Representation of Umami Taste in the Human Brain

I.E.T. de Araujo,[1,2] **M. L. Kringelbach,**[1,2] **E. T. Rolls,**[1,2] **and P. Hobden**[2]

[1]*Department of Experimental Psychology, University of Oxford, Oxford OX1 3UD; and* [2]*Oxford Centre for Functional Magnetic Resonance Imaging (FMRIB), John Radcliffe Hospital, Oxford OX3 9DU, United Kingdom*

de Araujo, I.E.T., M. L. Kringelbach, E. T. Rolls, and P. Hobden. Representation of umami taste in the human brain. *J Neurophysiol* 90: 313–319, 2003; 10.1152/jn.00669.2002. Umami taste stimuli, of which an exemplar is monosodium glutamate (MSG) and which capture what is described as the taste of protein, were shown using functional MRI (fMRI) to activate similar cortical regions of the human taste system to those activated by a prototypical taste stimulus, glucose. These taste regions included the insular/opercular cortex and the caudolateral orbitofrontal cortex. A part of the rostral anterior cingulate cortex (ACC) was also activated. When the nucleotide 0.005 M inosine 5′-monophosphate (IMP) was added to MSG (0.05 M), the blood oxygenation-level dependent (BOLD) signal in an anterior part of the orbitofrontal cortex showed supralinear additivity; this may reflect the subjective enhancement of umami taste that has been described when IMP is added to MSG. These results extend to humans previous studies in macaques showing that single neurons in these taste cortical areas can be tuned to umami stimuli.

INTRODUCTION

Recently, the taste referred to by the Japanese word *umami* has come to be recognized as a "fifth taste" (Baylis and Rolls 1991; Kawamura and Kare 1987) (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 and Kimizuka 1979; Yoshida and Saito 1969) 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 receptors for glutamate in lingual tissue with taste buds have been also recently found (Chaudhari et al. 2000). Umami taste is found in a diversity of foods like fish, meats, milk, tomatoes, and some vegetables, and is produced by the glutamate ion and also by some ribonucleotides (including inosine and guanosine nucleotides), which are present in these foods.

Besides their effects as unique tastants, umami substances have also been reported to show synergism, i.e., when two umami substances are mixed, the mixture effect is stronger than the sum of the effects given by the two substances (Rifkin and Bartoshuk 1980; Yamaguchi 1967). The synergism characteristic of umami occurs when MSG is combined with the ribonucleotide inosine 5′-monophosphate, IMP (or with its guanosine equivalent). The result of combining these two taste stimuli is a synergistic (i.e., supra-additive) effect in the subjective experience of taste intensity (Rifkin and Bartoshuk

1980; Yamaguchi 1967). The synergism can be demonstrated psychophysically even when appropriate ratio scales and correction for any nonlinearity in the psychophysical function are used (Rifkin and Bartoshuk 1980). Glutamate is high in concentration in foods such as tomatoes, green vegetables, and fish, and is relatively high in human breast milk; nucleotides are present in, for example, meat and in some fish such as tuna (Yamaguchi and Ninomiya 2000). The mixture of these components underlies the rich taste characteristic of many cuisines.

Some fibers in the taste nerves of rodents have been shown to have selective responses to umami tastants such as MSG (Ninomiya and Funakoshi 1987), and in macaques, it has been shown that single neurons in both the primary taste cortex in the insular/frontal opercular region and in the secondary taste cortex in the orbitofrontal cortex are selectively activated by MSG (Baylis and Rolls 1991; Rolls 2000), glutamic acid, or IMP (Rolls et al. 1996). Nothing is known, however, about the cortical responses to umami substances and their interactions in the human brain. We designed an event-related functional MRI (fMRI) experiment to investigate these questions.

METHODS

Subjects

Ten healthy right-handed subjects (of which 6 were males) participated in the study. Written informed consent from all subjects and ethical approval were obtained before the experiment.

