

# Neural contributions to the motivational control of appetite in humans

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## Abstract

The motivation to eat in humans is a complex process influenced by intrinsic mechanisms relating to the hunger and satiety cascade, and extrinsic mechanisms based on the appetitive incentive value of individual foods, which can themselves induce desire. This study was designed to investigate the neural basis of these two factors contributing to the control of motivation to eat within the same experimental design using positron emission tomography. Using a novel counterbalanced approach, participants were scanned in two separate sessions, once after fasting and once after food intake, in which they imagined themselves in a restaurant and considered a number of items on a menu, and were asked to choose their most preferred. All items were tailored to each individual and varied in their incentive value. No actual foods were presented. In response to a hungry state, increased activation was shown in the hypothalamus, amygdala and insula cortex as predicted, as well as the medulla, striatum and anterior cingulate cortex. Satiety, in contrast, was associated with increased activation in the lateral orbitofrontal and temporal cortex. Only activity in the vicinity of the amygdala and orbitofrontal cortex was observed in response to the processing of extrinsic appetitive incentive information. These results suggest that the contributions of intrinsic homeostatic influences, and extrinsic incentive factors to the motivation to eat, are somewhat dissociable neurally, with areas of convergence in the amygdala and orbitofrontal cortex. The findings of this study have implications for research into the underlying mechanisms of eating disorders.

## Introduction

The neural basis of the control of appetite has yet to be defined fully due to difficulties in disentangling genetically determined predispositions (Barsh *et al.*, 2000), biochemical signals (Schwartz *et al.*, 2000; Tschoop *et al.*, 2000), and affective and motivational factors (Dickinson & Balleine, 1994; Small, 2002). Using a subtractive-contrast imaging design, we have attempted to dissect two complementary contributions to the 'final common pathway' of food value and ensuing hunger. First, if one has not eaten for a long while, a cascade of homeostatic processes will induce perceptions of hunger. Secondly, if one is *not* hungry but is presented with stimuli associated with food (the smell or sight of preferred food), then this can elicit perceptions of hunger and concomitant bodily responses, such as salivation. They can be defined as 'intrinsic' and 'extrinsic' factors, respectively, as homeostatic-induced hunger largely arises from processes within the individual, whereas food preferences and the associated incentive properties of those foods are learnt from prior experience with the foods (Arana *et al.*, 2003). It has yet to be demonstrated whether in humans dissociable neural systems underlie these two contributions, which is

crucial for the understanding of both normal eating behaviour and the pathophysiology of eating disorders.

Research to date has implicated the hypothalamus and insula as key areas in the neural control of intrinsic processes (Burton *et al.*, 1976; Rolls, 1981; Kalra *et al.*, 1999; Liu *et al.*, 2000; Small *et al.*, 2001). The amygdala and orbitofrontal cortex (OFC) may also be activated in response to changes in intrinsic processes; largely because of the resulting change in the incentive value of stimuli, but the OFC may also be involved in feeding termination (O'Doherty *et al.*, 2000; LaBar *et al.*, 2001; Morris & Dolan, 2001; Small *et al.*, 2001; Tataranni & DelParigi, 2003). Recent imaging studies have shown that extrinsic processes appear to be subserved by the amygdala and the OFC (Gottfried *et al.*, 2003; Killgore *et al.*, 2003; Kringelbach *et al.*, 2003), which supports electrophysiological and lesion studies that suggest the amygdala codes for the emotional significance of the stimuli (Parkinson *et al.*, 2001; Balleine *et al.*, 2003), and the OFC uses this information to guide behaviour according to the current needs of the individual (Pickens *et al.*, 2003; Tremblay & Schultz, 1999; Baxter *et al.*, 2000; Pears *et al.*, 2003).

The aim of this study was to manipulate both intrinsic and extrinsic factors that contribute to food motivation in humans. The methods used allowed a naturalistic examination of the concomitant metabolic, psychological and neural processes of hunger and satiety through a novel counterbalanced approach. Positron emission tomography (PET) was used to scan participants (reading and choosing between high- and low-incentive food items from a series of restaurant menus)

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in separate sessions after fasting or after food intake. Food items were individually tailored on the basis of the replies to a food preference questionnaire presented prior to scanning sessions. It was hypothesized that increased activity of the hypothalamus, insula, amygdala and OFC would be associated with the state of hunger, whilst increased activity in the OFC would be associated with satiety (intrinsic factors). Only the amygdala and OFC would be activated by the prospect of high-incentive foods (extrinsic factor; Arana *et al.*, 2003). Furthermore, it was predicted that the two systems would converge in the amygdala and OFC, representing the global incentive value of food within the current context in order to direct appropriate action.

