Activation of the Human Orbitofrontal Cortex to a Liquid Food Stimulus is Correlated with its Subjective Pleasantness

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Single-neuron recording studies in non-human primates indicate that orbitofrontal cortex neurons represent the reward value of the sight, smell and taste of food, and even changes in the relative reward value, but provide no direct evidence on brain activity that is correlated with subjective reports of the pleasantness of food. In this fMRI investigation we report a significant correlation between the activation of a region of the human orbitofrontal cortex and the decrease in subjective pleasantness when a liquid food is eaten to satiety. Moreover, a cluster of voxels in the orbitofrontal cortex showed a decrease in its activation that was specific to the particular liquid food consumed in a meal, providing a neural correlate of sensory-specific satiety to a liquid whole food in humans. This sensory-specific reduction in activation of the orbitofrontal cortex correlating with subjective pleasantness is consistent with an important role for the orbitofrontal cortex in human emotion and motivation, and associated subjective states.

Introduction

The primate orbitofrontal cortex contains the secondary taste cortex, in that it receives projections directly from the primary taste cortex (Baylis *et al.*, 1994; Öngur and Price, 2000). This secondary taste cortex represents the reward value of taste, in that its taste neurons only respond to food when a monkey is hungry (Rolls *et al.*, 1989; Rolls, 1999, 2000). The orbitofrontal cortex also contains the secondary and tertiary olfactory cortical areas (Öngur and Price, 2000), and olfactory neurons in it represent the reward value of odor in that they only respond to the smell of a food if the monkey is hungry (Critchley and Rolls, 1996). The orbitofrontal cortex also has neurons in it that respond to the texture of fat in the mouth, and these neurons too only respond to fat in the mouth when the monkey is hungry. The primate orbitofrontal cortex also receives inputs from the inferior temporal cortical visual areas, and orbitofrontal cortex neurons with responses to the sight of food only respond to the sight of the food if hunger is present (Critchley and Rolls, 1996). In all these cases, the decrease in neuronal response to a food as the monkey is fed to satiety is partly specific to the food eaten, and this mechanism reflected in eating behavior is known as sensory-specific satiety (Rolls *et al.*, 1981a). Sensory-specific satiety refers to the fact that even after one food is fed to satiety, humans and other animals find other foods rewarding, and will still eat some of these other foods. Sensory-specific satiety could have evolved as a mechanism to encourage a varied diet, thus maximizing the probability of ingesting all of the nutrients necessary for survival, and may be a fundamental principle by which goal-directed behavior is controlled (Rolls, 1999).

Sensory-specific satiety is a particularly useful phenomenon for studying affective representation in the brain, as it provides a means of altering the affective value of a stimulus, without modifying its physical attributes. As a consequence, any differences observed between the representation of a particular food stimulus in the brain before and after satiety can be attributed to the change in the reward value. This controls for possible confounds such as increases in thirst, gastric distension and changes in blood glucose levels after feeding, by virtue of the fact that the neural response to another food, which is not eaten in the meal is also measured. Sensory-specific satiety effects are strongest when using quite different foods such as, for example, tomato juice (savory) and chocolate milk (sweet) (Rolls *et al.*, 1981a,b, 1982).

One aim of the present study was to use functional neuroimaging to obtain correlations between brain activity and the subjective emotion-related effects produced by whole food (i.e. taste, olfaction and texture) delivered in liquid form in a sensory-specific satiety paradigm. A second aim was to investigate which brain areas are activated by a whole food independently of satiation (and so might represent the whole range of sensory properties of the liquid food, including taste, olfactory, and texture components), and in which brain areas the responses to a liquid food were modulated by satiation (and so might reflect the affective properties of the whole food). A third aim was to extend our understanding of the brain regions that represent the reward value of food to humans. Studies that have investigated the effect of feeding to satiety on the responses of orbitofrontal cortex neurons to the taste (Rolls *et al.*, 1989), sight, odor (Critchley and Rolls, 1996) and texture (Rolls *et al.*, 1999) of food have shown that as the food is fed to satiety, there is a gradual decrease while a food is being fed to satiety in the neuronal response to that food yet a continuing neuronal response to other foods not being fed to satiety, and that this relative responsiveness of the neurons reflects the preference of the monkeys for the foods. It is thus the relative reward value of taste, olfactory, visual and texture stimuli that is represented in the orbitofrontal cortex. Further evidence for this was obtained in a study that also showed that neuronal responses in the macaque orbitofrontal cortex reflect relative reward preference (Tremblay and Schultz, 1999). However, there have been few previous neuroimaging studies that have investigated where the relative reward value of different stimuli is represented in the human brain, let alone of where the brain activity is directly correlated with the *subjective pleasantness* of the food. In one study, we showed that olfactory sensory-specific satiety resulted in less activation in the human orbitofrontal cortex to the odor of banana (O'Doherty *et al.*, 2000). In a recent PET study by Small *et al.* (Small *et al.*, 2001), the metabolism of the orbitofrontal cortex (and other brain regions) were found to alter after feeding chocolate to satiety, but due to the design of the experiment these changes could be related to the subjects' overall level of satiety rather than the pleasantness *per se*, and in addition, a sensory-specific satiety design was not used, so that the study does not address the changes that occur to different foods when one is eaten to satiety. That study also used water as a comparison stimulus, which made the results difficult to interpret,

because water in the mouth is known to activate many neurons in the primate orbitofrontal cortex (Rolls *et al*., 1990). In the present investigation we used an event-related fMRI approach so that with its reasonable temporal resolution responses to the sensory stimulation produced by a whole food could be measured; and used a tasteless solution as an appropriate control.

