Cerebral Cortex July 2008;18:1549-1559
doi:10.1093/cercor/bhm185
Advance Access publication December 1, 2007

How Cognition Modulates Affective Responses to Taste and Flavor: Top-down Influences on the Orbitofrontal and Pregenual Cingulate Cortices

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How cognition influences the affective brain representations of the taste and flavor of a food is important not only for understanding top-down influences in the brain, but also in relation to the topical issues of appetite control and obesity. We found using functional magnetic resonance imaging that activations related to the affective value of umami taste and flavor (as shown by correlations with pleasantness ratings) in the orbitofrontal cortex were modulated by word-level descriptors. Affect-related activations to taste were modulated in a region that receives from the orbitofrontal cortex, the pregenual cingulate cortex, and to taste and flavor in another region that receives from the orbitofrontal cortex, the ventral striatum. Affect-related cognitive modulations were not found in the insular taste cortex, where the intensity but not the pleasantness of the taste was represented. We conclude that top-down language-level cognitive effects reach far down into the earliest cortical areas that represent the appetitive value of taste and flavor. This is an important way in which cognition influences the neural mechanisms that control appetite.

Keywords: appetite, cingulate cortex, emotion, flavor, insular cortex, orbitofrontal cortex, taste

Introduction

The affective properties of food are an important source of human hedonic experience and are central to the regulation of motivated behavior such as food intake. The hedonic value of a food is strongly influenced by its sensory properties, with for example the pleasant flavor of some savory foods produced by a combination of a taste such as monosodium glutamate (MSG) and an odor such as the odor of vegetables (McCabe and Rolls 2007). Many studies have investigated the representations of taste and flavor sensory stimuli in the insular taste cortex, the orbitofrontal cortex, and the anterior cingulate cortex (Rolls and Baylis 1994; Critchley and Rolls 1996; Rolls et al. 1996; Small et al. 1999, 2004; O'Doherty et al. 2001; de Araujo et al. 2003c; Small and Prescott 2005; Gottfried et al. 2006; McCabe and Rolls 2007). However, our affective responses to environmental stimuli are not only dependent on their sensory properties, but also on high levels of cognitive and linguistic processing. Surprisingly, almost nothing is known about how cognitive processes can influence the hedonic properties of taste and flavor representations in the brain. Do for example cognitive descriptions at the level of language influence brain representations of flavor and taste only in higher order cognitive areas, or do these cognitive influences produce top-down biasing of early cortical, sensory representations? In the present study, we investigated this with functional magnetic resonance imaging (fMRI) by pairing a flavor stimulus and a taste stimulus with word descriptor labels that influenced the subjective pleasantness ratings of the stimuli.

There is little prior research investigating where in the brain cognition can influence the affective (pleasant vs. unpleasant) representations of flavor and taste. Previous neuroimaging research in humans has shown that cognitive modulation of the effects of an orthonasally delivered, non–food-related odor is present in regions such as the orbitofrontal cortex (de Araujo et al. 2005); that conditioned expectations could dampen the activation to a bitter taste stimulus of different intensities in the middle and posterior insula (Nitschke et al. 2006); and that brand knowledge evoked by a visual cue paired with the delivery of a beverage produced activations in memory-related brain regions such as the hippocampal and parahippocampal regions (McClure et al. 2004). However, no study has investigated where in the brain the affective value of food-related flavor and taste can be influenced by high-level cognitive processing.

Given the obesity epidemic and the medical risks associated with obesity, it is important to understand the different factors that determine the pleasantness of the taste and flavor of food and can thus influence the type of food that is eaten and how much is eaten (Krebs 2005; Schwartz and Porte 2005; Rolls 2007b, 2007c). This is the first study we know that investigates how word-level cognitive factors influence the affective representation of taste and flavor stimuli in the brain.

Methods

Overall Design

We investigated how top-down cognitive effects from the language level can influence hedonic representations of flavor and taste in the brain. We paired the same flavor and taste stimulus with word labels that were designed to influence the subjective pleasantness but not the intensity of the stimuli. We used a taste-only stimulus, MSG, which produces the taste of umami, and a flavor stimulus, MSG with vegetable odor, to investigate modulations in brain regions involved in the sensory and affective analysis of tastes and flavors related to food. To make our findings relevant to the brain mechanisms of food reward and thus the control of food intake we used taste and flavor stimuli that are present in many foods. Umami taste is found in a diversity of foods rich in glutamate like fish, meat, milk, and some vegetables including tomatoes and mushrooms, and is enhanced by some ribonucleotides (including inosine and guanosine nucleotides) (Yamaguchi 1967; Rifkin and Bartoshuk 1980), which are present in for example meat and some fish (Yamaguchi and Ninomiya 2000). We explicitly compared whether cognitive modulation effects are present in areas that represent the intensity but not the pleasantness of taste and flavor such as the insular primary taste cortex (Yaxley et al. 1988, 1990; Kringelbach et al. 2003), or in areas where neural activations are related to the reward value, that is the pleasantness, of taste and flavor such as the orbitofrontal cortex, pregenual cingulate cortex, and ventral striatum (Rolls 2006). An important part of our design was to investigate how activations to the

same sensory stimulus, a given taste and a given flavor, could be modulated when paired with 2 semantically different word labels.

The taste stimulus, consisting mainly of MSG which produced the taste of umami, was labeled on different trials as "rich and delicious taste" (MSGrich) or "monosodium glutamate" (MSGbasic) (see Table 1). Similarly, the flavor stimulus, produced by a combination of MSG and vegetable odor, was labeled on different trials as "rich and delicious flavor" (MSGVrich) or "boiled vegetable water" (MSGVbasic) (see Table 1). In addition, to investigate whether the brain areas where cognition modulates affective representations can be dissociated from those where sensory properties such as taste intensity are represented, we included a condition (MSG2) where we presented the taste stimulus at a higher concentration than in the MSGbasic condition accompanied by the same label. A further part of the design was to take psychophysical ratings of pleasantness and intensity of taste and flavor made on every trial by the subjects during the fMRI experiment, so that the subjective evaluation of the stimuli in terms of their pleasantness and intensity could be correlated with the fMRI blood oxygenation level–dependent (BOLD) signals measured on every trial. Moreover, to localize the primary taste cortex we included a tasteless control solution containing the main ionic components of saliva and which when subtracted from the effects produced by the taste stimulus allowed somatosensory and any mouth movement effects to be distinguished from the effects purely related to taste (O'Doherty et al. 2001; de Araujo et al. 2003a).

We formulated prior hypotheses based on previous neurophysiological and fMRI analyses of particular brain regions in which it would be of interest to test statistically whether cognitive modulation influenced the response to taste and flavor. These included the insular (primary) taste cortex and the orbitofrontal cortex which contains the secondary cortical taste area and also where olfactory and taste convergence to produce flavor is present (Rolls and Baylis 1994; Critchley and Rolls 1996; Rolls et al. 1996; Small et al. 1999, 2004; O'Doherty et al. 2001; de Araujo et al. 2003c; Small and Prescott 2005; McCabe and Rolls 2007), which have both been found to respond to umami taste (de Araujo et al. 2003a) and flavor (McCabe and Rolls 2007); the pregenual cingulate cortex which receives connections from the orbitofrontal cortex, contains taste neurons, and in which the activations correlate with the affective value of a number of sensory stimuli (Carmichael and Price 1996; Rolls Forthcoming a, Forthcoming b; Rolls et al. Forthcoming); and the ventral striatum which receives from the orbitofrontal and insular cortices (Fudge et al. 2005; Rolls 2005, 2006).

