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Umami: a delicious flavor formed by convergence of taste and olfactory pathways in the human brain

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Abstract

Umami taste is produced by glutamate acting on a fifth taste system. However, glutamate presented alone as a taste stimulus is not highly pleasant, and does not act synergistically with other tastes (sweet, salt, bitter and sour). We show here that when glutamate is given in combination with a consonant, savory, odour (vegetable), the resulting flavor can be much more pleasant. Moreover, we showed using functional brain imaging with fMRI that the glutamate taste and savory odour combination produced much greater activation of the medial orbitofrontal cortex and pregenual cingulate cortex than the sum of the activations by the taste and olfactory components presented separately. Supralinear effects were much less (and significantly less) evident for sodium chloride and vegetable odour. Further, activations in these brain regions were correlated with the pleasantness and fullness of the flavor, and with the consonance of the taste and olfactory components. Supralinear effects of glutamate taste and savory odour were not found in the insular primary taste cortex. We thus propose that glutamate acts by the nonlinear effects it can produce when combined with a consonant odour in multimodal cortical taste-olfactory convergence regions. We propose the concept that umami can be thought of as a rich and delicious flavor that is produced by a combination of glutamate taste and a consonant savory odour. Glutamate is thus a flavor enhancer because of the way that it can combine supralinearly with consonant odours in cortical areas where the taste and olfactory pathways converge far beyond the receptors.

Introduction

The taste referred to by the Japanese word umami has come to be recognized as a 'fifth taste' (Kawamura & Kare, 1987; Rolls, 2000; after sweet, salt, bitter and sour; umami captures what is sometimes described as the taste of protein). In fact, multidimensional scaling methods in humans (Yamaguchi & Kimizuka, 1979) have shown that the taste of glutamate (as its sodium salt monosodium glutamate, MSG) cannot be reduced to any of the other four basic tastes. Specific taste receptors for glutamate have been found (Chaudhari *et al*., 2000; Zhao *et al*., 2003; Maruyama *et al*., 2006). Umami taste is found in a diversity of foods rich in glutamate like fish, meat, milk, tomatoes and some vegetables, and is enhanced by some ribonucleotides (including inosine and guanosine nucleotides; Yamaguchi, 1967; Rifkin & Bartoshuk, 1980), which are present in for example meat and some fish (Yamaguchi & Ninomiya, 2000). The mixture of these components underlies the rich taste characteristic of many cuisines.

Glutamate does not act synergistically with other tastes (sweet, salt, bitter and sour; Yamaguchi & Kimizuka, 1979), and moreover when glutamate is presented alone as a taste stimulus, is not highly pleasant (Beauchamp & Pearson, 1991). The question then arises of how glutamate contributes to the delicious and pleasant quality of some foods (Roininen *et al*., 1996).

We show here that when glutamate is given in combination with a consonant, savory, odour (vegetable), the resulting flavor can be much more pleasant, and then investigate the brain mechanisms that underlie this. (Flavor is defined as a combination of taste and smell.) For the combination of smell and taste to be effective, the taste and olfactory signals must be brought together. From studies in nonhuman primates it is known that the primary taste cortex in the anterior insula contains neurons that respond to the taste and texture of what is in the mouth, but not its smell (Verhagen *et al*., 2004). Both the primary taste cortex and the pyriform (olfactory) cortex project forward into the orbitofrontal cortex, and it is here that bimodal taste and olfactory neurons are found (Rolls & Baylis, 1994). These flavor-responsive neurons are built by olfactory to taste association learning (Critchley & Rolls, 1996; Rolls *et al*., 1996). With human functional neuroimaging the primary taste area in the anterior insular taste cortex and the secondary taste cortex in the orbitofrontal cortex have been studied (Small *et al*., 1999; O'Doherty *et al*., 2001b; Faurion *et al*., 2005), and indeed have been found to respond to umami taste (de Araujo *et al*., 2003a). Olfactory areas have also been identified in the pyriform cortex and the orbitofrontal cortex (Zatorre *et al*., 1992; Zald & Pardo, 2000; Rolls *et al*., 2003; Verhagen & Engelen, 2006). Studies of where taste and smell are brought together in the human brain have started (Small & Prescott, 2005), and indeed it has been shown that there are areas in the orbitofrontal cortex and adjoining agranular (far anterior) insula that can be activated by both sucrose and strawberry (de Araujo *et al*., 2003c).

Materials and methods

Design

To examine how umami may act to enhance the pleasantness of foods, we performed this investigation in which umami taste was delivered

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alone or in combination with a consonant savory odour, vegetable. Part of the design was to allow a test of whether the activations of some brain regions to the combination was greater than to the sum of the gustatory and olfactory components. To indicate whether effects found with umami taste and vegetable odour were in some way specific to umami taste, a set of comparison stimuli was also used, namely NaCl alone or in combination with the vegetable odour. To provide an anchor and comparison stimulus for whether the taste and olfactory components were consonant, the umami taste was also presented in combination with a dissonant odour, rum. A further part of the design was to take psychophysical ratings of pleasantness, consonance, and fullness of flavor made on every trial by the subjects during the fMRI experiments, so that the subjective effects of the stimuli in terms of their pleasantness could be correlated with the BOLD signals measured on every trial.

Subjects

Twelve healthy volunteers (of whom six were males) participated in the study. Ethical approval (Central Oxford Research Ethics Committee) and written informed consent from all subjects were obtained before the experiment.

Stimuli

The set of stimuli was designed to allow umami taste (produced by 0.1 M monosodium glutamate and 0.005 M inosine 5′-monophosphate) to be tested alone or in combination with a complementary, savory, odour, for which vegetable odour (supplied by Firmenich SA) was used. This was to allow effects of the combination (MSGV in Table 1) to be compared to the effects of the gustatory (MSG in Table 1) or odour (tlV) components delivered separately. Part of the design was also to allow a test of whether the activation to the combination was greater than to the sum of the gustatory and olfactory components, as this supralinearity of activations can be an indication of combinatorial effects and convergence (de Araujo *et al*., 2003c). The vegetable odour component alone was delivered in tasteless solution (tlV in Table 1). To indicate whether effects found with umami taste and vegetable odour were in some way specific to umami taste, a set of somewhat similar stimuli was also used, namely NaCl alone or in combination with the vegetable odour. To provide an anchor and comparison stimulus for whether the taste and olfactory components were consonant, the umami taste was also presented in combination with a dissonant odour, rum (MSGR in Table 1). Finally, to allow the effects that were due to gustatory stimulation to be measured, a control tasteless solution (containing the main ionic components of saliva, 25 mM KCl + 2.5 mM $NaHCO_3$) was also used (tl in Table 1), which when subtracted from the effects of the other stimuli allowed somatosensory and any mouth movement effects to be subtracted from the effects produced by the other stimuli (O'Doherty *et al*., 2001b; 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*., 2001b; de Araujo *et al*., 2003a; de Araujo *et al*., 2003b).

