

# Changes in brain activity related to eating chocolate

## From pleasure to aversion

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### Summary

We performed successive H<sub>2</sub><sup>15</sup>O-PET scans on volunteers as they ate chocolate to beyond satiety. Thus, the sensory stimulus and act (eating) were held constant while the reward value of the chocolate and motivation of the subject to eat were manipulated by feeding. Non-specific effects of satiety (such as feelings of fullness and autonomic changes) were also present and probably contributed to the modulation of brain activity. After eating each piece of chocolate, subjects gave ratings of how pleasant/unpleasant the chocolate was and of how much they did or did not want another piece of chocolate. Regional cerebral blood flow was then regressed against subjects' ratings. Different groups of structures were recruited selectively depending on whether subjects were eating chocolate when they were highly motivated to eat and rated the chocolate as very pleasant [subcallosal region, caudomedial orbitofrontal cortex (OFC), insula/oper-

culum, striatum and midbrain] or whether they ate chocolate despite being satiated (parahippocampal gyrus, caudolateral OFC and prefrontal regions). As predicted, modulation was observed in cortical chemosensory areas, including the insula and caudomedial and caudolateral OFC, suggesting that the reward value of food is represented here. Of particular interest, the medial and lateral caudal OFC showed opposite patterns of activity. This pattern of activity indicates that there may be a functional segregation of the neural representation of reward and punishment within this region. The only brain region that was active during both positive and negative compared with neutral conditions was the posterior cingulate cortex. Therefore, these results support the hypothesis that there are two separate motivational systems: one orchestrating approach and another avoidance behaviours.

**Keywords:** feeding; taste; neuroimaging; motivation; orbitofrontal cortex

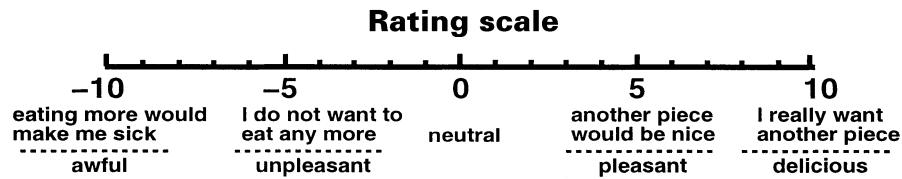
**Abbreviations:** ANOVA = analysis of variance; BA = Brodmann area; OFC = orbitofrontal cortex; rCBF = regional cerebral blood flow

### Introduction

Early cortical representations of visual, auditory and somatosensory information (e.g. 'primary' and 'secondary' areas) are in the unimodal neocortex. In contrast, the cortical representations of the chemical senses (taste and smell) are in the limbic and paralimbic cortex. This is true in primates (e.g. Tanabe *et al.*, 1975a, b; Pritchard *et al.*, 1986; Takagi, 1986; Price, 1990; Baylis *et al.*, 1995; Rolls *et al.*, 1996; Scott and Plata-Salaman, 1999) and in humans (Zatorre *et al.*, 1992; Jones-Gotman and Zatorre, 1993; Petrides and Pandya, 1994; Faurion *et al.*, 1999; Pritchard *et al.*, 1999; Small *et al.*, 1999). Thus, the representations of taste and smell are in regions of the brain that are thought to be important for

processing the internal and motivational state as well as the affective significance of external objects. Stimulation with taste and smell have been shown in neuroimaging studies to be potent elicitors of brain activity in limbic regions such as the amygdala, insula, orbitofrontal cortex, cingulate cortex and basal forebrain (e.g. Zatorre *et al.*, 1992; Small *et al.*, 1997b; Zald and Pardo, 1997; Sobel *et al.*, 1998; Zald *et al.*, 1998; Francis *et al.*, 1999; Royet *et al.*, 2000; Savic *et al.*, 2000).

Many neuroimaging studies have investigated brain activity evoked by affective stimuli, including chemosensory stimuli. For example, tastes (Zald *et al.*, 1998; Francis *et al.*, 1999),



**Fig. 1** Rating scale. Subjects used the rating scale to respond to two questions following ingestion of each piece of chocolate: (i) How pleasant or unpleasant was the piece of chocolate you just ate? (ii) How much would you like or not like another piece of chocolate?

flavours (Small *et al.*, 1997b), smells (Zald *et al.*, 1997; Francis *et al.*, 1999; Royet *et al.*, 2000), music (Blood *et al.*, 1999), sounds (Morris *et al.*, 1999a), faces (e.g. Morris *et al.*, 1996; Lane *et al.*, 1997; Phillips *et al.*, 1997), photographs (Lane *et al.*, 1997a; Paradiso *et al.*, 1999), pain (e.g. Coghill *et al.*, 1999; Tolle *et al.*, 1999) and touch (Francis *et al.*, 1999) have been investigated by functional neuroimaging in humans. However, in each case, different stimuli, or different stimulus intensities, had to be used to represent different hedonic valences. Recently O'Doherty and colleagues modulated the reward value of banana odour by having subjects eat bananas to satiety (O'Doherty *et al.*, 2000). Functional MRI was used to measure brain activity evoked by the same banana odour before and after feeding. Activity in the medial orbitofrontal cortex (OFC) decreased after satiety in response to the banana odour but not in response to a vanilla odour. This suggests that the medial OFC is preferentially activated to odours when they are rewarding. However, in this experiment the affective value was manipulated only from pleasant to neutral, leaving aversive unexplored. Furthermore, to our knowledge, no study has investigated the neuronal correlates of changes in the reward value of food produced by eating. Thus, despite the fact that much of the non-human animal literature of reward and stimulus–reward association learning is based upon feeding, the neural substrates of the affective and motivational components of feeding in humans remain relatively unexplored.

To investigate brain activity related to affective changes associated with feeding, we performed successive  $H_2^{15}O$ -PET scans on volunteers as they ate chocolate to beyond satiety. Thus the sensory stimulus was held constant, while its reward value, measured by affective ratings (Fig. 1; see also Methods), was manipulated by feeding. This paradigm is unique in that changes in regional cerebral blood flow (rCBF) can be attributed to changing reward value, independent of sensory input and behaviour (eating). Importantly, at the beginning of the experiment, eating the chocolate is consistent with the subjects' motivation, but as the chocolate is eaten to beyond satiety, behaviour comes to be inconsistent with subjects' motivation. Thus, the same act (eating) is both rewarding and punishing within this paradigm. However, because the change in reward value and motivational state necessarily occurs over time, the effects of order almost certainly contribute to neural activity.

Additionally, non-specific effects, such as autonomic and visceromotor changes, which are intrinsic to both eating and modulation of the reward value of food, were not assessed and thus cannot be disentangled from the overall neural response.