Stimuli and experimental design

Solutions consisted of 0.05 M MSG (the monosodium salt of L-glutamic acid), 0.005 M IMP (which in this experiment was used in a form without sodium ions), a combination of the two (MSGIMP made to contain a concentration of 0.05 M MSG and 0.005 M IMP), or glucose (1.0 M). These concentrations of MSG and IMP were chosen based on psychophysical investigations we performed on human subjects that indicated that enhancement was exhibited at these concentrations (see RESULTS). Furthermore, these concentrations are close to a midpoint of the sensitivity curves of single neurons to these stimuli in macaques (Baylis and Rolls 1991; Rolls et al. 1996). The glucose was used to reveal the brain areas activated by an exemplar of a prototypical type of taste, sweet, so that we could determine whether the umami stimuli activated similar areas. Glucose was used as the exemplar (rather than sucrose) because it has been used as the taste stimulus in many previous neurophysiological and some neuroimaging studies (O'Doherty et al. 2001b; Rolls et al. 1989, 1990; Yaxley

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et al. 1990), in which the effects of feeding to satiety were often of interest to investigate the brain mechanisms underlying appetite. Glucose was used in those studies because it is rapidly absorbed and can act as a satiety signal without further metabolism (Rolls 1999).

The experimental protocol consisted of an event-related interleaved design using these four taste stimuli as well as a tasteless control solution, which was delivered to the subject's mouth through five polythene tubes that were held between the lips. Each tube of approximately 1 m in length was connected to a separate reservoir via a syringe and a one-way syringe valve (supplied by Fisher Scientific).

At the beginning of each taste delivery, one of the four stimuli, chosen by random permutation, was delivered in 0.75-ml aliquots to the subject's mouth. Swallowing was cued by a visual stimulus after 10 s (following initial instruction and training). After a random delay of 2–10 s, a tasteless control solution (using the main ionic components of saliva: 25 mM KCl + 2.5 mM NaHCO$_3$) (O'Doherty et al. 2001b) was administered in exactly the same way, and the subject was cued to swallow again after 10 s. There was then a 2- to 10-s random delay period until the next taste was delivered. The tasteless solution was used as the comparison condition for the taste solution and allowed nontaste effects such as somatosensory effects produced by liquid in the mouth and the single tongue movement made to distribute the liquid throughout the mouth to be controlled for. This taste trial was repeated for each of the four tastes, and the whole cycle was repeated 12 times. It was a feature of the experimental design that a tasteless solution was used to control for nontaste (including somatosensory) effects of placing solutions in the mouth and that all activations analyzed took this into account by subtraction. The tasteless solution also provided a rinse for the preceding tastant.

During the experiment, subjects were asked to rate each of the taste stimuli for intensity using a visual analog scale anchored at −2 for very weak and +2 for very intense.

fMRI data acquisition

Images were acquired with a 3.0-T VARIAN/SIEMENS wholebody scanner at the Centre for Functional Magnetic Resonance Imaging at Oxford (FMRIB), where 14 T2* weighted echo-Planar imaging (EPI) slices were acquired every 2 s (TR = 2). We used the techniques that we have developed over a number of years to carefully select the imaging parameters to minimize susceptibility and distortion artifact in the orbitofrontal cortex as described in detail by Wilson et al. (2002). 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 +60 (A/P) to –38 (A/P). Acquisition was carried out during the task performance, which lasted a total of 25 min and 28 s, yielding 764 volumes in total. A whole brain T2* weighted EPI volume of the above dimensions and an anatomical T1 volume with slice thickness of 6 mm and in-plane resolution of 0.75 × 0.75 mm was also acquired. The acquisition protocol used in this study is similar to that used in previous studies from our laboratory in which we used fMRI to image the orbitofrontal cortex.

fMRI data analysis

The imaging data were analyzed using SPM99 (Wellcome Department of Cognitive Neurology, London). Preprocessing of the data used SPM99 realignment, reslicing with sinc interpolation, normalization, and spatial smoothing with a 10-mm full width at half-maximum isotropic Gaussian kernel and global scaling. The time series at each voxel was high-pass and low-pass filtered with a hemodynamic response kernel. A general linear model was then applied to the time course of activation of each voxel and linear contrasts were defined to test the specific effects of each condition. Voxel values for each contrast resulted in a statistical parametric map of the t statistic, which was then transformed into the unit normal distribution (SPM z). Group effects were assessed by conjunction analyses of subject-specific contrasts. Reported P values based on this group analysis for a priori regions of interest (i.e., the insula and the orbitofrontal cortex) were corrected for the number of comparisons made within each region (Worsley et al. 1996). Checks were performed using the estimated motion as a covariate of no interest to rule out the possibility of the observed results being due to motion-related artifact. Conjunction analysis (Friston et al. 1999) was then performed to reveal significant common activations for each effect of interest.

