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How the Brain Represents the Reward Value of Fat in the Mouth

Fabian Grabenhorst[1], Edmund T. Rolls, Benjamin A. Parris[2] and Arun A. d'Souza[3]

Department of Experimental Psychology, University of Oxford, Oxford OX1 3UD, UK, [1]Current address: Department of Psychology and Helen Wills Neuroscience Institute, University of California at Berkeley, CA 94720-3190, USA, [2]Current address: Psychology Research Group, School of Design, Engineering and Computing, University of Bournemouth, BH12 5BB Bournemouth, UK and [3]Current address: School of Psychology and Trinity College Institute of Neuroscience, Trinity College Dublin 2, Ireland

The palatability and pleasantness of the sensory properties of foods drive food selection and intake and may contribute to overeating and obesity. Oral fat texture can make food palatable and pleasant. To analyze its neural basis, we correlated humans' subjective reports of the pleasantness of the texture and flavor of a high- and low-fat food with a vanilla or strawberry flavor, with neural activations measured with functional magnetic resonance imaging. Activity in the midorbitofrontal and anterior cingulate cortex was correlated with the pleasantness of oral fat texture and in nearby locations with the pleasantness of flavor. The pregenual cingulate cortex showed a supralinear response to the combination of high fat and pleasant, sweet flavor, implicating it in the convergence of fat texture and flavor to produce a representation of highly pleasant stimuli. The subjective reports of oral fattiness were correlated with activations in the midorbitofrontal cortex and ventral striatum. The lateral hypothalamus and amygdala were more strongly activated by high- versus low-fat stimuli. This discovery of which brain regions track the subjective hedonic experience of fat texture will help to unravel possible differences in the neural responses in obese versus lean people to oral fat, a driver of food intake.

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

Introduction

The sensory and especially the hedonic effects of food are important drivers of food intake, and oversensitivity of the reward system to the sensory properties of food may be a driving factor in obesity (Davis et al. 2007; Franken and Muris 2005; Hetherington 2007; McGloin et al. 2002; Rolls 2005, 2007a, 2007b; Stice et al. 2008; Wardle et al. 2001). One of the sensory properties of food important in making it palatable is its fat texture (Drewnowski 1998). However, little is known about how the pleasantness of oral fat texture is represented in the brain. This is an important issue for evidence on the neural representation of the reward value of oral fat would provide a basis for investigations of whether the brains of obese people differ, inter alia, in their responsiveness to the pleasant, affective, reward value of oral fat texture. A previous investigation with a fatty oil (and comparisons with nonfat oral texture produced by carboxymethylcellulose) showed that fat texture is represented in areas of the human brain such as the taste and somatosensory insula, orbitofrontal cortex, and pregenual cingulate cortex (de Araujo and Rolls 2004). However, it is not known in which brain areas the subjective pleasantness of fat texture is represented and the extent to which these areas overlap with the areas that represent the pleasantness of food flavor, which include the orbitofrontal and pregenual cingulate cortex (Kringelbach et al. 2003; McCabe and Rolls 2007; Small et al. 2003). At the neuronal level, single neurons in the primary taste cortex in the insula, and in the orbitofrontal cortex, can reflect a convergence of effects produced by oral texture, including fat, and taste (Kadohisa et al. 2005; Rolls 2008; Rolls, Verhagen, and Kadohisa 2003; Verhagen et al. 2003, 2004).

The aim of this study was to investigate which areas of the human brain represent the subjective pleasantness of fat in the mouth and whether these areas overlap with the areas that represent the pleasantness of food flavor. We designed a protocol in which the oral effects of high- versus low-fat foods could be compared, by using dairy products that differed markedly in their fat content, and in which human participants provided ratings of the subjective pleasantness of the fat texture and separate ratings of the fattiness of what was in the mouth. The design included 2 flavors (vanilla and strawberry) of the high- and low-fat drinks and ratings of the subjective pleasantness of the flavor so that representations of the pleasantness of fat texture and of flavor could be compared in the same participants with interleaved trials.

Given the obesity epidemic and the medical risks associated with obesity (Flegal et al. 2005), it is important to understand the principles by which the pleasantness of the texture and flavor of food are processed in the brain and can thereby influence the type of food that is eaten and how much is eaten (Morton et al. 2006; Rolls 2007a, 2007b; Schwartz and Porte 2005).

Methods

Design

The flavor stimuli consisted of a pleasant vanilla-flavored dairy drink and, to provide for a range of pleasantness values in the investigation, a less pleasant strawberry-flavored dairy drink. Both types of flavor stimuli were presented as a low-fat version (0.1% fat milk) and a high-fat version (single cream, 18% fat) to produce a range of liquid food stimuli that differed in taste and olfactory and texture components. The drinks were made by taking either single cream or the low-fat milk as the base, and the flavor component was specified by vanilla food flavor and 5 g/100 mL (0.15 M) sucrose, or by strawberry food flavor without sucrose. The tasteless control/rinse solution contained the main ionic components of saliva (25 mM KCl + 2.5 mM $NaHCO_3$) that when subtracted from the effects produced by the taste stimulus allowed taste (or in the case of the high-fat stimuli taste and fat texture) effects to be distinguished from general somatosensory effects produced by introducing fluid into the mouth and any mouth movement (de Araujo, Kringelbach, Rolls, and Hobden 2003; O'Doherty et al. 2001b). Although this is a useful control condition (de Araujo, Kringelbach, Rolls, and Hobden 2003; de Araujo, Kringelbach, Rolls, and McGlone 2003; O'Doherty et al. 2001), in fact in the present study the main comparisons of interest were those between high- and low-fat stimuli and vanilla/sweet and strawberry flavor stimuli, and the rinse effects were not needed for these comparisons. Flavor stimuli were delivered

to the subject's mouth through Teflon tubes (one for each of the 4 stimuli and a separate tube for the tasteless rinse control) that were held between the lips. Each Teflon tube of approximately 3 m in length was connected to a separate reservoir via a syringe, and a one-way syringe activated check valve (Model 14044-5, World Precision Instruments, Inc, Stevenage, UK), which allowed 0.75 mL of any stimulus to be delivered at the time indicated by the computer.