Materials and Methods

Subjects and Materials

Ten healthy right-handed male subjects participated in the experiment. We chose to recruit only male subjects as female students are in some cases restrained eaters and eat little in a study of this type (Rolls and Rolls, 1997). The average age of the subjects was 28.5 (range: 22–38). Subjects refrained from eating for at least 6 h prior to arriving at the imaging center on the day of the experiment in the late afternoon. Prior to participation in the experiment, the subjects were pre-screened to ensure that they found both tomato juice and chocolate milk to be pleasant, and to ensure that they were not overweight or on a diet or planning to go on a diet. Both liquid foods are administrable in liquid form, palatable at room temperature and the clear difference in their flavor and texture helps to facilitate sensory-specific satiety effects and minimizes the likelihood of the subjects developing a generalized satiety to both liquid foods.

Before feeding, the subjects were placed in the scanner, and scanned while being presented with each of the two liquid food stimuli, as well as a tasteless control solution which was delivered to the subject's mouth through three polythene tubes that were held between the lips. Each tube of ~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). One reservoir contained the chocolate milk, another contained the tomato juice and a third reservoir contained a tasteless control solution with the main ionic components of saliva (consisting of 25 mM KCl and 2.5 mM $NaHCO_3$). We used a block design, with each epoch lasting 16 s. At the beginning of each epoch, 0.75 ml of one of the liquid foods (or the control solution) was delivered to the subject's mouth in under 0.5 s on average. The subject was then instructed to roll the stimulus around on the tongue, and was then cued to swallow the stimulus (using a visual cue) after 10 s. The stimuli were delivered in an interleaved manner for each epoch, such that the subjects received tomato juice in one epoch, followed by the tasteless control solution, followed by the chocolate milk, and then followed again by the tasteless control solution. This cycle was repeated 16 times. At three points during the imaging run, there was an additional 16 s period following the presentation of each stimulus (at cycles 4, 8 and 12), during which no taste stimulus was delivered. Instead, subjects were presented with a visual rating scale ranging from +2 (very pleasant) to –2 (very unpleasant) in 0.25 increments, and had to rate the subjective pleasantness of the preceding liquid food stimulus by moving a vertical bar to the appropriate point on the scale through the use of a button box.

After the initial scanning run, the subjects were taken out of the scanner and fed to satiety on one of the liquid foods. The subjects were instructed to consume the liquid foods for their lunch and were asked to drink as much as they could until they absolutely did not want to have any more. The liquid food was poured into a 150 ml cup and offered to the subject. Once the subject had consumed the contents of the cup, it was then refilled. This was repeated a number of times until the subject was completely satiated and refused the offer of an additional cup. To achieve a balanced design, five subjects were fed to satiety on tomato juice and five subjects were fed to satiety on the chocolate milk. Each subject was randomly allocated one of the two liquid foods for their meal and the subjects were not informed in advance (until after the first imaging run) which liquid food they would be invited to consume. Subjects fed to satiety on tomato juice consumed on average 915 ml (range 750–1100 ml), whereas subjects fed to satiety on chocolate milk consumed on average 1160 ml (range 900–1450 ml). This led to a highly significant decrease for both the hunger and thirst ratings across subjects. Each subject gave four ratings of hunger and four ratings of thirst throughout the experiment on a visual analog rating scale. The scale used for the subjective ratings ranges from +2 (very hungry/very thirsty) to –2 (not at all hungry/not at all thirsty). The four sets of ratings were taken at the following times: one set of ratings of both hunger and thirst was taken before the experiment started, another set of ratings was taken immediately after the first imaging run but before feeding, another set of ratings was taken immediately after feeding, and finally another set of ratings were taken at the end of the experiment. The average hunger rating just before feeding changed from 1.33 ± 0.18 (mean ± SEM) in the pre-satiety phase to –0.92 ± 0.32 just after feeding in the post-satiety phase ($P < 0.0009$; $t = 5.15$; d.f. = 8), while the average thirst ratings changed from 0.81 ± 0.22 (mean ± SEM) in the pre-satiety phase to –1.06 ± 0.32 in the post-satiety phase ($P < 0.0008$; $t = 5.20$; d.f. = 8). Once the subjects had finished their meal, they were then placed back into the scanner and the scanning procedure was repeated.

The details of the pleasantness and intensity ratings were as follows. Each subject gave 12 sets of pleasantness ratings and six sets of intensity ratings for each of the two stimuli during the experiment. (Intensity ratings were not taken while subjects were in the scanner.) During the pre-satiation phase seven sets of pleasantness ratings and four sets of intensity ratings were taken: three sets of pleasantness and intensity ratings were taken initially before the scanning session on a visual analog scale to ensure that the subjects were fully familiar with the rating scales. This was then followed by three sets of pleasantness ratings taken inside the scanner throughout the scanning session on a visual analog rating scale. One set of both pleasantness and intensity ratings was then taken outside the scanner after the scanning session just before feeding. During the post-satiation phase five sets of pleasantness ratings and two sets of intensity ratings were taken: one set of both pleasantness and intensity ratings were taken outside the scanner just after satiation, three sets of pleasantness ratings inside the scanner during the scanning session, and one set of both pleasantness and intensity ratings outside the scanner after the scanning session.