RESULTS

Behavioral data

The taste intensity ratings (using a visual analog scale anchored at −2 for very weak and +2 for very intense) taken in the experiment were −0.75 ± 0.38 for IMP (mean ± SE), 0.46 ± 0.36 for MSG, 0.92 ± 0.35 for MSG+IMP (MSGIMP), and 1.5 ± 0.50 for glucose. Statistically it was shown that the intensity of the taste of umami produced by the mixture of MSG and IMP was greater than that produced by the MSG alone (even if the rating scales are taken as implying that the threshold is at –2 on the rating scale used, paired t = 1.95, df = 9, $P < 0.04$; 1-tailed). We refer to this as taste enhancement within the domain of umami taste. Although the effect is not supralinear (or "synergistic"; if the rating scales are taken as implying that the threshold is at –2 on the rating scale used) on average across subjects with the relatively small number of subjects used, supralinearity has been found when larger psychophysical studies are performed (Rifkin and Bartoshuk 1980).

Responses to umami taste

The effects of umami taste as produced by the prototypical stimulus 0.05 M MSG on cortical activation in the group analysis are shown in Fig. 1, row 3, the activations produced by IMP (0.005 M) are shown in Fig. 1, row 2, and the activations produced by the sweet tastant 1 M glucose are shown in Fig. 1, row 1. For all stimuli, activation of the insular-opercular taste cortex, which is the putative human primary taste cortex, and the orbitofrontal cortex were found. The activation produced by IMP shows that umami, even when the solution administered contains no sodium ions, activates these areas of the cerebral cortex.

Activation was also found by all these taste stimuli in the group analysis in a part of the rostral anterior cingulate cortex, as shown in Fig. 1, *right*, ACC, and discussed in the DISCUSSION.