## Materials and methods

### Participants

Twelve right-handed male healthy volunteers (mean  $\pm$  SD age,  $26.3 \pm 7.2$  years; mean  $\pm$  SD body mass index,  $23.6 \pm 2.3$ ), with no previous history of neurological or psychiatric disorder, were recruited from a panel of volunteers at the Cognition and Brain Sciences Unit in Cambridge and through advertisements. Written, informed consent was obtained from all of the participants before commencing the study, which was approved by the Cambridge Local Research Ethics Committee and the United Kingdom Administration of Radioactive Substances Advisory Committee.

### Experimental design

A two-factor design (hunger state and incentive value) was used, with each participant being scanned on two separate occasions: once whilst satiated and once whilst hungry. The order of both sessions and trials within each condition was counterbalanced across participants. For the hunger condition, participants were asked to fast overnight ( $\approx 18$  h). For the satiated condition, participants were asked to eat until they were full (approximately an hour before the scheduled scanning slot) and to eat enough not to be hungry for the entire scanning time. A blood sample was taken prior to each PET session in order to measure plasma levels of glucose, leptin, insulin and free fatty acids. Visual analogue scales were given to the participants immediately before each PET session to obtain subjective ratings of 'hunger', 'fullness' and 'desire to eat' at that moment.

During both separate sessions, each participant received six consecutive scans at 8-min intervals. Two minutes and 15 s prior to the beginning of each scan, an instructional screen was presented to participants and the task began 15 s before the acquisition of data. Each participant was scanned in the presence of low background noise and dimmed ambient lighting. The task displays were presented on a touch-sensitive screen controlled by a Pentium microcomputer. The screen was mounted at a viewing distance so that the participant could touch all areas of the screen with the index finger of his right hand.

### Psychological task

During the scans, all participants were given the 'Restaurant Task', a program created using Visual Basic 6.0. Participants imagined that they were attending a restaurant for an evening meal, and were required to read and select food items from a menu that had been created using specific knowledge of each individual's food preferences, obtained by asking the participant to complete a food preference questionnaire at least a week prior to scanning. The task varied between two conditions of 'high' and 'low' incentive. The

high-incentive condition consisted of menu items that were predicted to be well liked by the participant, whereas the low-incentive condition consisted of food items that the person was predicted to be indifferent to. Foods that individuals disliked were omitted in order to avoid any aversive reactions. Menu items were matched across incentive conditions for style and sentence length. Each trial consisted of three menu items: three starters, three main courses or three desserts. A total of three screens could be presented for each trial. Participants were asked to consider each item and then make a choice, as they would in a restaurant, by touching their most preferred item. The latency for each decision was recorded and the number of screens seen during actual scan acquisition was also noted.

Following the second scanning session, the participant was asked to rate from 1 to 5 each menu item in terms of the incentive value, with 1 reflecting absolute indifference (i.e. an item not likely to be chosen in a restaurant) and 5 representing a high-incentive value (i.e. an item truly liked and inclined to be selected in a restaurant). The participant also rated the difficulty in making the choice between the three items presented on each trial, from 1 (difficult) to 5 (easy).

### Imaging acquisition and data analysis

PET procedures were conducted at the Wolfson Brain Imaging Centre (Addenbrooke's Hospital, Cambridge, UK), using the GE Advance System. For each scan, 35 image slices were produced at an intrinsic resolution of approximately  $4.0 \times 5.0 \times 4.5$  mm. Each participant received a 20-s i.v. bolus of  $\text{H}_2^{15}\text{O}$  through a forearm cannula at a concentration of 300 MBq/mL and a flow rate of 10 mL/min. With this method, each scan provides an image of regional cerebral blood flow (rCBF) integrated over a period of 90 s from when the tracer first enters the cerebral circulation. In addition, a three-dimensional magnetic resonance imaging (MRI) volume ( $256 \times 256 \times 128$  pixels, 3 mm thick) was acquired for each participant. Structural MRI scans obtained prior to the PET scans were used to exclude those with previously undetected brain pathology.

Scans from individual sessions were preprocessed separately, and then combined for the group statistical analysis, using SPM99 (provided by the Wellcome Department of Imaging Neuroscience, London, UK). Scans within each session were realigned to the first image from that session, and then the mean images of each session were co-registered. The scans were normalized for global rCBF value, and spatially normalized to the standard brain, based on those from the Montreal Neurological Institute. Finally, the scans were smoothed using a Gaussian kernel at 12 mm FWHM. In order to reduce scan order and movement artefacts, the movement parameters for the scans relative to the anterior commissure were calculated and added into the analysis as a covariate of no interest, together with a scan time order covariate. A total of three scans, each belonging to different participants, were not included in the analysis due to excessive movement during scanning.

