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Taste-olfactory convergence, and the representation of the pleasantness of flavour, in the human brain

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Abstract

The functional architecture of the central taste and olfactory systems in primates provides evidence that the convergence of taste and smell information onto single neurons is realized in the caudal orbitofrontal cortex (and immediately adjacent agranular insula). These higher-order association cortical areas thus support flavour processing. Much less is known, however, about homologous regions in the human cortex, or how taste–odour interactions, and thus flavour perception, are implemented in the human brain. We performed an event-related fMRI study to investigate where in the human brain these interactions between taste and odour stimuli (administered retronasally) may be realized. The brain regions that were activated by both taste and smell included parts of the caudal orbitofrontal cortex, amygdala, insular cortex and adjoining areas, and anterior cingulate cortex. It was shown that a small part of the anterior (putatively agranular) insula responds to unimodal taste and to unimodal olfactory stimuli, and that a part of the anterior frontal operculum is a unimodal taste area (putatively primary taste cortex) not activated by olfactory stimuli. Activations to combined olfactory and taste stimuli where there was little or no activation to either alone (providing positive evidence for interactions between the olfactory and taste inputs) were found in a lateral anterior part of the orbitofrontal cortex. Correlations with consonance ratings for the smell and taste combinations, and for their pleasantness, were found in a medial anterior part of the orbitofrontal cortex. These results provide evidence on the neural substrate for the convergence of taste and olfactory stimuli to produce flavour in humans, and where the pleasantness of flavour is represented in the human brain.

Introduction

The primary cortical structures involved in gustatory and olfactory processing have been the focus of considerable investigation in humans, particularly through functional neuroimaging methods such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) (Small *et al*., 1999; Zald & Pardo, 2000; O'Doherty *et al*., 2003). Not much is known, however, about brain regions that receive both taste and olfactory input and about how these two neural systems interact and support psychophysical processes such as flavour perception (Small *et al*., 1997).

In primates there are no known connections between the subcortical areas performing taste [e.g. the ventroposterior medial nucleus of thalamus, parvocellular part (VPMpc)] and olfactory (e.g. the olfactory bulb) processing (Sewards & Sewards, 2001). Nor are there direct inputs from both of these regions into a common part of the amygdala. Thus convergence between taste and olfactory inputs must be implemented in the cortex. In primates, the primary taste cortex is in the frontal operculum and the anterior insula, in that it receives afferents from VPMpc and contains taste neurons (Pritchard *et al*., 1986; Yaxley *et al*., 1990; Rolls, 1997; Scott & Plata-Salaman, 1999; Rolls & Scott, 2003). The primary taste cortex does not contain olfactory neurons (Kadohisa *et al*., 2003), and projects forward into a secondary cortical taste area in the caudal orbitofrontal cortex (OFC; Baylis *et al*., 1995), which contains taste neurons (Rolls *et al*., 1990). Olfactory inputs from the olfactory bulb reach a more anterior part of the insula than the primary taste cortex, the agranular insula, which is just at the caudal border of the OFC, and from there connections reach the OFC (Carmichael *et al*., 1994). In the OFC, convergence onto single neurons occurs (Rolls & Baylis, 1994) to build, by slow learning, a representation of flavour (Critchley & Rolls, 1996b; Rolls *et al*., 1996). Thus the caudal OFC, and possibly the adjoining agranular part of the anterior insula, is a candidate region to implement flavour processing in humans.

When food is consumed, first there is orthonasal stimulation by odour before the food is placed in the mouth, and then when the food is in the mouth there is retronasal stimulation from odour molecules via the posterior nares of the nasopharynx (Pierce & Halpern, 1996). Cerf-Ducastel & Murphy (2001) studied the cortical representation of olfactory retronasal stimulation in the human brain using fMRI, but did not attempt to use an odourless taste stimulus, nor this in combination with retronasal olfactory stimulation, to define unimodal taste areas, unimodal olfactory areas, and areas where both stimuli activate and potentially interact. The investigation of such convergence and interaction between taste and olfactory stimuli seems to be a necessary and important step towards disclosing the neural structures involved in flavour processing.

In this study we investigated, using event-related fMRI, three different aspects of taste and retronasal olfactory processing during

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flavour perception. First we aimed to reveal brain areas responding unimodally to taste stimuli, and to olfactory stimuli, and in addition, brain areas responding to both taste and olfactory stimuli. Second, we aimed to identify areas that responded nonlinearly to combinations of taste and olfactory stimuli, using this as a sign that these stimuli were interacting. Third, we were interested in the brain correlates of the perception of these complex combinations, that is the degree of consonance or congruence between the inputs produced through these two sensory modalities. These were assessed by a correlation analysis based on subjective ratings taken throughout the experiment. The taste and retronasal olfactory stimuli were delivered orally in aqueous solution, either separately or as complex mixtures. The results were compared with olfactory stimuli delivered orthonasally in a separate study, in order to help identify areas responding to unimodal olfactory stimuli, to unimodal taste stimuli, and to the combination of olfactory and taste stimuli.

Materials and methods

Subjects

Eleven healthy right-handed subjects (of whom six were males) participated in the study. Written informed consent from all subjects and ethical approval were obtained before the experiment from the Central Oxford Research Ethics Committee.

Stimuli

Two taste and two olfactory stimuli provided the basic set. The taste stimuli were 0.5 M sucrose (SIGMA) and 0.05 M monosodium glutamate (MSG; SIGMA). The olfactory stimuli were 20 p.p.m. strawberry odour (for use as a food flavour, and kindly supplied by Firmenich S.A., Geneva) and 25 p.p.m. of 1.9 % methional (a chicken-like flavour). The stimuli and concentrations were chosen based on psychophysical tests performed on a panel of subjects, and were in a midpoint of the response-intensity functions so that possible interactions could be revealed. All the stimuli were diluted and delivered in deionized water either as a taste + odour combination or as a simple stimulus. So in this case olfactory stimuli stimulated the retronasal pathway through the posterior nares of the nasopharynx. A tasteless solution (containing the main ionic components of saliva, 25 mM $KCl + 2.5$ mM $NaHCO_3$) was used as a control stimulus (O'Doherty *et al*., 2001b; de Araujo *et al*., 2003a). Tests were performed to verify that detection of olfactory stimuli was reliable only when the subjects' noses were open.

Experimental design

The experimental protocol consisted of an event-related interleaved design using in random order the four stimuli that consisted of taste + olfactory combinations ([sucrose + strawberry], [MSG + methional], [sucrose + methional] and [MSG + strawberry]); together with a taste-only stimulus, sucrose; an olfactory-only stimulus, strawberry odour; and a tasteless control solution. This set of stimuli was chosen: first, in order to limit the number of stimuli to what was feasible given the number of repetitions of each needed and the length of time that subjects were in the magnet; second, to enable consonant (e.g. [sucrose + strawberry]) and dissonant (e.g. [sucrose + methional]) combinations of stimuli to be compared; and third, to enable a combination of stimuli, [sucrose + strawberry], to be compared with each of its components, sucrose alone and strawberry alone. Stimuli were delivered to the subject's mouth through seven polythene tubes that were held between the lips, and the odours were thus delivered by the retronasal route in aqueous solution. 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 Ltd, UK), which allowed 0.75 mL of any stimulus to be delivered manually under computer instruction.

