus of the thalamus, which projects gustatory fibers to the primary taste cortex (Pritchard 2011). This result is consistent with the results of our DCM analysis showing the effect of taste was first registered in the MI. An anatomical study suggested that only a small portion of cells respond to taste stimuli in the primary taste cortex (Scott and Plata-Salaman 1999). This feature of primary taste cortex would be reflected in our observation that the response in the MI was smaller than the response in the AI during the taste quality identification task.

Although the location of the primary taste cortex in humans has been a controversial issue, our results collectively suggest that the human primary taste cortex is located in a part of the MI.

The laterality of the taste system

Since the response to taste during the passive condition was observed only in the right MI, our results appeared to indicate a predominance of the right insula. However, the laterality of the gustatory system in the human brain has yet to be clarified, since the pathway from the thalamus to the primary taste cortex in humans has not been established (Kobayashi 2006).

In a previous magnetoencephalography study of patients whose chorda tympani nerve had been severed on the right side, the results suggested that unilateral gustatory stimulation activated the taste cortex bilaterally in humans (Onoda et al. 2005). Another clinical study suggested that the central gustatory pathway ascends ipsilaterally from the medulla to the pons, branches at the upper pons, and then ascends bilaterally from the midbrain to the cerebral cortex (Onoda et al. 2012). By contrast, a recent fMRI study suggested a predominance of ipsilateral processing for taste in the insula/operculum. (Iannilli et al. 2012). Faurion et al. (1999) reported that unilateral projection was observed in the inferior part of the insula of the dominant hemisphere, according to the participant's handedness.

In the case of the present study, our taste delivery system did not show any laterality of the stimulation size of the tongue (Nakamura et al. 2011). However, only at the lower threshold, we detected brain response to taste in the left insula during the passive event, [−40, −6, 14] ($P = 0.002$, $t = 3.33$, cluster size = 6, thresholded at $P < 0.01$ with small volume correction (S.V.C.) using search volume = 10 mm sphere at [−40, −6, 14])). Since our participants were all right handed, our result showed preference for an ipsilateral path.

The effect of the task

The effect of the taste quality identification task resulted in significant response in the bilateral AI (Table 1). This result is consistent with that of a previous study contrasting the identification task with the passive tasting task (Bender et al. 2009). Therefore, neural activity in the AI may be modulated by the effect of attention to taste.

Voluntary attention, a top-down, goal-directed influence, refers to our ability to intentionally attend to something, such as finding an object with particular features (Corbetta et al. 2008). Projections from attentional control systems appear to affect the excitability of cortical neurons coding the features of stimuli. fMRI studies have provided evidence that attention to visual stimuli modulates visual perception. For example, attention to the color of a visual stimulus modulates brain activity in the anterior and medial color-selective areas of the collateral sulcus and fusiform gyrus (Beauchamp et al. 1999). Additionally, attention to motion of a visual stimulus modulates perception of motion as indicated by activity levels in V5, a motion-sensitive area located in the extrastriate cortex (Miki et al. 2001). Based on these psychological phenomena in visual perception, attention to taste quality modulated activity in the area that processed taste quality. Moreover, a previous clinical study by Pritchard et al. (1999) showed that damage to the AI caused taste recognition deficits, suggesting that human insular taste cortex contributes to quality coding. According to these previous results and our findings, the AI appears to play an important role in coding taste quality.

Connectivity between the gustatory region and prefrontal cortex

Our DCM results indicated that in Model 3 (the most favorable model), the connection from the MI to AI was significantly greater than zero ($P < 0.05$; Table 2). This result is consistent with some previous studies. An anatomical study reported abundant local intra-insular connections between agranular (anterior part of the insula) and dysgranular insula (posterior part of the insula) in the monkey brain (Friedman et al. 1986). A recent neuroimaging study used resting state functional connectivity MRI to parcellate the human insular lobe based on clustering of functional connectivity patterns. They identified 3 insular subregions functionally connected with each other: a posterior region, a dorsal anterior to middle region, and a ventral anterior region (Deen et al. 2011). These findings of significant effective connectivity from the MI to AI appear to suggest a hierarchical processing of taste from the MI to AI.