Blood flow changes between experimental conditions were estimated for each voxel according to the general linear model using SPM99. A number of anatomically specific *a priori* hypotheses were tested about activation patterns in the hypothalamus, amygdala and the OFC within defined subtractions. In particular, activation was expected in all three regions when testing the main effect of hunger (Hunger–Satiety), in the OFC for the main effect of satiety (Satiety–Hunger), and the amygdala and OFC when testing the main effect of incentive (High–Low). In the latter case, a prediction was made regarding the role of the medial sector of the OFC, specifically. This prediction was based on evidence from both non-human primate research (Iversen &

Mishkin, 1970; Tremblay & Schultz, 1999) and human neuroimaging (Elliott *et al.*, 2000; O'Doherty *et al.*, 2001; Small *et al.*, 2001), which suggests that functions of the medial and lateral OFC can be dissociated, and that the medial OFC, in particular, is involved in the processing of reward value.

Accordingly, small volume corrections were applied (Worsley *et al.*, 1992, 1996), using *vol\_corr* software (Brett, MRC Cognition & Brain Sciences Unit, 1999). The volume of the hypothalamus (bilateral) was set as a box with the dimensions 10 × 12 × 10 mm as per Arnow *et al.* (2002), resulting in an intensity threshold of  $t = 2.84$ , corresponding to a corrected probability of  $P < 0.05$ . A region of interest was created for the amygdala using MRICro version 1.35 (Rorden & Brett, 2000). The calculated volume of the amygdala region of interest (ROI) was 4435 mm<sup>3</sup> and the corresponding intensity threshold for significance ( $P < 0.05$ , corrected) was  $t = 3.28$ . For the main effect of incentive only, a ROI for just the medial OFC was constructed. A conservative estimate for the volume was set at 12,000 mm<sup>3</sup>, resulting in a corrected threshold of  $t = 3.46$ . For all other comparisons, a separate ROI was constructed to include all of the OFC with a calculated volume of 21,486 mm<sup>3</sup>. Accordingly, the intensity threshold for significance ( $P < 0.05$ , corrected) was set to  $t = 3.6$ .

In addition to the main effects of hunger state and incentive, the interaction between these effects was investigated. All scans were included in the analysis, in which the effect of hunger on incentive was examined ([Hunger: High–Low] – [Satiety: High–Low]). Previous research suggests convergence of these factors in the OFC (Rolls *et al.*, 1989; O'Doherty *et al.*, 2000).

Finally, for the rest of the brain, an exploratory search was conducted, so the statistical threshold for reporting a peak as significant was set at  $P < 0.05$ , corrected for multiple comparisons across the whole brain.

### Behavioural statistical analysis

Non-parametric behavioural data (incentive and difficulty ratings) were analysed using Wilcoxon signed ranks test and Mann–Whitney *U*-test, as applicable. Parametric data, such as response time (i.e. time duration from menu screen onset to the onset of the next trial) and the number of screens reached during the different conditions were analysed using a repeated-measures ANOVA. Analysis was conducted using SPSS (version 10).

## Results

### Biochemical data

Blood samples taken prior to scanning demonstrated that most participants had been in the appropriate physiological state for each condition. As expected, insulin levels after food intake were significantly higher, compared with those in the fasting condition ( $z = -2.666$ ,  $P = 0.008$ ). Plasma glucose levels remained in the normal range for all the participants, with higher levels after eating. However, this difference was not significant ( $z = -1.955$ ,  $P = 0.51$ ), probably due to the counteracting effects of the rise in insulin. Levels of free fatty acids were significantly elevated in the fasting state compared with levels after eating, as would be expected ( $z = -2.666$ ,  $P = 0.008$ ). Levels of plasma leptin were not significantly different for the two states ( $z = -1.823$ ,  $P = 0.068$ ), in line with its main role as an adiposity signal rather than a satiety signal (Schwartz *et al.*, 2000). Over the course of the experiment, one participant was excluded from the study after insulin levels were shown not to be elevated for the satiated condition, suggesting he had not eaten when instructed (Table 1).

TABLE 1. Mean levels of plasma glucose, insulin, leptin and free fatty acids

	Hunger condition	Satiety condition
Glucose mmol/L	4.5 ± 0.2	5.3 ± 0.3
Insulin pmol/L	30.0 ± 6.3	191.9* ± 28.0
Leptin µg/L	2.6 ± 0.8	2.8 ± 0.9
FFAs µmol/L	675.3 ± 108.1	205.1* ± 32.9

Data are presented as mean ± SEM. \*Difference between the means significant at  $P \leq 0.05$ .