Participants

Twelve healthy volunteers (6 males and 6 females, age range 21–35) participated in the study. Ethical approval (Central Oxford Research Ethics Committee) and written informed consent from all subjects were obtained before the experiment. The participants were asked not to eat for 3 h before the experiment.

Stimuli

The taste and flavor stimuli were chosen based on previous fMRI studies (de Araujo et al. 2003a; McCabe and Rolls 2007) as well as on a preliminary psychophysical investigation with 30 subjects which was conducted to ensure that the subjective ratings of the stimuli could be modulated by the word labels. The taste stimulus consisted of 0.1 M MSG + 0.005 M inosine 5′-monophosphate which produced the taste of umami. The flavor stimulus consisted of a combination of umami taste (as produced by the same concentration of MSG and inosine 5′-monophosphate) and a consonant, savory, vegetable odor (supplied by Firmenich S.A., Geneva) (see Table 1). The vegetable odor used combines supralinearly with umami taste to produce a rich and delicious flavor (McCabe and Rolls 2007). In addition, to investigate the effects of the concentration of the tastant on brain activations, we included a condition where we presented the taste stimulus at the higher concentration of 0.4 M (accompanied by the label "monosodium glutamate"). Both the taste and flavor stimuli were prepared using distilled water. An important aim of the design of this study was to allow for the localization of the primary taste cortex. For this purpose, we included a tasteless control solution containing the main ionic components of saliva (25 mM KCl + 2.5 mM $NaHCO_3$) which when subtracted from the effects produced by the taste stimulus allowed somatosensory and any mouth movement effects to be distinguished from the effects purely related to taste (O'Doherty et al. 2001; de Araujo et al. 2003a). This is an important control condition that we have pioneered to allow taste areas to be shown independently of any somatosensory effects produced by introducing a fluid into the mouth (O'Doherty et al. 2001; de Araujo et al. 2003a, 2003b). The tasteless solution was accompanied by the visual display of a red cross.

Table 1
Stimuli and abbreviations

MSGrich	0.1 M MSG + 0.005 M inosine 5′-monophosphate	"Rich and delicious taste"
MSGbasic	0.1 M MSG + 0.005 M inosine 5′-monophosphate	"Monosodium glutamate"
MSGVrich	0.1 M MSG + 0.005 M inosine 5′-monophosphate + 0.4% vegetable odor	"Rich and delicious flavor"
MSGVbasic	0.1 M MSG + 0.005 M inosine 5′-monophosphate + 0.4% vegetable odor	"Boiled vegetable water"
MSG2	0.4 M MSG + 0.020 M inosine 5′-monophosphate	"Monosodium glutamate"

To investigate the effects of cognitive labels on the neural taste and flavor representations, the taste or flavor stimulus was accompanied on different trials by different word labels. The instructions given to the subjects stated that we were interested in the evaluation of pleasant tastes and flavors, and in the components that influence the pleasantness of different foods such as vegetable soup. To measure the cognitive effects of a word label on taste, the taste stimulus described above was labeled on different trials as "rich and delicious taste" or "monosodium glutamate." Similarly, the flavor stimulus described above was labeled on different trials as "rich and delicious flavor" or "boiled vegetable water." The word labels were designed to modulate the affective, that is hedonic, value of the stimuli and were presented on a backprojection screen simultaneously with the delivery of the taste and flavor stimuli. The participants were not informed about whether the taste and flavor stimuli delivered into the mouth were the same or different on different trials, and were not told the composition of the stimuli.

Experimental Protocol

During the fMRI experiment the subjects gave psychophysical ratings of pleasantness and intensity on every trial, so that correlation analyses between the ratings and the brain activations could be performed. Contrast analyses were performed for the fMRI data as described in the Results to measure the effects of the word labels on the activations produced by the taste and flavor stimuli.

The experimental protocol consisted of an event-related interleaved design presenting in random permuted sequence the 5 experimental conditions described above. The number of experimental conditions was chosen to be feasible given the number of repetitions of each condition needed and the length of time that subjects were in the magnet, but at the same time to allow the analyses described in this paper to be made. Stimuli were delivered to the subject's mouth through 4 teflon tubes (one for each of the 3 taste or flavor stimuli, and a separate tube for the tasteless rinse control) that were held between the lips. The odor in the flavor condition was thus delivered by the retronasal route in aqueous solution. This allowed for the flavor to be produced in a natural way. Each teflon tube of approximately 3 m in length was connected to a separate reservoir via a syringe and a one-way syringe activated check valve (Model 14044-5, World Precision Instruments, Inc), which allowed 0.75 mL of any stimulus to be delivered at the time indicated by the computer.

At the beginning of each stimulus delivery, one of the 3 experimental solutions chosen by random permutation was delivered in a 0.75-mL aliquot to the subject's mouth (and was cued by a small red cross on a visual display). Swallowing was cued after 7 s by a small green cross on the visual display (following initial instruction and training). After a delay of 2 s, the subject rated each of the oral stimuli for pleasantness (with +2 being very pleasant and –2 very unpleasant), and for intensity

(0 to +4). The ratings were made with a visual analog rating scale in which the subject moved the bar to the appropriate point on the scale using a button box. Each rating period was 4 s long. Subjects were pretrained in the use of the rating scales. After the intensity rating the small red cross indicated the delivery of the tasteless control solution that was also used as a rinse between stimuli, and this was administered in exactly the same way as a test stimulus and the subject was cued to swallow after 7 s by the green cross. There was then a 4-s delay period before the next trial started. Each experimental condition was presented in permuted sequence 9 times. The instruction given to the subject was to move the tongue once as soon as a stimulus or tasteless solution was delivered (at the time when a red cross was turned on) in order to distribute the solution round the mouth to activate the receptors for taste and smell, and then to keep still for the remainder of the 7-s red cross period until the green cross was shown, when the subject could swallow. This procedure has been shown to allow taste effects to be demonstrated clearly with fMRI, using the procedure of subtracting any activation produced by the tasteless control from those produced by a taste or other stimulus (O'Doherty et al. 2001; de Araujo et al. 2003a, 2003b; de Araujo and Rolls 2004).