TABLE 1 Stimuli and abbreviations

MSG	0.1 M MSG + 0.005 M inosine 5′monophosphate
MSGV	0.1 M MSG + 0.005 M inosine 5′monophosphate + 0.4% vegetable odour
NaCl	0.1 M NaCl
NaClV	0.1 M NaCl + 0.4% vegetable odour
MSGR	0.1 M MSG + 0.005 M inosine 5′monophosphate + 2% rum
odour tl	25 mM KCl + 2.5 mM $NaHCO_3$ (tasteless control)
tlV	25 mM KCl + 2.5 mM $NaHCO_3$ + 0.4% vegetable odour

Experimental protocol

The effects in the experiment were measured by psychophysical ratings of pleasantness, consonance, and fullness of flavor made on every trial by the subjects during the fMRI experiments; by fMRI contrasts showing the effects of the combination vs. the sum of the taste and olfactory components; and by fMRI correlation analyses between each of the three psychophysical ratings made throughout the experiment and the brain activations produced by the stimulus being delivered.

The experimental protocol consisted of an event-related interleaved design using in random permuted sequence the six stimuli described above and shown in Table 1. This number of stimuli was chosen to be feasible given the number of repetitions of each stimulus needed and the length of time that subjects were in the magnet, but at the same time to allow the analyses described under 'stimuli' to be made. Stimuli were delivered to the subject's mouth through seven Teflon tubes (one for the tasteless rinse control described below) that were held between the lips, and the odours were thus delivered by the retronasal route in aqueous solution. Each Teflon tube of approximately three meters 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 manually at the time indicated by the computer.

At the beginning of each taste delivery, one of the six stimuli 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 a visual display (following initial instruction and training). After a delay of 2 s, the subject was asked to rate each of the oral stimuli for pleasantness (with +2 being very pleasant and −2 very unpleasant), for fullness and richness of flavor (0 to +4), and for consonance of the taste and olfactory components (+2 for consonant, 0 if there is no special consonance or dissonance of any taste and olfactory components, and −2 for dissonant). The ratings were made with a visual analogue rating scale in which the subject moved the bar to the appropriate point on the scale using a button box. Each rating period was 5 s long. After the last 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 2 s delay period allowed for swallowing followed by a one-second gap until the start of the next trial. A taste trial was repeated for each of the six stimuli, and the whole cycle was repeated nine times (with the subjective ratings analyses using trials 2–9 as a precaution to ensure that each subject was used to giving ratings with the button box used in the fMRI environment). 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 activations produced by the

tasteless control from those produced by a taste or other stimulus (O'Doherty *et al*., 2001b; de Araujo *et al*., 2003a; de Araujo *et al*., 2003b; de Araujo & Rolls, 2004). All contrasts reported below had the tasteless control condition subtracted.

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 28 T2* weighted EPI coronal slices with in-plane resolution of 3 × 3 mm and between plane spacing of 4 mm were acquired every 2 s (TR = 2). We used the techniques that we have developed over a number of years (e.g. O'Doherty *et al*., 2001b; de Araujo *et al*., 2003a) and as described in detail by Wilson *et al*. (2002) to carefully select the imaging parameters in order to minimize susceptibility and distortion artefact 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 25 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 −50 (A/P). Acquisition was carried out during the task performance yielding 939 volumes in total. A whole brain T2* weighted EPI volume of the above dimensions, and an anatomical T1 volume with coronal plane slice thickness 3 mm and in-plane resolution of 1.0 × 1.0 mm was also acquired.

fMRI data analysis

The imaging data were analysed using SPM2 (Wellcome Institute of Cognitive Neurology). Preprocessing of the data used SPM2 realignment, reslicing with sinc interpolation, normalization to the MNI coordinate system (Montreal Neurological Institute; Collins *et al*., 1994), and spatial smoothing with an 8 mm full width at half maximum isotropic Gaussian kernel. The time series at each voxel were low-pass filtered with a haemodynamic 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 modelled as single impulse response functions and then convolved with the canonical haemodynamic response function (HRF, Friston *et al*., 1994; duration 0). 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 dataset were then entered into second-level, random effects analyses accounting for both scan-to-scan and subject-to-subject variability. More precisely, the sets of individual statistical maps corresponding to a specific effect of interest were entered as covariates in multiple regression models (ANOVA without a constant) as implemented in SPM2, 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 (blood oxygenation-level dependent) 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 SPM2. Reported *P*-values for each cluster based on this group analysis are fully corrected (fc) for the number of comparisons (resels) in the entire volume ('whole-brain' multiple comparisons, Worsley *et al*., 1996). We supplement these by describing a small number of further activations corresponding to clusters of voxels significant when corrected for the number of comparisons made within each region [small volume correction (svc) applied with a sphere of 8 mm chosen to be greater than or equal to the spatial smoothing kernel, Worsley *et al*., 1996], in order to provide an indication of effects appearing in further brain areas such as the orbitofrontal and anterior cingulate cortex, anterior insular (primary taste) cortex, and ventral striatum shown to be of interest because of activations found in prior studies in reward paradigms or because neurophysiological, lesion, or connection evidence links them to taste or olfactory processing (Small *et al*., 1999; O'Doherty *et al*., 2001b; de Araujo *et al*., 2003a; de Araujo *et al*., 2003b; de Araujo & Rolls, 2004; Kringelbach & Rolls, 2004; Rolls, 2005a, 2006; Verhagen & Engelen, 2006; Zald & Rauch, 2006). The per cent change in the BOLD signal for different stimuli within regions of interest identified from the contrast analyses were extracted using the SPM Marsbar toolbox documented at http://marsbar.sourceforge.net/. The supralinearity contrasts consisted for example of a comparison of the response to MSGV compared to the sum of the responses to MSG and the vegetable odour (tlV) presented separately.