At the beginning of each taste delivery, one of the six 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 delay of 3 s, the subject was asked to rate each of the taste stimuli three times for consonance, pleasantness and intensity by using three separate visual analogue rating scales anchored at -2 for very incongruent/unpleasant/weak, and $+2$ for very congruent/pleasant/intense. Each rating period was 5 s long. The tasteless control solution containing the main ionic components of saliva (25 mM $KCl + 2.5$ mM $NaHCO_3$) was then administered in exactly the same way as the test stimulus and the subject was cued to swallow again after 10 s. 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 (de Araujo *et al*., 2003a; O'Doherty *et al*., 2001b). There was then a 3-s delay period allowed for swallowing followed by a 1-s gap until the start of the next trial. This taste trial was repeated for each of the six stimuli, and the whole cycle was repeated nine times.

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 14 $T2^*$ weighted EPI slices 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*., 2001a; de Araujo *et al*., 2003a; Rolls *et al*., 2003a; Rolls *et al*., 2003b) to carefully select the imaging parameters in order to minimize susceptibility and distortion artefact in the OFC 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 yielding 1008 volumes in total. A whole brain $T2^*$ weighted EPI volume of the above dimensions and an anatomical T1 volume with slice thickness 1.5 mm and in-plane resolution of 1.5×1.5 mm was also acquired.

fMRI data analysis

The imaging data were analysed using SPM99 (Statistical Parametric Mapping; Wellcome Institute of Cognitive Neurology). Pre-processing of the data used SPM99 realignment, reslicing with sinc interpolation, normalization to MNI coordinate system (Montreal Neurological Institute) (Collins *et al*., 1994), used throughout this paper, and spatial smoothing with an 8-mm full width at half maximum isotropic Gaussian kernel and global scaling. The time series at each voxel were high-pass and low-pass filtered with a haemodynamic 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 across distinct stimulus conditions and second-level, random effects analysis. Reported *P*-values based on this group analysis for *a priori* regions of interest (e.g.

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-correlated artifact. Reported *P*-values based on this group analysis for *a priori* regions of interest were corrected for the number of comparisons made within each region using the small volume correction (SVC) procedure (Worsley *et al*., 1996). The regions of interest were defined *a priori* to be over the anatomical boundaries bilaterally of the insula/operculum, orbitofrontal cortex, and amygdala.

As mentioned above, subjects gave ratings for consonance, pleasantness and stimulus intensity on every trial. This allowed performance of a correlation analysis aiming to reveal brain areas significantly covarying with the subjective ratings for stimuli congruence or consonance. This analysis was performed in each subject's individual data through a parametric modulation analysis and the resulting parametric maps were entered into a second-level, random effects analysis. Pleasantness and intensity ratings were modelled as effects of no interest by including the relevant parameters as columns in the design matrix.

Results

Behavioural data

The consonance ratings given by the subjects for each stimulus delivered throughout the experiment were as follows (mean ± SEM): sucrose, 0.34 ± 0.08; strawberry, 0.16 ± 0.11; [sucrose + strawberry], 0.99 ± 0.11; [MSG + methional], 0.17 ± 0.22; [MSG + strawberry], -0.57 ± 0.17; [sucrose + methional], -0.38 ± 0.22. We note that the two consonant combinations ([sucrose + strawberry] and [MSG + methional]) were rated positively, while the dissonant combinations ([sucrose + methional] and [MSG + strawberry]) were rated negatively. A pairwise comparison between the two classes of stimuli results in a *t*-value of 5.02, significant at $P < 0.0001$. (Pairwise *t*-tests were performed to test particular hypotheses). In addition, supra-additivity was found for some of the consonance ratings. For example, the consonance of the combination of [sucrose + strawberry] was significantly greater than the sum of the unimodal components sucrose and strawberry ($P < 0.0001$).

The pleasantness ratings were as follows (mean ± SEM): sucrose, 0.6 ± 0.1; strawberry, 0.28 ± 0.06; [sucrose + strawberry], 1.19 ± 0.11; [MSG + methional], -0.8 ± 0.16; [MSG + strawberry], -0.7 ± 0.14; [sucrose + methional], -0.01 ± 0.23. It is interesting to note that the above ratings show that while the combination [MSG + methional] was rated positively with respect to consonance it was perceived as rather unpleasant by the subjects. This shows that subjects were able to dissociate between consonance and pleasantness, perceiving them as distinct attributes of the stimuli. Thus potentially the experimental design could reveal parts of the brain in which the activation was correlated with either consonance or pleasantness. In addition, supra-additivity was found for some of the pleasantness ratings. For example, the pleasantness of the combination of [sucrose + strawberry] was significantly greater than the sum of the unimodal components sucrose and strawberry ($P < 0.001$).

The intensity ratings were as follows (mean ± SEM): sucrose, 2.6 ± 0.04; strawberry, 1.54 ± 0.23; [sucrose + strawberry], 2.95 ± 0.11; [MSG + methional], 2.6 ± 0.19; [MSG + strawberry], 2.38 ± 0.15; [sucrose + methional], 2.98 ± 0.1. These ratings were rescaled into the interval (0–4), where 0 = very weak and 4 = very intense. We found that the rated intensity of the combination [sucrose + strawberry] was greater than that of the unimodal sucrose ($t = 2.95$, $P < 0.01$). [Note that the intensity ratings were mapped into a (0–4) scale, and that the intensity of the stimulus was what was being rated]. While this effect is not surprising, it does show that the retronasal strawberry odour was significantly intense when present with sucrose to increase the intensity rating compared to that for sucrose alone.

fMRI data

Main effects

Initially a group analysis was performed on each individual stimulus in order to reveal the brain areas responding significantly to the stimuli. In general, activations were found for all six stimuli (bilaterally unless otherwise stated) in the amygdala, insular cortex and adjoining frontal operculum, ventral striatum, caudal OFC, and an anterior region of the anterior cingulate cortex (ACC). Figure 1 shows the effects of [sucrose + strawberry], sucrose alone, and strawberry alone (all with the control subtraction of the effects of the tasteless solution) in four different brain regions; the amygdala and frontal operculum bilaterally (column 1), the caudal orbitofrontal cortex (second column), and the anterior ACC (third column). The third column also shows ventral forebrain activations (which extend for the [sucrose + strawberry] combination from the posterior end of the OFC at $Y = 30$ to $Y = 0$ which is approximately 5 mm behind the anterior commissure). Table 1 summarizes the results of this main effects analysis. Most of the activations were found bilaterally.