We predicted that rCBF would be modulated by the reward value of the stimulus in chemosensory regions, including the insula/operculum and orbitofrontal cortex, reflecting the involvement of these regions in both sensory and limbic aspects of the neural representation of food. Additionally, we expected that structures proposed to be involved in the initiation of feeding, such as the striatum and dopaminergic midbrain (Rolls, 1993), would be selectively active when subjects were motivated to eat chocolate and that the prefrontal cortex, which has been proposed to be involved in the decision to terminate eating (Tataranni *et al.*, 1999), would become increasingly active as subjects became increasingly motivated not to eat. We also predicted modulation of rCBF in limbic areas previously implicated in the positive and negative evaluation of sensory stimuli, and reward and punishment, including the subcallosal region, OFC, cingulate cortex, basal ganglia and anterior temporal lobe structures. Finally, we studied positive or negative changes in linear rCBF in specific brain regions as an indication of the extent to which that region is either preferentially activated by eating chocolate when it is 'pleasant and rewarding' versus 'unpleasant and punishing' or vice versa.

## Methods

### Pilot study

Pilot testing was conducted to determine what type of chocolate to use. Fifteen healthy subjects were asked to rank 20 kinds of chocolate from the most to the least pleasant. Lindt bittersweet (50% cocoa) and Lindt milk chocolate were consistently ranked as the most pleasant; however, subjects who preferred the bittersweet did not like the milk chocolate and subjects who preferred the milk chocolate did not like the bittersweet chocolate. In the PET experiment we therefore decided to give subjects the choice between Lindt bittersweet and milk chocolate. Two subjects chose bittersweet and seven subjects chose milk chocolate.

## Subjects

Nine healthy, right-handed volunteers who claimed to be chocolate-lovers participated in this study. Status as a chocolate-lover was determined by rating the subject on a scale from 1 to 10, where 10 referred to 'chocoholic' and zero was neutral; all subjects' ratings fell between 8 and 10. Five were women and four were men. All had eaten breakfast ~4.5 h prior to scanning, which took place in the early afternoon (12.30 hours). Hunger ratings, made on a scale of 1–10, where 10 corresponded to starving, 0 to very full and 5 to neither hungry nor full, indicated that subjects were in the range of not hungry to mildly hungry (ratings between 5 and 7) at the beginning of the experiment. All subjects gave informed consent to participate in the study, which was approved by the Ethics Committee of the Montreal Neurological Hospital.

## PET study

PET scans were performed with a Siemens HR+ scanner in 3D acquisition mode, using the  $H_2^{15}O$  water bolus technique to measure rCBF (Raichle *et al.*, 1983). Each subject also received an MRI scan for anatomical registration of PET data (Collins *et al.*, 1994) and resampling into a standardized stereotaxic coordinate system (Talairach and Tournoux, 1988).

Subjects underwent seven identical 'chocolate scans'. In each, ~10 s before scanning, subjects were given one square of chocolate and instructed to eat it by letting it melt in their mouth. Immediately after the scan was completed, subjects indicated how pleasant or unpleasant they found that piece of chocolate [question (i)] and how much they would like or not like to have another piece [question (ii)], using the rating scale shown in Fig. 1. Independent pilot testing with 20 subjects had suggested that these aspects of affective evaluation of chocolate were different. Specifically, subjects commonly reported that the chocolate still tasted pleasant but that they did not want to eat any more. Therefore, in the final version of the paradigm we included both ratings in order to capture as much information as possible about the subjects' subjective state. There were two main goals of these ratings. First, we wanted to have a measure of subjective state to determine how much chocolate to feed each subject. Secondly, we wanted to be able to regress rCBF against a value other than scan number in case changes in subjective affective state did not decrease in a linear fashion. Prior to the next scan, subjects were fed chocolate, one square at a time, making both ratings after eating each piece, until the rating dropped by at least two points. There was a rest period of at least 5 min between the termination of eating and the beginning of the next scan, to reduce the possibility of habituation. In total, subjects ate between 16 and 74 squares of chocolate, corresponding to between half and two-and-a-half 85 g bars of chocolate.

In addition to the chocolate scans, we included three control scans to address potential order effects. Specifically,

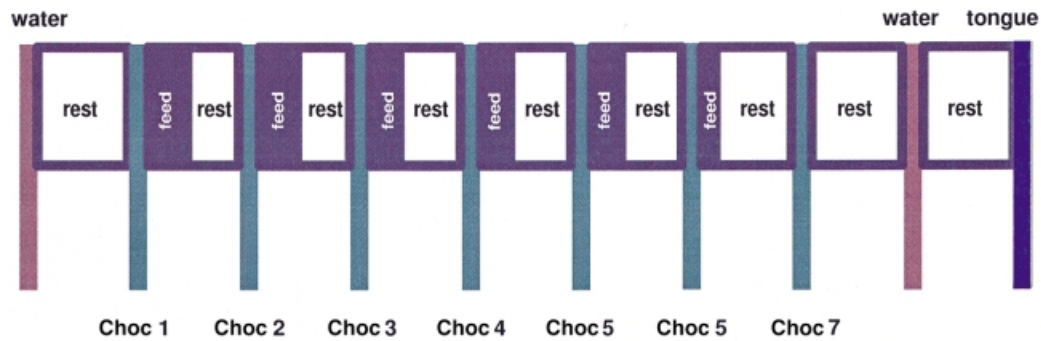
one 'water scan' (5 ml of water was injected slowly into the subject's mouth over the course of the scan) was included before the first ('water-pre') and after the last ('water-post') chocolate scan. In the final scan, subjects were asked to move their tongue as though they had chocolate in their mouth, making a total of 10 scans. The entire protocol is depicted in Fig. 2.

## Data analysis

Regression maps (Paus *et al.*, 1996) were calculated to assess the significance of the relationship between affective ratings and rCBF. Regression analysis involves correlating rCBF with incremental changes in a specific experimental variable. The data set for this analysis consisted of normalized CBF values obtained in each subject during each of the seven chocolate scan conditions, yielding a total of 63 image volumes. The effect of variation in affective rating (ii) was assessed by means of analysis of covariance, with subjects as a main effect and the affective rating as a covariate. The following model was fitted:  $E(y_{ij}) = a_i + b_P s_{ij}$ , where  $y_{ij}$  is the normalized CBF of subject  $i$  on scan  $j$ , and  $s_{ij}$  is the motivation rating at scan  $j$ . The subject effect ( $a_i$ ) is removed and the parameter of interest is the slope  $b_P$  of the effect of the change in affective rating on CBF. Values equal to or exceeding a criterion of  $t = 4.4$  for unpredicted peaks were deemed significant ( $P < 0.05$ , two-tailed). This yielded a false-positive rate of 0.025 in 200 resolution elements (which has dimensions of  $14 \times 14 \times 14$  mm for the main analysis) if the volume of brain grey matter is  $500 \text{ cm}^3$  (Worsley *et al.*, 1996). For predicted peaks, values equal to or exceeding a criterion of  $t = 3.2$  were considered significant, yielding a false-positive rate of 0.025 in 1.5 resolution elements in  $2 \text{ cm}^3$  (Worsley *et al.*, 1996).