### Behavioural data

As shown by the mean self-ratings on the visual analogue scales in Fig. 1, all participants reported significantly greater hunger ( $z = -2.934$ ,  $P = 0.003$ ) and lower fullness ratings ( $z = -2.803$ ,  $P = 0.005$ ), and a stronger desire to eat ( $z = -2.807$ ,  $P = 0.005$ ) after the overnight fast. In addition, food items in the high-incentive condition were rated to be of higher incentive than those in the low-incentive condition, confirming that the food items had been appropriately categorized ( $z = -2.936$ ,  $P = 0.003$ ; see Fig. 2). Furthermore, subjects overall judgement of choice difficulty was not significantly different across conditions [incentive ( $z = -1.513$ ,  $P = 0.130$ ), hunger ( $z = -0.415$ ,  $P = 0.678$ ); see Fig. 2].

No significant differences were observed for response time per menu screen across the conditions (hunger: mean = 44.90, SE = 3.00; satiety: mean = 43.12, SE = 2.57;  $F_{1,10} = 0.482$ ,  $P = 0.503$ ) (high incentive: mean = 43.41, SE = 2.61, low incentive: mean = 44.61, SE = 2.61;  $F_{1,10} = 0.558$ ,  $P = 0.472$ ). Participants viewed on average three screens within each trial, and no difference was found between the number of screens read in each PET acquisition across all conditions ( $P > 0.05$ ).

### Neuroimaging data

#### Regions of activation associated with manipulation of intrinsic motivational factors

To investigate the rCBF changes associated with hunger and satiety, the six scans within each imaging session were compared directly

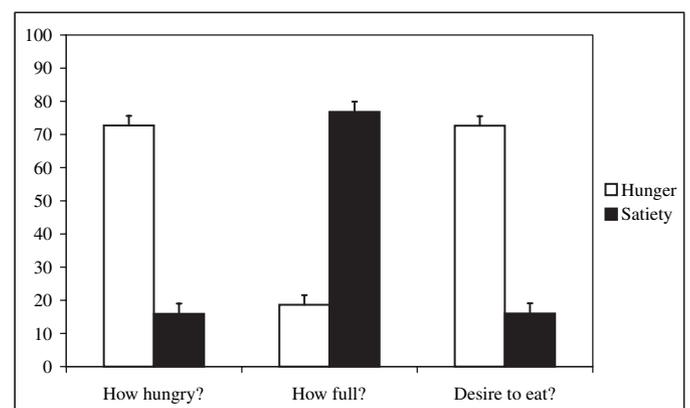


FIG. 1. Self-report ratings for hunger, fullness and desire to eat. Average subject ratings (with SE bars) on visual analogue scales given prior to each scanning session (after fasting 'Hunger' and after food intake 'Satiety'). The scales were as follows: How hungry do you feel? From not at all hungry (0 mm) to as hungry as I have ever felt (100 mm); How full do you feel? From not at all full (0 mm) to as full as I have ever felt (100 mm); How strong is your desire to eat now? From none at all (0 mm) to strongest I have ever felt (100 mm).