Brain areas activated by both taste and olfactory stimuli

A systematic comparison between taste and olfactory activations was performed through conjunction analysis (Friston *et al*., 1999), as follows. We first assessed common brain areas activated by sucrose (unimodal taste) and by strawberry (unimodal olfactory, using retronasal delivery) by performing a conjunction analysis across these two conditions (using a group analysis). This conjunction analysis showed significant activations by both the taste and the olfactory stimuli each delivered unimodally in the amygdala (bilaterally), right frontal operculum, right anterior insula, and right caudal orbitofrontal cortex. The analysis revealed that right amygdala activations resulted in higher *Z*-scores than in the left amygdala ($Z = 5.39$, $P < 0.05$ corrected for multiple comparisons for the peak voxel in the right amygdala and $Z = 4.17$, $P < 0.0001$ uncorrected in the left amygdala) (see Fig. 2A). Right frontal operculum activations were found at (62, 1, 18), $Z = 5.4$, $P < 0.05$ corrected (Fig. 2A); right far anterior (agranular) insular activations were found at (45, 15, −8), $Z = 3.2$, $P < 0.001$ uncorrected (Fig. 2B, circled); and right caudolateral orbitofrontal cortex at (36, 25, −6), $Z = 3.2$, $P < 0.001$ uncorrected (see Fig. 2C).

To reveal areas activated by unimodal taste but not by unimodal olfactory stimuli, conjunction analysis was performed for the contrast [sucrose − strawberry] across all 11 subjects. Significant activations were found in the frontal operculum, as shown in Fig. 2D. This activation is significant at $P < 0.05$, corrected for SVC (by defining a 20-mm sphere around the peak voxel; MNI coordinates (−36, 12, 12), $Z = 4.06$). The implication is that the frontal operculum/insula area at this level anterior ($Y = 3$ to $Y = 14$) is a unimodal taste cortex. This area has been found to be consistently activated in previous taste imaging studies (Small *et al*., 1999; O'Doherty *et al*., 2001b; de Araujo *et al*., 2003a), and is thought to be not targeted by projections from primary olfactory areas (see Sewards & Sewards, 2001).

Taste and olfaction interactions

To reveal brain areas responding to positive interactions between taste (sucrose) and olfactory (strawberry) stimuli, we defined the contrast

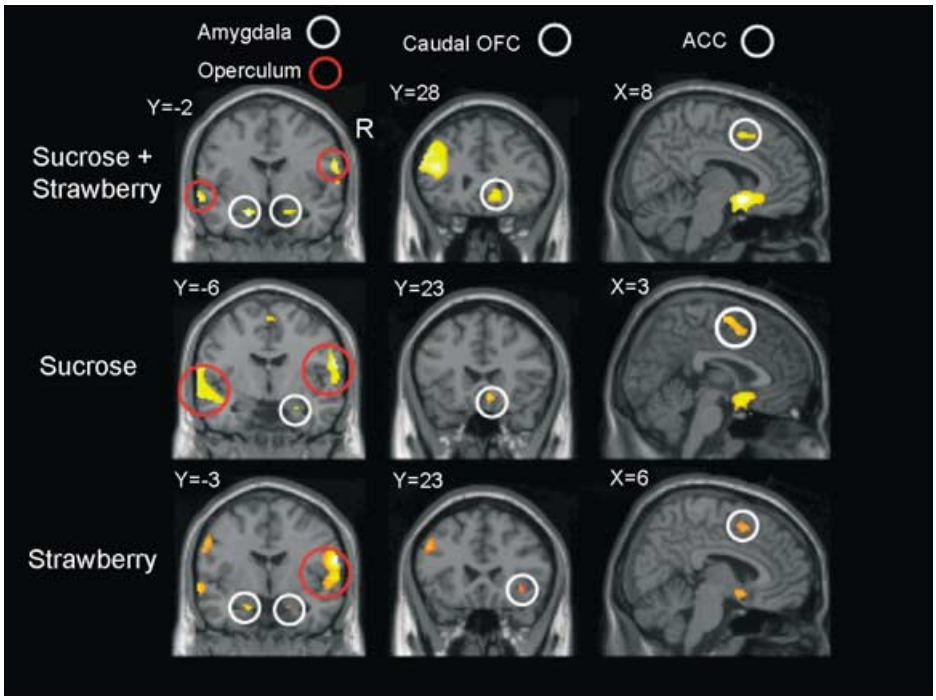
Amygdala
Operculum
Caudal OFC
ACC
Y=-2
R
Y=28
X=8
Sucrose +
Strawberry
Y=-6
Y=23
X=3
Sucrose
Y=-3
Y=23
X=6
Strawberry

FIG. 1.

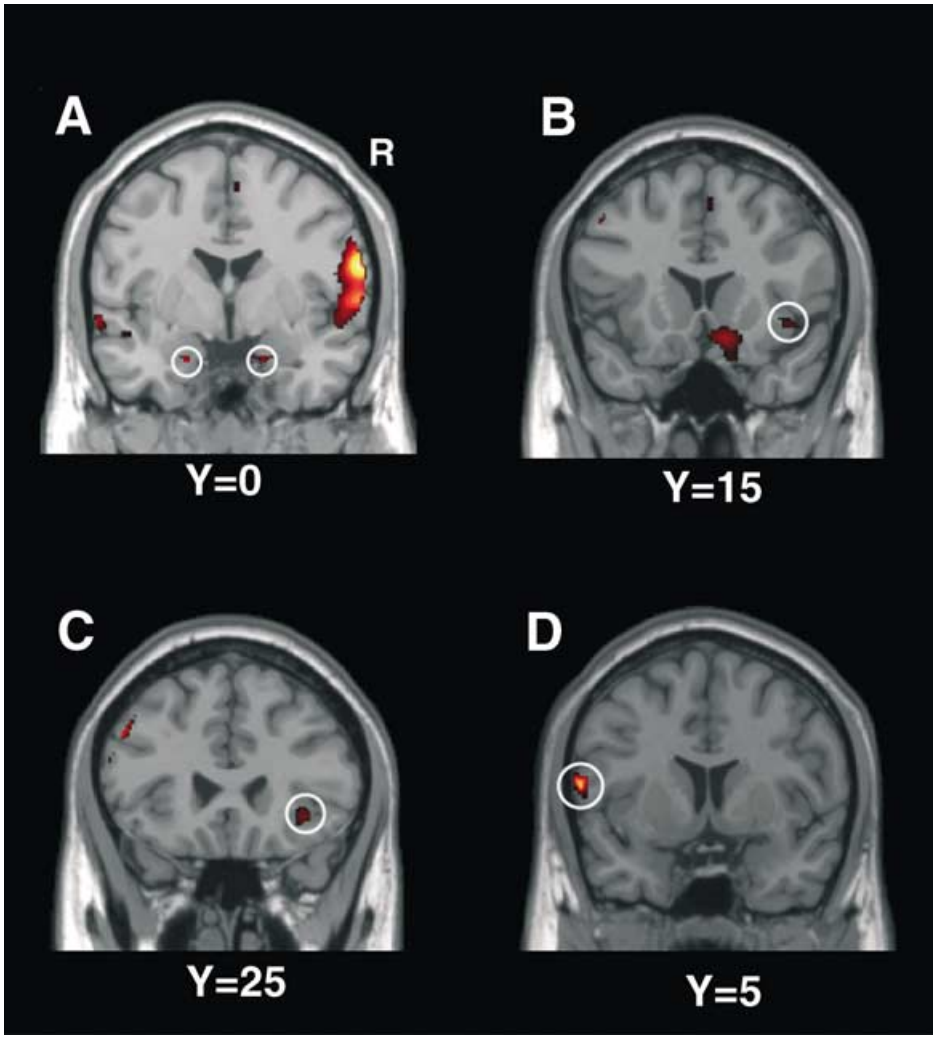
A
R
B
Y=0
Y=15
C
D
Y=25
Y=5

FIG. 2.