Since satiety is a phenomenon that unfolds over time, we introduced several measures to decipher non-specific time effects from time effects associated with satiety. First, we employed covariation, a statistical technique designed to dissociate linearly related variables and then partial out the effect of the selected variable. Whereas this significantly reduces the likelihood of false-positive errors, it also increases the likelihood of false-negative errors due to the high degree of multicollinearity between scan order and affective ratings. Secondly, three control scans (water-pre, water-post and tongue movement) were also included in our study design to isolate scan order effects. Specifically, rCBF between the two water scans, which were identical except for their order in the experiment, could be compared in areas of interest (determined by the regression analysis and predictions); if there was no difference in activation in a region, we reasoned that linear increases or decreases were unlikely, because of the effect of scan order.

Finally, subtraction analysis (Worsley *et al.*, 1992) was performed to identify regions that may have responded non-linearly to increasing satiety. Specifically, the fourth chocolate scan, with affective ratings near neutral, was subtracted from



**Fig. 2** Pictorial representation of protocol. Purple bars represent water PET scans and turquoise bars represent chocolate PET scans. The tongue movement scan is represented by a blue bar. Interscan intervals consist of a feeding period and a rest period. The amount of chocolate eaten to produce the required decreases in affective ratings obtained from questions (i) and (ii) decreased gradually as the experiment progressed. This is depicted by the shrinking feed periods. Colour-coded bar graphs in Fig. 3 correspond to the colour scheme used here.

the first and last chocolate scans, in which affective ratings were high regardless of valence. These three chocolate scans (Choc 1, Choc 4 and Choc 7) were also each subtracted from the first scan (water-pre) and the ninth scan (water-post).

## Results

Regression of rCBF in each of seven chocolate scans (Choc 1 – Choc 7) against the ratings to question (ii) ('How much would you like or not like another piece of chocolate?') revealed significant rCBF decreases (as ratings changed from positive to negative) in the midline subcallosal region and midbrain; bilaterally, the inferior and middle temporal gyri, dorsal insula/frontal operculum, caudomedial OFC and caudate nucleus; on the right, in the occipitotemporal gyrus, dorsal insula/frontal operculum and ventral insula; and on the left, in the thalamus and putamen (Table 1) (Fig. 3A–C). When this analysis was performed with the ratings to question (i) ('How pleasant or unpleasant was the piece of chocolate you just ate?'), similar results were obtained. Therefore, we report only the results from the ratings given to question (ii).

When the regression equation was performed with scan order covaried out, only the subcallosal area, inferior temporal gyri and left insula remained significant. This analysis suffers from a propensity to false-negative error due to the shared variance associated with the linear relationship between the psychophysical ratings and scan order. Therefore, the areas that remain after this more stringent analysis are robustly related to the psychophysical ratings but not to scan order. However, given the likelihood of false-positive errors, we also considered peaks in the context of the literature (see Discussion).

Subtraction of the water-pre scan from the water-post scan revealed similar activity bilaterally in the dorsal insula, right ventral insula, thalamus, midbrain, left ventral striatum and hippocampus, suggesting that rCBF changes were due to eating chocolate as opposed to scan order (Table 2). This relationship is depicted graphically in Fig. 3. Specifically,

graphs of absolute rCBF changes in each of the 10 scans were constructed for spherical volumes with an 8 mm radius surrounding a given peak. Graphing the data in this way illustrates that rCBF was sensitive to condition and not simply scan order in many of the predicted peaks that were not significant after scan order was factored out.

Since the subcallosal peak was very large in both extent and magnitude, and since it is in a heterogeneous cortical region, in heterogeneous cortex, the data were reanalysed with reduced blurring (9 mm full width half maximum) to ascertain if there were in fact multiple areas of activity. In addition to the initial subcallosal peak, this analysis resulted in the emergence of bilateral caudomedial orbitofrontal activations, probably corresponding to area 13 (Table 1). Both peaks remained significantly active with scan order covaried out ( $t = 3.6$  on the right and  $t = 3.8$  on the left).

Regions where rCBF increased as ratings moved from positive to negative included the precentral gyri [Brodmann area (BA) 4] and the medial frontal gyri (BA 6, 8) [on the right, two peaks within the caudolateral OFC; on the left, the inferior (area 45/46) and middle frontal gyri (BA 6)] (Fig. 3D and Table 2). When the regression was performed with scan order covaried out of the equation, the peaks within the motor and premotor areas disappeared. In contrast, rCBF changes were greater in all other locations (Table 2). Additionally, two peaks in the anterior cingulate cortex that almost reached significance in the original regression were clearly significant with scan order covaried out. This was also true of blood flow in the right parahippocampal gyrus (BA 28/36). Areas where there were no rCBF differences between water-pre and water-post include the right supplementary motor area, caudolateral orbitofrontal cortex, cingulate, parahippocampal gyrus and left inferior frontal gyrus. For areas exhibiting rCBF increases during the experimental scans, this relationship is depicted graphically in Fig. 3.

To identify regions that may have responded non-linearly to increasing satiety, we performed subtraction analyses

**Table 1** rCBF decreases with decreasing reward value

Area	t-Value		Coordinates		
	Choc 1-7	Water <sup>†</sup>	x	y	z
Subcallosal region	11.4 <sup>‡</sup>	9.78	-1	25	-19
Left inferior temporal gyrus	6.1 <sup>‡</sup>	2.7	-49	-42	-21
Right inferior temporal gyrus	4.9 <sup>‡</sup>	5.4	52	-37	-19
Right dorsal insula/operculum*	6.1	1.3	36	1	15
Left dorsal insula/operculum*	4.3 <sup>‡</sup>	-1.0	-43	-4	13
Right lateral occipitotemporal gyrus/cerebellum	6.0	3.4	41	-59	-23
Left lateral occipitotemporal gyrus/cerebellum	5.2	3.6	-46	-64	-24
Right middle temporal gyrus	5.8	2.5	55	-56	13
Left middle temporal gyrus	4.9	2.0	-56	-62	6
Left thalamus*	5.3	1.0	-7	-26	9
Right caudomedial OFC	4.8 <sup>‡</sup>	4.7	16	27	-19
Left caudomedial OFC	5.3 <sup>‡</sup>	5.3	-18	25	-18
Midbrain*	4.4	1.4	3	-28	-13
Left putamen	4.2	1.5	-29	1	6
Right ventral insula	4.1	1.3	37	0	-7
Left caudate nucleus	3.9	1.0	-12	10	5
Right caudate nucleus	3.2	2.9	15	20	9
Left hippocampus	3.3	2.0	-27	-28	-7