To analyze whether there are areas of overlap of the activations produced by the umami stimuli and the glucose used as a prototypical taste stimulus, we show in Fig. 1, row 5, the conjunction across stimulus conditions and subjects (Friston et al. 1999) of the effects produced by MSG, IMP, MSGIMP, and glucose. Activations (significant at the $P < 0.05$ level, corrected for multiple comparisons) were found at the rostral border of the insula, which by comparison with the macaque, is likely to be the primary taste cortex, and in a part of the
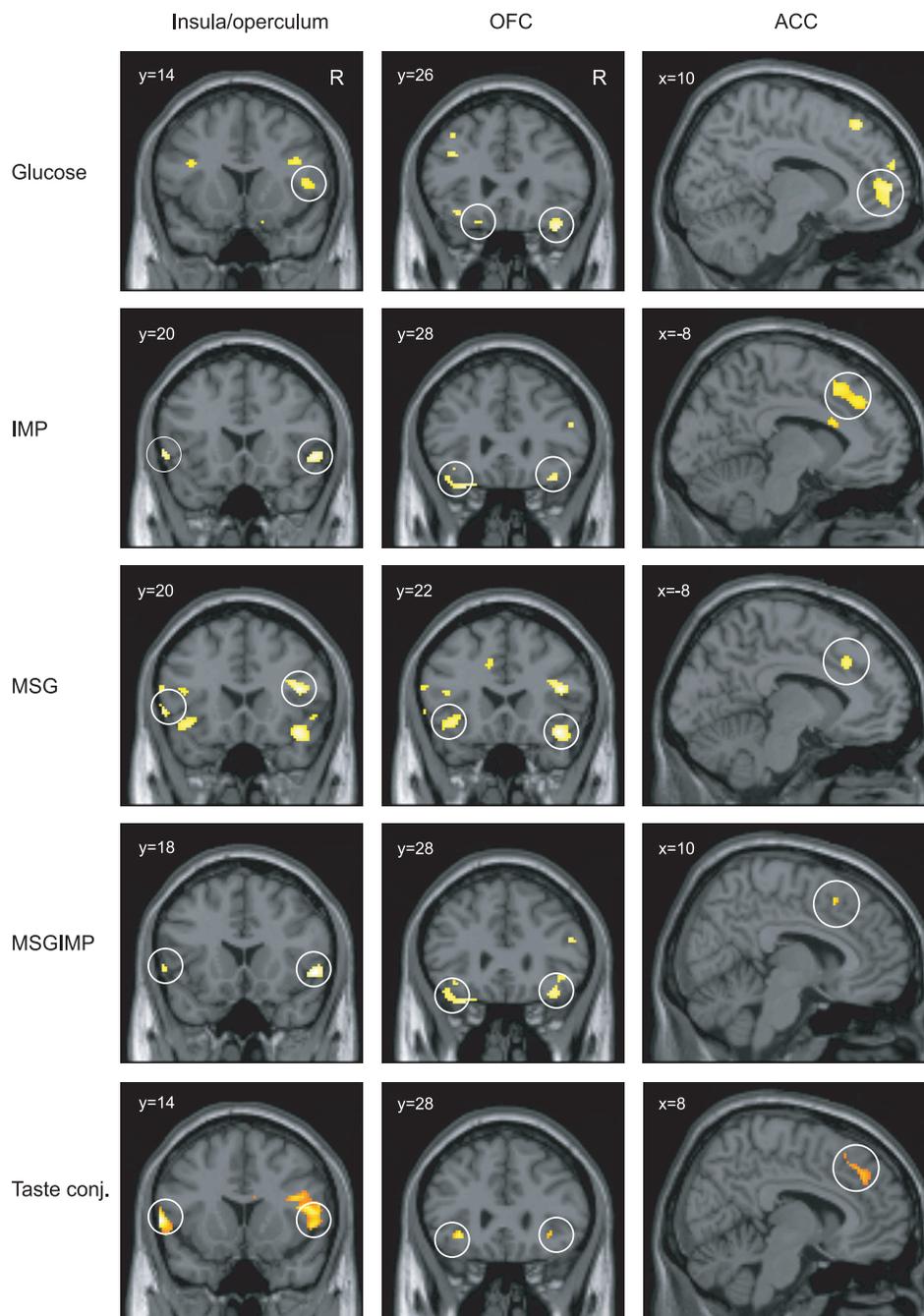
FIG. 1. Activations produced in the rostral insula/operculum, the orbitofrontal cortex (OFC), and the anterior cingulate cortex (ACC) by the tastants 1 M glucose, 0.005 M inosine 5′-monophosphate (IMP), 0.05 M monosodium glutamate (MSG), a combination of the MSG and IMP (MSGIMP), and the conjunction of all tastants. In the group analysis used, the peak of each of these activations is significant at $P < 0.05$ corrected (S.V.C), but to show the full extent (circled) of the activated regions of these brain structures, the figure shows the activations thresholded at $P < 0.001$ uncorrected. Group size included all subjects in all cases except for the IMP condition for the OFC brain area, where 1 subject was not included because no activation was found in the OFC in this condition, and interestingly, the subject reported a low perceived intensity of the IMP. The y and x values are with respect to the MNI coordinate system (Collins et al. 1994).

orbitofrontal cortex, which is likely to be a secondary taste cortical area (Baylis et al. 1994; Rolls 2000). The analysis thus shows that rather similar cortical areas were activated by the glucose and umami taste stimuli, providing evidence that umami is specifically activating regions that are demonstrably activated by classical taste stimuli.

To reveal the main effects produced by the three umami stimuli (umami taste), we show in Fig. 2 the conjunction across stimulus conditions and subjects (Friston et al. 1999) of the effects produced by MSG, IMP, and MSGIMP. Significant activations (at the $P < 0.05$ corrected for multiple comparisons) were found in the primary taste cortex (insula/operculum), putative secondary taste cortex (caudolateral orbitofrontal cortex), and in a region of the rostral anterior cingulate cortex.