Results

Ratings

The ratings of pleasantness, consonance, and fullness of flavor are shown in Fig. 1. The pleasantness ratings were significantly different between the stimuli (one-way within subjects ANOVA, $F_{6,66} = 2.49$, $P = 0.031$), as were the consonance ($F_{6,66} = 5.71$, $P < 0.00003$) and fullness of flavor ratings ($F_{6,66} = 21.24$, $P << 0.001$). The combination of MSG and vegetable odour was rated as more pleasant than MSG alone (paired *t*-test $P < 0.015$ in a planned comparison. We confirmed that the rating data were suitable for parametric analysis by showing that the ratings were close to normally distributed, and made the further check by applying a nonparametric Wilcoxon test to the comparison just described, which was significant at 0.036). The combination of MSG and vegetable odour was rated as more pleasant than the combination of NaCl and vegetable odour as shown in Fig. 1, and it was shown in a two-way ANOVA that the increase of pleasantness was greater when vegetable was added to MSG than when vegetable was added to NaCl (which actually produced a decrease in pleasantness, as shown in Fig. 1) (interaction in a within subjects two-factor ANOVA, $F_{1,11} = 22.05$, $P < 0.001$). Similar interaction effects of adding vegetable to MSG when compared to the effect of adding vegetable to NaCl were found for consonance ($F_{1,11} = 12.03$ $P < 0.005$), and for fullness of flavor ($F_{1,11} = 5.92$, $P < 0.03$). Further, *posthoc* tests showed that the MSG plus vegetable (MSGV) was more consonant ($P < 0.01$) and more full in flavor ($P < 0.001$) than the MSG alone. Further, for this particular set of taste and olfactory stimuli, the pleasantness and consonance ratings were correlated significantly ($r = 0.53$, $P < 0.001$).

For the functional imaging results, we first consider the main effects of the taste and related stimuli, and after that show contrasts to reveal where the combination of MSG with odour is especially effective. The activations shown are minus the rinse control, and are fully corrected

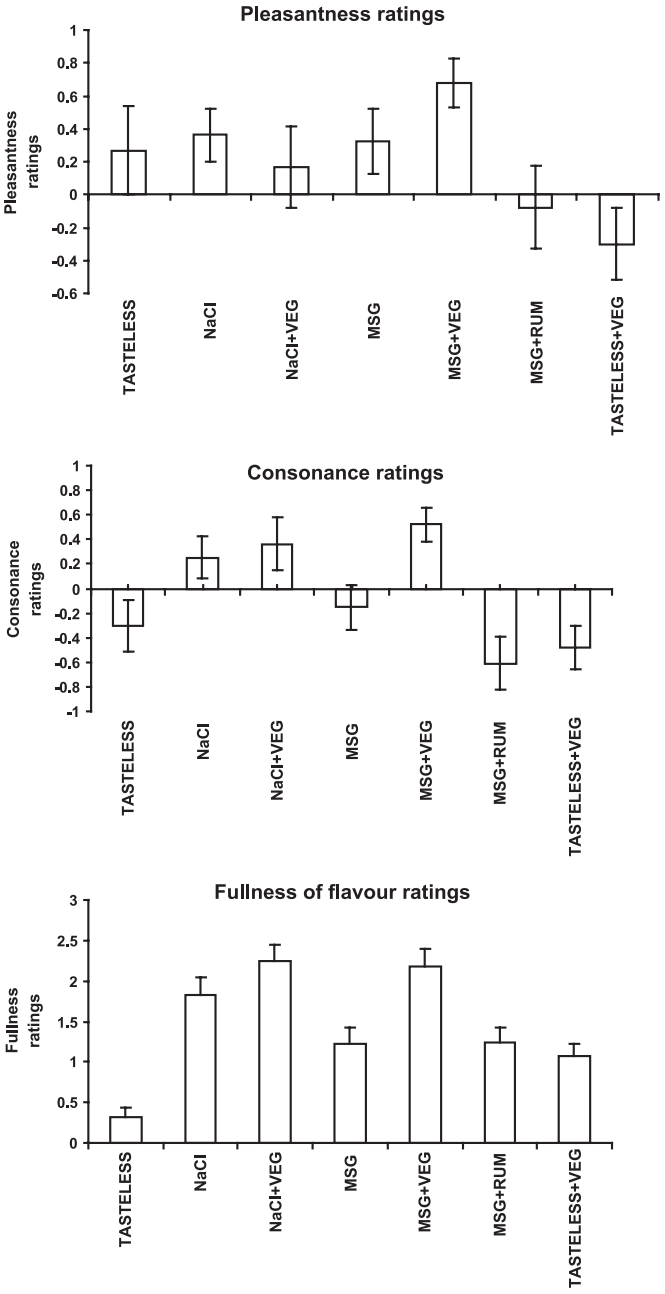

FIG. 1. The ratings of pleasantness, consonance, and fullness of flavor (means ± SEM).

(fc) or small volume corrected (svc) with the significance level indicated.

MSG and NaCl taste

As expected, the MSG condition resulted in activation in the primary taste cortex, for example at ([34 24 −6] Z = 3.94, fc $P < 0.001$). This is illustrated in Fig. 2, which shows a coronal plane image taken through the taste insula. The same image shows that some activation is also present in area 6 ([46 22 28] Z = 3.73, fc $P < 0.001$) and in the dorsal part of the anterior cingulate cortex ([8 6 56] Z = 3.94, fc $P < 0.001$). Activations were also found in the mid-orbitofrontal cortex at ([24 36 −16] Z = 3.01, svc $P < 0.01$). NaCl also activated

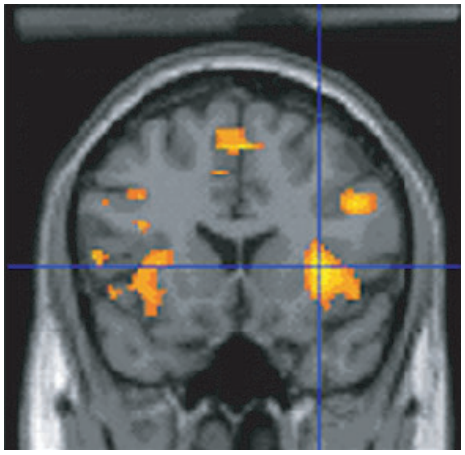

FIG. 2. MSG-r, the taste of MSG minus the tasteless condition, showing activation of the primary taste cortex at the anterior end of the insula [34 24 −6] (fc $P < 0.001$).

the primary taste cortex as expected ([−40 16 −2) Z = 3.17, svc $P < 0.005$), the orbitofrontal cortex ([12 42 −28] Z = 3.21, svc $P < 0.006$), and area 6 ([−38 20 20] Z = 5.07, fc $P << 0.001$).