Our DCM results also indicated that connectivity from the MI to AI and from the MFG/FEF to AI were enhanced by the effect of the taste quality identification task. The FEF relates to covert and overt shifts of attention (Schall 2004). Previous studies used visual search tasks to identify attention-related activity. Those studies suggested that the FEF was involved in the guidance of visual attention (Bisley 2011). A recent study suggested the indirect modulation of the gustatory cortex, with a strong influence coming from the FEF via the anterior cingulate cortex (Veldhuizen et al. 2012). Therefore, the FEF may be involved not only in visual attention, but also in allocating attention for various modalities. Taken together, these results suggest that the MFG/FEF may be one of the regions that plays a role in controlling attention to taste quality, and that under the effect of attentional modulation to taste quality, a hierarchical processing of taste from the MI to AI is enhanced. However, from the results of the present study, we cannot rule out the possibility that this modulation of attention to taste quality was not a specific phenomenon related to attention to taste quality, but rather an effect of attention to other features of taste or a general effect of attention to other sensations. Additional research is needed to elucidate the full interactions between attention networks and taste perception.

Summary

We attempted to localize the primary taste cortex within the insula using an attentional paradigm in an fMRI experiment. Our results indicated that the human primary taste cortex is located in the MI. The results of conventional GLM analysis suggested that passive tasting resulted in activation of the right MI. The most favorable model selected by DCM analysis indicated that the effect of taste directly influenced the MI. BMS results at the family level suggested that the taste inputs entered into the MI. Our results further suggest that since the effect of attention to taste quality on neural activity was observed in the AI rather than in the MI, the AI also takes part in processing taste quality. Additionally, we observed that the MFG/FEF was recruited to perform the taste quality identification task, which may indicate that the MFG/FEF is one of the regions that play a role in controlling the attention to sensory information.

Acknowledgments We thank Prof. Yuzo Ninomiya, Section of Oral Neuroscience, Graduate School of Dental Sciences, Kyushu University.

References

Arnsten AF (2009) Toward a new understanding of attention-deficit hyperactivity disorder pathophysiology: an important role for prefrontal cortex dysfunction. CNS Drugs 23(Suppl 1):33–41. doi:10.2165/00023210-200923000-00005

Beauchamp MS, Haxby JV, Jennings JE, DeYoe EA (1999) An fMRI version of the Farnsworth–Munsell 100-Hue test reveals multiple color-selective areas in human ventral occipitotemporal cortex. Cereb Cortex 9:257–263

Bender G, Veldhuizen MG, Meltzer JA, Gitelman DR, Small DM (2009) Neural correlates of evaluative compared with passive tasting. Eur J Neurosci 30:327–338. doi:10.1111/j.1460-9568.2009.06819.x

Bisley JW (2011) The neural basis of visual attention. J Physiol 589:49–57. doi:10.1113/jphysiol.2010.192666

Buchel C, Friston KJ (1997) Modulation of connectivity in visual pathways by attention: cortical interactions evaluated with structural equation modelling and fMRI. Cereb Cortex 7:768–778

Cauda F, D'Agata F, Sacco K, Duca S, Geminiani G, Vercelli A (2011) Functional connectivity of the insula in the resting brain. Neuroimage 55:8–23. doi:10.1016/j.neuroimage.2010.11.049

Cerf-Ducastel B, Van de Moortele PF, 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

Corbetta M, Patel G, Shulman GL (2008) The reorienting system of the human brain: from environment to theory of mind. Neuron 58:306–324. doi:10.1016/j.neuron.2008.04.017

Craig AD (2008) Interception and emotion: a neuroanatomical perspective. In: Lewis M, Haviland-Jones JM, Barrett LF (eds) Handbook of emotions, 3rd edn. The Guilford Press, New York, pp 272–290

De Araujo IE, Rolls ET (2004) Representation in the human brain of food texture and oral fat. J Neurosci 24:3086–3093. doi:10.1523/JNEUROSCI.0130-04.2004

de Araujo IE, Kringelbach ML, Rolls ET, Hobden P (2003a) Representation of umami taste in the human brain. J Neurophysiol 90:313–319. doi:10.1152/jn.00669.2002

de Araujo IE, Kringelbach ML, Rolls ET, McGlone F (2003b) Human cortical responses to water in the mouth, and the effects of thirst. J Neurophysiol 90:1865–1876. doi:10.1152/jn.00297.2003

de Araujo IE, Geha P, Small DM (2012) Orosensory and homeostatic functions of the insular taste cortex. Chemosens Percept 5:64–79. doi:10.1007/s12078-012-9117-9