The only significant difference in activation between glucose and umami stimuli (as revealed by masking the statistical maps at $P < 0.05$) was found in a ventral part of the rostral anterior cingulate cortex, which was activated reliably by glucose but not by any of the umami stimuli. This activation is shown in Fig. 1. Given the role of this region of the ACC in motivation and emotion-related behavior (Bush et al. 2000), it is notable that the glucose stimulus was clearly rated as being the most pleasant tastant to all subjects (glucose = 1.54 ± 0.17, MSGIMP = 0.5 ± 0.31, MSG = 0.22 ± 0.32, IMP = -0.4 ± 0.32, with $+2$ = very pleasant, -2 = very unpleasant). Comparisons performed subsequent to an ANOVA showed that the glucose was significantly more pleasant than any of the umami stimuli ($P < 0.0001$ in each case using a post hoc pairwise t-test comparison).
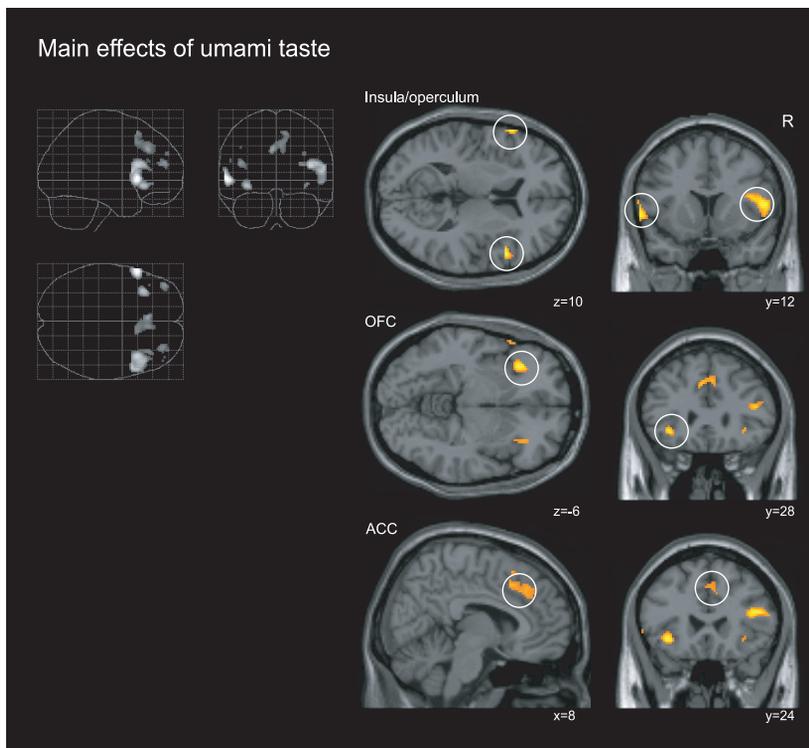
FIG. 2. Cortical activations produced by umami tastants. Group conjunction statistical analysis was applied to reveal common areas activated by the umami tastants (IMP, MSG, MSGIMP). *Left*: results from the SPM99 analysis are shown in a glass brain. *Right top*: axial and coronal section through the primary taste cortex ($x,y,z = 54,12,10$; $z = 5.21$; $-58,18,2$; $z = 6.15$, with $z = 4.5$ corresponding to a group-corrected P value of <0.05) are shown with the activations thresholded at $P < 0.0001$ for extent. *Right middle*: axial and coronal section through the caudal orbitofrontal cortex ($-34,26,-6$; $z = 4.84$). *Right bottom*: saggital and coronal section through the anterior cingulate cortex ($-4,30,36$; $z = 4.35$, S.V.C.).

Combination of MSG and IMP

Given the evidence that IMP (or its guanosine equivalent) and MSG can show synergism psychophysically (Rifkin and Bartoshuk 1980), we performed a contrast to investigate whether any brain areas are significantly more strongly activated by the MSGIMP combination than by the sum of the effects of MSG alone and IMP alone. Figure 3 shows the results of a stringent group analysis (based on the conjunction of activations in individual subjects) (Friston et al. 1999) thresholded for the group conjunction test at $P < 0.001$, which