\*Peaks shown in Fig. 3. <sup>†</sup>t-Values from the subtraction water-pre minus water-post. <sup>‡</sup>The value of t remained significant when scan order was covaried out of the regression equation.

comparing CBF in scans with corresponding ratings that differed the most from neutral (Choc 1 and Choc 7) with CBF in scans where ratings were near neutral (water-pre, water-post and Choc 4). Eight subtractions were performed and are summarized in Table 3. A peak located in the posterior cingulate cortex was present in both affective chocolate scans (Choc 1 and Choc 7) compared with the neutral chocolate scan (Choc 4) and in both water baseline scans (water-pre and water-post) compared with the neutral chocolate scan. In some cases the *t* value was slightly below significance (Table 3 and Fig. 3E). However, we did not covary non-linear time effects out of the equation, and these cannot be precluded from an interpretation of this result.

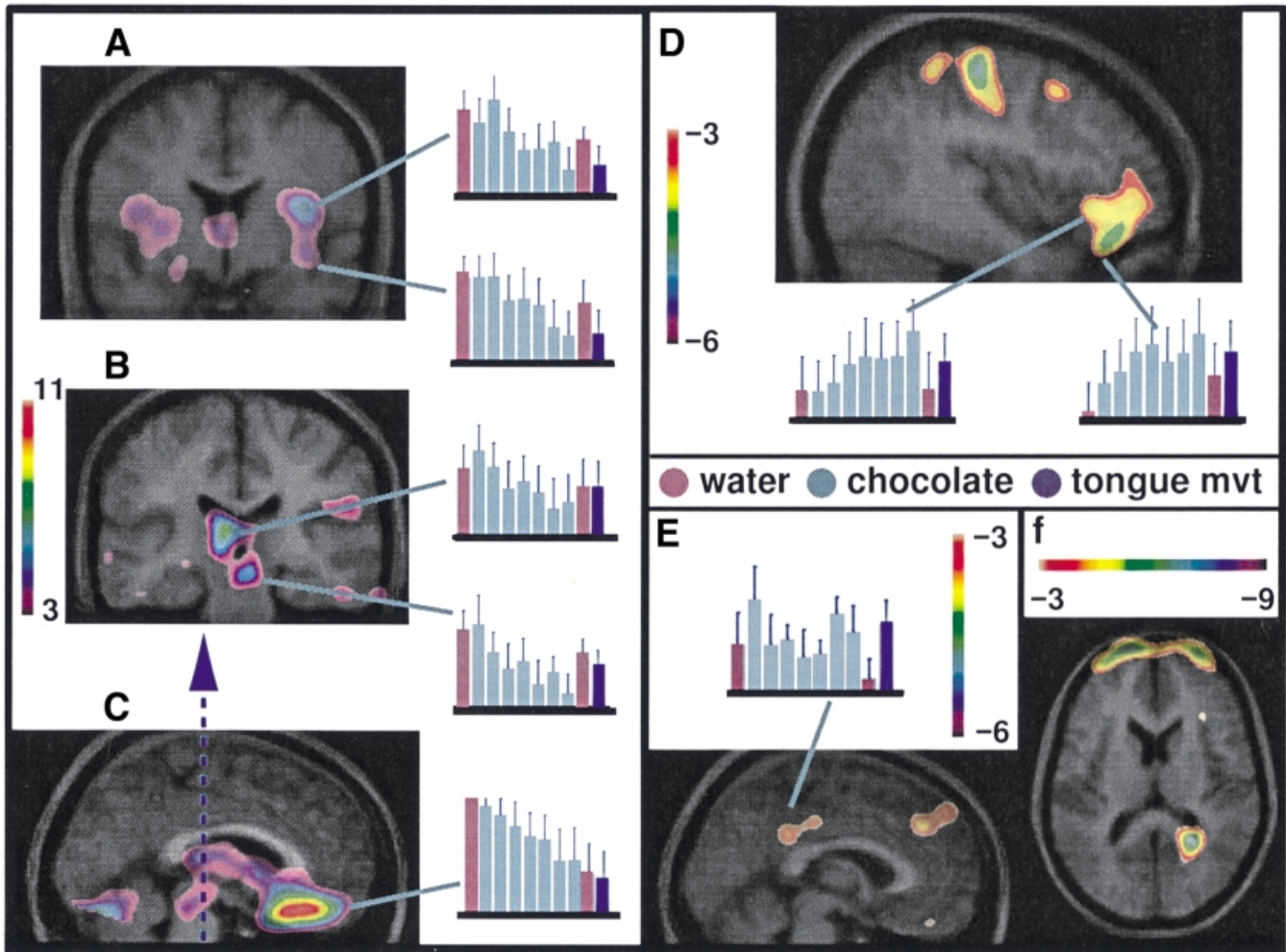
Repeated measures analysis of variance (ANOVA) of the psychophysical data revealed a significant interaction, indicating that the difference in slope between the ratings given in response to question (i) and question (ii) was significant [ $F(1,8) = 22, P = 0.002$ ]. Thus, motivation to eat declined more rapidly and to a greater extent than evaluation of pleasantness (Fig. 4). While these scales are only ordinal, it was nevertheless clear that there were points during the experiment when subjects did not want to eat chocolate but still found the chocolate pleasant. Since the psychophysical results indicated a difference in these two aspects of evaluation (at a single point in time) but the original regressions of each type of rating with blood flow did not reveal any differences, we compared the results of both analyses [rCBF regressed against ratings from questions (i) and (ii)] with scan order covaried out of the equation. In effect, these analyses reduced the total variance, increased sensitivity and allowed a more direct comparison between

rCBF related to the two different ratings. The comparison revealed a peak in the retrosplenial sulcus close to the isthmus (at 26, -54, 12), which correlated with ratings given to question (ii) to a greater extent than ratings given to question (i) ( $t = -8.7$  compared with  $t = -3.7$ ) (Fig. 3F). Specifically, blood flow increased with increasing motivation not to eat. This region has been shown recently to be part of the retrosplenial limbic cortex (Morris *et al.*, 1999).

A repeated measures ANOVA was also carried out to compare psychophysical data from nine pilot subjects who performed the identical experiment but who were sitting at a table as opposed to lying in a scanner with the data from subjects who participated in the PET study. There was no difference in the affective ratings between the groups [ $F(1,15) = 0.007, P = 0.97$ ]. This indicated that the pleasantness of chocolate and the motivation to eat declined at the same rate regardless of the experimental context. Consequently, it is unlikely that there was an interaction between the increasing unpleasantness of lying in the scanner and the increasing unpleasantness of the chocolate.