MSG and vegetable odour (MSGV)

The MSG plus vegetable (MSGV) condition again produced activation of the insular taste cortex ([−38 14 2] Z = 3.46, fc $P < 0.02$), and in addition produced activation of the ventral striatum ([14 10 −8] Z = 3.29, svc $P = 0.004$) illustrated in Fig. 3, the orbitofrontal cortex ([14 44 −26] Z = 3.56, svc $P = 0.005$), and area 6 ([−40 22 24] Z = 4.25, fc $P < 0.001$). Figure 3 shows the ventral striatal activation, but also some of the insular taste cortex activation is visible, as is activation more dorsally in the dorsal part of the anterior cingulate cortex ([10 6 54] Z = 4.29, fc $P < 0.001$). The NaCl plus vegetable (NaClV) condition also activated the primary taste cortex ([−40 12 0] Z = 3.99, fc $P < 0.001$), and also the pregenual cingulate cortex ([12 24 −8] Z = 3.48, svc $P = 0.005$), the dorsal part of the anterior cingulate cortex ([−2 8 54] Z = 4.56, fc $P = 0.04$), and the lateral prefrontal cortex ([−42 42 8] Z = 4.56, fc $P = 0.04$) where taste has been shown to produce activation in a previous study (Kringelbach *et al.*, 2004).

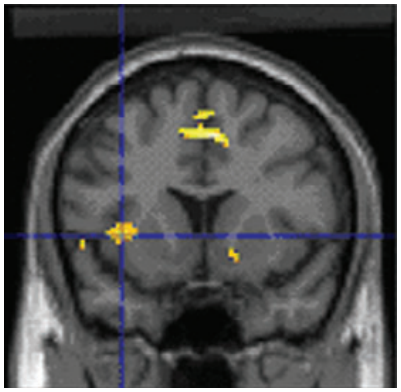

FIG. 3. Activation in the ventral striatum ([14 10 −8] svc $P < 0.004$) produced by the combination of MSG and vegetable odour. The same slice shows some of the activation in the (anterior part of the) insular taste cortex ([−38 14 2] fc $P < 0.02$); and also activation in the dorsal part of the anterior cingulate cortex ([10 6 54] fc $P < 0.001$).

Supralinearity for a combination of MSG and vegetable odour

A main focus of this investigation was on whether the combination of MSG taste with a consonant odour, vegetable, might produce selective activations of some brain regions. To test this, we show in Fig. 4A a contrast of the effects of the mixture of MSG and vegetable (MSGV), with the sum of the activations to MSG and vegetable presented separately. This contrast thus is of supralinear additivity. This reveals a highly significant effect in the medial orbitofrontal cortex centred at