reveals a significant cluster with 30 voxels in the left lateral orbitofrontal cortex ($x,y,z = -44,34,-18$; $z = 3.49$). Furthermore, it was found that this activation is significant using corrected statistics ($P < 0.05$ with a small volume correction). Thus supra-linear additivity in the blood oxygenation-level dependent (BOLD) signal was found in this anterior part of the orbitofrontal cortex (Fig. 3). The supra-linear additivity in the BOLD signal is further demonstrated by the time courses for each of the umami taste stimuli in this significant cluster of voxels in the orbitofrontal cortex, as shown in Fig. 4*A*. (The
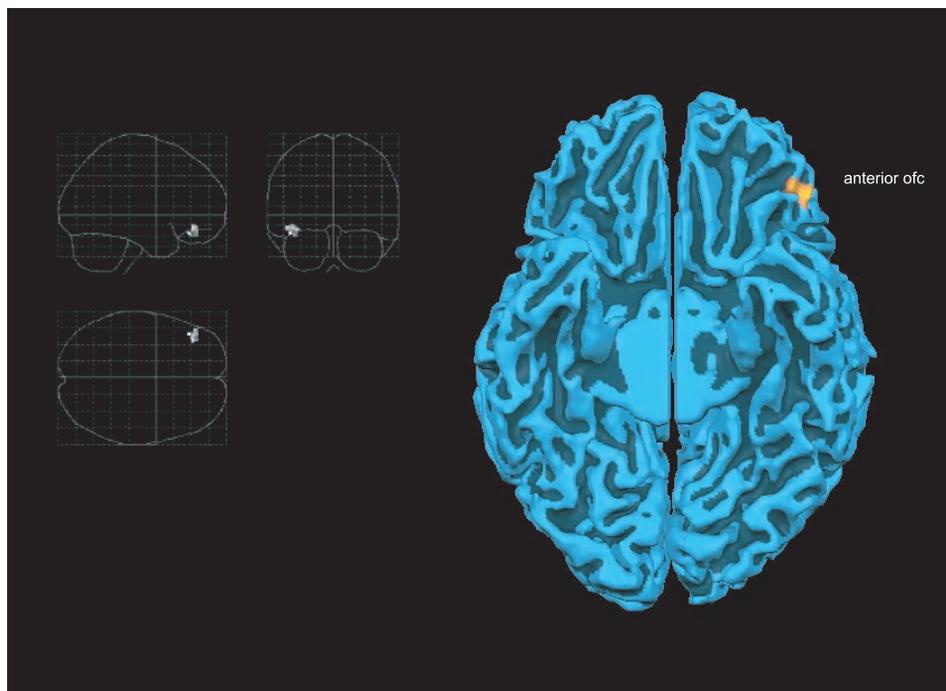

FIG. 3. Effects produced by a combination of umami tastants. Results of an SPM analysis to show brain regions where significantly larger activations were found to the combination taste stimulus MSG and IMP (MSGIMP) than to the sum of the activations produced by MSG and IMP delivered separately. The statistical analysis revealed a region of the orbitofrontal cortex ($-44,34,-18$; $z = 3.49$, $P < 0.05$ corrected for multiple comparisons with S.V.C. *Left*: unmasked results in a glass brain. *Right*: activation in the anterior orbitofrontal cortex (OFC) is shown rendered on the ventral surface of human cortical areas with the cerebellum removed.
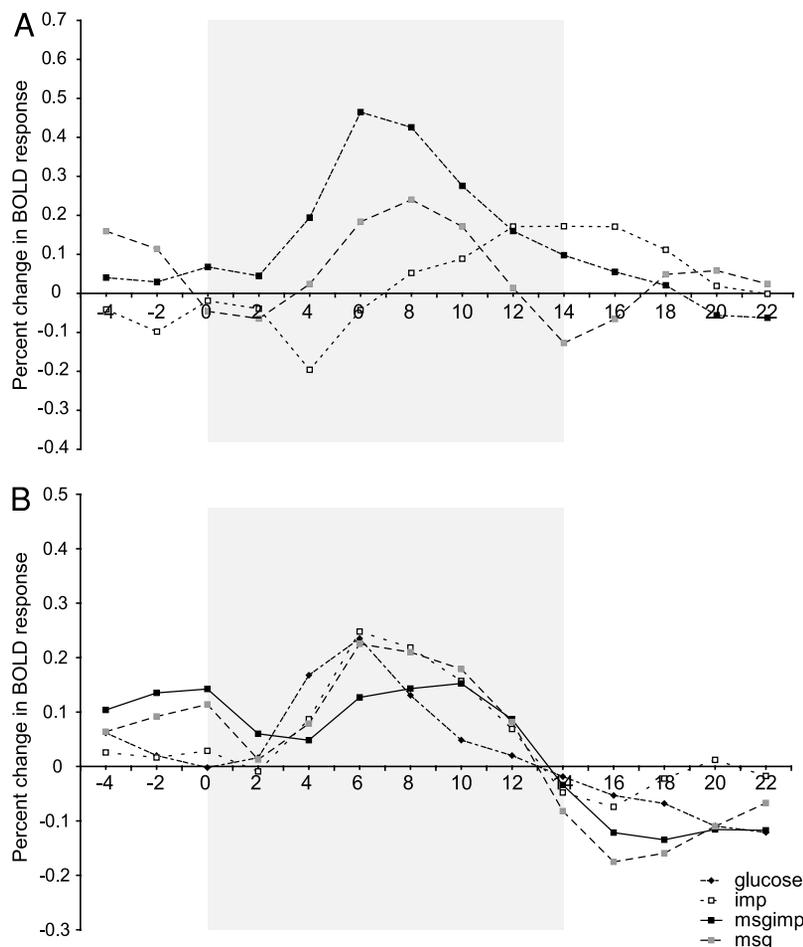
FIG. 4. Timecourses of cortical activation to taste. *A:* time course (averaged across all 10 subjects) within the significant cluster of 30 activated voxels in the orbitofrontal cortex in the group analysis from the supra-additivity contrast showing the percent change in BOLD signal for MSGIMP, MSG, and IMP compared with the tasteless control. Peak voxel of the cluster was at ($-44,34,-18$; with $z = 3.49$). *B:* time course (averaged across all 10 subjects) within the significant cluster of voxels in the insular/opercular taste cortex (from the main effects of taste contrast shown in Fig. 2, group effect across all 10 subjects, $P < 0.05$, corrected for multiple comparisons) averaged over a group of 53 voxels in the primary gustatory cortex ($x,y,z = 52,12,10$; $z = 5.48$). Percent changes in the BOLD signal for glucose, MSG, IMP, and MSGIMP compared with the tasteless control are shown. The taste stimuli were delivered at time 0. The time axis is in s.

