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Trying to Detect Taste in a Tasteless Solution: Modulation of Early Gustatory Cortex by Attention to Taste

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Abstract

Selective attention is thought to be associated with enhanced processing in modality-specific cortex. We used functional magnetic resonance imaging to evaluate brain response during a taste detection task. We demonstrate that trying to detect the presence of taste in a tasteless solution results in enhanced activity in insula and overlying operculum. The same task does not recruit orbitofrontal cortex (OFC). Instead, the OFC responds preferentially during receipt of an unpredicted taste stimulus. These findings demonstrate functional specialization of taste cortex in which the insula and the overlying operculum are recruited during taste detection and selective attention to taste, and the OFC is recruited during receipt of an unpredicted taste stimulus.

Key words: baseline shift, fMRI, gustatory cortex, humans, insula

Introduction

The process of selective attention serves to bring relevant aspects of the sensory world into focus in the service of goal-directed behavior (Posner 1980; Posner et al. 1980; Mesulam 1981). For example, finding a lost friend in a crowd will be faster and more accurate when attention is directed to a salient feature, such as his red-and-white–striped sweater. Selective attention is thought to be achieved through up-regulation of activity in relevant and down-regulation in irrelevant sensory cortical areas. For example, activity in early visual areas increases during active discrimination as opposed to passive viewing of the same stimulus set (Shulman et al. 1997) and it increases when directional cues effectively bias attention toward the part of the visual scene where a target is expected to occur (Gitelman et al. 1999; Small, Gitelman, et al. 2003). Functional magnetic resonance imaging (fMRI) studies of visual attention indicate that attentional modulation occurs in primary visual cortex (Gandhi et al. 1999; Kanwisher and Wojciulik 2000). Likewise, probing the world for a sound in silence (Voisin et al. 2006), a sight in an empty visual scene (Kastner et al. 1999; Hopfinger et al. 2000), or an odor in odorless air (Zelano et al. 2005) results in activation of the respective primary sensory cortical region. This activation is thought to represent a shift in baseline processing so that incoming sensory signals that are the focus of goal-directed behavior can be amplified (Kanwisher and Wojciulik 2000). The goal of the current study was to investigate whether trying to detect a taste in a tasteless solution (i.e., in the absence of a taste stimulus) would activate primary gustatory cortex (PGC).

Although the neural correlates of selective attention to taste have not been examined, the existence of selective taste attention has been demonstrated behaviorally. In a study by Marks and colleagues, subjects attempted to detect taste under 2 different conditions. In one condition, subjects were informed that there was a probability of 0.75 that they would receive a sweet taste stimulus on each trial and a probability of 0.25 that they would receive a sour taste stimulus. In the second condition, these probabilities were reversed. Thus, information about quality was used to direct a "taste search." The authors reported lower detection threshold for the taste that was the focus of the search. In other words, directing attention to the taste quality resulted in enhanced sensitivity to that taste, thus demonstrating the existence of selective attention to taste (Marks and Wheeler 1998; Marks 2002). Here we used fMRI to investigate the neural response to taste and tasteless solutions when subjects tasted passively

or performed a taste search. Stimuli included weak taste (sweet, salty, or sour—see Materials and methods) and tasteless solutions (individually tailored artificial saliva), but analyses focus on tasteless events, so that we could focus on isolating baseline shifts, indicative of top–down processing separate from sensory processing. Based on studies in other modalities, we reasoned that searching a tasteless solution for the presence of a taste should activate PGC.

Materials and methods

Subjects

Fourteen right-handed subjects (11 women, 3 men, mean age 26.2 ± 3.0 years with a mean Edinburgh Handedness Inventory score of 89 [Oldfield 1971]) gave informed consent to participate in our study that was approved by Yale University School of Medicine Human Investigation Committee. All subjects reported having no known taste, smell, neurological, or psychiatric disorder. Three (of the original 17) subjects were excluded because movements during scanning exceeded a predetermined limit of 1 mm of movement in any direction.

Taste stimuli and delivery

A stock tasteless solution was created containing 2.5 mM sodium bicarbonate and 25 mM potassium chloride (O'Doherty et al. 2001) as well as 3 weaker versions (at 25%, 50%, and 75% of the original concentration). The sweet solution consisted of 5.6×10^{-1} M sucrose, the salty solution consisted of 1.8×10^{-1} M sodium chloride, and the sour solution consisted of 1.0×10^{-2} citric acid dissolved in distilled water. In a pilot study, pleasantness and subjective intensity of the tastes were rated by 10 subjects. Pleasantness was rated on a visual analogue line scale of 100 mm with the label ''most unpleasant sensation ever'' at the left anchor point (0), the label ''neutral'' in the middle (50), and the label ''most pleasant sensation ever'' at the right anchor point (100) (Lawless and Heymann 1999). Subjective intensity was rated on the general Labeled Magnitude Scale (Green et al. 1996). This is a vertical line scale of 100 mm with the label ''barely detectable'' at the lower anchor and the label ''strongest imaginable sensation'' at the upper anchor. In between these labels, the following words were quasi-logarithmically spaced: ''weak'' (6 mm), moderate (17 mm), strong (35 mm), and very strong (53 mm). Pleasantness of sweet, sour, salty, and tasteless was rated as 72 (±10), 50 (±11), 46 (±14), and 49 (±2), respectively, indicating that all stimuli were perceived as neutral or moderately pleasant. The subjective intensities of the stimuli were rated as 28 (±16), 20 (±10), 23 (±13), and 3 (±3) for sweet, sour, salty, and tasteless solutions, respectively. This indicated that the taste stimuli were rated similarly moderate to strong in subjective intensity and that the tasteless stimulus was between barely detectable and weak in subjective intensity. Stimuli were all delivered as 0.4 ml of solution over 4 s (Figure 1A) from the syringe pumps as described in Figure 2A.