Ratings assessed outside the scanner were taken following an identical procedure to that employed when the subject was in the scanner. There were no significant differences ($P > 0.05$; paired *t*-tests on means) in the pleasantness ratings given by subjects whether assessed in or outside the scanner, when comparing the means across subjects. These results show that even in the unusual, noisy and somewhat uncomfortable environment of the scanner, subjects nevertheless found the liquid food stimuli to be as subjectively pleasant as they did when outside the scanner.

MRI Acquisition

Imaging was conducted using a 3.0 T VARIAN/SIEMENS (Palo Alto, CA) whole-body scanner at the Oxford Centre for Functional Magnetic Resonance Imaging (FMRIB, Oxford, UK). Fourteen T_2*-weighted coronal EPI slices were acquired every 2 s ($T_R = 2$ s). The following parameters were carefully selected in order to minimize susceptibility and distortion artifact in the orbitofrontal cortex (Wilson *et al*., 2002). Firstly, the data were acquired in a coronal rather than axial slicing direction, as this aligned the slices to be perpendicular to the predominant direction of the intrinsic susceptibility induced field gradients, and helps to minimize through plane dephasing. Secondly, the voxel resolution was minimized by using 3 mm in-plane resolution and a 7 mm slice thickness which results in less phase cancellation than would be produced by lower voxel resolutions. Thirdly, a relatively low T_E of 25 ms was selected to decrease the signal dropout, as less phase dispersion is created across the voxels. Fourthly, each subject was individually shimmed using both linear and second order shimming to minimize static field inhomogeneities in the orbitofrontal cortex. Finally, geometric distortion was minimized by using a specialist head insert gradient coil (Magnex SGRAD III, Abingdon, UK) with a relatively high gradient switching frequency of 960 Hz.

The total number of functional volumes acquired in each imaging run was 564 which corresponds to a total imaging time of 18 min and 48 s. Coverage was obtained from +60 (A/P) to –38 (A/P). The same imaging protocol was used for both the pre- and post-satiety runs. After the second run, a full-brain EPI (3 mm in-plane resolution, 7 mm slice thickness) and a structural T_1 volume were acquired (0.75 mm in-plane resolution, 7 mm slice thickness).

Image Analysis

The image analysis was carried out using SPM99 (Wellcome Institute of Cognitive Neurology, London, UK) implemented in Matlab (Mathworks, Inc., Sherborn, MA). One subject was excluded from the analysis (who

had consumed tomato juice to satiety) due to excessive motion during the post-satiety imaging run. The data were corrected for motion (the volumes from the second imaging run were aligned to the volumes from the first imaging run), globally normalized (and resampled to 2 × 2 × 2 voxels) using FLIRT (Jenkinson and Smith, 2001), and spatially filtered (using FWHM of 10 mm). Low and high pass temporal filtering were also applied to the data. A statistical parametric map was generated for each individual subject by fitting a box-car function to each combined dataset, convolved with the hemodynamic response function and its temporal derivative. When constructing the model the 'OFF' (*control*) periods were modeled explicitly at the times where the tasteless solution was delivered. The stimulus deliveries were classified into pre- and post-satiety and according to whether the subject was fed on the stimuli. If the subject was fed on tomato juice, the deliveries of tomato juice before satiation were classified as preFed and those after satiation was classified as postFed, while the deliveries of chocolate milk before satiation were classified as preUnFed and those after satiation were classified as postUnfed. Similarly, if the subject was fed on chocolate milk, the deliveries of chocolate milk before satiation were classified as preFed and those after satiation was classified as postFed, while the deliveries of tomato juice before satiation were classified as preUnFed and those after satiation were classified as postUnfed.

In the SPM99 analysis, the main effects of liquid in the mouth (independently of satiation) were investigated by performing a contrast for individual subjects for the areas activated by liquid food in the mouth (which could be produced by the taste, texture or smell of the liquid food stimulus) relative to the control condition (tasteless solution in the mouth). The contrast used was (preFed-control) + (preUnfed-control) + (postFed-control) + (postUnfed-control).

To test for sensory-specific satiety-related effects, the data were split into two groups according to what liquid food the subjects were fed, and for these two groups brain regions with changes specific to the food eaten to satiety were modeled by the contrast: [(preFed + preUnfed + postUnfed)/3 – postFed] (O'Doherty *et al.*, 2000), and a further conjunction analysis of the results from the two groups was then performed. 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-correlated artifact.

In order to determine the brain regions which showed activation that correlated with the subjective pleasantness of the liquid foods as rated by the subjects only when in the scanner, another model was constructed in which the six pleasantness ratings made for each stimulus were used as regressors by setting up a time series in which the size of the hemodynamic response function at each trial was set to the magnitude of the pleasantness subjective rating made by the subject for that stimulus (for each subject's dataset, the six pleasantness ratings given to the chocolate milk and six pleasantness ratings given to the tomato juice in the scanner were interpolated across the dataset). This model was then fitted to the functional data for each subject and a second level random effects group analysis was conducted. A simple contrast of the effects of this parametric series then yielded those voxels, which showed changes in BOLD activation that was significantly correlated with the changes in the subjective ratings made by each subject during the experiment. The average change of the BOLD signal produced by liquid food in the mouth at the voxels showing a significant correlation between the pleasantness ratings and the BOLD signal was also obtained. This was calculated by subtracting the maximum intensity of the peak voxels in each significantly activated cluster in the correlation analysis from the average intensity value for that voxel across the whole time series for each condition.