Each trial started with a visual cue displayed for 1 s to indicate to the subjects that a flavor stimulus will be delivered. Then at $t = 1$ s, a blue cross was shown, and a flavor stimulus (chosen in a random permuted sequence through the set of stimuli that was then followed by a new random permutation) was delivered into the mouth and left there for a 7-s flavor period. After this period, at $t = 8$ s, a green 2 s cross-cued the subjects to swallow. After this period, ratings were made with visual analog rating scales in which the subject moved a bar to the appropriate point on the continuous scale using a button box. Subjects rated the flavor stimuli on separate scales for pleasantness of flavor, pleasantness of texture (with +2 being very pleasant and −2 very unpleasant), and fattiness (with 0 being very low in fat and +4 being very high in fat). The subjects were instructed to rate the fattiness of the stimuli independent of how pleasant the stimuli were. Each rating period was 4 s long. Preexperiment training in the protocol and use of the rating scales allowed the participants to rate the pleasantness of texture separately from the fattiness of a stimulus. After the last rating (at $t = 22$ s), a small visual cue indicated the delivery of the tasteless control/rinse solution that was administered in exactly the same way as the test stimuli. Swallowing was again cued by a visual stimulus. The instruction given to the subject was to move the tongue once as soon as a stimulus or tasteless solution was delivered (at the time when a blue visual stimulus was turned on) in order to distribute the solution round the mouth to activate the receptors for taste, smell, and oral texture and then to keep still for the remainder of the 7 s until a green cue indicated when the subject could swallow. There was then a 4-s delay period before the next trial started. Each experimental stimulus was presented in permuted sequence 12 times, interleaved with other trials on which thermal stimuli were applied to the hand as part of another investigation. This general protocol and design has been used successfully in previous studies to investigate activations and their relation to subjective ratings in cortical areas (de Araujo, Kringelbach, Rolls, and Hobden 2003; de Araujo, Kringelbach, Rolls, and McGlone 2003; de Araujo, Rolls, et al. 2003; Grabenhorst et al. 2008).

Participants

Fourteen healthy volunteers (9 male and 5 female, mean age 24 y) participated in the study. Ethical approval (Central Oxford Research Ethics Committee) and written informed consent from all subjects were obtained before the experiment. The participants were asked not to eat for 3 h before the experiment, and the experiments were performed at approximately lunchtime, so that the participants were sufficiently hungry to want to eat.

fMRI Data Acquisition

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

fMRI Data Analysis

The imaging data were analyzed using statistical parametric mapping (SPM)5 (Wellcome Trust Centre for Neuroimaging, London, UK). Preprocessing of the data used SPM5 realignment and unwarping, reslicing with sinc interpolation, normalization to the Montreal Neurological Institute coordinate system (Collins et al. 1994), and spatial smoothing with a 6-mm full width at half maximum isotropic Gaussian kernel. The time series at each voxel were low-pass filtered with a hemodynamic response kernel. Time series nonsphericity at each voxel was estimated and corrected for (Friston et al. 2002), and a high-pass filter with a cutoff period of 128 s was applied. In the single-event design, a general linear model (GLM) was then applied to the time course of activation where the onset of the oral stimulus effects (at $t = 2$ s in each trial) was modeled with an impulse response function and then convolved with the canonical hemodynamic response function (Friston et al. 1994). (The oral stimulus was delivered at $t = 1$ s, and the 1-s delay for the analysis was to allow the oral stimulus to be distributed in the mouth.) Linear contrasts were defined to test specific effects. Time derivatives were included in the basis functions set. Following smoothness estimation (Kiebel et al. 1999) in the first stage of analysis condition-specific experimental effects (parameter estimates, or regression coefficients, pertaining to the height of the canonical hemodynamic response function) were obtained via the GLM in a voxel-wise manner for each subject. In the second (group random effects) stage, subject-specific linear contrasts of these parameter estimates were entered into a factorial design, where one factor was fat content (high fat vs. low fat) and the second factor was flavor (vanilla vs. strawberry). The regression analyses of the functional magnetic resonance imaging (fMRI) blood oxygen level–dependent (BOLD) signal with given parameters of interest (e.g., the pleasantness ratings) were performed at the second level through applying one-sample t tests to the first-level subject-specific SPMs resulting from performing linear parametric modulation as implemented in SPM5. When a regression analysis was being performed with the parametric modulator pleasantness of texture ratings, the pleasantness of flavor ratings was included as covariates and vice versa. We specified the GLM so that the second parametric modulator in the model was orthogonalized with respect to the first as implemented in SPM5, and any shared variance was assigned to the first parametric modulator. We confirmed that all results of these analyses were not altered by reversing the order in which the parametric modulators were entered in the GLM. For example, all correlations reported for the pleasantness of texture ratings were still significant when any shared variance was assigned to the pleasantness of flavor ratings and vice versa. For the correlations with the pleasantness of oral texture, separate regressors for the vanilla and strawberry flavors were implemented at the first (subject) level, and the effects for the oral texture were combined at the second (group) level. For the correlations with the pleasantness of flavor, separate regressors for the high- and low-fat versions were implemented at the first (subject) level, and the effects for the flavor were combined at the second (group) level. We focus our analysis on brain regions where there were prior hypotheses and applied small volume (false discovery rate) corrections for multiple comparisons for which $P < 0.05$ (though the exact corrected probability values are provided) (Genovese et al. 2002) with a radius corresponding to the full width at half maximum of the spatial smoothing filter used. These brain regions with prior hypotheses specified in this way were as follows: regions within the orbitofrontal and anterior cingulate cortex, anterior and midinsular cortex, ventral striatum, hypothalamus, and amygdala in which we and others have found activations in previous studies to taste and flavor stimuli (de Araujo, Kringelbach, Rolls, and Hobden 2003; de Araujo, Kringelbach, Rolls, and McGlone 2003; de Araujo and Rolls 2004; Kringelbach and Rolls 2004; O'Doherty et al. 2001b; Rolls 2005, 2006; Small et al. 2003; Small and Prescott 2005; Small et al. 1999). In addition to the statistical criterion just described for a significant effect calculated for the peak voxel of a region of activation in an a priori defined region based on earlier findings, we used the additional statistical test (see Gottfried et al. 2002; O'Doherty et al. 2003, 2006) that the results reported were in global contrast and/or correlation analyses significant using the criterion of $P < 0.001$ uncorrected (uc) for multiple comparisons and with a cluster size >3 voxels, and these additional statistics confirmed the same effects in the a priori regions in all cases in this paper unless otherwise stated. All results that were significant within the areas of interest for all the analyses performed are

included in the Results section. For voxels where significant correlations were found between the percentage BOLD signal and the ratings in the SPM regression analysis using the criteria described above, we produced graphs to show how the ratings were related to the percentage BOLD signal. These were produced for each subject by taking the average of the BOLD response in the 3 time bins at 4-, 6-, and 8-s after stimulus onset (when the hemodynamic response function has high values), on each trial, and the corresponding rating. For each subject, the means were calculated in discretized ranges of the rating function (e.g., −2 to −1.75, −1.75 to −1.5, etc), and then these values were averaged across subjects.