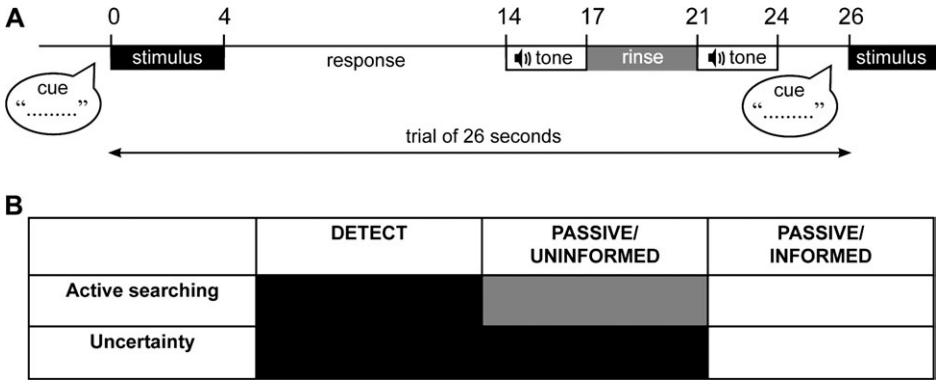

Figure 1 Experimental design. **(A)** Timeline of events within a trial. Events lasted 26 s. Each event began with a 1-s auditory cue. In condition DETECT, the auditory cue was "liquid," after which a solution "stimulus" (1 of the 3 tastes or tasteless) was presented (0.4 ml over 4 s). Once delivery was complete, the subject indicated whether or not he or she had tasted something by pressing a button. After the 10-s response time, the sounding of a 3-s tone indicated the window during which subjects should swallow. This was followed by 4-s rinse of tasteless solution (0.4 ml) and then a second swallow tone. In condition PASSIVE/UNINFORMED, as in condition DETECT, the subject received the auditory cue "liquid"; however, in this condition they were instructed to taste passively and randomly press a button during the response period. In PASSIVE/INFORMED, the cue was "sweet," "salty," "sour," or "tasteless," and thus the subject was accurately informed about the identity of the stimulus. In this condition, the subject was also required to make random button presses. **(B)** Graphic depiction of the variables being manipulated in this experiment. Variables are listed vertically in the first column and conditions are listed horizontally in the top row. Saturation indicates predicted engagement of variables across conditions. In condition DETECT, subjects are unaware of the identity of the upcoming stimulus and must actively probe the solution for the presence of a taste. Hence, this condition involves active probing and uncertainty. In condition PASSIVE/UNINFORMED, subjects are unaware of the identity of the upcoming stimulus. Therefore, the condition includes uncertainty. Although subjects are asked not to probe the stimulus, we reasoned that they might be tempted to probe the solution despite the instructions, and therefore, we color the variable gray to acknowledge the possibility that some active probing may occur. In condition PASSIVE/INFORMED, the subject is informed about stimulus identity. Therefore, there is no uncertainty, and also there should be no active probing. Comparison of DETECT and PASSIVE/UNINFORMED should isolate regions only engaged by active probing, whereas comparison of DETECT with PASSIVE/INFORMED should isolate regions engaged by active probing and uncertainty.

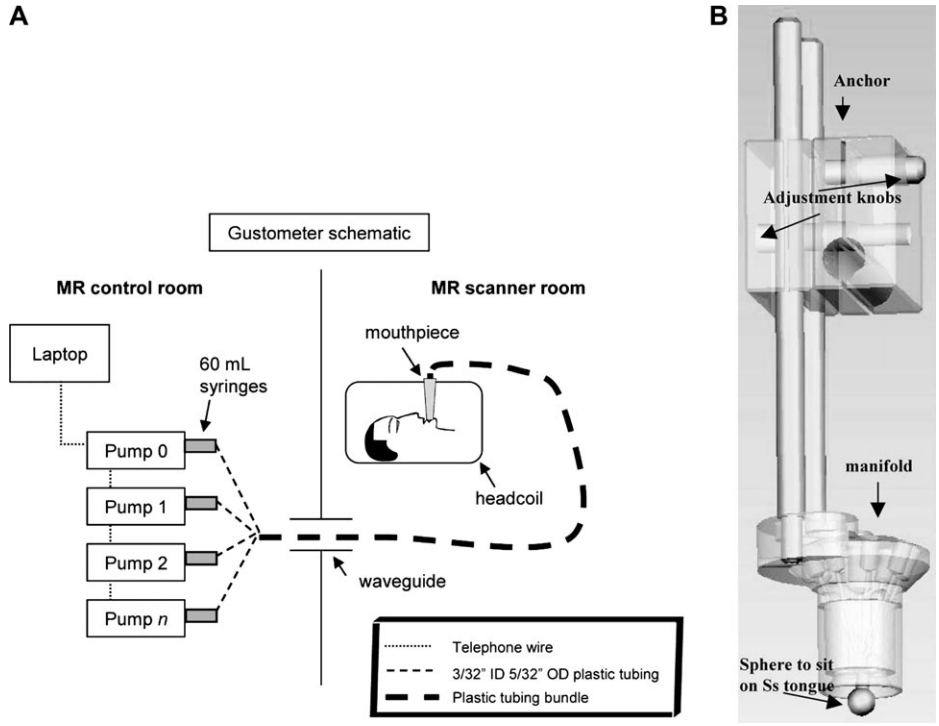

Figure 2 The setup for delivery of gustatory stimuli. **(A)** The gustometer system. **(B)** The gustatory manifold.

The gustometer system is a fully portable device that consists of a laptop computer that can control up to 11 independently programmable BS-8000 syringe pumps (Braintree Scientific, Braintree, MA) to deliver precise amounts of liquid stimulus to the supine subject at precisely timed intervals and durations. The pumps, which infuse liquids at rates of 6–15 ml/min, are controlled by programs written using Matlab 6.5.1 (MathWorks Inc., Sherborn, MA) and Cogent2000 v1.25 (Wellcome Department of Cognitive neurology, London, United Kingdom). Each pump holds a 60-ml syringe connected to a 25-foot length of Tygon beverage tubing (Saint-Gobain Performance Plastics, Akron, OH) with an inside diameter of 3/32″ All tubing terminates into a specially designed Teflon, fMRI-compatible custom designed gustatory manifold (Figure 2B), which is anchored to the MRI head coil and interfaces with the subject. The gustometer manifold was designed to deliver up to 9 taste solutions and 1 tasteless rinse. The stimulus inlets are arrayed around a center inlet through which the rinse liquid is delivered. All tastants and rinses pass through 1-mm channels that converge at a central point at the bottom of the manifold for delivery to the tongue tip. To prevent the subject's tongue from coming in contact with the 1-mm holes and to ensure the liquids flow directly onto the tongue a 7-mm plastic sphere is positioned directly under the 1-mm holes. The subject's tongue rests up against the bottom surface of the sphere to receive the stimulus, which drips onto the sphere and rolls off the surface to the tongue. Tactile stimulation is held constant across all events (i.e., delivery of the different tastants and the tasteless solutions) by the use of the sphere. Four vent holes on the bottom of the manifold prevent the subject from drawing or sucking the stimulant through the manifold at uncontrolled times or rates. The gustometer manifold is mounted by rigid tubing onto an anchoring block that clamps onto the bars of the head coil. The anchor height and horizontal positions are adjustable via 2 knobs accessible to the subject and the experimenter to achieve the most comfortable position. The manifold is then locked in place for the duration of the scanning run.

Experimental design

All subjects first participated in a screening and training session in the mock scanner. The purpose of this session was to select an appropriate ''tasteless'' solution, to familiarize subjects with the task, and to identify subjects who found it uncomfortable to swallow in the supine position. Because water activates taste cortex (Frey and Petrides 1999; Zald and Pardo 2000) and has a taste (Bartoshuk et al. 1964), we used artificial saliva as our tasteless stimulus. Subjects were first presented with several variants of a tasteless solution (with similar ionic components as saliva) and were required to choose the one that ''tasted most like nothing.'' Subjects then performed a mock run in the fMRI simulator. During mock and actual scanning, the liquid stimuli were delivered using our custom-built gustometer and gustatory manifold (see Figure 2).