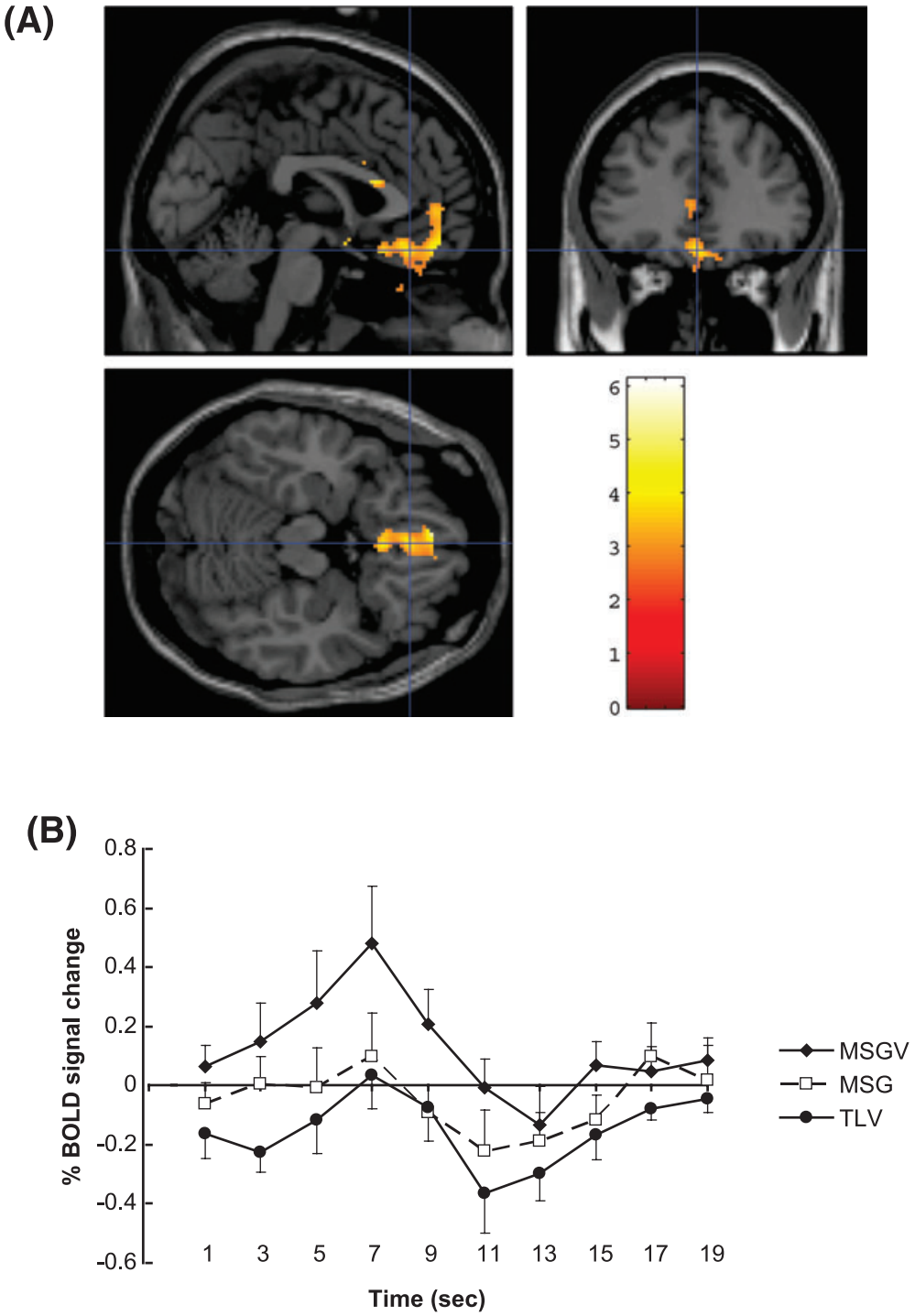

FIG. 4. (A) Supralinear additivity between MSG and vegetable odour. A contrast of the mixture of MSG and vegetable (MSGV) with the sum of the activations to MSG and vegetable presented separately. This reveals a highly significant effect in the medial orbitofrontal cortex centred at [−6 52–14] fc $P = 0.002$, with the activation extending up into the pregenual cingulate cortex. (B) Timecourse of the activations in the pregenual cingulate cortex at [−6 52 −14] produced by the combination of MSG and vegetable odour (MSGV), by MSG alone, and by the vegetable odour alone (tlV). The timecourses were computed across subjects using Marsbar for the region that showed significant effects in the supralinearity contrast at $P = 0.002$ shown in Fig. 4A. The mean across subjects per cent BOLD for this analysis was MSGV = 0.485%, MSG = 0.097%, and tlV = 0.035%. The taste stimuli were delivered at time 0, and the means and SEM percentages are shown for 2-s bins.

([−6 52 −14] Z = 3.96, fc $P = 0.002$), which extends up into the pregenual cingulate cortex. The timecourse of these activations is shown in Fig. 4B. In addition, a part of the ventral striatum/olfactory tubercle showed significant supralinear activation ([0 2 −14] Z = 3.25, svc $P = 0.05$; Fig. 5). It was notable that there was no evidence of this supralinearity in the taste insula, nor in the agranular insula.

Supralinearity for a combination of NaCl and vegetable odour

To investigate whether the supralinearity of MSG and vegetable was special to this combination, we ran a similar analysis for the supralinearity of NaCl with vegetable. The contrast was of the mixture of NaCl and vegetable (NaClV), with the sum of the activations to NaCl and vegetable presented separately. This contrast revealed no supralinear activation in any part of the brain, apart from a barely significant supralinearity in the NaClV condition in the medial orbitofrontal cortex ([−2 26 −18] Z = 2.79, svc $P = 0.05$), but this is shown below to be less than that produced by MSGV. The implication of this result is that an important part of the way in which MSG works is that it can produce supralinear activation with vegetable odour, and that this is not an important property of another taste stimulus (used as a control), NaCl when combined with vegetable odour. (In addition as shown by the ratings in Fig. 1, NaClV is not more pleasant than NaCl alone.)

Supralinearity for MSG and vegetable odour vs. supralinearity of NaCl and vegetable odour

To estimate further whether the supralinearity found in areas such as the medial OFC and pregenual cingulate cortex was special to the combination of MSG and vegetable odour, we performed a contrast of the supralinearity of MSGV minus the supralinearity of NaClV. [This was calculated by defining two independent contrasts at the first (single subject) level, for the supralinearity of MSGV = [MSGV − (MSG + V)], and the supralinearity of NaClV = [NaClV − (NaCl + V)]. Then at the second level, the group analysis, we defined a within-subjects ANOVA with these two supralinearity regressors. Sphericity correction was applied, and a *t*-test was performed between the two conditions.] The results of this contrast showing significant effects in the medial orbitofrontal cortex ([10 42 −22] Z = 3.37 fc $P = 0.02$) are shown in Fig. 6. To check whether this supralinearity effect was in the same brain region as that for the supralinearity for MSGV, we performed a mask analysis and showed that there was overlap of the activations produced by the supralinearity analysis for MSGV and the supralinearity analysis for MSGV–NaClV in the medial orbitofrontal cortex, with the peak activation in the area of overlap at [−4, 52, −12] (Z = 4.19 svc $P < 0.001$). (The SPM mask analysis was performed at the second (group) level by using a multiple regression model to build two covariates based on the first level analyses for each subject, for the supralinearity of MSGV and for the supralinearity of MSGV-NaClV, and then masking one with the other as provided for in SPM2). There were also significant effects in the inferior agranular insula at ([−48 6 −18] Z = 3.52 fc $P < 0.001$). This contrast also showed a significant result in the ventral striatum ([2 16 −18] Z = 2.95 svc $P = 0.03$).

The interpretation of the greater supralinearity for MSGV in the medial orbitofrontal cortex might be that in this region the activations reflect some attribute of the stimulus, such as its pleasantness, which might be much higher for the combination than for the components separately. To investigate this, we performed the correlation analyses that are described below, to investigate what attributes of the stimuli correlated with the activations in the medial orbitofrontal cortex.

Correlation with pleasantness ratings

The pleasantness ratings were correlated with activations in the pregenual cingulate cortex ([−4 54 10] Z = 2.69, svc $P = 0.05$; see Fig. 7), and in addition Fig. 7 shows correlations also in the medial orbitofrontal cortex (peak at [6 40–16] Z = 2.77). Consistent with the correlation found in this dataset between the ratings of pleasantness and consonance (see Results, ratings), similar correlations with the consonance ratings were also found in the pregenual cingulate cortex

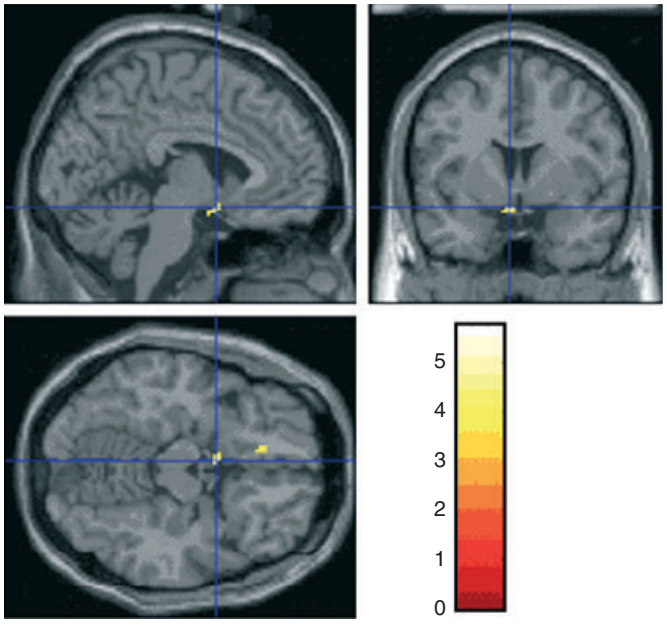

FIG. 5. Supralinear additivity between MSG and vegetable odour. A contrast of the mixture of MSG and vegetable (MSGV) with the sum of the activations to MSG and vegetable presented separately shows activation in a part of the ventral striatum/olfactory tubercle at [0 2 −14] 0.05 (svc).