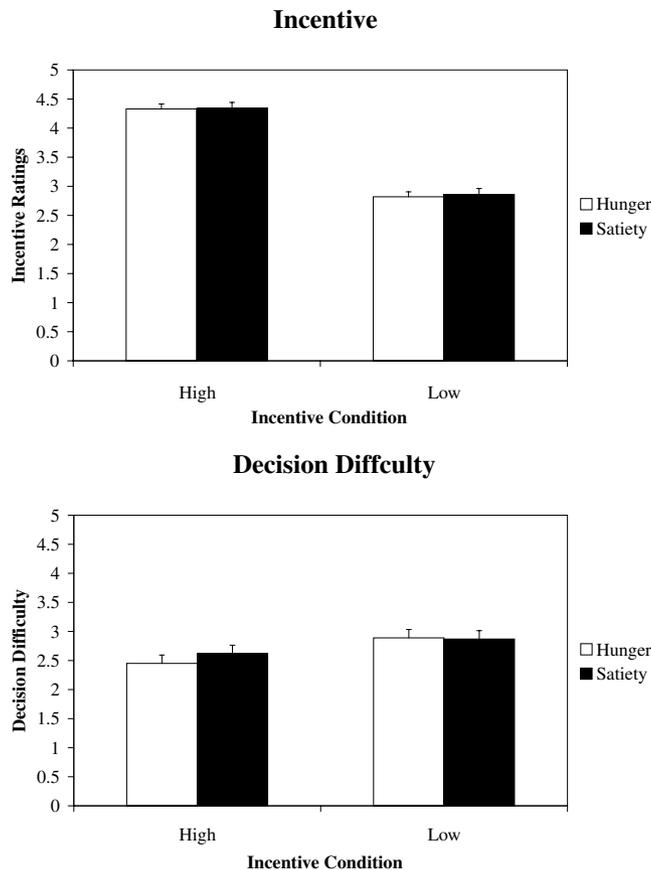


FIG. 2. Subject-rated behavioural measures. Incentive – average subject ratings (with SE bars) of incentive value of menu items in each condition; ‘High’ for high-incentive items and ‘Low’ for low-incentive items; ‘Hunger’ after fasting and ‘Satiety’ after food intake. Higher scores on the scale of 1–5 indicated a higher incentive value for menu items. Decision difficulty – average subject ratings (with SE bars) of the difficulty of the decision between menu items in each condition (as above). Lower scores on the scale of 1–5 indicated a more difficult decision was made when choosing between menu items.

(collapsed across incentive). As hypothesized, when contrasted with satiety, hunger was associated with significant rCBF changes in the hypothalamus, amygdala and insula cortex and, in addition, significantly greater rCBF in bilateral striatum, anterior cingulate, thalamus and brain stem (Table 2; Fig. 3). When contrasted with hunger, satiety, as predicted, was associated with significantly greater rCBF in the lateral OFC, as well as bilateral occipital cortex, inferior temporal cortex and posterior temporal cortex (Table 2; Fig. 3).

#### Regions of activation associated with manipulation of extrinsic motivational factors

To investigate the rCBF changes associated with incentive, all of the 12 scans from both imaging sessions were compared directly, regardless of hunger state. As hypothesized, the comparison between the high- and low-incentive conditions (High–Low) revealed greater activation in the vicinity of the amygdala that marginally missed criterion, according to our significance threshold (Table 2). For this contrast, significantly greater activation was also found in the left medial OFC, in the gyrus rectus, according to Chiavaras & Petrides (2000) (Table 2, Fig. 4). When activity associated with low incentive was subtracted from high incentive, no significant differences were observed.

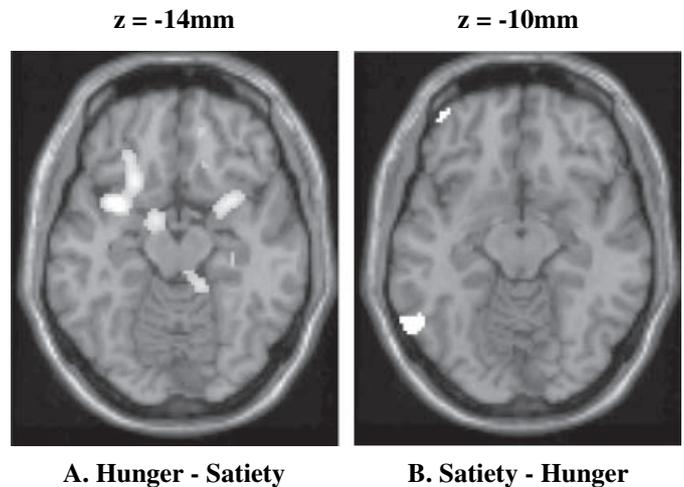


FIG. 3. Significant rCBF changes in the contrast between Hunger and Satiety. (A) Horizontal slice ( $z = -14$  mm) depicting the hypothalamus, which shows increased rCBF after fasting (Hunger condition) than after food intake (Satiety condition). This slice also shows increased rCBF in the insula cortex; see Table 2 for coordinates and  $t$ -values. (B) Horizontal slice ( $z = -10$  mm) depicting the lateral OFC, which shows increased rCBF after food intake (Satiety condition) than after fasting (Hunger condition). PET data were superimposed on to a standard normalized brain volume from SPM99.

An additional area of activation was observed in the left OFC in the interaction between hunger and incentive value ( $t = 3.53$ ), that missed significance marginally according to our corrected threshold of  $t = 3.6$ ,  $P < 0.05$ ; Fig. 5A. This peak lies approximately on the anterior orbital gyrus (according to probabilistic maps of Chiavaras & Petrides, 2000). For high incentive trials, more activation was

TABLE 2. Significant changes in rCBF in comparison between hunger and satiety, high and low incentive, and the interaction across those factors