TABLE 1. Activations produced by unimodal taste (sucrose) and retronasal olfactory (strawberry) stimuli, and by their combination (cf Fig. 1)

Side /Location	Coordinates (MNI, peak)	*Z*-score	*P*-Value
Sucrose + Strawberry – Tasteless solution			
R Caudomedial OFC	14, 26, −6	3.94	<0.05 (SVC)
R Anterior Insula	42, 18, −6	4.02	<0.03 (SVC)
L Anterior Insula	−31, 22, 0	4.13	<0.005 (SVC)
R Operculum	64, −4, 20	5.19	<0.05 (C)
R Frontal Operculum	64, 14, 16	4.29	<0.01 (SVC)
R Ventral Forebrain	8, 8, −10	5.85	<0.01 (C)
L Amygdala	−18, −2, −24	5.91	<0.01 (C)
R Amygdala	20, −4, −24	4.35	<0.001 (SVC)
R ACC	8, 11, 49	3.39	<0.001 (U)
L DLPFC	−42, 28, 20	5.38	<0.01 (C)
L Anterior OFC	−32, 50, −10	2.81	<0.005 (U)
Sucrose – Tasteless solution			
R Caudomedial OFC	10, 22, −12	3.64	<0.0001 (U)
R Anterior Insula	45, 15, −9	3.96	<0.01 (SVC)
R Operculum	64, −4, 20	6.67	<0.01 (C)
L Operculum	−62, −10, 14	5.40	<0.05 (C)
R Ventral Forebrain	8, 8, −12	6.10	<0.01 (C)
L Amygdala	−18, 0, −26	3.40	<0.001 (U)
R Amygdala	20, −4, −24	5.52	<0.05 (C)
R ACC	6, 6, 50	3.54	<0.0001 (U)
Strawberry odour – Tasteless solution			
R Caudolateral OFC	38, 23, −7	3.10	<0.001 (U)
R Anterior Insula	45, 15, −8	2.95	<0.005 (U)
R Operculum	64, −4, 20	6.01	<0.01 (C)
R Ventral Forebrain	8, 8, −12	3.89	<0.001 (U)
L Amygdala	−20, −4, −24	5.01	<0.05 (C)
R Amygdala	18, −2, −26	3.94	<0.005 (SVC)
R ACC	6, 10, 52	3.63	<0.001 (U)

C, corrected for multiple comparisons; MNI, Montreal Neurological Institute; SVC, small volume correction (see Methods); U, uncorrected for multiple comparisons.

{[sucrose + strawberry] − [sucrose alone + strawberry alone]}. This tests whether the activation produced by the mixture is significantly greater than the sum of any activations produced by the two unimodal components presented alone. This contrast was applied to each individual subject data and the resulting statistical parametric maps were inserted into a second-level, random effects analysis (Worsley *et al*., 1996). Significant activations left from this contrast show brain areas that are activated more by the combined odour + taste stimulus than by the sum of any activations produced by each separately, and is a way in neuroimaging studies of detecting interactions between different stimuli due to their convergence onto the same neural processing system.

The random effects analysis revealed that an area of the left anterior OFC was more strongly activated by the combination [sucrose + strawberry odour] than by the sum of any activations to the two stimuli (see Fig. 3). This activation is significant at $P < 0.05$ corrected for small volume correction (see Materials and methods; MNI coordinates (−32, 50, −10), $Z = 3.92$). No other cluster was found to be significant at this statistical threshold.

Brain areas with activations correlating with the consonance and pleasantness ratings

A second-level (random-effects) analysis was performed to show brain areas with activations correlating with the subjective ratings taken during the experiment. In the SPM analysis, both pleasantness and consonance were included as covariates in the model. Significant areas correlating with the consonance (Fig. 4A) and pleasantness (Fig. 4B) ratings were found in the rostral medial orbitofrontal cortex. For the consonance correlation the peak activation in the cluster was (0 46 −17), $Z = 5.09$, significant at $P < 0.05$ (corrected for multiple comparisons). In this case the pleasantness ratings were modelled as effects of no interest. For the pleasantness correlation the peak activation was found at (2, 52, −15), $Z = 4.14$, $P < 0.05$ SVC. Neither effect was due to any confound with intensity, for no correlations of brain activation with the stimulus intensities (which were deliberately kept within a limited range) were found. To elucidate further these results, Fig. 4C shows the relation between the blood oxygen level dependent (BOLD) signal from the cluster of voxels in the medial orbitofrontal cortex shown in Fig. 4A and the subjective consonance ratings. Figure 4C shows a very clear relation between the consonance ratings and the activations of these medial orbitofrontal cortex voxels.

Discussion

This study aimed to reveal how the human brain represents flavour, by disclosing which areas respond to either taste or retronasal olfactory stimuli, and which brain areas respond to both. In particular we were interested in knowing if the findings could be compared with what is known about taste–odour interactions in nonhuman primates. We have shown that taste and olfactory inputs in the human brain converge in particular in the far anterior (putatively agranular) insular cortex, the caudal OFC, the amygdala, the ventral forebrain (a region extending from the far caudal OFC to 5 mm behind the anterior commissure), and in the ACC and adjoining areas. We have also shown that positive interactions between taste and (retronasally delivered) odour stimuli are represented in a lateral part of the anterior orbitofrontal cortex, and that subjective judgements of congruence between taste and smell stimuli correlate with activity in a medial part of the anterior orbitofrontal cortex.

To obtain further evidence on the activation produced by retronasal odourant presented in aqueous solution (circled region in Fig. 2B) in the far anterior (putatively agranular) insular cortex (shown to be also activated by taste stimuli) is activated by olfactory stimuli, we also analysed the activations produced in this brain region by odours presented orthonasally using an olfactometer in a related study (Rolls *et al*., 2003a). Eleven healthy right-handed subjects participated in the

FIG. 1. Main effects analyses. Group effects for the comparisons: row 1, [sucrose + strawberry odour − tasteless]; row 2, [sucrose − tasteless]; row 3, [strawberry odour − tasteless] in four different brain regions: column 1, frontal operculum and amygdala; column 2, the caudal region of the orbitofrontal cortex (OFC); column 3, a posterior part of the anterior cingulate cortex (ACC) region close to the supplementary motor cortex (SMA). The images were thresholded at $P < 0.0001$ for illustration. In the coronal sections, R indicates the right side of the brain. Column 3 also shows activation in the basal forebrain extending from the caudal orbitofrontal cortex to behind the anterior commissure. The middle column top row shows in addition an area of the left dorsolateral prefrontal cortex activated by the stimulus [sucrose + strawberry odour − tasteless], which was also activated in the other conditions at $Y = 28$ (not shown).