Results

Ratings of the Pleasantness of Oral Texture, Flavor, and Fattiness

The ratings of the pleasantness of texture and flavor, and of the fattiness of the stimuli, obtained during the neuroimaging are shown in Figure 1. A within-subjects analysis of variance (ANOVA) ($F_{1,13}$ = 14.8, P = 0.002) followed by post hoc least square difference tests (accompanied by a Kolmogorov–Smirnov test for normality) showed that the texture of the high-fat stimulus was rated as more pleasant than the low-fat stimulus for each of the 2 flavors. There was also, as part of the design to reveal potential correlations with the pleasantness of flavor, higher rated pleasantness of vanilla than strawberry flavor ($F_{1,13}$ = 14.8, $P < 1 \times 10^{-6}$). Both these were significant as main effects in the ANOVA. As is evident in Figure 1, within the flavor vanilla, there was a significant difference of the rated pleasantness of texture ($P = 1 \times 10^{-3}$). The same was the case within the flavor strawberry (P = 0.026). (Also, no significant interaction was found between the factors flavor and texture in the pleasantness of texture ratings ($F_{1,13}$ = 1.03, $P > 0.3$.) Because the effect of high versus low fat on pleasantness ratings was found separately for each of the 2 flavors, vanilla and strawberry (and there was no interaction); the psychophysical data show that the high-fat version of each drink was rated as more pleasant than the low-fat version and thus that the high-fat version was more pleasant than the low-fat version for each of the 2 flavors. Thus, some of the fMRI analyses tested within each of the 2 flavors whether some brain regions had activations that were correlated with the pleasantness of the fat texture. The correlations between the ratings of the pleasantness of texture and the pleasantness of flavor within each subject across trials were low and nonsignificant (with an average correlation of r = 0.11, which had the same value when calculated separately for vanilla and strawberry), indicating that the subjects were able to independently rate the pleasantness of these different sensory properties of the stimuli.

Figure 1*b* shows that within each flavor, the high-fat stimulus was rated as more fatty than the low-fat stimulus ($F_{1,13}$ = 55.9, $P < 5 \times 10^{-5}$; for vanilla, $P = 3 \times 10^{-5}$; for strawberry, $P = 5 \times 10^{-4}$). Contrast analyses to identify brain regions with activations to high versus low fat therefore focused on contrasts within each flavor, and the same approach was used with the regression analyses to identify brain regions with activations related to the rated fattiness of the oral texture stimulus.

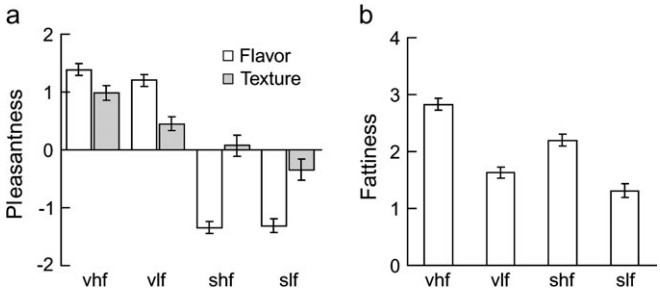

Figure 1. The psychophysical ratings of the pleasantness of flavor and oral texture (*a*) and fattiness (*b*) obtained during the neuroimaging (mean across participants ± standard error of the mean). vhf—vanilla high fat; vlf—vanilla low fat; shf—strawberry high fat; slf—strawberry low fat.

fMRI Data

For the analysis of the fMRI data, we aimed to identify brain regions where neural activity correlates with the subjective pleasantness of texture and flavor. The ratings of the pleasantness of texture and flavor were used as subject-specific regressors for neural activity in SPM regression analyses (see Methods). In addition, to illustrate how activity at the sites identified in these analyses is related to the range of pleasantness rating values, we extracted from locations where significant correlations were found in the SPM regression analyses the percentage BOLD signal as a function of pleasantness ratings. This method of using subjective ratings as regressors for neural activations has previously been used to successfully identify brain areas where activity reflects the subjective affective value of stimuli (de Araujo, Kringelbach, Rolls, and Hobden 2003; de Araujo, Kringelbach, Rolls, and McGlone 2003; de Araujo, Rolls, et al. 2003; Grabenhorst et al. 2007, 2008; Rolls and Grabenhorst 2008; Rolls, Grabenhorst, and Parris 2008). We focus our analyses on brain regions where there were prior hypotheses as described in the Methods. A list of other brain regions where significant effects were found is provided in Supplementary Table 1.

Brain Regions with Representations of the Pleasantness of Oral Fat Texture

The Midorbitofrontal Cortex

Activity in the midorbitofrontal cortex was correlated with the subjective pleasantness of fat texture as shown in Figure 2*a* which shows the statistical map for the SPM regression analysis ([32, 34, −14], z = 3.38, P = 0.013). The results show where the pleasantness of fat texture is represented in that they were obtained for the high- and low-fat versions with the vanilla flavor that differed in texture pleasantness (see Fig. 1) and also included the flavor ratings as a covariate in the SPM analysis. The diagram in Figure 2*c* shows that activity in the midorbitofrontal cortex was positively related to the pleasantness of texture ratings over a wide range of pleasantness values. The only other brain region where there was a significant positive correlation with the pleasantness of texture as the parametric regressor was the anterior cingulate cortex, as described later.

Consistent with this relation to the pleasantness of oral fat texture, activations in this midorbitofrontal cortex region were larger for the vanilla high- versus low-fat stimulus (Fig. 2*d*,*f*) as shown by a significant effect in an SPM contrast analysis ([34, 38, −10], z = 3.46, P < 0.001). If this region represents the pleasantness of the texture of fat, then the large response shown in Figure 2*f* to high- versus low-fat vanilla stimuli but not to high- versus low-fat strawberry stimuli can be understood as reflecting how pleasant these stimuli were in terms of their fat texture,

which was high for high-fat vanilla as shown in Figure 1*a*. This brain region thus represents the affective value of oral fat texture especially when it is pleasant, and a similar point can be made for the pregenual cingulate area that represents the pleasantness of pleasant high-fat stimuli, as shown below. Interestingly, a different region of the orbitofrontal cortex did show a significant difference between the high- and low-fat versions of the strawberry stimuli at [–26, 42, –12], $z = 3.71$, $P = 0.012$, which reflects a difference in pleasantness that is mainly in the negative range of ratings. This is consistent with our earlier finding that some parts of the orbitofrontal cortex seem to represent the pleasantness and unpleasantness of stimuli at least partly independently (Grabenhorst et al. 2007).