timecourses across all 10 subjects are shown in Fig. 4*A* with respect to the tasteless solution.) This shows in these voxels a greater activation by MSGIMP than by either alone. For comparison, Fig. 4*B* shows the time courses for the largest peak in the main effects comparison for umami taste for the insular/operculum taste region shown in Fig. 2, and it is evident that the MSGIMP response was not especially prominent in the insular/opercular taste cortex.

DISCUSSION

The results of this study show that the taste of umami activates generally similar brain regions to another and prototypical tastant, glucose, including the putative human primary taste cortex in the anterior insular/opercular region, and the putative secondary taste cortex in the orbitofrontal cortex. The taste effects of umami were shown to be independent of the necessity of administered sodium ion by our use as a stimulus of inosine 5′-monophosphate (Sigma I-2879, which contains no sodium ion). The fact that cortical taste areas shown to be activated by glucose were also activated by the umami stimuli provides additional evidence that umami works in generally the same way as other tastants and is consistent with umami being considered as a "fifth taste."

The new findings described here in humans are supported by single-neuron recordings in nonhuman primates (macaques), which have shown that umami tastants activate single neurons in the primary and secondary taste cortices, and that these neurons can be shown to be tuned to umami tastants in a way that does not reflect their responsiveness to the sodium ion (Baylis and Rolls 1991; Rolls 2000; Rolls et al. 1996). The populations of neurons with responses to umami tastants such as MSG and IMP were shown to be separate from the populations activated by the four other prototypical tastants, sweet (glucose), salt (NaCl), bitter (quinine), and sour (HCl) (Rolls et al. 1996).

Second, this study uncovered a part of the human orbitofrontal cortex that showed strong supralinear additivity in the BOLD signal produced by the combination of MSG and IMP (the MSGIMP condition) compared with the sum of the MSG and IMP BOLD signals. This region was just anterior (with a peak at $y = 34$) to the part of the orbitofrontal cortex showing effects in the main comparison between taste and tasteless solution (with a peak at $y = 26$).