Results

Subjective Sensory-specific Satiety Effects

As shown in Figure 1*A*, the subjects showed very clear evidence of sensory-specific satiety in that the subjective pleasantness of the liquid food eaten decreased markedly from pre- to post-satiety, whereas the pleasantness of the liquid food not eaten did not show such a decrease. The sensory-specific decrease in the pleasantness of the liquid food eaten to satiety relative to the liquid food not eaten was highly statistically significant [as shown by a repeated measures two-way ANOVA, $F(1,8) = 62.3$, $P < 0.0002$]. On the other hand, no significant changes were found in the perceived intensity of the liquid food stimuli when comparing pre- to post-satiety ratings ($P > 0.05$), indicating that it is the perceived pleasantness and not the perceived intensity of the liquid food that decreases following satiation (Rolls *et al.*, 1983).

Brain Areas with Activation that Is Correlated with the Changes in Subjective Pleasantness Ratings that Occur to the Liquid Foods within Each Individual

We were able to directly correlate the changes in the BOLD signals throughout the brain with the subjective pleasantness that occurred during the experiment in individual subjects. The correlation was made possible by the fact that each subject provided 12 ratings of the pleasantness of the liquid foods which could be correlated with the values of the BOLD signal in different voxels taken at corresponding times. The mean pleasantness ratings obtained from all subjects are shown in Figure 1*C*. To perform the correlation analysis the subjective pleasantness ratings made in the scanner by each subject to each liquid food were interpolated across the whole time series, and used as regressors in a general linear model fitted to the changes in BOLD signal in each voxel. This enabled us to determine whether the changes in BOLD signal in any region of the orbitofrontal cortex or other brain area were correlated with the changes in the subjective pleasantness of the liquid food stimuli following satiety.

The random effects group analysis across all nine subjects revealed a highly significant correlation of the pleasantness ratings with activation of the left orbitofrontal cortex (with the peak of the cluster found at $x, y, z = -22, 34, -8$; $z = 4.06$, $P < 0.05$, small volume correction). The orbitofrontal cortex site of this correlation with the pleasantness ratings is shown in Figure 2, together with a graph of the fitted hemodynamic responses in the region plotted against the pleasantness ratings. A region in the right orbitofrontal cortex (Talairach coordinates $x, y, z = 12, 26, -28$, z-score = 2.85) was also found to correlate with the subjective ratings, but just below the significance level chosen. We performed a further analysis of the activation in the peak voxels identified by the correlation with subjective ratings. The results of this analysis are shown in Figure 1*B*, where the mean change in the BOLD signal for peak voxels in this area is plotted for the responses to the two liquid foods before and after feeding to satiety. As can be seen from Figure 1*B*, the BOLD signal shows a clear sensory-specific satiety related profile, decreasing markedly for the liquid food eaten following satiety, but showing no such decrease for the liquid food that was not eaten in the meal.

The mean percent change in BOLD signal produced by the two liquid foods in this region showed a significant effect of sensory-specific satiety across subjects [a repeated measures two-way ANOVA (liquid food eaten versus liquid food not eaten × hungry versus satiated) revealed a highly significant two-way interaction: $F(1,8) = 39.3$; $P < 0.0005$]. The extent to which the activation in this region is related to the subjects' own subjective pleasantness ratings of the two liquid foods can be appreciated by comparing the percentage change in the BOLD signal to the subjects' own subjective pleasantness ratings (see Fig. 1).

Some other brain areas were also found to show correlations between the BOLD signal and the pleasantness changes asso-