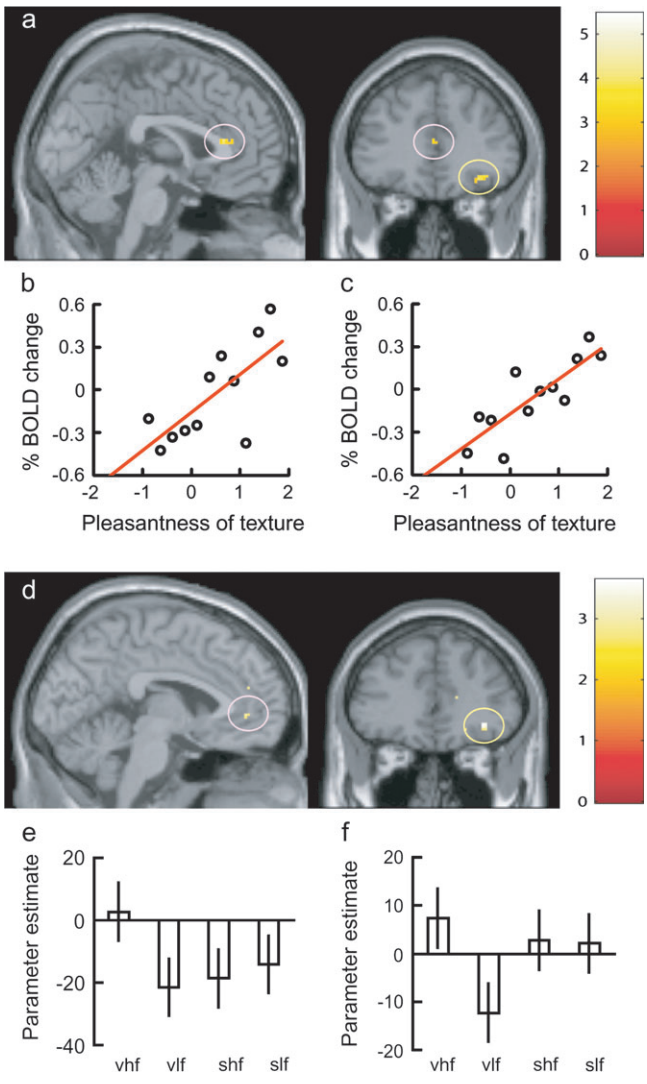

Figure 2. Brain regions in which the activations were correlated with the subjective pleasantness of fat texture: midorbitofrontal cortex ([32, 34, −14], $z = 3.38$, $P = 0.013$) (*a*, yellow circle; *c*, showing the relation between the percentage change in the BOLD signal and the rating of the pleasantness of the texture) and anterior cingulate cortex ([2, 30, 14], $z = 3.22$, $P = 0.016$) (*a*, pink circles, and *b*). (*d*) Contrast of high versus low fat for the vanilla stimuli. The contrast shows significant effects in the midorbitofrontal cortex (*d*, yellow circle; *f*, showing the parameter estimates from this analysis) and the anterior, pregenual cingulate cortex (*d*, pink circle, and *e*). The convention in this figure and the following figures is that the brain images show the sites where significant effects were found in the SPM regression or contrast analysis, and the plots below show the correlation or parameter estimate data at these sites that correspond to and are based on the significant SPM analysis.

Interestingly, activity that was correlated with the subjective pleasantness of flavor was found in the midorbitofrontal cortex as shown in Figure 3*a,c* ([22, 36, –10], $z = 3.87$, $P = 0.004$) in a region that was close to that shown in Figure 2 as having activations related to the subjective pleasantness of oral fat texture. Thus, the midorbitofrontal cortex region has representations of both the pleasantness of oral texture and flavor.

The Anterior Including Pregenual Cingulate Cortex

Activity in the anterior cingulate cortex was correlated with the subjective pleasantness of fat texture as shown in Figure 2*a* ([2, 30, 14], $z = 3.22$, $P = 0.016$). The results show where the pleasantness of fat texture is represented in that they were obtained for the high- and low-fat versions with the vanilla flavor that differed in texture pleasantness (see Fig. 1) and also included the flavor ratings as a covariate in the SPM analysis. The diagram in Figure 2*b* shows that the activity was positively related to the pleasantness of texture ratings over a wide range of pleasantness values.

Consistent with this relation to the pleasantness of oral fat texture, activations in this anterior cingulate cortex region were also correlated with the subjective ratings of fatty texture ([0, 30, 12], $z = 2.87$, $P = 0.035$), and the effect extended into the pregenual cingulate cortex, as shown in Figure 2*d,e*, by the high- versus low-fat contrast analysis with the pleasant flavor vanilla ([–4, 46, –4], $z = 3.67$, $P < 0.001$). This pregenual cingulate cortex region is known to be activated by a number of pleasant stimuli (Grabenhorst et al. 2008; Rolls 2009b; Rolls and Grabenhorst 2008; Rolls, Grabenhorst, and Parris 2008).

In this context, it was very interesting that a region of the anterior cingulate cortex close to that shown in Figure 2 as having activations related to the pleasantness of oral fat texture also had activations that were correlated with the pleasantness of flavor ([8, 30, 16), $z = 3.09$, $P = 0.037$), as shown in Figure 3*a,b*. Similarly, the region of pregenual cingulate cortex shown in Figure 2 as having activations related to oral fat texture also had nearby activations that were correlated with the pleasantness of flavor ([12, 50, –8], $z = 2.98$, $P = 0.013$).

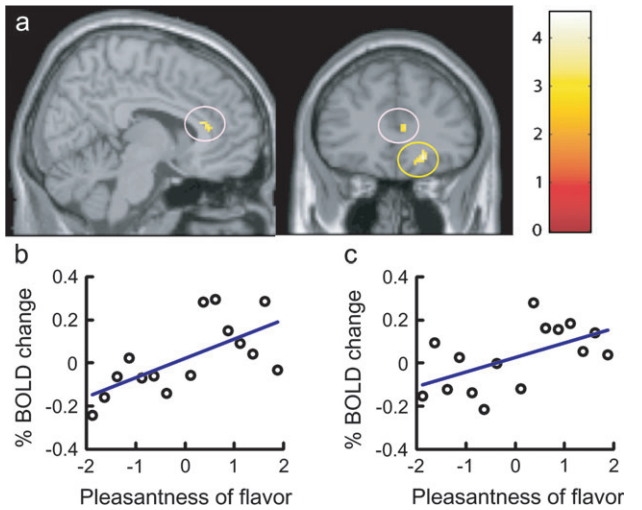

Figure 3. Brain regions with activations correlated with the subjective ratings of flavor pleasantness: midorbitofrontal cortex ([22, 36, −10], $z = 3.87$, $P = 0.004$) (*a*, yellow circle, and *c*) and anterior cingulate cortex ([8, 30, 16), $z = 3.09$, $P = 0.037$) (*a*, pink circle, and *b*).