Comparisons and regions	Left/right	Co-ordinates			$t$ -value
		$x$	$y$	$z$	
<b>Hunger–Satiety</b>					
Hypothalamus*	L	-10	-2	-14	4.21
Amygdala*	R	16	-6	-30	4.42
Insula*	L	-32	8	-14	5.11
Brain stem (NST)		0	-26	-34	6.39
Striatum (caudate and putamen)	R	16	4	2	8.73
Thalamus	L	-6	-18	12	5.56
Caudate	L	-12	-4	16	6.95
Anterior cingulate	R	8	36	26	5.71
<b>Satiety–Hunger</b>					
Orbitofrontal cortex*	L	-42	56	-12	4.84
Occipital cortex	R	38	-76	16	7.15
	L	-32	-68	22	5.73
Inferior temporal cortex	R	58	6	-30	5.85
Posterior temporal (fusiform)	R	42	-44	-22	5.71
<b>Incentive (High–Low)</b>					
Amygdala*	L	-10	-6	-8	3.27†
Orbitofrontal cortex*	L	-8	42	-20	3.46
<b>Interaction between intrinsic and extrinsic factors (Hunger: High–Low) – (Satiety: High–Low)</b>					
Orbitofrontal Cortex*	L	-26	56	-10	3.53†

All peaks survive a significance threshold of  $P < 0.05$  (except † marginally missed criterion). \**A priori* hypothesis regarding these regions.

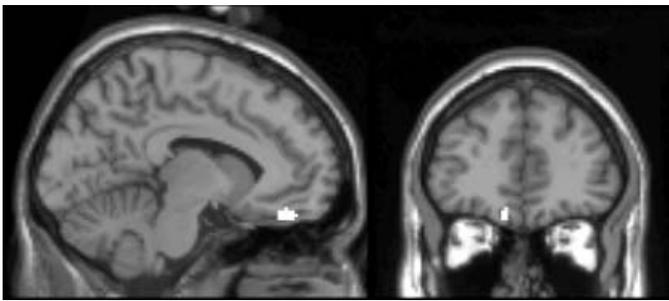


FIG. 4. Significant rCBF changes in the main effect contrast of incentive value. Sagittal and coronal sections illustrating an area of the left OFC, which showed increased activation in the high incentive condition; see Table 2 for coordinates and  $t$ -value. This area is almost identical to the location of activity observed for the equivalent contrast in an associated study (Arana *et al.*, 2003; Fig. 2B).

observed in this area during hunger relative to satiety, as shown in Fig. 5B.

## Discussion

This study compared the neural substrates underlying intrinsic and extrinsic processes contributing to the motivation to eat. Areas of increased activation during the intrinsic state of hunger included the hypothalamus, amygdala, striatum, insula and anterior cingulate cortex (ACC). Given the previous literature implicating these regions in the

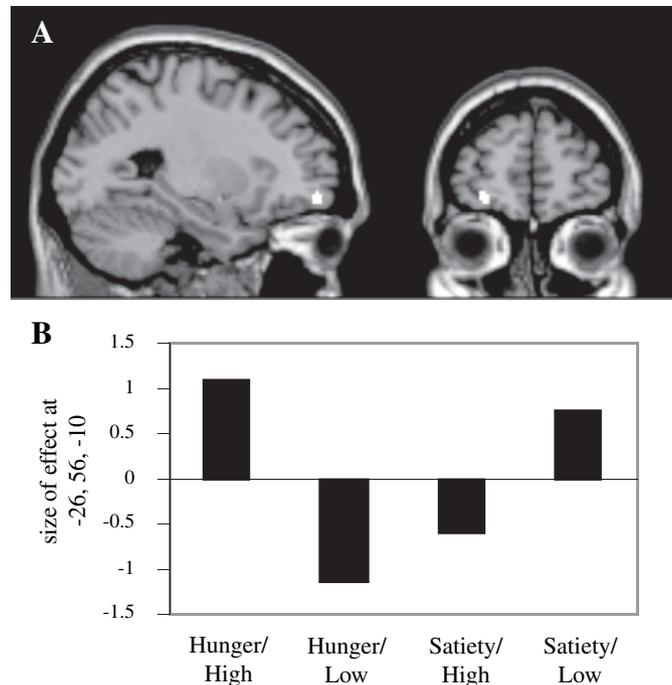


FIG. 5. The interaction between incentive value and hunger state. (A) Sagittal and coronal sections depicting a distinct area of the left OFC, which showed increased activation in the interaction between hunger state and incentive value; see Table 2 for coordinates and  $t$ -value. (B) The pattern of interaction between hunger state and incentive value is shown by this condition-specific plot: the conditions were Hunger/High Incentive, Hunger/Low Incentive, Satiety/High Incentive and Satiety/Low Incentive.

regulation of appetite (see below), it is unlikely that these effects reflect mere vascular changes related to food intake. In the reverse contrast, during a state of satiety, lateral orbitofrontal and temporal cortical areas showed increased activation, illustrating that there is a significant change in brain activity as the intrinsic state of the person shifts from hunger to satiety. Far fewer areas were sensitive to the extrinsic incentive properties of foods, with enhanced activations when imagining high-incentive foods only seen in the medial OFC and in the vicinity of the amygdala, corroborating that shown by Arana *et al.* (2003) using the same restaurant menu task. Thus, it would appear that the neural substrates underlying the mechanisms by which intrinsic and extrinsic factors influence motivation to eat show both neural dissociation and convergence.