fMRI Data Acquisition

Images were acquired with a 3.0-T VARIAN/SIEMENS whole-body scanner at the Centre for Functional Magnetic Resonance Imaging at Oxford (FMRIB), where 27 T_2^*-weighted EPI coronal slices with in-plane resolution of 3 × 3 mm and between plane spacing of 4 mm were acquired every 2 s (time repetition = 2). We used the techniques that we have developed over a number of years (O'Doherty et al. 2001; de Araujo et al. 2003a) and as described in detail by Wilson et al. (2002) we carefully selected the imaging parameters in order to minimize susceptibility and distortion artifact in the orbitofrontal cortex. The relevant factors include imaging in the coronal plane, minimizing voxel size in the plane of the imaging, as high a gradient switching frequency as possible (960 Hz), a short echo time of 28 ms, and local shimming for the inferior frontal area. The matrix size was 64 × 64 and the field of view was 192 × 192 mm. Continuous coverage was obtained from +62 (*A*/*P*) to −46 (*A*/*P*). A whole brain T_2^*-weighted echo planar imaging volume of the above dimensions, and an anatomical T_1 volume with coronal plane slice thickness 3 mm and in-plane resolution of 1 × 1 mm was also acquired.

fMRI Data Analysis

The imaging data were analyzed using SPM5 (Wellcome Institute of Cognitive Neurology). Preprocessing of the data used SPM5 realignment, reslicing with sinc interpolation, normalization to the MNI Montreal Neurological Institute coordinate system (Collins et al. 1994), and spatial smoothing with a 6-mm full width at half maximum isotropic Gaussian kernel. The time series at each voxel were low-pass filtered with a hemodynamic response kernel. Time series nonsphericity at each voxel was estimated and corrected for (Friston et al. 2002), and a high-pass filter with a cut-off period of 128 s was applied. In the single event design, a general linear model was then applied to the time course of activation where stimulus onsets were modeled as single impulse response functions and then convolved with the canonical hemodynamic response function (Friston et al. 1994). Linear contrasts were defined to test specific effects. Time derivatives were included in the basis functions set. Following smoothness estimation (Kiebel et al. 1999), linear contrasts of parameter estimates were defined to test the specific effects of each condition with each individual dataset. Voxel values for each contrast resulted in a statistical parametric map of the corresponding *t* statistic, which was then transformed into the unit normal distribution (SPM Z). The statistical parametric maps from each individual data set were then entered into second-level, random effects analyses accounting for both scan-to-scan and subject-to-subject variability. More precisely, the sets of individual statistical maps corresponding to a specific effect of interest were entered as covariates in multiple regression models as implemented in SPM5, and the corresponding group effects were assessed by applying linear contrasts (again following smoothness estimation) to the (second-level) parameter estimates generating a *t*-statistics map for each group effect of interest. The correlation analyses of the fMRI BOLD signal with given parameters of interest (e.g., the pleasantness ratings) were performed at the second-level through applying one-sample *t*-tests to the first-level *t*-maps resulting from performing linear parametric modulation as implemented in SPM5. We report results for brain regions where there were prior hypotheses as described under Overall Design, namely in the parts of the orbitofrontal and anterior cingulate cortex, insular primary taste cortex, and ventral striatum in which we and others have found activations in previous studies to taste and flavor stimuli (Small et al. 1999, 2003; O'Doherty et al. 2001; de Araujo et al. 2003a, 2003b; de Araujo and Rolls 2004; Kringelbach and Rolls 2004; Rolls 2005, 2006; Small and Prescott 2005) and applied small volume corrections for multiple comparisons (Worsley et al. 1996) with a radius corresponding to the full width at half maximum of the spatial smoothing filter used. (We note that this is suitable for small brain regions such as the ventral striatum, or for parts of larger structures where there is a predefined part that is of interest based on earlier studies, which applies in our study to the parts of the medial orbitofrontal cortex, anterior cingulate cortex, and anterior insular cortex investigated; see Rolls et al. 2003a; de Araujo and Rolls 2004; de Araujo et al. 2005; McCabe and Rolls 2007). Peaks are reported for which $P < 0.05$, though the exact corrected probability values (Worsley et al. 1996) are given in Table 2. All the results shown in Table 2 and described in this paper also met the additional criterion that the activations were significant at $P < 0.001$ uncorrected with a cluster size >10 voxels.

For the time course plots, we located activations within the a priori regions of interest and extracted event-related responses from the peak voxel for that subject. These single-subject time courses were then averaged across subjects.

Table 2
Coordinates for activations found in different brain regions

Brain area	*x*	*y*	*z*	*Z* score	*P* value
Insular taste cortex ($y = 22$ to $y = 6$)					
MSGVrich-rinse	38	16	6	4.15	0.001
	−32	14	4	3.46	0.001
MSGVbasic-rinse	38	14	4	3.83	0.001
MSGrich-rinse	34	16	4	4.32	0.001
MSGbasic-rinse	34	16	2	3.92	0.001
MSG2–MSGbasic	30	20	−6	3.32	0.027
	−30	20	−4	3.96	0.003
	−36	6	0	3.86	0.002
Conjunction (MSGrich-rinse, MSGbasic-rinse)	34	16	4	4.50	0.001
Conjunction (MSGrich-rinse, MSGbasic-rinse, MSG2–MSGbasic)	36	14	4	3.89	0.002
	−38	6	6	3.49	0.010
Positive correlation with intensity (MSG2, MSGbasic)	−30	20	−4	3.15	0.026
Orbitofrontal cortex					
MSGVrich–MSGVbasic	−8	28	−20	3.36	0.039
Positive correlations with pleasantness (MSGrich, MSGbasic)	−28	52	−2	3.09	0.016
(MSGbasic, MSG2)	−6	42	−26	3.05	0.044
(MSGVrich, MSGVbasic, MSGrich, MSGbasic)	18	20	−8	3.44	0.021
Positive correlation with intensity (MSGVrich, MSGVbasic)	14	24	−12	3.26	0.043
Negative correlations with intensity (MSGrich, MSGbasic)	−26	30	−14	3.58	0.005
(MSGbasic, MSG2)	−8	56	−18	2.50	0.040
Cingulate cortex					
MSG2–MSGbasic	−10	36	10	3.49	0.016
Positive correlations with pleasantness (MSGrich, MSGbasic)	4	44	−2	3.24	0.016
Ventral striatum					
MSGVrich–MSGVbasic	−6	6	−14	3.19	0.033
MSGrich–MSGbasic	2	12	−10	3.40	0.037
Positive correlations with pleasantness (MSGVrich, MSGVbasic)	−12	2	−2	3.00	0.042
(MSGrich, MSGbasic)	−6	10	−16	3.64	0.006
(MSGbasic, MSG2)	−6	2	−18	3.12	0.021
(MSGVrich, MSGVbasic, MSGrich, MSGbasic)	−10	4	−16	4.38	0.001
Positive correlation with intensity (MSGVrich, MSGVbasic)	−20	8	−2	3.01	0.021

Results

Cognitive Effects on the Ratings of Pleasantness and Intensity

The ratings of the pleasantness and intensity of the stimuli obtained during the neuroimaging are shown in Fig. 1. A within-subjects analysis of variance (ANOVA) ($F_{4,11} = 10.2$, $P < 0.001$) followed by post hoc least significant difference (LSD) tests (accompanied by a Kolmogorov–Smirnov test for normality) showed that the MSG was rated as significantly more pleasant when labeled "rich and delicious taste" than when labeled "monosodium glutamate" ($P = 0.002$). Similarly, the MSGV was rated as significantly more pleasant when labeled "rich and delicious flavor" than when labeled "boiled vegetable water" ($P = 0.003$). In contrast, the labels did not produce significant differences in the intensity ratings for the MSG ($P = 0.273$) or the MSGV ($P = 0.526$) (post hoc LSD tests after a within-subjects ANOVA of the intensity ratings). These findings provide clear evidence that the cognitive labels were modulating the perceived taste and flavor in this investigation. The MSG2 was rated as significantly more intense than the MSGbasic ($P < 0.001$) (with the within-subjects ANOVA for the intensity ratings ($F_{4,11} = 63.1$, $P < 0.001$), and as significantly less pleasant ($P < 0.001$). In this case, the labels were identical ("monosodium glutamate"), and this provides evidence that the perceived taste reflected also the properties of the stimuli (0.1 M vs. 0.4 M MSG). There was no correlation between the pleasantness and intensity ratings apart from for the MSG2 (0.4 M MSG) condition, for which the pleasantness was negatively correlated with the intensity ($r = -0.97$, df = 11, $P < 0.001$).