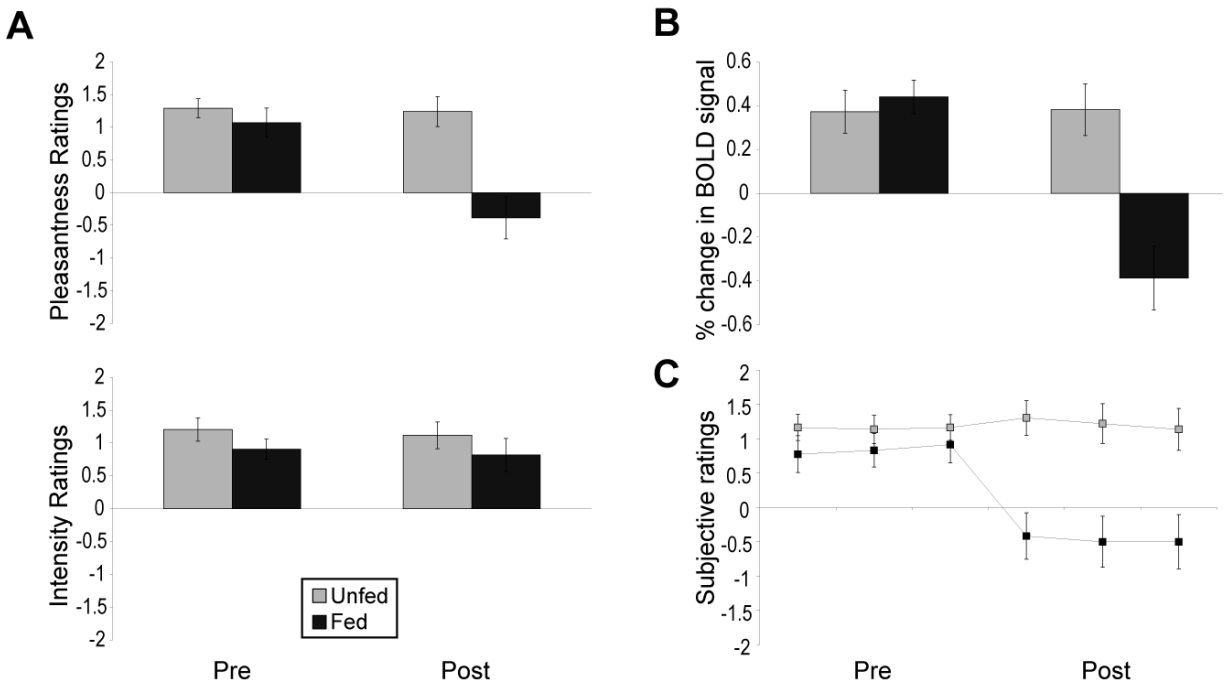

Figure 1. Subjective pleasantness and intensity ratings and mean percent change in the BOLD signal. (*A*) The average change in the subjective pleasantness and intensity ratings for the food fed and the food unfed for all nine subjects. The pleasantness ratings pre-satiety for each of the food stimuli were averaged over the seven ratings taken inside and outside the scanner and the pleasantness ratings post-satiety were averaged across five ratings across the nine subjects. Thus each pleasantness data-point pre-satiety is averaged across 63 values, while each data-points post-satiety is averaged over 45 values. The intensity ratings pre-satiety for each of the food stimuli were averaged over the four ratings taken inside and outside the scanner and the intensity ratings post-satiety were averaged across two ratings across the nine subjects. Thus each intensity data-point pre-satiety is averaged across 36 values, while each data-point post-satiety is averaged over 18 values. (*B*) The mean percent change in the BOLD signal across subjects of peak voxels in the OFC that showed a significant correlation with the subjective pleasantness ratings taken in the scanner before and after satiety. (*C*) The mean subjective pleasantness ratings taken during the experiment while in the scanner to show the subjective data that were obtained for correlation analysis with the BOLD signal. The error bars depict the standard error of the mean. The scale used in the figure for the subjective pleasantness ratings ranges from +2 (very pleasant) to –2 (very unpleasant), and for the intensity ratings ranges from +2 (very intense) to –2 (very weak).

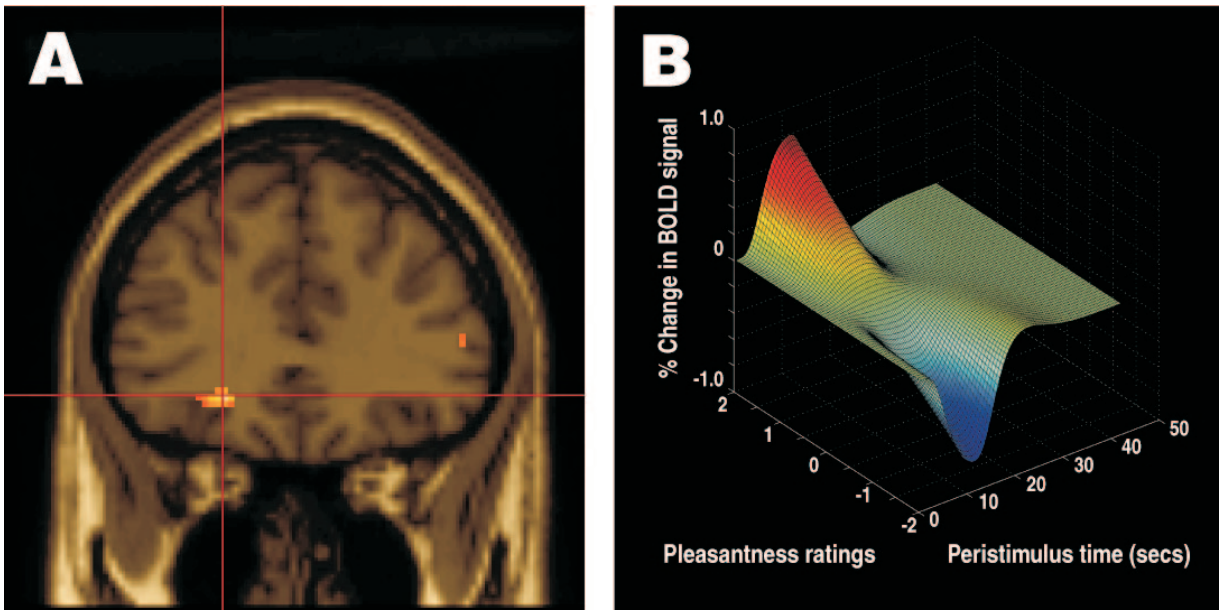

Figure 2. Areas of the human OFC correlating with pleasantness ratings. (*A*) Coronal section through the region of the orbitofrontal cortex from the random effects group analysis showing the peak in the left orbitofrontal cortex (Talairach coordinates *x*, *y*, *z* = –22, 34, –8, *z*-score = 4.06), in which the BOLD signal in the voxels shown in yellow was significantly correlated with the subjects' subjective pleasantness ratings of the foods throughout the experiment. A region in the right orbitofrontal cortex (Talairach coordinates *x*, *y*, *z* = 12, 26, –28, *z*-score = 2.85) just below significance chosen was also found to correlate with the subjective ratings. (*B*) Plot of the magnitude of the fitted hemodynamic response from a representative single subject against the subjective pleasantness ratings (on a scale from –2 to +2) and peristimulus time in seconds.