## Discussion

Eating chocolate while its reward value was manipulated by feeding resulted in differential engagement of the limbic, neocortical and chemosensory areas (Fig. 3). Thus, different groups of structures were recruited selectively, depending on whether subjects were eating chocolate when they were highly motivated to eat and rated the chocolate as very pleasant or whether they ate chocolate despite being satiated.



**Fig. 3** Cortical regions demonstrating significant rCBF correlations with affective rating for question (ii). Regression analyses were used to correlate rCBF from averaged PET data (Choc 1 minus Choc 7) with affective ratings taken immediately after these scans (see Methods). Correlations are shown as  $t$  statistic images superimposed on corresponding averaged MRI scans. The  $t$  statistic ranges for each set of images are coded by colour bars, one in each box. Bar graphs represent normalized CBF in an 8 mm radius surrounding the peak. The y-axis corresponds to normalized activity and the bars along the x-axis represent scans. The three colours represent scan type and correspond to the coloured bars in Fig. 2. Each bar graph corresponds to activations indicated by a turquoise line. (A) Coronal section taken at  $y = 1$  showing the decrease in rCBF in the primary gustatory area (bilaterally in the anterior insula/frontal operculum and in the right ventral insula). (B) Coronal section taken at  $y = -26$  showing decreases in rCBF in the left thalamus and medial midbrain (possibly corresponding to the ventral tegmental area). (C) Sagittal section taken at  $x = -1$  showing decreases in rCBF in the subcallosal region, thalamus and midbrain. (D) Sagittal section taken at  $x = 42$  showing the increase in rCBF in the right caudolateral orbitofrontal cortex. Activation is also evident in the motor and premotor areas. (E) Sagittal section taken at  $x = 8$  showing an increase in rCBF in the posterior cingulate gyrus (peak at 8, -30, 45) in subtraction analysis Choc 1 – water-post (see Table 3 and Results section). This was the only region where CBF was consistently greater in affective scans regardless of valence, compared with the neutral chocolate scan (Choc 4) and the two water baseline scans (water-pre and water-post). (F) Horizontal section at  $z = 12$  showing an increase in rCBF in the retrosplenial cortex (area 30) that correlated with affective rating (ii) but not the affective rating (i) when scan order was covaried out of the regression analysis (see Results and Methods).

### The cortical chemosensory areas

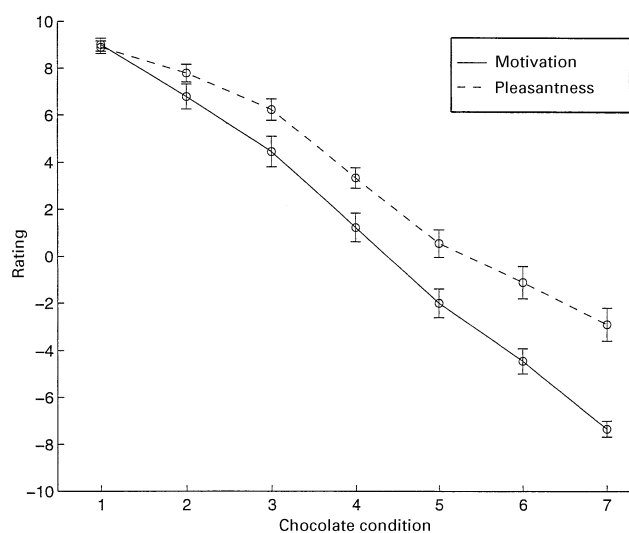
As predicted, activity in regions that probably correspond to the cortical gustatory areas was modulated by changes in the reward value of the chocolate (Fig. 3A and D), suggesting overlapping representation of sensory and affective processing of taste in humans. Specifically, as the reward value of the chocolate decreased, rCBF decreased bilaterally in the insula in regions shown by previous neuroimaging

studies to represent the primary gustatory area (Kinomura *et al.*, 1994; Small *et al.*, 1997a, b, 1999; Zald *et al.*, 1998; Faurion *et al.*, 1999; Francis *et al.*, 1999). In contrast, rCBF increased with decreasing reward value in a region of the caudolateral OFC, which has been implicated in gustatory processing in humans (Small *et al.*, 1997a, b, 1999) and has been suggested to represent a secondary gustatory area by Rolls and colleagues (Rolls *et al.*, 1990). When scan order

**Table 2** rCBF increases with decreasing reward value

Area	t-Value		Coordinates		
	Choc 1-7	Water <sup>†</sup>	x	y	z
Left precentral gyrus	-5.9	-3.9	-29	-26	57
Right precentral gyrus	-5.7	-3.4	21	-23	65
Right supplementary motor area	-5.8	-2.2	11	30	55
Left middle frontal gyrus	-5.4	-3.9	-28	17	50
Medial frontal gyrus	-4.9	-3.1	-1	-25	66
Right caudolateral orbitofrontal cortex*	-4.3 <sup>‡</sup>	-3	41	34	-19
Right caudolateral orbitofrontal cortex*	-4.2 <sup>‡</sup>	0	44	27	-5
Left inferior frontal gyrus	-4.0	-1.4	-48	30	3
Right cingulate cortex	-3.1 <sup>‡</sup>	-2	15	24	31
Cingulate cortex	-3.0 <sup>‡</sup>	-1	1	-7	33
Right parahippocampal gyrus	-2.8 <sup>‡</sup>	0	31	-21	-21

\*Peaks shown in Fig. 3. <sup>†</sup>t-Values from the subtraction water-pre minus water-post. <sup>‡</sup>The value of t remained significant when scan order was covaried out of the regression equation.



**Fig. 4** Average affective rating to questions (i) and (ii) across the seven chocolate conditions. Dotted line depicts ratings to question (i) (Pleasantness) and the solid line represents ratings to question (ii) (Motivation). Error bars represent the standard error of the mean. Ratings correspond to the rating scale shown in Fig. 1. Repeated measures ANOVA revealed a significant interaction, indicating that the slopes of the two lines are different (see Results).

was covaried out of the regression equation, rCBF changes in the left anterior insula and bilaterally in the caudolateral OFC remained significant. Thus, even when scan order was covaried out, modulation was observed in the cortical gustatory areas. Moreover, there was no difference in rCBF in these regions in the comparison of the two water scans, performed at the beginning and end of the session, indicating that rCBF changes were probably related to the changes in the affective and motivational value of the chocolate and not simply to an effect of scan order (see Results and Fig. 3).