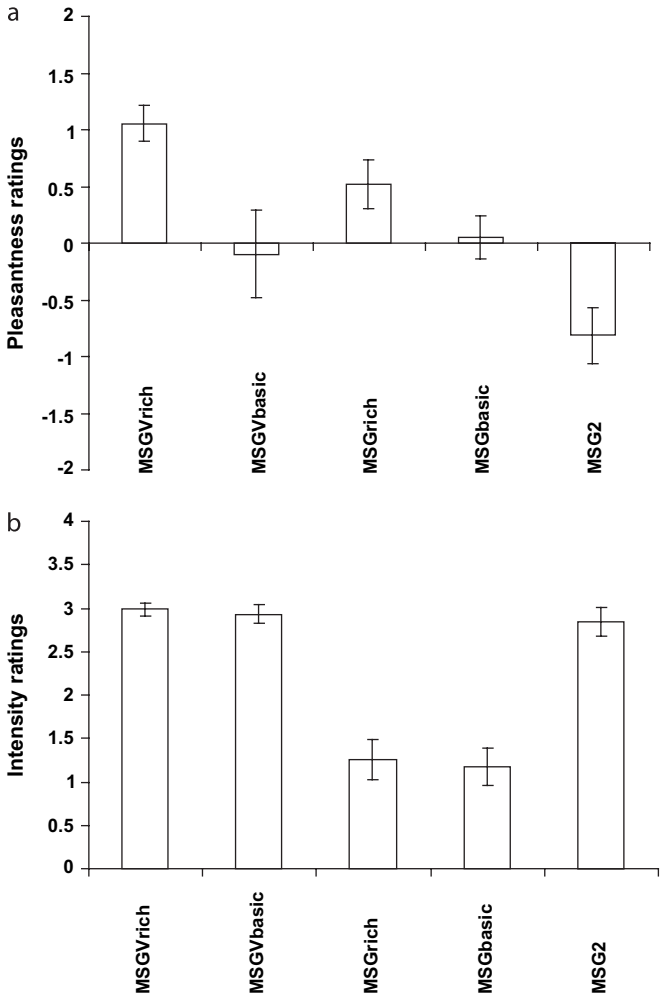

Figure 1. The ratings of pleasantness (*a*) and intensity (*b*) for the taste and flavor stimuli (means ± SEM). For abbreviations see Table 1. The taste stimulus MSG was rated as significantly more pleasant when labeled "rich and delicious taste" than when labeled "monosodium glutamate." Similarly, the flavor stimulus MSGV was rated as significantly more pleasant when labeled "rich and delicious flavor" than when labeled "boiled vegetable water." In contrast to the effects on the pleasantness ratings, the labels did not produce significant differences in the intensity ratings for the taste and flavor stimuli. These findings provide clear evidence that the cognitive labels were modulating the perceived pleasantness, but not the intensity of the taste and flavor. The more concentrated taste stimulus MSG2 was rated as significantly less pleasant and more intense than the identically labeled taste stimulus MSGbasic. In this case, the labels were identical ("monosodium glutamate"), and this provides evidence that the perceived taste reflected also the properties of the stimuli (low vs. high concentration).

Localization of the Insular Primary Taste Cortex

To locate the primary taste cortex, we used the contrast of MSG2–MSGbasic (which had the identical label but different MSG concentrations), and this showed significant effects in the anterior insular cortex with a number of separate peaks at for example [30 20 –6] and [–36 6 0] as shown in Table 2 identifying this region as insular taste cortex (consistent with earlier studies; e.g., McCabe and Rolls 2007), and showing that this region reflects the concentration of the tastant (with the BOLD signal time course to MSG2 included in Fig. 2*b*). Evidence consistent with this identification is that a conjunction of the activations produced by MSGrich-rinse and MSGbasic-rinse showed activations in the same region (see Table 2). Because the tasteless control solution has been subtracted from the first 2 terms in this conjunction, these contrasts (and the conjunction of them) show where the taste cortex is located, by subtracting the effects of somatosensory stimulation produced when the tastant is introduced into the mouth. Moreover, the conjunction of this analysis with MSG2–MSGbasic resulted in the effects shown in Fig. 2*a*, which clearly identifies a substantial region at the anterior end of the insula that is activated by taste, and which had peaks at [34 16 4] and [–38 6 6].

Representation of Intensity but no Affective Cognitive Modulation in the Insular Primary Taste Cortex

The activation in the region of insular taste cortex just identified (see Fig. 2*a* and Table 2) was correlated with the intensity ratings (but not the pleasantness ratings) obtained for the MSG2 and MSGbasic stimuli ($y = 20$ in Table 2).

There was no significant effect of the rich versus basic word labels in this area of taste cortex (as illustrated by the BOLD signal time course for MSGVrich and MSGVbasic shown in Fig. 2*b* and the corresponding peaks shown in Fig. 2*c*), nor of the correlations of the brain activations with the pleasantness ratings of the taste or flavor as modulated by the word labels.

Cognitive Modulation of Affective Taste and Flavor Representations in the Orbitofrontal and Pregenual Cingulate Cortices

The human medial orbitofrontal cortex and pregenual cingulate cortex are considered together, as there are considerable similarities in how these areas responded to the taste and flavor