Deen B, Pitskel NB, Pelphrey KA (2011) Three systems of insular functional connectivity identified with cluster analysis. Cereb Cortex 21:1498–1506. doi:10.1093/cercor/bhq186

Fajardo C, Escobar MI, Buritica E, Arteaga G, Umbarila J, Casanova MF, Pimienta H (2008) Von Economo neurons are present in the dorsolateral (dysgranular) prefrontal cortex of humans. Neurosci Lett 435:215–218. doi:10.1016/j.neulet.2008.02.048

Faurion A, Cerf B, Le Bihan D, Pillias AM (1998) fMRI study of taste cortical areas in humans. Ann NY Acad Sci 855:535–545

Faurion A, Cerf B, Van De Moortele PF, 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

Frank GK, Oberndorfer TA, Simmons AN, Paulus MP, Fudge JL, Yang TT, Kaye WH (2008) Sucrose activates human taste pathways differently from artificial sweetener. Neuroimage 39:1559–1569. doi:10.1016/j.neuroimage.2007.10.061

Friedman DP, Murray EA, O'Neill JB, Mishkin M (1986) Cortical connections of the somatosensory fields of the lateral sulcus of macaques: evidence for a corticolimbic pathway for touch. J Comp Neurol 252:323–347. doi:10.1002/cne.902520304

Friston KJ, Harrison L, Penny W (2003) Dynamic causal modelling. Neuroimage 19:1273–1302. doi:10.1016/S1053-8119(03)00202-7

Grabenhorst F, Rolls ET (2008) Selective attention to affective value alters how the brain processes taste stimuli. Eur J Neurosci 27:723–729. doi:10.1111/j.1460-9568.2008.06033.x

Grabenhorst F, Rolls ET, Bilderbeck A (2008) How cognition modulates affective responses to taste and flavor: top-down influences on the orbitofrontal and pregenual cingulate cortices. Cereb Cortex 18:1549–1559. doi:10.1093/cercor/bhm185

Guest S, Grabenhorst F, Essick G, Chen Y, Young M, McGlone F, de Araujo I, Rolls ET (2007) Human cortical representation of oral temperature. Physiol Behav 92:975–984. doi:10.1016/j.physbeh.2007.07.004

Haase L, Cerf-Ducastel B, Buracas G, Murphy C (2007) On-line psychophysical data acquisition and event-related fMRI protocol optimized for the investigation of brain activation in response to gustatory stimuli. J Neurosci Methods 159:98–107. doi:10.1016/j.jneumeth.2006.07.009

Iannilli E, Singh PB, Schuster B, Gerber J, Hummel T (2012) Taste laterality studied by means of umami and salt stimuli: An fMRI study. Neuroimage 60:426–435. doi:10.1016/j.neuroimage.2011.12.088

Kami YN, Goto TK, Tokumori K, Yoshiura T, Kobayashi K, Nakamura Y, Honda H, Ninomiya Y, Yoshiura K (2008) The development of a novel automated taste stimulus delivery system for fMRI studies on the human cortical segregation of taste. J Neurosci Methods 172:48–53. doi:10.1016/j.jneumeth.2008.04.009

Kobayakawa T, Ogawa H, Kaneda H, Ayabe-Kanamura S, Endo H, Saito S (1999) Spatio-temporal analysis of cortical activity evoked by gustatory stimulation in humans. Chem Senses 24:201–209

Kobayakawa T, Saito S, Gotow N (2012) Temporal characteristics of neural activity associated with perception of gustatory stimulus intensity in humans. Chem Percept 5:80–86. doi:10.1007/s12078-012-9123-y

Kobayashi M (2006) Functional organization of the human gustatory cortex. J Oral Biosci 48:244–260. doi:10.2330/joralbiosci.48.244

Kobayashi M, Takeda M, Hattori N, Fukunaga M, Sasabe T, Inoue N, Nagai Y, Sawada T, Sadato N, Watanabe Y (2004) Functional imaging of gustatory perception and imagery: "top-down" processing of gustatory signals. Neuroimage 23:1271–1282. doi:10.1016/j.neuroimage.2004.08.002