Bringing together representations of the sensory properties of food is likely to be important in determining the palatability of a food, which can be enhanced by particular combinations of the sensory properties, including sweet and fat, as occurs in foods such as ice cream and chocolate. To investigate whether there are common areas in the brain in which both the pleasantness of oral fatty texture and the pleasantness of flavor (e.g., the flavor of the sweet vanilla) are represented, we inclusively masked the brain areas where activations were correlated with the pleasantness of oral texture with the brain areas where activations were correlated with the pleasantness of flavor. As shown in Figure 4*a*, parts of the pregenual cingulate cortex had overlapping representations. For this area of overlap, the peaks of the correlations were for texture [6, 32, –6], $z = 2.92$, $P = 0.002$, uc, and for flavor [10, 42, 0], $z = 2.83$, $P = 0.04$. The graphs underneath show that the percentage change in the BOLD signal for both the pleasantness of oral fatty texture and the pleasantness of flavor (with its taste and olfactory attributes) was similar in this common region, implying a similar scale in this brain region for the subjective reward value of the texture and flavor properties of the stimuli.

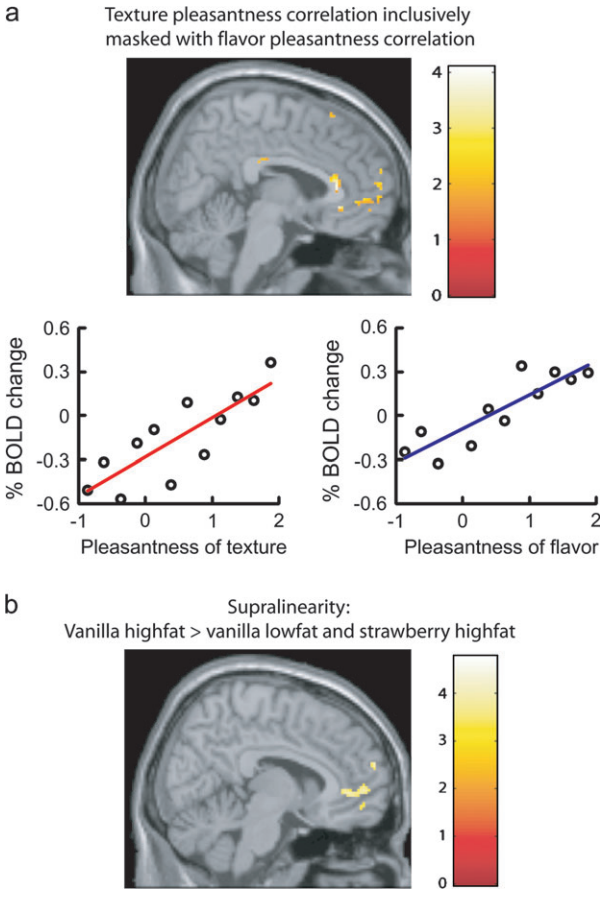

Figure 4. *a*) Inclusive masking ($P < 0.05$) of brain areas where activations were correlated with the subjective pleasantness of fat texture and of flavor revealed common areas in the pregenual cingulate cortex. For this area of overlap, the peaks of the correlations were for texture, [6, 32, −6], $z = 2.92$, $P = 0.002$, uc, and for flavor [10, 42, 0], $z = 2.83$, $P = 0.04$. The graphs underneath show that the relationship between the percentage change in the BOLD signal and the subjective ratings was similar for both the pleasantness of oral fatty texture and the pleasantness of flavor (with its taste and olfactory attributes). (*b*) Regions of the pregenual cingulate cortex showing supralinear responses to the combination of fat texture and sweet vanilla flavor compared with the sum of the components (high-fat strawberry and low-fat vanilla) with peaks at [8, 42, 0], $z = 3.68$, $P = 0.002$, and [−6, 50, −4], $z = 3.81$, $P = 0.001$.

If stimuli combine supralinearly, this can indicate convergence of the stimuli to produce a new representation of the combination that can act differently to the sum of the parts. We tested whether any brain regions might show such a supralinear combination effect of fat texture and flavor (taste plus smell, as defined in the vanilla/sweet and the strawberry/nonsweet stimuli). (This test was performed in SPM as part of a factorial design of high- vs. low-fat texture and vanilla/sweet flavor vs. strawberry/nonsweet flavor. The test specified was for whether the high fat with vanilla/sweet flavor produced a greater activation than the sum of the texture component [using high fat strawberry] and the flavor component [using vanilla/sweet in the low-fat stimulus].) As shown in Figure 4*b*, regions of the pregenual cingulate cortex showed supralinear effects for fat texture and sweet vanilla flavor (with peaks at [8, 42, 0], $z = 3.68$, $P = 0.002$, and [–6, 50, –4], $z = 3.81$, $P = 0.001$).

In this investigation, the only common area for the representation of the pleasantness of fat texture and the pleasantness of flavor shown by the masking approach was the anterior and pregenual cingulate cortex, although activations related to the pleasantness of fat texture and the pleasantness of flavor were found close together in the midorbitofrontal cortex, as described above. The only area in this investigation showing a supralinear representation of fat texture and flavor was the pregenual cingulate with the extent shown in Figure 4*b*.

Brain Regions with Representations of Fattiness

Lateral Hypothalamus and Adjoining Amygdala

The orbitofrontal cortex projects to the lateral hypothalamus as well as to the pregenual cingulate cortex. In this context, it was of interest that a contrast of high fat versus low fat in the factorial design including high versus low fat and vanilla versus strawberry flavor revealed a significant effect in the lateral hypothalamus ([8, –8, –2], $z = 3.04$, $P = 0.048$) as shown in Figure 5*a*. The parameter estimates showing the effects for each stimulus in Figure 5*b* showed effects related to the high- but not the low-fat stimuli independently of flavor. This result was extended by a positive correlation ($z = 3.20$, $P = 0.033$) in the same region with the subjective rating of the fattiness of the stimuli. The lateral hypothalamus also had activations correlated with the pleasantness of flavor ([14, –12, –6], $z = 3.58$, $P = 0.006$).