## Neural basis of intrinsic motivational factors

In agreement with evidence implicating the hypothalamus in the regulation of eating (Burton *et al.*, 1976; Kalra *et al.*, 1999; Tataranni *et al.*, 1999), greater activation of the hypothalamus was found during hunger compared with satiety. The spatial resolution of PET does not allow identification of the individual hypothalamic nuclei activated, though the interfundibular, paraventricular nucleus and the lateral hypothalamus have been implicated (Kalra *et al.*, 1999). Furthermore, the significant activation of the insular cortex during hunger found in this study supports the accumulating evidence for its role in human appetite. Previous studies have demonstrated insular involvement in neural responses to hunger (Tataranni *et al.*, 1999; Morris & Dolan, 2001) and food stimuli (LaBar *et al.*, 2001), the modulation of reward value of food (Balleine & Dickinson, 2000; Small *et al.*, 2001) and the assignment of valence to visceral cues (Gordon *et al.*, 2000), in addition to increased neural activity to tastes (Kinomura *et al.*, 1994; Zald *et al.*, 1998), flavours (Small *et al.*, 1997; Kobayashi *et al.*, 2002) and smells (O'Doherty *et al.*, 2000). In fact, it has been suggested that autonomic, sensory and affective representations of stimuli overlap in the insular cortex (Small *et al.*, 2001).

Adaptive preparatory processes underlie the motivation to eat (Capaldi, 2001). This is demonstrated by activity in the striatum, in which neurons are activated largely by the expectation of reward, particularly the initiation and execution of feeding-related movements, but also in anticipating and detecting the reward itself (Rolls *et al.*, 1983; Schultz *et al.*, 2000). In this study, the striatum was strongly activated in response to hunger, which supports other imaging studies where activity in the striatum decreased in response to satiety (Gautier *et al.*, 2000, 2001; Small *et al.*, 2001), and the suggestion that one role of the striatum, along with areas such as the insula, is to initiate feeding (Small *et al.*, 2001). It is noteworthy that the contrast between hunger and satiety produced strong activation in this region, whereas the manipulation of high and low incentive did not. This may be because the menu items were only imagined rather than consumed during the study.

It is thought that other areas of the brain implicated in anticipatory processes are dissociable from those implicated in receipt of reward, in this case food (Everitt, 1990; Burns *et al.*, 1993; O'Doherty *et al.*, 2002). Whereas the hypothalamus directly controls and responds to the state of hunger, the amygdala may only respond to hunger if the person is anticipating food. Thus, the response of the amygdala in the hunger state in the present study may reflect the increased saliency of the restaurant menu items when hungry (Hamann *et al.*, 1999; Morris & Dolan, 2001). This also agrees with anecdotal comments from several participants, who found it was easier to imagine the menu items when hungry.

The ACC was also significantly activated during hunger. Anatomically, regions of the ACC are connected to the amygdala, ventral striatum, hypothalamus, insula and OFC (Devinsky *et al.*, 1995), a network associated with visceromotor and endocrine functions (Bush *et al.*, 2000) and is similar to the network activated in this, and other, studies in response to hunger (Tataranni *et al.*, 1999). As the ACC has been argued to underlie body weight and diet regulation (Hu *et al.*, 2002), the increased activity in this area may reflect the monitoring of the nutritional status of the individual. Further, the ACC is also implicated in error detection and response conflict (Bush *et al.*, 2000; van Veen & Carter, 2002), and so may compare the current nutritional state of the individual with the consequences of ingesting prospective food items; a function particularly pertinent to those with eating disorders. Indeed, this area has been shown to be significantly activated in response to food stimuli in those with recovered and chronic anorexia nervosa (Uher *et al.*, 2003).

In contrast to those areas activated by hunger, increased activation was found in the lateral OFC in association with satiety. A number of studies have demonstrated that sensory-specific satiety is reflected in activity of the OFC, as the value of the food decreases during consumption (Rolls *et al.*, 1989; Critchley & Rolls, 1996; O'Doherty *et al.*, 2000). Although no food was ingested in this study, the decreasing reward value of the food imagined whilst in a state of satiety may have led to this response. Satiety may be one source of inhibition when making choices between desirable food items, and it has been suggested previously that the prefrontal cortex, including the lateral OFC, is involved with the inhibition of responses (Elliott *et al.*, 2000). Indeed, lateral orbitofrontal activation was also seen in the associated study, in which it was argued that in order to make the choice between desirable food items, subjects had to suppress responses to two of the items in order to choose the third (Arana *et al.*, 2003). Furthermore, other studies have suggested an inhibitory role for the prefrontal cortex in the termination of feeding itself, thereby resulting in a state of satiety (Nozoe *et al.*, 1995; Tataranni *et al.*, 1999; Small *et al.*, 2001).