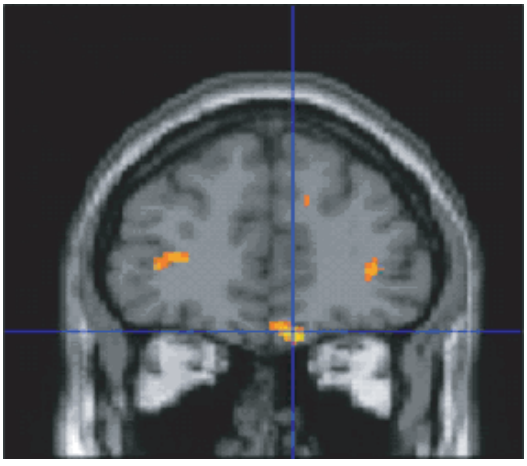

FIG. 6. A contrast of the supralinearity of MSGV − the supralinearity of NaClV. (The exact contrast was [MSGV − (MSG + V)] − [NaClV − (NaCl + V)].) Activation was found in the medial orbitofrontal cortex [10 42 −22] fc 0.02.

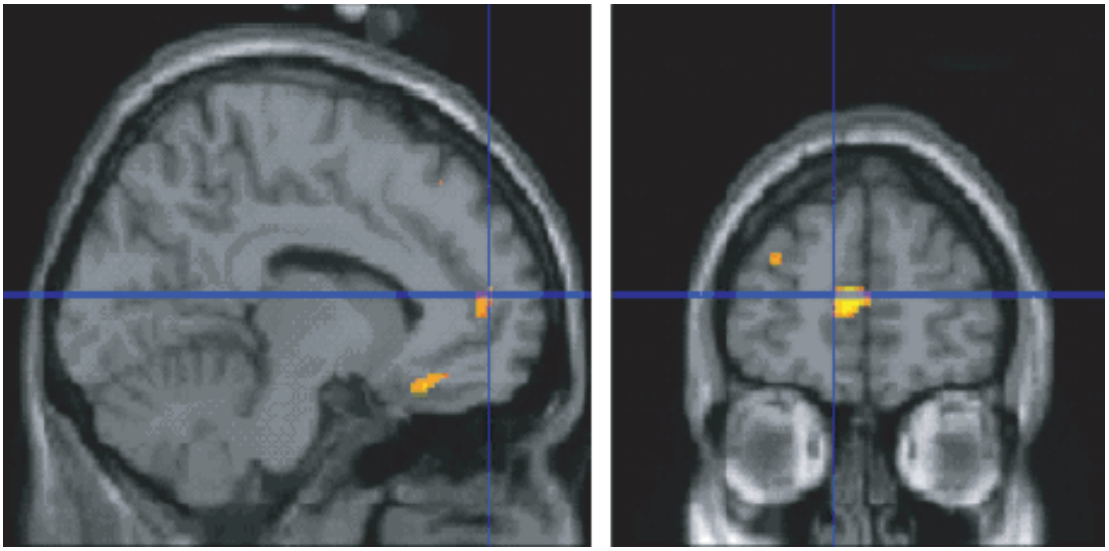

FIG. 7. A positive correlation with the pleasantness ratings was found in the pregenual cingulate at [−4 54 10] svc 0.05 and in the medial orbitofrontal cortex at [6 40 −16].

([−4 50 10] Z = 2.23, svc $P = 0.04$) and medial orbitofrontal cortex ([−2 36 −28] Z = 2.47, svc $P = 0.03$).

Correlation with fullness of flavor ratings

Correlations with the fullness of the flavor were found in the ventral striatum/olfactory tubercle ([−14 6 −20] Z = 3.54, svc $P = 0.006$), as shown in Fig. 8. Correlations were also found in the medial orbitofrontal cortex ([−20 32 −16] Z = 3.23, svc $P = 0.02$). Correlations with fullness of flavor were also found in the parietal somatosensory operculum ([−46–8 14] Z = 3, svc $P = 0.02$).

Negative correlations with ratings

Activations in a part of the caudo-lateral orbitofrontal cortex that were negatively correlated with consonance were found at ([28 46 2] Z = 3.34, svc $P < 0.01$). Activations in a nearby part of the lateral orbitofrontal cortex that were negatively correlated with fullness were also found at ([30 42 2] Z = 3.58, svc $P = 0.005$). Thus the lateral orbitofrontal cortex was activated more by the less consonant stimuli, which tended to be less pleasant as shown in Fig. 1. Some negative correlation with consonance was found in the ventral striatum at ([12 0 −12] Z = 3.48, svc $P = 0.01$), as shown in Fig. 9. Thus the ventral striatum is not exclusively activated by consonant/pleasant stimuli.

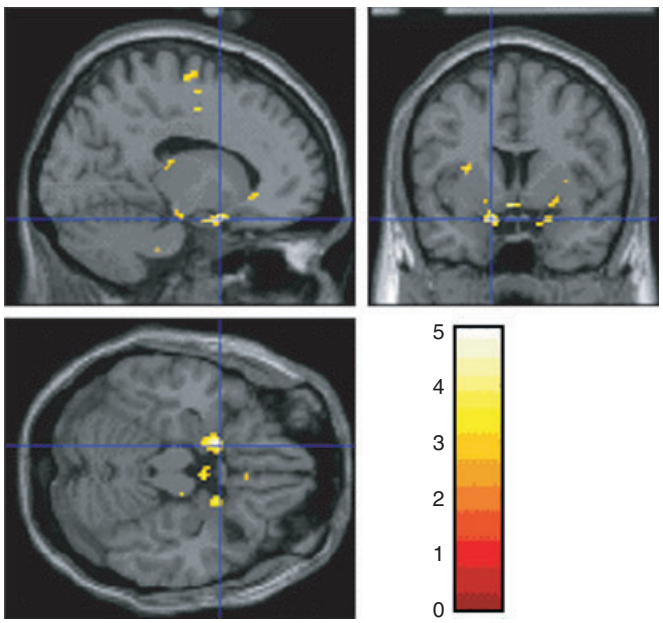

FIG. 8. Correlation with the subjective ratings of the fullness of the flavor in the ventral striatum/olfactory tubercle ([−14 6 −20] svc $P = 0.006$).