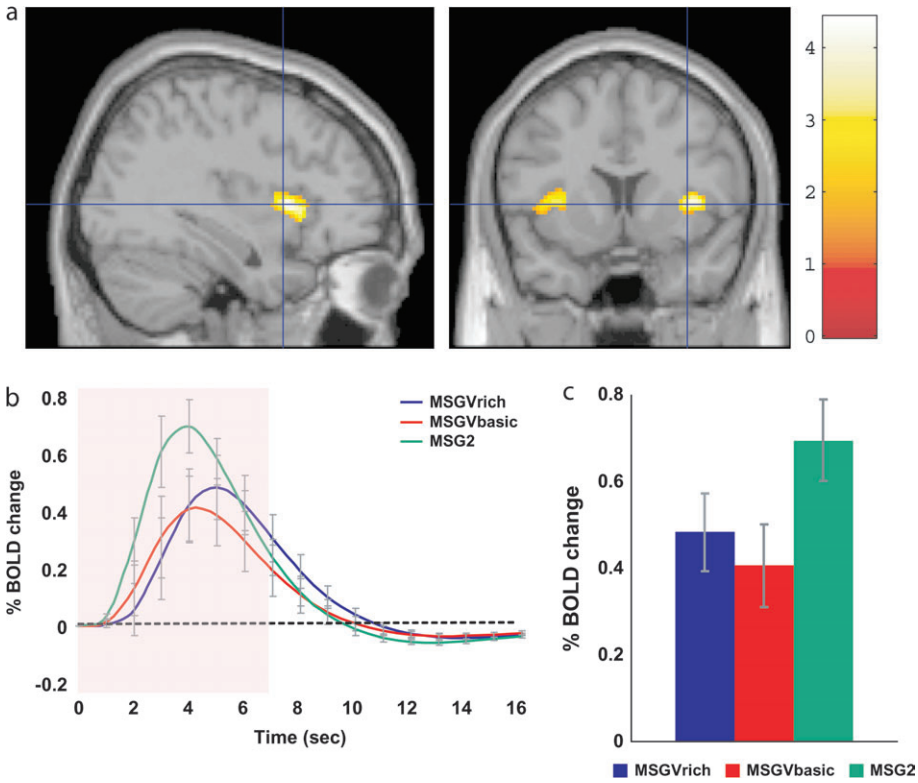

Figure 2. Insular taste cortex. (*a*) A conjunction analysis of the activations produced by the taste of MSG (from the conditions MSGrich-rinse and MSGbasic-rinse) shows the location of the insular primary taste cortex [34 16 4]. Subtraction of the tasteless control was performed, as this is a better control than subtracting effects produced by water, for there are neurons tuned to water in the primary taste cortex (Yaxley et al. 1990), and water relative to a tasteless control activates the human primary taste cortex (de Araujo et al. 2003b). (*b*) The time course of the BOLD signals for the conditions MSGVrich, MSGVbasic, and MSG2 in the insular taste cortex. (*c*) The peak values of the BOLD signal (mean across subjects ± SEM) were not different in this region for the flavor stimulus under the different labels (MSGVrich vs. MSGVbasic), but the effect of the more concentrated solution (MSG2) was larger (LSD post hoc tests both $P < 0.05$ following a significant ANOVA $F_{2,22} = 4.63$, $P = 0.021$).

stimuli in this study, as well as to many other positively affective stimuli in previous studies (de Araujo et al. 2003b; de Araujo and Rolls 2004; Rolls 2005, 2007a, Forthcomingb, Guest et al. 2007; McCabe and Rolls 2007; Rolls and McCabe 2007). The evidence comes both from contrasts that reveal effects of cognitive modulation, and from correlations with the pleasantness ratings where the only factor influencing the pleasantness ratings was the cognitive label.

The contrast MSGVrich versus MSGVbasic showed significant effects in the medial orbitofrontal cortex, in that this region was activated more strongly when the stimulus was labeled "rich and delicious flavor" than when it was labeled "boiled vegetable water" (at [–8 28 –20] Fig. 3*a*; the BOLD signal for the 2 conditions is shown in Fig. 3*b*, and the peaks were significantly different as shown in Fig. 3*c*). Thus, the word labels influenced the activations produced by the flavor in this area. Moreover, activations in the medial orbitofrontal cortex reflected the pleasantness of the stimuli, as shown by a correlation with the subjective pleasantness ratings of the stimuli (MSGVrich, MSGVbasic, MSGrich, and MSGbasic) (see Fig. 3*d* which shows the BOLD signal as a function of the ratings, and Table 2 for the coordinates of the peak voxel of what was an extensive area bilaterally), and, as also shown in Table 2, there was a correlation in the orbitofrontal cortex between the pleasantness ratings to MSG when the factor influencing the pleasantness was the word label as the conditions were MSGrich and MSGbasic. Thus, in the orbitofrontal cortex the activations to taste and flavor were modulated by the word labels, and the cognitive modulation was of activations that were related to the pleasantness of these stimuli.

Cognitive modulation of activations produced by the taste stimulus was found in an area closely related to the medial orbitofrontal cortex, the pregenual cingulate cortex (Fig. 4*a*). There was a significant difference in the BOLD signals produced by the taste under the labels MSGrich and MSGbasic, in that the taste produced a higher response when labeled "rich and delicious taste" than when labeled "monosodium glutamate" (Fig. 4*b*,*c*), and this was also supported by the contrast analysis for MSGrich versus MSGbasic (Fig. 4*a*). Activations in the pregenual cingulate cortex were also positively correlated with the pleasantness ratings given to MSGrich and MSGbasic demonstrating that it is the affective value of the taste that is represented in this area ([4 44 –2] Fig. 4*d*). Moreover, the taste stimulus was identical for this correlation analysis, showing that the word labels were influencing the affective representation in this area.

In contradistinction to the insular primary taste cortex, there was less evidence for correlations to the rated intensity of the taste or flavor stimuli in the orbitofrontal cortex and pregenual cingulate cortex. Indeed, the main correlations with intensity that were found were negative correlations with intensity in the medial [–8 56 –18] and mid [–26 30 –14] orbitofrontal cortex. These correlations with intensity may reflect the fact