In the light of the much discussed issue of hemispheric specialization (Davidson 1992), it is potentially of interest to note that, in the group analysis, the region of the orbitofrontal cortex showing supra-linear additivity in the BOLD signal is on the left side of the human brain. This is consistent with the suggestion corroborated by clinical findings (Pritchard et al. 1999) that gustatory processing involves the left side of the human brain (Craig 2002). However, it should be noted that in some of the individual subjects, the supra-linear additivity effects were also seen in the right orbitofrontal cortex. Further, we note that, as shown in Figs. 1 and 2, there is very clear

evidence of the representation of taste bilaterally in the human brain.

The relative activations by the different umami tastants (MSG, IMP, and the mixture) were similar in the insula/operculum and main area of the taste orbitofrontal cortex (peak at $y = 26$), but were much larger to the MSGIMP combination in the more anterior area (peak at $y = 34$), as shown by the time course data shown in Fig. 4. This supra-linear change in BOLD signal for the mixture MSGIMP compared with the MSG and IMP may reflect underlying supra-addivity effects in the neuronal firing rates. Although there is some evidence that the BOLD signal reflects the underlying neuronal firing rates (Hyder et al. 2002; Smith et al. 2002), there is also evidence that the BOLD signal reflects in addition the inputs to and processing within a brain area (Logothetis et al. 2001).

The actual interaction between MSG and IMP may be expressed in part in the taste receptors themselves, or there may be somewhat different receptors for the different umami tastants (Chaudhari et al. 2000; Lin and Kinnamon 1998), but in any case, the results of this study show that there is a part of the human orbitofrontal cortex in which supra-linear additivity shows up very strongly in the statistical analysis. The fact that this part of the human orbitofrontal cortex statistically reflects supra-additive effects between umami tastants evident in the BOLD signal makes it likely that activity in this part of the orbitofrontal cortex is especially relevant to the perceived sensation of umami taste and to the behavioral preferences for umami taste. The role of this part of the human cerebral cortex in the taste of umami could arise because it is able to provide a nonlinear amplification of the MSG and IMP inputs already combined in the taste receptors, or it could be that this part of the cortex is able to combine information from partly separate umami channels to produce the large response to the combination of MSG and IMP. This will be an interesting issue for future investigations.

The evidence described here that the orbitofrontal cortex represents umami taste (literally "delicious" in Japanese) is consistent with other evidence that the orbitofrontal cortex also represents information about the reward value of other primary and secondary reinforcers including taste (O'Doherty et al. 2001b; Small et al. 1999), odor (Zald and Pardo 1997; Zatorre et al. 1992), and even abstract monetary rewards (O'Doherty et al. 2001a).

The activation of the cingulate cortex found in this study by the taste stimuli is of interest. For example, we have found that pleasant olfactory stimuli activate a far anterior part of the anterior cingulate cortex, with aversive olfactory stimuli a slightly more posterior region (de Araujo et al. 2002). The far rostral anterior cingulate area activated by glucose shown in Fig. 1 is close to the area in which pleasant olfactory stimuli are represented. The cingulate area activated by umami taste is in the anterior cingulate cortex, a little behind the region activated by glucose (see Fig. 1). Further, the anterior cingulate cortex has been shown to be activated by motivationally relevant affective stimuli including pleasant touch (Rolls et al. 2003), and there is evidence from animal studies that it is involved in a range of motivationally oriented unconditioned behaviors and emotional learning (Cardinal et al. 2002; Devinsky et al. 1995). In addition the anterior, ventral cingulate cortex (Brodmann's areas 24a/b and 25) in humans seems to be involved in the pathology of depression in humans, as well as in the control of normal mood (Drevets et al. 1997), and in responding to emotionally significant stimuli, such as cocaine-associated cues in drug abusers (Childress et al. 1999).

Other affective stimuli have been shown to activate nearby parts of the anterior cingulate (Bush et al. 2000). However, it is not clear from these imaging studies whether the cingulate activation reflects a sensory representation of the stimuli, some more general affective or even arousal reaction to the stimuli, or some behavioral response or response selection or response inhibition. We now have reason to believe that the activation shown in this study of the human cingulate cortex by taste stimuli reflects sensory inputs produced by the tastants, because in studies now in progress in macaques, taste neurons with classical taste cell properties in a corresponding region of the macaque rostral anterior cingulate cortex are being found, and interestingly, these cingulate taste cells are hunger dependent, and in particular, reflect sensory-specific satiety in the same way as orbitofrontal cortex taste neurons (Rolls et al. 1989).

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