A long-event–related design was used (Small, Gregory, et al. 2003; Small et al. 2004) and is depicted and described

in Figure 1A. Neural responses to taste and tasteless solutions were assayed under 3 different conditions (see Figure 1B). Each condition consisted of blocks of 6 trials. Trials were 26 s in duration and included an instruction, receipt of a solution, a response, a swallow, receipt of a rinse, and a final swallow (Figure 1A). At the beginning of each block, subjects heard an instruction particular to each condition. In condition DETECT, this instruction was "Detect." During training, subjects had learned that this cue meant that they should probe the solutions presented during this block of trials for the presence of a taste. During each trial in condition DETECT, subjects heard the word "liquid," which instructed them that the solution was about to be administered. They were then required to probe the solution for a taste percept and to press button A if it contained a taste and button B if it was perceived to be tasteless. Two control conditions were employed. In control condition PASSIVE/UNINFORMED, the trials were identical to DETECT, but the instruction at the beginning of the block was "Randomly Press." In the training session, subjects had been instructed that they should not probe solutions for a taste during these blocks and that they should make a random button press during the response period. This baseline is well matched to the experimental condition. However, we reasoned that it was possible that some subjects might try to detect even though they were instructed not to. Therefore, we included a second baseline condition "PASSIVE/INFORMED." In this condition, the general instruction was the same as in PASSIVE/UNINFORMED (i.e., they heard "Randomly Press"), but during each trial subjects were accurately informed about the identity of the stimulus (i.e., they heard "sweet," "salty," "sour," or "tasteless" just prior to delivery) and were told to make a random button response. Because subjects were accurately informed about the stimulus identity, there was no need for active probing. However, providing knowledge also resulted in this baseline differing from DETECT in terms of uncertainty about the identity of the upcoming taste (likely to cause anticipatory taste attention or expectation). By including both baselines, we were able to ensure true passive perception of tasteless while also being able to examine effects related to stimulus uncertainty or anticipatory attention (Figure 1B).

Each condition had 2 levels (taste and tasteless). There were equivalent numbers of taste and tasteless events, and these were presented randomly. Collapsing across the different taste qualities, this created 6 different events: 1) DETECT*taste*, 2) DETECT*tasteless*, 3) PASSIVE/UNINFORMED*taste*, 4) PASSIVE/UNINFORMED*tasteless*, 5) PASSIVE/INFORMED*taste*, and 6) PASSIVE/INFORMED*tasteless*. Each event lasted 26 s, each run consisted of 18 events, and each subject underwent 6 runs. Subjects used a button box that had 4 buttons beneath the left middle, left index, right middle, and right index fingers. Half the subjects were instructed to press either of the left-hand buttons if they detected a taste and either of the right-hand buttons if they detected no taste. The other half of the subjects received reversed instructions (right hand: taste; left hand: no taste).

fMRI scanner

The images were acquired on a Siemens 3 T Trio magnetom scanner. Echoplanar imaging was used to measure the blood oxygenation-level–dependent (BOLD) signal as an indication of cerebral brain activation. A susceptibility-weighted single-shot echoplanar method was used to image the regional distribution of the BOLD signal with TR, 2000 ms; TE, 20 ms; flip angle, 90°; field of view (FOV), 220 mm; matrix, 64×64; slice thickness, 3 mm; and acquisition of 40 contiguous slices. Slices were acquired in an interleaved mode to reduce the cross-talk of the slice selection pulse. At the beginning of each functional run, the MR signal was allowed to equilibrate over 6 scans for a total of 12 s, which were then excluded from analysis. The anatomical scan used a T1-weighted 3D FLASH sequence (TR/TE, 2530/3.66 ms; flip angle, 20°; matrix, 256×256; 1-mm thick slices; FOV, 256; 176 slices).

fMRI analysis and statistics

Data were analyzed on LINUX workstations under the Matlab Software (MathWorks, Inc.) using SPM2 (Wellcome Department of Cognitive Neurology). Functional images were time acquisition corrected to the slice obtained at 50% of the TR. All functional images were then realigned to the scan immediately preceding the anatomical T1 image. After segmentation, the images (anatomical and functional) were then normalized to the Montreal Neurological Institute template of gray matter, which approximates the anatomical space delineated by Talairach and Tournoux (1998). Functional images were smoothed with a 10-mm full width half maximum isotropic Gaussian kernel. For time series analysis on all subjects, a high-pass filter (128) was included in the filtering matrix (according to convention in SPM2) in order to remove low-frequency noise and slow drifts in the signal, which could bias the estimates of the error. Condition-specific effects at each voxel were estimated using the general linear model. The response to events was modeled by a canonical hemodynamic response function, consisting of a mixture of 2 γ-functions that emulate the early peak at 5 s and the subsequent undershoot. The temporal derivative of the hemodynamic function was also included as part of the basis set to enable examination of differences in timing between various events (Henson et al. 2002). We defined our events of interest as miniblocks of 12.5-s duration from taste onset to swallow (see Figure 1A). The swallow and the rinse were modeled as events of no interest.

Within-group comparisons were performed using random-effects models for all comparisons in order to account for intersubject variability. Parameter estimate images from designated contrasts were entered into second-level random-effects analyses using 1-sample Student's *t*-tests. SPM assigns significance *t*-fields from all analyses using the theory of

Gaussian random fields (Friston et al. 1995; Worsley and Friston 1995). Activations of a cluster size > 3 in predicted areas were reported at $P_{\text{uncorrected}} = 0.001$ and activations in unpredicted areas were reported at $P_{\text{cluster level-corrected}} = 0.05$.

Results

Behavior

Subjects detected taste and tasteless solutions with a mean accuracy of 98 ± 2% in condition DETECT. In order to verify that they were not performing a detection task during the passive conditions, we also calculated mean accuracy for "correct responses" in these conditions. The average accuracy score in PASSIVE/INFORMED was 50 ± 1% and in PASSIVE/UNINFORMED 46 ± 1%, suggesting that subjects followed the instructions and were pressing the buttons randomly.

Neuroimaging: tasting in the absence of taste

To test the prediction that searching for the presence of a taste in a tasteless solution induces greater activity in early gustatory cortex compared with passive receipt of a tasteless solution, we first built gustatory-specific functional masks using the taste–tasteless contrast from individual subjects. This was then used as an inclusive mask for the contrasts DETECT*tasteless*–PASSIVE/UNINFORMED*tasteless* and DETECT*tasteless*–PASSIVE/INFORMED*tasteless* to limit tests for attention effects to taste-responsive regions of cortex.