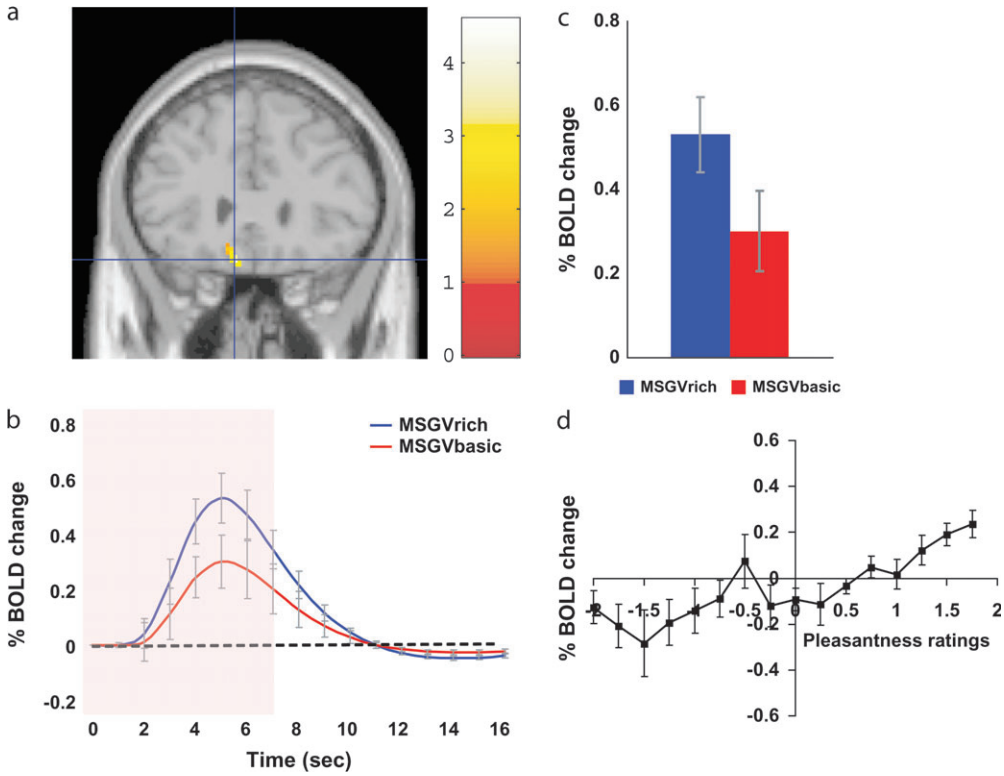

Figure 3. (*a*) The medial orbitofrontal cortex was more strongly activated when the flavor stimulus was labeled "rich and delicious flavor" (MSGVrich) than when it was labeled "boiled vegetable water" (MSGVbasic) ([−8 28 −20]). (*b*) The time course of the BOLD signals for the 2 conditions. (*c*) The peak values of the BOLD signal (mean across subjects ± SEM) were significantly different ($t = 3.06$, df = 11, $P = 0.01$). (*d*) The BOLD signal in the medial orbitofrontal cortex was correlated with the subjective pleasantness ratings of taste and flavor, as shown by the SPM analysis (Table 2), and as illustrated in (*d*) (mean across subjects ± SEM, $r = 0.86$, $P < 0.001$).

that the more intense stimuli (such as MSG2) tended to be rated as less pleasant, and indeed some of these parts of the orbitofrontal cortex were correlated positively with the pleasantness ratings (see for example the correlation based on MSG2 and MSGbasic pleasantness ratings in Table 2 [−6 42 −26]). There is thus an interesting difference in the representations in the insular primary taste cortex, where intensity is an important property of the representation, and the orbitofrontal cortex and pregenual cingulate, where pleasantness is more apparent in the representations.

Cognitive Modulation of Affective Taste and Flavor Representations in the Ventral Striatum

Cognitive modulation of taste and flavor was also found in the ventral striatum, and this was related to the effects of the cognitive modulations in making the taste and flavor stimuli more pleasant. For example, the ventral striatum was significantly more activated by the flavor stimulus when labeled "rich and delicious flavor" than when labeled "boiled vegetable water" and activations were positively correlated with the pleasantness ratings in these conditions (see Fig. 5*a*,*b* and Table 2) [−12 2 −2]. Corresponding effects were found for taste (see Fig. 5*c*,*d*, and Table 2 [−6 10 −16] and [2 12 −10]). No negative correlations with taste or flavor pleasantness were found in the ventral striatum. We note that the term ventral striatum includes the nucleus accumbens and olfactory tubercle, and the activations shown in Fig. 5 extend up into the nucleus accumbens, and are posterior to the orbitofrontal cortex (Mai et al. 2004).

Discussion

The main conclusion is that when the taste or flavor stimulus is identical, its pleasantness can be altered by the word-level cognitive labels as shown by the change in the subjective ratings (Fig. 1), and this cognitive modulation is expressed in brain areas such as the orbitofrontal cortex and pregenual cingulate cortex (Figs 3 and 4). An implication is that cognition modulates the affective representations of taste and flavor by a top-down modulating influence on the first cortical areas that represent the affective value of taste and flavor. Cognitive factors can thus have a fundamental influence on how the hedonic value of the taste and flavor of a food is represented early in cortical processing, and in this way may be important in the selection and consumption of foods.

An interesting finding was that these modulations by cognition of the affective experience of the taste and flavor stimuli (as shown by the subjective ratings) were not expressed in changes that were evident in the insular primary taste cortex. In contrast, we did find that the concentration of the MSG did modulate activations in the insular taste cortex (Fig. 2), and the subjective ratings of the intensity of the stimuli (which varied on a trial by trial basis) were correlated with the activations in the insula (see Table 2). Thus the perceived intensity and not the pleasantness of taste may be represented in the insular taste cortex, and this is consistent with studies manipulating the pleasantness of taste by for example feeding to satiety, in macaque neurophysiological (Yaxley et al. 1988; Rolls 2006) and human neuroimaging studies (Kringelbach et al. 2003; Small et al. 2003). (We note that the rat may be

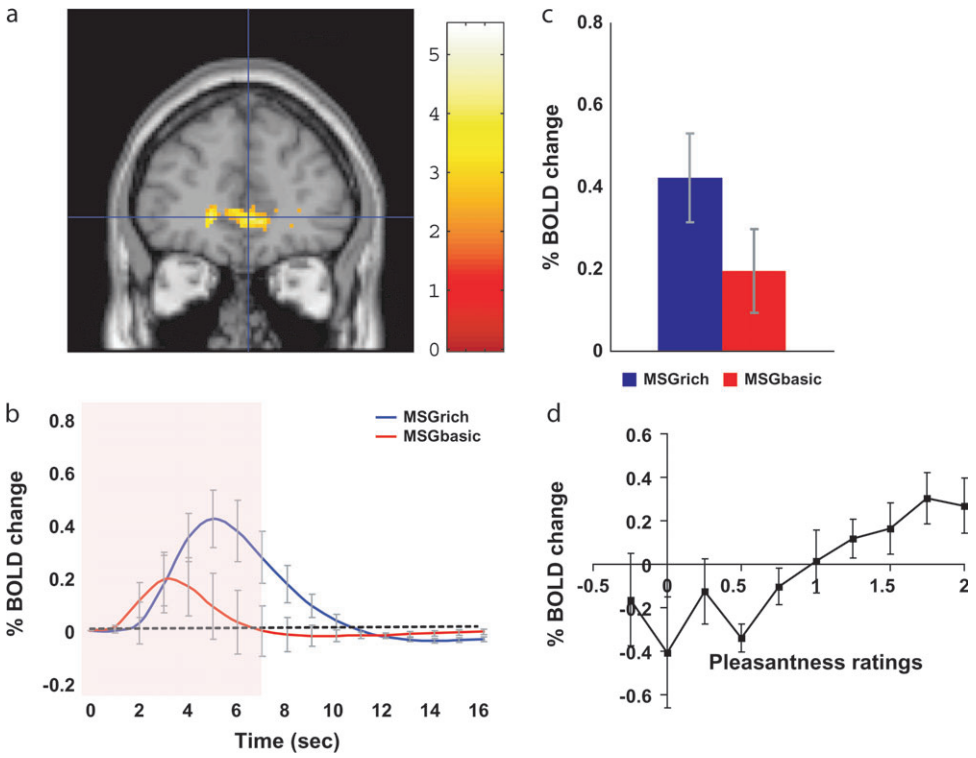

Figure 4. (*a*) The pregenual cingulate cortex was more strongly activated when the taste stimulus was labeled "rich and delicious taste" (MSGrich) than when it was labeled "monosodium glutamate" (MSGbasic) ([0 46 2] $z = 2.78$ $P = 0.05$). (*b*) The time course of the BOLD signals for the 2 conditions. (*c*) The peak values of the BOLD signal (mean across subjects ± SEM) were significantly different ($t = 3.02$, df = 11, $P = 0.01$). (*d*) The BOLD signal in the pregenual cingulate cortex was correlated with the subjective pleasantness ratings of taste, as shown by the SPM analysis (Table 2), and as illustrated in (*d*) (mean across subjects ± SEM, $r = 0.84$, $P = 0.002$).

a less good model of taste processing in humans, in that not only are there differences in the anatomy of the rat taste pathways, but also there is evidence that in the rat insular taste cortex and even as early as the nucleus of the solitary tract the responses may be influenced by the affective value of the stimuli when these are altered by for example altering satiety; Giza and Scott 1983; Norgren 1984; Katz et al. 2001; Rolls and Scott 2003; Rolls 2005.)