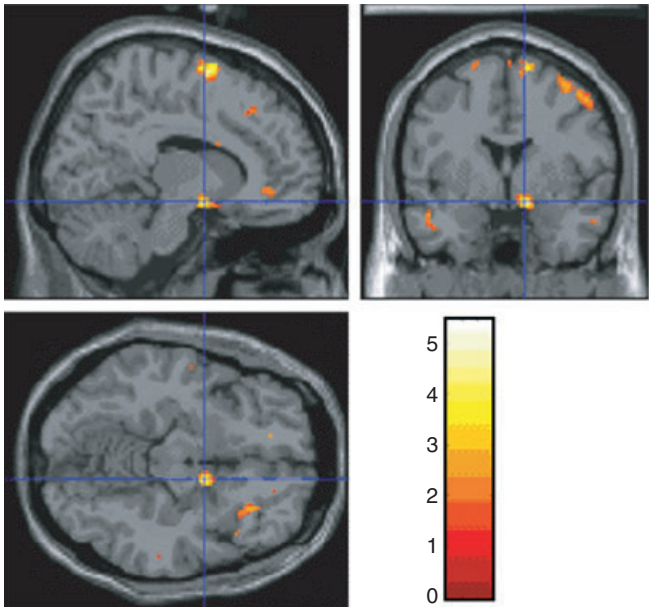

FIG. 9. A negative correlation with the consonance ratings was found in the ventral striatum [12 0 −12] svc 0.01.

Vegetable odour alone

The vegetable odour alone (tIV in Table 1, analysed as for the other stimuli with the tasteless control subtracted) activated a region centred at ([36 28 −10] Z = 3.89, svc $P < 0.003$) extending from the lateral orbitofrontal cortex through to the agranular insula. This activation is centred at the same region activated by unpleasant odours delivered by olfactometer (Rolls *et al*., 2003). The activation continued posteriorly to [36 15 −9], so included some of what is probably the insular primary taste cortex, which is centred close to $y = 18$ (de Araujo *et al*., 2003a). Although single neurons in the primary taste cortex do not respond to olfactory stimuli in macaques (Verhagen *et al*., 2004), activations at the anterior-posterior level of the insular taste cortex in humans are produced by olfactory stimuli in some studies (Gottfried *et al*., 2002; Verhagen & Engelen, 2006) though in other studies the olfactory activations do not extend back into what has been defined by using taste stimuli as putative primary taste cortex (de Araujo *et al*., 2003a; de Araujo *et al*., 2003c; Rolls *et al*., 2003), and a relevant factor in this may be whether a task in being performed (Gottfried *et al*., 2006).

Ventral premotor area

It was notable that a part of the ventral premotor cortex area 6 was activated by the simple contrasts involving taste (e.g. MSG-r, NaCl-r, and MSGV-r) (from [−52 −10 42] posteriorly extending anteriorly to [−40 22 24]). This region was not activated in the supralinearity comparisons. This ventral premotor region does receive inputs from the opercular/insular region (Cipolloni & Pandya, 1999).

Discussion

A fascinating finding of this study was that although the taste of MSG alone was not very pleasant, and the vegetable odour alone was unpleasant, the combination of the MSG with a vegetable odour was pleasant (see Fig. 1), and the pleasantness ratings were reflected in the activations found in the medial orbitofrontal and pregenual cingulate cortex (Fig. 7). To investigate where this interaction between taste and smell took place for this particular combination of umami taste and smell, we performed supralinearity analyses between the MSG and vegetable odour combination (tested vs. the sum of the components), and found supralinear additivity in the medial orbitofrontal cortex that extended up towards the pregenual cingulate cortex (Fig. 4A). Moreover, this supradditivity occurred for the MSG and vegetable combination, but was very much less (and significantly less) for a NaCl and vegetable combination in the medial orbitofrontal cortex (Fig. 6). Thus the medial orbitofrontal and pregenual cingulate cortices are important sites of interaction between MSG and a vegetable odour, which in combination produced a pleasant flavor. The NaCl and vegetable combination was not more pleasant than the NaCl alone (see Fig. 1). (In a two-way ANOVA the increase of pleasantness was greater when vegetable was added to MSG than when vegetable was added to NaCl.)

Supraadditive activation for taste-olfactory combinations has been found before (e.g. for sweet taste and strawberry odour in for example the medial orbitofrontal cortex (de Araujo *et al*., 2003c), and for sweet taste and vanilla in for example the anterior cingulate and orbitofrontal cortex (Small *et al*., 2004)). However, the interest of the present study is that the supraadditive activations were for a very different type of flavour, savoury flavour produced by a combination of MSG and vegetable odour, and that this combination produced a very pleasant flavour from components that separately were mildly pleasant or unpleasant. These findings lead us to propose that MSG acts as a flavor enhancer, because it can when presented in combination with at least some savory odours, produce supralinearity of olfactory and MSG activations. Moreover, both the pleasantness and supralinear additivity effects with this savoury odour were special for MSG when compared to NaCl. The results thus indicate that MSG when combined with appropriate odours can act particularly well, even relative to NaCl, as a flavour enhancer, and that these effects are realized far on in taste and olfactory processing in the brain, in the orbitofrontal cortex and a region to which it projects (Carmichael & Price, 1996), the pregenual cingulate cortex.

We now consider the possibility that the medial orbitofrontal cortex supralinearity might be understood in terms of greater perceived pleasantness and/or consonance of the combination of MSG and vegetable compared to each of the separate components. However, we note that the supraadditive effect in terms of the BOLD signals in the medial orbitofrontal cortex is an effect found by the statistical analysis for the combination of MSG and vegetable odour. This may be reflected in the pleasantness of the combination (which is correlated with activations in the medial orbitofrontal cortex), and in a sense the supralinearity reflects the fact that the combination is more pleasant than the components. The two ways of thinking about this are not very different, for both acknowledge that the pleasantness and/or consonance may not be related in a linear way to the activations produced by each of the components when presented separately. In any case, the new findings in this paper show that in the medial orbitofrontal cortex the combination of MSG and vegetable odour is related to the pleasantness of the combination compared to the separate components, and that the combination produces supralinear effects in the medial orbitofrontal cortex.