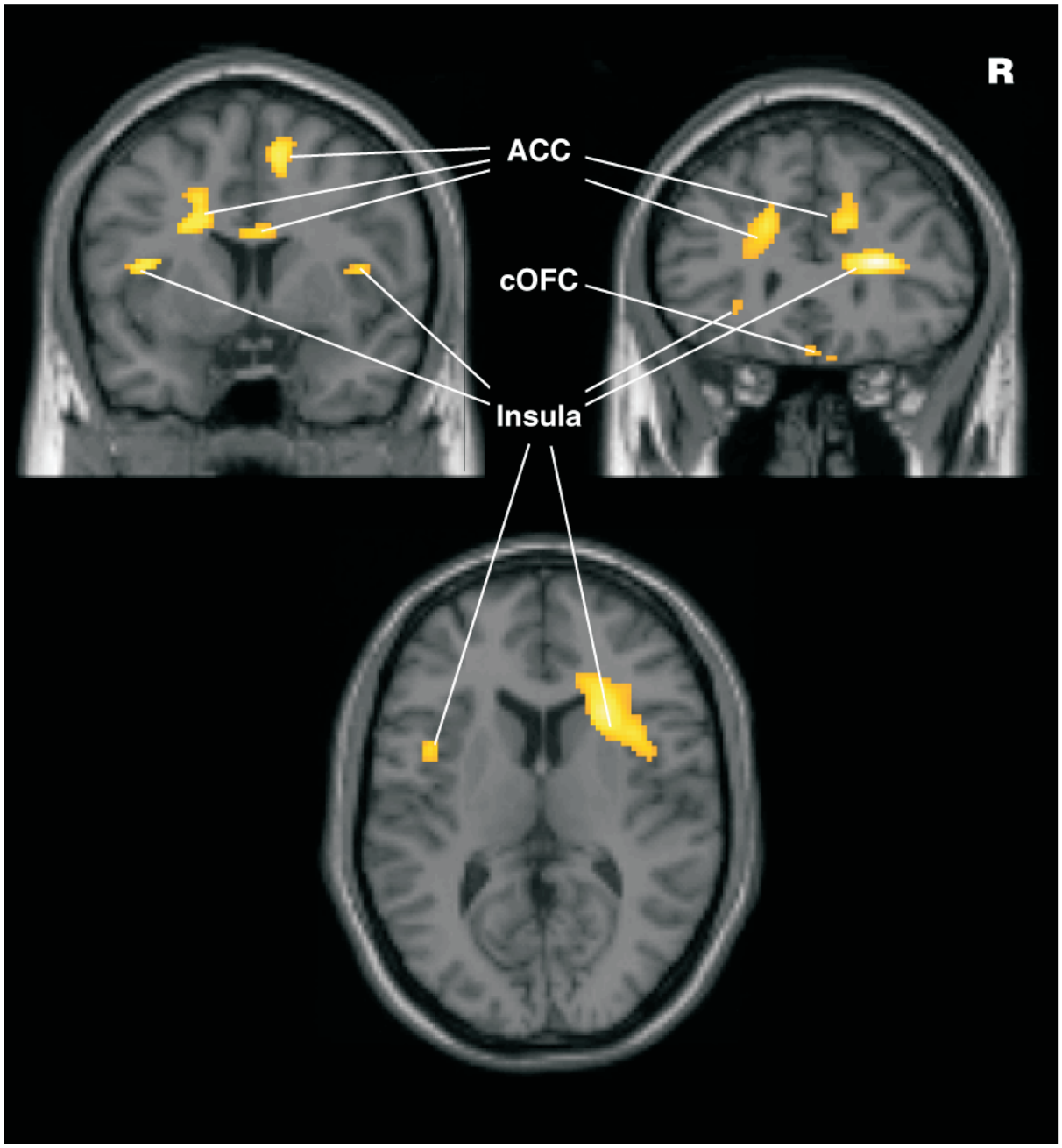

Figure 3. Brain areas activated by the flavor of liquid food. The figure shows those areas activated by the main effect of the flavor of liquid food, i.e. food minus control tasteless solution ($P < 0.05$, corrected for multiple comparisons). Most significantly areas of bilateral insula/operculum were activated by the flavor of liquid food along with regions of the caudal orbitofrontal cortex (cOFC) and anterior cingulate cortex (ACC). Coronal slices are shown above, and axial below.

ciated with sensory-specific satiety, albeit below the rigorous statistical threshold applied ($P < 0.05$, corrected for multiple comparisons). These areas include the posterior dorsal insula in what is a putative somatosensory region, part of the somatosensory cortex (SI) (in the face area), and also bilaterally in part of what is putatively higher order somatosensory cortex, SII, in the parietal operculum.

Brain Areas Activated by the Flavor of Liquid Food

The experimental paradigm allowed further conclusions to be reached about how the effects of liquid food in the mouth, which will have taste, texture and olfactory components, is represented in the brain. These components will contribute to the flavor of the liquid food (which we consider for the purposes of this paper to be a sensation contributed to by two or more of these components). Figure 3 shows the areas activated by the liquid whole food compared with the control tasteless solution (the main effect analysis described in Materials and Methods). (All areas shown are significant at $P < 0.05$ corrected for multiple com- parisons.) The most significant activation was found in the anterior insula (peaks at $x, y, z = 26, 26, 14$; $z > 8$), which is part of the putative human primary taste cortex. Activations were also found in relatively caudal parts of the orbitofrontal cortex (16, 38, –22; $z = 5.48$; cluster size: 28) and (2, 30, –22; $z = 4.64$; cluster size: 8) (just anterior to the insula/operculum). In this caudal part of the orbitofrontal cortex the activation to the liquid

whole foods was independent of the state of satiation. Other highly significant activations were also found in regions of the (right) anterior cingulate cortex (16, 20, 36; z = 5.26 and 16, 8, 58; z = 4.93), where also there was no effect of feeding to satiety.