Increased activation of inferior and posterior temporal cortical areas were also associated with satiety, areas that have been associated previously with hunger (Fisher, 1994; Tataranni *et al.*, 1999; Gautier *et al.*, 2000, 2001; LaBar *et al.*, 2001). This may be a reflection of hunger and satiety being particular points in a cascade of responses to food intake (Blundell, 1990). Furthermore, in this study a similar area of the fusiform gyrus was activated during satiety as was activated during hunger in LaBar *et al.* (2001); the visual response to the food stimuli in the latter study was thought to vary according to the hunger state. Together with the increased activation in the occipital cortex in this study, activation of these predominantly visual areas during satiety suggests that imagining the food items was different in the two states. It could be argued that perhaps this was more difficult when in a satiated state, inducing enhanced activation; which agrees with the anecdotal comments of participants as previously mentioned.

### Neural basis of extrinsic motivational factors

Imagining a prospective meal composed of highly valued foods (i.e. the main effect contrast of high–low incentive menus) produced activation in the vicinity of the left amygdala and a region of the left medial OFC. These results are strengthened by comparison with an associated study (Arana *et al.*, 2003), in which activation of corresponding areas was found using an independent data set. That study demonstrated that the functions of the amygdala and OFC could

be differentiated; activity in the amygdala positively correlated with the magnitude of the incentive value of menu items (also see LaBar *et al.*, 2001; Gottfried *et al.*, 2003), whereas activity in the OFC not only responded to high-incentive stimuli, but also when information regarding incentive value informed choice (also see Schoenbaum *et al.*, 1998, 1999; Bechara *et al.*, 1999; Tremblay & Schultz, 1999; Baxter *et al.*, 2000; Pears *et al.*, 2003; Pickens *et al.*, 2003).

When determining the neural mechanisms underlying the regulation of motivation by both intrinsic and extrinsic factors, a further area of the OFC was activated, which was lateral and anterior to the 'incentive' peak. More activation was found during hunger relative to satiety when high-incentive food items were considered, although hunger alone did not activate the OFC. This finding suggests that the OFC plays a role in goal selection, on the basis of both motivational and physiological state.

### Conclusion

This study has demonstrated that the neural substrates of motivation to eat are distributed in a 'network' of midbrain, diencephalic and cortical areas. Activity in some nodes of the network reflect specifically the influence of either intrinsic or extrinsic factors on motivation, while others may act as a final common pathway. There is now some consensus regarding the neuroanatomy of intrinsic appetitive function: from the physiological response in the brain stem, to the more complex motivational and affective responses in the hypothalamus, amygdala, striatum, insula and prefrontal cortex. Each area plays a distinct but integrated role in the process, either as a relay of information such as the medulla (Jean, 1991) or as a homeostatic centre such as the nuclei of the hypothalamus (Kalra *et al.*, 1999). The substrates of extrinsic processes are embedded in this network; specifically the amygdala and OFC are implicated in the processing of appetitive incentive stimuli and the subsequent production of goal-directed behaviour, in this case when the goal is to find or choose between desirable foods.

The implications of understanding this network are widespread both in terms of increasing our knowledge regarding the normal regulation of intrinsic and extrinsic factors on the motivation to eat, and also using this information to understand disorders in which this system is dysfunctional. The extent to which intrinsic and extrinsic factors contribute to a disorder may vary. Anorexia nervosa, for example, is characterized by food restriction (Huse & Lucas, 1984); an extrinsic contribution occurs in those with the disorder who report increased anxiety around high-calorie foods, a response that has been shown to be associated with elevated rCBF in the medial temporal lobe (Gordon *et al.*, 2001). Prader–Willi syndrome is characterized by excessive eating due to an abnormal satiety response to food intake (Holland *et al.*, 1993). This leads to an 'insatiable appetite', which is likely to be due to abnormal processing in the intrinsic network; but such is the drive to eat in this syndrome, extrinsic factors may also contribute.

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## Abbreviations

ACC, anterior cingulate cortex; MRI, magnetic resonance imaging; OFC, orbitofrontal cortex; PET, positron emission tomography; rCBF, regional cerebral blood flow; ROI, region of interest.

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