In the contrast DETECT*tasteless*–PASSIVE/UNINFORMED*tasteless*, the uncertainty about the upcoming stimulus is held constant so that any resulting differential activity must be related to active searching for a taste (i.e., top–down modulation by selective attention) rather than uncertainty. This analysis resulted in activity within the left anterior to middorsal insula and overlying frontal and Rolandic operculum at the base of the precentral gyrus (midIns/Fop) (−39, 0, 6) and bilateral parietal operculum (Pop) (−60, −12, 30; 63, −30, 21) (Figure 3A, B and Table 1). The peak in the left midIns/Fop is posterior to the area shown to receive taste afferents from the thalamus in the macaque (Pritchard et al. 1986). However, it does overlap with taste peaks from other human neuroimaging studies (Kinomura et al. 1994; Faurion et al. 1998, 1999; Frey and Petrides 1999; Small et al. 1999; Barry et al. 2001; Cerf-Ducastel et al. 2001; O'Doherty et al. 2001; De Araujo, Kringelbach, Rolls, and Hobden 2003; De Araujo, Kringelbach, Rolls, and McGlone 2003; De Araujo, Rolls, et al. 2003; Small, Gregory, et al. 2003; Schoenfeld et al. 2004; Ogawa et al. 2005; Marciani et al. 2006; Nitschke et al. 2006), and it is in the exact region we identified in our 1999 review (Small et al. 1999) as the main taste-responsive region in human brain. This finding, taken in conjunction with previous reports (e.g., see the reports mentioned above, especially Frey and Petrides [1999]), raises the possibility of interspecies differences in insular representation of taste.

The posterior parietal peaks correspond to the region that is frequently identified in magnetoencephalography (MEG) (Kobayakawa et al. 1996, 1999; Onoda et al. 2005) as responding to taste stimulation, as well as in fMRI studies (Cerf-Ducastel et al. 2001; Ogawa et al. 2005; Nitschke et al. 2006).

To evaluate which regions outside the gustatory cortex were active during attention to taste, we recalculated the contrast without inclusive masking (i.e., enabling evaluation of regions that do not encode taste sensation). We predicted that, as with visual attention, a large-scale heteromodal network including the posterior parietal cortex, frontal eye fields (FEF), and cingulate gyrus (Mesulam et al. 2005) would be coactivated with the insula and overlying operculum. Activity within predicted spatial attention network was found in FEF (51, 0, 51) and area 32 of the dorsal anterior cingulate cortex (ACC) (3, 6, 51) (Figure 3D and Table 1). Unpredicted significant activations ($P_{\text{cluster level-corrected}} < 0.001$) were observed in the cerebellum (−18, −57, −27) and several subcortical areas including the thalamus (12, −6, 6) and substantia nigra (−3, −27, −15) (Figure 3C,E,F and Table 1).

In the contrast DETECT*tasteless*–PASSIVE/INFORMED*tasteless*, both the uncertainty about the upcoming stimulus and active searching for a taste is varied, and as such this contrast isolates regions responding to attention for a taste and taste uncertainty. This analysis revealed several peaks in bilateral insula/operculum within the taste-inclusive mask (Table 1 and Figure 4A), including regions anatomically homologous to the 2 projection sites for thalamic taste afferents in nonhuman primates (Pritchard et al. 1986). In the left hemisphere, we observed peaks in 3 regions of dorsal mid to anterior insula that extend into overlying frontal and Rolandic opercula (−33, 30, 6; −39, 9, 3; and −39, 0, 6) and 1 in Pop (−60, −15, 9) (Figure 4A and Table 1). In the right hemisphere, we observed one peak at the junction of the anterior insula and frontal operculum (33, 18, 9) and one in the frontal operculum proper (54, 6, 9) (Figure 4A and Table 1). The peaks in the left middorsal insula at the junction with overlying frontal and Rolandic opercula (from $y = 0$ and $y = 9$; see Table 1 and Figure 4A) overlap with the insula activation isolated in the previous analysis (Figure 3B).

As predicted, when the analysis was repeated without inclusive masking of the taste–tasteless contrast, several peaks were observed in the frontoparietal attention network, including the IPS, FEF, dorsal ACC, and posterior cingulate cortex (PCC) (see Table 1 and Figure 4B). The peaks in FEF and dorsal ACC overlapped with the peaks identified in DETECT*tasteless*–PASSIVE/UNINFORMED*tasteless*.

Uncertainty

To isolate areas that respond preferentially to receipt of unpredicted taste and tasteless solutions (i.e., knowledge of upcoming taste), we subtracted PASSIVE/INFORMED *tasteless* from PASSIVE/UNINFORMED *tasteless*. This contrast did not result in insular activation even when the