Brain Areas Showing Sensory-specific Effects to the Flavor of Liquid Food

Another way to investigate the brain areas in which satiety influences the representation of liquid food is to compare the brain activations produced by liquid foods when hungry and satiated (rather than performing a correlation with subjective pleasantness as described above). This approach was taken by analyzing the brain areas that showed sensory-specific satiation effects, that is where the brain activation was less to a liquid food eaten to satiety in a meal compared with the activation produced by a different liquid food not eaten to satiety (see Materials and Methods for the specification of the contrast used to reveal sensory-specific satiety effects).

We were also interested in the satiation effects of food type and we therefore divided the dataset into two groups according to what liquid food the subjects were asked to consume. It was found that very similar regions of the orbitofrontal cortex were activated in the sensory-specific satiety contrast for both tomato juice (–26, 45, –8; z = 3.83) and for chocolate milk (–24, 42, –12; z = 3.37). This was further confirmed by performing a conjunction of the two contrasts, which showed that a region of the orbitofrontal cortex (–33, 44, –12; z = 3.22) showed sensory-specific satiety effects for both the chocolate milk and for the tomato juice. In addition, bilateral regions of the posterior insula (48, –14, 22; z = 5.05; –30, –14, –6; z = 5.46) and ventral striatum (24, 16, –6; z = 5.37; –24, 10, 0; z = 5.61) were activated only in the group of subjects who were fed on chocolate milk, and showed a sensory-specific satiety-related change of activation for the chocolate milk.

Discussion

The results of this study show that there is a significant correlation between the activation of a region of the human orbitofrontal cortex and the subjective pleasantness reported by humans produced by the flavor of a liquid food. The results were obtained in conditions in which the subjective pleasantness of a liquid food could be altered by allowing human subjects to eat a liquid food to satiety. The results show moreover that the sensory-specific nature of the pleasure is represented in the human orbitofrontal cortex, and emphasize the importance of sensory-specific alterations in the pleasure and reward value of stimuli that influence human behavior (Rolls, 1999). To our knowledge, this is the first time that a direct correlation has been reported between a subjective state of pleasure induced by a primary (unlearned) reinforcer and the activation of a brain area measured in an event-related fMRI design where individual activations are produced each time the stimulus is delivered. In an earlier study we showed that olfactory sensory-specific satiety produced by eating banana to satiety produced a sensory-specific reduction in the activation of the human orbitofrontal cortex to the odor of banana (O'Doherty *et al.*, 2000), but that study did not include a correlation with subjective pleasantness ratings. The results of the current study extend the earlier finding by using complex liquid food stimuli with at least three sensory qualities (odor, taste and texture). This led to the interesting result that although the activations produced by the delivery of the taste, odor and texture combination produced by the liquid food activated quite extensive brain areas (see Fig. 3) (which are likely to be more extensive than those activated by olfactory stimuli alone) (O'Doherty *et al.*, 2000; de Araujo *et al.*, 2002), nevertheless the effects that were related to sensory-specific satiety were found in the present multimodal food stimulus study still mainly in the orbitofrontal cortex (though with some effect also to only the chocolate in a postero-ventral part of the insula). Moreover the present study showed how the activity in a more anterior region of the orbitofrontal cortex is directly correlated with the subjective pleasantness of the liquid food.

A number of previous neuroimaging studies have reported activation in the human orbitofrontal cortex to different types of primary and secondary (learned) rewards and punishers. These include rewarding and aversive tastes (Zald *et al.*, 1998; O'Doherty *et al.*, 2001b), pleasant and aversive odors (Zatorre *et al.*, 1992; Zald and Pardo, 1997), olfactory stimuli in a sensory-specific satiety paradigm (O'Doherty *et al.*, 2000), pleasant touch (Francis *et al.*, 1999), sexually arousing stimuli (Redouté *et al.*, 2000), positive and negative feedback (Elliott *et al.*, 1997), pleasant music (Blood *et al.*, 1999), and monetary reward (Thut *et al.*, 1997; O'Doherty *et al.*, 2001a) and punishment (O'Doherty *et al.*, 2001a). These findings, together with the results from this study, support the notion that the orbitofrontal cortex is involved in representing many different types of reinforcer. The present study advances our understanding by showing a direct correlation between the subjective pleasure produced by rewarding stimuli and the activation of the human orbitofrontal cortex and other brain areas. Although the most significant correlation was found with a region in the left orbitofrontal cortex, a correlation was also found with a similar region in the right orbitofrontal cortex, and thus the present results do not support strong lateralization in the cortical response in humans, which is consistent with findings from non-human primates (Rolls *et al.*, 1989; Critchley and Rolls, 1996; Tremblay and Schultz, 1999). These studies reported neurons located in posteriomedial area 11, close to area 14, and in area 12 and 13, that reflect reward preferences, and the region found in the present study may correspond to these areas in macaques. The exact nature of neuronal activity in the dorsolateral prefrontal cortex in relation to reward has been less explored especially in relation to satiety (Watanabe *et al.*, 2002), and further exploration of this in imaging studies would be of interest.