FIG. 2. (A–C). Areas in the cortex activated by both unimodal taste and unimodal olfactory stimuli as revealed by a group conjunction analysis for the comparison [sucrose − tasteless] AND [strawberry odour − tasteless]. Significant activations were found: (A) in the frontal operculum and bilaterally in the amygdala (circled); (B) in the far anterior, agranular, insula (circled) (basal forebrain activation is also visible); (C) in the caudolateral orbitofrontal cortex (circled). (D) Conjunction analysis across all 11 subjects for the comparison [sucrose taste − strawberry odour] revealed a significant activation in the frontal operculum area (circled; ranging from $Y = 3$ to $Y = 14$), providing evidence that this region is activated by taste and not by odour. Images were thresholded at $P < 0.0001$ for illustration.

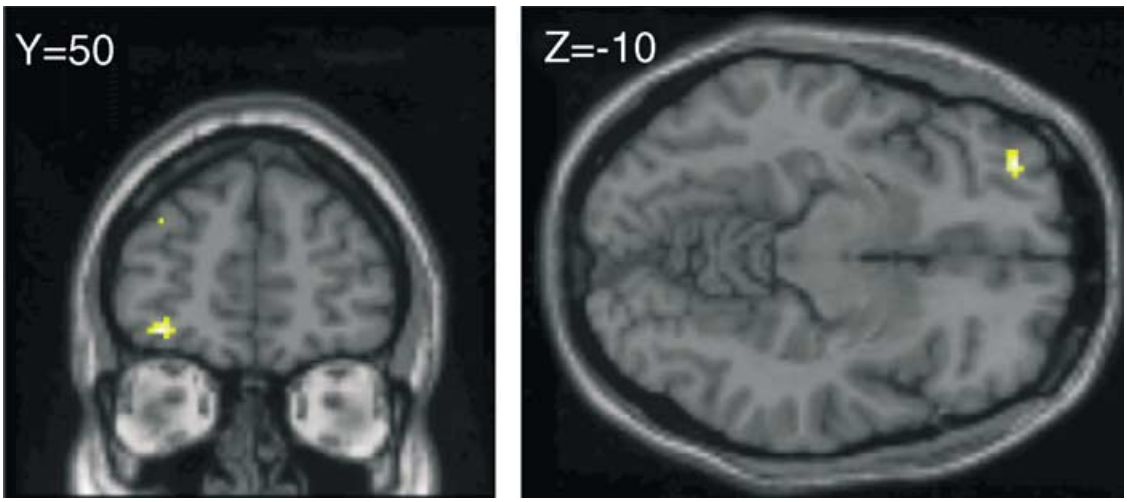
Y=50
Z=-10

FIG. 3.

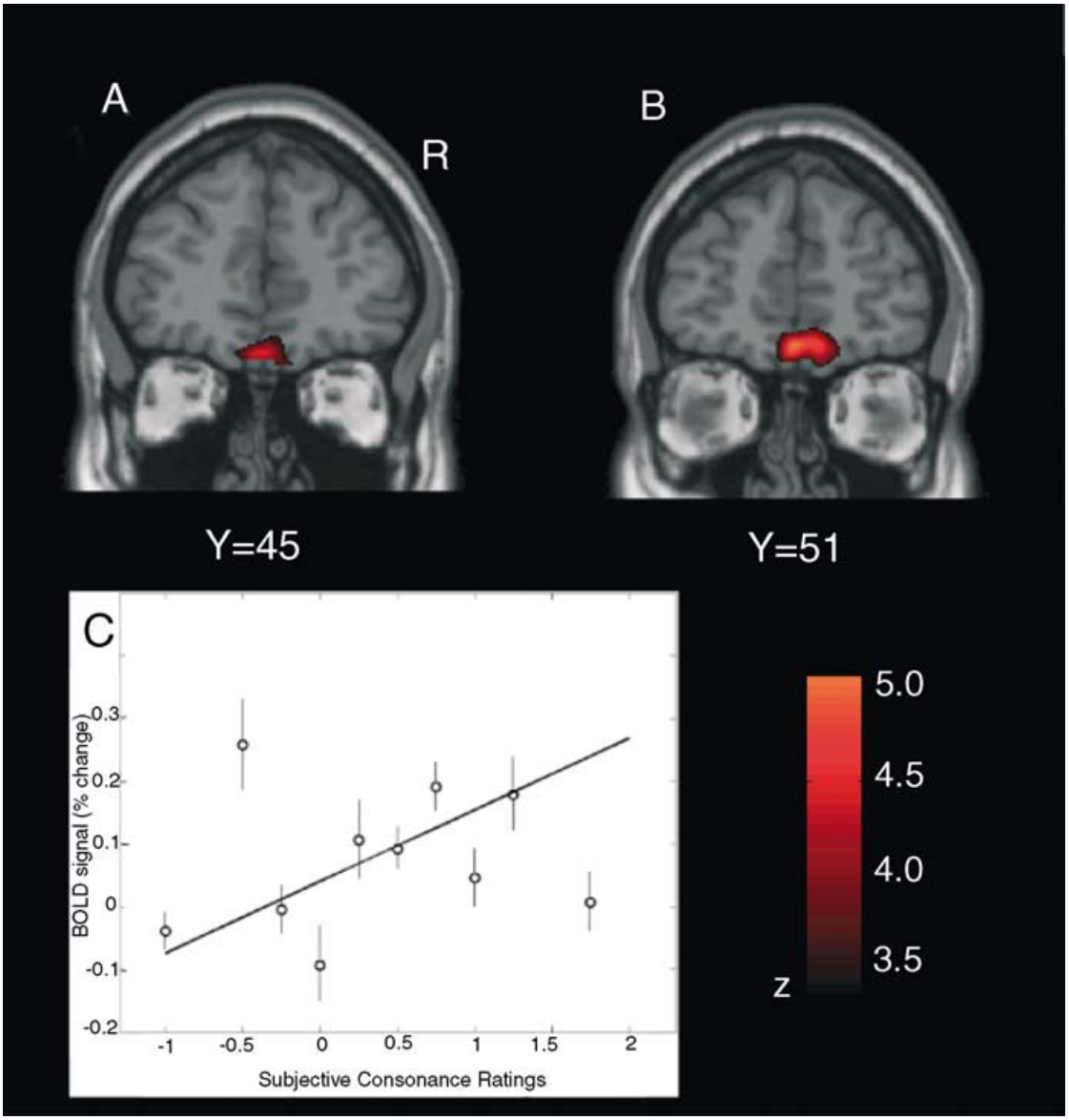
A
R
B
Y=45
Y=51
C
BOLD signal (% change)
0.3
0.2
0.1
0
-0.1
-0.2
-1
-0.5
0
0.5
1
1.5
2
Subjective Consonance Ratings
5.0
4.5
4.0
3.5
z

FIG. 4.