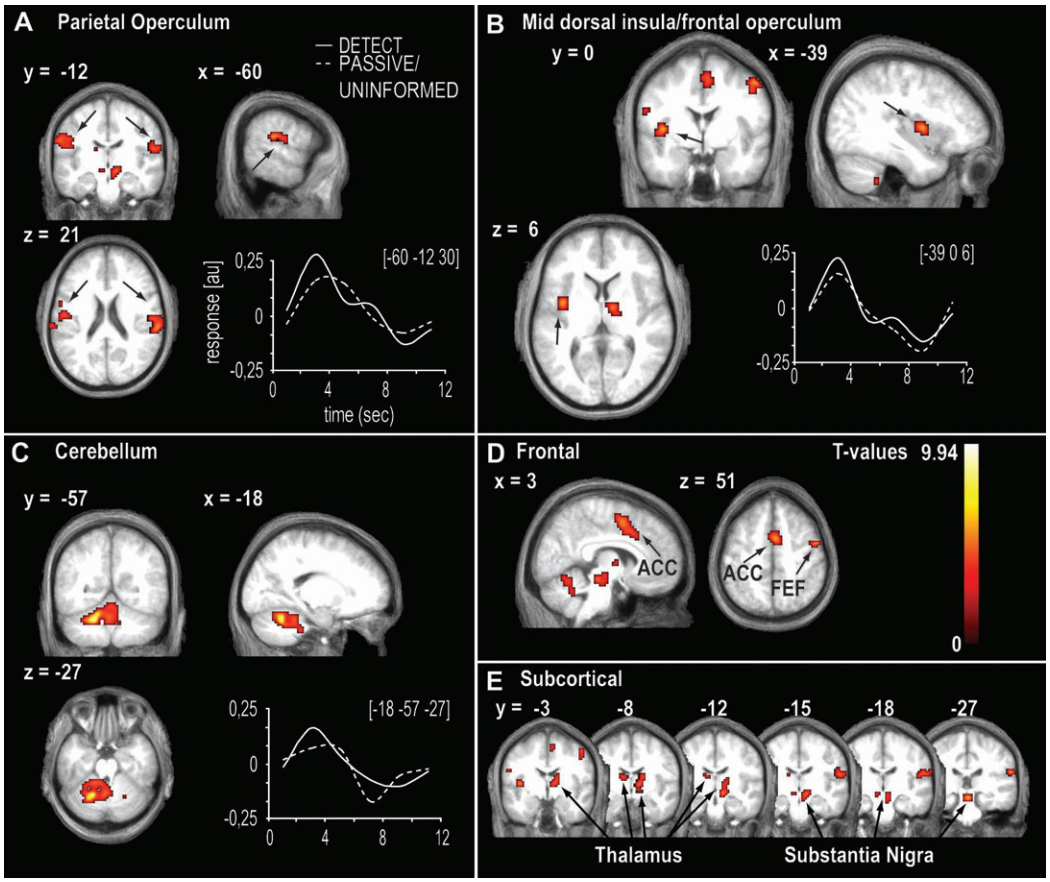

Figure 3 Results from random-effects analysis of DETECT*tasteless*–PASSIVE/UNINFORMED*tasteless*. The color bar in panel D represents the *t* values (from 0 to 9.94) representative of all panels. Graphs represent extracted response in arbitrary units on the *y* axis of graphs over time in seconds on the *x* axis. The solid line represents the response in DETECT and the dashed line the response in PASSIVE/UNINFORMED. **(A)** Coronal, saggital, and axial sections showing activity in left parietal operculum (−60, −12, 30; $Z = 3.91$; $P_{\text{uncorrected}} < 0.001$). **(B)** Coronal, saggital, and axial sections showing activity in the left middorsal insula and frontal operculum (−39, 0, 6; $Z = 4.18$; $P_{\text{uncorrected}} < 0.001$). **(C)** Coronal, saggital, and axial sections showing activity in cerebellum (−18, −57, −27; $Z = 5.21$; $P_{\text{cluster level-corrected}} < 0.05$). **(D)** Saggital and axial sections showing activity in spatial attention network (FEF: 51, 0, 51; $Z = 4.12$; $P_{\text{uncorrected}} < 0.001$; ACC: 3, 6, 51; $Z = 4.09$; $P_{\text{uncorrected}} < 0.001$). **(E)** Coronal sections showing activation in several midbrain areas, including the thalamus (12, −6, 6; $Z = 3.92$; $P_{\text{cluster level-corrected}} < 0.05$) and substantia nigra (−3, −27, −15; $Z = 4.28$; $P_{\text{cluster level-corrected}} < 0.05$).

threshold was dropped to $P < 0.01$. We did observe activity in the orbitofrontal cortex (OFC) (39, 57, −6; $Z = 4.51$; $P_{\text{uncorrected}} < 0.001$), IPS (39, −63, 51; $Z = 3.41$; $P_{\text{uncorrected}} < 0.001$), PCC (3, −24, 30; $Z = 4.32$; $P_{\text{uncorrected}} < 0.001$), and ACC (6, 30, 30; $Z = 3.52$; $P_{\text{uncorrected}} < 0.001$) for this contrast. We also observed a peak in the OFC when we compared PASSIVE/UNINFORMED*taste*–PASSIVE/INFORMED*taste* (24, 51, −9; $Z = 3.52$; $P_{\text{uncorrected}} < 0.001$). When we performed the reverse contrast for tasteless, we identified a small but nonsignificant peak in the left ventral mid insula (−36, −6, −9; $Z = 2.42$; $P_{\text{uncorrected}} = 0.008$), suggesting that this region of insula may preferentially encode taste attention compared with uncertainty.

Supra-additive effects of taste and attention

The attention-related analyses were restricted to tasteless events. Similar patterns of activation were observed when we repeated these analyses with the taste events. We do not report these results as they do not add any new information and because we were primarily interested in identifying baseline shifts in early cortical regions, which can only be detected in a tasteless solution (Kanwisher and Wojciulik 2000). However, we were interested in knowing if there were regions where taste perception and attention to taste interact. Therefore, to determine which areas responded supra-additively to taste and attention, we contrasted the response in DETECT*taste* with the responses generated in PASSIVE/UNINFORMED*taste* + DETECT*tasteless*. In this analysis, the attention condition is contrasted with the passive condition in which the subject is uncertain about the quality of the taste they will next receive, equating uncertainty for both tasks. Here we observed activity in the ACC (0, 15, 27) (see Table 2 and Figure 5A). We also contrasted DETECT*taste* – (PASSIVE/INFORMED*taste* + DETECT*tasteless*), which isolated activity

Table 1 Activations from DETECT*tasteless* MINUS the PASSIVE tasks

Contrast	Region	MNI[a] coordinates			Cluster size in mm^3	*Z* values	$P_{uncorrected}$ values
		x	*y*	*z*			
DETECT*tasteless*–PASSIVE/ UNINFORMED*tasteless*							
Inclusive mask[b]	Middorsal insula/frontal operculum	−39	0	6	6.2	4.18	1.47×10^{-5}
	Parietal operculum	−63	−30	21	6.9	4.09	2.17×10^{-5}
		−57	*−15*	*18*		3.74	
		−60	−12	30	7.5	3.91	4.57×10^{-5}
		−51	*−12*	*24*		3.77	
		−69	*−27*	*24*		3.63	
		−60	−30	36	4.3	3.15	8.05×10^{-4}
No mask	Frontal						
	Middle frontal gyrus/FEFs[b]	51	0	51	6.4	4.12	1.93×10^{-5}
		57	*3*	*36*		3.32	
	Cingulate						
	ACC[b]	3	6	51	7.4	4.09	2.12×10^{-5}
		6	*12*	*42*		3.58	
	Subcortical						
	Substantia nigra[c]	−9	−18	−9	4.5	3.20	6.77×10^{-4}
		3	−27	−15	7.4	4.28	9.38×10^{-6}
		12	*−12*	*−9*		3.95	
	Thalamus[c]	*12*	*−6*	*6*		3.92	
		−12	−6	15	5.6	3.66	1.26×10^{-4}
	Cerebellum[c]	−18	−57	−27	8.6	5.21	9.69×10^{-8}
		−30	*−45*	*−33*		4.00	
		0	*−54*	*−30*		3.86	
DETECT*tasteless*–PASSIVE/ INFORMED*tasteless*							
Inclusive mask[b]	Anterior insula	33	18	9	5.2	3.39	3.46×10^{-4}
		−33	30	6	5.4	4.01	2.9×10^{-5}
	Middorsal insula/frontal operculum	−39	9	3	4.5	3.18	7.48×10^{-4}
		−39	0	6	4.5	3.13	8.87×10^{-4}
	Frontal operculum	54	6	9	6.6	3.50	2.29×10^{-4}
	Parietal/frontal operculum	−60	−15	9	6.8	4.36	6.51×10^{-6}
No mask	Parietal						
	Intra parietal sulcus[b]	−51	−36	51	7.0	4.68	1.42×10^{-6}
	Frontal						
	Superior/middle frontal gyrus[c]	−33	36	24	7.6	4.21	1.27×10^{-5}
		−39	*39*	*12*		3.50	
		−33	*43*	*9*		3.49	
	Middle frontal gyrus/FEFs[b]	45	3	51	6.3	3.69	1.14×10^{-4}

Table 1 Continued

Contrast	Region	MNI[a] coordinates			Cluster size in mm^3	*Z* values	$P_{uncorrected}$ values
		x	*y*	*z*			
	Cingulate						
	ACC[b]	6	24	33	8.4	5.06	2.08×10^{-7}
		−3	*15*	*51*		3.79	
		6	*15*	*60*		3.54	
	PCC[b]	3	−27	30	7.4	4.59	2.16×10^{-6}

Italics indicate that a peak falls under the same cluster as the preceding peak.
[a]Montreal Neurological Institute.
[b]T-map thresholded at $P_{uncorrected} = 0.001$.
[c]Unpredicted areas are reported only at $P_{cluster\ level\text{-}corrected} = 0.05$, if complemented by a peak in the opposite hemisphere, then this peak is reported as well at $P_{uncorrected} = 0.001$.