Electrical stimulation of the human insula elicits alterations in gastrointestinal motility, taste hallucinations and a variety

of sensations associated with the digestive tract (Penfield and Faulk, 1955). Neuroimaging studies have shown this region to be sensitive to various processes related to feeding, including odour (Zatorre *et al.*, 1992; Small *et al.*, 1997b; Fulbright *et al.*, 1998; Francis *et al.*, 1999), taste (Small *et al.*, 1999), tongue somatosensory stimulation (Pardo *et al.*, 1997), swallowing (Hamdy *et al.*, 1999), facial expressions of disgust (Phillips *et al.*, 1997), thirst (Denton *et al.*, 1999) and hunger (Tataranni *et al.*, 1999). In accordance with these studies, O'Doherty and colleagues recently reported that odour-induced insular activation may be attenuated following satiation with the food related to that odour (in one of six subjects in their study) (O'Doherty *et al.*, 2000). The anterior insula is also consistently activated in studies using emotionally salient tasks or sensory stimulation (e.g. Breiter *et al.*, 1997; Kosslyn *et al.*, 1996; Lane *et al.*, 1997b; Thut *et al.*, 1997; Coghil *et al.*, 1999; Morris *et al.*, 1999a). The overlapping representation of affective, sensory and autonomic functions in the insular region is consistent with our result in supporting a role for the insula in feeding behaviour and underscoring the fact that the primary gustatory area may be better conceptualized as the ingestive cortex as opposed to a strictly sensory area. However, the multimodal nature of this region also raises the possibility that the insular modulation we observed may be related to numerous aspects of feeding in addition to the changes in reward value of the chocolate.

Taste-responsive cells in the monkey are not modulated by satiety until the OFC (Rolls *et al.*, 1988, 1989); furthermore, OFC taste cells decrease firing with satiety (whereas we report increased blood flow in an analogous region of OFC). There are several explanations for the discrepancy between the single-cell recordings and our findings. First, there are many examples of interspecies differences in the gustatory system. For example, in rats, physiological state has been shown to modulate the taste response as early as the brainstem (Jacobs *et al.*, 1988).

**Table 3** *t*-Values of activity in the posterior cingulate cortex in affective compared with neutral scans

Area	Ch1–Ch4	Ch7–Ch4	Ch1–wpre	Ch1 wpost	Ch4–wpre	Ch4–wpost	Ch7–wpre	Ch7–wpost
Posterior cingulate gyrus	3.2	2.8	3.3	3.9*	–	–	2.5	3.8

Ch = Choc; wpre = water-pre; wpost = water-post. \*Peak shown in Fig. 3.

Secondly, it is possible that our results are not contradictory but reflect a manifestation of the different scopes of the two methods (single-cell recording versus PET). For example, the electrophysiological studies could be biased in that cells must first display a response to taste in order to be investigated, and thus cells that increase response in the OFC with satiety could be missed. Or perhaps both response profiles exist in the human and are simply not discernible by PET. Finally, the representation of taste in the insula and OFC is sparse (~4% of the cells respond to taste) (Yaxley *et al.*, 1990). Consequently, it is impossible to know if the CBF changes we observed reflect activity of taste neurones per se rather than the modulation of cells responding to reward value or some autonomic aspect associated with being fed chocolate. In any case, the differential engagement of the cortical gustatory areas suggests that in humans taste cells have access to information regarding the internal state and reward value of the stimulus. Such an organization represents a departure from classical notions of sensory organization, which is based mostly upon examination of the visual and auditory modalities, both of which have primary cortical representation in the unimodal neocortex.

Differential activity was not observed in the primary olfactory region, thought to be located in the pyriform region of humans (Zatorre *et al.*, 1992; Small *et al.*, 1997b; Dade *et al.*, 1998; Sobel *et al.*, 1998; for review, see Zald and Pardo, 2000; Zatorre and Jones-Gotman, 2000). This area does not appear to be sensitive to olfactory sensory-specific satiety (O'Doherty *et al.*, 2000), although it is sensitive to subtle cognitive manipulations (Dade *et al.*, 1998) and different parameters associated with sniffing (Sobel *et al.*, 1998). The pyriform region has also been characteristically difficult to image with PET because of rapid habituation of the odour-induced response (Sobel *et al.*, 2000). Therefore, our failure to observe modulation may reflect the insensitivity of PET to temporal events as opposed to insensitivity of the region to changes in reward value or perceptual experience. Activity was observed in a region of the medial OFC that may correspond to the putative secondary olfactory area (Zatorre *et al.*, 1992). Here activity decreased as motivation to eat decreased. This result is consistent with single-cell recording studies of olfactory sensory-specific satiety in this region (Critchley and Rolls, 1996) and with the functional MRI study by O'Doherty and colleagues reporting that the response of the medial OFC to an odour decreases after subjects eat a related food to satiety (Doherty *et al.*, 2000). However, bimodal taste and smell-responsive cells and neurones that respond to the presence of fat in the mouth

have been found throughout the caudal OFC (Rolls and Baylis, 1994; Rolls *et al.*, 1999), suggesting that neural processing in this area may give rise to flavour perception in monkeys. Therefore, the changes observed in OFC activity may represent this region's involvement in flavour processing, as opposed, or in addition, to unimodal taste and smell processing.

We speculate that one reason for this integrated relationship between sensory and limbic processing of taste is that the brain regions involved in the processing of sensory stimuli that are primarily reinforcing, such as tastes and pain, developed in tandem with the limbic structures for the common purpose of avoiding danger (i.e. toxins and bodily harm) and incorporating nutrients for survival. This integrated relationship may account for phenomena such as single-trial conditioned taste aversion learning, in which the insula has been implicated (Gutierrez *et al.*, 1999) and for which there are clear adaptive advantages. It may also support addictive ingestive behaviour, including overeating and drug abuse, as well as the generation of drive and craving states (e.g. hunger and addiction). For example, Wise suggests that the brain circuitry underlying addiction originally developed to subserve feeding behaviour (Wise, 1997). Our results support this hypothesis, as the structures selectively active when ratings indicated that the chocolate had a strong positive valence overlap considerably with areas where increases in rCBF were evoked by cocaine versus saline injection (subcallosal region, caudate, putamen, thalamus, hippocampus, insula and ventral tegmentum) (Breiter *et al.*, 1997). Moreover, in addition to hunger (Tataranni *et al.*, 1999) and thirst (Denton *et al.*, 1999), both the insula and the OFC have been implicated in drug cravings (Wang *et al.*, 1999). In the present study, both the insula and the caudomedial OFC were active only when subjects were highly motivated to eat the chocolate. Interestingly, chocolate has been identified as the single most craved food in studies of food cravings (Rozin *et al.*, 1991), and chocolate addiction has been described (Hetherington and MacDiarmid, 1993).