The amygdala (in a region bordering the ventral forebrain and substantia innominata) was also more strongly activated by the high versus low fat in the contrast analysis for the vanilla flavor ([24, 0, –12], $z = 3.29$, $P = 0.031$) as shown in Figure 5*a,c*.

Ventral Striatum

The orbitofrontal cortex, pregenual cingulate cortex, and amygdala project to the ventral striatum (Ferry et al. 2000). In this context, it was of interest that activations in the ventral striatum were correlated with the subjective ratings of oral fat texture ([–8, 20, –16], $z = 4.59$, $P < 0.001$, Figure 6*a,b*), extending the finding of a previous study that the ventral striatum was activated by oral fat texture independently of viscosity (de Araujo and Rolls 2004). Although activations in the ventral striatum were not significantly correlated with the pleasantness of fat texture, it was found that in a region of the

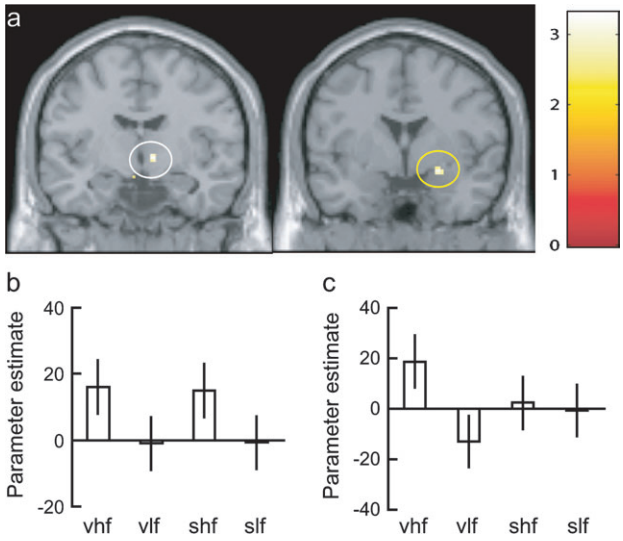

Figure 5. Brain regions with activations related to fat texture: Higher responses to high- versus low-fat stimuli were found in the lateral hypothalamus ([8, −8, −2], z = 3.04, P = 0.048) (*a* and *b* show the parameter estimates for the effect analyzed in a factorial design) and amygdala/ventral forebrain ([24, 0, −12], z = 3.29, P = 0.031) (*a*, *c*).

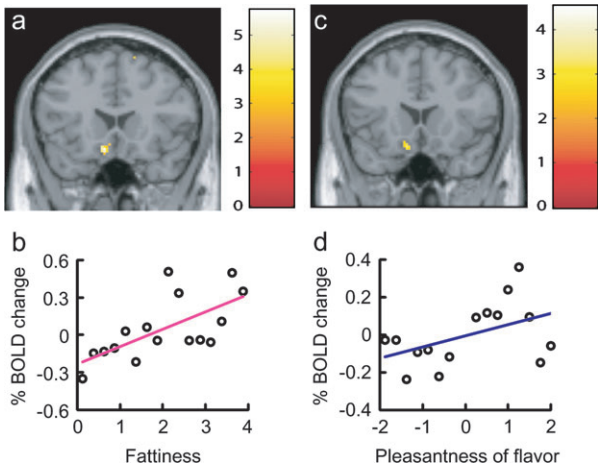

Figure 6. Activity in the ventral striatum was correlated with the subjective ratings of fattiness ([−8, 20, −16], z = 4.59, P < 0.001) (*a*, *b*) and the subjective pleasantness of flavor ([−12 22 -16], z = 3.26, P = 0.016) (*c*, *d*).

ventral striatum close to that shown in Figure 6*a* as having activations related to the oral fat texture, activations were correlated with the pleasantness of flavor, as shown in Figure 6*c,d* ([−12, 22, −16), z = 3.26, P = 0.016).

Brain Regions with Representations of the Unpleasantness of Fat Texture

Insula and Frontal Operculum

Two brain regions in which activity was negatively correlated with the pleasantness of fat texture were the far anterior, agranular, insula ([26, 24, −6], z = 3.70, P = 0.011) and the frontal operculum/overlying cortex ([56, 12, 8], z = 3.34, P = 0.017), as shown in Figure 7*a,b*. The results shown were found for the high- and low-fat versions of both the vanilla and strawberry flavors and also had the flavor ratings as a covariate, so show

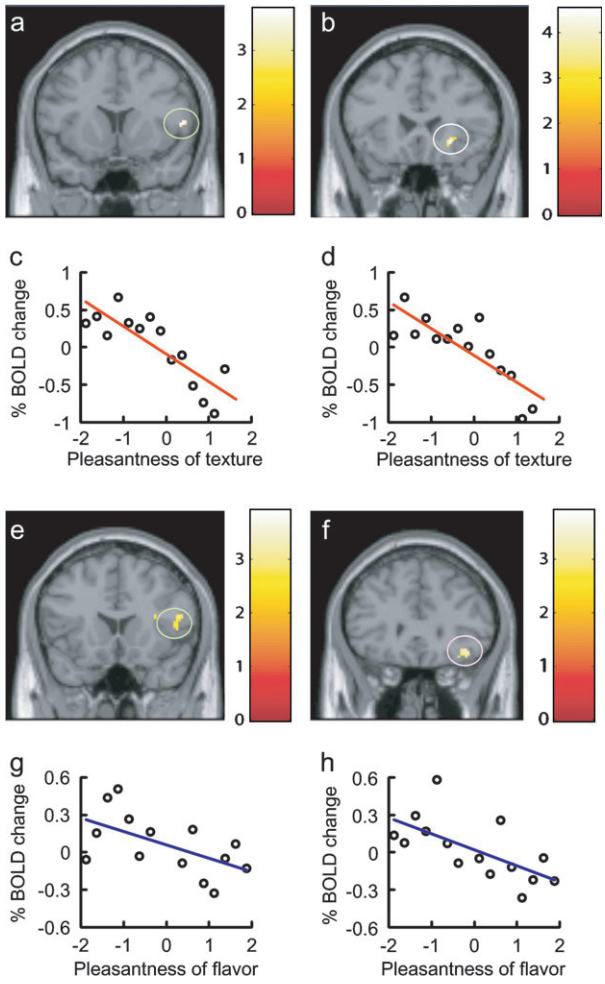

Figure 7. Brain regions in which the activations were negatively correlated with the pleasantness of fat texture: frontal operculum/overlying cortex ([56, 12, 8], z = 3.34, P = 0.017) (*a*, *c*) and far anterior, agranular insular cortex ([26, 24, −6], z = 3.70, P = 0.011) (*b*, *d*). Negative correlations between activity and the pleasantness of flavor were found in the frontal operculum/overlying cortex ([50, 18, 16], z = 4.17, P < 0.001) (*e*, *g*) and the lateral posterior orbitofrontal cortex ([32, 32, −18], z = 3.64, P < 0.001) (*f*, *h*).