Furthermore, the results of this study demonstrate a number of important points regarding the cortical processing of sensory versus affective properties of a liquid whole food. First, the activations shown in Figure 3 are in brain areas where the activation was not hunger dependent. It is of interest that these include not only the anterior insula, which is probably the human primary taste cortex, but also the immediately adjacent far caudal orbitofrontal cortex. The human anterior insula is known to respond to gustatory stimuli (O'Doherty *et al.*, 2001b; Small *et al.*, 1999). This is consistent with the neurophysiological evidence in macaques of a primary taste cortical area in the insula and adjoining frontal operculum (Sudakov *et al.*, 1971; Scott *et al.*, 1986). Indeed, this region is the primary taste cortex in non-human primates, in that it is the area of cortex known to receive taste afferents from the VPMpc nucleus (ventral posterior medial nucleus, parvocellular part) of the thalamus (Pritchard *et al.*, 1986; Baylis *et al.*, 1994; Rolls and Scott, 2003). In macaques, it has been shown that the primary taste cortex, in the anterior insula, has hunger independent neuronal responses (Yaxley *et al.*, 1988). The adjoining caudolateral orbitofrontal cortex region may be an anterior continuation of the primary taste cortex in humans, but may also be involved in olfactory effects produced by the liquid whole food, in that we have found activation in this region in a different experiment in which odors were presented

in an olfactometer. It is known that this region is anatomically a transitional region between the insula and orbitofrontal cortex (Öngur and Price, 2000). Both these regions may thus represent the sensory and not the affective properties of a liquid whole food.

Second, a posterior region of the anterior cingulate cortex is also activated by the flavor of a liquid whole food independently of its affective value (i.e. of whether the subject is hungry or satiated) (the cingulate area shown in Fig. 3).

Third, it was found in a food-specific satiation contrast for chocolate milk that in addition to the orbitofrontal cortex, significant effects were also found in regions of the posterior insula and ventral striatum. This indicates that some of the findings of activation of striatum and insula in a study of the pleasantness of chocolate when eaten 'beyond' satiety striatum by Small and colleagues (Small *et al.*, 2001) could be due to food-specific effects rather than the intrinsic pleasantness of food *per se* (Schultz *et al.*, 2000).

It is important to note that in neurophysiological recordings in primates the orbitofrontal cortex neurons diminish their response after satiety (Critchley and Rolls, 1996), while in this fMRI study we find that not only does the activation to the liquid food decrease after it is eaten to satiety (which parallels the neurophysiological finding), but also the BOLD signal may decrease below the baseline. However, the baseline in the BOLD signal in this experiment is the average across the whole experiment, and thus does not directly correspond to the spontaneous firing activity of neurons measured in neurophysiological experiments, and indeed probably corresponds to activity above the spontaneous firing rate. The results of this study are therefore compatible with earlier neurophysiological results, although further research on the detailed interpretation of deactivations in fMRI studies is needed.

Although this study has focused on the orbitofrontal cortex, it should also be noted that other regions are also involved in the control of feeding. One such region is the hypothalamus, an area which receives extensive afferent connections from the orbitofrontal cortex (Rempel-Clower and Barbas, 1998) and which has been implicated in the control of food intake and satiety as a result of lesion studies and neurophysiological investigations (Burton *et al.*, 1976; Clark *et al.*, 1991; Grossman, 1975; Rolls, 1999). In a recent neuroimaging study, time dependent changes in activation were found in this area following glucose intake to satiety (Liu *et al.*, 2000). This region has also been shown to contain neurons with sensory-specific satiety related responses to the sight or taste of food (Rolls *et al.*, 1986), and this hypothalamic region receives inputs from the orbitofrontal cortex and amygdala (Öngur and Price, 2000).

The results described here thus indicate that a region of the human orbitofrontal cortex shows sensory-specific satiety related changes to the flavor of liquid food, which has taste, texture and olfactory components, and that because of the power of the statistics used, this finding generalizes to the general population although it should be noted that only right-handed males were tested. The activation in this region relates closely to the subjects' own subjective ratings of the pleasantness of the liquid food stimuli, such that the greater the BOLD signal in this region, the more pleasant the subject found the liquid food stimulus. These findings suggest that the human orbitofrontal cortex, as with non-human primates, plays an important role in representing the reward value of liquid food stimuli. More generally, these findings have important implications for understanding the neural basis of affect, by suggesting that the human orbitofrontal cortex is a brain region that is involved in representing the subjective pleasantness of a stimulus, which may be important in influencing whether a food is selected as a goal for action. We further note that the regions of the orbitofrontal cortex that were found to have activations that correlate with the pleasantness of the liquid food stimuli were anterior to the caudolateral areas of the orbitofrontal cortex that were activated in relation to the main effects of the liquid food stimuli (i.e. where the activations were independent of satiety and therefore reward value). This would suggest a posterior–anterior axis in the orbitofrontal cortex, where more complex processing such as affective value and pleasantness are represented in more anterior regions. Further, although the results we describe are in the context of the sensory-specific changes in the pleasantness of a liquid food that occur during food-motivated behavior, we hypothesize that sensory-specific reductions in the affective quality of sensory stimuli are a general property of reward systems in the brain (Rolls *et al.*, 1999).

Notes

We thank Prof. Paul Matthews, and Drs Steven Smith, Peter Jezzard, Stuart Clare and Irene Tracey for their help and assistance. This research is supported by the MRC (to FMRIB, to the IRC for Cognitive Neuroscience, by a Program Grant to ETR, and by a studentship to J.O'D); the Danish Research Agency, Aarhus, Denmark (to M.L.K.); the Oxford McDonnell–Pew Centre for Cognitive Neuroscience; and by Firmenich SA.

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