### **Feeding-related circuitry**

The observation that the primary gustatory area and the chemosensory regions of the OFC are modulated by satiety suggests that these areas play a role in feeding behaviour in addition to sensory processing. The striatum, which has been proposed as a crucial structure for the initiation of feeding (Rolls, 1993), receives feeding-related projections from both the insula (Chikama *et al.*, 1997) and the caudomedial OFC



(Haber *et al.*, 1995), which is itself connected to the laterally located secondary gustatory area (Carmichael and Price, 1996). In the present study, rCBF in the dorsal striatum and caudomedial OFC decreased as motivation to eat declined. This result is also in accordance with the results of Tataranni and colleagues, who reported activity in these regions in a comparison of eyes closed resting and hungry with eyes closed resting and satiated (Tataranni *et al.*, 1999). These results suggest that the insula, striatum and caudomedial OFC are part of the neural network underlying the initiation of feeding. Interestingly, whereas we observed that activity in the midbrain (in the region of the ventral tegmental area) and subcallosal region correlated with eating chocolate when it is judged as pleasant, Tataranni and colleagues observed no change in these regions in the hungry state compared with the satiated state. One difference between the present study and the study by Tataranni and colleagues is that the subjects in our study received a rewarding stimulus during scanning, whereas their subjects were scanned after eating. This discrepancy is consistent with the proposal that the dopaminergic midbrain mediates the reward value of food (e.g. Mirenowicz and Shultz, 1996; Richardson and Gratton, 1998; Ahn and Phillips, 1999).

In contrast, rCBF in several motor and premotor areas, the left lateral prefrontal cortex (left middle and inferior frontal gyri), the bilateral OFC, the right anterior cingulate and the right parahippocampal gyrus increased with satiety. The anterior cingulate and parahippocampal gyrus have been reported to be involved in the affective evaluation of sensory stimuli (discussed below), but to our knowledge have not been implicated directly in feeding. Tataranni and colleagues reported rCBF increases with satiety in the dorsolateral prefrontal cortex and speculated that, since the prefrontal cortex has been shown to participate in the inhibition of inappropriate behaviours, this region may be important in decisions to terminate feeding (Tataranni *et al.*, 1999). Our result supports this hypothesis, and also suggests that, as in non-human primates (Rolls, 1997), the caudolateral OFC may also be a part of the neural network underlying feeding termination.

Regional CBF changes were not observed in the amygdala. The amygdala has been shown previously to be activated by aversive tastes (Zald *et al.*, 1998), smells (Zald *et al.*, 1997) and flavours (Small *et al.*, 1997a), and single-cell recording studies in the monkey suggest that at least some taste cells are sensitive to satiety (Yan and Scott, 1996). There is also some evidence that the human amygdala is sensitive to sensory-specific satiety of odours (O'Doherty *et al.*, 2000). There are several reasons why we may not have observed activity here. First is the potential for interspecies differences. Secondly, it is possible that excitatory and inhibitory activity cancelled each other out, rendering changes undetectable by PET (Yan and Scott, 1996). However, it is also possible that the amygdala is involved in evaluation of the affective valence of chemosensory stimuli when the association should be more permanent. Thus, amygdala activation is seen in

response to aversive tastes or to odours such as intestinal gas (Zald *et al.*, 1997), which will always be aversive, and in rats it is involved in conditioned taste aversion learning (e.g. Yamamoto *et al.*, 1994). In contrast, affective evaluation corresponding to satiety must be flexible, as satiety is transient, varying with a changing internal state. Our results, specifically the activity observed in the caudolateral (secondary gustatory area) and caudomedial OFC, are in agreement with the suggestion of Rolls and colleagues, based on the results of electrophysiological experiments in monkeys of stimulus reversal learning, that the orbitofrontal cortex is more important for flexible stimulus–reward associations (e.g. Rolls, 1993).

## *Affective evaluation*

### *Subcallosal region*

The largest area of rCBF change observed in our study was in the subcallosal region. This was also the most robustly activated region in a similarly designed study using musical dissonance to modulate the affective valence of a tune (Blood *et al.*, 1999). In both studies, regression analysis revealed that rCBF decreased as pleasantness decreased, as a function of either increasing satiety or increasing dissonance. Clinical evidence indicates that damage to this region results in disruption of goal-directed actions, which are guided by motivational and emotional factors (for review, see Damasio, 1994), and in rats it has been demonstrated that damage to the medial OFC results in the inability of a cue to access representational information about the incentive value of associated reinforcement (Gallagher *et al.*, 1999). Together, these results suggest that the subcallosal medial prefrontal region subserves a variety of behaviours guided by motivational and emotional factors, including feeding. rCBF in the caudomedial OFC also followed this pattern of activity (i.e. rCBF decreased with increasing satiety or dissonance), which is consistent with the postulated involvement of this area in stimulus–reward association learning (e.g. Rolls, 1996). A final similarity between our study and the musical study by Blood and colleagues was increasing rCBF in the right parahippocampal region as the stimuli became more unpleasant. In the study of musical dissonance, the subcallosal region, caudomedial OFC and parahippocampal gyrus were activated even though scan order was counterbalanced, and in the present study all three regions were still significantly activated when scan order was covaried out of the regression.

### *Medial versus lateral OFC activity*

The opposite pattern of rCBF was observed in the medial compared with the lateral OFC. As eating chocolate changed from rewarding to aversive, rCBF decreased in the medial OFC and increased in the immediately adjacent lateral OFC. Above, we have interpreted these results in relation to the chemosensory literature and our specific predictions regarding

feeding. However, the same region of the OFC that is implicated in taste and smell is thought to be involved in stimulus–reward association learning (e.g. Iversen and Mishkin, 1970; Rolls, 1996) in monkeys, and human neuroimaging studies of emotional state, reward, punishment and the affective evaluation of non-chemosensory stimuli consistently report OFC activation (e.g. Thut *et al.*, 1997; Blair *et al.*, 1999; Blood *et al.*, 1999; Morris *et al.*, 1999; Rogers *et al.*, 1999; Damasio *et al.*, 2000; O’Doherty *et al.*, 2001). Moreover, since food is often used as the primary reinforcer in stimulus–reward association learning paradigms, Carmichael and Price have suggested that higher-order processing of the sensory attributes of food in the OFC may provide the sort of hedonic representation that underlies much of what is meant by the term ‘reward’ (Carmichael and Price, 1996).