where the unpleasantness of fat texture is represented. Figure 7*c,d* show that for both brain regions the activations were negatively correlated with the pleasantness of texture ratings over a wide range of pleasantness values. Several parts of the insula showed this activation related to the unpleasantness of fat texture, including a ventral part of the insula ([44, 0, −18], z = 3.67, P = 0.006, P < 0.001 uc) and a midposterior part of the insula ([60, 8, 4], z = 3.52, P = 0.005, P < 0.001 uc). These insular areas did not correspond to the primary taste cortex identified using a tasteless solution as a control and shown to have activations related to the concentration of the tastant (Grabenhorst et al. 2008). The insular regions with activations correlated with the unpleasantness of the oral fat texture were shown to be more activated by the low-fat strawberry (parameter estimate = 24.1) than by the high-fat strawberry (15.6), and little difference was found for the parameter estimates of low- versus high-fat vanilla (−5.1 and −5.4), so that these regions were especially activated by unpleasant oral stimuli, and their activations represent how unpleasant the stimuli are as influenced by their fat content.

The frontal opercular region shown in Figure 7 also had activations negatively correlated with the pleasantness of flavor (analysed as described above) ([50, 18, 16], $z = 4.17$, $P < 0.001$), as shown in Figure 7*e,g*.

Lateral Orbitofrontal Cortex

A lateral part of the orbitofrontal cortex/inferior frontal gyrus (area 47) ([–48, 32, –2], $z = 3.35$, $P = 0.014$) and a part of midorbitofrontal cortex ([16, 38, –20], $z = 3.62$, $P = 0.007$) also had activations that were correlated with the unpleasantness ratings of the oral texture. The lateral posterior orbitofrontal cortex also had activations negatively correlated with flavor pleasantness ([32, 32, –18], $z = 3.64$, $P < 0.001$), as shown in Figure 7*f,b*. The orbitofrontal cortex receives inputs from insular and frontal opercular areas (Baylis et al. 1995). The lateral orbitofrontal cortex is known to be activated by a number of aversive stimuli, including unpleasant odors (Rolls, Kringelbach, and de Araujo 2003), monetary loss (O'Doherty et al. 2001a), and an angry face expression received as a social negative reinforcer (Kringelbach and Rolls 2003), and it is thus of interest that as shown here it is activated also by unpleasant oral texture.

Discussion

These new findings on where the pleasantness of oral fat texture is represented are important for understanding the principles by which the pleasantness of the texture and flavor of food are processed in the brain and how these processes may differ in obesity. One region identified was the midorbitofrontal cortex (Fig. 2*a*) where activity correlated with the ratings of the pleasantness of oral texture based on texture differences produced by high- versus low-fat stimuli. Confirmation that this region is involved in representations of fat texture is that it was activated more by high-fat than by low-fat stimuli (as illustrated in Fig. 2*d,f*) (cf. de Araujo and Rolls [2004]). Interestingly, activations in the same region also correlated with the ratings of the pleasantness of flavor, as shown in Figure 3*a,c*. In a previous study, the same region was also activated more by the flavor of a complex whole food (chocolate milk or tomato juice) when hunger was present and when the food was pleasant compared with after the food was eaten to satiety (Kringelbach et al. 2003).

This midorbitofrontal cortex region thus represents both the pleasantness of fat texture and the pleasantness of flavor, and consistent with this, there is convergence of the effects of oral fat texture and flavor onto single neurons in the primate orbitofrontal cortex (Rolls et al. 1999; Verhagen et al. 2003), where in addition neurons respond to the taste and smell of food only when hunger is present (Critchley and Rolls 1996; Rolls et al. 1989). This convergence provides for neurons to be activated by particular combinations of taste and oral texture, and thus for particular combinations of taste and oral texture to become pleasant or unpleasant, and to show sensory-specific satiety (Rolls 2005). This computational principle provides a reason why activations to oral texture and taste are found in overlapping areas within the orbitofrontal and pregenual cingulate cortices (Rolls 2005). This region is also implicated in differences between individuals in their responsiveness to the reward value of food for this region was more activated in chocolate cravers than noncravers by the sight of chocolate (Rolls and McCabe 2007).

Part of the interest of the new findings is that having identified a brain region where the pleasantness of oral fat texture is represented, it will now be of interest in relation to the study of obesity to examine whether this part of the brain is more activated by fat stimuli in obese than in nonobese, as part of the important goal of unraveling some of the brain processing that may contribute to the tendency to become obese. The midorbitofrontal cortex is thus a key area important in responses to the affective properties of food that drive appetite and food intake. Moreover, it is a key stage in processing, for earlier cortical stages that project to the orbitofrontal cortex such as the primary taste and olfactory cortex are implicated in representations of the sensory properties of foods such as intensity, and the orbitofrontal cortex in turn projects to other brain areas (Carmichael and Price 1996; Ferry et al. 2000; Price 2006) where the pleasantness of food is represented, such as the anterior/pregenual cingulate cortex, ventral striatum, lateral hypothalamus, and amygdala (see below and Rolls and Grabenhorst [2008]). We conceptualize this brain area as a region involved in representing the reward and subjective affective value of sensory stimuli (Rolls 2005; Rolls and Grabenhorst 2008).