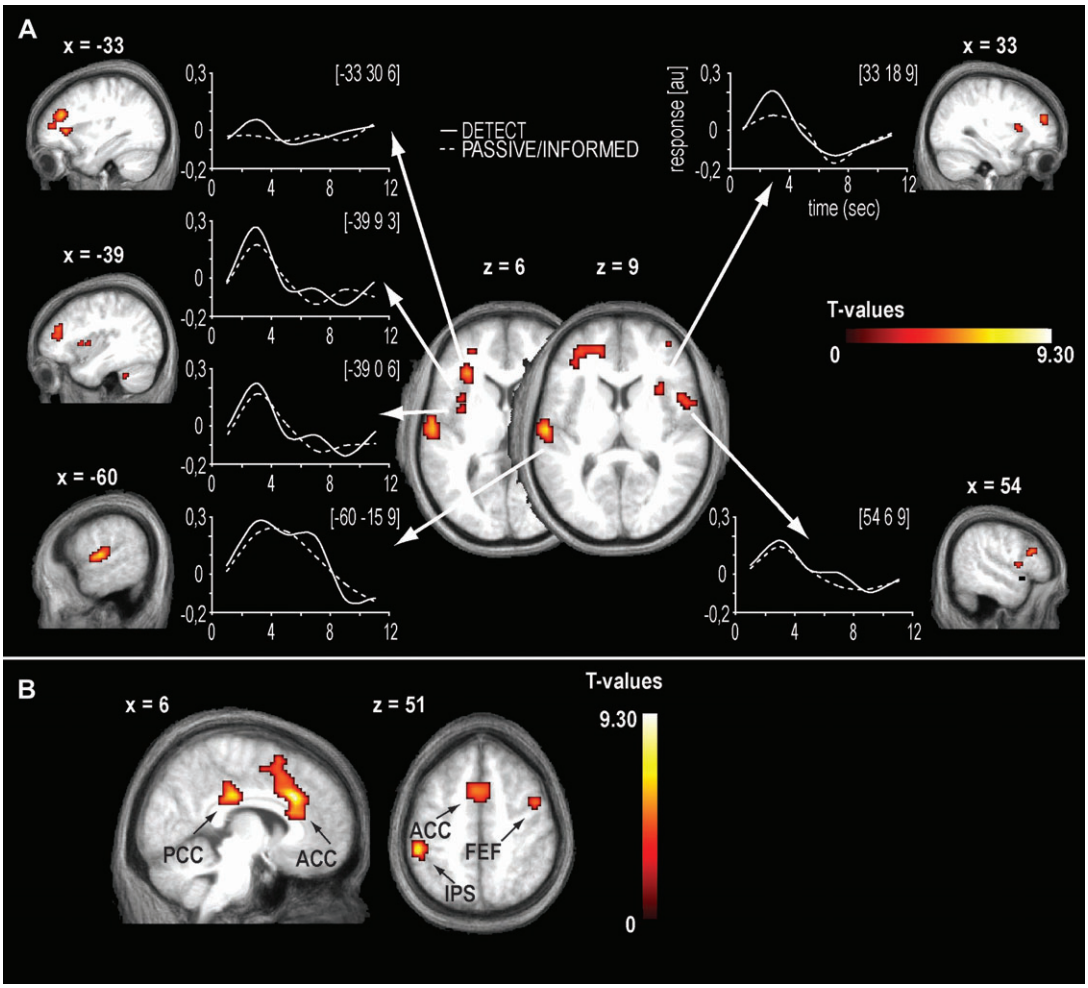

Figure 4 Results from random-effects analysis of DETECT*tasteless*–PASSIVE/INFORMED*tasteless*. The color bar in panel A represents the *t* values (from 0 to 9.30) representative of both panels. Graphs represent extracted response in arbitrary units on the *y* axis of graphs over time in seconds on the *x* axis. The solid line represents the response in DETECT and the dashed line the response in PASSIVE/INFORMED. **(A)** Activations in the left anterior, dorsal mid insula, and parietal operculum (−33, 30, 6; $Z = 4.01$; $P_{uncorrected} < 0.001$; −39, 9, 3; $Z = 3.18$; $P_{uncorrected} < 0.001$; −39, 0, 6; $Z = 3.13$; $P_{uncorrected} < 0.001$; and −60, −15, 9; $Z = 4.36$, $P_{uncorrected} < 0.001$) in left sagittal and axial sections. Activations in the right anterior insula and frontal operculum (33, 18, 9; $Z = 3.39$; $P_{uncorrected} < 0.001$ and 54, 6, 9; $Z = 3.50$; $P_{uncorrected} < 0.001$) in right saggital and axial sections. **(B)** Saggital and axial sections showing activity in spatial attention network (ACC, PCC, IPS, and FEF, see Table 1).

Table 2 Activations from the supra additive effects of taste and attention

Contrast	Region	MNI[a] coordinates			Cluster size in mm^3	*Z* values	$P_{uncorrected}$ values
		x	*y*	*z*			
DETECT*taste* − (PASSIVE/UNINFORMED*taste* + DETECT*tasteless*)[b]	ACC	0	15	27	5.4	4.05	2.59×10^{-5}
	ACC	−15	21	36	4.6	3.57	1.77×10^{-4}
DETECT taste − (PASSIVE/INFORMED*taste* + DETECT*tasteless*)[b]	OFC	−27	27	−15	6.1	4.03	2.84×10^{-5}
		−21	*36*	*−15*		4.59	
	ACC	0	18	24	5.9	3.97	3.56×10^{-5}
	Parietal precuneus	3	−63	30	5.1	3.49	2.42×10^{-4}
	Posterior cingulate gyrus	−6	−36	12	4.3	3.22	6.31×10^{-4}

Italics indicate that a peak falls under the same cluster as the preceding peak.
[a]Montreal Neurological Institute.
[b]T-map thresholded at $P_{uncorrected} = 0.001$.