Kringelbach ML, de Araujo IE, Rolls ET (2004) Taste-related activity in the human dorsolateral prefrontal cortex. Neuroimage 21:781–788. doi:10.1016/j.neuroimage.2003.09.063

Maldjian JA, Laurienti PJ, Kraft RA, Burdette JH (2003) An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets. Neuroimage 19:1233–1239

Maldjian JA, Laurienti PJ, Burdette JH (2004) Precentral gyrus discrepancy in electronic versions of the Talairach Atlas. Neuroimage 21:450–455

Martin RE, Goodyear BG, Gati JS, Menon RS (2001) Cerebral cortical representation of automatic and volitional swallowing in humans. J Neurophysiol 85:938–950

McCabe C, Rolls ET (2007) Umami: a delicious flavor formed by convergence of taste and olfactory pathways in the human brain. Eur J Neurosci 25:1855–1864. doi:10.1111/j.1460-9568.2007.05445.x

Mesulam MM, Mufson EJ (1982) Insula of the old world monkey. I. Architectonics in the insulo-orbito-temporal component of the paralimbic brain. J Comp Neurol 212:1–22. doi:10.1002/cne.902120102

Miki A, Liu GT, Modestino EJ, Liu CS, Bonhomme GR, Dobre CM, Haselgrove JC (2001) Functional magnetic resonance imaging of the visual system. Curr Opin Ophthalmol 12:423–431

Nakamura Y, Goto TK, Tokumori K, Yoshiura T, Kobayashi K, Nakamura Y, Honda H, Ninomiya Y, Yoshiura K (2011) Localization of brain activation by umami taste in humans. Brain Res 1406: 18–29. doi:10.1016/j.brainres.2011.06.029

Nitschke JB, Dixon GE, Sarinopoulos I, Short SJ, Cohen JD, Smith EE, Kosslyn SM, Rose RM, Davidson RJ (2006) Altering expectancy dampens neural response to aversive taste in primary taste cortex. Nat Neurosci 9:435–442. doi:10.1038/nn1645

O'Doherty J, Rolls ET, Francis S, Bowtell R, McGlone F (2001) Representation of pleasant and aversive taste in the human brain. J Neurophysiol 85:1315–1321

Ogawa H, Wakita M, Hasegawa K, Kobayakawa T, Sakai N, Hirai T, Yamashita Y, Saito S (2005) Functional MRI detection of activation in the primary gustatory cortices in humans. Chem Senses 30:583–592. doi:10.1093/chemse/bji052

Onoda K, Kobayakawa T, Ikeda M, Saito S, Kida A (2005) Laterality of human primary gustatory cortex studied by MEG. Chem Senses 30:657–666. doi:10.1093/chemse/bji059

Onoda K, Ikeda M, Sekine H, Ogawa H (2012) Clinical study of central taste disorders and discussion of the central gustatory pathway. J Neurol 259:261–266. doi:10.1007/s00415-011-6165-z

Penny WD, Stephan KE, Daunizeau J, Rosa MJ, Friston KJ, Schofield TM, Leff AP (2010) Comparing families of dynamic causal models. PLoS Comput Biol 6:e1000709. doi:10.1371/journal.pcbi.1000709

Petrides M, Alivisatos B, Pandya ND, Evans AC (1996) Gustatory cortex: comparative architectonic analysis in the human and the macaque brain and functional data. NeuroImage 3:S344. ISSN 1053-8119. doi:10.1016/S1053-8119(96)80346-6

Pritchard TC (2011) Gustatory system. In: Mai JK, Paxinos G (eds) The human nervous system, 3rd edn. Academic Press, London, pp 1187–1218

Pritchard TC, Macaluso DA, Eslinger PJ (1999) Taste perception in patients with insular cortex lesions. Behav Neurosci 113:663–671

Rolls ET (2007) Sensory processing in the brain related to the control of food intake. Proc Nutr Soc 66:96–112. doi:10.1017/S0029665107005332

Rudenga K, Green B, Nachtigal D, Small DM (2010) Evidence for an integrated oral sensory module in the human anterior ventral insula. Chem Senses 35:693–703. doi:10.1093/chemse/bjq068