experiment. The odours used were linalyl acetate (floral, sweet), geranyl acetate (floral) and alpha-ionone (woody, slightly food-related), hexanoic acid, octanol and isovaleric acid, the former three odours being considered to be 'pleasant' and the latter three ones 'unpleasant'. The odours were matched to be of similar intensity. A continuous airflow olfactometer was used to deliver a given odourant for a period of 8 s, followed by 24-s of pure air (control condition). All odours were presented birhinally. In order to show brain areas activated by orthonasal olfactory stimuli, a conjunction analysis was performed across the six olfactory conditions [alpha-ionone − control] and [lynalyl acetate − control] and [geranyl acetate − control] and [isovaleric acid − control] and [octanol − control] and [hexanoic acid − control]. The control condition was the clean air flow, and was used to remove possible effects of the orthonasal air stream. Orthonasal olfactory activations were found in the right far anterior (agranular) insular cortex (see Fig. 5A; (45, 15, −9), $Z = 4.07$, $P < 0.01$ SVC). The latter is the exact location (shown in Fig. 2B) found for activations in both [sucrose − tasteless] ($P < 0.05$ corrected, see Fig. 5B) and [strawberry odour − tasteless] ($P < 0.001$ uncorrected) contrasts indicating that this region of the right far anterior (agranular) insula is a site of unimodal taste and (retronasal/orthonasal) olfactory coactivation and thus potentially of convergence (although it must be noted that this region is close to and adjoins the caudal orbitofrontal cortex region showing taste/olfactory convergence from which it is difficult to separate given the spatial filtering used of 8 mm in the anterior-posterior direction). For direct comparison, Fig. 5C shows that there is a part of the far anterior (agranular) insular cortex at $Y = 15$ (and very close to the boundary with the caudal orbitofrontal cortex) that is activated by this retronasal strawberry and unimodal sucrose (MNI coordinates (45, 15, −9); this is the region marked by the cross-lines). The timecourses of the activations measured in these voxels and corresponding to these effects are shown in Fig. 5D, to show that these three different stimulus conditions activate the same brain region in the far anterior (putatively agranular) insular cortex. Thus this far anterior, probably agranular, part of the insular cortex just where it joins the orbitofrontal cortex does receive both taste and olfactory (whether produced retronasally or orthonasally) inputs. Part of the value of the direct comparison provided in Fig. 5A of the effects of orthonasal olfactory stimuli is that this does help to provide clear evidence that the putative agranular insula is a region that responds to odourants when there is nothing in the mouth, and so can be concluded to be a region that can be activated by olfactory stimuli that have no intraoral accompaniment. A close comparison between the orthonasal activations and the activations described in this study is facilitated by the facts that the same imaging system, the same acquisition parameters, the same image resolution, the same spatial filtering, and the same normalization to MNI space were used. Activations in Fig. 5B and C are also shown in the ventral forebrain.

A far anterior, cytoarchitectonically agranular, part of the macaque insula (labelled Ia in Fig. 6) where it adjoins the caudal orbitofrontal cortex receives anatomical connections from the primary olfactory system, as demonstrated by anterograde tracer injections in the macaque piriform cortex (Carmichael *et al*., 1994). This region is very close to the caudal orbitofrontal cortex area that has been defined as the secondary taste cortex by virtue of receiving direct projections from the primary taste cortex (Baylis *et al*., 1995). This secondary cortical taste area is in area 12 and 12/PrCo according to the labelling used in Fig. 6. This same general region is known to contain single neurons in macaques that respond to both taste and olfactory stimuli (Rolls & Baylis, 1994) and where olfactory–taste association learning to produce flavour representations occurs (Rolls *et al*., 1996). (The area extends anteriorly well into the orbitofrontal cortex, as shown by Rolls & Baylis (1994), Rolls *et al*. (1996), and Critchley & Rolls (1996b). This transitional agranular far anterior insular/caudal orbitofrontal cortex area (labelled Ia in Fig. 6) probably corresponds to the region in humans shown to receive olfactory (as confirmed by orthonasal as well as retronasal delivery) and taste inputs in this investigation in humans (see Fig. 6, and also Ongur *et al*., 2003).

Although there has been a previous neuroimaging study on retronasal olfactory stimulation (Cerf-Ducastel & Murphy, 2001), the study described here is the first we know to have analysed activations using both unimodal and bimodal taste and olfactory stimuli, and to have compared retronasal with orthonasal application of olfactory stimuli.

The part of the insular/opercular taste cortex shown to be activated by sucrose in Fig. 1 middle row left centred on the anterior-posterior region $Y = 0$ to $Y = 5$ may be a part of the taste cortex which is unimodal. In confirmation of this, no activation by the orthonasal olfactory stimuli was found in the main part of the opercular/insular taste cortex (Rolls *et al*., 2003a) in the region where activation was produced by the retronasal strawberry stimulus shown in the bottom left slice in Fig. 1A at $Y = -3$. The implication is that this opercular/insular area around $Y = 0$ is in fact not a region that is activated by pure orthonasal olfactory stimuli alone. Its activation by the retronasal strawberry could be because when the odour is delivered in this way, and is combined with some intraoral stimulation including somatosensory inputs which may be produced by the odours in solution or, though the concentration at 25 p.p.m. is likely to be far too low, possibly by minimal taste inputs. [The same conclusion, of no activation of this part of the insula/operculum, was reached when only the three pleasant orthonasal odours were used in the conjunctional analysis just described instead of the six odours, using the dataset described by Rolls *et al*. (2003a)]. This taste insular/opercular region at $Y = 0$ was activated by the retronasally delivered strawberry olfactory stimulus in aqueous solution (Fig. 1, bottom row, left), but this activation may, by comparison with the effects of orthonasally delivered olfactory stimuli, be ascribable to the combination of a retronasal odour and somatosensory inputs produced by liquids in the mouth with a further possible contribution of minor taste or somatosensory inputs produced by the olfactory stimulus in the mouth. (We did control for nontaste related inputs in this study by always using a tasteless control which produced similar somatosensory and tongue movements. The activation described by Cerf-Ducastel & Murphy (2001) in this region by retronasal odour presented in aqueous solution could of course just be due to a taste-related activation by water, which is known to activate

FIG. 3. Interaction effects produced by adding strawberry odour to a sucrose solution. A second-level, random effects analysis based on individual contrasts (for the comparison [sucrose + strawberry mixture] − [sucrose alone + strawberry odour alone]) revealed a significant activation in a lateral part of the left anterior orbitofrontal cortex. The images were thresholded at $P < 0.0001$ for illustration.

FIG. 4. Brain areas where activations were correlated with the subjective ratings for stimulus [taste–odour] consonance and pleasantness. (A) A second-level, random effects analysis based on individual contrasts (the consonance ratings being the only effect of interest) revealed a significant activation in a medial part of the anterior orbitofrontal cortex. (B) Random effects analysis based on the pleasantness ratings showed a significant cluster of activation located in a (nearby) medial part of the anterior orbitofrontal cortex. The images were thresholded at $P < 0.0001$ for illustration. (C) The relation between the BOLD signal from the cluster of voxels in the medial orbitofrontal cortex shown in A and the subjective consonance ratings. The analyses shown included all the stimuli included in this investigation. The means and standard errors of the mean across subjects are shown, together with the regression line, for which $r = 0.52$.