We thus propose, based on the neuroimaging results described here, that the enhancement of MSG when paired with at least some odours is realized by combining taste and olfactory inputs in the brain, in particular in the medial orbitofrontal cortex and pregenual cingulate cortex. Consistent with this, it is known at the single neuron level in macaques that it is in the orbitofrontal cortex where taste and olfactory inputs combine to activate the same single neurons (Rolls & Baylis, 1994), and this effect occurs in part by olfactory to taste association learning (Critchley & Rolls, 1996; Rolls *et al*., 1996). The orbitofrontal cortex has onward connections to the anterior cingulate cortex (Vogt & Pandya, 1987; Van Hoesen *et al*., 1993; Carmichael & Price, 1995; Carmichael & Price, 1996; Rolls, 2007), and the effects found in the pregenual cingulate cortex in this study may reflect this connectivity.

Consistent with the point that bimodal olfactory and taste neurons are not found in the macaque insular, primary, taste cortex (Verhagen *et al*., 2004), supralinear interactions of MSG and vegetable odour were not found in the insular taste cortex, although this cortical area was certainly activated by the MSG, the NaCl, and by these when they were presented in combination with vegetable (as illustrated in Figs 2 and 3). Thus the primary taste cortex does not appear to be the brain region in humans and macaques where MSG produces flavor enhancement by combining with a consonant odour. Primary olfactory areas such as the pyriform cortex did not show supralinear effects of taste and odour combinations in this study. This is consistent with the fact that in an earlier study, it was the intensity of odour that was correlated with activations in the pyriform cortex, whereas the pleasantness of odours was correlated with activations in the medial orbitofrontal cortex, and the unpleasantness of odours with activations in the lateral orbitofrontal cortex (Rolls *et al*., 2003). In this study in some other areas with olfactory inputs there was some evidence of interaction with MSG, for example in the olfactory tubercle/ventral striatum area, which had a significant (with svc) supralinear effect of

MSGV (Fig. 5), and which had a correlation with the fullness of the flavor as shown in Fig. 8.

The activation of the lateral orbitofrontal cortex was negatively correlated with the consonance and fullness of flavor of the stimuli. As shown at the start of the Results section, the ratings of pleasantness were correlated with those of consonance. These findings may be related to earlier studies showing activation of the lateral orbitofrontal cortex with unpleasant olfactory stimuli delivered from an olfactometer (Rolls *et al*., 2003), although clear mediolateral hedonic mapping was not found in a study with sweet vs. salt taste (O'Doherty *et al*., 2001b). However, activation of the lateral orbitofrontal cortex is produced by other unpleasant stimuli, including losing money (Elliott *et al*., 2000; O'Doherty *et al*., 2001a; Remijnse *et al*., 2005) and not obtaining an expected reward in a visual discrimination reversal task with face expressions as the reinforcers (Kringelbach & Rolls, 2003). Although all these nonreward or punishing stimuli activate the lateral orbitofrontal cortex (and many of them also more dorsal parts of the anterior cingulate rather than the pregenual cingulate; Rolls, 2005a, 2007), we know from single neuron recording studies in macaques that different stimuli do activate different populations of neurons (e.g. taste, olfactory, oral texture, oral temperature, visual, and even auditory), so that the representations of which reinforcer has been delivered is specified in the orbitofrontal cortex at the neuronal level (Rolls, 2005a, b).

Some evidence for supralinear effects of MSG with vegetable odour were also found in the ventral striatum (see Fig. 5). Here the activation was not especially related to the pleasantness of the stimuli [and indeed part of the ventral striatum [6 2–6] had activation that was negatively correlated with the consonance of the stimuli (see Fig. 9)]. We note that the ventral striatum receives major inputs from the orbitofrontal cortex and amygdala, and activity in the ventral striatum in part reflects inputs from these regions (Rolls, 2005a). The supralinear responses in this region to MSGV, together with a strong correlation with the fullness of flavor (Fig. 9), and without strong correlations with pleasantness, are consistent with the hypothesis that the ventral striatum activation reflects strong or salient stimuli.

The part of ventral premotor cortex area 6 that was activated in this study by the taste stimuli [and in previous studies with taste/oral somatosensory stimuli including water in the mouth (de Araujo *et al*., 2003b)] is known to receive inputs in macaques from the insular (primary) taste cortex (Cipolloni & Pandya, 1999). This region also receives somatosensory inputs from much of the length of the frontoparietal opercular cortex (Cipolloni & Pandya, 1999), so is not concerned mainly with taste or flavor processing. Consistent with this view, in this study the ventral premotor area did not show activation that was related to the supralinear flavor combination effects of MSG with vegetable, nor did it have any correlation with the pleasantness, consonance, or fullness of the flavor. Instead, its activation may be more related to preparation for movements, and indeed mirror neurons are found in the ventral premotor cortex (Iacoboni, 2005; Binkofski & Buccino, 2006). Further, electrical stimulation in the mouth region of the ventral premotor cortex in macaques can cause the hand to move to the mouth (Graziano & Gross, 1998). Thus the taste input to this region may be concerned with possible actions to sensory stimuli in the mouth, rather than with the perceptual and hedonic analysis of flavor.

To conclude, this is the first study we know in which the taste-olfactory brain mechanisms related to the delicious flavor of umami have been investigated. The findings lead us to propose that conceptually umami can best be thought of as a flavor enhancement effect produced by a combination of MSG/inosine monophosphate taste with a consonant odour. We thus suggest that MSG should be described as a flavor enhancer, because of the way it combines supralinearly with consonant odours such as vegetable. Other consonant odours might include fish and meat odours (Yamaguchi & Ninomiya, 2000), so that umami flavor comes, probably by olfactory-taste associative learning (Critchley & Rolls, 1996; Rolls *et al*., 1996), to represent the flavor of protein. This hypothesis is consistent with the fact that MSG alone is not very pleasant (see Fig. 1, and Beauchamp & Pearson, 1991), and does not enhance the taste of other gustatory stimuli such as sweet, salt, bitter and sour (Yamaguchi & Kimizuka, 1979). The present study also leads to the view that (when compared to salt), MSG is especially effective in enhancing the pleasantness of the flavor, and also the consonance and the fullness of flavor (see Fig. 1). Moreover, the results lead us to propose that the flavor enhancing effects of MSG are realized particularly in multimodal areas such as the orbitofrontal cortex and pregenual cingulate cortex, where supralinear interactions between MSG and vegetable odour were very highly significant (see Fig. 4A), and where activations were correlated with the rated pleasantness of the stimuli.

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Abbreviations

Fc, fully corrected; MSG, monosodium glutamate; MSGV, MSG plus vegetable; NaClV, NaCl and vegetable; svc, small volume correction.

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