Schall JD (2004) On the role of frontal eye field in guiding attention and saccades. Vision Res 44:1453–1467. doi:10.1016/j.visres.2003.10.025

Schoenfeld MA, Neuer G, Tempelmann C, Schussler K, Noesselt T, Hopf JM, Heinze HJ (2004) Functional magnetic resonance tomography correlates of taste perception in the human primary taste cortex. Neuroscience 127:347–353. doi:10.1016/j.neuroscience.2004.05.024

Scott TR, Plata-Salaman CR (1999) Taste in the monkey cortex. Physiol Behav 67:489–511

Small DM (2010) Taste representation in the human insula. Brain Struct Funct 214:551–561. doi:10.1007/s00429-010-0266-9

Small DM, Prescott J (2005) Odor/taste integration and the perception of flavor. Exp Brain Res 166:345–357. doi:10.1007/s00221-005-2376-9

Small DM, Zald DH, Jones-Gotman M, Zatorre RJ, Pardo JV, Frey S, Petrides M (1999) Human cortical gustatory areas: a review of functional neuroimaging data. NeuroReport 10:7–14

Smits M, Peeters RR, van Hecke P, Sunaert S (2007) A 3 T event-related functional magnetic resonance imaging (fMRI) study of primary and secondary gustatory cortex localization using natural tastants. Neuroradiology 49:61–71. doi:10.1007/s00234-006-0160-6

Stephan KE, Penny WD, Daunizeau J, Moran RJ, Friston KJ (2009) Bayesian model selection for group studies. Neuroimage 46:1004–1017. doi:10.1016/j.neuroimage.2009.03.025

Stephani C, Fernandez-Baca Vaca G, Maciunas R, Koubeissi M, Luders HO (2011) Functional neuroanatomy of the insular lobe. Brain Struct Funct 216:137–149. doi:10.1007/s00429-010-0296-3

Tzourio-Mazoyer N, Landeau B, Papathanassiou D, Crivello F, Etard O, Delcroix N, Mazoyer B, Joliot M (2002) Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. Neuroimage 15:273–289. doi:10.1006/nimg.2001.0978

Veldhuizen MG, Small DM (2011) Modality-specific neural effects of selective attention to taste and odor. Chem Senses. doi:10.1093/chemse/bjr043

Veldhuizen MG, Bender G, Constable RT, Small DM (2007) Trying to detect taste in a tasteless solution: modulation of early gustatory cortex by attention to taste. Chem Senses 32:569–581. doi:10.1093/chemse/bjm025

Veldhuizen MG, Nachtigal D, Teulings L, Gitelman DR, Small DM (2010) The insular taste cortex contributes to odor quality coding. Front Hum Neurosci 4:58. doi:10.3389/fnhum.2010.00058

Veldhuizen MG, Albrecht J, Zelano C, Boesveldt S, Breslin P, Lundstrom JN (2011) Identification of human gustatory cortex by activation likelihood estimation. Hum Brain Mapp 32:2256–2266. doi:10.1002/hbm.21188

Veldhuizen MG, Gitelman D, Small DM (2012) An fMRI study of the interactions between the attention and the gustatory networks. Chem Percept 5:117–127. doi:10.1007/s12078-012-9122-z

Verhagen JV, Engelen L (2006) The neurocognitive bases of human multimodal food perception: sensory integration. Neurosci Biobehav Rev 30:613–650. doi:10.1016/j.neubiorev.2005.11.003

Wagner A, Aizenstein H, Frank GK, Figurski J, May JC, Putnam K, Fischer L, Bailer UF, Henry SE, McConaha C, Vogel V, Kaye WH (2006) Neural correlates of habituation to taste stimuli in healthy women. Psychiatry Res 147:57–67. doi:10.1016/j.pscychresns.2005.11.005

Worsley KJ (2001) Statistical analysis of activation images. In: Jezzard P, Matthews PM, Smith SM (eds) Functional MRI: an introduction to methods. Oxford University Press, Oxford, pp 251–270

Yaxley S, Rolls ET, Sienkiewicz ZJ (1990) Gustatory responses of single neurons in the insula of the macaque monkey. J Neurophysiol 63:689–700

Zald DH, Pardo JV (2000) Cortical activation induced by intraoral stimulation with water in humans. Chem Senses 25:267–275