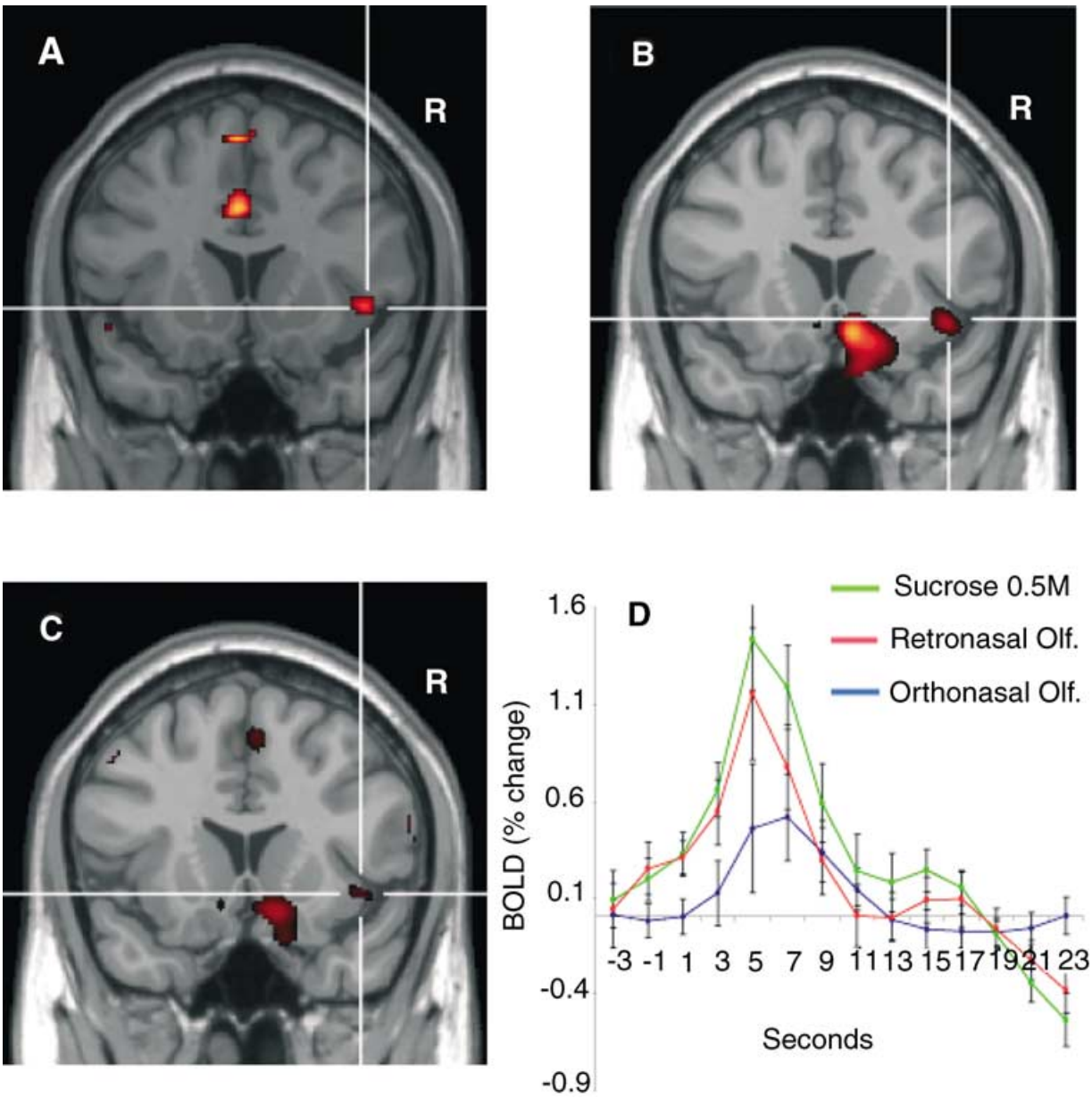

FIG. 5. Coronal slices through the anterior insular cortex showing small region in this brain area found to receive convergent orthonasal olfactory and gustatory input (MNI coordinates (45, 15, −9); this is the region marked by the cross-lines). (A) Responses to orthonasal olfactory stimuli (revealed in a conjunction analysis across [lynalyl acetate – control] and [alpha-ionone – control] and [geranyl acetate – control] and [isovaleric acid – control]) and [octanol – control] and [hexanoic acid – control] from the study of Rolls *et al*. (2003a), using a continuous air-flow olfactometer). (B) Responses to [0.5 M sucrose – tasteless]. (C) The same brain region is activated by a conjunctive comparison of [sucrose – tasteless] and [retronasally administered strawberry odour – tasteless]. (D) Timecourses of activation corresponding to these effects, showing that these three different stimuli activate the same site in the far anterior (putatively agranular) insular cortex at $Y = 15$. The units on the abscissa are in seconds, and on the ordinate are percent of BOLD signal change. Activation in B and C is also shown in the ventral forebrain.

the primary taste cortex, (de Araujo *et al*., 2003b). We further note that the activation produced by orthonasal olfactory stimulation described by Poellinger *et al*. (2001) as being in the frontal operculum is in fact right at the anterior end of the frontal operculum at Talairach coordinates (43, 12, 3) in a region that is very close to the region which we described as agranular insular and where we obtained activation by six different orthonasal olfactory stimuli. Their region is thus several mm anterior to the opercular unimodal taste region at $Y = 0$ to $Y = 5$ in MNI coordinates being discussed here.) It may be that even that at the very low concentration of odour used, 25 p.p.m. of strawberry odour, there was some somatosensory input, and this may be difficult to eliminate if the stimuli are delivered in aqueous solution, as inevitably they will be when eating a real food, the situation at which this study is aimed. Our suggestion thus is that the insular/opercular region at $Y = 0$ in humans is a taste and not olfactory area. It is in the same brain region in humans as the primary taste cortex of macaques to which we believe it corresponds. To enable these areas to be understood in humans by reference to macaques in which the anatomy and physiology has been well established, we show coronal sections through these regions in macaques in Fig. 6. The primary taste cortex of macaques, as defined by anterograde tracing from the taste thalamus (Pritchard *et al*., 1986) and by the presence of taste neurons (Yaxley *et al*., 1990; Rolls, 1997; Scott & Plata-Salaman, 1999; Rolls & Scott, 2003), and labelled G in Fig. 6, is in the anterior insular and adjacent frontal opercular cortex.