Indeed, the pregenual/anterior cingulate cortex was also shown here to have activations related to the ratings of the pleasantness of oral fat texture (Fig. 2*a,b*) and also to respond more to high fat than low fat (Fig. 2*d,e*, cf. de Araujo and Rolls [2004]) with activations correlated with the subjective ratings of fattiness and to have activations related to the pleasantness of flavor (Fig. 3*a,b*). Further, the pregenual cingulate cortex also had areas in which the pleasantness of fatty texture and the pleasantness of flavor overlapped, as shown in Figure 4*a*. Moreover, these representations of the pleasantness or subjective reward value of the oral texture and flavor representations were on a similar scale, as suggested by the similar slopes of the percentage BOLD change as a function of the rated pleasantness shown in Figure 4*a*. Further, parts of the pregenual cingulate cortex also showed supralinear activation by a combination of high fat and pleasant flavor (a combination of sweet and vanilla) as shown in Figure 4*b*. (This combination, sweet, vanilla, and fat, happens to be present also in a highly palatable food, vanilla ice cream.) The pregenual cingulate cortex also contains neurons that respond to taste in macaques (Rolls 2008), and thus can be designated as an area of tertiary taste cortex, and is activated in humans by pleasant sweet (de Araujo and Rolls 2004) and umami (Grabenhorst et al. 2008; McCabe and Rolls 2007) taste. In previous studies, the pregenual cingulate cortex also showed supralinear activation to the pleasant combination of umami taste and a consonant vegetable odor (McCabe and Rolls 2007), as well as the combined sight and taste of chocolate in chocolate cravers (Rolls and McCabe 2007), suggesting that this brain area responds strongly to food stimuli that are highly pleasant. We conceptualize this brain area as a region involved in receiving information about the reward and subjective affective value of sensory stimuli and in then contributing with other parts of the cingulate cortex to the selection of actions (Rolls 2009a; Rolls and Grabenhorst 2008; Rushworth et al. 2007).

It is of interest that activations in the ventral striatum also have correlations with the subjective ratings of fattiness (Fig. 6*a,b*) and the pleasantness of flavor (Fig. 6*c,d*) (cf. Grabenhorst et al. 2008), for this region receives from the orbitofrontal cortex and anterior cingulate cortex (Ferry et al. 2000), and is

also implicated in interfacing reward representations to action selection (Kelley 2003; Rolls 2005). Further, the administration of μ-opioid agonists in this region enhances the intake of fat (Kelley et al. 2002).

The lateral hypothalamus was shown to be influenced by the oral sensory properties of fat, for it was activated more by high-fat than by low-fat stimuli (Fig. 5*a,b*), and activations in the lateral hypothalamus were correlated with the subjective ratings of oral fattiness. The hypothalamus is implicated in the molecular machinery involved in responsiveness to peripheral hunger and satiety signals (Morton et al. 2006; Schwartz and Porte 2005), and the present finding emphasizes that the hypothalamus is a brain region in which such signals can be interfaced to the sensory stimuli that provide for the reward and affective value of food. This convergence of sensory stimuli produced by food, and hunger/satiety signals, also probably occurring in the orbitofrontal cortex, is crucial in producing food reward and food-affective signals, which are fundamental to the control of appetitive responses to food and thus in food intake and body weight control (Rolls 2005, 2007a, 2007b).

Another new finding was that some brain areas had activations negatively correlated with the pleasantness ratings of the oral texture, including the frontal operculum (Fig. 7*a,c*) and the far anterior, agranular insula (Fig. 7*b,d*). These areas thus reflected the unpleasantness of the oral texture stimuli. Activations in the frontal operculum/overlying cortex were also negatively correlated with the pleasantness of flavor (Fig. 7*e,f*). These areas were not part of the primary taste cortex in the rostral insula (located at y = 4–20 mm [Grabenhorst et al. 2008]). The agranular insula is topologically in the posterior orbitofrontal region that receives input from both the primary taste cortex and the pyriform (primary olfactory) cortex and is known to be activated by combinations of taste and odor (de Araujo, Rolls, et al. 2003), which could produce a flavor that is unpleasant or pleasant. The frontal operculum/overlying cortex area at y = 12 is just lateral to the taste cortex in the insula and at least in macaques is probably an oral somatosensory area (Pritchard et al. 1986; Scott et al. 1986). Activations in the frontal operculum and adjacent anterior insular cortex were in previous investigations related to the relative unpleasantness of odors (Grabenhorst and Rolls 2009), the expectation of low monetary reward outcomes (i.e., low expected value), and the uncertainty of reward (Rolls, McCabe, and Redoute 2008), as well as risk prediction and risk prediction error (Preuschoff et al. 2008). Together, these findings suggest that this brain region can be activated by different types of aversive events.

An interesting finding was that the pleasantness of oral (fat) texture was represented for pleasant oral stimuli (the vanilla flavor) in areas such as the midorbitofrontal cortex and pregenual cingulate cortex (Figs 2 and 4), whereas the pleasantness of oral (fat) texture for oral stimuli that were less pleasant (the strawberry flavor) was represented in brain areas such as the insula (Fig. 7). Thus, some brain areas such as the midorbitofrontal cortex and pregenual cingulate cortex represent the pleasantness of oral fat texture for pleasant stimuli, whereas other brain areas such as the insula represent the unpleasantness of fat texture (with larger activations to low-fat stimuli) when the oral stimuli are unpleasant.

Another interesting finding was that some brain regions (such as the hypothalamus and amygdala, Fig. 5) reflect the subjective fattiness of oral texture stimuli and not their affective value (pleasantness). Thus, the brain has subjective representations both of how fatty an oral texture stimulus is and how pleasant it is. This separation between representations of the identity of a stimulus and its affective value is advantageous, for the pleasantness of a stimulus may vary independently of its fattiness, as when, for example, a high-fat food is eaten to satiety. This is an important principle in the control of food intake, and it is of interest that it is found for fat as well as for other properties of oral stimuli such as their taste, odor, and flavor (Rolls 2005, 2009a).

These findings are potentially of relevance to understanding some of the factors underlying the obesity epidemic (Flegal et al. 2005; Krebs 2005) and how sensory properties of food such as oral fat texture become represented in terms of the subjective hedonic value, become related to the hypothalamic molecular mechanisms that reflect peripheral hunger and satiety signals (Morton et al. 2006; Schwartz and Porte 2005), and can contribute to driving excessive food intake (Davis et al. 2007; Franken and Muris 2005; Hetherington 2007; McGloin et al. 2002; Rolls 2005, 2007a, 2007b; Stice et al. 2008; Wardle et al. 2001). This is the first study we know in which brain regions involved in the representation of the subjective pleasantness of oral fat have been identified. This is potentially important as a step toward understanding whether obese people have higher activity in brain systems that represent the pleasantness of palatable and energy-dense foods, such as high-fat foods, and the importance of oral fat texture in this.

Supplementary Material

Supplementary Table 1 can be found at: http://www.cercor.oxfordjournals.org/.

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Notes

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Address correspondence to Prof Edmund T. Rolls, Oxford Centre for Computational Neuroscience, Oxford, UK and International Digital Laboratory, University of Warwick, CV4 7AL, UK. Email: edmund.Rolls@oxcns.org.

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