In contrast, the perceived pleasantness and not the intensity of taste and flavor are represented in the orbitofrontal cortex and pregenual cingulate cortex (Kringelbach et al. 2003; Small et al. 2003; Rolls 2006; McCabe and Rolls 2007). A completely new but consistent finding of the present study in this context is that when cognitive word labels modulate the pleasantness of taste, they do so not in the insular taste cortex, but in areas such as the orbitofrontal and pregenual cingulate cortex which contain secondary and tertiary cortical taste areas (Rolls 2006, 2007b). The orbitofrontal and pregenual cingulate cortices represent the affective value of many different sensory rewards, including taste, olfactory, flavor, visual, and somatosensory stimuli (Kringelbach 2005; Rolls 2005, 2007; Padoa-Schioppa and Assad 2006), and our results indicate that the affective representation of flavor and taste in these areas is not only influenced by bottom-up sensory inputs and information about the current motivational status, for example whether or not hunger is present (Kringelbach et al. 2003), but is also strongly dependent on cognitive factors from as high as the language level that we suggest operate by the same mechanisms of top-down biasing that operate in attention (Rolls and Deco 2002; de Araujo et al. 2005). The regions of the orbitofrontal cortex in which affective cognitive modulation effects of taste and flavor were found (as shown either by contrasts, or correlations with pleasantness ratings that were modulated by the affective cognitive labels) were close to those known to be activated by taste (e.g., the negative correlation with intensity based on MSGbasic and MSG2 in this study), or by flavor or smell (e.g., the region where consonance rating correlations with flavor are found at [–2 36 –28] in a previous study; McCabe and Rolls 2007). We note that the macaque orbitofrontal cortex area "12o" contains taste responsive neurons (Rolls et al. 1990, 2003b; Verhagen et al. 2003; Kadohisa et al. 2004, 2005), receives from the primary taste cortex (Baylis et al. 1995), and projects to pregenual cingulate cortex area 32 (Carmichael and Price 1996), thus providing a route for taste information to reach the pregenual cingulate cortex. We note that although taste and olfactory neurons are found throughout the mid and lateral orbitofrontal cortex of macaques, these areas appear to extend more medially in humans, extending to the midline (Rolls Forthcominga). These orbitofrontal cortex areas are at least in macaques distinct from the pregenual cingulate cortex that forms part of area 32, which is more dorsal, and in which taste neurons have now been described (Rolls Forthcominga; Rolls et al. Forthcomingb). Correspondingly, Fig. 3*a* shows that the activation related to cognitive modulation of flavor is in the medial orbitofrontal cortex, and not in the subgenual cingulate cortex or pregenual cingulate cortex. For completeness, we further note that macaque area 32 may correspond to a region a little more ventral to this in humans in the subgenual region (Ongur et al. 2003), and that activations with positively affective stimuli including the combination of MSG taste and vegetable