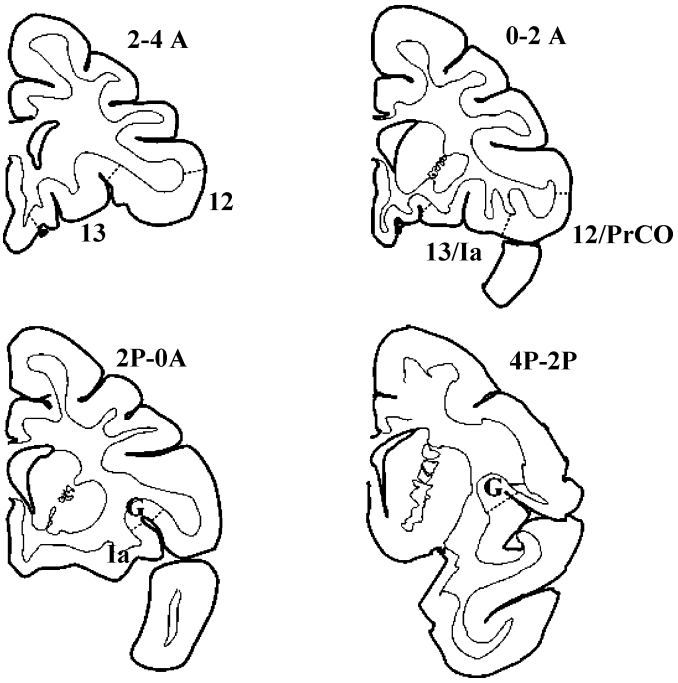

FIG. 6. Coronal slices through the transition area between the caudal part of the orbitofrontal cortex and the anterior insula in the rhesus monkey. Coordinates in the anterior-posterior direction are with respect to the sphenoid (see Aggleton & Passingham, 1981). G, primary taste cortex (extends posterior); Ia, agranular part of the insula; PrCO, precentral opercular cortex; 12, 13, areas of the orbitofrontal cortex. The approximate boundaries of the regions are indicated by dashed lines. The regions are labelled using the nomenclature of Carmichael & Price (1994).

The primary taste cortex of macaques is now known to contain neurons that respond to taste and/or somatosensory inputs which convey information about the texture of food in the mouth, and does not have olfactory or visual responses (Kadohisa *et al*., 2003). In these respects it may be very similar to the human insular/opercular taste cortex at $Y = 0$. Activation in this region by unimodal taste stimuli has also been found by de Araujo *et al*. (2003a), O'Doherty *et al*. (2001b) and Small *et al*. (1999), including water in the mouth (de Araujo *et al*., 2003b).

The caudal orbitofrontal cortex, a main site for olfactory/gustatory convergence in macaques as just described, contains in humans a posterior part (close to $Y = 25$) that responds to sucrose taste and to the [sucrose + strawberry] combined stimulus (see Fig. 1, middle column). At a more anterior level of the orbitofrontal cortex (at $Y = 50$) is the region where there is an activation to the combined [sucrose + strawberry] stimulus which is greater than the sum of the taste or olfactory components, which in this case alone produced little or no activation (see Fig. 3). At a similar level ($Y = 45$, but more medially) is the region where the BOLD signal correlates with the subjective rating of the consonance of the stimuli (Fig. 4A). At a similar level anteriorly ($Y = 50$, and again medially) is the part of the OFC where the BOLD signal correlates with the subjective rating of the pleasantness of the stimuli (Fig. 4B). This medial OFC region is close to that which activation has been shown to be related to other affectively positive stimuli such as pleasant odours (Zatorre *et al*., 1992; Zald & Pardo, 1997; Anderson *et al*., 2003; Rolls *et al*., 2003a), taste (O'Doherty *et al*., 2001b; Small *et al*., 2001), pleasant touch (Rolls *et al*., 2003b), monetary reward (O'Doherty *et al*., 2001a), and intraoral water under fluid deprivation (de Araujo *et al*., 2003b). There is additional strong evidence at the level of the single neuron that neurons in the OFC respond in relation to the reward value of taste (Rolls *et al*., 1989), olfactory, and visual stimuli (Critchley & Rolls, 1996a; Rolls *et al*., 1996; Rolls, 1999, 2000).

With respect to the amygdala, anterograde tracers placed into the olfactory bulb label axons in the anterior cortical nucleus of the amygdala and periamygdaloid cortex (Carmichael *et al*., 1994); and projections from the primary taste cortex reach the central nucleus of the amygdala (Scott & Plata-Salaman, 1999). The primate amygdala contains taste neurons (Rolls & Scott, 2003), and activation of the human amygdala by a pleasant taste, glucose, and an aversive taste, saline, has been described (O'Doherty *et al*., 2001b). Activation of the human amygdala by both olfactory and taste stimuli is described here for the first time.

The anterior cingulate activations shown in this study are in regions known to respond to odours (Rolls *et al*., 2003a) and taste stimuli (de Araujo *et al*., 2003a). It is known that areas 23/24 of the ACC receive projections from the agranular part of the insula as shown by axonal tracer methods (Vogt & Pandya, 1987), and this could be one source of such inputs. Another possible source is the orbitofrontal cortex (Cavada *et al*., 2000).

One of the goals of our study was to determine which brain areas show non–linear interactions between taste and olfactory stimuli, i.e. which areas are more strongly activated by the combination [sucrose + strawberry] odour than by the sum of any activations produced by the two stimuli presented separately. The analysis reveals significant activation of this type in a part of the left anterior OFC. Interestingly, an adjacent region was shown to respond to the enhancement of umami taste produced by adding 5′-ribonucleotides to monosodium glutamate (de Araujo *et al*., 2003a). The primate OFC is known to be a site of multimodal integration (Rolls, 1999, 2000) and neurons in this area are involved in encoding information about the sensory properties of complex combinations of stimuli. The activation produced by the olfactory–taste combination stimulus in this study in comparison with the sum of any activation produced by each separately is the type of evidence obtainable by fMRI that two stimuli interact, and thus provides evidence that this region is an important area in humans too not only of functional convergence of taste and olfactory stimuli, but also of effects produced by particular combinations of taste and olfactory stimuli.

Finally, we aimed in this study to assess the representation in the human brain of the affective and hedonic properties of taste–olfactory stimulus combinations. In particular we were interested in determining which brain areas are involved in representing the degree of 'consonance' or 'matching' between taste and olfactory stimuli. A correlation analysis using the subjective ratings as parameters revealed a significant activation in the anterior medial OFC (Fig. 4). This result is consistent with other evidence that the OFC also represents information about the reward value of primary and secondary reinforcers including taste (O'Doherty *et al*., 2001b; Small *et al*., 2001), odour (Zatorre *et al*., 1992; Zald & Pardo, 1997; Anderson *et al*., 2003; Rolls *et al*., 2003a), somatosensory (Rolls *et al*., 2003b) and even abstract monetary rewards (O'Doherty *et al*., 2001a). Also, we have found that pleasant olfactory stimuli activate a far anterior part of the medial OFC, with aversive olfactory stimuli a slightly more posterior region (Rolls *et al*., 2003a). The area activated in the correlation analysis shown in Fig. 4 is close to the area in which pleasant olfactory stimuli are represented.

In conclusion, the far anterior (putatively agranular) insular cortex, the caudal OFC, the amygdala, and the ACC seem likely from this investigation to support flavour perception. Of these, it is the OFC which shows the most interesting evidence of being closely related to the representation of flavour, in that a part of this region showed activation to combined olfactory and taste stimuli that was greater than

the sum of any activation produced by each alone, and a nearby part of the medial OFC has activations that are correlated with the subjective consonance between olfactory and taste stimuli (such as sweet and strawberry), and with the pleasantness of the olfactory and taste stimuli and their combination.

Abbreviations

ACC, anterior cingulate cortex; MNI, Montreal Neurological Institute; MSG, monosodium glutamate; OFC, orbitofrontal cortex; PET, positron emission tomography; SMA, supplementary motor area; SPM, Statistical Parametric Mapping; SVC, small volume correction.

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