A similar dissociation between medial and lateral OFC activity has been noted by O’Doherty and colleagues (O’Doherty *et al.*, 2001). In their study, subjects performed an emotion-related visual reversal-learning task while undergoing functional MRI scanning. Lateral OFC activation was found in response to a punishing outcome, whereas medial OFC activation occurred in response to a rewarding outcome. These results suggest that the neural representations of reward and aversion are separated within these regions. Elliott and colleagues have also described a dissociation between medial and lateral OFC function based on a review of functional neuroimaging studies conducted in their laboratory (Elliott *et al.*, 2000). These authors suggest that the medial OFC is involved in monitoring and holding in mind reward values, whereas the lateral OFC is recruited when a response previously associated with a reward has to be suppressed. Our results partially support this notion. Here, the medial OFC is active when subjects report that eating chocolate is rewarding. During this time, their behaviour is in accordance with their will. As their desire to eat decreases and their behaviour (eating) comes to be inconsistent with their will (indicated by their affective ratings), the medial OFC activity decreases and the lateral OFC activates. Thus, in the present study, lateral OFC activity occurs when the desire to stop eating must be suppressed in order to conform to the demands of the experiment.

### *Posterior cingulate cortex*

Subtraction analysis (see Results) revealed only one significant non-linear effect in this experiment. Specifically, rCBF in the posterior cingulate cortex was higher when subjects rated chocolate as highly pleasant or highly unpleasant than when they rated it as neutral (Table 3 and Fig. 3E). As further verification of this effect, we compared the pleasant and unpleasant chocolate scans individually with the two neutral water baseline scans (water-pre and water-post) (Table 3). The effect held: both chocolate scans activated the posterior cingulate to a greater extent than did the neutral water scans. This result is in accordance with Maddock, who,

in a recent review of the neuroimaging literature, concluded that this is the brain area that is most consistently activated by emotionally salient stimuli, regardless of valence (Maddock, 1999). Thus, our finding suggests at least some overlap between the brain regions involved in processing positive and negative valenced stimuli. However, since this is the only region we observed with such an rCBF response profile, our study supports the notion (LeDoux, 1996) that different neural substrates underlie two motivation systems, one dealing with positive/appetitive stimuli and a second dealing with negative/aversive stimuli.

Finally, in the present study, the subjects’ ratings in response to question (ii) (‘How much would you like, or not like to have another piece of chocolate?’) decreased faster and to a greater extent than their ratings to question (i) (‘How pleasant or unpleasant was the chocolate that you just ate?’) (Fig. 4). In other words, there was a point in time at which subjects reported that the chocolate tasted pleasant, yet they did not want to eat any more. Although question (i) required the subject to think about the pleasantness of the chocolate eaten immediately prior to the question, whereas question (ii) required the subject to report how motivated they were to eat a piece of chocolate in the immediate future, we feel the ratings we have collected capture two different subjective states that cannot be accounted for by time alone. Berridge and colleagues have described a dissociation between taste reactivity measures (characteristic responses to pleasant or aversive tastes) and acceptance or rejection behaviours in rats (for review, see Berridge, 1996). These two states are described as ‘liking’ and ‘wanting’, respectively. It is possible that the ratings we have gathered depict these two dimensions of affective evaluation, question (i) addressing liking and question (ii) addressing wanting. We therefore decided to pursue our psychophysical result. When scan order was covaried out of the regression equation, a region of the retrosplenial cortex, probably corresponding to limbic area 30 (Morris *et al.*, 1999b), was identified that correlated to a greater extent with ratings given to question (ii) compared with ratings given to question (i). While this finding is certainly preliminary, we speculate that this region of the brain may form part of a neural substrate for the subjective difference between finding the chocolate pleasant but not wanting to eat any more (Fig. 3F). This interpretation is consistent with Berridge’s proposal that there are separate neural systems underlying wanting and liking (Berridge, 1996).

### *Strengths and weakness of the paradigm*

The paradigm employed here to evaluate affective changes associated with feeding is unique because the same stimulus was used to evoke the entire affective spectrum (positive and appetitive to negative and aversive). At the beginning of the experiment, eating the chocolate was consistent with subjects’ motivation, but as the chocolate was eaten to beyond satiety, behaviour came to be inconsistent with the subjects’

motivation. Thus, the same act (eating) is both rewarding and punishing within this paradigm and corresponding neural activity can be assessed. However, since our subjects were instructed to eat beyond satiety (in order to make the act of eating chocolate punishing), the paradigm did not mimic the natural satiation associated with normal termination of a meal in this study.

The major limitation of this paradigm is that, since affective changes associated with feeding occur over time, order effects almost certainly contributed to our results. However, time—and thus order—effects are inherent to the process of affective change associated with eating to satiety (and beyond). We attempted to address order effects by including ‘control’ water and tongue-movement scans at the beginning and at the end of the experiment and by employing covariation, a statistical technique designed to dissociate linearly related variables and then partial out the effect of the selected variable. Nevertheless, we acknowledge that neither of these techniques controls for order completely. Additionally, non-specific effects, such as autonomic and visceromotor changes, which are intrinsic to both eating and the modulation of the reward value of food, were not assessed and thus cannot be disentangled from the overall neural response.

Finally, we chose to collect affective ratings immediately after each scan, as opposed to during each scan. This choice was based on our decision to avoid confounding reward-related processing in the OFC and decision-making-related activity in the OFC. The disadvantage of this decision is that ratings reflected the subjective state immediately after eating the chocolate as opposed to the subjective state during the scan. However, given that changes in ratings occurred steadily and gradually, it is unlikely that these two states differed significantly.

## Conclusion

We observed differential recruitment of brain regions depending on whether subjects ate chocolate when they were highly motivated to eat and rated the chocolate as pleasant, or whether they were highly motivated not to eat and rated the chocolate as unpleasant. The only brain region that was active during both positive and negative compared with neutral conditions was the posterior cingulate cortex. Thus, the present study supports the hypothesis that different neural substrates underlie two motivation systems, one dealing with positive/appetitive stimuli and a second with negative/aversive stimuli. This functional dissociation was particularly apparent in the OFC, where the rCBF decreased in the medial OFC and increased in the lateral OFC as the reward value of chocolate changed from pleasant to aversive. This pattern of activity indicates that there may be a functional segregation of the neural representation of reward and punishment within these regions.

As predicted, modulation was seen in cortical chemosensory areas including the insula and OFC, suggesting that these chemosensory regions contribute to feeding behaviour

by encoding changes in the value of food reward in addition to sensory processing. This result is important because it demands a reconceptualization of these regions as heteromodal ingestive cortices with overlapping representations of sensory and affective processing of taste and smell, which departs from classical notions of primary and secondary sensory areas. Additionally, we observed activity in several brain regions previously implicated in feeding by studies with non-human animals including the striatum, midbrain and OFC. These results provide a reference against which future studies of eating disorders and obesity in humans may be compared.

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