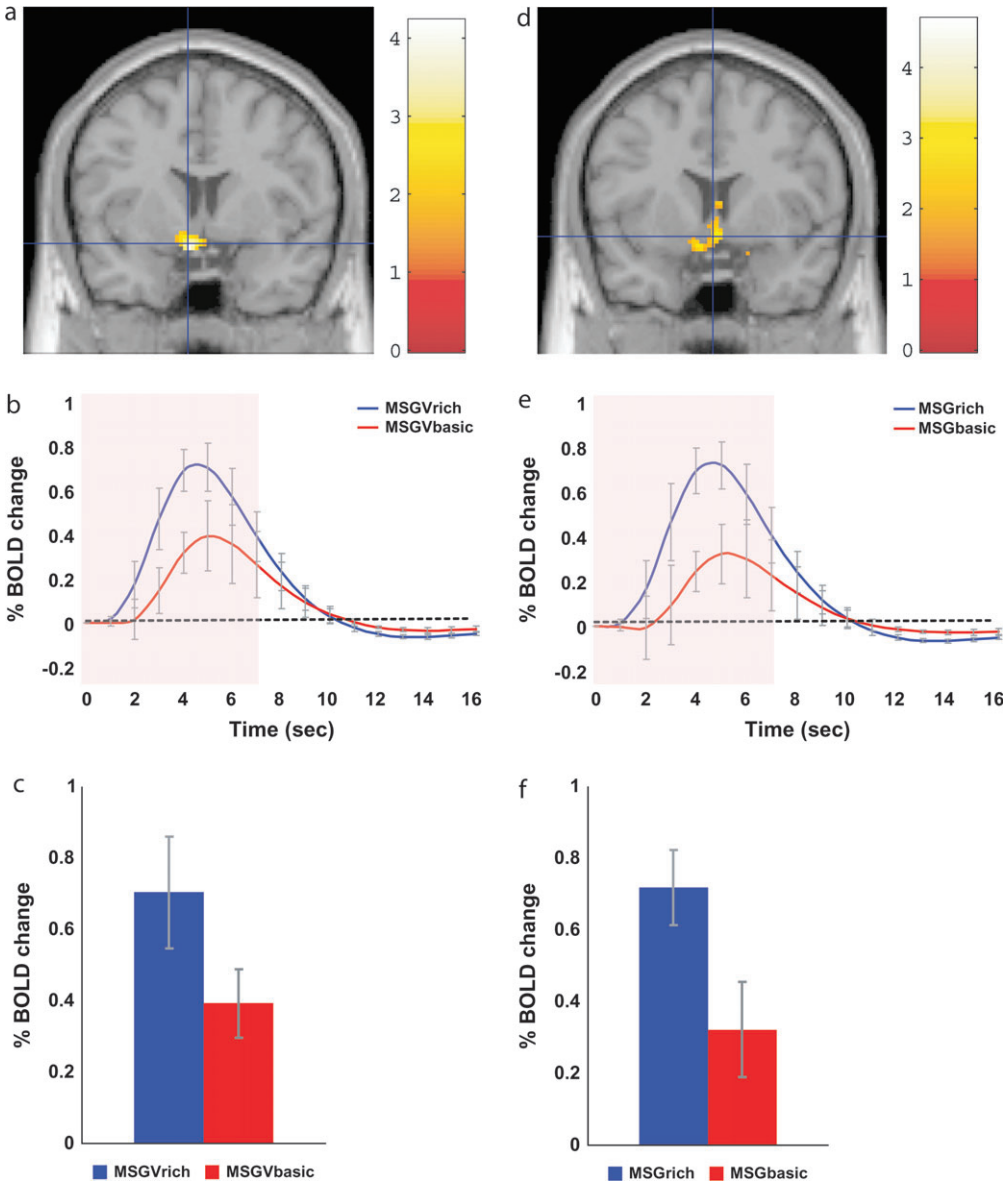

Figure 5. Ventral striatum. (*a*) The ventral striatum was significantly more activated by the flavor stimulus MSGV when labeled "rich and delicious flavor" than when labeled "boiled vegetable water" [−6 6 −14]. As shown in Table 2, the activations in this region were also correlated with the pleasantness ratings. (*b*) The time course of the BOLD signals for the 2 conditions. (*c*) The peak values of the BOLD signal (mean across subjects ± SEM) were significantly different ($t = 2.71$, df = 11, $P = 0.02$). (*d*) The ventral striatum was significantly more activated by the taste stimulus MSG when labeled "rich and delicious taste" than when labeled "monosodium glutamate" [2 12 −10]. As shown in Table 2, the activations in this region were also correlated with the pleasantness ratings. (*e*) The time course of the BOLD signals for the 2 conditions. (*f*) The peak values of the BOLD signal (mean across subjects ± SEM) were significantly different ($t = 3.14$, df = 11, $P = 0.001$).

odor used in the present study often activate a continuous regions extending from the medial orbitofrontal cortex through the subgenual cingulate region to the pregenual cingulate cortex (McCabe and Rolls 2007).

In a previous study it has been shown that visual symbols that had been associated with different concentrations of a bitter taste can modulate activity in the insula (Nitschke et al. 2006). However, the insular activations described in that study were not identified as being in the taste cortex by a taste localizer consisting of a taste stimulus with a tasteless rinse control subtracted. Moreover, the activations appeared to be posterior to the taste cortex, and were described as being in the middle or posterior insula, whereas the taste cortex, as shown here and elsewhere (de Araujo et al. 2003a), is in the human anterior insula. Other neuroimaging studies have shown effects of attentional modulation in primary sensory cortex in the visual and olfactory modalities (Gandhi et al. 1999; Zelano et al. 2005), and in a taste detection study, more activation of the insular cortex was reported when participants were instructed to try to detect a taste stimulus than when instructed to randomly respond or in other control conditions (Veldhuizen et al. 2007). We did not observe cognitive modulation in primary sensory cortex in the present study, and this may be related to our use of word labels which were designed to modulate the hedonic value of the stimuli, which is not represented in the primary cortical areas (as shown for example by the lack of correlation of insular taste cortex activations with pleasantness ratings in this study, and by the

correlation of activations in the pyriform cortex with intensity but not pleasantness ratings of odors; Rolls et al. 2003a). Instead, we found modulation effects in the orbitofrontal cortex which includes the secondary taste cortex and is also the first stage in cortical processing where the affective value of sensory stimuli, including taste, is represented.

An interesting finding was that cognitive modulation of both taste and flavor processing was found in the ventral striatum, and when subjective pleasantness was modulated by the cognitive word labels, the pleasantness ratings were correlated with activity in the ventral striatum. The ventral striatum receives inputs from regions such as the orbitofrontal and pregenual cingulate cortex (Ferry et al. 2000), and also from the (particularly agranular) insula (Fudge et al. 2005), and given the results described here, the cognitive modulation of affective representations in the ventral striatum is likely to originate in the orbitofrontal cortex and pregenual cingulate cortex rather than the insular taste cortex. The ventral striatum is thought to play a role in the effects of conditioned incentive stimuli on behavior (Cardinal et al. 2002; Everitt and Robbins 2005), and the present study adds to this by showing that unconditioned stimuli such as flavor, as well as taste (O'Doherty et al. 2002, 2006) activate the human nucleus accumbens, and also that cognitive, word level, modulation of taste and flavor representations are found in the ventral striatum. Given its functions in behavioral responses to incentive stimuli, the cognitive modulation of taste and flavor representations described here may be one way in which the effects of these cognitive modulations on behavior are produced (Cardinal et al. 2002; Everitt and Robbins 2005; Rolls 2005). Thus, in principle cognitive factors, and not just conditioned incentive learning, can influence reward representations in the ventral striatum, and this may be relevant to understanding the brain systems and processes involved in addiction (Everitt and Robbins 2005; Volkow and Wise 2005).

The effects of the word labels were found in many cases in areas where activity covaried with changes in the taste stimulus, showing that top-down cognitive effects were expressed in brain regions that were responding to the actual sensory stimuli. For example, in the pregenual cingulate cortex the activations reflected the sensory stimuli and not just the word labels, in that 0.4 M MSG (MSG2) produced more activation than 0.1 M MSG (MSGbasic), even though both were associated with the same label. Consistent evidence that the pregenual and orbitofrontal cortex areas represent taste and flavor is that they are activated by these stimuli when no cognitive label is present (de Araujo et al. 2003a; de Araujo and Rolls 2004; McCabe and Rolls 2007; Rolls Forthcomingb). Moreover, in a study of the effects of top-down cognitive word label inputs on olfactory processing, it was found that the effects of the word labels alone were small, with much larger effects when the sensory olfactory inputs were present (de Araujo et al. 2005), as has been found in attentional studies (Deco and Rolls 2005). Similar arguments apply to the orbitofrontal cortex, where the word labels altered the responses to the flavor stimulus, and where the pleasantness ratings were correlated with the BOLD signals to the taste and flavor stimuli as influenced by the 2 word labels, yet where the sensory stimuli were represented, as shown by the negative correlation with intensity based on the high and low concentrations of MSG.

This investigation provides evidence on the mechanisms by which the pleasantness of food, which in turn may influence the tendency to overeating and obesity (Rolls 2007b, 2007c), can be cognitively influenced. This is a very important area for study, because obesity and the diseases related to it have become an international epidemic (Schwartz and Porte 2005). The present study emphasizes the importance of cognitive factors in determining the pleasantness of a food. Even a simple label at the word level can have effects on the representation of the taste and flavor components of food far down into cortical processing. This emphasizes how fundamental the influences of cognition may be on the control of the pleasantness of food, and thus of what foods are eaten (which might be healthy and nutritious or not), and of how much of a food is eaten (which may be increased if cognition had come to label a food as especially pleasant). An implication of the present study is that it will always be very important to provide the appropriate cognitive context when there is an opportunity to influence the type of food that is selected for ingestion and the amount that is eaten. This could be in the context of optimizing diet, which in the context of the increasing incidence of obesity, is a matter of great public interest and concern (Krebs 2005), for the present investigation shows that cognitive factors directly modulate the brain mechanisms that determine the pleasantness of the taste and smell of food, and therefore its selection.

In conclusion, cognitive influences from the language level reach far down to the first cortical areas at which the pleasantness of taste and flavor are made explicit in the representations. This is a fundamental aspect of brain design, revealed by this investigation which combined for the first time word-level cognitive inputs, carefully specified taste and flavor stimuli, and separation of affective from intensity-related representations.

Funding

International Glutamate Technical Committee research grant; and Gottlieb-Daimler- and Karl Benz-Foundation grant to F.G.

Notes

The investigation was performed at the Centre for FMRIB at Oxford University, and we thank Peter Hobden for his help. *Conflict of Interest*: None declared.

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