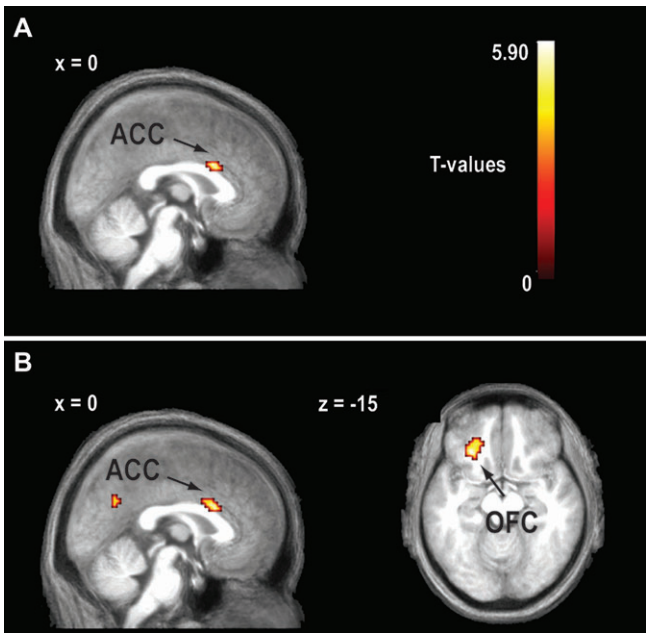

Figure 5 Results from random-effects analyses of supra-additive taste and attention to taste. The color bar in panel A represents the *t* values (from 0 to 5.90) representative of both panels. **(A)** Saggital section of ACC activity in DETECT*taste* contrasted with PASSIVE/UNINFORMED*taste* + DETECT*tasteless*) (Table 2). **(B)** Saggital and axial sections of ACC and OFC activity in DETECT*taste* constrasted with PASSIVE/INFORMED*taste* + DETECT*tasteless* (Table 2).

in a different region of the ACC (0, 18, 24) (area 24) and in caudolateral OFC (−27, 27, −15) (see Table 2 and Figure 5B). This again suggested selective recruitment of OFC when the identity of the stimulus is uncertain.

Tongue movement

Although tongue movement was restricted throughout the experiment (due to the gustatory manifold, see Figure 2), we reasoned that in task DETECT, subjects may have moved their tongue more to explore the oral cavity for taste than in the passive tasks. In an attempt to rule out the possibility that differences in tongue movements contributed to the observed insular activity, we conducted a control experiment to isolate regions that respond to when subjects moved the tongue 10 times in 5 s (TM10) versus a condition when they moved the tongues 5 times in 5 s (TM5). Eleven new subjects were scanned. A tone was used to cue subjects to move the tongue. Ten tones were played, and subjects received alternating instructions to move the tongue from side to side after every other tone (TM5) or after every tone (TM10). Comparison of TM10–TM5 produced bilateral activity in the primary sensorimotor cortex (66, −3, 33; $Z = 3.37$; $P_{uncorrected} = 0.000$; 66, −12, 15; $Z = 3.07$; $P_{uncorrected} = 0.001$; and −63, −18, 42; $Z = 2.93$; $P_{uncorrected} = 0.002$). Additional peaks were observed in the claustrum (−27, −6, 15; $Z = 2.81$; $P_{uncorrected} = 0.002$; which did not overlap with insular peaks) and in the cerebellum (−15, −63, −18; $Z = 2.75$; $P_{uncorrected} = 0.003$), but no activity was found in the insula. Furthermore, we did a small volume search with a sphere of 15-mm radius using the coordinates of the peaks in Figures 3 and 4 and Table 1 as centroids. We observed no areas of overlap. This experiment shows that differences in tongue movement between DETECT and passive tasks is unlikely to account for the differential response in the insula.

Task difficulty

Because of the concern that differences in task difficulty might provide an alternative explanation for the differences observed in detection versus passive tasks, we turned to unpublished data recently collected in a complementary study of Bender G, Meltzer J, Gitelman D, Small DM (in preparation). In this experiment ($n = 15$), subjects performed task DETECT, in addition to 3 other tasks. In one of the additional tasks, the subject was asked to identify the taste

quality (QUAL) (e.g., "is the liquid sweet, salty, or sour?"). Both tasks involve taste evaluation, but response times are longer for QUAL than for DETECT (2 [task: DETECT or QUAL] × 2 [taste: taste or tasteless] within-subjects analysis of variance; $F(1, 14) = 23.518$; $P = 0.000$), indicating that QUAL is likely a more difficult task. The 2 tasks (QUAL-*tasteless*–DETECT*tasteless* [Bender G, Meltzer J, Gitelman D, Small DM, in preparation]) did not produce differential activation of the insula, even when thresholding at $P_{\text{uncorrected}} = 0.005$ (this contrast is not reported in that manuscript because there were no significant findings). Furthermore, we did a small volume search with a sphere of 15-mm radius using the coordinates of the peaks in Table 1 as centroids. We observed only 1 area of overlap in the superior/middle frontal gyrus at 60, 21, 15 ($Z = 2.6$). These findings do not support a role for task difficulty as a cause of the differential insula response during detection versus passive tasting.

Discussion

As predicted, the results from this study demonstrate that trying to detect a taste in a tasteless solution results in activation of early gustatory cortex, specifically the midIns/Fop as well as the Pop (Figures 3A,B and 4A). This finding supports the possibility that multiple regions within the insula and operculum are important for taste detection and selective attention to taste. In contrast, the caudolateral OFC was not recruited when trying to detect a taste in a tasteless solution. Rather, consistent with prior work, the response in this region appeared to be preferentially sensitive to receipt of solutions when their identity was uncertain (Berns et al. 2001).

Probing the world for a sound in silence (Voisin et al. 2006), a sight in an empty visual scene (Kastner et al. 1999; Hopfinger et al. 2000), or an odor in odorless air (Zelano et al. 2005) results in activation of the respective primary sensory cortical region. This is consistent with our observation of increased activity in taste-responsive regions of insula and operculum when searching for taste in a tasteless solution. The primary projection from taste thalamus in the macaque is to the anterior insula and overlying frontal operculum (Pritchard et al. 1986). We observed activity here in DETECT*tasteless*–PASSIVE/INFORMED*tasteless.* However, when uncertainty was matched, the attention effect was limited to midIns/Fop and parietal operculum. This region is frequently activated to taste (Small et al. 1999). Taste intensity, detection, and identification are changed after lesions that include this area of insular cortex (Pritchard et al. 1999; Mak et al. 2005). Responses in this region increase with perceived intensity (Small, Gitelman, et al. 2003), and a companion study from our laboratory indicates that this region responds more to taste stimulation compared with tasteless stimulation irrespective of task (Bender G, Meltzer J, Gitelman D, Small DM, in preparation). This area has also been reported to be the first region to respond after taste stimulation in an fMRI study (Ogawa et al. 2005). Taken together, these data indicate that the midIns/Fop plays an important role in human gustation.

We also observed activity bilaterally in the Pop (Figures 3A and 4B). This region has been proposed to represent primary taste cortex in the humans because in several MEG studies this area shows the earliest response to taste stimulation (Kobayakawa et al. 1996, 1999). One problem with this proposal is that there is no evidence for a gustatory projection from thalamus to posterior insula/parietal operculum in primates or humans (Mesulam et al. 1983; Pritchard et al. 1986). Furthermore, Petrides and Pandya (1994) have described the existence of a small granular zone in the anterior insula and frontal operculum, which is the site of the primary termination of gustatory afferents, in both monkey and humans. Taken together, these findings indicate that both Pop and midIns/Fop are important for detecting taste stimuli and that both regions are modulated by selective attention to taste. However, in the absence of evidence for a taste projection to the posterior region, we propose that this area is primarily important for oral somatosensation and that its recruitment in our task may reflect attention to the mouth rather than attention to taste. We note that this does not mean that the Pop is unimportant for taste detection or selective attention to taste but rather that detection and selective attention may recruit gustatory and somatosensory systems, with the midIns/Fop corresponding to the taste response and the Pop to the somatosensory response. Future studies are needed to further explore the possibility and nature of functional specialization of these areas.

Our insular finding has important implications for future gustatory paradigm design. Several studies in which a taste detection task has been employed fail to isolate responses in the insula and overlying operculum (Small et al. 1997a, b; Zald et al. 1998). The current result suggests that this is because the sensory effect of taste may be insufficient to be observed above the attentional effect to taste, which occurs in the same region. This possibility is in accordance with single-cell recording studies showing that only a small percentage of cells within the gustatory insula/operculum actually respond to taste (Scott and Plata-Salaman 1999) and with data from an fMRI study showing greater BOLD response in the anterior insula for ageusic patients as compared with controls (Hummel et al. 2006). In agreement with our suggestion, Hummel et al. (2006) explained this latter finding by the larger effort patients made to perceive taste compared with controls.

To our knowledge, attention activation surpassing sensory activation in early cortical regions has not been observed in other modalities. For example, attentional modulation in the visual system has been reported to be around 25% of the sensory signal (Gandhi et al. 1999; Kanwisher and Wojciulik 2000). There are several possible factors that may contribute to this potentially taste-specific effect. First, the gustatory insular cortex is heteromodal with only a small subset of neurons encoding taste (Smith-Swintosky et al. 1991; Hamdy

et al. 1999; Zald and Pardo 1999; Katz et al. 2002; De Araujo and Rolls 2004; Verhagen et al. 2004; Watanabe et al. 2004; Kadohisa et al. 2005; Rolls 2005). In contrast, early visual, auditory, and somatosensory cortical regions are, if not exclusively, then certainly dominantly concerned with sensory representation of their respective modality. Thus, the proportion of sensory neurons in cortical regions may determine the relative magnitude of sensory versus attentional effects. Second, the heteromodal taste cortex is not only sensory cortex but is also postulated to play a critical role in interoceptive awareness (Critchley et al. 2004). Thus, a relatively weaker sensory response may be coupled with a relatively greater attentional response.

As can be observed in the plots of the BOLD signal over time in Figures 3 and 4, there is activity in insula and overlying operculum in response to the tasteless solutions under the PASSIVE conditions (dashed lines). Although we recognize that we cannot exclude the possibility that the individually tailored tasteless solutions may still have had a weak taste, this activity does not necessarily reflect gustatory activation. As was indicated above, the insula and overlying operculum are heteromodal cortical zones. Some of the neurons are bimodal and respond, for example, to oral somatosensation and mouth movement (Scott and Plata-Salaman 1999). Thus, the activity in these areas could reflect the representation of the somatosensory aspects of the tasteless solution. It is exactly this characteristic that makes the tasteless solution a better control stimulus than water taste or a no-taste resting baseline.

Top–down modulation of mid to posterior dorsal insular cortex by breaches of taste expectancy has been described by Nitschke et al. (2006). In their study, subjects were led to believe that they would receive a mildly aversive bitter taste but unexpectedly received a highly aversive bitter taste. The magnitude of insular and overlying opercular responses was less when compared with a condition where they were not misled about the same taste stimulus. This result is consistent with the current report, in that this region is sensitive to top–down modulation. However, here the finding was in response to tasteless events and is thus likely due to a baseline shift in activity rather than to modulation of the processing of a sensory signal. Additionally, we observed activity irrespective of whether subjects were informed about the stimulus identity, indicating that the region did not appear to be selectively or preferentially responsive to manipulations of cue predictability. Rather, we found that activity in a more anterior region of insula was driven by uncertainty (Figure 4A). The reason for this discrepancy is not apparent. However, there are a number of notable differences between the study of Nitschke et al. (2006) and the present one: our analyses are based on tasteless solutions, whereas theirs were based on taste solutions; our taste stimuli were weak and moderately pleasant or aversive, whereas their stimuli included a highly aversive bitter taste; and finally, our cues were not misleading, whereas in their study cues were misleading. Future studies will be needed to determine the importance of these or other variables in predicting the precise location of insular response to taste and to top–down modulation of taste.

Trying to taste in the absence of taste stimulation did not lead to increased activity in the OFC. This is consistent with its designation as a higher order gustatory region, characterized by responses to changes in subjective pleasantness (O'Doherty et al. 2001; De Araujo, Rolls, et al. 2003; Kringelbach et al. 2003; Small, Gregory, et al. 2003). Furthermore, the OFC has been reported to be preferentially sensitive to taste predictability (Berns et al. 2001). In agreement with this, we observed activity in the OFC during taste uncertainty. These findings are consistent with functional specialization in taste cortex in humans and with the insula/operculum designated as PGC and OFC as higher order cortex.

We observed a supra-additive response to taste stimulation and attention to taste in the ACC that was present irrespective of whether the baseline condition controlled for uncertainty (Figure 5). This region is frequently activated by taste, smell, and flavor stimulation (Zald et al. 1998; O'Doherty et al. 2001; De Araujo, Rolls, et al. 2003; Small, Gregory, et al. 2003; Small et al. 2004; Marciani et al. 2006). Furthermore, this exact region shows supra-additive responses to perception of congruent taste–odor pairs compared with the sum of the response to independent stimulation of the taste and the odor (Small et al. 2004). Thus, evidence is mounting to support the possibility that the ACC should be considered as part of the taste and flavor network.

We also note that we isolated activity in the canonical spatial attention network FEF, IPS, dorsal ACC, and PCC during attention to taste. The spatial attention network is thought to up-regulate baseline activity in sensory cortex (Mesulam et al. 2005). This finding adds support to the notion that the attention network is not modality specific but a more general large-scale heteromodal network important for attending to the internal and external environments (Grefkes and Fink 2005).

Conclusions

In summary, the present results show that trying to detect a taste in a tasteless solution results in enhanced activity in the insula and overlying operculum but not in higher order gustatory cortex in the OFC. We propose that the insula activation represents the neural correlate of selective attention to taste. In contrast, we observed preferential activation of OFC when subjects were uncertain about the next taste sensation, providing further evidence for the importance of this region in taste predictability. Taken together, these findings support the existence of functional specialization in human gustatory cortex.

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